mons pubis. These glands are *stimulated by* epinephrine carried in the blood stream, called *Non-Thermal Sweating*. Atropine does not inhibit this secretion.

Sweating is controlled by direct or reflex stimulation of the centres in the spinal cord, medulla, hypothalamus or cerebral cortex.

In the initial stages, sweating is initiated by the discharge of impulses from the motor cortex. In later stages, rise in hypothalamus temperature acts upon detectors at the hypothalamic level. Spinal centres exist for segmental control of sweating.

The rate of evaporation of water is influenced inversely by the degree to which the atmosphere is already saturated with water *i.e.* by its relative humidity. Therefore, a man can maintain normal body temperature in an atmosphere of over 100°C provided the air is perfectly dry while in damp atmosphere a temperature of 50°C causes body temperature to rise rapidly; *that is why one feels hotter on a humid day*.

Rate of sweating may be as high as 1.6 L per hour. If it were all evaporated this would remove over 900 kcal of heat from the body per hour. Therefore, heat loss by vaporization of water varies from 30-900 kcal per hour.

TEMPERATURE REGULATING MECHANISMS

These mechanisms involve the reflex thermoregulatory responses. They include *autonomic, somatic, endocrine and behavioural changes*. One group of responses cause increase in heat loss and decreased heat production; whereas the others cause decrease in heat loss and increased heat production (Fig. 63.3).

1. THERMOREGULATORY RESPONSES ACTIVATED BY EXPOSURE TO COLD (via posterior hypothalamus)

A. *Increase Heat Production*

1. *Shivering*. It is an involuntary response of skeletal muscles contraction and can increase the muscle metabolism up to 3 times. It may try to maintain the body temperature at 28°C when body temperature falls below the critical level of 23°C.

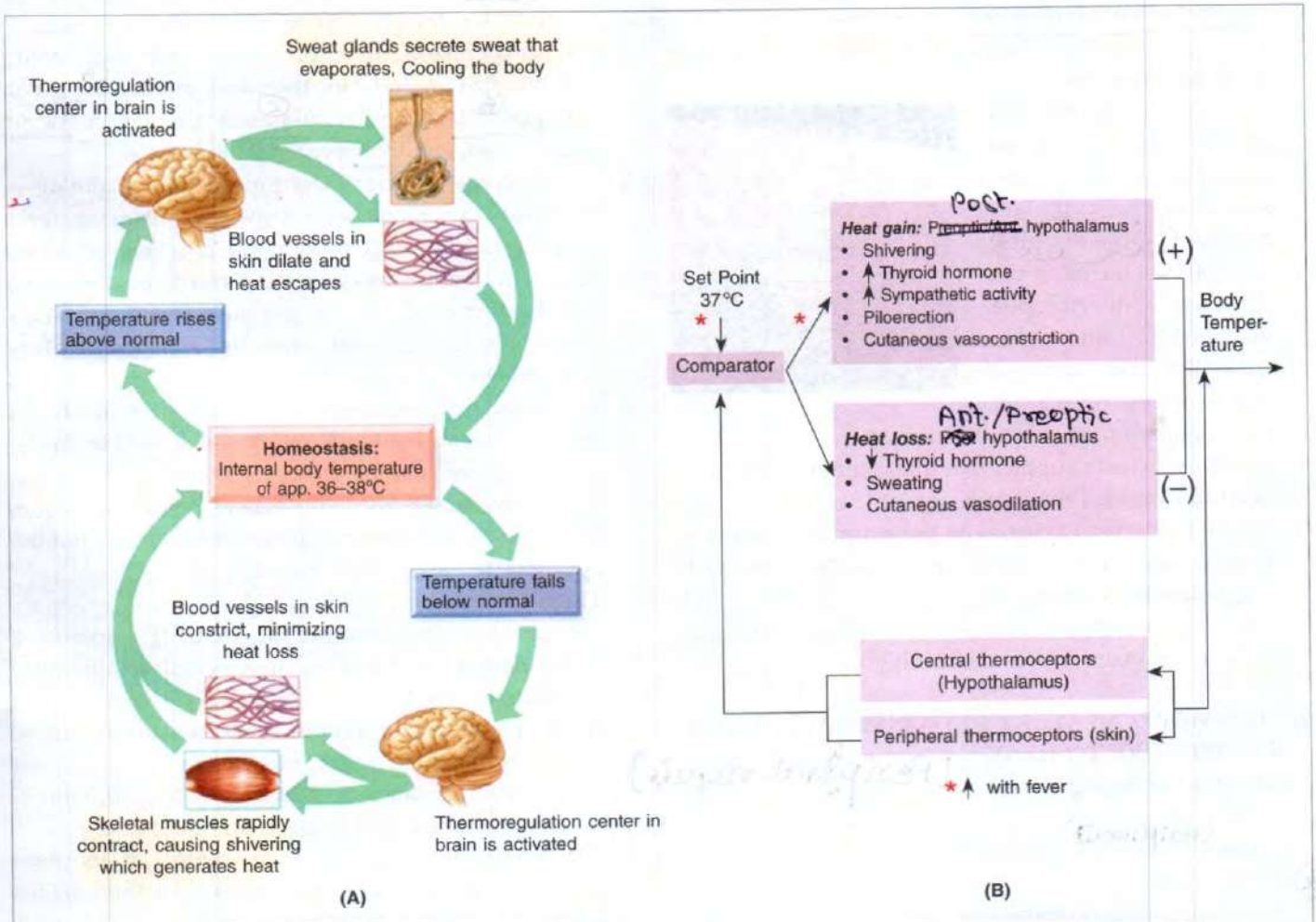


Fig. 63.3 Temperature regulation (A) Mechanisms; (B) Summary

2. *Hunger* increases food intake and thereby increases sympathetic discharge.
3. *Increase Voluntary Activity* because of semiconscious increase in motor activity *e.g.* foot stamping and dancing up and down on a cold day.
4. *Increase TSH secretion* from anterior pituitary.
5. *Increase Catecholamine* (epinephrine and nor-epinephrine) secretion from adrenals.

B. *Decrease Heat Loss*

1. *Cutaneous Vasoconstriction due to*
   (i) exposure to cold – 'Local response'
   (ii) increase catecholamine secretion from adrenal medulla – 'Generalised reflex response'.

   When cutaneous blood vessels are cooled, they become more sensitive to catecholamines and the arterioles and venules constrict. This directs blood away from the skin into deeper veins *i.e.* venae comitantes which run along the side of arteries. Therefore, heat is transferred from the warm arterial blood to the cold venous blood coming from the extremities and is carried back to body without reaching the skin (***counter current heat exchange***) (page 547). This keeps the tips of the extremities cold but conserves body heat.
2. *Curling up* 'in a ball' decreases body surface exposed to the environment.
3. *Horripilation i.e.* erection of the hairs due to contraction of piloerector muscle attached to the hair results in Goose Pimples. *Horripilation* increases the thickness of the trapped air, therefore, heat transfer across this layer is reduced and heat loss (or in a hot environment, heat gain) is decreased.

Humans, usually supplement this layer of hair with a layer of clothes. Therefore, magnitude of heat transfer across the clothing depends on its texture and thickness thereby determining how warm or cool the clothes feel. For example, dark clothes absorb radiated heat and feel warm whereas light-coloured clothes reflect heat back to the exterior thus feel cool.

2. THERMOREGULATORY RESPONSES ACTIVATED BY EXPOSURE TO HEAT (via anterior hypothalamus)

A. *Increase Heat Loss*

1. Cutaneous vasodilatation
2. Sweating
3. Increase in respiration.
4. Nor-epinephrine

B. *Decrease Heat Production*

1. Anorexia, decreases sympathetic discharge and decrease BMR
2. Apathy and inertia decreases body activity as a whole
3. Decrease TSH secretion from anterior pituitary.

The above mentioned mechanisms which get activated by exposure to cold or heat are controlled by ***Nervous System*** *and* ***Endocrines****.*

I. Role of Nervous System

The thermoregulatory responses which control heat production and heat loss from the body are primarily integrated in the hypothalamus.

1. The **afferents** (signals) that activate the hypothalamic temperature regulating centres come from two sources:
   (i) *Temperature-sensitive cells in the anterior hypothalamus*, which get stimulated by exposure to high temperature.
   (ii) *Cutaneous temperature receptors*, specially cold receptors, which get stimulated by exposure to cold (for details, refer to page 864).
2. **Efferents** project to the somatic and autonomic nervous system and can, therefore, modify muscular and glandular activity, cutaneous circulation, sweat secretion and pulmonary ventilation.
3. The response of body heat production to cooling is modified by interactions between cutaneous and central stimuli. Heat production is increased when head temperature falls below a given threshold value, but the threshold for the response is lower and its magnitude is decreased when the skin temperature is increased.
4. In general, *cutaneous temperature receptors* are much less important than the temperature sensitive cells in the anterior hypothalamus. However, by acting along with the *hypothalamic receptors* the skin receptor can shorten the latent period between changes in heat loss and the appropriate thermoregulatory response.
   Thus,
   (i) the skin receptors are of value in promoting responses to rapid environmental temperature changes, and
   (ii) the hypothalamic receptors compensate for changes in endogenous heat production and prevent overcompensation by skin reflexes (e.g. promotion of shivering by cooling the skin).
5. *The anterior hypothalamus is the 'centre' for responses to rising temperature and the posterior hypothalamus the 'centre' for responses to falling temperature.*

Evidences

(i) **Localized stimulation of *anterior hypothalamus*** results in:
   (a) anorexia
   (b) cutaneous vasodilatation
   (c) sweating, and
   (d) increase in respiration via ANS

   Its lesion lead to hyperthermia, and core temperature increases to 43°C.

(ii) **Localized stimulation of *posterior hypothalamus*** results in:
   (a) shivering due to increased muscular activity via somatic nervous system
   (b) cutaneous vasoconstriction, increase HR, increase BP and pupillary dilatation via ANS; and
   (c) hunger

   Its lesion causes body temperature to fall towards that of environment because both cold and hot regulating mechanisms are destroyed as anterior hypothalamus fibers pass via the posterior hypothalamus, therefore, person becomes *poikilothermic* (page 581).

6. There is some evidence that *5-HT (serotonin)* is a synaptic mediator in the centres controlling the mechanisms activated by 'cold'; and *nor-epinephrine* plays a similar role in those activated by 'heat'.

II. Role of Endocrines

1. *Adrenal Medulla* – Exposure to cold reflexely stimulates epinephrine secretion that stimulates metabolism and decreases heat loss. Epinephrine effect is rapid and of short duration.
   Evidence: Adrenal medullectomized rats die faster than normal controls when exposed to cold.
2. *Thyroid*
   Exposure to cold via hypothalamic TRH (thyroid releasing hormone) and pituitary thyrotrophin causes stimulation of thyroid secretion. This increases heat production, mobilizes glycogen and stimulates gluconeogenesis.
   Its effect is slowly developing but much more prolonged.
   In *cretin* and *myxoedematous patients*, body temperature is subnormal, therefore, they prefer hot environment.
   Evidence: Rats exposed to low temperatures (7-12°C) for more than 3 weeks develop hyperplasia of thyroid gland and increase in metabolic rate by 16%; while thyroidectomised rats under same environmental condition showed very little increase in metabolic rate.
3. *Adrenal Cortex*: Exposure to external heat or cold, stimulates secretion of adrenal corticoids.

APPLIED ASPECT

A. FEVER (HYPERTHERMIA)

Mechanism of Development of Fever

When fever occurs, the thermoregulatory mechanisms behave as if they were adjusted to maintain body temperature at a higher than normal level *i.e. as if the* ***thermostat*** *had been* ***reset*** to a new point above 37°C. The temperature receptors then signal that the actual temperature is below the new set point, and temperature-raising mechanisms are activated. This produces chilly sensations or even shivering due to cutaneous vasoconstriction.

However, the nature of the response depends on the ambient temperature. The temperature rise is due to:

(1) increase heat production, if in a cold environment, and to
(2) decrease heat loss, if in a warm environment.

Pathogenesis of Fever

1. Endotoxin from bacteria
2. Inflammation, and
3. Other pyrogenic stimuli

↓ These act on

↓ *Monocytes*
Macrophages
Kupffer cells
to produce

↓ *Cytokines* and *Interleukin-1* (a polypeptide, called **Endogenous Pyrogen**)

↓

(i) Enters brain, direct effect on 'preoptic area of hypothalamus' to cause increase synthesis of probably prostaglandins which produce fever. 'Aspirin' by inhibiting synthesis of prostaglandins (specially PGE_2), decreases the fever.
(ii) Acts on lymphocytes to activate the immune system
(iii) Stimulates bone marrow and causes neutrophil release
(iv) Proteolysis in muscle ⇒

(Also see to page 447)

Benefits of fever

1. **Inhibits bacterial growth.**
   Before the advent of antibiotics, fever was artificially induced for the treatment of *neurosyphilis* and proved

to be beneficial. Hyperthermia benefits individuals infected with:

(i) anthrax
(ii) pneumococcal pneumonia [LAP]
(iii) leprosy
(iv) various fungal, rickettsial and viral diseases.

2. Increases antibody production.
3. Decreases tumour growth.

However, very high temperatures are harmful. When core temperature is more than 41°C (106°F) for prolonged periods it may cause permanent brain damage. When it is more than 43°C death occurs due to heat stroke.

Cause? → Excess physical activity ← common in Mid-east
→ Excess temp

Important Note

Mutation of the gene coding for ryanodine receptors (page 164) leads to excess Ca^{2+} release during muscle contraction. This increases heat production in the muscle and causes marked rise in body temperature, called *Malignant Hyperthermia*. A phenomenon commonly triggered by stress.

Cause: HALOTHANES - anaesthetic drugs

B. HYPOTHERMIA (94°F)

When the skin or the blood is cooled enough to lower the body temperature, it results in

(1) metabolic and physiologic processes to slow down
(2) decreases respiration and heart rate
(3) decreases BP, and
(4) loss of consciousness.

At core temperature of about 28°C ability to spontaneously return the temperature to normal is lost, but the individual continues to survive and, if rewarmed with external heat, returns to a normal state.

⇒ If not treated ⇒ Gangrene ← FROST BITE ← Ischaemia of periph

Use

Humans tolerate body temperature of 21-24°C (70-75°F) without permanent ill effects, and induced hypothermia has been used extensively in surgery. In hypothermic patients, the circulation can be stopped for relatively long periods because the O_2 needs of the tissues are greatly reduced. BP is low and bleeding is minimal. It is possible under hypothermia to stop and open the heart and to perform other procedures, specially brain operations.

Artificial hypothermia

Study Questions

1. **Give physiological basis of:**
   (i) Subnormal body temperature in old age
   (ii) Maximum heat production after ingestion of proteins
   (iii) One feels hotter on a humid day
   (iv) Hypothyroid patients prefer hot environment
   (v) Aspirin is given to decrease fever
   (vi) One feels chilly in a relatively warm room with cold walls
   (vii) Shivering.
2. **Write short notes on:**
   (i) Factors affecting body temperature
   (ii) Heat production and heat loss processes
   (iii) Specific dynamic action of food
   (iv) Brown fat
   (v) Vaporization of water from the body
   (vi) Mechanism of sweating and its control
   (vii) Thermoregulatory response activated by thermal stress
   (viii) Neural and humoral mechanisms controlling body temperature
   (ix) Pathophysiology of fever
   (x) Benefits of hypo- and hyperthermia.
   (xi) Thermal receptors
3. **Give the physiological significance of:**
   (i) Comfortable zone temperature
   (ii) Thermal and non-thermal sweating
4. **Why is regulation of body temperature required?**
5. **Mention the sites from where core temperature can be recorded.**
6. **How much calories of heat are required by a person weighing 70 kg to raise his body temperature by 1°C?**

- Physical barrier
- Temp. regulation
- Excretion of waste material
- Prevention of UV rays
- Fluid-Electrolyte balance

7. Give the contribution of each process that transfers heat away from the body.
8. How many calories of heat are removed from the body by vaporization of 1 mL of water?
9. What amount of heat is lost via perspiration?
10. What will happen and why to body temperature if:
    (i) Anterior hypothalamus is destroyed locally.
    (ii) Posterior hypothalamus is destroyed locally.
11. Depict diagrammaticals:
    (i) Temperature regulting mechanism
    (ii) Balance between factors increasing heat production and heat loss

MCQs

1. Regulation of body temperature is required:
   (a) To obtain neutral zone temperature
   (b) To speed up chemical reactions within the body
   (c) Because enzyme system of body has narrow temperature range to function
   (d) To prevent body invasion by bacteria
2. Oral temperature:
   (a) An accurate index of body temperature
   (b) Remains fairly constant under different conditions
   (c) Closely correlated with rise of temperature in subclavian artery
   (d) Thermoregulatory receptors are sensitive to it
3. Lower and upper lethal core temperatures respectively are:
   (a) 5°C below and above the normal
   (b) 7°C below and above the normal
   (c) 26°C and 43.5°C
   (d) 30°C and 41°C
4. A major factor resulting in increase in body temperature during exercise is:
   (a) Heat dissipating mechanisms inefficient
   (b) Enormous thermogenesis
   (c) Vasoconstriction in non-working muscles
   (d) Resetting of thermostat
5. BMR is dependent on:
   (a) Body weight
   (b) Surface area
   (c) Amount of adipose tissue
   (d) Amount of lean body mass
6. A major source of heat production in infants is:
   (a) Increased muscular activity
   (b) Brown fat
   (c) Increased sympathetic activity
   (d) Specific dynamic action of food
7. At environmental temperature of 36°C, most important mechanism of heat loss is by:
   (a) Sweating (b) Radiation (c) Conduction (d) Insensible perspiration
8. Vaporization of 1 gm (about 1 mL) of water removes approx. ..... of heat:
   (a) 200 calories (b) 400 calories (c) 600 calories (d) 800 calories
9. Heat loss process of the body *not* directly under physiological control is:
   (a) Radiation from body
   (b) Conduction and convection to surroundings
   (c) Vaporization of sweat
   (d) Warming of inspired air
10. One feels hotter on a humid day because:
    (a) Rate of sweating increases
    (b) Surrounding temperature is more
    (c) Heat loss by the body via process of radiation decreases
    (d) Rate of evaporation of water from body decreases
11. Body temperature will rise sharply when exposed in an atmosphere of:
    (a) Over 100°C, dry air
    (b) 50°C, damp air
    (c) 25°C, dry air
    (d) 25°C, damp air
12. A person who has been cold acclimatized shows all changes *except*:
    (a) Hypothermic response
    (b) Increased vascular insulation
    (c) Initiation of shivering at lower temperature
    (d) Decreased metabolism

13. *False* statement regarding horripilation:
(a) Seen during exposure to cold
(b) Activated by anterior hypothalamus
(c) Results in goose pimples
(d) Increase the thickness of the trapped air

14. Integration of temperature information by the nervous system occurs mainly in the:
(a) Spinal cord
(b) Hypothalamus
(c) Amygdala
(d) Peripheral receptors

15. Which area of hypothalamus functions as thermostat?
(a) Preoptic
(b) Paraventricular
(c) Dorso medial
(d) Lateral

16. During the course of febrile illness, shivering is usually associated with which of the following?
(a) A recent increase in the hypothalamic set point temperature
(b) A recent reduction in the hypothalamic set point temperature
(c) Rising body temperature
(d) Falling body temperature

17. Pyrogens raise body temperature by:
(a) Setting the thermostat to higher level
(b) Releasing interleukins
(c) Decreasing peripheral heat liberating mechanism
(d) Causing peripheral vasoconstriction

18. Profound hypothermic signs include all *except*:
(a) Slow breathing
(b) Bradycardia
(c) Hypotension
(d) Hyperactivity

19. Neutral (or comfortable) zone temperature is:
(a) Ambient temperature at which no active temperature regulatory mechanism operates
(b) Normal is 27 ± 2°C
(c) Also called critical air temperature
(d) All of the above

20. Rectal temperature is higher than oral temperature by ..... °C:
(a) 0.5-1
(b) 1-2
(c) 2-3
(d) 3-4

21. Circadian fluctuation in body temperature may occur in healthy individuals upto ... °C:
(a) 0.5
(b) 1.5
(c) 2.0
(d) Not seen

22. During severe exercise, core temperature may rise by .... °C:
(a) 3-4
(b) 4-5
(c) 5-6
(d) 6-7

23. How many Kcals are required by a person weighing 70 kg to raise his body temperature by 1°C?
(a) 7
(b) 14
(c) 28
(d) 56

24. Normally, insensible water loss (perspiration) through skin per day is:
(a) 400-600 mL
(b) 600-800 mL
(c) 800-1000 mL
(d) 1000-1200 mL

25. Insensible water loss (perspiration) will be absent if humidity is:
(a) 50%
(b) 70%
(c) 90%
(d) 100%

26. Shivering can increase the rate of heat production upto ..... times:
(a) 2
(b) 3
(c) 5
(d) 8

27. The anterior hypothalamus is the cenre for responses to:
(a) Rising body temperature
(b) Falling body temperature
(c) Increased heat production
(d) Decreased heat loss

28. Aspirin decreases the body temperature by:
(a) Inhibiting interleukin-1
(b) Inhibiting pyrogens release
(c) Killing fever producing organisms
(d) Inhibiting prostaglandin synthesis

Answers

1. (c)	2. (c)	3. (c)	4. (d)	5. (b)	6. (b)	7. (b)	8. (c)	9. (d)	10. (d)
11. (b)	12. (d)	13. (b)	14. (b)	15. (a)	16. (a)	17. (b)	18. (d)	19. (d)	20. (a)
21. (b)	22. (a)	23. (d)	24. (d)	25. (d)	26. (b)	27. (a)	28. (d)		

Unit VIII

METABOLISM AND NUTRITION

Chapter 64: Principles of Energy Metabolism

Important definitions
Phases of catabolism
Chemical reaction
Enzymes
Energy liberation and transfer
Biological oxidation

Chapter 65: Carbohydrate Metabolism

Carbohydrates of food
Digestion and absorption of carbohydrates
Intermediary metabolism of carbohydrates
Regulation of blood glulcose level

Chapter 66: Fat Metabolism

Classification of lipids
Digestion and absorption of neutral fats
Fate of fat after absorption
Relation of liver to fat metabolism
Fatty acid catabolism: Ketone bodies
Utilization and catabolism of 'active acetate'
Free fatty acid metabolism
Cholesterol metabolism – Atherosclerosis
Integration of fat and carbohydrate metabolism

Chapter 67: Protein Metabolism

General: definitions; nitrogen balance; essential amino-acids; urinary sulphates; digestion and absorption amino acid pool
Metabolism of amino-acids and nucleic acid; Gout.

Chapter 68: Food and Nutrition

Food Vs nutrition
Constituents of normal diet
Nutritional needs of the body in terms of calories
Balanced diet
Principles of diet planning.
Applied: PCM (Kwashiorkor; Marasmus); undernutrition and starvation.

Chapter 69: Antioxidant Nutrients, Free Radicals and Physiology of Aging

Antioxidant nutrients
Free radical-formation and diseases they produce
Age related changes
Theories of aging
Factors that will delay aging

Chapter 64

Principles of Energy Metabolism

I. Definitions: Catabolism; Anabolism
II. Phases of catabolism
III. Chemical reactions
IV. Enzymes
V. Energy liberation and transfer
VI. Biological oxidations

DEFINITIONS

The term ***metabolism*** (a Greek word) means *a change* and refers to all the chemical and energy transformations that occur in the body. It comprises two processes: *catabolism* and *anabolism*.

1. ***Catabolism*** or ***dissimilation*** is the total breakdown process underwent by a foodstuff to produce the final end products. Catabolic processes liberate energy because the energy content of a complex foodstuff is greater than that of its simpler degradation products.
2. ***Anabolism*** or ***assimilation*** is building up of storage, structural and functional materials from simple foodstuffs or intermediates.

PHASES OF CATABOLISM

Catabolism proceeds in *three* major phases as follows:

(A) Phase I

(i) This corresponds to the processes of intestinal digestion and absorption and the similar processes in tissues when stored material is mobilized for catabolism. For example: polysaccharides are converted to simple hexose sugars; fats to glycerol and fatty acids; proteins to amino acids.

(ii) Relatively little energy is liberated in this phase of metabolism.

(B) Phase II

(i) The various end products from phase I are partially oxidised to form CO_2, H_2O, nitrogenous waste products, and one of the three acids: *acetic acid*, *α-ketoglutaric acid* and *oxaloacetic acid*.

(ii) During this phase, about one-third of the available energy of complete catabolism is released.

(C) Phase III

(i) It represents a final metabolic 'cyclical' pathway *common to all three acids*. This pathway is called the ***citric acid cycle*** after one of the chief intermediates, citric acid.

(ii) It results in oxidation of three acids to CO_2 and H_2O with the release of the remaining two-thirds of the available chemical energy.

(iii) It provides a set of related and interchangeable intermediates through which the major metabolic materials can be transformed one into the other.

CHEMICAL REACTIONS

Since the energy content of the ***reactants*** and ***products*** are usually different, and because energy can neither be created nor destroyed, energy must either be added or released during a chemical reaction. For example, the reaction in which carbonic acid (*energy content:* 155 Kcal/ mol) breaks down into CO_2 (94 Kcal/ mole) and water (57 Kcal/mol) with the release of 4 Kcal of energy per mole of reactants. The energy that is released appears as heat energy, the energy of increased molecular motion.

$$\underset{\text{Reactant}}{H_2CO_3} \longrightarrow \underset{\text{Products}}{CO_2 + H_2O} + 4 \text{ Kcal/mol}$$

(155 Kcal per mol)

(94 Kcal/mol) + (57 Kcal/mol)

1. *Determinants of Reaction Rates* (Table 64.1)

Table 64.1: Determinants of Reaction Rates

Factor	Effect
(i) Reactant concentration	(i) Higher concentration, faster reaction rate
(ii) Activation energy*	(ii) High activation energy, slower reaction rate
(iii) Temperature	(iii) Higher temperature, faster reaction rate
(iv) Catalyst	(iv) Increases reaction rate

* In order for a chemical reaction to occur, reactant molecules must acquire enough energy (the ***activation energy***) to enter an activated state in which some of the chemical bonds can be broken. This energy is released when the products are formed.

2. *Reversible and Irreversible Reactions*

(i) In every chemical reaction there are two reactions going on simultaneously: a *forward* reaction in which *reactants* are converted to *products* and a *reverse* reaction, in which *products* are converted to reactants.

(ii) As a reaction progresses, rate of the forward reaction decreases (as concentration of *reactants* decreases) and simultaneously the rate of reverse reaction will increase (as the concentration of *product* molecules increases). Finally, the reaction will reach a state of ***chemical equilibrium*** in which the forward and reverse reaction rates are equal. At this stage there will be no further change in the concentration of *reactants* and *products*.

(iii) **Characteristics features**

(a) *Reversible reactions*

$A + B \rightleftharpoons C + D$ +small amount of energy

at chemical equilibrium, ***product*** concentrations are only slightly higher than ***reactant*** concentrations.

(b) *Irreversible reactions*

$E + F \longrightarrow G + H$ + large amount of energy

Here, at chemical equilibirum, almost all *reactant* molecules have been converted to *product*.

Note

Although all chemical reactions are reversible to some extent, those reactions that release large amount of energy are said to be irreversible reactions.

3. *Law of Mass Action*

(i) The concentrations of *reactants* and *products* also play an important role in determining the direction in which the net reaction proceeds. Its direction can be altered by *lowering* the concentration of one of the participants. Thus, lowering the concentration of one of the *products* will drive the net reaction in the forward direction and *vice versa*.

(ii) The effects of *reactant* and *product* concentrations on the direction in which the net reaction is proceeding is called as the ***law of mass action*** (Fig. 64.1).

ENZYMES

1. The *catalysts* are called enzymes (meaning '***in yeast***', the first enzyme was discovered in yeast cells). The

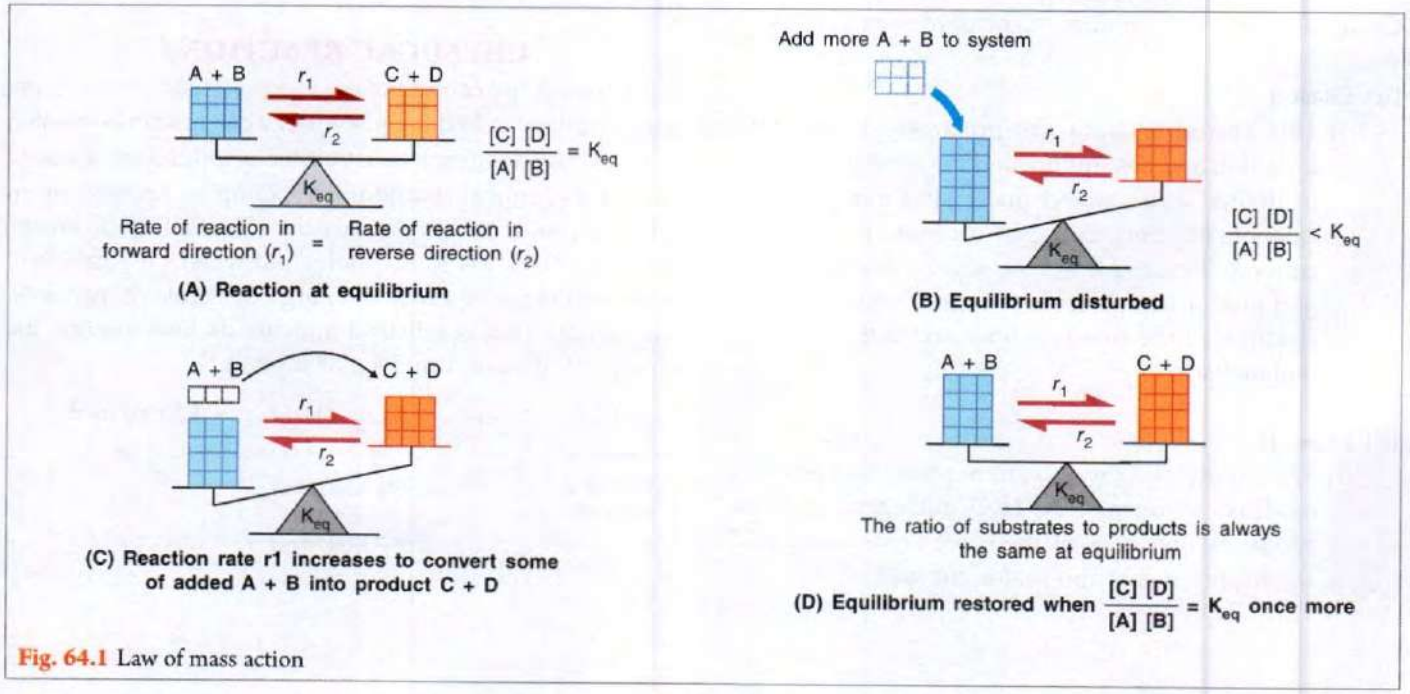


Fig. 64.1 Law of mass action

enzymes are protein molecules and so an enzyme is also called as ***protein catalyst***.

2. The enzyme combines with *reactant* (substrate) to form an *enzyme-reactant (substrate) complex*, which breaks down to release *products* and *enzyme*.

$$\underset{\textit{(reactant)}}{R} + \underset{\textit{(enzyme)}}{E} \rightleftharpoons \underset{\substack{\textit{enzyme}\\\textit{reactant}\\\textit{complex}}}{ER} \rightleftharpoons \underset{\textit{product}}{P} + \underset{\textit{enzyme}}{E}$$

At the end of the reaction, the enzyme is free to undergo the same reaction with additional *reactant* molecules.

3. ***Characteristic features of enzymes***
   (i) It undergoes *no* net chemical change as a consequence of the reaction it catalyses.
   (ii) The binding of *reactant* to an enzyme's active site has the properties of: *chemical specificity, affinity, competition* and *saturation* (see below)
   (iii) An enzyme cannot cause a reaction to occur but it increases the rate of a chemical reaction by lowering the *activation energy* of the reaction.
   (iv) It increases both the *forward* and *reverse* rates of a chemical reaction and thus does not change the *chemical equilibrium*.
   (v) It lowers the *activation energy* of a reaction but does not alter the net amount of energy that is added to or released by the reactants in the course of the reaction.

Note

The catalytic activity of an enzyme can be extremely large. For example, a single molecule of an enzyme can convert approx. 1,00,000 *reactant* molecules to *products* in 1 sec.

4. ***Cofactors and Coenzymes***
   (i) Many enzymes are inactive in the absence of small amounts of other substances called ***Cofactors***. The Cofactor is either a trace metal (such as Mg^{2+}, Fe^{2+}, Fe^{3+}, Zn^{2+}, Cu^{2+} or PO_4^{3-}) or an organic molecule that directly participate as one of the *reactant* in the reaction being catalyzed and is termed as ***Coenzyme***.

   (ii) ***Enzyme-Coenzyme system***
   A single Coenzyme molecule can be used over and over again to transfer molecular fragments from one reaction to another. For example:

$$R\text{-}2H + \text{Coenzyme} \overset{\textit{enzyme}}{\rightleftharpoons} R + \text{Coenzyme-}2H$$

The two H-atoms that are transferred from a reactant (R_1) to the Coenzyme can be transferred from the Coenzyme to another reactant (R_2) with the help of a second enzyme. The second reaction converts the Coenzyme back to its original form which becomes available to accept two more H-atoms **(Fig. 64.2)**.

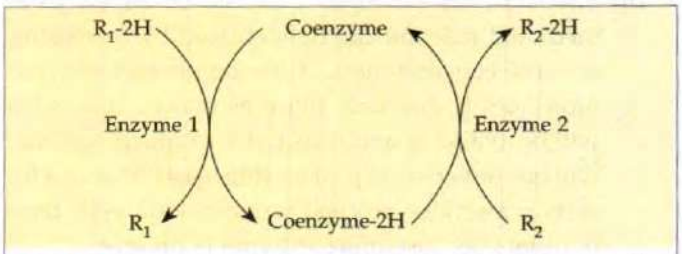


Fig. 64.2 The transfer of 2H-atoms from R_1-2H to R_2 by way of a Coenzyme. Enzyme 2 regenerates the original Coenzyme that can now reapeat the cycle.

   (iii) Coenzymes are derived from vitamins (page 630). A few of the Coenzymes, the vitamins from which they are derived and the chemical group they transfer are listed in **Table 64.2**.

5. ***Regulation of Enzyme-Mediated Reactions***
Factors that affect the rate of an enzyme-mediated reactions are:
   (i) ***Substrate (reactant) concentration:*** The rate of an enzyme-mediated reaction increases as the substrate (*reactant*) concentration increases until it reaches the maximal rate despite further increase in substrate concentration **(Fig. 64.3)**.

Note

Since Coenzymes are substrates in enzyme reactions, changes in Coenzyme concentration also affect a reaction rate by the same saturation mechansim.

Table 64.2: Derivation of Coenzymes

Coenzyme	Vitamin from which derived	Transferred chemical group
(a) Nicotinamide adenine dinucleotide (NAD^+)	Niacin (Vitamin B_4)	Hydrogen (-2H)
(b) Flavin adenine dinucleotide (FAD)	Riboflavin (vitamin B_2)	Hydrogen (-2H)
(c) Coenzyme A (CoA)	Pantothenic acid	Acetyl groups (—C—CH_3) ‖ O
(d) Tetrahydrofolate	Folic acid	Methyl group (—CH_3)

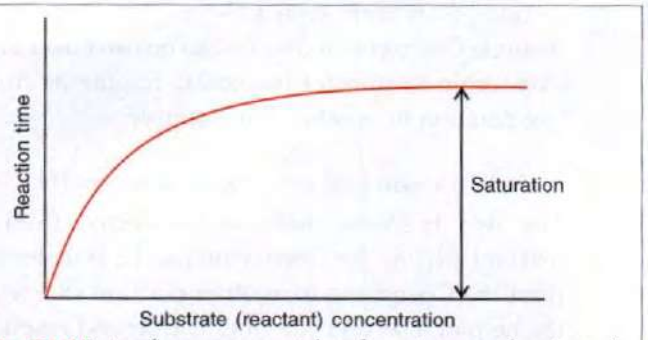


Fig. 64.3 Rate of an enzyme-catalyzed reaction as a function of substrate concentration

(ii) ***Enzyme concentration:*** The rate of an enzyme-mediated reaction can be increased by increasing enzyme concentration. If the number of enzyme molecules is doubled, twice as many active sites will be available and thus twice as much *substrate* will be converted to *product* **(Fig. 64.4)**. This is why certain reactions proceed faster in some cells than in others because more enzyme is present.

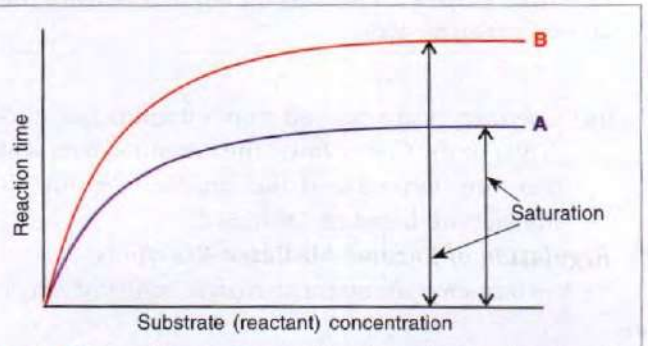


Fig. 64.4 Rate of an enzyme-catalyzed reaction as a function of substrate concentration at two enzyme concentrations A and B. (Enzyme conc. B is twice enzyme conc. A, so produces twice the maximal reaction rate.)

Note

Changing the concentraion of enzymes is a relatively slow process, generally requiring several hours. Regulation of gene transcription is the primary mechanism for altering most enzyme concentrations.

(iii) ***Enzyme activity:*** The rate of an eznyme-mediated reaction can be altered when the properties of an enzyme's active site are altered. The increased affinity of the enzyme's binding site will result in an increase in the number of active sites that contain bound substrate. **(Fig. 64.5)**

Note

The major modulators of enzyme activity are the products of metabolism and chemical messengers such as hormones. The activity of an enzyme can be altered by more than one agent.

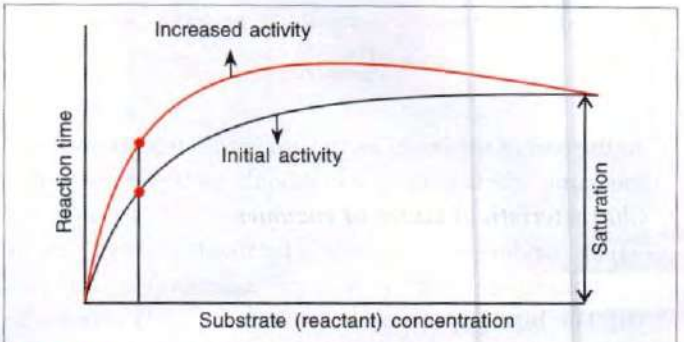


Fig. 64.5 Rate of enzyme-catalyzed reaction as a function of enzyme activity. Note that increasing the enzyme's affinity does not increase the maximal rate of the enzyme-mediated reaction.

Note

Since body temperature is normally maintained nearly constant, changes in temperature are not used directly to alter the rates of metabolic reactions. However, during fever and exercise, increase in temperature increases the rates of all metabolic reactions.

ENERGY LIBERATION AND TRANSFER

1. The *unit of energy* is the same as that of heat. The standard unit of heat is the ***calorie (cal)***. It is *defined* as the amount of heat energy necessary to raise the temperature of 1 gm of water by 1 degree celsius, *e.g.* from 15 to 16°C. This unit is also called the *gram calorie, small calorie or standard calorie*. The unit commonly used in medicine is the ***Calorie (Kilocalorie, Kcal)***, which equals 1000 small calories (cal).

   Factors affecting calories requirement: Refer to page 629.

A chemical reaction which liberates heat is said to be *exothermic* and one which takes in heat is *endothermic*.

Notes

1. Energy production can be calculated by indirect calorimetry, i.e. by measuring O_2 consumption per unit of time (page 432).
2. Small calorie is written with a small 'c' where as kilocalorie with capital 'C'.

2. A *complex molecule* has a higher energy content than the atoms or simpler molecules from which it is built because of the energy of formation of the chemical bonds which holds it together; this ***bond-energy*** is liberated when the bonds are broken.

3. (i) 'Most' of the organic phosphates when hydrolysed, an energy equivalent to approx. 2-3 kcal/mol is liberated as heat and such a compound is called ***low energy phosphate compound (R-ph)***. *For example:* glucose 1-phosphate and glucose 6-phosphate; fructose diphosphate; phosphoglyceraldehyde; monophosphoglyceric acid; adenosine monophosphate (AMP).
   (ii) When 'some' organic phosphates are hydrolysed, energy equivalent to approx. 10-12 kcal/mol is liberated and these phosphates are called ***high energy phosphate compounds (R-ph)***. *For example:* adenosine diphosphate (ADP); adenosine triphosphate (ATP); creatine phosphate; diphosphoglyceric acid; phosphopyruvic acid; acetyl phosphate.
4. ***Role of high-energy phosphates***
   (i) The energy of catabolism, instead of immediately being lost as heat, is used to synthesize high energy phosphate compounds *e.g.* ATP. These compounds are stored, and the energy 'locked up' in them is utilized as and when required.
   (ii) High energy phosphate is the sole source of energy that cells can use directly. It is used to perform work (muscular, osmotic, secretory) and to liberate heat which helps in maintaining the body temperature.
5. ***High energy esters: Coenzyme A***

One other group of metabolic intermediates of the high energy type are the acyl derivatives (R-CO–) of mercaptans (HS-R'). On hydrolysis to acid R-COOH and mercaptan HS-R', there is a large energy release of 8-10 kcal/mol. The most important metabolic intermediates of this type are the acyl derivatives of ***Coenzyme A*** (A for acylation). For example: pyruvic acid (CH_3.CO.COOH), has a higher energy content than acetic acid (CH_3.COOH). When pyruvic acid is oxidised metabolically to acetate, the released energy is not wasted as heat. Instead, the actual product is the 'Coenzyme-A', *ester of acetic acid (acetyl-CoA)*, a high energy compound. Acetyl-CoA is also known as ***active acetate*** because its acetyl group combines readily with substances in reactions that would otherwise require outside energy. From the point of view of energies, *formation of 1 mol of any acyl-CoA compound is equivalent to the formation of 1 mol of ATP.*

BIOLOGICAL OXIDATIONS

1. *Oxidation* is the combination of a substance with O_2 or loss of hydrogen, or loss of electron. Conversely, combination of a substance with hydrogen, or loss of O_2 or gain of electron is called ***reduction***.
2. One common form of biological oxidation is ***Dehydrogenation reaction*** *i.e.* removal of hydrogen from an R—OH group forming R=O.
   (i) For a given reaction, a specific *dehydrogenase enzyme* catalyzes the transfer of the 2H to the appropriate Coenzyme acceptor, which is thereby reduced. Such oxidations are: 'anaerobic', dependent only on the supply of Coenzyme and not on the oxygen itself.
   (ii) The commonest Coenzyme acceptor for dehydrogenation reaction is nicotinamide adenine dinucleotide (NAD); in the reduced form, NAD.2H, the hydrogen is attached to the nicotinamide portion of the molecule.
   (iii) Some dehydrogenase enzymes cannot function with NAD; instead, they require phosphate derivative of NAD, called NADP as their hydrogen acceptor. Nicotinamide is one of the vitamins of the B-complex group, it cannot be synthesized by the GIT and must be supplied in the diet.
   (iv) *Examples of biological dehydrogenation i.e.* ***oxidative reactions***
      (a) The *oxidation of lactic acid to pyruvic acid*, with NAD as hydrogen carrier. This is a fully 'reversible' reaction without energy liberation.
      (b) The *oxidation of phospho-glyceraldehyde to phosphoglyceric acid*, an important energy-liberating step along the pathway of glucose metabolism.
      (c) The *oxidative decarboxylation of pyruvic acid*. An important energy-liberating stage of phase II metabolism is the oxidative conversion of the ketoacid pyruvic acid (CH_3.CO.COOH) to acetyl CoA and CO_2 (page 604). This is an 'irreversible' reaction.
3. Energy is continuously cycled through ATP molecules in a cell. There are also two mechanisms by which energy can be transferred to ATP:
   (i) ***Oxidative phosphorylation*** in which inorganic phosphate is coupled to ADP to form ATP; and
   (ii) ***Substrate phosphorylation***, in which a phsophate group in a organic metabolic intermediate is transferred to ADP to form ATP. One such pathway is glycolysis (details page 601).

Note

Oxidative phosphorylation requires the presence of oxygen, whereas substrate phosphorylation does not. Most of the ATP in the body is formed by oxidative phosphorylation.

4. ***Respiratory chain oxidation – oxidative phosphorylation***

(i) Production of ATP associated with oxidation by the **flavoprotein-cytochrome system** is called oxidative phosphorylation This process occur only in the mitochondria. 90% of the O_2 consumption at rest in mitochondria is mainly coupled to ATP synthesis. Each enzyme in the chain is reduced and then reoxidized as the hydrogen is passed down the lane.

(ii) The hydrogen released from various substrates by the action of dehydrogenases becomes attached temporarily to a Coenzyme *e.g.* NAD, NADP or FAD. Finally, the H has to be transferred elsewhere to regenerate the Coenzyme. This subsequent transfer of hydrogen to molecular oxygen forming water involves a chain of enzymes, the final enzyme in the chain is *cytochrome c oxidase* (***the respiratory chain oxidation***) **(Fig. 64.6)**. The overall reaction is:

$$NAD.2H + 1/2\ O_2 \xrightarrow{many\ steps} NAD + H_2O$$

(iii) During the oxidation of one molecule of reduced coenzyme via this respiratory chain, metabolic energy equivalent to 3 ATP molecules is generated. The chief links of the respiratory chain are flavoproteins, cytochromes and cytochrome oxidase; together they form ***flavoprotein-cytochrome system***, *i.e.* a chain of enzymes that transfers hydrogen to oxygen, forming water. This process occurs on the inner membranes of mitochondria which contain a group of proteins called as:

(a) *Flavoproteins* – These are metal containing enzymes which catalyse the transfer of hydrogen from reduced coenzymes to the FAD.

(b) *Cytochromes* – These are pigments of conjugated proteins carrying iron-porphyrin prosthetic groups.

(c) *Cytochrome c oxidase* – This enzyme catalyses the reduction of its own iron-porphyrin prosthetic group by reduced cytochrome, thus generating the (oxidised) cytochrome; which transfers 2H to $1/2\ O_2$ forming H_2O.

The coenzymes and flavins are reduced by addition of 2H atoms, but the iron-containing cytochromes are reduced by electron transport (change of ionic charge). A hydrogen atom removed during a dehydrogenation reaction undergoes 'acidic ionization' to give a proton (positively charged, denoted by H^+) and an electron (equally but negatively charged, denoted by ε').

$$\underset{\text{atom}}{H} \rightleftharpoons \underset{\text{proton}}{H^+} + \underset{\text{electron}}{\varepsilon'}$$

5. Of the total energy released during electron transport along the cytochrome chain, 40% is transferred to ATP while the remaining 60% appears as heat.

Important Note

If oxygen is not available to the cytochrome system, ATP cannot be formed since the flow of electron through the cytochrome chain depends on the ultimate donation of electrons to oxygen. The cause of death from cyanide poisoning is blockage of electron transfer to O_2 and thus failure to form adequate amounts of ATP by the mitochondria to maintain cell functions.

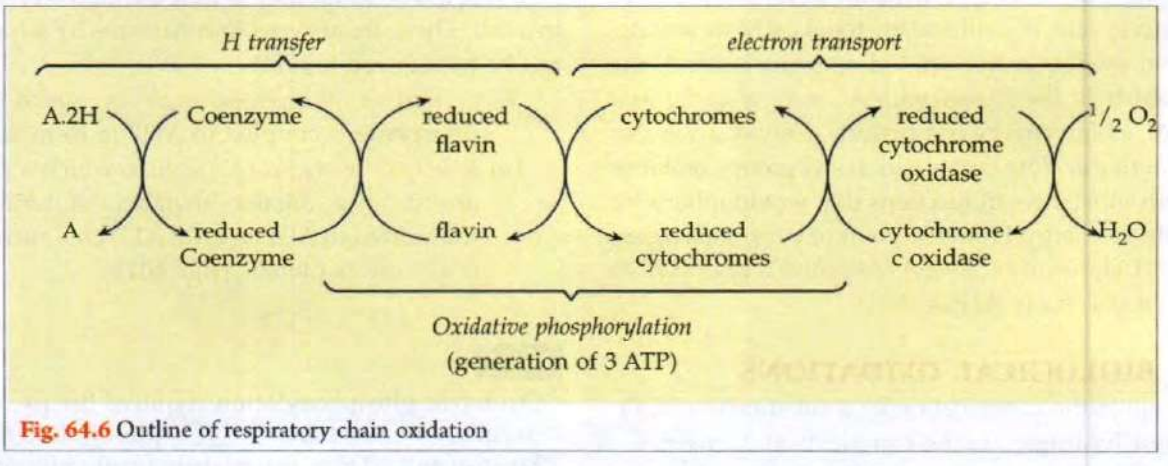


Fig. 64.6 Outline of respiratory chain oxidation

Note

Each enzyme in the chain is reduced and then reoxidized as the hydrogen is passed down the line.

Study Questions

1. **Give physiological basis of:**
   (i) anabolism and catabolism
   (ii) various phases of catabolism
   (iii) Reversible and irreversible reactions
   (iv) Enzymes and Coenzymes
   (v) Low and high energy phosphate compound
   (vi) Cofactor and Coenzyme.
2. **Write short notes on:**
   (i) Factors determining chemical reaction rates
   (ii) Characteristics of enzymes
   (iii) Coenzyme A
   (iv) Active acetate
   (v) Dehydrogenation reaction
   (vi) Oxidative reactions
   (vii) Oxidative phosphorylation
   (viii) Flavoprotein-cytochrome system.
3. **Give characteristic features of various phases of metabolism.**
4. **What are enzymes? Give their salient features.**
5. **What is the unit of energy? How is it liberated and transferred?**
6. **Give an account of "Respiratory chain oxidation". Give its physio-clinical significance.**

MCQs

1. **Phase I of catabolism corresponds to:**
   (a) Liberation of about 1/3rd of the available energy
   (b) Oxidation of a product to form CO_2 and H_2O
   (c) Processes of intestinal digestion and absorption of a product
   (d) Citric acid cycle
2. **A major portion of energy by catabolism of a foodstuff is released during:**
   (a) Process of intestinal digestion and absorption
   (b) Its oxidation to CO_2 and H_2O
   (c) Final stage of metabolism
   (d) Its mobilization for storage in tissues
3. **Low energy phosphate compound when hydrolysed liberate approx. ..... Kcal/mol. as heat:**
   (a) 2-3 (b) 10-12 (c) 15-20 (d) 25-30
4. ***Not true* of high energy phosphate compounds:**
   (a) Liberate 10-12 kcal/mol on hydrolysis
   (b) Examples include creatine phosphate, ADP and ATP
   (c) Is the sole source of energy that cells can use directly
   (d) The released energy is not wasted as heat
5. **One mole of ATP on conversion to AMP releases ..... calories:**
   (a) 1000-1200 (b) 2000-2400 (c) 3000-3600 (d) 4000-4800
6. **Oxidative phosphorylation is defined as:**
   (a) Transfer of H^+ to appropriate Coenzyme acceptor
   (b) Oxidation of lactic acid to pyruvic acid, with NAD and hydrogen carrier
   (c) Electrons moved from H^+ atom and transferred to O_2 with release of excess energy used to convert ADP to ATP
   (d) Oxidative decarboxylation of pyruvic acid
7. ***Not true* of flavoprotein-cytochrome system:**
   (a) A chain of enzymes that transfer oxygen to hydrogen
   (b) It operates in the mitochondria
   (c) Oxidation by this system is called oxidative phosphorylation
   (d) Results in production of ATP
8. ***Not* a high energy phosphate is:**
   (a) ATP (b) Creatine phosphate (c) ADP (d) Glucose-6-Phosphate
9. **Enzyme which catalyses the transfer of H^+ atoms to NAD is known as:**
   (a) Co-enzyme (b) Dehydrogenase (c) Cytochrome oxidase (d) Flavoprotein

Answers

1. (c) 2. (c) 3. (a) 4. (d) 5. (a) 6. (c) 7. (a) 8. (d) 9. (b)

Chapter 65

Carbohydrate Metabolism

I. Carbohydrates of food

II. Digestion and absorption of carbohydrates

III. Intermediary metabolism of carbohydrates:
Glycogenesis; Glycogenolysis; Glycolysis; Citric acid cycle (Kreb's cycle); Hexose monophosphate shunt; Gluconeogenesis

IV. Regulation of blood glucose level

CARBOHYDRATES OF FOOD

Refer to GIT Unit, page 259.

DIGESTION AND ABSORPTION OF CARBOHYDRATES

Refer to GIT Unit, pages 259.

INTERMEDIARY METABOLISM OF CARBOHYDRATES

The following reactions occur in the body: *Glycogenesis; Glycogenolysis; Glycolysis; Citric acid cycle* (Kreb's cycle, tricarboxylic acid cycle); *Hexose monophosphate shunt* and *Gluconeogenesis.*

(A) GLYCOGENESIS, *the synthesis of glycogen from glucose.*

Salient features

(1) Glucose is converted to glycogen in most tissues of the body, specially in liver and muscle. Liver content of glycogen is 60 gm (4% by weight of liver) which increases to 5% after a high carbohydrate meal, and decreases with fasting. The glycogen content in resting muscle is 150 gm (0.7 - 1% by weight of muscles).

Important Note

The brain cells contain little glycogen and depend on a continuous supply of glucose for their high metabolic activity.

(2) Glycogen is a polysaccharide (MW 5,000,000) consisting of many hundreds of glucose units joined together by glycosidic linkages. It is a suitable form to store carbohydrates because:

(i) it is insoluble and so exerts no osmotic pressure;
(ii) it cannot diffuse from its storage sites;
(iii) it has a higher energy level than a corresponding weight of glucose;
(iv) it is readily broken down to glucose in the liver to enter the blood, and in many tissues (including the liver) it is degraded to other lower intermediates which produce energy;
(v) the glycogen in muscle is consumed during muscular activity but is not easily re-converted to glucose even when hypoglycemia is marked.

(3) Glucose entry from the blood into most of the body cells is facilitated by insulin. Within the cells glucose is phosphorylated to form glucose 6-phosphate. This phosphorylation process is accompanied by the enzyme ***hexokinase***, and in the liver by an additional enzyme ***glucokinase***. ATP acts as a phosphate donor and Mg^{2+} are required. This is an "irreversible" reaction.

$$\underset{+\ ATP}{Glucose} \xrightarrow[Mg^{2+}]{Hexokinase} \underset{+\ ADP}{Glucose\ 6\text{-}phosphate}$$

Glucose 6-phosphate is then converted to glucose 1-phosphate by *phosphoglucomutase.* Glucose 1-phosphate reacts with uridine triphosphate (UTP) to form uridine diphosphate glucose (UDPG) which serves as the source of glucose from which glycogen is formed by ***polymerization*** under the influence of the enzyme *glycogen synthetase.* The

final reactions concerned with glycogen synthesis are irreversible. Glycogen synthesis is promoted by insulin (page 747).

(4) *Sources of liver glycogen.* Liver glycogen is formed from:

(i) The hexoses monosaccharide – end products of carbohydrates digestion *i.e.* glucose, fructose, galactose.

(ii) *Intermediates* of carbohydrate breakdown, specially lactic acid and pyruvic acid.

(iii) Glycerol derived from the hydrolysis of neutral fats.

(iv) *Intermediates* derived from the breakdown of the amino-acids which enter into the *general metabolic pool.*

Important Note

The quickest way of building up liver glycogen is by raising the blood glucose level; this is best achieved by the I.V. injection of glucose.

(5) *Role of liver glycogen:*

(i) It is the only immediately available reserve of blood glucose.

(ii) High liver glycogen content,

(a) decreases the rate of deamination of amino acids in the liver and the amino acids remain available for protein synthesis; and

(b) decreases the rate of ketone bodies formation from long chain fatty acids.

(iii) It helps in detoxification by acetylation or glucuronide formation of many substances.

(iv) It protects the body against the harmful effects of many poisons *e.g.* ethyl alcohol, arsenic and bacterial toxins.

(B) **GLYCOGENOLYSIS**, *the conversion of glycogen to glucose.*

This reaction *occurs mainly in the liver.*

(1) Glycogen breakdown is brought about by *phosphorylase.* How? **(Fig. 65.1)** First, the enzyme adenylyl cyclase is activated and catalyses the formation of cyclic 3′–5′ AMP (cAMP) from ATP; second, cAMP converts inactive *phosphorylase b* to active *phosphorylase a* which forms glucose 1-phosphate from glycogen. Glucose 1-phosphate is then converted to glucose 6-phosphate by *phosphoglucomutase.*

(2) In the liver, but not in muscle, the specific enzyme *glucose 6-phosphatase* removes phosphate from the glucose 6-phosphate and promotes the entry of free glucose into the blood. Epinephrine and glucagon promote hepatic glycogenolysis by stimulating adenylyl cyclase.

(3) Epinephrine also activates adenylyl cyclase in skeletal muscle but since muscle lacks glucose 6-phosphatase, the glucose 6-phosphate enters either the *Embden-Meyerhof* pathway or the *hexose monophosphate shunt* pathway, forming lactic acid.

(4) ACTH activates adenylyl cyclase in the adrenal cortex but not in the liver or skeletal muscle.

{**Applied:** In *McArdle's syndrome (myophosphorylase deficiency glycogenosis),* there is marked muscular weakness, pain and stiffness on exercise resulting in exercise intolerance. The muscle glycogen content is raised due to deficiency of muscle phosphorylase; hence glycogen cannot be broken down to provide energy for muscular contraction. The glucose delivered to the muscles via the circulation is just sufficient to meet their routine resting demand.}

(C) **Glycolysis** ***(Embden-Meyerhof Pathway)****, the oxidation (breakdown) of glucose or glycogen to pyruvic acid and/or lactic acid by Embden-Meyerhof pathway* **(Fig. 65.2)**. The pathway is a series of either 10 or 11 enzymatic reactions. These reactions take place in the cytosol and can occur either in the presence or the absence of oxygen. *In the presence of oxygen* (***aerobic glycolysis***), the glycolytic pathway ends with pyruvic acid; whereas *in the absence of oxygen* (***anaerobic glycolysis***), pyruvic acid is converted to lactic acid.

Glucose 6-phosphate, whether formed by breakdown of glycogen or by phosphorylation of glucose,

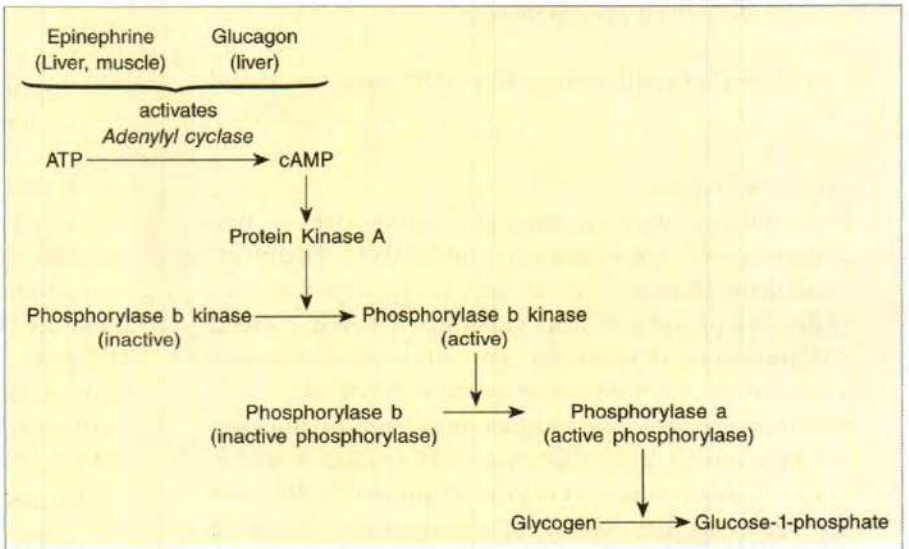


Fig. 65.1 Steps in formation of active phosphorylase. Glucagon has similar action in liver but *not* in skeletal muscle

undergoes the following changes in the conversion to pyruvic acid.

(1) *Glucose 6-phosphate* —(Phosphohexose Isomerase)→ *Fructose 6-phosphate*

Fructose and mannose enter the metabolic pathway here after phosphorylation by independent reactions.

(2) *Fructose 6-phosphate* —(Phosphofructokinase, ATP)→ *Fructose 1,6-diphosphate*

(3) *Fructose 1,6-diphosphate* —(Aldolase)→ Dihydroxy acetone phosphate (DHAP) + 3-phospho-glyceraldehyde

DHAP can be converted to glycerol phosphate which can be incorporated into triglycerides and phospholipids. If no glycerol is formed DHAP is converted to 3-phosphoglyceraldehyde (triose) so that two molecules of this 'triose' are available for the next reaction.

(4) *3-phosphoglyceraldehyde* —(in 3 stages)→ *3-phosphoglyceric acid*

Stage (i) : 3 phosphoglyceraldehyde + HO-ph
⟶ 1,3-diphosphoglyceraldehyde
Stage (ii) : 1,3 diphosphoglyceraldehyde + NAD,
⟶ 3 diphosphoglyceric acid + NAD.2H
Stage (iii) : 1,3 diphosphoglyceric acid + ADP ⟶
3 phosphoglyceric acid + ATP

(5) 3-phosphoglyceric acid ⟶ 2-phosphoglyceric acid (*lower energy phosphate*) ⟶ phospho-enolpyruvic acid (*high energy phosphate*).

(6) Phosphoenolpyruvic acid + ADP ⟶ pyruvic acid + ATP

Energy Production

1. Each glucose unit of 'glycogen' gives rise to two molecules of 3-phosphoglyceraldehyde. Therefore, catabolism of one glucose unit of glycogen to two molecules of pyruvic acid generates 4 newly formed ATP molecules (2 formed at step 4(iii) and two at step 6). All these reactions occur in the absence of O_2 and thus represent *anaerobic* production of energy. However, one high energy phosphate from ATP is used in step 2. Thus when pyruvic acid is formed ***anaerobically*** from glycogen, the net release of metabolically available energy is equivalent to 3 ATP = approx. 40 kcal/mol of glucose.
2. If the process starts from free blood 'glucose', the net release is only 2 ATP, since high energy phosphate of one ATP is used in the hexokinase reaction (page 600).
3. In addition, 6 moles of ATP will be generated by the respiratory chain oxidation of the 2 moles of reduced coenzyme formed in step 4(ii). *Thus if the catabolism proceeds **aerobically** the energy production from one free glucose to pyruvic acid is 8 ATP. But if the process is **anaerobic**, there will be no respiratory phosphorylation and only 2 ATP will be produced.*

Fate of Pyruvic Acid

Pyruvic acid is a key substance in phase II metabolism (page 593). It gets further transformed into: lactic acid, glucose, oxaloacetic acid and acetyl-Coenzyme A.

1. ***Conversion of pyruvic acid to lactic acid***
   (i) In the presence of adequate oxygen, pyruvic acid is broken down to CO_2 and H_2O, and the reduced Coenzyme (NAD.2H) is reoxidised to NAD.
   (ii) Under conditions of relative O_2 lack (such as during maximal exercise), all the NAD would soon be converted to reduced form, NAD.2H. However, pyruvic acid acts as a temporary H store *i.e.* pyruvic acid dehydrogenates (oxidises) the (reduced) NAD.2H back to (oxidised) NAD. The pyruvic acid in the process itself is reduced to lactic acid

NAD.2H + pyruvic acid ⟶ NAD + lactic acid

Therefore, under anaerobic conditions, the muscle glycogen can be broken down into lactic acid to produce energy without the NAD being completely saturated with H. When the oxygen supply is restored, the reaction

pyruvic acid ⇌ (*lactate dehydrogenase, anaerobic condition* / ***aerobic condition***) lactic acid

is reversible (the same enzyme and coenzyme are involved whichever way the reaction is moving).

2. ***Reconversion of pyruvic acid to glucose***
Formation of glucose from pyruvic acid can only occur if energy is provided by ATP. The complete oxidation of 2 molecules of pyruvic acid or lactic acid provides more than enough energy to rebuild 10 molecules of pyruvic acid into 5 molecules of glucose.
3. ***Conversion of pyruvic acid to oxaloacetic acid (OAA)***

Pyruvic acid + CO_2 ⇌ (β-carboxylase, present in most cells) Oxaloacetic acid

The formation of 'OAA' requires ATP energy.

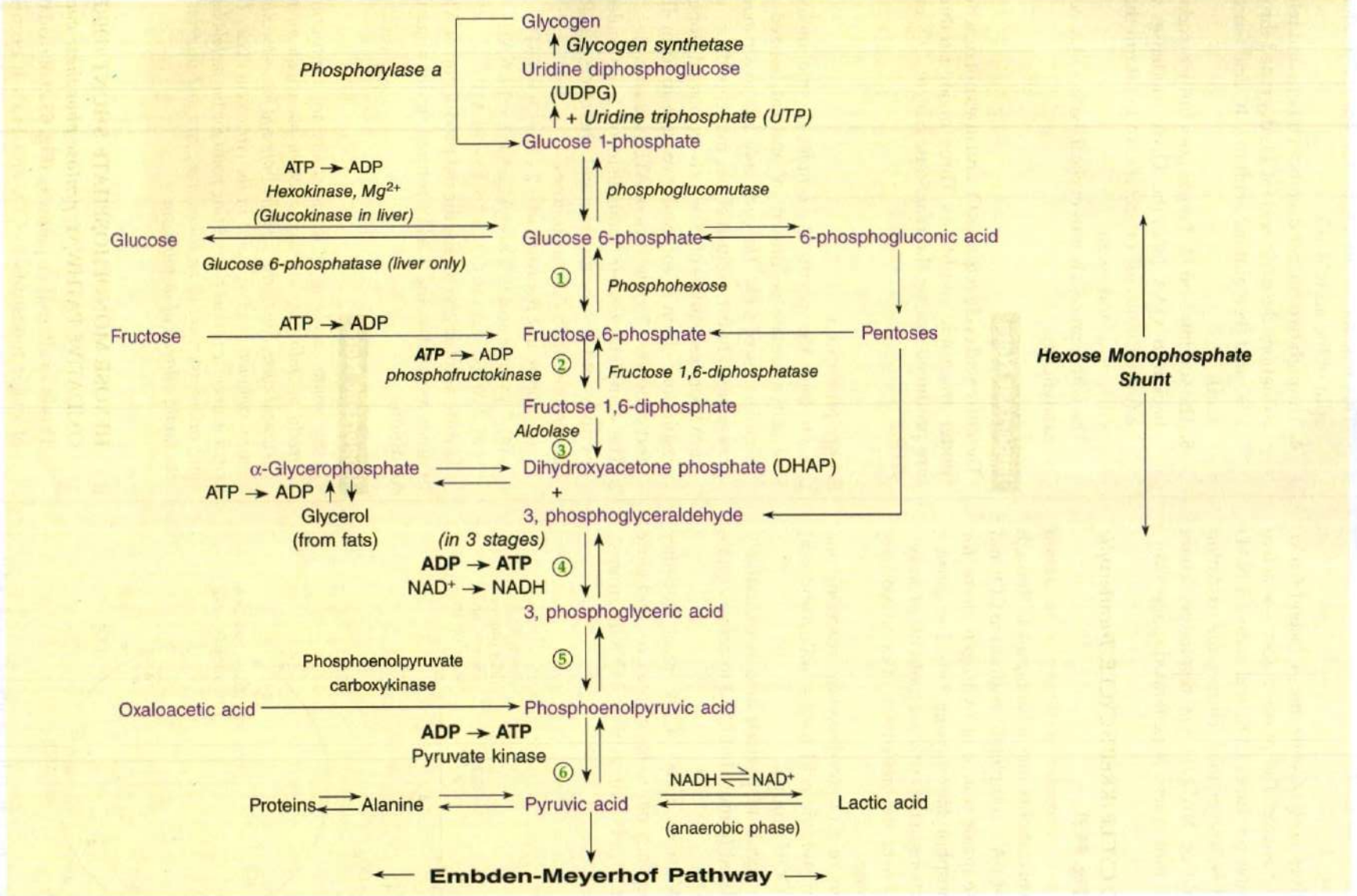


Fig. 65.2 Outline of carbohydrate metabolism (For Abbreviations and numbers ① to ⑥, refer to the text, page 602)

Note

Glycolysis to pyruvic acid occurs outside the mitochondria; pyruvic acid then enters the mitochondria and is metabolized.

4. *Conversion of pyruvic acid to acetyl-Coenzyme A*

Pyruvic acid gives acetyl-Coenzyme A (acetyl CoA), also called *active acetate*. The pyruvic acid → active acetate conversion produces CO_2, and reduced NAD (NAD.2H), and is 'irreversible'. During the oxidation of one molecule of NAD.2H via respiratory chain oxidation, 3ATP molecules are generated (page 598).

(D) CITRIC ACID CYCLE (KREB'S CYCLE, *Tricarboxylic acid cycle*) (Fig. 65.3)

This is the **final common pathway** of oxidation (breakdown) of carbohydrate, fat and protein through which acetyl-CoA is completely oxidised to CO_2 and H_2O. It is the major source of hydrogen atoms for oxidative phosphorylation (page 598). The starting point for reactions in the cycle is a molecule of acetyl-CoA, derived from the breakdown of carbohydrates, fats and proteins.

1. By addition of CO_2 (carboxylase reaction) one molecule of pyruvic acid forms oxaloacetic acid (4C; two COOH groups).
2. Another molecule of pyruvic acid is oxidatively decarboxylated (removal of CO_2) to active acetate (Acetyl-CoA).
3. The 'OAA' and acetyl CoA react together (condensing enzyme) to form free CoA and citric acid (6C = a tricarboxylic acid *i.e.* 3 COOH groups).

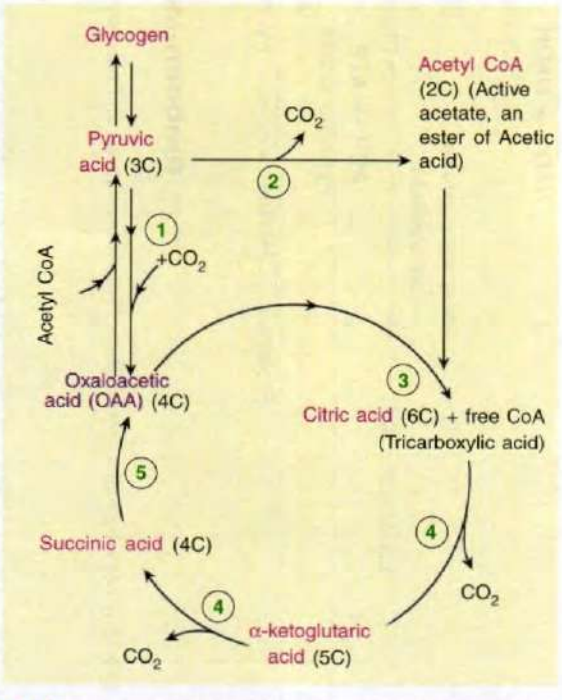


Fig. 65.3 The Kreb's citric acid cycle (tricarboxylic acid cycle) (Refer to text above for numbers 1 to 5)

This reaction is driven by the energy-producing split of the acetyl-CoA.

4. Through two further decarboxylations and related oxidations the citric acid (6C) is degraded through a 5C acid (ketoglutaric acid) to a 4C acid (succinic acid).
5. The succinic acid (4C) undergoes further oxidation back into 'OAA' (4C); the 'OAA' condenses with a further molecule of acetyl-CoA to reform the 6C citric acid, and so on.

The whole process is thus cyclical, with 'OAA' acting catalytically.

Important Note

The citric acid cycle requires O_2 and does not function under anaerobic conditions. Three major products are produced during the reactions: *H atom*, CO_2 and *ATP*.

Energy production

1. Each time the circuit is completed, one molecule of active acetate is 'drawn in' and catabolized into 2 molecules of CO_2. *The cycle only acts under* ***aerobic*** *conditions* (almost exclusively in mitochondria); each turn liberates 8 atoms of H, which are passed along the respiratory chain to molecular oxygen to form $4H_2O$ and generate 12 molecules of ATP (see above).
2. The complete ***aerobic*** catabolism of 2 molecules of pyruvic acid *i.e.* one glucose unit, therefore, results in generation of 38 ATP, as follows:
   (i) glucose to 2 pyruvic acid = 2 + (2 × 3) = 8 ATP
   (ii) 2 pyruvic acid to 2 Acetyl-CoA = 2 × 3 = 6 ATP
   (iii) 2 Acetyl- CoA to CO_2 = 2 × 12 = 24 ATP

During **aerobic** glycolysis, the net production of ATP is 19 times as great as the 2 ATPs formed under **anaerobic** conditions.

Important Note

Many amino acids after deamination are transformed directly or indirectly into acids which participate in the citric acid cycle. Similarly, carbohydrate and fat metabolism have a common meeting point in the citric acid cycle. The citric acid cycle is thus the meeting point for the metabolism and interconversion of carbohydrates, fats and proteins – the final pathway of metabolism.

(E) HEXOSE MONOPHOSPHATE SHUNT (DIRECT OXIDATIVE PATHWAY; *pentose phosphate cycle*)

This is an alternative pathway **(Fig. 65.2)** of oxidation of major foodstuffs to CO_2 and H_2O. It occurs in some tissues such as the liver, lactating mammary gland, and adipose tissue.

First step is the oxidation of glucose 6-phosphate to phosphogluconic acid, followed by oxidative decarboxylation to 5C pentose phosphates. The H from these oxidation is passed to NADP. The pentose phosphates are either used for the synthesis of nucleotides or are transformed by complex cycle of reactions back to glucose phosphate (fructose 6-phosphate).

The overall catabolism (6 pentose phosphate ⟶ 5 glucose phosphate) can be represented as:

glucose 6-phosphate + 12 NADP + 6 H_2O
⟶ 6 CO_2 + 12 NADP.2H + phosphate.OH.

Aerobic reoxidation of the reduced Coenzyme generates 12 × 3 = 36 ATP.

(F) **GLUCONEOGENESIS**, *the formation of glucose or glycogen from non-carbohydrate sources.* The principal substrates for gluconeogenesis are glucogenic amino acids, lactic acid and glycerol (page 607).

METABOLISM OF OTHER HEXOSES

1. *FRUCTOSE*

(i) Part of it is ingested and a part is released from sucrose in the intestine by the enzyme *invertase*. It is metabolised in the body, particularly by adipose tissue as under.

(ii) A small amount is phosphorylated by *hexokinase* to form fructose 6-phosphate. In liver and muscle another enzyme, *fructokinase*, effects the transfer of phosphate from ATP to form fructose-1-phosphate.

(iii) Fructose-1-phosphate is split into dihydroxyacetone phosphate and glyceraldehyde. Glyceraldehyde is then phosphorylated and together with dihydroxyacetone phosphate it enters the 'Embden-Meyerhof pathway' for glucose metabolism. Fructose-1-phosphate may also form fructose 1,6-diphosphate **(Fig. 65.2)**.

(iv) In liver and kidney, fructose 1,6-diphosphate can be converted to fructose 6-phosphate, and thence to glucose.

2. *GALACTOSE*

It is liberated from lactose in the intestine by the enzyme *lactase*. It is readily converted in the liver to glucose. The reactions involved are given in **Fig. 65.4**.

Uridine diphosphoglucose is converted to glycogen and thence by glycogenolysis to glucose. The utilization of galactose is dependent on insulin. For synthesis of lactose in the mammary gland, galactose is converted to UDP-galactose which condenses with glucose 1-phosphate to form lactose 1-phosphate. The latter is hydrolysed to form lactose.

Important Note

Galactosaemia, **an inherited metabolic disorder in which there is a deficiency of the enzyme (phosphogalactose uridyl transferase) which converts galactose 1-phosphate to UDP-galactose. Ingested galactose accumulates in the blood, and causes serious disturbances in growth and development.**

REGULATION OF BLOOD GLUCOSE LEVEL

General

1. Normal fasting peripheral venous blood glucose level is 70-90 mg/dL. After the ingestion of meals rich in carbohydrates, it rises temporarily to 110-130 mg/dL; while, after 24 hours of fasting, the level is maintained at 50-60 mg/ dL. In arterial blood the glucose level is about 20 mg/ dL higher than in the venous blood.
2. *Hypoglycemia* (low blood glucose) is harmful to the brain as is cerebral hypoxia; on the other hand, *hyperglycemia* is not harmful.
3. Of the total glucose ingested:
   (i) 5% is immediately converted into glycogen in the liver,
   (ii) 30-40% is converted into fat, and
   (iii) 50-60% is metabolized in muscles and other tissues.

Factors regulating blood glucose (Table 65.1 and Fig. 65.5)

1. The liver is the main organ in regulating the blood glucose. The final products of digestion (glucose, fructose and galactose) pass via the portal vein to the liver where fructose and galactose are converted to glucose. The liver serves as a receiving, manufacturing, storing and distributing centre for glucose, which is then carried by the blood to all parts of the body for utilization. The 'secretion' of glucose by the liver raises the blood glucose, and removal of glucose by actively

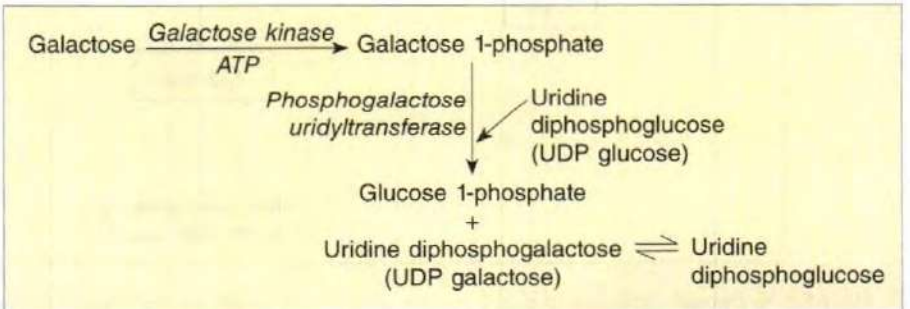


Fig. 65.4 Steps involved in the formation of glucose from galactose

Table 65.1: Factors affecting blood glucose

Tend to raise (during hypoglycemia)	Tend to lower
1. Hunger	1. Satiety; starvation
2. Glucose absorption from GIT	2. Insulin (page 747) (a) ↑ glucose oxidation (b) ↑ glycogen deposition (c) ↑ lipogenesis (d) ↓ gluconeogenesis (glycosuria - in diabetes)
3. Hepatic glycogenolysis (a) Epinephrine (b) Glucagon	3. Muscular exercise
4. Gluconeogenesis (in liver)	
5. Insulin antagonists *i.e.* decreased uptake of glucose by tissues (a) Growth hormone (b) Cortisol	

metabolizing tissues lower blood glucose, therefore,

(i) when the blood glucose is high, the liver takes up glucose and stores it as 'glycogen' under the influence of insulin (page 747); and

(ii) when the blood glucose is low, output from the liver to the blood stream increases. The liver thus functions as a ***glucostat*** maintaining a constant circulating level of glucose.

2. *Liver as Glucostat: Mechanism*

Hepatic cells are freely permeable to glucose, therefore,

(i) at normal blood glucose level of 70-90 mg/dL, the liver is a net producer of glucose;

(ii) at 150 mg/dL, the rates of uptake and output of glucose are equal.

The reactions in hepatic cells to changes in blood glucose levels are controlled by primitive control mechanisms *e.g.* intermediary metabolites; ratios of oxidized to reduced Co-enzymes; availability of ATP or ADP etc.

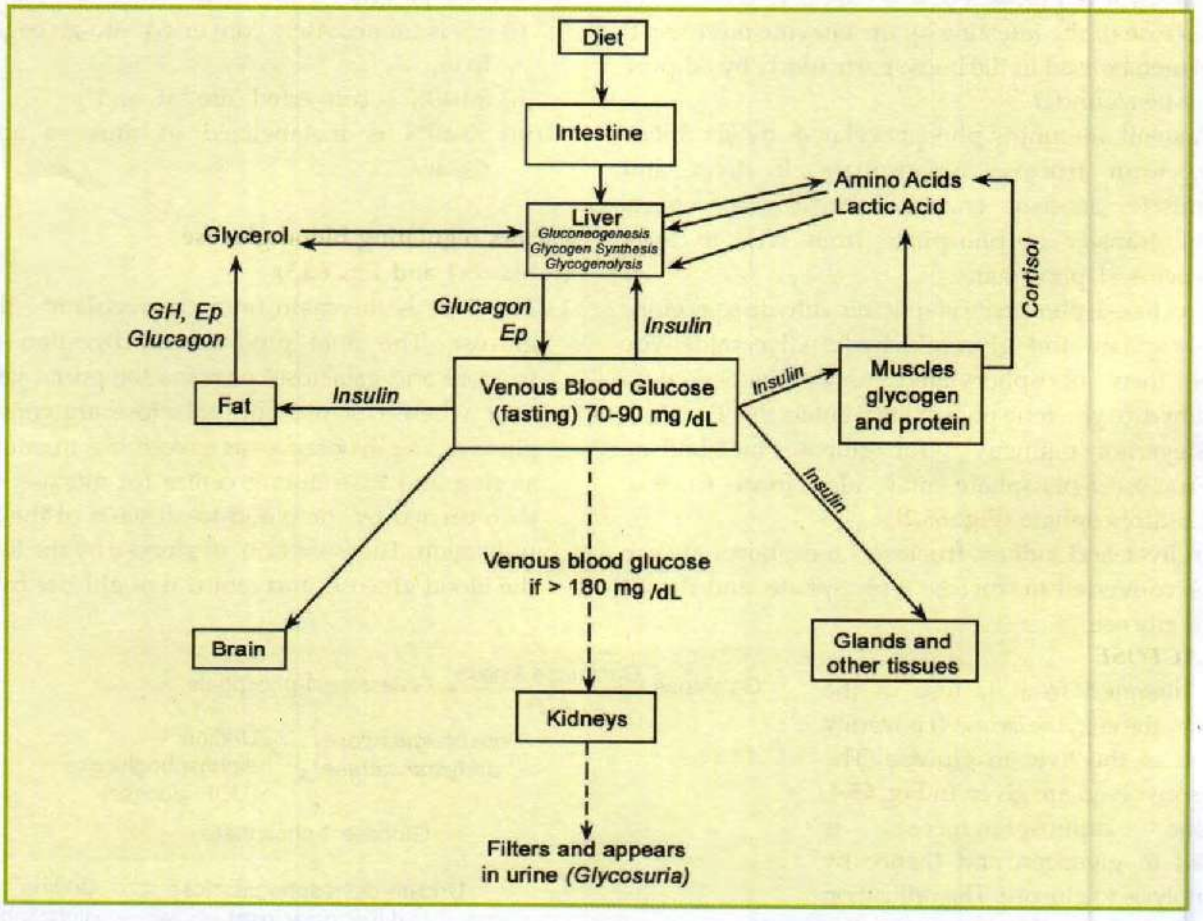


Fig. 65.5 Hormonal regulation of blood glucose concentration (Ep: Epinephrine; GH: growth hormone)

Important Note

The major cause of hyperglycemia in diabetes mellitus is derangement of the glucostatic function of the liver, secondary to insulin deficiency.

3. *Factors which increase blood glucose:*
   (i) Hunger – It is aroused by the metabolic need of the body and promotes eating.
   (ii) Increased glucose absorption from the 'GIT' tend to raise the blood glucose; this is seen during hypoglycemia.
   (iii) *Hepatic glycogenolysis* – It is the first compensatory response to hypoglycemia (occurs within minutes). It is promoted by (a) epinephrine and (b) glucagon. Both these cause glycogen breakdown by activating phosphorylase via adenylyl cyclase and cAMP (page 601).
   In the liver *glucose-6-phosphatase* acts on glucose-6-phosphate to release glucose which enters the blood, the activity of glucose-6-phosphatase is increased by hypoglycemia, and at the same time *glucokinase* activity is depressed, thus decreasing glycogen synthesis.
   Epinephrine also promotes glycogenolysis in muscle; but because of the lack of glucose-6-phosphatase in the muscle, glycolysis occurs and leads to the lactic acid formation. The lactic acid enters the blood and in the liver forms the substrate for gluconeogenesis. Glucagon does not cause glycogenolysis in muscle.
   (iv) *Gluconeogenesis* (mainly in the liver).
   It occurs over hours and even days. The substrate for gluconeogenesis are the non-nitrogenous portions of certain amino acids, lactic acid from muscle, and glycerol from split triglycerides in adipose tissue. Gluconeogenesis is under hormonal control.
      (a) Glucagon, besides promoting glycogenolysis, also increases gluconeogenesis from amino acids (page 742).
      (b) Epinephrine increases gluconeogenesis indirectly by inhibiting the secretion of insulin (page 737).
      (c) Cortisol promotes gluconeogenesis (page 719):
      – by favouring the release of amino acids from proteins in muscle and bone; and
      – by inducing the synthesis of gluconeogenic enzymes in the liver.
   (v) Insulin antagonists – cortisol and growth hormone reduce the uptake of glucose by tissues (insulin antagonist action).
4. *Factors which decrease blood glucose*
   (i) Satiety and starvation, stops food intake.
   (ii) Insulin – It is the most important hypoglycemic factor, secreted by the β-cells of the pancreatic islets.
   Actions:
      (a) It lowers blood glucose mainly by promoting transport of glucose from ECF into cells.
      (b) Inside cells glucose undergoes a variety of metabolic changes, such as oxidation, deposition as glycogen and conversion to fat (lipogenesis) or amino acids.
      Insulin activates enzymes which produce all these changes and controls influences of the hormones which tend to raise the blood glucose level (for details, refer to page 747).
   (iii) Muscular exercise – It produces tissue hypoxia, thereby decreases blood glucose levels by promoting transport of glucose from ECF into the cells.

Important Note

Epinephrine, glucagon, cortisol, ACTH and growth hormone also promote lipolysis. The FFA so released, provides an alternative fuel to glucose in muscle and also reduces glucose uptake. Thus, these hormones help to maintain the blood glucose level:
(i) by increasing glucose inflow into the blood; and
(ii) by reducing its outflow into the tissues.

Study Questions

1. **Give physiological basis of:**
   (i) Glycogenesis, glycolysis, glycogenolysis and gluconeogenesis
   (ii) Carboxylase reaction
   (iii) Oxidative decarboxylation
2. **Name the major sites of glycogenesis. Mention the steps involved in its formation.**
3. **Name the form in which carbohydrates get stored in the body and explain why.**

4. **Persons suffering from liver diseases are advised to take high carbohydrate diet. Why?**
5. **What is the main site of glycogenolysis? Can it occur in skeletal muscle?**
6. **Write short notes on (give line diagram, wherever necessary):**
   (i) Final common pathway of metabolism
   (ii) McArdle's syndrome
   (iii) Embden-Meyerhof pathway
   (iv) Phosphorylation of glucose
   (v) Hexose monophosphate shunt
   (vi) Galactosaemia
   (vii) Liver as glucostat
   (viii) Factors influencing blood glucose level.
   (ix) Aerobic and anaerobic glycolysis
7. **With the help of line diagram, mention the steps involved during citric acid cycle.**
8. **List the reactions that occur in the body during the intermediating metabolism of carbohydrates. Briefly describe physio-clinical significance of any one of them.**
9. **Give physiological basis of:**
   (i) Brain cells depend on a constant supply of oxygen for their activity.
   (ii) Liver is only immediate available resource of blood glucose.
   (iii) Aerobic glycolysis produces more energy than that is produced by anaerobic pathway.
   (iv) Citric acid cycle cannot function under anaerobic conditions.

MCQs

1. **Glycogen is a suitable form to store carbohydrates because:**
   (a) It is soluble and exerts little osmotic pressure
   (b) It has a higher energy level than a corresponding weight of glucose
   (c) It is easily converted to glucose in the muscles
   (d) All of the above
2. **The number of ATP molecules generated in the conversion of glycogen to lactate is:**
   (a) 2 (b) 14 (c) 36 (d) 38
3. **Aerobic versus anaerobic energy production from one free glucose to pyruvic acid is:**
   (a) 4:1 (b) 1:4 (c) 3:1 (d) 1:3
4. **The common pathway for metabolism of carbohydrate, fat and protein in mitochondria is:**
   (a) Succinyl CoA (b) Kreb's cycle
   (c) Acetyl CoA (d) Embden-Meyerhof pathway
5. **The total number of ATP formed during complete aerobic breakdown of one molecule of glucose is:**
   (a) 6 (b) 8 (c) 24 (d) 38
6. **During hypoglycemia, synthesis of new glucose molecules takes place at a relatively rapid rate in:**
   (a) Liver (b) Skeletal muscle (c) Brain (d) Pancreas
7. **Of the total glucose ingested, what percentage gets converted into fat:**
   (a) Nil (b) 10-20% (c) 20-30% (d) 30-40%
8. **First compensatory response to hypoglycemia is:**
   (a) Increased hunger (b) Increased glucose absorption from GIT
   (c) Increased hepatic glycogenolysis (d) Increased hepatic gluconeogenesis
9. **Muscular exercise is helpful to diabetic patient because:**
   (a) Controls influence of hormones which tend to raise blood glucose level
   (b) Oxidises intracellular glucose
   (c) Promotes glucose transport from ECF into the cells
   (d) Helps conversion of glucose to glycogen
10. **Quickest way of building up liver glycogen is by:**
    (a) Raising blood glucose level (b) I.V administration of triglycerides
    (c) Injection of epinephrine (d) Administration of thyroxine
11. **McArdle's syndrome is characterized by:**
    (a) Exercise intolerance (b) Depletion in muscle glycogen
    (c) Decrease delivery of glucose to muscles (d) All of the above

12. Byproduct of anaerobic glycolysis is:
(a) Pyruvic acid (b) CO_2 (c) Lactic acid (d) Water only

13. In citric acid cycle, the number of hydrogen atom formed per molecule of glucose is:
(a) 16 (b) 20 (c) 24 (d) 28

14. Not *a true* statement about citric acid cycle:
(a) Pathway through which Acetyl-CoA is completely oxidised to CO_2 and H_2O
(b) Final common pathway of oxidation of foodstuff
(c) Can act under aerobic as well as anaerobic conditions
(d) Oxaloacetic acid acts as a catalyst during the whole process

15. During aerobic glycolysis, the net production of ATP is ..... times as great as under anaerobic conditions:
(a) 2 (b) 4 (c) 8 (d) 19

16. Galactosaemia:
(a) It is due to deficiency of enzyme galactose kinase
(b) An inherited metabolic disorder
(c) Associated with accumulation of galactose-1-phosphate in blood
(d) Produces severe digestive disturbances

17. Gluconeogenesis is promoted by:
(a) Insulin (b) Calcitonin (c) Growth hormone (d) Gonadotrophin

18. Alternative fuel to glucose in the muscle is:
(a) Glycogen (b) Creatine phosphate (c) Free fatty acids (d) Amino acids

Answers

1. (b)	2. (a)	3. (a)	4. (b)	5. (d)	6. (a)	7. (d)	8. (c)	9. (c)	10. (a)
11. (a)	12. (c)	13. (a)	14. (c)	15. (d)	16. (b)	17. (c)	18. (c)		

Chapter 66

Fat Metabolism

I. Classification of Lipids
II. Digestion and Absorption of Neutral fats
III. Fate of fat after absorption: Fat stores; Blood fat
IV. Relation of liver to fat metabolism: Fatty liver
V. Fatty acid catabolism: Ketone bodies; Ketosis
VI. Utilization and catabolism of 'Active acetate'
VII. Free fatty acid metabolism
VIII. Cholesterol metabolism: Applied aspect: Atherosclerosis
IX. Integration of fat and carbohydrate metabolism

CLASSIFICATION OF LIPIDS

Refer to page 261, GIT Unit

DIGESTION AND ABSORPTION OF NEUTRAL FATS

Refer to page 261, GIT Unit

FATE OF FAT AFTER ABSORPTION

After absorption, fat is treated in various ways:

1. It undergoes *complete oxidation* in the tissues to produce energy, CO_2 and H_2O. When 1 gm of mixed fat is completely burnt to CO_2 and H_2O, approx. 9 kcal of heat is produced; during metabolic catabolism of fat, a large proportion of this energy is made available to the body as high-energy phosphate ATP. Active acetate (Acetyl-CoA) is an intermediate and can be used in acetylation reactions (page 614) and for the synthesis of acetoacetic acid (page 613).
2. Fat is *built into the structures of* all tissues (page 261). The *structural lipid* consists of the following:
   (i) *Lecithins* (and the related cephalins)
   (ii) *Cholesterol esters* of fatty acids (cholestrides)
   (iii) *Sphingomyelins and cerebrosides*. These are specialized lipids of the CNS.

The fatty acids in (i) and (ii) are mainly *unsaturated* and are essential constituents of all cell membranes; in addition, lecithin is a component of the myelin sheath of nerve fibers.

Important Note

In *starvation*, the neutral fat in the depots is called upon and used for producing energy, but structural lipids are unaffected.

3. *Fat is stored as neutral fat* (triglycerides) in the ***fat stores*** *i.e.* adipose cells of the fat depots. There are two types of adipose tissue: *white* and *brown*. The main differentiating features between the two are given in **Table 66.1**.
4. *Sources of depot fat:* The neutral fat in adipose tissue is derived from two main sources:
   (i) from food fat, and
   (ii) from carbohydrate.

Important Note

Potatoes are rightly condemned as fattening, though the fat content of potatoes is almost nil (0.1%); clearly the fat which gets deposited is derived from carbohydrates.

5. *Blood fat:* Page 264.

RELATION OF LIVER TO FAT METABOLISM

Salient features:

1. When fats are to be used in the body they are withdrawn from the fat stores (the adipose tissue cells), and passed to the liver; the fat content of the liver may be little altered, as the fat is broken in the liver as fast as it arrives.
2. The neutral fat in the liver is broken down by liver lipase into glycerol and fatty acids *(phase I metabolism of fat)*.
   (i) The glycerol is utilized via the pathways of carbohydrate metabolism;
   (ii) The fatty acids are oxidised to acetyl-CoA *(phase II metabolism of fat)* (page 613, ***β-oxidation of fatty acids)***.

These fragments are either (a) completely oxidised to CO_2 and H_2O with energy production *(phase III fat metabolism)*

Table 66.1: White and brown adipose tissues compared

White adipose tissue (White fat depot)	Brown adipose tissue (Brown fat depot)
1. It comprises large fat cells which contain a single fat droplet.	1. It comprises small fat cells containing several small fat droplets.
2. Its fat cells contain *less* number of mitochondria with low cytochrome content, therefore, appears white.	2. Its fat cells contain *numerous* mitochondria with high cytochrome content, therefore, appears yellowish-brown or red brown.
3. *Sites:* It is found scattered throughout the body.	3. It is more *abundant in infants* and is found as a thin sheath between the scapulas, around the neck; behind the sternum; around the kidney and adrenal gland.
4. It forms 10-15% of the body weight and represents the *biggest stores of energy* in the body. Its oxygen consumption is approximately 8 mL/100 gm/min.	4. It makes up a small percentage of total body fat and is responsible for much increased oxygen consumption and heat production on exposure to cold (page 583).
5. *Innervation:* the principal sympathetic innervation is solely to the blood vessels and to some of the fat cells.	5. Fat cells as well as the blood vessels have very rich sympathetic innervation.
6. It is under hormonal control (growth hormone, insulin and catecholamine) and its main role is in the maintenance of free fatty acid concentration in the blood.	6. Stimulation of sympathetic nerve releases nor-epinephrine which acts via β-adrenergic receptors to activate a lipase. This in turn splits triglyceride, and increased fatty acid oxidation in the mitochondria increases the heat production (Fig. 66.1).

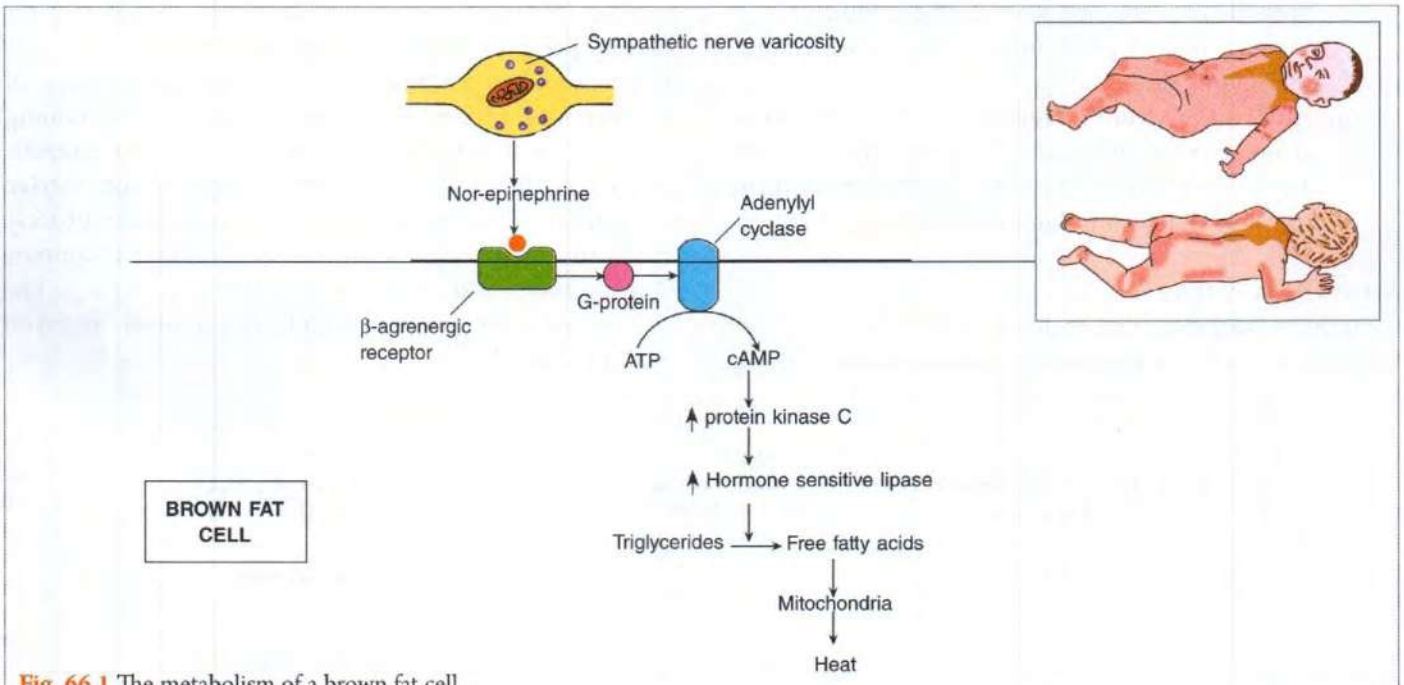


Fig. 66.1 The metabolism of a brown fat cell
(Activation of β-adrenergic receptors on the cell surface leads to signal chain that results in an increased breakdown of triglycerides. These are metabolized in the mitochondria to generate heat.) (**Inset:** Location of brown fat in infants)

or (b) recombined to give a ketone, acetoacetic acid; this latter process is called ***ketogenesis***.

3. *During carbohydrate deficiency*, the liver can:
   (i) increase the metabolism of fat including the production of aceto-acetic acid for energy utilization in tissues and thus 'spare' the available carbohydrates; and
   (ii) convert some small part of the fat into glucose or glycogen.
4. When the 'neutral' fat content of the liver is increased, the condition is called a ***fatty liver*** (details, page 238).

The condition is characterized by a grossly enlarged liver containing massive deposition of neutral fat. The fatty liver is seen in: (i) diet rich in fat and (ii) during starvation.

(i) ***Fatty liver due to diet rich in fat:*** high fat diet which is also deficient in ***lipotropic factors*** (see below). Under such circumstances, fat becomes the principal source of energy for the body and the uptake of fat by the liver exceeds markedly than its rate of despatch. The fat content of the 'fatty liver' is considerably decreased by administration of:

(a) methionine or protein rich in methionine; or
(b) choline or related substance 'betaine'; or
(c) lecithin (which contains choline).

Role of Lipotropins – A substance which reduces the amount of liver fat is called a ***lipotropin (lipotropic factor)***. The lipotropins are effective because they contain choline or because they promote choline synthesis.

(a) Methionine is a methyl donor. It supplies methyl groups to cholamine (ethanolamine) to form choline.
(b) Betaine (a methylated glycine derivative) is also a methyl donor.
(c) Lecithin contains choline and liberates it on hydrolysis.

Role of choline – It promotes the conversion of liver fat into choline containing phospholipids (*e.g.* lecithins) which are more readily transferred from the liver into the blood in the combined form (*i.e.* as a part of phospholipid molecules-lecithin, sphingomyelin).

(ii) ***Fatty liver due to starvation:*** Here the stress of metabolism also falls on fat *i.e.* the fat in the depots. As lipotropins are not available in adequate amounts, fat accumulates in the liver.

Effects of fatty liver

The effects are mainly due to depressed functional activity of the liver cells secondary to the decreased blood supply of the swollen cells. The effects are:

(1) Reduced glycogenesis;
(2) Diffused hepatic fibrosis (or ***cirrhosis of liver***) *i.e.* death of many liver cells and their replacement by scar tissue. The scarring, by interfering with hepatic blood supply, further aggravates the condition. The major causes of cirrhosis of liver are:
   (i) in **severe malnutrition** due to deficiency of fat, protein and lipotropin in the diet, and
   (ii) **alcoholic cirrhosis**. The liver is initially 'fatty' and later shows fibrosis. The essential cause is a diet deficient in lipotropins aggravated by their defective absorption from the intestine.

FATTY ACID CATABOLISM: β-OXIDATION OF FATTY ACIDS

1. The neutral fat (triglyceride) in the liver is hydrolyzed as required, releasing glycerol and long-chain fatty acids, the majority containing 16 or 18C atoms; for example, palmitic, stearic and oleic acids.
2. The next stage is breakdown, mainly in the liver, of these long carbon chains into 'fragments' containing two carbon atoms each. Thus 16C chain of palmitic acid produces 8 fragments of acetyl-CoA (***active acetate***). This breakdown is an oxidative process (occurs in mitochondria), where 2-carbon fragments are serially split off the fatty acids (*β-oxidation*). The *sequence of reactions* involved in this process are given in **Fig. 66.2**:

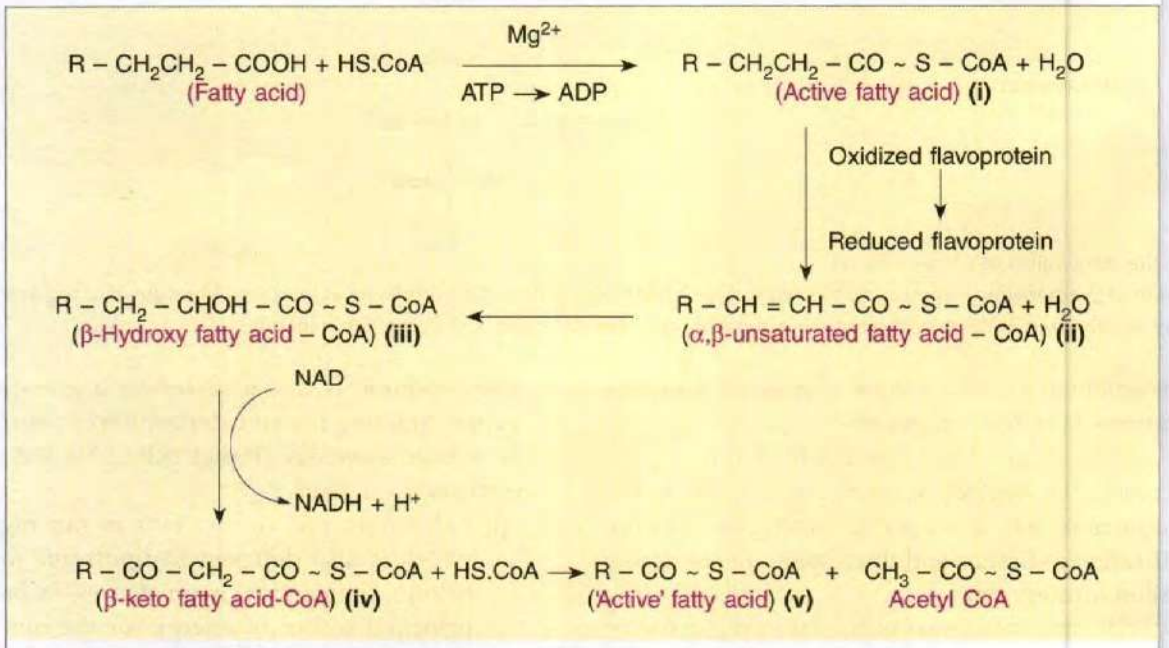


Fig. 66.2 Sequence of reaction involved during β-oxidation of fatty acid chain to acetyl-CoA
(R = Rest of fatty acid chain; for '(i)' to '(v)', refer to text above)

(i) activation of fatty acid *i.e.* fatty acid has to be converted to its high energy CoA;
(ii) dehydrogenation;
(iii) hydration of CoA ester;
(iv) cleavage at the β-carbon atom with another molecule of CoA;
(v) splitting off of acetyl-CoA, leaving the carbon chain with 2C less but still as a CoA ester.

3. The whole process gets repeated and another acetyl-CoA splits off, and so on down the chain. The C chain of fatty acid is thus split off, 2C at a time, from the acid end.

Important Note

The proportion of acetyl-CoA forming acetoacetic acid rather than being immediately oxidised to CO_2 is determined by the rate of the simultaneous carbohydrate catabolism in the liver. If the rate of carbohydrate catabolism is depressed, as in diabetes mellitus or starvation, then the proportion of acetoacetic acid formed rises, and ketosis may develop.

4. *Ketone bodies*

The *ketone bodies* or *acetone bodies* are the substances, which form a metabolically related group, *e.g.* acetoacetic acid, β-hydroxybutyric acid and acetone **(Fig. 66.3)**.

(i) **Acetoacetic acid** is formed during the catabolism of (a) long chain fatty acids from fat, and (b) certain essential amino acids.
(ii) **β-hydroxybutyric** acid is the reduction product of acetoacetic acid; the two acids are freely interconvertible.
(iii) **Acetone** also arises from acetoacetic acid by spontaneous and non-reversible decarboxylation (loss of CO_2), a reaction which occurs chiefly in the lungs and bladder.

Note

β-hydroxybutyric acid is 'not a ketone', though it is metabolically derived from acetoacetic acid.

Important Note

The liver unlike other tissues contians a deacylase.Thus it is the only organ which produces ketone bodies on a significant scale. All the tissues, with the exception of the brain and liver itself, can catabolise acetoacetic acid to CO_2, H_2O and usable energy.

5. *Ketosis*

(i) The normal non-fasting blood ketone level is 0.5–2 mg/dL; fasting of 2 or 3 days increases this level by fifty folds.
(ii) The amount of circulating ketone bodies depends upon the balance between:
  (a) Ketone bodies formation by the liver, and
  (b) Ketone bodies catabolism by the tissues.
  There is, however, a maximum amount of fat which the tissues can use (mostly as acetoacetic acid), namely, about 2.5 gm of fat/kg/day, equivalent to 175 gm of fat/day in a 70 kg man.
(iii) The ***rate of ketogenesis*** in the liver varies greatly according to circumstances. If ketogenesis proceeds at an unduly high rate, exceeding the rate at which catabolism can be carried on by the tissues, then ketones accumulate in the blood, called ***ketosis***. This may lead to the excretion of ketone bodies in the urine. In extreme ketosis, the urinary output may reach 100-120 gm/day (*normal:* 1 mg/day).
(iv) ***Causes of ketosis***
  (a) With a **low glycogen and a high fat content in the liver** *e.g.* on a high fat, low carbohydrate diet or in starvation; the liver glycogen reserves are exhausted and depot fat is being utilized. Under these conditions fat becomes the 'principal substrate of the liver cell' to an excessive ketone body formation.
  (b) Injection of anterior pituitary extracts, specially **growth hormone**. It causes fat depot to mobilize and large amount of fat is brought to the liver. Glucose catabolism is simultaneously depressed, and liver glycogen is decreased due to its conversion into blood glucose.
  (c) **Diabetes mellitus**. Ketosis develops in this condition secondary to insulin deficiency which mobilizes the free fatty acids from the fat depot and increases the flow of fat to the liver. It also decreases glucose catabolism and glycogen deposition in the liver.

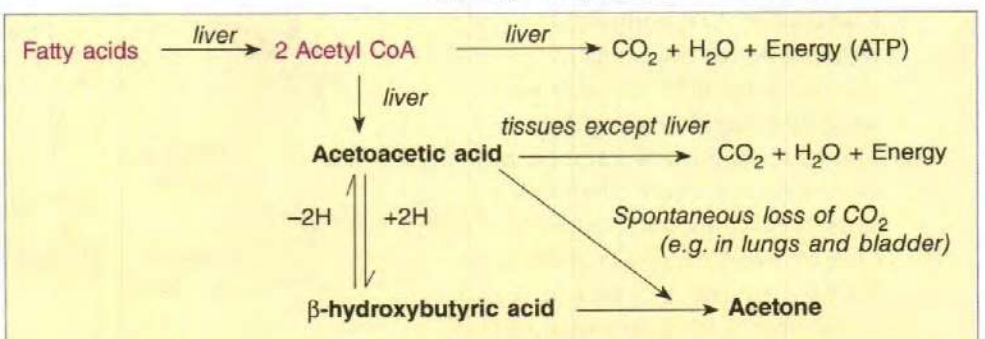


Fig. 66.3 Inter-relationship of the 'ketone bodies'

(v) ***Symptoms and signs of ketosis***

(a) Produces a metabolic acidaemia (blood pH may fall to 7.0) which stimulates respiration producing deep and rapid (*Kussmaul*) breathing (page 752).

(b) Increased excretion of ketone bodies in the urine (*ketonuria*) causes increased urinary excretion of NH_4^+, and later of Na^+; severe Na^+ and water loss leads to severe dehydration, which is made even worse by the vomiting induced by acidaemic ketosis.

UTILIZATION AND CATABOLISM OF 'ACTIVE ACETATE'

'Active acetate' units are highly reactive, and as they are formed they immediately undergo the following changes **(Fig. 66.4)**.

1. ***Self-condensation to give acetoacetic acid.*** The random self-condensation of two acetyl-CoA forms the 4C compound, *acetoacetic acid*. This is carried in the circulation to other tissues which can catabolise it.

2. ***Catabolism to CO_2 and H_2O.*** Acetyl-CoA and acetoacetic acid are completely catabolised by entering the krebs citric acid cycle. The long C chain of the fatty acids is appropriate for storage purposes only.

(i) Acetyl-CoA from fatty acid is metabolized in exactly the same way as that formed by the oxidative decarboxylation of pyruvic acid (from carbohydrate) (page 604). As a result, energy is liberated which is made available to the body through the high-energy ATP.

(ii) ***Energy production*** – The energy of fatty acid catabolism appears as ATP during the respiratory reoxidation of the Coenzyme hydrogen carriers reduced during the aerobic chain cleavage and the aerobic citric acid cycle. Six carbon atoms of a chain catabolised through 3 acetyl-CoA to 6 CO_2 produce a total of 44 ATP, compared with the 38 for 6C atoms as glucose (page 605). ***There is no anaerobic metabolism of fat.***

(iii) The main step in the catabolism of aceto-acetic acid in the tissues is its re-splitting into two acetyl-CoA by free CoA; these are then oxidised by the enzymes of the krebs citric acid cycle present in the tissue concerned.

3. ***Acetylation reaction*** – the active acetyl-CoA can be employed by the body in acetylating reactions *e.g.* the synthesis of acetylcholine or acetylation of amines during their 'detoxification' by the liver.

Choline + Acetyl CoA + glucose + ATP
↓ *Choline acetyl transferase (choline acetylase)*
Acetyl choline
(occurs in all cholinergic neurons)

4. ***Use as building unit for body components.*** C atoms from acetic acid or any other compounds giving rise to Acetyl-CoA can be built into: (i) cholesterol; (ii) haem porphyrins, and (iii) the intermediates of the citric acid cycle.

5. ***Resynthesis of fatty acids.*** 'Acetic acid units', from any source, can be built up into long-chain fatty acids, and thence into fat. This occurs by the stepwise addition of 2C acetyl-CoA units to the acid end of a carbon chain. The process requires a supply of H from reduced NADP, ATP, and of CO_2 as a catalyst. Its mechanism is not the reverse of fatty acid breakdown.

FREE FATTY ACID METABOLISM

Free fatty acids (FFA) are provided to body tissues and fat cell by chylomicrons (page 263) and VLDL (page 53). They circulate bound to albumin and are a major source of energy. The supply of FFA to body tissues is *regulated* by:

1. ***Lipoprotein lipase*** which breaks down *circulating* triglyceride (Chylomicrons and VLDL) thereby increase

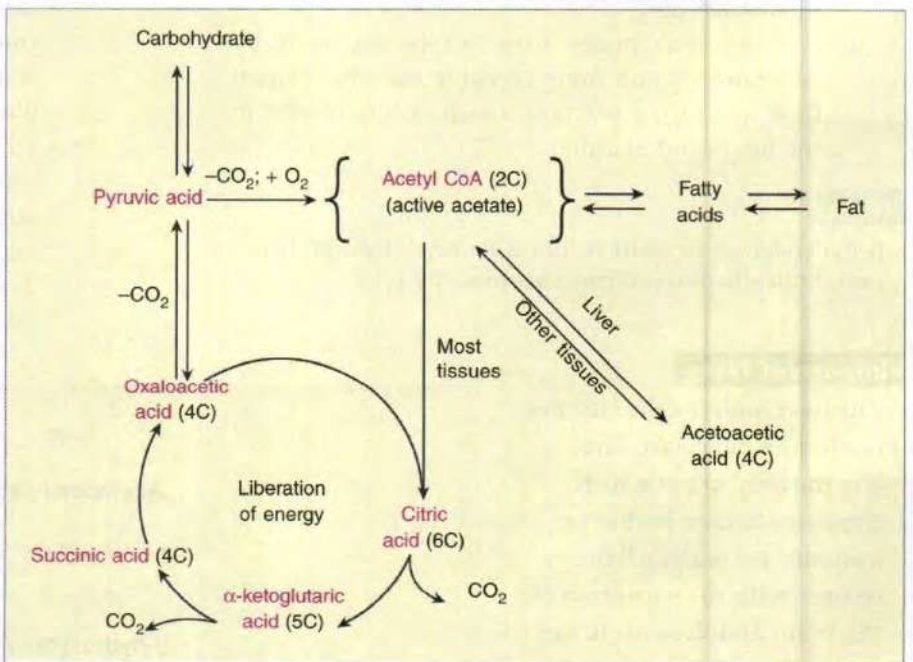


Fig. 66.4 The formation and catabolism of fat

FFA and glycerol in the fat cells. Its activity is increased by feeding and decreased by fasting and stress.

2. *Hormone sensitive lipase* which catalyzes the breakdown of ***stored*** triglyceride into FFA and glycerol. Its activity is
   (i) increased by: Catecholamine (Ep, NE), glucagon, cortisol, growth hormone, thyroid hormone, fasting and stress; and
   (ii) decreased by: Insulin, prostaglandin E and feeding (Fig. 66.5).

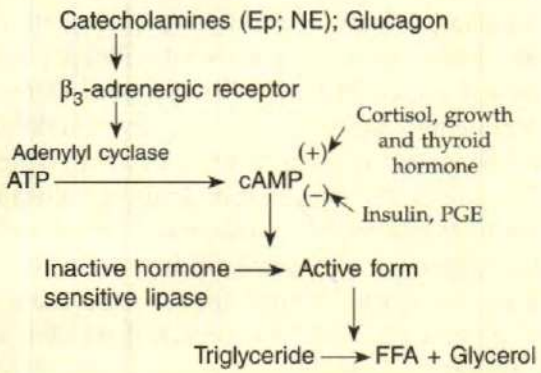
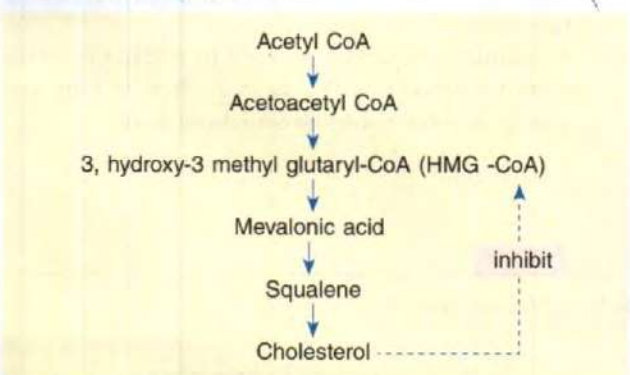


Fig. 66.5 Mechanisms which alter the activity of the hormone sensitive lipase in fat cells
(+): stimulation; (–): Inhibition

CHOLESTEROL METABOLISM

1. *Cholesterol synthesis*



Cholesterol inhibit is own synthesis via negative feedback mechanism by inhibiting ***HMG-CoA reductase*** enzyme.

2. Normal plasma cholesterol level: 120-200 mg/dL

Note

Incidences of atherosclerosis and its complication increases in linearlity with increase in the plasma cholesterol levels.

3. Thyroid hormones and oestrogens decreases plasma cholesterol level by increasing the number of LDL receptors in the liver, whereas its level are increased by biliary obstruction and in diabetes mellitus.
4. Cholesterol lowering drugs acts by
   (i) inhibiting mobilization of FFA from fat depots; and
   (ii) ***Statins*** (such as lovastatin) which reduce cholesterol synthesis by inhibiting HMG-CoA.
5. ***Applied:*** *Atherosclerosis* (Fig. 66.6)
   It is characterized by infiltration of cholesterol underneath the tunica intima of the arterial wall. This is followed by a complex sequence of changes involving smooth muscle cells, platelets, macrophages and inflammatory mediators that produces proliferative lesions which finally ulcerate and calcify (called *arteriosclerosis*). This predisposes to myocardial infarction, cerebral thrombosis, ischaemic gangrene of the extremities etc.

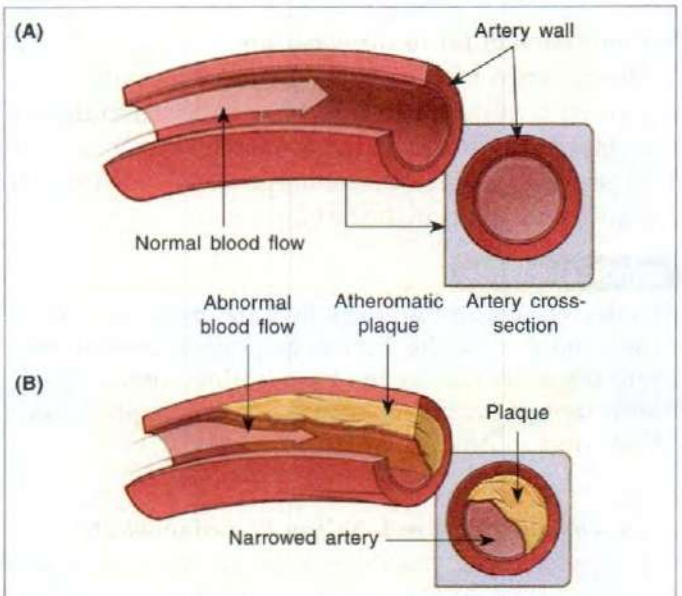


Fig. 66.6 Narrowing of artery following atherosclerosis
(A) Normal artery; (B) Narrowing of artery

Note

HDL (page 53) picks up cholesterol from peripheral tissues and transports into the liver thus lowering plasma cholesterol. This is why the individuals who have higher HDL levels, have a lower incidence of myocardial infarction.

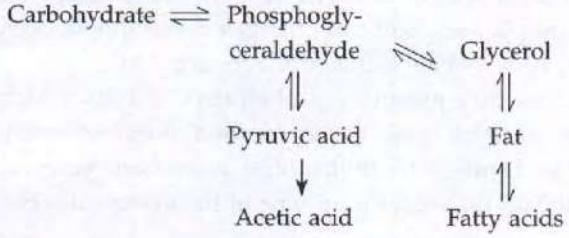
INTEGRATION OF FAT AND CARBOHYDRATE METABOLISM

A. *Conversion of carbohydrate to fat*

(1) The pathways of carbohydrate and fat metabolism meet at the common intermediate acetic acid (acetyl-CoA). Since fatty acid is reversibly formed from acetyl-CoA, the way is open for the transformation of carbohydrate via pyruvic acid and acetic acid

into fatty acids. This transformation is stimulated by insulin and inhibited by anterior pituitary hormones.

(2) Glycerol from the breakdown of fat is converted into phosphoglyceraldehyde and joins the main pathway of carbohydrate metabolism. This reaction is 'reversible' allowing carbohydrate to be used for the synthesis of glycerol when this is needed for the deposition of fatty acids as body fat.



B. *Conversion of fat to carbohydrate*

The glycerol of fats can join the reversible pathway of carbohydrate metabolism and thus be built into glucose or glycogen. This would allow the formation of only 12 gm of blood glucose from 100 gm of fat, much greater conversion occurs in the fasting animal.

Important Note

Under conditions of carbohydrate deficiency, the chief function of the liver is to provide acetoacetic acid for utilization by the tissues, thus 'sparing' the utilization of the blood glucose which is required for CNS metabolism.

C. *Dependence of fat metabolism on carbohydrate*

1. The complete catabolism of fat via acetyl-CoA requires available supply of 'OAA' to catalyse the krebs cycle. This must be supplied from a source other than fat, since the pyruvic acid ⟶ acetic acid reaction is irreversible. The chief source of 'OAA' is carbohydrate via pyruvic acid and the carboxylase reaction (page 598). Therefore, the complete catabolism of fats in the liver requires the simultaneous oxidation of carbohydrate *i.e. the fats burn in the flame of the carbohydrates.*
2. Any change which reduces the rate of carbohydrate oxidation in the liver will decrease the rate of complete oxidation of acetyl-CoA locally, without reducing its rate of formation; in fact, its rate of formation may increase if the fat is the only available energy source. However, highly reactive acetyl-CoA fragments cannot accumulate, they undergo self condensation to form aceto-acetic acid.
3. The lower the rate of carbohydrate utilization in the liver relative to fat utilization, the greater is the production of aceto-acetic acid.
4. If the tissues cannot catabolise the increased supplies of aceto-acetic acid which reach them then ketosis develops.

Important Notes

(i) Starvation, diabetes mellitus, and other conditions that lead to ketosis all involve a decrease in the normal ratio of carbohydrate to fat utilization in the liver (Page 613).

(ii) The acetone odour in the breath of children who have been vomiting is due to ketosis of starvation.

(iii) I.V. administration of glucose in relatively small amounts abolishes the ketosis, that is why the *carbohydrate* is said to be anti-ketogenic.

Study Questions

1. **Name the main sites from where fats get absorbed. Mention its fate after absorption.**
2. **Write short notes on:**
   (i) Brown fat (ii) Fatty liver (iii) Lipotrophin / lipotropic factor
   (iv) Cirrhosis of liver (v) β-oxidation of fatty acids (vi) Catabolism of active acetate
   (vii) Free fatty acid metabolism (viii) Cholesterol metabolism (ix) Interconversion of fats and carbohydrates
   (x) Active acetate (xi) Types of adipose tissues
3. **Give the physiological basis of:**
   (i) Potatoes are fattening (ii) There is no anaerobic metabolism of fats
   (iii) Fats burn in the flame of carbohydrate (iv) Carbohydrate is said to be antiketogenic
   (v) Acetone odour in the breath following vomiting (vi) Development of atherosclerosis.
   (vii) In starvation, structural fats are not called upon for production of energy.
4. **Name the ketone bodies. Give their inter-relationship.**
5. **How can a person develop ketosis? Mention its signs and symptoms.**
6. **How much fats depend on carbohydrates for their metabolism?**
7. **Depict diagrammatically "metabolism of a brown fat cell".**

MCQs

1. **Among various lipids present, the most abundant source of potential chemical energy is in the form of:**
   (a) Triglycerides (b) Free fatty acid (c) Cerebrosides (d) Lecithins
2. **Adipose tissue cells:**
   (a) Contain plenty of mitochondria (b) Contain triglycerides in a liquid state
   (c) Responsible for much increased oxygen consumption (d) Are abundant in infants
3. **Stored fat is usually transported from one part of the body to another in the form of:**
   (a) Triglycerides (b) free fatty acids (c) Glycerol (d) Neutral fat
4. **White fat depot *differs* from brown fat depot in all of the following *except*:**
   (a) Fat is stored as triglycerides (b) Scattered throughout the body
   (c) Forms 10-15% of body weight (d) Represents the biggest stores of energy in the body.
5. **Ketone bodies are formed mainly in the:**
   (a) Skeletal muscle (b) Stomach (c) Liver (d) Kidney
6. **Fasting of 2 or 3 days increases normal blood ketone level by ..... folds:**
   (a) 5 (b) 15 (c) 25 (d) 50
7. **Beta oxidation is defined as:**
   (a) Formation of Acetyl-CoA from fatty acid (b) Formation of Acetyl-CoA from pyruvic acid
   (c) Formation of Acetyl-CoA from amino acid (d) Formation of Acetyl-CoA from lactic acid
8. **Under normal conditions, amount of glucose that can be formed from 100 gm of fat is:**
   (a) 5-6 gm (b) 10-12 gm (c) 18-20 gm (d) 25-30 gm
9. **Acetone odour in breath of children who have been vomiting is due to:**
   (a) Starvation (b) Ketosis (c) Respiratory alkalosis (d) Metabolic acidosis
10. **Myelin which surrounds fast conducting axon is composed mainly of:**
    (a) Sphingomyelin (b) Cephalin (c) Lecithins (d) Cholestrides
11. **Potatoes are fattening because:**
    (a) Fat content is high (b) Provide a good source of depot fat
    (c) Increase uptake of fat by body cells (d) All of the above
12. **Adipose tissue cells:**
    (a) Contain plenty of mitochondria (b) Contain triglycerides in a liquid state
    (c) Responsible for much increased oxygen consumption (d) Are abundant in infants
13. ***Not* an effect of fatty liver:**
    (a) Reduced glycogenesis (b) Cirrhosis of liver
    (c) Increased choline synthesis (d) Decreased hepatic blood flow
14. **Which of the following organs *does not* utilise ketone as a means of energy?**
    (a) Kidney (b) Skeletal muscles (c) Heart (d) Liver
15. **The following is *true* about brain metabolism:**
    (a) Use free fatty acid in starvation (b) In resting state, 60% of the total energy is provided by fats
    (c) Ketone bodies are used in starvation (d) Has no energy store
16. **In extreme ketosis, urinary output of ketone bodies may reach:**
    (a) 100 mg/day (b) 1 gm/day (c) 10 gm/day (d) 100 gm/day
17. **Carbohydrate is said to be anti-ketogenic because:**
    (a) Increases ketone bodies catabolism (b) Causes fat depot to mobilize
    (c) Decreases rate of ketogenesis in the liver (d) All of the above

Answers

1. (a) 2. (b) 3. (b) 4. (a) 5. (c) 6. (d) 7. (a) 8. (b) 9. (b) 10. (a)
11. (b) 12. (b) 13. (c) 14. (d) 15. (a) 16. (d) 17. (c)

———OOO———

Chapter
67

Protein Metabolism

I. General: proteins; amino acids; digestion and absorption of proteins; amino acid pool; nitrogen balance; essential amino acids; urinary sulphates

II. Metabolism of amino acids: urea formation; creatine and creatinine

III. Nucleic acid metabolism: purine; pyrimidines; nucleosides; nucleotides; Gout

GENERAL

A. PROTEINS

The proteins are complex molecules built mainly from α-amino acid linked together in chains. The linkage between the amino acids is called *peptide bond;* molecules built up from many (upto 100) amino acids are called *polypeptides.* Proteins consist of several polypeptide chains, cross-linked between specific amino acid units. Chains containing 2-10 amino acids are called *peptides.*

B. AMINO ACIDS

The principal amino acids obtained by breakdown of proteins are:

1. ***Neutral amino acids*** – they contain one NH_2 (basic) group and one COOH (acidic) group which mutually neutralize each other.
   Types:
   (i) Amino acids with unsubstituted C chains: glycine, alanine, valine, leucine, isoleucine.
   (ii) Hydroxyl-substituted amino acids: serine, threonine.
   (iii) Sulphur containing amino acids: cysteine, cystine (oxidative product of cysteine), methionine.
   (iv) Aromatic amino acids, derived from alanine: phenylalanine, tyrosine, thyroxine, triiodothyronine.
2. ***Acidic amino acids*** – amino acids with acidic (—COOH) side chain: aspartic acid, asparagine, glutamic acid, glutamine.
3. ***Basic amino acids*** – amino acids with basic (—NH_2) side chain: arginine, lysine, histidine.
4. ***Imino acids*** – contains imino group but no amino group: proline, hydroxyproline.

C. DIGESTION AND ABSORPTION OF PROTEINS

Refer to page 264, GIT Unit.

D. AMINO ACID POOL

Most of the tissue proteins (*structural* as well as *functional* protein) are continuously undergoing disintegration to release amino acids. The amino acids derived from food (exogenous protein) and those derived from the tissue break down (endogenous protein) enter the circulation forming general ***amino acid pool*** (Fig. 67.1). It represents an availability of amino acid building units. From this *common amino acid pool,* amino acids are taken up by the cells, if a cell takes up as much amino acid as it loses, it is in a state of *dynamic equilibrium;* if the loss is greater, the cell degenerates; if the gain is greater, the cell grows. The proteins of the body are in a state of *dynamic equilibrium i.e.* a balance between simultaneous breakdown and synthesis. The *endogenous protein* turnover rate is about 80-100 gm/day being greatest in intestinal mucosa, followed by kidney, liver, brain and muscle in that order.

E. NITROGEN BALANCE

The body is in *nitrogenous equilibrium* when the nitrogen intake in the food over a given period exactly equals the nitrogen lost in the excreta over the same period. 95% of the nitrogen intake is in the form of dietary protein; the nitrogen loss is mainly via the urine as urea, ammonia, uric acid etc. and, to a minor extent, in the faeces.

A subject in nitrogenous equilibrium is said to be in *nitrogen balance:*

(i) a subject whose intake of nitrogen is greater than the output (*e.g.* in growth, recovery from illness or administration of anabolic steroids) is said to have a ***positive*** nitrogen balance; and

(ii) a subject whose intake of nitrogen is smaller than the output (*e.g.* in starvation, forced immobilization) is said to have a ***negative*** nitrogen balance.

Important Note

It is impossible to maintain *nitrogen equilibrium* on diets which are deficient in any one or more amino acids of specific type (*essential amino acids*), no matter how much protein is consumed. This is why nitrogen balance becomes negative whenever a single *essential amino acid* is omitted from the diet.

F. ESSENTIAL AMINO ACIDS

These are the amino acids needed for replacement and growth, but which cannot be synthesized by the body in amounts sufficient to fulfil its normal requirements. The rest of the amino acids are the *non-essential amino acids* and can be synthesized in the body. It has been found that the following amino acids are indispensable for human adults under normal conditions: ***valine, leucine, isoleucine, threonine, methionine, phenylalanine, tryptophan, lysine, histidine*** *and* ***arginine***.

Important Note

Exclusion of any one of these *essential amino acids* leads to a negative nitrogen balance, fatigue, loss of appetite, and nervous irritability. Histidine and arginine are required under conditions of growth or other physiological stress (because of the limited capacity of the body to synthesize them).

G. SPECIFIC METABOLIC ROLES OF AMINO ACIDS

1. *Amino acids* are the building units of all the tissue proteins including the enzymes and many of the hormones.
2. *Glycine* is a fundamental building unit, and an inhibitory transmitter in the spinal cord.
3. *Arginine* is responsible for urea formation and helps in creatine synthesis.
4. *Histidine* is the precursor of histamine.
5. *Phenylalanine* can be irreversibly converted to tyrosine which is the precursor for thyroxine, epinephrine, nor-epinephrine and melanin pigment.
6. *Tryptophan* is essential for the formation of 5 HT (serotonin).
7. *Methionine*, *cysteine* and *cystine* are the only important source of sulphur and are used for the formation of organic sulphates or taurine.

H. URINARY SULPHATES

The sulphur compounds of urine are derived mainly from the sulphur containing amino acids (methionine, cysteine and cystine) of the dietary and tissue proteins. The sulphur is excerted in urine in the following forms:

1. *Inorganic sulphate* – Sulphur containing amino acids of the *amino acid pool* that are not used in protein synthesis are completely oxidised and the sulphur as sulphate ions (SO_4^{2-}) are excreted in urine, with an equivalent amount of cations (Na^+, K^+, NH_4^+). The normal range of urinary output is 0.3–3 gm of sulphate ions per day.
2. *Ethereal sulphate* – The urine contains small amounts of organic sulphate esters, R-O-SO_3H (ethereal sulphates), where R is the aromatic radicals. These are the forms in which many phenols (oestrogen, steroids, indoles and drugs like aspirin) are detoxicated and excreted in urine. The conjugation of the phenol with sulphate from amino acids takes place in the liver.
3. *Neutral sulphur e.g.* cystine, mercaptans are found in the urine in traces.

METABOLISM OF AMINO ACIDS

Amino acids can be catabolized to provide energy for ATP synthesis. Amino-acids contain nitrogen atoms (in their amino group) is addition to carbon, hydrogen and oxygen atoms. Once the nitrogen containing amino group is removed from most amino acids, the remainder of the amino acid can be metabolized to intermediates capable of entering either the glycolytic or citric acid cycle pathways.

A. METABOLISM OF AMINO ACIDS INVOLVES THE FOLLOWING REACTIONS: (Fig. 67.1)

1. *Oxidative deamination*

Amino acids which are not used as such undergo 'oxidative deamination', primarily in the liver. The overall reaction is the transformation (removal) of an amino acid R.CH(NH_2).COOH, to the corresponding *keto-acid*, R.CO.COOH. This involves an oxidation (or dehydrogenation) to give α-imino acid, followed by hydrolysis liberating '*ammonia*' (NH_3).

$CH_3.CH(NH_2)\,COOH + NAD$

Alanine — *amino acid oxidase* — coenzyme (H carrier)

$CH_3.C(:NH)COOH + NAD.2H$

α-imino acid — reduced coenzyme

$CH_3C\,(:NH)\,COOH + H_2O$

$CH_3.CO.COOH + NH_3$

pyruvic acid

The ammonia thus formed is then used up in the synthesis of other amino acids or excreted as urea.

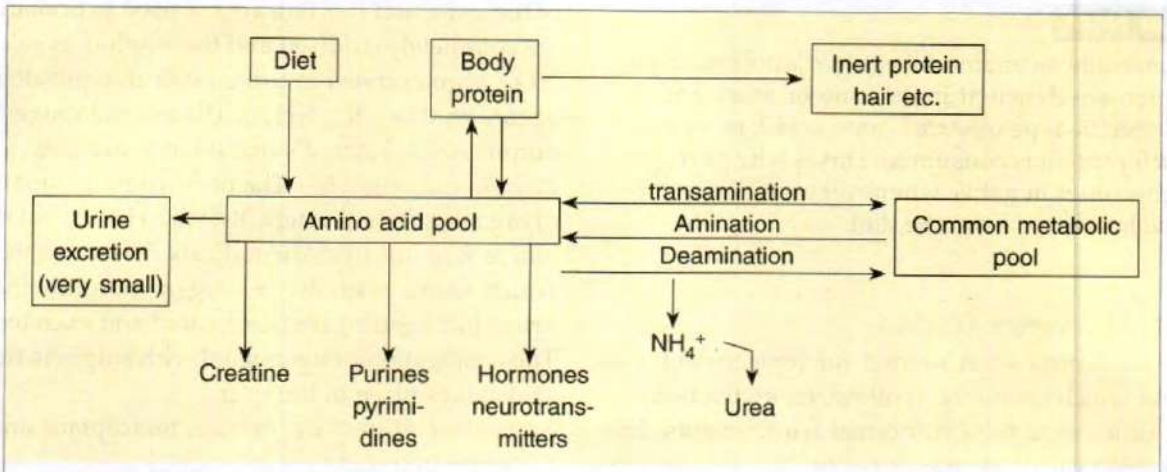
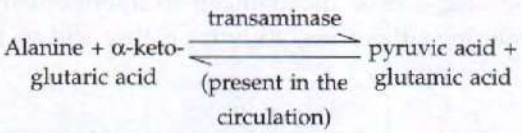


Fig. 67.1 Amino acid metabolism

2. ***Transamination***

It is the process in which deamination of an amino acid to corresponding ketoacid is coupled with the simultaneous amination of another ketoacid to an amino acid *e.g.*



Transamination is 'reversible'. Thus plays an important role in both the breakdown of amino-acids and their synthesis from non-protein sources; for example, from ketoacids of the citric acid cycle.

Important Note

The serum level of certain transaminases, specially of glutamic-oxaloacetate transminase (SGOT) and aspartate aminotransferase (AST), are markedly increased in disease conditions involving injury to large numbers of metabolically active cells such as in *myocardial infarction*.

3. ***Amination of non-nitrogenous residues***

Amino acids from the *amino acid pool* are continually being broken down by deamination, and the processs of direct amination or transamination are used to resynthesize some of these amino acids. Products of deamination formed at one site can be reaminated elsewhere and so re-enter the 'amino acid pool'.

4. ***Ammonia***

Ammonia formed by the kidney tubule cells, mainly from glutamine, diffuses into the lumen of the tubules and act as a hydrogen ion acceptor.

B. UREA FORMATION

1. The excess of ammonia which is formed by deamination and not used for reamination is converted into urea. Ammonia is very toxic to cells whereas 'urea' is harmless even in very high concentrations. *The liver is the only site of urea formation*, and that urea once formed is not destroyed in the body.
2. Urea formation in the liver consists of the union of 2 moles of NH_3 and one mole of CO_2 with the elimination of H_2O. This takes place directly through the ***Krebs urea cycle*** in which 'non-protein' amino acid *Ornithine* acts as a catalyst to form *Citrulline* **(Fig. 67.2)**. This reacts with a second mole of NH_3 to give arginine; the amidine group of arginine is split off as urea by hydrolytic enzyme 'arginase', and ornithine is regenerated to continue the cycle.

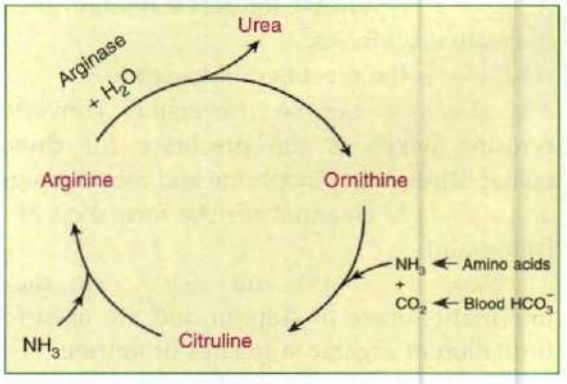


Fig. 67.2 Krebs urea cycle or Ornithine cycle

Important Note

In severe liver disease the blood urea nitrogen (BUN) level falls and blood NH_3 rises.

C. FATE OF NON-NITROGENOUS RESIDUES FROM AMINO ACIDS

The non-nitrogenous residues remaining after deamination enter the 'common metabolic pool' and are either completely catabolised to CO_2 or are built up into other body constituents.

In general, *the essential amino acids* (page 619) *are glucogenic i.e.* they give rise to compounds that can readily be converted to glucose; all the *non-essential amino acids are ketogenic i.e.* they give rise to ketone bodies (page 613).

Applied Aspect

In certain conditions, oxidative mechanisms of amino-acids are deranged by the blockage at different points. This results in the urinary excretion of intermediate metabolites are as follows:

1. ***Phenylketonuria*** – It is a form of *idiocy* in which there is an inability to convert phenylalamine to tyrosine, therefore, phenylalanine accumulates, and phenyl pyruvic acid (the deamination product of phenylalanine) appears in the urine (also refer to page 732).
2. ***Alcaptonuria*** – Here, a normal metabolite from tyrosine appears in the urine; such urine darkens considerably when alkaline is exposed to air and may turn almost black.

D. SIGNIFICANCE OF NITROGEN CONTAINING CONSTITUENTS IN URINE

Mixed proteins contain an average of 16% of nitrogen, almost all of which is excreted in the urine. The chief nitrogen containing waste products in urine are: urea, creatinine, creatine, ammonium ions and uric acid. A small amount of amino acids are also lost from the body through the urine.

1. ***Urea*** – Urea is formed in the liver from ammonia derived from amino acids (see above).
   (i) On a **normal protein intake** (the 'amino acid pool' is contributed by the ingested food), the urinary urea is mainly of food origin *i.e.* exogenous proteins. Within limits, the urea output varies directly with the recent protein intake. On a normal mixed diet, an adult's excretion of urea is 15-50 gm/day (= 7-23 gm of urea nitrogen).
   (ii) On a **protein-free diet** but adequate in energy content, the amino acids are contributed to the 'pool' by breakdown of tissue proteins only *i.e.* endogenous proteins. Amino acids from this endogenous proteins cannot be rebuilt into the proteins from which they come, because one or more of the required essential amino acid needed for the protein synthesis has been utilized elsewhere; moreover, these amino acids cannot be stored and are irreversibly broken down producing first ammonia and then urea which appears in the urine. Thus, the urinary urea on a 'protein-free diet' is wholly 'endogenous' and is approximately 4 gm of urea/day.
   (iii) In **complete starvation**, tissue protein (specially muscle protein) is broken down into amino acids on a much larger scale than in (ii) above. Most of this is deaminated and the residues utilized for energy purposes and to maintain the blood sugar level. Therefore, urea excretion is on a much larger scale because tissue protein is not being used as "fuel".
2. ***Creatine and creatinine***
   (i) Creatine occurs in greatest concentration in skeletal muscle, with lesser amounts in heart muscle, brain and uterus. In resting muscle, creatine exists largely as ***creatine phosphate*** *(phosphocreatine)*, a high energy compound. This is formed by the reaction of creatine with ATP (reversible reaction) **(Fig. 67.3)**. The energy of carbohydrate catabolism in muscle is initially made available as ATP which reacts with creatine to form ADP and large amounts of creatine phosphate. During exercise, the reaction is reversible, maintaining the supply of ATP (an immediate source of energy for muscle contraction).

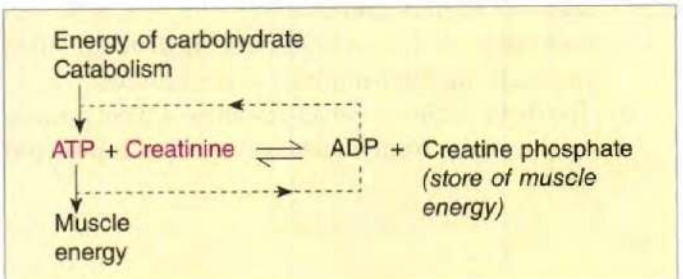


Fig. 67.3 Creatine phosphate as an energy store

   (ii) Creatine is synthesized in the liver from arginine, glycine and methio-nine. Creatine gets phosphorylated by ATP to give creatine phosphate, some of which lost to the body by a slow, spontaneous transformation to 'creatinine' is excreted in urine.
   (iii) ***Creatinuria*** *i.e.* excretion of creatine in urine. Creatine is not a normal constituent of the urine but may appear in the following conditions:
      (a) **In children**, creatinuria may be associated with the low storage power of the muscles for creatine at an early age.

(b) **Pregnancy** – there is a continuous creatinuria during pregnancy, which rises to a maximum of 1.5 gm/day after delivery; when it is derived from the involuting uterus.

(c) **Myopathies** – creatinuria occurs because of the low storage power of the muscles.

(d) In any condition in which unusual **breakdown of the tissues** (specially muscles) occurs, *e.g.* in starvation (muscles substance is broken down for energy purposes), uncontrolled diabetes mellitus, thyrotoxicosis and fever (from the increased metabolic rate).

(iv) **Excretion of creatinine** – Creatinine is formed in the body exclusively from creatine via creatine phosphate; therefore, the urinary output of creatinine increases during exercise.

3. ***Ammonium ions*** (NH_4^+) – Refer to page 553.
4. ***Amino acids*** – traces of many amino acids and small peptides are found in normal urine; mainly they come from the breakdown of tissue protein (endogenous excretion).
5. ***Uric acid*** – This is the only end product from the metabolism of purines and nucleic acids which normally appears in the urine (page 623).

NUCLEIC ACID METABOLISM

A. General (also refer to page 265)

1. ***Purines***
   (i) The major purines found in nucleotides and nucleic acids are adenine and guanine. *'Uric acid' is the final oxidation product of all purines;* intermediate oxidation products are hypoxanthine and xanthine.
   (ii) The diet contributes small amounts of 'free' purines to the body from meat extract, tea, coffee and cocoa.
2. ***Pyrimidines*** – the major pyrimidines found in nucleotides and nucleic acid are cytosine, uracil and thymine.
3. ***Nucleosides and nucleotides***
   (i) When a purine or pyrimidine is linked to a sugar residue the resulting compound is called a ***nucleoside*** (purine or pyrimidine + Ribose or 2-deoxyribose = nucleoside).
   (ii) If the sugar residue is also phosphorylated a ***nucleotide*** results *i.e.* nucleoside + phosphoric acid residue = nucleotide. Therefore,
      (a) adenine-ribose = adenosine
      (b) adenine-ribose phosphate = adenosine monophosphate (AMP)
      (c) adenine-ribose phosphate-phosphate = adenosine diphosphate (ADP)
      (d) adenine-ribose-PO_4-PO_4-PO_4 = adenosine triphosphate (ATP)
      (e) hypoxanthine-ribose = inosine
   (iii) ***Nucleotides functions***
      (a) as Coenzyme-like activators or carriers of biologically important substances (page 595), and
      (b) as building units for the nucleic acids.
4. ***Nucleic acids*** – the fundamental unit of the nucleic acid is a *nucleotide*. Many nucleotides forming double-helical structure of 2 polynucleotide chains = nucleic acid.
   (i) 'Nucleic acid' contains phosphate, a pentose sugar (ribose) and 4 nitrogenous bases – *adenine, guanine, cytosine* and *uracil*. 'Thymonucleic acid' contains phosphate, deoxyribose and 4 nitrogenous bases – adenine, guanine, cytosine and thymine. These two nucleic acids are named ***ribonucleic acid (RNA)*** and ***deoxyribonucleic acid (DNA)*** respectively **(Fig. 67.4)**. DNA is restricted to the cell nuclei,

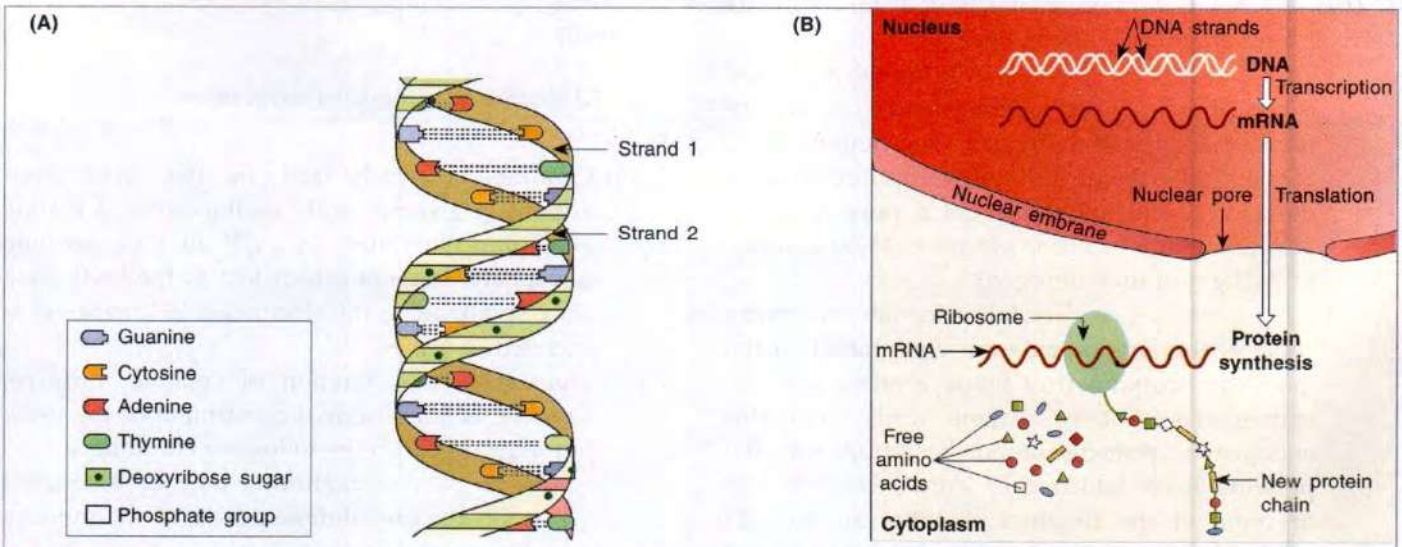


Fig. 67.4 (A) Deoxyribonucleic acid (DNA); (B) The relationship between DNA, RNA and protein synthesis

whereas RNA is found both in the nucleus and in the cytoplasm.

(ii) Both DNA and RNA are macromolecules with molecular weights of 50,000.

RNA is in dynamic equilibrium with the amino acid pool, but DNA, once formed, is metabolically stable throughout life.

B. Nucleic Acid Metabolism

1. Mammalian tissue cells synthesize both RNA and DNA. RNA is continuously being broken down by enzyme systems within the cell. Most of the DNA is metabolically stable during the life of the cell. However, the maturation of nucleated RBCs to form non-nucleated discs involves the destruction of the nucleus and this contributes a considerable proportion of the purines and pyrimidines freed from cells.
2. The cellular foodstuffs which are rich in nuclei (liver, kidney, pancreas, yeast) are likewise rich in nucleic acids. These are digested in the duodenum and small intestine, with liberation of nucleotides, nucleosides and 'free' purines and pyrimidines.
3. The 'purine' bases adenine and guanine are catabolized to uric acid, most of which is excreted (see below). The 'pyrimidine' bases are completely degraded to urea and simple carbon compounds.
4. *Metabolism of purines*
   (i) Purine nucleotides are released during the breakdown of tissue nucleic acids, food nucleic acids and tissue nucleotides, and are further split by specific enzymes, liberating free purine bases. These bases can either be reconverted to their respective nucleotides, oxidised to 'uric acid' as a final product or excreted. The enzyme xanthine oxidase converts xanthine to uric acid (Fig. 67.5).

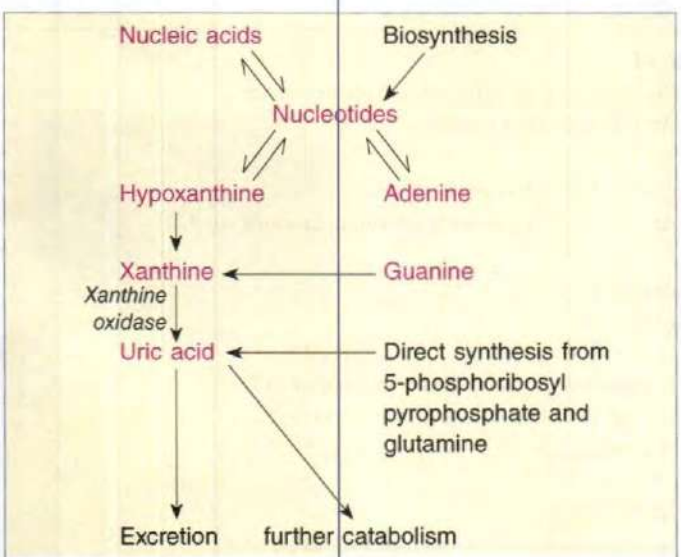


Fig. 67.5 Oxidative formation of uric acid

(ii) The immediate precursor of uric acid is *xanthine*, which arises from guanine or hypoxanthine. Adenine does not give rise to hypoxanthine directly, but can do so via the corresponding nucleotides.

Uric acid is also synthesized from *5-phosphoribosyl pyrophosphate* (5-PRPP) and *glutamine*.

(iii) *Normal* blood uric acid level is 2-4 mg/dL, which gets affected by:
   (a) Ingestion of purine rich diet has no effect on the blood uric acid in normal individuals, but raises it in cases of renal insufficiency.
   (b) In uraemia – increases.
   (c) In leukaemia considerable break-down of nuclei of WBCs occurs and the blood uric acid is raised.

(iv) Excretion of Uric acid
   (a) The output of uric acid in urine on a normal diet is 0.75-1 gm/day, on a purine-free diet, it falls by 50% to about 0.4-0.5 gm/day.
   (b) Normally, 98% of the filtered uric acid is reabsorbed. Its excretion is decreased when the diet has a low purine content, a low protein content, a low calorific value or consists of fat rather than carbohydrate.

Applied Aspect: GOUT

[A] Gout is characterised by:

1. Excess of uric acid in the blood.
2. In normal persons 'metabolic pool' of uric acid is 0.7-1.3 gm which increases to 2-4 gm.
3. Deposition of sodium monourate in articular and non-articular structures, producing ***tophi*** (Fig. 67.6).
4. Recurring attacks of acute arthritis. These are due to deposition of microcrystals of monosodium urate

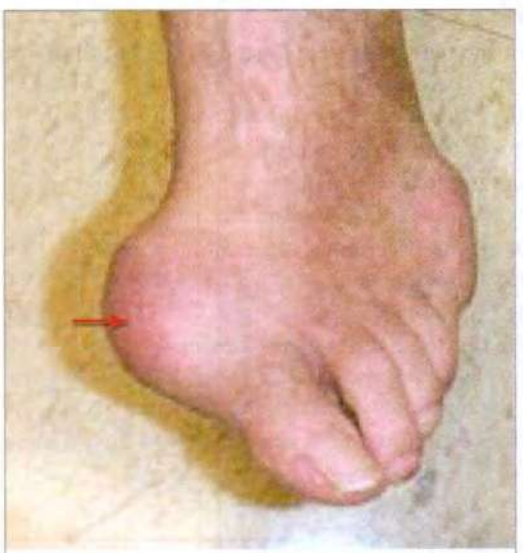


Fig. 67.6: Gout : tophi formation in great toe

in and around the structures of the affected joints. The joint most commonly affected in early stages is metatarsophalangeal joint of the great toe.

[B] Types: primary and secondary gout.

(i) *Primary gout:* Here, increased formation of uric acid occurs from simple carbon and nitrogen compound without intermediary incorporation into nucleic acids.

(ii) *Secondary gout:* There is an increased breakdown of nucleic acids leading to an excess of the end-product, uric acid; it occurs in polycythaemia, chronic leukaemias and pernicious anaemia.

Study Questions

1. **Name essential amino acids. Why are they so called? Also give their physiological significance.**
2. **Write short notes on:**
   (i) Common amino acid pool
   (ii) Nitrogen balance
   (iii) Reaction involved in amino acid metabolism
   (iv) Formation of urea
   (v) Phenylketonuria
   (vi) Alcaptonuria
   (vii) Creatinuria
   (viii) Nuclei acid metabolism
   (ix) Uric acid formation
   (x) Gout
   (xi) Oxidative deamination and transamination
   (xii) Differentiate between RNA and DNA
3. **Name nitrogen containing wastes in urine. Give their physiological significance.**
4. **Give physiological basis of:**
   (i) Amino acids derived from endogenous proteins cannot be rebuilt into the protein from which they come.
   (ii) Creatinuria seen after delivery.
5. **Give the source and amount of urea in the urine:**
   (i) on a normal diet
   (ii) on a protein free diet
   (iii) in complete starvation.
6. **Give the normal blood uric acid level. What do you infer if it is found to be high in an individual?**
7. **Depict diagrammatically:**
   (i) Kreb's urea cycle
   (ii) Creatine phosphate as an energy store
   (iii) Structure of DNA

MCQs

1. **Amino acids are transported in the blood mainly in the form of:**
   (a) Plasma proteins
   (b) In combination with a carbohydrate carrier
   (c) In combination with a phospholipid carrier
   (d) Amino acids themselves
2. **The essential amino acids:**
   (a) Are found in all dietary proteins
   (b) Can be formed in the body
   (c) Must be present in the diet
   (d) Are necessary to provide adequate amounts of ATP
3. **Of all the precursors of urea, most toxic is:**
   (a) Citrulline
   (b) Arginine
   (c) Ammonia
   (d) Ornithine
4. **Urea in the liver is formed from:**
   (a) Two ammonia moles and one mole of CO_2
   (b) Two ammonia moles and two mole of CO_2
   (c) One ammonia moles and one mole of CO_2
   (d) One ammonia moles and two mole of O_2
5. **In an individual on a normal mixed diet, daily urea excretion in urine is:**
   (a) 1-15 gm
   (b) 15-50 gm
   (c) 50-100 gm
   (d) Above 100 gm

6. **Blood uric acid level increases in all of the following conditions, *except*:**
   (a) Ingestion of purine rich diet (b) Uraemia
   (c) Leukaemia (d) Renal insufficiency
7. **When energy is derived from creatine phosphate to cause muscle contraction, what is the first step in this transfer of energy?**
   (a) The creatine phosphate transfers energy to the cross bridges
   (b) The creatine phosphate cause the power stroke of the cross bridges
   (c) The creatine phosphate transfers its energy to the actin filament
   (d) The energy of the creatine phosphate is used to convert ADP into ATP
8. **The constituents of ATP are all *except*:**
   (a) Adenine (b) Ribose (c) Phosphate (d) Ribulose
9. **Gout is characterized by all of the following, *except*:**
   (a) Tophi formation
   (b) Recurrent acute arthritis
   (c) Great toe joints most commonly affected
   (d) Increased renal excretion of uric acid
10. **Which amino acid can proteinate and deproteinate at neutral pH?**
    (a) Serine (b) Asparagine (c) Glutamine (d) Histidine
11. ***Not true* of urea:**
    (a) Formed from excess of ammonia (b) Very toxic to the body cells
    (c) Liver is the only site of its synthesis (d) Once formed, is not destroyed in the body
12. ***Not a true* statement regarding non-essential amino acid:**
    (a) All are glucogenic (b) All are ketogenic
    (c) Can be synthesized in the body (d) Required to fulfil normal body requirements
13. **Urinary urea on a protein-free diet is:**
    (a) 4-5 gm of urea/day (b) 5-15 gm of urea/day
    (c) 15-50 gm of urea/day (d) 50-100 gm of urea/day
14. **Organ whose function is disturbed by accumulation of urea precursors is:**
    (a) Brain (b) Liver (c) Kidney (d) Heart

Answers

1. (d) 2. (c) 3. (c) 4. (a) 5. (b) 6. (a) 7. (d) 8. (d) 9. (d) 10. (a)
11. (b) 12. (a) 13. (a) 14. (a)

Chapter 68

Food and Nutrition

I. Introduction: Food Vs Nutrition
II. Constituents of a normal diet
III. Nutritional needs of the body in terms of calories
IV. Balanced diet
V. Principles of diet planning
VI. Applied aspect:
A. Deficiency diseases: PCM (kwashiorkor; marasmus) B. Undernutrition and starvation

INTRODUCTION

1. The knowledge of food and nutrition has a direct bearing on the maintenance of sound health of an individual. *Food* is a complex mixture of various substances which help:
   (i) the production of heat and energy for body work and activities;
   (ii) the growth, repair and maintenance of body tissues;
   (iii) the digestive system to work well.
2. *Nutrition* is a dynamic process in which the food that is consumed is digested, its nutrients are absorbed and finally distributed to all body tissues for proper utilization.
3. *Essentials of a diet*
   (i) An adequate diet has an energy value sufficient to provide for:
      (a) the requirements of the basal metabolism
      (b) the stimulating action of the food-stuffs, and
      (c) the need of varying degrees of muscular work.
   (ii) It must have adequate amount of the constituents of normal diet (see below), all in suitable proportions.
   (iii) Adequate additional provision must be made for children, requirements of menstruation, pregnancy, lactation, illness and old age.

CONSTITUENTS OF A NORMAL DIET

The dietary constituents of food are: *proteins, fats, carbohydrates, vitamins, minerals, dietary fibre* and *water*. Most of the foods contain all these constituents but in varying proportion. Food can be classified on the basis of their predominant function as:

1. *Energy yielding foods:* These foods are rich in carbohydrates and fat, *e.g.*, cereals, sugars, oil.
2. *Body building foods:* These foods are rich in proteins, *e.g.* milk and its products, pulses, meat, etc.
3. *Protective foods:* These foods are rich in proteins, vitamins and minerals, *e.g.*, milk, egg, green leafy vegetables, fruits etc.

A. PROTEINS

Proteins are complex organic nitrogenous compounds. They are indispensable constituents of the diet because they are the only source of the amino acids including the *essential amino-acids;* these are: valine, lysine, leucine, isoleucine, phenylalanine, methionine, threonine, tryptophan, histidine and arginine (also see to page 619).

Functions

1. Build up new tissues during the period of growth or pregnancy and lactation;
2. Are essential for repair and maintenance of worn out body tissues;
3. Provides the raw material for the synthesis of certain substances *e.g.*, antibodies, haemoglobin, enzymes, hormones and plasma proteins;
4. Provide 10-15% of the energy during emergencies *e.g.*, starvation, inadequate food intake.

Sources (Fig. 68.1)

(i) *Animal sources:* milk and milk products, eggs, meat, fish etc.
(ii) *Plant sources:* pulses, cereals, dry fruits, nuts, beans, etc.

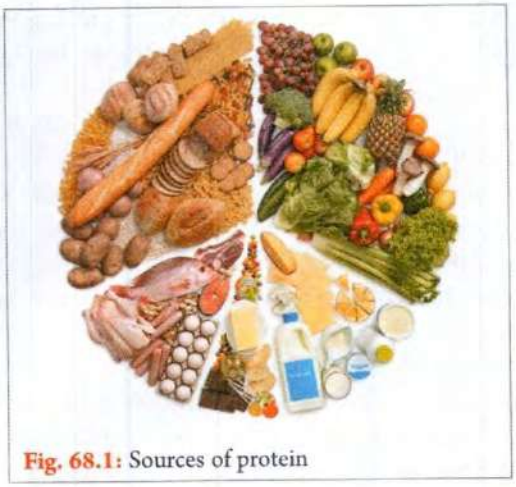


Fig. 68.1: Sources of protein

In general, the individual *proteins of animal tissues* closely resemble those of human tissues in their amino acid composition and they can be employed more economically for repair and growth; thus are called proteins of *high biological value*. Conversely, *proteins of vegetable foods* frequently have a very different type of amino-acid pattern and cannot be employed so economically built up into human tissues; such proteins are, therefore, called proteins of *low biological value*.

Proteins of 'high' and 'low' biological value are sometimes called ***first class*** (Grade I) and ***second class*** (Grade II) ***proteins*** respectively. But it should be remembered that many animals build up their muscles from the proteins of the vegetable origin.

Daily requirements

The protein intake should be 1.0 gram/kg body weight for an adult, some of it in the form of animal protein. An extra amount of protein (1.5-2 gm/kg body weight) should be added in: debiliating diseases; children and in pregnant and lactating women.

B. FATS

Fats are composed of fatty acids and contain carbon, hydrogen and oxygen. They are concentrated sources of energy. 1 gm of fat yields approx. 9 kcal of energy.

Functions

1. **Improve the palatability** *i.e.*, flavour and taste of food.
2. **Are essential for absorption of fat soluble vitamins** such as **Vitamins A, D, E and K.**
3. **Provide support** to body internal vital organs such as heart, kidneys, lungs, brain and liver.
4. Stored fats beneath the skin **provides insulation** against cold *i.e.*, prevents heat loss from the body.
5. Provide ***Essential Fatty Acids*** (EFA) which help in growth promotion, maintenance of skin integrity and reduce blood cholesterol. ('EFA' are: *linoleic acid; linolenic acid and arachidonic acid.*)

Note

Individuals with diet deficient in EFA fail to grow, develop skin and kidney lesions, and become infertile.

Sources (Fig. 68.2)

(i) *Animal sources:* ghee, butter, fish, oils. In general, they are poor sources of essential fatty acids but are good sources of retinol and cholecalciferol (vitamins A and D respectively).

(ii) *Plant sources:* groundnut, mustard, cotton seed, rape seed and coconut oil. These are all rich sources of essential fatty acids.

Fig. 68.2: Sources of fat

When vegetable oils are hydrogenated, the liquid oils are converted into semi-solid and solid fat, known as ***vanaspati oil/ghee*** (*e.g.*, Dalda, Rath, etc.). The **disadvantage** of hydrogenation is that the content of the valuable 'essential fatty acids' present in vegetable oils is drastically reduced.

When natural fats are treated with steam, alkalies etc., the free fatty acid, and rancid material present in oils are removed, the process is known as *'refining'* and ***Refined oils*** are produced. Refining improves the quality and taste of oil. Refined oils are free from odour and colour and are as safe as raw oils.

Daily requirements

The fat should provide at least 20% of the total energy in a day. This could come to 10-20 grams of fat per day. Young children need 25% extra amount of fats.

C. CARBOHYDRATES

Carbohydrates form the main bulk of diet and are the chief source of energy. They are also essential for the oxidation of fats and for the synthesis of certain *non-essential amino acids*. They are a cheap and readily obtainable food.

Sources (Fig. 68.3)

(i) *Starches:* these are 'complete sugar', present in abundance in cereals and millets, roots and tubers.

(ii) *Sugars:*

(a) monosaccharides *e.g.* glucose, fructose, galactose,

(b) disaccharides *e.g.*, sucrose, lactose and maltose.

(iii) *Cellulose* or dietary fibre: This is the fibrous substance lining fruits, vegetables and cereals. It is the indigestible component of carbohydrate with hardly any nutritive value.

Fig. 68.3: Sources of carbohydrates

Daily requirements

Carbohydrate intake should be in the range of 300-500 gm (between 50% to 70% of total energy intake). It should be sufficient to prevent the need for protein breakdown to provide energy.

D. VITAMINS

Characteristic features

1. Vitamins are complex chemical organic substances of high biological activity, required by the body in very small amounts in normal metabolism and act as a catalyst in various body processes.
2. They cannot be manufactured in the body in sufficient amounts, therefore, they have to be supplied through the diet (Fig. 68.4).

Fig. 68.4: Sources of vitamins

3. Vitamins are divided into two major groups as:
   (i) *Fat soluble vitamins* – Vitamins A, D, E and K; and
   (ii) *Water soluble vitamins* – Vitamins of B group (vitamin B-complex) and Vitamin C.
4. They appear to be *indispensable* for certain specific functions of the body; in most cases their mode of action has been fairly clearly defined.
5. They do not contribute to the energy of the body; in many cases they mobilize energy.
6. Deficiency of a vitamin can arise in two ways:
   (i) 'primary' deficiency, due to inadequate intake of vitamin or its precursor over a prolonged period of time; or
   (ii) 'conditioned' deficiency arising on an adequate diet through other factors which decrease absorption or prevent release, or increase utilization or excretion.
7. (i) Vitamin B-complex group consists of a series of water soluble organic substances which are found in all cells (the important ones are: *thiamine* (B_1), *Riboflavin* (B_2), *Niacin* (B_4), *Pyridoxine* (B_6), *Pantothenic acid, Biotin, folic acid and cyanocobalamin* (B_{12}).
   (ii) They are involved in the oxidation of the foodstuffs, and are, therefore, indispensable for the normal functioning of all tissues.
   (iii) Most members of this group of vitamin can be synthesized by the intestinal bacteria.

E. MINERALS

1. The body contains some 50 minerals which serve specific functions in the body. The mineral constituents of the body amount to 4.3-4.4%, largely in the skeleton.
2. The important minerals include: Calcium, phosphorus, iron, sodium, potassium and magnesium.
3. Some minerals are required by the body in very small amounts *e.g.*, iodine, zinc, manganese, copper, cobalt and fluorine. They form a part of every cell and fluid in the body and are required for growth, repair and regulation of vital body functions. For example:
   (i) *Zinc* is present in insulin and in many enzymes; its deficiency causes skin ulcers, depresses immune response and hypogonadal dwarfism.
   (ii) *Copper* occurs in blood combined with an α-globulin, forming the protein ceruloplasmin; its deficiency causes anaemia, changes in ossification and increases S.cholesterol.
   (iii) *Manganese* is required in many enzyme systems.
4. Conversely, some minerals produce toxicity when present in the body in excess *e.g.*, iron overload causes haemochromatosis; copper excess causes brain damage.

5. Some important vitamins and minerals essential to human nutrition along with their *sources, functions deficiency symptoms* and their *prevention* in human are listed in the **Table 68.1**.

Important Note

Very large doses of the fat soluble vitamins are toxic (as occurs with consumption of vitamin pills/ supplements), called Hypervitaminosis. In general, it is characterized by: anorexia, diarrhoea, headache, hepato-splenomegaly, irritability, bone sclerosis and neuropathies.

F. DIETARY FIBRE

The carbohydrates (*e.g., pectin, cellulose, hemicellulose*) and some non-carbohydrate substances (*e.g., lignin*) are collectively called *dietary fibre* (also see to page 256). It resists digestion and is found in vegetables, fruits and grains. The fibre absorbs water, which increases the bulk of the intestinal contents and facilitates intestinal movements and thus the defecation. Fibres also have a role in weight reduction and cholesterol lowering. Its **deficiency leads to** constipation, cancer of colon, colonic diverticulosis, heart disease and gall bladder stones.

The most practical way of including sufficient fibre in diet are **(Fig. 68.5)**:

(i) Whole cereals should be preferred to refined cereals.

(ii) Whole pulses should be preferred to those from which the husk has been removed.

(iii) Fruits and vegetables that can be eaten with the skin intact should be eaten as such.

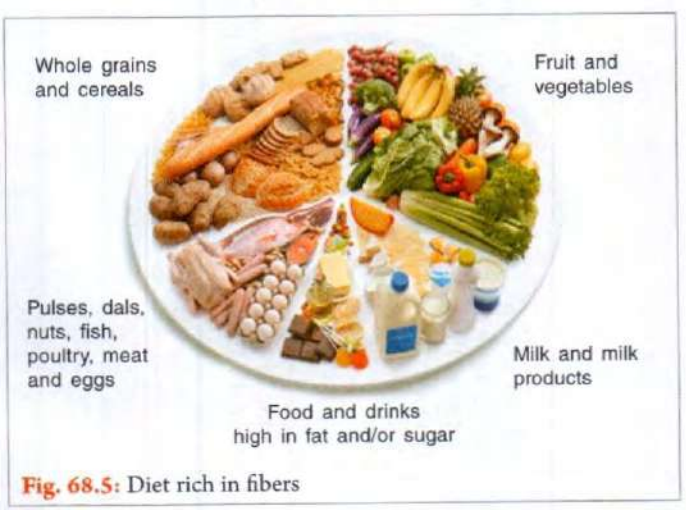


Fig. 68.5: Diet rich in fibers

G. WATER

Water is an essential requirement for life. It is the medium in which most of the chemical activities in the body take place. More than 70% of the body weight is imply because of the water it has. Loss of water upto 10% of total body water, makes a person feel extremely tired and fatigued. More than 20% loss may result in death. Water occurs in all natural food, most of it comes from that we drink.

NUTRITIONAL NEEDS OF THE BODY IN TERMS OF CALORIES

1. The physiological **calorie value** of food for different nutrients is:

Carbohydrate (sugar, starch)	:	4 kcal/gm
Protein (mixed)	:	4 kcal/gm
Fat	:	9 kcal/gm

(1 kcal = 4.2 kJ)

2. There are wide variations in individual **calories requirements** even among persons living under similar conditions. The total calories requirements for Indian at 'rest' (*i.e.* under complete physical and mental rest called ***Basal Metabolic Rate - BMR***) as given by ICMR (Indian Council of Medical Research) are:

(i) for men : 38-40 kcal/hour/m^2 BSA = 1500-2000 kcal/day

(ii) for women : 33-35 kcal/hour/m^2 BSA = 1200-1500 kcal/day.

(Also refer to page 596)

Note

Mental activity involves no expenditure of energy.

3. **Factors affecting calories requirement:**

(i) *Age*

(a) *Infants* require about 750 kcal/day during first 3 months of life, rising to 1000 kcal/day at 10-12 months.

(b) *Children* and *young adults* grow very fast and thus the following calories requirements have been proposed.

Age (years)	*kcal/day*
1–3	1500
4–6	1800
7–9	2200
10–12	2700
13–15	3100
16–20	3500

(c) *Old age* – with advancing age the BMR falls, and the amount of physical activity decreases, therefore, calories requirement decreases.

(ii) *Sex:* Recommended daily requirements of calories of a woman are about 20% lower than those of a man of the same age.

(iii) *Body size and weight:* Both BMR and the calories requirements of mechanical work are directly proportional to the body weight.

Table 68.1: Vitamins and Minerals Essential to Human Nutrition

Vitamin (1)	Daily Requirements (2)	Sources (3)	Function/Action (4)	Deficiency Symptoms (5)	Prevention and control of deficiency (6)
VITAMINS					
1. Vitamin A (Retinol)	Infants 300-400 µg of retinol equivalent: Adults 750 µg; Children 400–600 µg; Pregnancy 750+400 µg; Lactation 750+400 µg (one I.U. of Vitamin A = 0.3 µg of Retinol).	Yellow vegetables and fruits (carrots, pumpkin, mangoes, papaya, bananas, liver, egg yolk, ghee, cheese, milk and its products, eggs, fish, fish liver oil.	1. Constituents of visual pigment (page 1105) which helps in normal vision. 2. Maintains epithelial cells of skin and mucous membrane. 3. Associated with growth especially regulates skeletal growth. 4. Protects body against infections.	1. Resistance to infection decreases. 2. Dry Scaly Skin ***(Toad skin)***. 3. ***Night blindness*** *i.e.*, inability to see in dim light. 4. ***Xerophthalmia*** (dry eye) characterized by (i) dry conjunctiva. (ii) ***Bitot's Spots*** (greyish, rough and raised patches on conjunctiva). (iii) Cornea becomes dry, hazy like ground glass with ulceration. (iv) ***Keratomalacia*** (softening of a part or whole of the cornea).	1. Diet improvement – regular intake of green leafy vegetables. 2. Oral administration of 200,000 I.U. of vitamin A drops every 6 months to pre-school children.
2. Vitamin D, Cholecalciferol *(antirachitic vitamin)*	Infants and children 10 µg; adults 7.50 µg; lactation 15 µg [1 µg of cholecalciferol = 40 I.U. ov vitamin D]	Fish, liver, fish liver oils, eggs, butter, milk and its products; generated in the skin by action of ultra-violet rays of sunlight.	1. Increases intestinal absorption of calcium and phosphate. 2. Mineralization of bones and teeth.	***Rickets*** in children and ***Osteomalacia*** in adults. *Rickets* is characterised by bony deformities in growing children. *Osteomalacia* is characterized by generalized body pain especially over bones.	1. Infants and children are exposed to the sun under appropriate conditions. 2. Prophylaxis vitamin D supplements during first two years of life.
3. Vitamin E *(Anti-sterility vitamin)*	15 I.U. (= 10 mg) for normal adults.	Milk, oils, eggs, meat, leafy vegetables.	1. Antioxidant. 2. Cofactors in electron transport in cytochrome chain.	*Sterility*, muscles wasting and Ataxia, foetal death, testicular degeneration and hemolysis of red blood cells in animals.	Widely distributed in foods, therefore, no deficiency symptoms are produced in humans.

Table 68.1: Vitamins and Minerals Essential to Human Nutrition

Vitamin (1)	Daily Requirements (2)	Sources (3)	Function/Action (4)	Deficiency Symptoms (5)	Prevention and control of deficiency (6)
4. Vitamin K *(Anti-haemorrhagic vitamin)*	Average diet combined with that formed by intestinal bacteria (approx. 30 µgm)	Green leafy vegetables, cereals, fruits; synthesized by bacteria in GIT.	Catalyzes γ-carboxylation of glutamic acid to activate clotting factors especially prothrombin.	Marked prolongation in blood clotting time leading to generalised bleeding tendencies.	Administration of single oral dose of vitamin K to premature infants.
5. Vitamin B-complex group (i) Vitamin B_1 (Thiamine)	Children: 0.5-1.0 mg Adults: 1.0-1.5 mg Pregnancy and lactation: 1.5-2 mg	Meat, fish liver, eggs, milk, cereals, pulses, grains, nuts, fruits, yeast, vegetables.	Cofactor in decarboxylation of acids, thus helps in carbohydrate utilization and maintenance of good appetite and digestion. [nervous tissue uses glucose as their primary source of energy].	***Beri-beri***, neurological and mental disturbances *e.g.* anaesthesia, loss of reflexes, paralysis in legs, insomnia, anxiety, depression, cardiomegaly, signs of cardiac failure.	1. Use of parboiled or undermilled rice. 2. Addition of thiamine rich food to the diet.
(ii) Vitamin B_2 (Riboflavin)	2 mg	Liver, milk, meat, beer, green leafy vegetables, pulses, germinating cereals, also synthesized by bacteria in large intestine.	1. Constituent of *'flavo-protein'* which helps in tissue oxidation and respiration. 2. Helps in protein, fat and carbohydrate metabolism.	***Glossitis***, cheilosis, soreness of the tongue, redness and burning sensation in the eyes, dermatitis.	Adequate intake of riboflavin rich foods.
(iii) Vitamin B_4 (Niacin)	10-15 mg	Yeast, meat, kidney, liver, cereals, pulses, germinating seeds, green vegetables, also synthesized in the body.	Constituent of coenzyme NAD^+, $NADP^+$ and thus concerned with many of the important enzyme producing reactions of metabolism. This helps in normal functioning of skin, intestinal tract and nervous system.	1. ***Pellagra***-characterized by 3Ds: (a) Dermatitis (b) Diarrhoea (c) Dementia (Memory loss) 2. Glossitis, mental disorders with polyneuropathy	Adequate intake of niacin rich foods.
(iv) Vitamin B_6 (Pyridoxine)	1.5 mg for normal adults.	Yeast, wheat, corn, liver, cereals, legumes.	1. Forms prosthetic groups of decarboxylases and transami-nases. 2. Converted in the body into pyridoxal phosphate. These help in metabolism of amino-acids, fats and carbohydrates.	Convulsions, hyperirritability, dizziness and vomiting.	Administration of drugs (INH, oral contraceptives) produces Vitamin B_6 deficiency. These drugs must be supplemented with Vitamin B_6.

(iv) *Physical activity:* Daily calories requirement increases with the type of physical activity (Table 68.2).

(v) *Climate*

(a) People eat less where the environmental temperature exceeds 25°C, the energy intake should be reduced by 5-10%.

(b) In cold climate, the calories requirements should be increased by only 3% for every 10°C of mean external temperature below the reference temperature since protection against cold is achieved by clothing and by heating.

(vi) *Specific dynamic action (SDA) of food* - page 582

(vii) *Thyroid hormones* - page 688

(viii) *Catecholamines* - page 738

Table 68.2: Calories requirements of physical activity

Work level	Additional calories requirements
1. 'Light' work, such as most domestic work	10%
2. 'Moderate' work, such as gardening, tennis, cycling, carpentry etc.	20%
3. 'Heavy' work, such as coal mining, loading, football, athletics, etc.	30%
4. 'Very heavy' work, such as, black-smith work, swimming, hill climbing etc.	40%

BALANCED DIET

A diet which contains different types of food in such quantities and proportions that the need for energy, proteins, fats, carbohydrates, vitamins and minerals is adequately met for maintaining health, is called ***balanced diet*** (Fig. 68.6).

If the diet is deficient in any of these nutrients, ***malnutrition*** results and individual might suffer from physical and mental growth retardation. To stay healthy and strong, a person should eat food that provides adequate amounts (neither too little nor too much) of various nutrients according to nutritional requirements.

Balanced diet requirements are closely related to age, sex, body build, occupation of the individual and in pregnant and lactating women (Table 68.3). Balanced diets formulated by the ICMR are recommended by adopting universally energy requirements of an Indian *reference man and woman*. An Indian reference man is an apparently healthy individual between 20-39 years of age, weighing 55 kg. with body surface area 1.62 sq. metres, whereas a reference woman weighs 45 kg with body surface area 1.40 sq. metres.

PRINCIPLES OF DIET PLANNING

No food is perfect though most foods contain more than one nutrient. In general, a mixed diet consisting of foodstuff from different food groups is likely to be adequate in protein, vitamins and minerals, if it is adequate as regards energy needs.

In formulating diet for any individual, the following broad principles should be adopted:

1. It should be a *'fibre' rich balanced diet* and must provide the required recommended daily calories.
2. Of the total calories requirements, at least 50% should be provided by carbohydrate; 25-30% from proteins and 20-25% from fats.
3. Cost of the diet should be reasonably low.
4. The diet should be such that it can be prepared easily.
5. As far as possible, locally and seasonally available foods should be used; this will reduce the cost of the diet.
6. The menu should be frequently changed to avoid monotony.

APPLIED ASPECT

A. DEFICIENCY DISEASES

Health is affected not only by diseases but also by an *unbalanced* food. A balanced diet is necessary for good

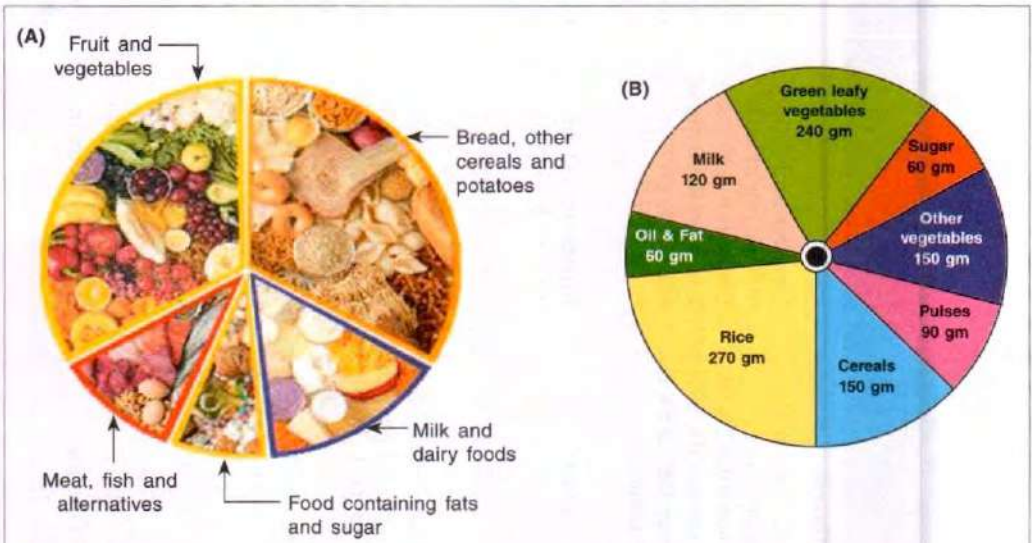


Fig. 68.6 Daily requirements of different types of food in an adult (A and B)

Table 68.3: Balanced diets according to Age and Sex (all values in grams) (Source: ICMR)

Food item	Children (either sex)			Reference man	Reference woman
	1-3 years	4-6 years	10-12 years		
1. Cereals	175	270	420	460	410
2. Pulses	35	35	45	40	40
3. Leafy vegetables	40	50	50	40	100
4. Other vegetables	20	30	50	60	40
5. Roots and tubers	10	10	30	50	50
6. Milk and milk products	300	250	250	150	100
7. Oil and fat	15	25	40	40	20
8. Sugar and jaggery	30	40	45	30	20

Notes

1. An additional of 10% allowances during 'pregnancy' or during 'light work' have been recommended.
2. An additional of 20% allowances during 'lactation' or during (moderate work) have been recommended.
3. An additional of 30% allowances during 'heavy work' have been recommended.

health. Inadequate amount of food leads to insufficient nutrition. The condition coming out of this is called Malnutrition or Undernutrition. Going by the *Progress of Nations* the level of malnutrition in India is among the highest in the world. As many as 5000 children in the country die of malnutrition every day.

Malnutrition is more marked in vulnerable sections of the population *i.e.*, pregnant women, nursing mothers, infants and children, especially in lower and middle classes. It manifests itself in various forms of deficiency diseases.

Note

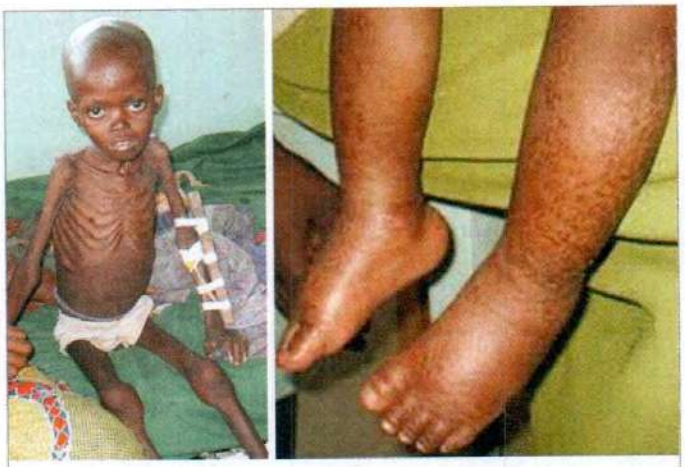
Diseases due to vitamins and mineral deficiencies and their prevention are given in Table 68.1, pages 630–633.

Diseases due to Energy Deficiency

It leads to so called ***Protein Energy Malnutrition*** (PEM). The term 'PEM' is misnomer because protein deficiency alone is very uncommon. The real deficiency is that of food energy which is measured in terms of 'calorie'. PEM is, therefore, referred to as ***Protein Calorie Malnutrition*** (PCM).

Protein Calorie Malnutrition (PCM)

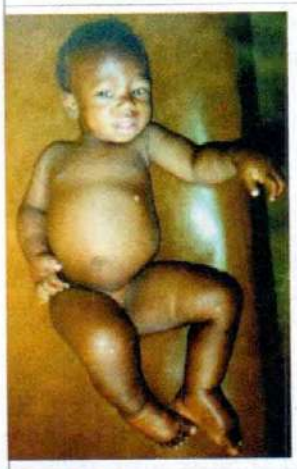
Protein calorie (energy) malnutrition is the *commonest form* of malnutrition in India. Infants and young children between 1 to 3 years of age are the most frequent sufferers. It may lead to permanent mental and physical disabilities in children who survive. The most serious forms of PCM are ***Kwashiorkor*** and ***Marasmus***. The main differentiating features of two forms of PCM are given in Table 68.4 and Fig. 68.7.



(A) Kwashiorkor, results from gross protein deficiency

Characteristic features

1. Generalized oedema *i.e.* swelling present all over the body.
2. Swollen face (moon like)
3. Hair: sparse, straight with loss of pigment
4. Generalized skin changes:
   (i) areas of skin pigmentation alternating with scaling
   (ii) areas of decreased pigmentation



(B) MARASMUS, results from severe calorie malnutrition

Characteristic features

1. Absence of oedema
2. Marked muscular wasting, Ribs are conspicuously visible
3. Brittle (fragile) hair
4. Small sunken face (monkey like)
5. Severe growth retardation:
   (i) Limbs are thin (look like sticks)
   (ii) Absence of fat from the buttocks

Fig. 68.7 Two major forms of Protein-Calorie Malnutrition (PCM)

Table 68.4: The main differentiating characteristic features of two forms of PCM

Principal Features	Kwashiorkor	Marasmus
1. Major causative factor	Gross protein deficiency	Severe calorie malnutrition
2. Weight as percentage of normal	60% to 80%	Below 60%
3. Oedema	Present all over the body	Absent
4. Muscular wasting	Occasionally seen	Severe
5. Growth retardation (physical and mental)	Less	Severe
6. Appetite	Poor	Usually good
7. Skin changes	Depigmentation of skin all over the body	Loose with loss of elasticity
8. Hair	Sparse, straight, greyish or reddish	Brittle (fragile)
9. Face	Swollen, *moon like face*	Small sunken; *monkey like face*
10. Diarrhoea	Often present	May be present
11. Anaemia	Present	May be present
12. Liver enlargement	Frequent, secondary to 'fatty liver'	Absent
13. Occurrence and outcome	Less common occurrence with serious outcome, may be fatal	Common occurrence with less serious outcome

The major causative factors of PCM

1. An inadequate diet, both in quantity and quality; primarily due to poverty.
2. Infectious and parasitic diseases such as repeated diarrhoea and chest infections, worms infestation, measles.
3. Poor environmental conditions.
4. Adverse cultural practices like premature termination of breast feeding; use of over-diluted milk; late weaning of the child.

Preventive Measures

1. Health promotion/health education.
   (i) promotion of breast feeding and correct feeding practices;
   (ii) better mother health care during pregnancy;
   (iii) family planning and spacing of births.
2. Provision of specific protection (immunization) against infectious diseases.
3. Early detection and treatment of diarrhoea, chest infections and PCM.
4. Rehabilitation of the sufferers by providing follow-up care.

B. UNDERNUTRITION AND STARVATION

Undernutrition and starvation lead to wasting of the body with marked loss of adipose tissue and of muscle.

Causes

1. Insufficient food in the diet.
2. Severe disease of the GIT such as malabsorption syndrome. This prevents absorption of nutrients even if the dietary supply is adequate.
3. Infection and toxaemias. They reduce appetite or interfere with normal metabolism.

Body changes

During starvation, even if no physical work is being done, approx. 1500 kcal will be needed daily. During the first few days the glycogen stores of the liver are called upon. The main source of energy is the fat reserves and tissue proteins. So as long as fat is available tissue protein is 'spared'. Death occurs after about 4 weeks, when the body weight is reduced by 50%. The ***major effects*** of undernutrition and starvation on the body are:

1. *Blood sugar* – this is maintained at a 'steady state' level almost to the end. It is formed in the liver from amino acid residues, glycerol (from fats) and lactic acid (from partial catabolism of muscle glycogen).
2. *Body fat*
   (i) The neutral fats (triglycerides) which are found in adipose tissue are used in starvation. The increased breakdown of fat in the adipose tissue depots releases free fatty acids (FFA) which can provide energy for muscular contraction and thus help to conserve the blood glucose for the brain which cannot utilize FFA.
   (ii) The mobilized FFA are taken to the liver, where it is either completely catabolised or transformed into ketone bodies. The 'complex lipid' which forms part of the cell structure is spared till the end.
   (iii) Owing to the lack of carbohydrate, ketogenesis is stimulated and ketone bodies pass into the blood

from the liver faster than they are disposed off by the tissues. There is thus a *ketosis* and ketone bodies appear in the urine (page 613).

3. ***Tissue protein***
   (i) Tissue protein is hydrolyzed to amino acid. The increased breakdown of 'endogenous' protein occurs chiefly in the muscles and glands; the brain and heart lose only 3% of their bulk; muscle, liver and spleen lose 30, 55 and 70% respectively. This is controlled through the action of adrenal cortex.
   (ii) The amino acids which enter the 'common pool' serve:
      (a) to maintain the structure and so functional efficiency of the essential organs;
      (b) to preserve the normal blood sugar level; the conversion of amino acids to sugar occurs in the liver.
   (iii) Nitrogen excretion during the first week of starvation averages approx. 10 gm/day; during the second or third week it may fall to a considerably low value.
4. ***Water***

Intracellular water is decreased but extracellular water is not correspondingly reduced so that a relative excess accumulates, producing *oedema*. Water retention is promoted by:
   (i) reduction in plasma protein level;
   (ii) fall in tissue tension secondary to loss of fat.
5. ***Failure of hormone and enzyme production***

Many of the body's hormones and all enzymes are proteins (except Ribozyme). Therefore, during prolonged starvation the synthesis of protein hormones and enzymes is reduced causing:
   (i) delayed puberty and amenorrhoea in girls;
   (ii) loss of libido and impotence in males;
   (iii) marked atrophy of the thyroid gland due to reduced secretion of 'thyrotropic' hormone;
   (iv) diarrhoea due to reduced formation of digestive enzymes.
6. ***CVS***
   (i) The marked bradycardia due to thyroid deficiency;
   (ii) peripheral blood flow and venous pressure and systemic arterial B.P. are reduced.
7. ***Metabolic rate*** – the BMR is reduced, partly due to smaller mass of active tissues and partly due to thyroid deficiency. Thus, energy amounting to about 400 kcal is saved daily.
8. ***Hunger***

In 'semi-starved' people, the hunger sensation becomes progressively increased (strong contractions of the empty stomach give rise to a sense of hunger – 'hunger pains').

Study Questions

1. **Write briefly on:**
   (i) role of vitamins in maintenance of health
   (ii) scurvy
   (iii) importance of zinc and copper in diet
   (iv) balanced diet
   (v) dietary fibre
   (vi) xerophthalmia
   (vii) beri-beri
   (viii) sprue
   (ix) principles of formulating diet
   (x) factors affecting calories requirement
   (xi) calories requirements of physical activity.
   (xii) food and nutrition
   (xiii) first and second class proteins
   (xiv) vanaspati and refined oil
   (xv) dental caries and dental fluorosis
   (xvi) skimmed and toned milk
   (xvii) kwashiorkor and marasmus.
2. **Mention deficiency symptoms due to:**
   (i) Vitamin D (ii) Vitamin K (iii) Vitamin C (iv) Niacin.
3. **Name the dietary constituents of normal food. Classify food on the basis of their functions.**
4. **Give the main sources, daily requirement and functions of:**
   (i) proteins (ii) fats (iii) carbohydrates.
5. **Name the essential amino acids and fatty acids. Why are they called so?**
6. **Define protein calorie malnutrition. Enumerate the main factors which precipitate it. How can it be prevented?**

7. **Mention the major effects of starvation on the body. How long can a person survive with complete starvation?**
8. **Define a reference man and woman. Give its physiological significance.**

MCQs

1. **A major function of proteins in diet is:**
   (a) Body growth and repair
   (b) Maintenance of plasma protein level
   (c) Haemoglobin synthesis
   (d) To provide energy
2. ***Not* an essential fatty acid:**
   (a) Linoleic acid (b) Linolenic acid (c) Stearic acid (d) Arachidonic acid
3. **Dietary fibre derived from non-carbohydrate source is:**
   (a) Pectin (b) Lignin (c) Cellulose (d) Hemicellulose
4. **Vitamin A deficiency symptoms include all of the following, *except*:**
   (a) Xerophthalmia
   (b) Generalized body pain
   (c) Bitot's spots
   (d) Decreased resistance to infection
5. **Rickets is characterized by:**
   (a) Generalized body pain
   (b) Pain over bones
   (c) Bony deformities
   (d) Marked muscular weakness
6. **Salient feature of thiamine deficiency is:**
   (a) Decreased cardiac output
   (b) Accelerated venous return
   (c) High sleeping pulse rate
   (d) Systolic hypertension
7. **Glossitis and burning sensation in the eyes is most commonly seen in deficiency of:**
   (a) Thiamine (b) Riboflavin (c) Niacin (d) Pyridoxine
8. **Which vitamin is essential for synthesis of amino acids in the body?**
   (a) Vitamin B_1 (b) Vitamin B_2 (c) Vitamin B_6 (d) Vitamin B_{12}
9. **During germination of pulses, concentration of which of the following vitamins increases considerably?**
   (a) Vitamin C (b) Niacin (c) Folic acid (d) All of the above
10. **Beer supplies ..... kcal of energy per gram:**
    (a) 7 (b) 17 (c) 70 (d) 107
11. **Balanced diet is one which:**
    (a) Contains different types of food-stuffs
    (b) Is not deficient in any of the nutrients
    (c) Contains all nutrients in adequate amounts and proportions for maintaining health
    (d) Is sufficient for physical and mental growth
12. **Kwashiorkor differs from Marasmus in all of the following *except*:**
    (a) Major causative factor is severe calorie malnutrition
    (b) Generalised oedema
    (c) Depigmentation of skin
    (d) Diarrhoea often present
13. **Daily protein intake should be:**
    (a) 0.5 gm/kg body weight
    (b) 1 gm/kg body weight
    (c) 1.5 gm/kg body weight
    (d) 2 gm/kg body weight
14. **Dietary fibre play an important role in:**
    (a) Facilitate intestinal movements
    (b) Weight gain
    (c) Raises blood cholesterol
    (d) All of the above
15. **Not a function of vitamin A:**
    (a) Constituent of visual pigment
    (b) Maintains epithelial cells of skin
    (c) Increases intestinal absorption of calcium
    (d) Regulates skeletal growth
16. **Deficiency of which vitamin is *not* known in newborns?**
    (a) C (b) D (c) E (d) K
17. ***Salient feature* of thiamine deficiency is:**
    (a) Decreased cardiac output
    (b) Accelerated venous return
    (c) High sleeping pulse rate
    (d) Systolic hypertension
18. **A low convulsive threshold in humans may be an indication of deficiency of:**
    (a) Pyridoxine (b) Thiamine (c) Aldosterone (d) Glucocorticoids

19. **In vitamin C deficiency wound healing is poor because of:**
    (a) Poor blood vessels development
    (b) Poor connective tissue synthesis
    (c) Poor neurophil function
    (d) Excessive collagen formation
20. **Water is safe for drinking with fluorine concentration of ..... parts per million (ppm)**
    (a) 1 (b) 2 (c) 3 (d) 4
21. **The best and most complete of all foods is:**
    (a) Fruits
    (b) Green leafy vegetables
    (c) Milk and milk products
    (d) Cereals
22. **Broad principle adopted in formulating a diet is:**
    (a) It should be fiber rich balanced diet
    (b) Of the total calories requirements 50% should be provided by carbohydrates, 25% by proteins and 25% by fats
    (c) Locally and seasonally available food should be used
    (d) All of the above
23. **All of the following parameters decreases during starvation *except*:**
    (a) Heart rate
    (b) Hunger
    (c) Peripheral blood flow
    (d) Systemic arterial BP

Answers

1. (a)	2. (c)	3. (b)	4. (b)	5. (c)	6. (b)	7. (b)	8. (c)	9. (d)	10. (a)
11. (c)	12. (a)	13. (b)	14. (a)	15. (c)	16. (c)	17. (b)	18. (a)	19. (b)	20. (a)
21. (c)	22. (d)	23. (b)							

Chapter 69

Antioxidant Nutrients, Free Radicals and Physiology of Aging

I. Antioxidant nutrients
II. Free radicals: formation and diseases they produce
III. Physiology of Aging
   A. Age related changes
   B. Theories of aging
   C. Factors that will delay aging

ANTIOXIDANT NUTRIENTS

1. *Antioxidants* are group of chemical compounds that can deactivate the ***free radicals*** (see below) and prevent their formation. They also stimulate the immune system to increase our protection against all diseases.
2. These nutrients stop fats from undergoing autoxidation and reacts with a free radical much more rapidly than the body components do.
3. The ***major antioxidant nutrients*** include the following **(Fig. 69.1)**:

Fig. 69.1 Antioxidant foods (**Note:** Foods of different colours)

(i) Vitamin E.
(ii) Vitamin C (functions mainly as an electron donor).
(iii) Betacarotene (provitamin) and vitamin A.
(iv) Bioflavonoids (various members of the B-complex vitamins).
(v) Lipoic acid and glutathione, sulphur-containing compounds that can act as hydrogen atom donors.
(vi) *Minerals.* They are not direct antioxidants but are needed to make the ***antioxidant enzymes.***
   (a) **Selenium** – helps to make *glutathione peroxidase.*
   (b) **Manganese** – produces *superoxide dismutase* which dismutates the superoxide anion radical in the mitochondria. This enzyme is important for people with arthritis because it is also an anti-inflammatory agent.
   (c) **Zinc and copper** – form *superoxide dismutase* in the cytoplasm.
   (d) **Iron** – forms the *catalase* which converts hydrogen peroxide into water.
   (e) **Chromium** – reduces free radical formation during the energy production process.
(vii) *Accessory antioxidants:* pyenogenol, Co-enzyme Q-10 and curcuminoids.

Important Note

If we consume less than the optimal amounts of the antioxidant nutrients, we increase the risk of heart disease, cancer, arthritis, cataracts and many other diseases.

FREE RADICALS

A. Definition

Free radicals are very reactive molecules or fractions of molecules. These free radicals exist independently with only one electron in one or more orbitals. Such a lone electron is called an ***unpaired*** electron. Since all other

molecules have electron pairs, therefore, each time a free radical reacts with a molecule, it forms another radical.

B. How do free radicals form?

1. Normal body processes, such as metabolism that utilize oxygen to turn food into energy, remove electrons from oxygen atoms one electron at a time. This leaves the oxygen atom, with an unpaired extra (or lone) electron in comparison with a normal atom of oxygen. This extra electron is highly reactive and can initiate a ***chain reaction*** of thousands of free radical reactions within seconds.
2. The free radicals are formed mainly from oxidation products of foods under the influence of radiation or food additives, or when the foods are not sufficiently protected by certain vitamins. When we are healthy, free radicals are balanced by our *antioxidant defence system* **(Fig. 69.2)**.
3. Free radical *chain reactions* take place in our body countless times a day. Cigarette smoking, pollutants, sunlight, radiations and even emotional stress can cause free radicals formation and free radical chain reactions.

C. Common free radicals of biological importance

1. Hydrogen atom.
2. Oxygen molecule.
3. Superoxide anion.
4. Hydroxyl (most damaging radical to body components).
5. Alkoxyl and peroxyl.
6. Nitric oxide.
7. Peroxy nitrate.

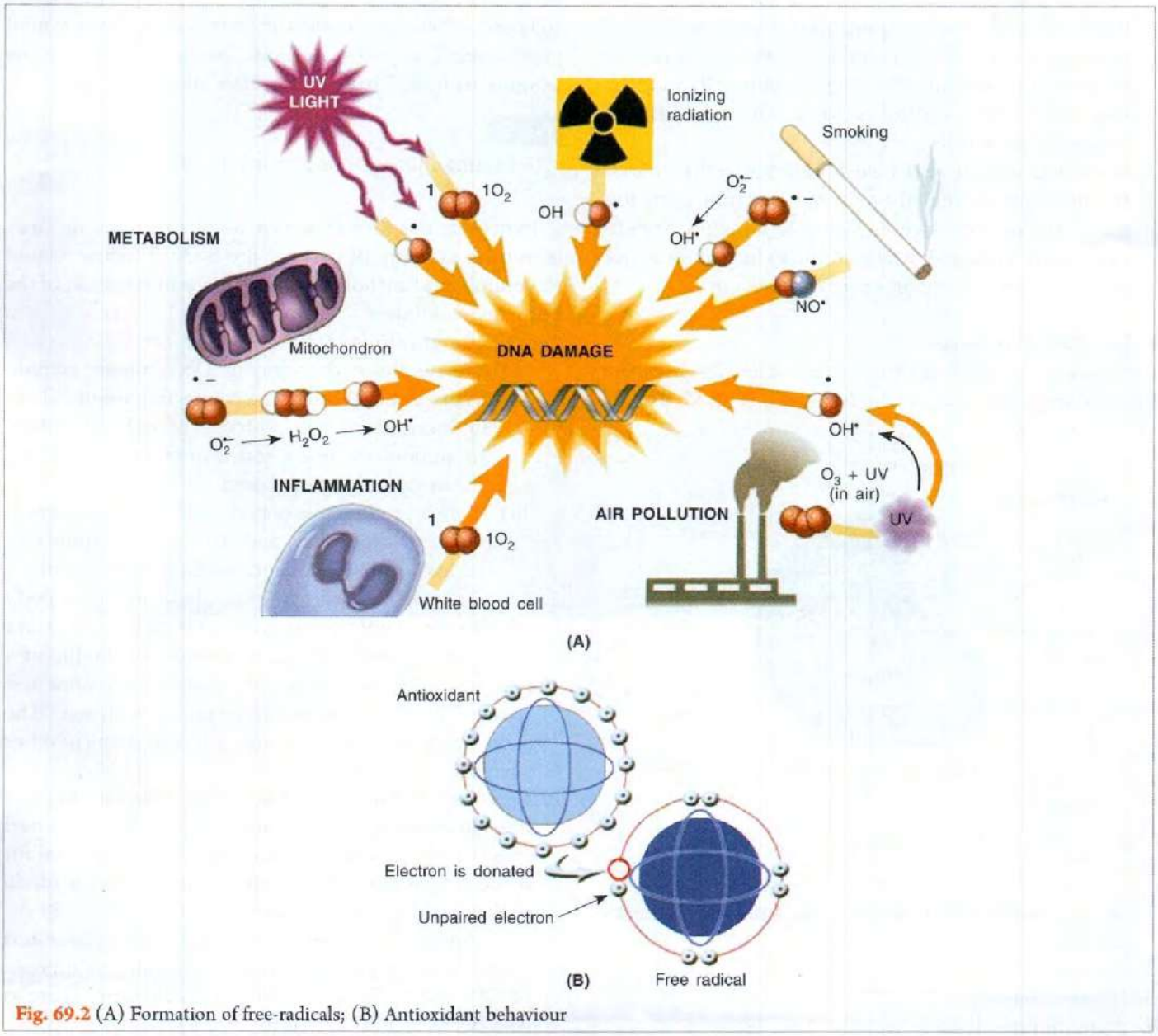


Fig. 69.2 (A) Formation of free-radicals; (B) Antioxidant behaviour

Important Note

A major factor in increased free radical generation in our bodies is due to the fact that most of us eat far too many calories to our needs. As more food is eaten, more oxygen is required to burn it, and as more oxygen is used, more free radicals are produced.

D. How free radicals produce damage?

1. Tens to thousands of free radicals are produced in the body every second. These are so dangerous that critical body components, such as DNA (the genetic material that directs the manufacture of each cell) can be altered by them. Free radicals damage DNA in genes by oxidizing the DNA nucleic acid bases (adenine, thymine, guanine and cytosine) that hold the double strands of the helical-shaped DNA molecules.
2. Free radicals causes oxidation of fatty compounds (lipids) that are vital components of hormones and cell membranes. If cellular membranes are damaged, the cells may not recognize the neighbouring cells and they may grow out of control of these normal conditions forming cancer cells.
3. Free radicals can also fuse proteins together, *cross-linking* them so that they do not function normally. For example, excessive exposure to sunlight, stiffens skin and can cause skin cancer due to formation of free radicals from ultraviolet energy of the sun.

E. Free radical diseases

Free radicals are the sole cause of only a few diseases, but they are involved in all of the following **(Fig. 69.3)**:

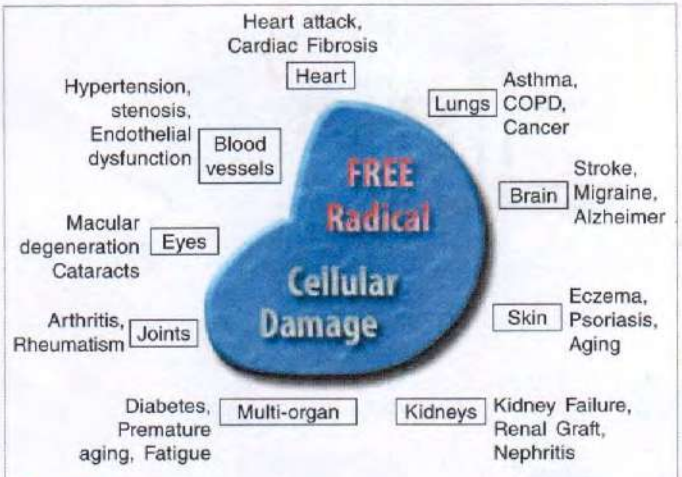


Fig. 69.3 Diseases due to free-radicals

1. Aging, disorders of premature aging, immune deficiency of aging.
2. Cancers.
3. Heart diseases.
4. Autoimmune diseases.
5. Rheumatoid arthritis.
6. Radiation injury.
7. Cataracts.
8. Retinopathy.
9. Parkinson's disease.

PHYSIOLOGY OF AGING

Aging is described as the process that reduces the number of healthy cells in the body, therefore, the body loses its ability to respond to a ***challenge*** (external or internal stresses) to maintain homeostasis.

A. AGE RELATED CHANGES

The body loses its ability to reproduce some of its cells, and as cells are destroyed they are not always replaced. In addition, there is a stiffening of tissues. The loss of cells and stiffening of tissues age our bodies. The maximal physiological capacity of most organ system reduces progressively and irreversibly after 30 years of age.

Note

The human life span is about 110-120 years.

However, the rate at which body functions declines is not the same in all parts of the body. The age related structural and functional changes in various organs of the body are as follows.

1. *Changes at cellular level*
   (i) A generalised decrease in DNA repair activity occurs in body cells. The connective tissues show an increase in the stiffness of collagen fibers throughout the body and also an increase in the rate of hydrolysis of elastin.
   (ii) There is gradual loss of body cells, being greatest in nerve, muscle, kidney and glands. This accounts for the loss of their function (about 0.6% per year).
2. *Loss of body reserve.* An example of how the body losses reserve with aging is that fasting blood glucose levels remain fairly constant throughout the life of a healthy individual. However, glucose tolerance test (page 753) shows a loss of response with age. The same holds true for the recovery mechanisms of other systems.
3. *Immune mechanisms.* The aging process impairs the immune system, primarily due to decreased effectiveness of cellular immunity, which is crucial for protection against viruses and tumours. This leads to higher incidences of cancer in old age.
4. *GIT.* An overall decline in the capacity to digest and absorb the nutrients is seen due to atrophy of mucosa of GIT and reduction in enzyme secretions. There is also decrease in the molitity of the GIT.

5. *Cardiovascular system.* The heart becomes stiffer and less efficient as a pump, while arteries lose elasticity and offer greater resistance to blood flow. This, in turn, decreases blood flow to most organs.
6. *Respiratory system.* An overall decline of respiratory functions, such as ventilation, exchange of gases as well as regulation of respiration is seen with advancing age.
7. *Excretory system.* A decrease in number of nephrons and decreased blood flow to kidneys with advancing age makes the kidney less efficient as filter.
8. *Endocrine system.* In general, number of target cells decreases with decreased sensitivity of receptors to hormones. This results in reduction of physiological response of many of the hormones in the body with the advancing age.

Note

Some of the normal aging results from decreased growth hormone secretion (page 663). As one ages, the average plasma concentration of GH decreases.

9. *Nervous system*
   (i) The aged brain has lost a large percentage of cells in several key neural pathways, therefore, reaction time is longer, learning becomes less efficient and short-term memory becomes less reliable.
   (ii) The function of various neuro-transmitters decreases. This is responsible for many old age nervous dysfunctions like Alzheimer's (page 1040) and Parkinson's disease (page 997).
   (iii) Various special sensations like smell, taste, vision and hearing also decline with age.

Important Note

The greatly diminished physiological capacities of each organ system mean that old people are far more apt to die if subjected to such stresses as infection, accidental injury or environmental factors like extreme cold or heat and even air pollution.

Some of the *diseases of aging* are heart disease, cancer, arthritis, cataract and allergic disorders.

B. THEORIES OF AGING

Many theories of aging have been postulated through the years. Some of them are:

1. *Death hormone and limited cell replication theory.* The production of a *death hormone* is built into our genes and is released late in life. However, human cells are capable of a limited number of cell divisions and that their potential to replicate decreases with age.
2. *Cross-link theory.* In our cells a large number of smaller molecules have very specific functions; everything works fine as long as every molecule does its job. The ***'cross-linking' agents*** can link two or more of these molecules together with strong bonds. When this happens, the molecules can no longer do their work. *Cross-linking agents* are formed in the body from normal molecules when they are subjected to radiations or air pollution or when normal metabolic reactions are hampered by toxic chemicals like alcohol or heavy metals.
3. *Collagen theory.* This theory holds that aging is due to cross-linking between collagen molecules and fibrous molecules that support bone, tendon and connective tissue; these collagen molecules then shrink and strangle healthy cells.
4. *DNA damage theory.* It states that aging is due to an accumulation of damage done to the DNA molecule. When damage is done repeatedly and is carried over into new cells, the DNA becomes less efficient. *Cross-linking agents* (see above), radiation and the lack of necessary building materials for the construction of the DNA during cell divisions are causes of DNA damage. (*Proof:* Abnormal chromosomes are formed when the animals are exposed to radiation.)

Important Note

The body also has a DNA repair mechanism that can restore the DNA to normal if all required conditions are fulfilled. Good nutrition can supply the building materials for the DNA repair mechanism. *Junk foods* and highly processed foods are low in nucleic acids.

5. *Free radical theory* (*Most acceptable*). It states the aging is due to the damaging effect of *free radicals* on living tissues (for details, refer to **Fig. 69.4**).
6. *Metabolic products theory.* The accumulation of oxidation products in our cells makes us tired. Some of these metabolic products can form free radicals and cross-linking agents. Our body needs rest (in the form of sleep) to get rid of these products, called ***body's cleansing mechanism*** and return to a state of equilibrium.

Important Note

For the cleansing mechanism to work properly, we must have adequate nutrition, a sufficient amount of bodily fluid and a normal BMR. Drinking a glass of water and taking a light meal before retiring is, therefore, an advisable measure. A full stomach interferes with the BMR and may also prevent good sexual functioning.

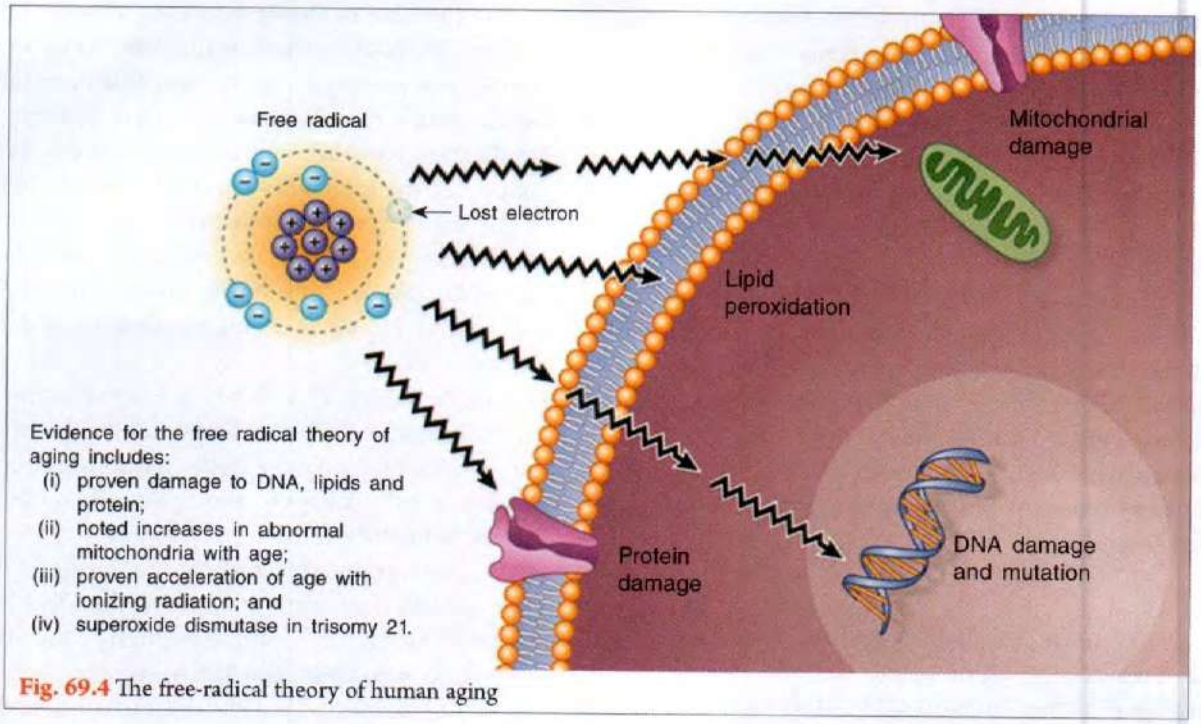


Fig. 69.4 The free-radical theory of human aging

7. ***Stress theory.*** This theory states that the body and the cells can tolerate a certain amount of stress. The point at which stress changes into ***distress*** differs from one individual to another. Distress can affect the rate of cell division, hormone levels and many other functions.

Important Note

A healthier body is more resistant to distress than a sick or fragile one. That is why good healthy practices (exercise and hygiene) and nutrition are so important.

8. ***Immunologic theory.*** Life span decrease has been associated with a number of factors that can hamper immune responses, such as cigarette smoking, obesity and distress. This theory states that aging is due to decreasing immunological functions with age.
   Our immune system has two major types of cells, the ***B-cells*** and ***T-cells***. The *T-cells*, when pass through the thymus, become ***'killer' cells*** and can destroy microorganisms and cancer cells. While the B-cells deactivate the chemicals that are produced by these cancer cells. As the thymus shrinks with age, the effectiveness of the T-cells also decreases. Many nutrients have been associated with increasing immune functions; that include: vitamins A, C, E, folic acid and minerals like selenium, zinc, calcium and magnesium.
9. ***Cybernetic theory.*** This theory suggests that aging is due to an increasing loss of control by the nervous system over all functions of the body.
   The neuroendocrines, from the hypothalamus to the pituitary and the thyroid, trigger the release of many hormones that control the functioning of the body. An imbalance of certain neurotransmitters (specially serotonin, nor-epinephrine and dopamine), in the neuroendocrines is a result of the aging process.

Note

In the synthesis of neurotransmitters in the brain, nutrients and polyunsaturated fatty acids play key roles.

C. FACTORS THAT WILL DELAY AGING

If we can control the rate of deleterious reactions that impair the stability of living system, we can control the aging process. Some of the important factors that increase life span will also delay aging. The factors are:

1. ***Not smoking cigarettes.*** Cigarette smoking causes increase formation of free radicals (page 640).

Note

Cigarette smoking is the largest avoidable cancer and heart disease risk factor.

2. ***Maintaining normal weight.*** Eating low-fat nutritious foods instead of high-fat junk foods can save a person from 900 to 1500 calories per day. This is equivalent to 0.5-1 kg per week.
   The *calorie-restricted diets* decreases the body metabolism with decreased formation of protein cross-links and decreased production of free radicals. In addition, such

diets are enriched with vitamins and minerals, therefore, calorie restriction acts at very fundamental level to genuinely slow the aging process (page 640).

Important Note

Calorie-restricted individuals act younger, look younger and, by objective physiological standards of aging, actually are younger. However, many discomforts of calorie restriction are: sleeplessness, hunger, aggression and anxiety.

3. *Regular Exercise*
   (i) Exercise is an absolute for the prevention of heart disease, diabetes and blood sugar disorders.
   (ii) Exercise is one of the most important and healthful way of relieving stress. It can also eliminate depression. People who suffer from depression also age faster and look older. Eliminating depression is, therefore, an established anti-aging procedure.
   (iii) When we exercise, the main source of energy is the burning of glucose. B-complex group of vitamins are important to burn glucose effectively. Stress in general increases the need for the vitamin B-complex. That is why the B-complex group of vitamins are termed the ***stress vitamins***.
4. *Overall good nutrition.* The life span increase attributable to high-quality nutrition is anywhere from 10 to 20 years (for details, refer to theories of aging). Antioxidants are responsible for delaying aging (page 640).

Study Questions

1. **Define and explain:**
   (i) Antioxidant nutrients
   (ii) Free radicals
   (iii) Aging
2. **Write briefly about:**
   (i) Age related changes and recent theories postulated to explain aging
   (ii) Role of nutrition and exercise in delaying aging
   (iii) Differences between free-radical and DNA damage theory of aging
3. **What will happen:**
   (i) If you consume less than the optimal amounts of antioxidant nutrients?
   (ii) If we eat too much?
   (iii) If excess of free radicals are generated in the body?
4. **Give physiological basis of:**
   (i) Formation of free radicals.
   (ii) How damage is done by the free radicals?
   (iii) Old persons are far more apt to die if subjected to stresses.
   (iv) Abnormal chromosomes are formed when the animals are exposed to radiation.

MCQs

1. **Antioxidant vitamins include all *except*:**
   (a) Vitamin E (b) Vitamin C
   (c) Vitamin A (d) Vitamin D
2. **Low blood manganese concentration may lead to:**
   (a) Arthritis (b) Diarrhoea
   (c) Anaemia (d) Cirrhosis liver
3. **Most damaging free radical to body components:**
   (a) Hydrogen atom (b) Oxygen molecule
   (c) Hydroxyl (d) Nitric oxide
4. **A major factor in increased free radical generation in our bodies is:**
   (a) Overeating (b) Lack of physical activity
   (c) Improper sleep (d) Decreased consumption of antioxidant nutrients

5. **Age related changes include the changes in following *except*:**
   (a) GFR
   (b) Haematocrit
   (c) Brain atrophy
   (d) GTT
6. **Rate at which loss of body cells occurs with aging is:**
   (a) 0.6-1% per year
   (b) 2-3% per year
   (c) 4-5% per year
   (d) Above 5% per year
7. **Most acceptable theory of aging is:**
   (a) Limited cell replication theory
   (b) DNA damage theory
   (c) Free radical theory
   (d) Immunological theory
8. **The role of chromium in the body is:**
   (a) Reduces free radical formation
   (b) Erythropoiesis
   (c) Growth
   (d) Spermatogenesis
9. ***False* about free radicals:**
   (a) Are very reactive molecules
   (b) Exists as unpaired electron
   (c) Formed mainly from oxidation of foodstuffs during energy production process
   (d) Not formed in a healthy individual
10. **Free radicals are *not* involved in which of the following diseases?**
    (a) Parkinson disease
    (b) Autoimmune diseases
    (c) Bacterial infections
    (d) Radiation injury
11. **Junk foods or highly processed foods may result in premature aging because:**
    (a) Low in nucleic acid
    (b) More generation of free radicals
    (c) Enriched with calories
    (d) All of the above
12. **Immune system can be strengthened by increased consumption of:**
    (a) Vitamins A and C
    (b) Folic acid
    (c) Minerals like zinc and calcium
    (d) All of the above

Answers

1. (d) 2. (a) 3. (c) 4. (a) 5. (b) 6. (a) 7. (c) 8. (a) 9. (d) 10. (c)
11. (d) 12. (d)

Unit IX

THE ENDOCRINE SYSTEM

Spelling: "HORMONE

↳ Start from End → Begin (Chapters) – Dr. Sujaya

• Compare & Study – Func. & Disorders very imp. (make tab. columns) ['MASTER' TABULAR COLUMN] – Dr. Srikanth.

Chapter 70: General Principles of Endocrinology

Definition, chemistry and characteristics of a hormone; Hormone assays; mechanism of action and regulation of secretion of hormones; control versus regulation.

Chapter 71: The Pituitary Gland

Physiological anatomy, the pituitary hormones; Anterior pituitary: actions and control of secretion of growth hormone, gigantism, acromegaly, dwarfism; Physiology of growth; Actions and control of secretion of prolactin; Posterior pituitary: actions and control of secretion of ADH and oxytocin, SIADH, diabetes insipidus; Milk-let down reflex, Intermediate pituitary: MSH; Effects of hypophysectomy, pituitary insufficiency.

Chapter 72: The Thyroid Gland

Physiological anatomy; formation, secretion, transport, metabolism, regulation of secretion and actions of thyroid hormone; Goiter, myxoedema, cretinism, Grave's disease; Anti-thyroid drugs; Thyroid function tests.

Chapter 73: The Parathyroids, Calcitonin and Vitamin D

Calcium metabolism; Phosphate metabolism; Physiology of bone; Hormones regulating calcium metabolism (parathormone, calcitonin and vitamin D); Rickets, osteomalacia, tetany, hypo and hyper-parathyroidism.

Chapter 74: The Adrenal Cortex

Physiological anatomy; Biosynthesis, transport, metabolism and excretion of adrenocortical hormones, regulation of glucocorticoids secretion, actions of glucocorticoids (cortisol), Cushing's syndrome; Mineralocorticoids: Aldosterone, actions and regulation of secretion; Applied aspect: primary and secondary hyperaldosteronism (Conn's Syndrome) and adrenocortical insufficiency (Addisóns' disease); Sex hormone – Adrenal virilism.

Chapter 75: The Adrenal Medulla

Physiological anatomy; Catecholamines: biosynthesis, metabolism, excretion, regulation of secretion and actions; Applied: hypo and hypersecretion (phaeochromocytoma).

Chapter 76: Pancreas

Physiological anatomy; Glucagon: actions and regulation of secretion; Insulin: structure and species specificity, regulation of secretion, mechanism of action; Applied: pathophysiology of diabetes mellitus, glucose tolerance test, clinical types; hypoglycemia, hyperglycemic versus hypoglycemic coma.

Chapter 77: The Thymus

Chapter 78: The Pineal Gland: Melatonin

Chapter 79: Local Hormones: A-ch, Prostaglandin, 5-HT, Histamine

31st: Intro to endocrines & ant. pituitary Dr Padmapriya

1st: Ant. pituitary. Dr. Padmapriya

4th: Post. pituitary Dr. Jyothi

5th: Thyroid. Dr. Sujaya

6th: Thyroid Dr. Sujaya

7th: Pancreatic hormones - 1 Dr. Pushpakrishna

8th: Pancreatic hormones - 2 Dr. Pushpakrishna

11th: Parathyroid & Ca metabolism. - 1 Dr. Nalina

12th: Parathyroid & Ca metabolism - 2 Dr. Nalina

13th: Adrenal cortex - 1 Dr. Veena

15th: Adrenal cortex - 2 Dr. Veena

18th: Adrenal medulla Dr. Parimala

19th: Physiology of stress & physiology of Growth Dr. Veena

Chapter 70

General Principles of Endocrinology

I. Introduction
II. Definition and characteristics of a hormone
III. Chemistry or classification of hormones
IV. Hormone assays
V. Mechanisms of hormone action
VI. Regulation of secretion of hormones
VII. Control versus regulation

INTRODUCTION

Cell function is broadly controlled by two mechanisms: *nervous* and *endocrinal*.

1. **Neural Control** is due to the spread of depolarization through the nerve. It has *rapid action* (much shorter latent period) and it affects certain groups of cells for a short period.
2. **Endocrinal Control** is by release of physiologically active substances called ***hormones*** directly into the blood stream. It has *slower action* (*i.e.* much longer latent period) and it affects number of cells over a longer period.

The term *Endocrine* is derived from a Greek word. It means *I separate within* and the glands are called ***Endocrine*** or ***Ductless Glands*** because they secrete physiologically active substances called hormones directly into the bloodstream.

The *important endocrine glands* include **(Fig. 70.1)**:

1. the hypothalamus
2. the anterior pituitary (adenohypophysis)
3. the posterior pituitary (neurohypophysis)
4. the Islets of Langerhans in the pancreas
5. the adrenal cortex
6. the adrenal medulla
7. the thyroid
8. the parathyroid
9. the kidney
10. the ovary and testis.

The other organs with endocrine function and the hormones they produce are:

	Organ	*Hormone*
1.	Heart	Atrial natriuretic peptide (ANP)
★ 2.	GIT	Cholecystokinin-pancreozymin (CCK-PZ), Secretin; and Vasointestinal peptide (VIP)
★ 3.	Kidney	1,25-Dihydroxycholecalciferol (1,25 DHCC)
4.	Pineal gland	Melatonin
5.	Skin	Calciferol (vitamin D_3).
★ 6.	Liver	Insulin-like growth factors (IGF-I and II).
7.	Platelets	Platelet-derived growth factor (PDGF)
★ 8.	Lymphocytes	Interleukins

DEFINITION AND CHARACTERISTICS OF A HORMONE

1. *Definition:* The word hormone (Greek word meaning *I excite or arouse*), was introduced by *Starling* in 1905 and was first used in reference to 'secretin' and 'gastrin'. Hormones are secretory products of *ductless (endocrine)* glands released directly into the circulation in *small amounts* in response to a *specific stimulus* and on delivery in circulation produces response on the *Target Cells* (cells that respond to the hormone) or organs.
2. Hormones interact with their target cells via ***receptors***, which are large protein molecules with specific binding sites for specific hormones. Generally, there are 2000-100,000 receptor molecules per target cell. (*Note:* If there are no hormone receptors in a tissue, its cells cannot respond.)
3. Hormones act on their targets cells in one of the three basic ways:
   (i) by controlling the rates of enzymatic reaction (*see below*);
   (ii) by controlling the ions or molecules across cell membranes, or
   (iii) by controlling gene expression and synthesis of proteins.

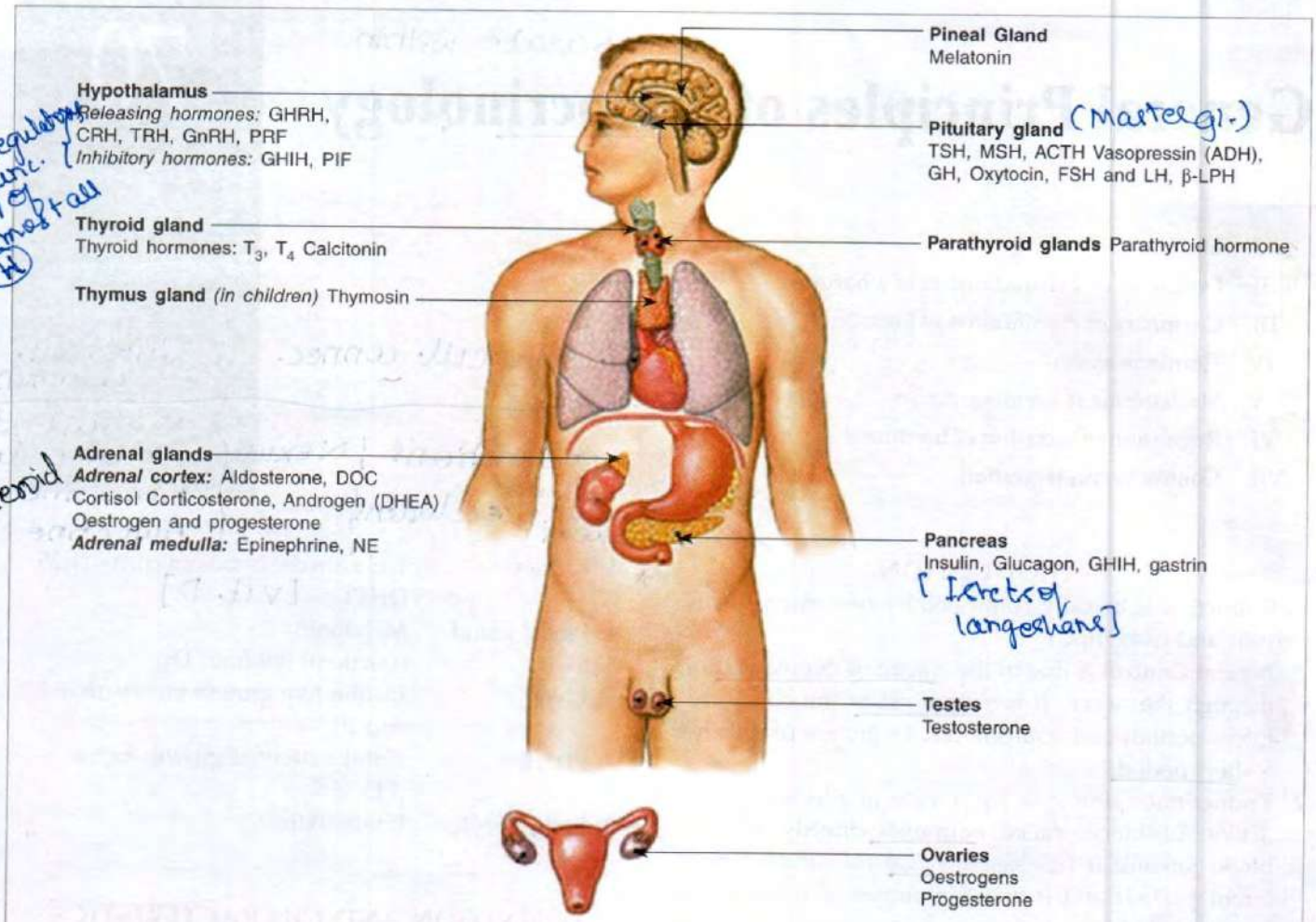


Fig. 70.1 The major endocrine glands and the hormones they secrete (abbreviations as given in the text)

4. Hormones regulate existing fundamental bodily processes but *do not* initiate cellular reactions as such. As regulators, hormones stimulate or inhibit the rate and magnitude of biochemical reactions by their control of enzymes and thereby cause morphological, biochemical and functional changes in the target tissues. For example, a hormone does not provide energy but it modulates energy producing processes and regulates the circulating levels of energy producing substrates such as glucose, fatty acids, etc.
5. Hormones are usually secreted into the circulation in extremely *low concentrations* (nanomolar: 10^{-9} M to picamolar: 10^{-12} M), while metabolic end-products (*e.g.* CO_2, H^+ etc.) are secreted in large amounts and are thus called ***Parahormones***.
6. Hormones have a much *longer latent period* than that associated with neurons following their stimulation. For example, following the injection of oxytocin, milk ejection occurs in a few minutes; while following the application of a stimulus to a nerve, the muscle contracts within few milliseconds.
7. Most hormones are metabolised rapidly after secretion and they get *inactivated* mainly in the liver and kidney.
8. Pheromones: Refer to page 1058.
9. Hormone interactions:
The hormones interact at their target cells in three ways: *synergism, permissiveness* and *antagonism*.
   (i) In *synergism*, two (or more) hormones interact at their targets so that the combination produces a result that is greater than additive.
   Example:

(a) Epinephrine	elevates blood glucose	5 mg/dL
(b) Glucagon	elevates blood glucose	10 mg/ dL
(c) a+b	elevates blood glucose	22 mg/ dL

   Thus the combined effect of the two hormones is greater than the sum of the effects of the two hormones individually. This is also known as **potentiation**.

(ii) In *permissiveness*, one hormone cannot fully exert its effects unless a second hormone is present.
Example

(a) Thyroid hormone alone	No development of reproductive system.
(b) Reproductive hormones alone	Delayed development of reproductive system.
(c) a+b	Normal development of reproductive system.

(iii) In *antagonism*, two hormones are considered functional antagonists if they have opposite physiological actions.
Example: Both glucagon and growth hormone raise the concentration of glucose in the blood, and both are antagonistic to insulin, which lowers the concentration of glucose in the blood.

10. ***Regulation of receptors*** : Receptors are themselves subject to physiological regulation (page 6). The ***number*** of receptors a cell has and the ***affinity*** (*i.e.*, the strength) of the receptors for their specific messenger can be decreased or increased. For example:
(i) when a *high* extracellular concentration of messenger is maintained chronically, the total number of receptors for that messenger may decrease; a phenomenon of *down-regulation*. It has the effect of reducing the target cell's responsiveness to high concentration of messengers and thus represents a local negative-feedback mechanism (Also see to page 749).
(ii) Cells exposed chronically to very *low* concentration of a messenger may come to have many more receptors for that messenger, thereby developing supersensitivity to it. A phenomenon of *up-regulation*. Example: *Denervation hypersensitivity* (page 189).
Down-regulation and *up-regulation* are made possible because there is a continuous degradation and synthesis of receptors. Membrane-bound receptors are *internalized i.e.*, taken into the cell by means of endocytosis, and are either broken down or reinserted back into the membrane along with newly synthesized receptors during exocytosis.

Important Notes

1. There are many disease process in which the number of receptors or their affinity for messenger becomes abnormal. For example: Myasthenia gravis page 158).
2. Mutation in hormone receptor may result in functional *hormone resistance* that develops over a time. In type 2 DM, target tissues for insulin gradually becomes more and more resistant to its actions secondary to reduced activation to tyrosine kinase - page 749.

CHEMISTRY or CLASSIFICATION OF HORMONES

In general, hormones are *divided into* three major classes:
1. Steroids
2. Proteins and polypeptides
3. Amino acid derivatives (or) Amines

1. **Steroids** are hydrophobic, lipid soluble substances, synthesized from acetate or cholesterol in the cytoplasm and mitochondria. They are not stored for more than a few minutes in the endocrine cells of synthesis, and for continued action within the body steroid hormones must be continuously synthesized. After being released into general circulation, steroids circulate in the plasma, bound to transport proteins. The half life of steroids varies from 60 minutes to 100 minutes. *Examples* include:
   (i) Adrenocortical hormones (mineralocorticoids; and glucocorticoids).
   (ii) Male and female sex hormones (androgen, oestrogen, progesterone).
   (iii) 1,25-dihydroxycholecalciferol (Vitamin D_3).
2. **Proteins and Polypeptide** hormones generally are water soluble and circulate unbound in plasma. These are synthesized on ribosomes which are attached to endoplasmic reticulum. These hormones are stored as zymogen granules in golgi apparatus for hours or days and are released by *exocytosis*. Their half life varies from 5-6 minutes to 60 minutes. *Examples* include:
   (i) Anterior and posterior pituitary hormones
   (ii) Hypothalamic hormones
   (iii) Parathyroid hormone, calcitonin, insulin, glucagon, gastrin, secretin and angiotensin.
3. **Amino Acid Derivatives** (*i.e.* amino acids with halogens). They include epinephrine, norepinephrine (tyrosine/phenylalanine with CH_3), triiodothyronine (T_3) and thyroxine (T_4 – tyrosine with iodine). Most of the thyroid hormones (T_4 and T_3) are bound to transport proteins and have a biological half life of approx. 7-9 days. Epinephrine and norepinephrine exist in plasma either in the free form or in conjugation with sulphate or glucuronide and their circulatory half life is approx. 1-3 minutes.

Summary
Refer to **Table 70.1**.

HORMONE ASSAYS

Biological assay of hormonal activity is needed when new synthetic products are being compared with natural hormones. Biological assay systems can record the minute concentrations of hormones which occur in circulating

Table 70.1: Comparison of Steroids, Peptides and Amino Acid Derivatives

Parameter	Steroid hormones	Peptide hormones	Amino Acid Derivatives hormones
Examples	Sexsteroids (oestrogen, progestgerone, androgen) cortisol,	Insulin, parathyroid	(a) Catecholamines (b) Thyroid hormones
1. Derived from	Cholesterol	Three or more amino acids	Tyrosine(mainly) or tryptophan
2. Synthesis and storage	Synthesized on demand from precursors	Made in advance and stored in secretory vesicles	Made in advance and stored in secretory vesicles
3. Transport in blood	Bound to carrier proteins	Dissolved in plasma	(a) is dissolved in plasma (b) is bound to carrier
4. Half life (i.e. how long a hormone is active in the body).	Long (60-90 minutes)	Short (few minutes)	(a) is very short, few seconds. (b) is long (7-9 days)
5. Location of receptors	Cytoplasm or nucleus	Cell membrane surface	For (a): cell membrane For (b): nucleus
6. Response to receptor - ligand binding	Activation of genes for transcription and translation	Activation of second messenger system via cAMP.	For (a) activation of second messenger system, for (b) activation of genes for transcription and translation
7. General target response	Induction of new protein synthesis	Rapid, modification of existing proteins and induction of new protein synthesis	(a): Modification of existing proteins (b): Induction of new protein synthesis

blood. The various separation techniques which are available include the following:

1. **Solvent extraction**
2. **Chromatography**
3. **Molecular sieving**
4. **Chemical or immunological techniques**. These include:
   (i) *fluorescence* methods for catecholamines;
   (ii) *gas-liquid chromatography* for steroid hormones;
   (iii) *radio-active isotopes e.g.* ^{131}I and ^{125}I for thyroid hormones.
5. **Competitive radioassay** (saturation analysis). It includes ***radioimmunoassay***, widely applied to all the protein and peptide hormones, which can be detected in concentrations of µg/L or ng/L. It is done with antibody as the binding protein.
   Principle: The binding sites on antibody or other high affinity protein are saturated with radio-labelled hormone *e.g.* ^{131}I and incubated in the cold with material containing unlabelled (free) hormone **(Fig. 70.2)**. The competition between labelled and 'free' hormones for the binding sites reduces the proportion of bound radioactive hormone and increases the proportion of 'free' radioactive hormone. As concentration of unlabelled hormone increases, the ratio of bound labelled hormone to free labelled hormone decreases.
   Advantage: This method has high sensitivity and high specificity.

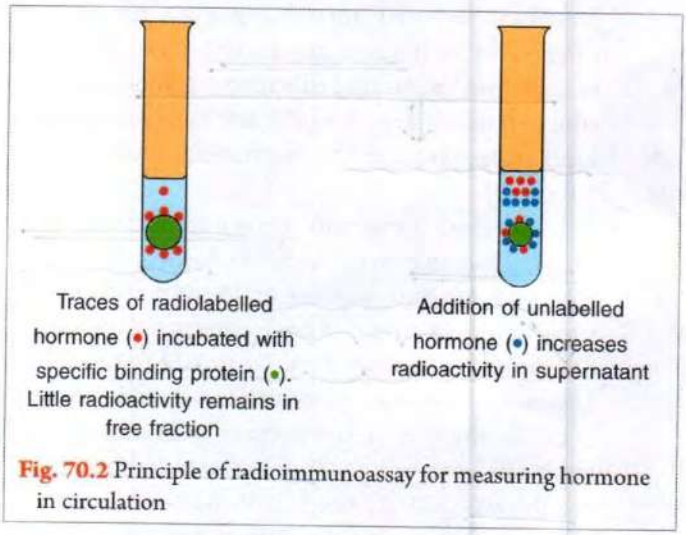


Fig. 70.2 Principle of radioimmunoassay for measuring hormone in circulation

6. ***Enzyme Linked Immunosorbent Assay (ELISA)***. *Basic principle* for measuring the concentration of a hormone **(Fig. 70.3)**.
   (i) AB_1 and AB_2 are antibodies that recognize the hormone (H) at different binding sites.
   (ii) A third antibody (AB_3) is added to recognize AB_2 and is linked to an enzyme (E) that converts a specific substrate (S) to a product (P).
   (iii) The product (P) can be easily detected by calorimetric or fluorescent optical methods.
   (iv) The amount of 'P' formed is proportional to the amount of hormone present in the sample.

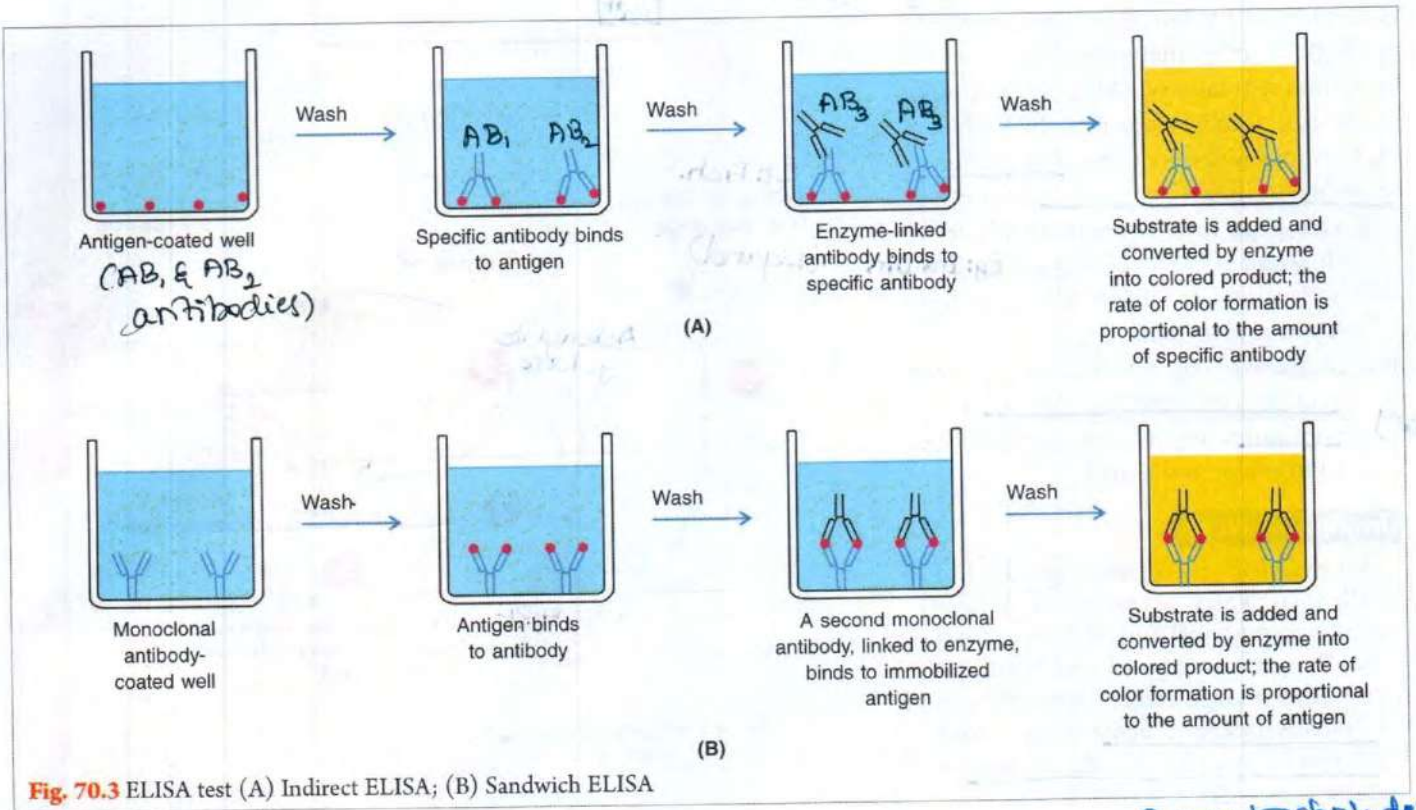


Fig. 70.3 ELISA test (A) Indirect ELISA; (B) Sandwich ELISA

(v) As the each molecule of enzyme catalyzes the formation of many thousands of product molecules, even small amount of hormone molecules can be detected.

Advantages

(i) ELISA does not employ radioactive isotypes
(ii) It is an accurate method for assessing hormone levels.
(iii) Cost effective

7. *Cytochemical assays.* Genesis of hormone can be detected in slices cut out of the endocrine gland, then incubating in an ascorbate-enriched culture medium. This test is much more sensitive than competitive radioassay, but is more complicated and time-consuming. However, it is very useful in measuring the minute basal levels of hormone secretion.

MECHANISMS OF HORMONE ACTION

A. OVERVIEW

1. Only cells with receptors for a specific hormone respond; those cells lacking the specific receptors are unaffected. Hormone receptors found on the target cell membrane are termed *external receptors*, and those within the cytoplasm and nucleus are termed *internal receptors*.
2. Hormones and receptors interact in the following ways to affect intracellular metabolism.
   (i) Polypeptide hormones bind to a *fixed* receptor at the outer cell surface.
   (ii) Steroids bind to a specific *mobile* receptor in the cytoplasm.
   (iii) Thyroid hormones combine with a *nuclear* receptor.
3. Hormone-sensitive cells respond to high concentrations of certain hormones by reducing the number of receptors on the cell surface. For example, elevated ambient insulin concentration causes a loss or inactivation of insulin receptors in liver cells, fat cells and WBCs.

B. HORMONE-RECEPTOR INTERACTION

Two mechanisms for 'hormone-receptor coupling' operate:
(1) cAMP mediated hormone activity, and
(2) Transcription and translation effects.

1. cAMP mediated hormone activity

Most proteins and polypeptide hormones (page 651), many amino acid derivatives, specially catecholamines, and some of prostaglandins (because of their large size, cannot enter the cells); they act as the ***first messenger*** and exert their effect by combining with specific fixed receptor site over the outer surface of the cell membrane, thereby activate the enzyme *adenylyl cyclase* on the inner surface of the membrane **(Fig. 70.4)**. This increases formation of intracellular cAMP from ATP. cAMP, the ***second messenger***, is a basic regulator of cell metabolism, it acts by conversion of inactive *protein kinases* to their active form (page 601). Protein kinases catalyses the phosphorylation of proteins thereby alters their forms and activity. Adenylyl cyclase

is stimulated by low [Ca^{2+}] but inhibited by high [Ca^{2+}]; therefore, [Ca^{2+}] is an important regulator of cAMP concentration in the cell. cAMP transmits the signal of the hormone and may bring about different functions in different target cells; such as:

(i) change in membrane permeability to different substances or ions
(ii) activation or inactivation of rate limiting enzymes
(iii) increased or decreased protein synthesis by action on ribosomes
(iv) regulation of release of hormones from endocrine gland.

Important Note

Once cAMP is formed inside the cell, it activates a *cascade of enzyme reactions* (pages 95 and 656). Thus even small concentration of the hormone can have a large effect. (Also refer to *G-protein-linked hormone receptors* and *calcium-calmodulin second messenger system* page 22)

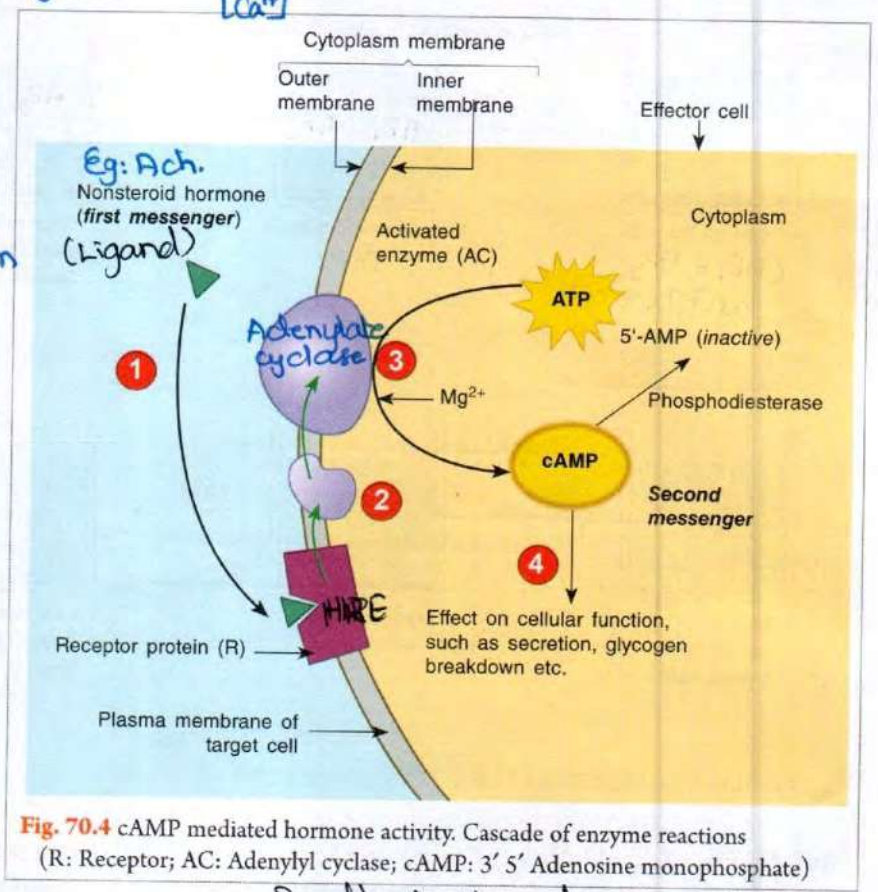


Fig. 70.4 cAMP mediated hormone activity. Cascade of enzyme reactions (R: Receptor; AC: Adenylyl cyclase; cAMP: 3′ 5′ Adenosine monophosphate)

2. Transcription and Translation Effect

Steroid hormones (page 714); 1,25 DHCC (page 704) and thyroid hormones being lipid soluble can easily enter into the target cells and exert their effect by combining to a specific *cytoplasmic* receptor protein in a target cell *i.e.* cell that responds to the hormone **(Fig. 70.5)**. Each receptor molecule binds two molecules of hormone, forming a *complex* that enters the nucleus and becomes attached to the chromatin, the genetic material. The *complex* reacts with DNA, stimulates the ***transcription*** (*i.e.* formation of mRNA) of a particular gene, and specific messenger RNA (mRNA) synthesis increases. The specific mRNA enters the cytoplasm, where it directs the ribosomes to synthesize specific proteins (***translation***). These proteins may be enzymes, structural proteins, receptor proteins or secretory proteins.

Important Note

Heat Shock Proteins (HSP) *i.e.*, a group of intracellular proteins whose amount increased when cells are exposed to heat and various stresses. These proteins help the cells to survive a variety of stresses, thus also called as *stress proteins*.

Mode of action: Specially the steroid hormones receptors (glucorticoids, oestrogen and progesterone) bound to *HSP* and cover the DNA-binding domain. When the steroid binds to the receptors, it forms changes to release the *HSP*, thus exposing the DNA-binding domain.

REGULATION OF SECRETION OF HORMONES

Regulation of secretion of hormones is brought about by two mechanisms: *direct* and *nervous control*.

A. DIRECT CONTROL

Some of the hormone secretion is regulated by the blood concentration of the substances which are directly controlled by the hormones themselves. For example: Insulin secretion from pancreatic β-islets of Langerhans is promoted by a rise in blood glucose level and glucagon secretion from α-cells by a fall in blood glucose level. These responses keep the blood glucose levels within narrow limits inspite of variations in carbohydrate intake in the diet, since insulin lowers and glucagon raises blood glucose.

B. NERVOUS CONTROL

Hormonal secretion from endocrine glands is largely controlled by the CNS. Most of the 'neurotransmitters' are concerned with rapid transmission of stimulation or inhibition over short distances. The CNS contains neurons which synthesize and release *peptides*. The highest concentrations of such neurons are found in the hypothalamus where they release peptide hormones. Thus the term ***neurosecretion*** refers to the actions of all

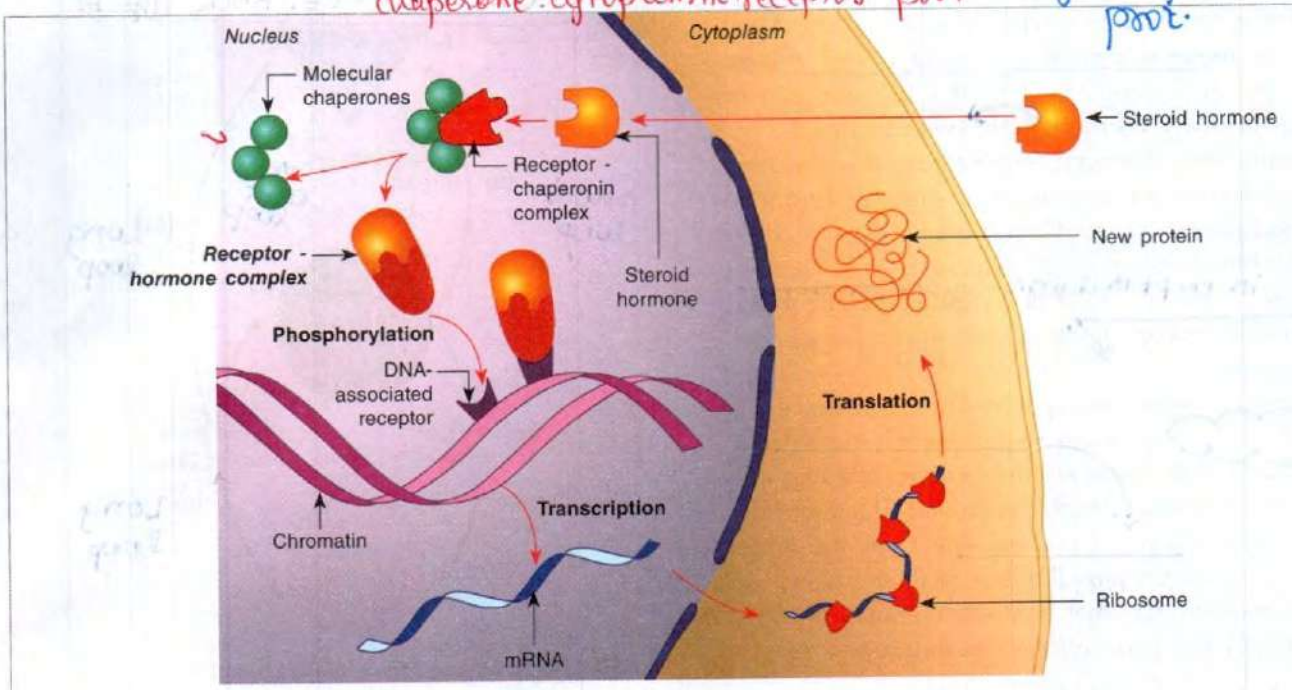


Fig. 70.5 Steroid hormones action on target cell. The hormone is separated by receptor molecule; '*receptor-hormone complex*' enters the nucleus and becomes attached to the chromatin to stimulate 'transcription'; on ribosomes, mRNA is translated into new protein.

neurons which act by release of chemical agents, whether as *neurotransmitter* or as *neuroendocrine transducers* (*i.e.* endocrine glands that convert neural signals into hormonal signals, page 761) **(Fig. 70.6)**. Neural control of endocrine glands occurs by three mechanisms:

1. ***Direct innervation via ANS.*** For example:
   (i) Pancreatic islets of Langerhans have a postganglionic parasympathetic innervation.
   (ii) Adrenal medullary cells innervation by pre-ganglionic (cholinergic) sympathetic fibers.
2. ***Neurosecretory neurons control of the posterior lobe.*** Depolarization of neurosecretory cells of the posterior pituitary by A-ch released at synapses on the cell bodies of these neurons causes release of ADH and oxytocin.
3. ***Neurosecretory neurons control of the anterior pituitary.*** The hypothalamic regulation of the anterior pituitary is achieved through *peptidergic neurons* which

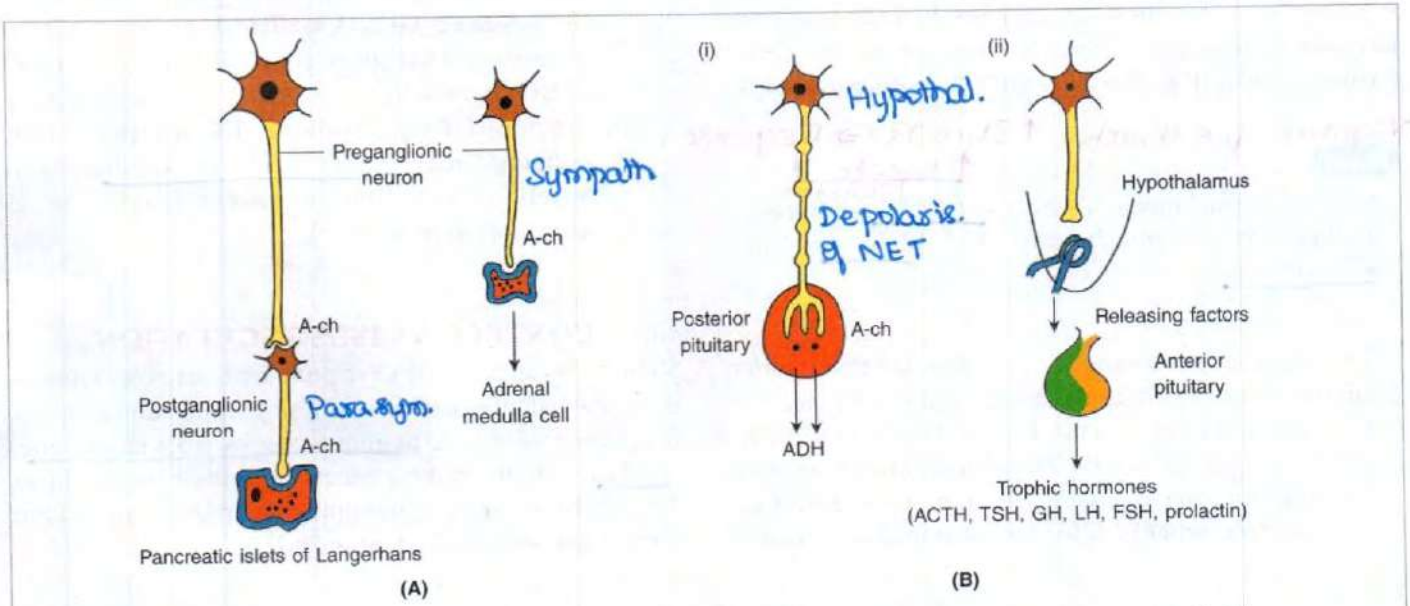


Fig. 70.6 Neuroendocrine transducers. (A) direct innervation via autonomic fibers; (B) neurosecretory neurons control of the (i) posterior pituitary and of (ii) anterior pituitary

synthesize and secrete *specific releasing factors*. They enter the ***hypothalamic-hypophysial portal system*** (page 660) and stimulate or inhibit the secretion of anterior pituitary hormones into systemic blood.

Important Note: Hormones secreted into portal system have a distinct advantage, as a dose of hormone secreted into general circulation is rapidly diluted by the total blood volume of 5L. The same dose secreted into tiny volume of blood flowing through the portal system remains concentrated, while it is taken directly to its target.

The hypothalamo-adenohypophysial system serves as a *cascade amplifier* i.e. a few *nanograms* of hypothalamic releasing hormone promotes the secretion of *micrograms* of adenohypophysial trophic hormone which, in turn, may release *milligrams* of hormone from the target organs (Also refer to page 95). This fact helps to explain how hormones (and other messangers) can be effective at extremely low extracellular concentration.

Important Note

The hypothalamus receives neuronal connections from many regions of the CNS. This explains why the nervous activity can influence secretion of pituitary hormones.

C. FEEDBACK CONTROL

In addition to control by the CNS the secretion of anterior pituitary hormones is regulated by ***'feedback' control*** (page 3) effects of the hormones secreted by the target organs; the feedback control mechanisms are of two types: *negative* and *positive*. In the ***negative feedback*** control the *response* is opposite to the *original stimulus;* it is important for survival. Conversely, in the ***positive feedback*** control, the *response* is the same as that of the *original stimulus* (**Fig. 82.6**, page 806) (Also refer to page 5).

Note

Negative feedback **mechanism are self-limiting whereas** ***positive feedback*** **mechanism are explosive and self-reinforcing**

The target organ hormones act either on the anterior pituitary or on the hypothalamus, usually by *negative feedback* control, which occurs at three levels (**Fig. 70.7**).

(i) ***Long Loop Feedback.*** Peripheral gland hormones and substances arising from tissue metabolism can exert what is called *long-loop* feedback control

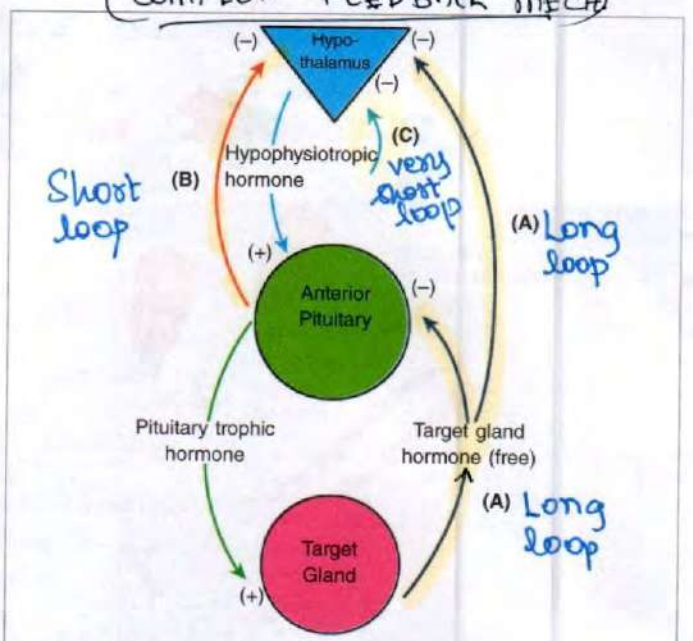


Fig. 70.7 Negative 'feedback control' of hormone secretion. long loop (A); short loop (B) and ultra-short loop (C) feedback mechanisms.
{(+): stimulation; (–): negative feedback control mechanism}

on both the hypothalamus and the anterior lobe of the pituitary gland. *Long-loop* feedback *usually is negative* but occasionally can be *positive* and is particularly important in the control of thyroidal, adrenocortical and gonadal secretions.

(ii) ***Short Loop Feedback.*** Negative feedback also can be exerted by the anterior pituitary trophic hormones on the synthesis or release of the hypothalamic releasing or inhibiting hormones, which collectively are called ***Hypophysiotropic Hormones*** *e.g.* GHRH, GHIH (page 662); PRF, PIF (page 671); TRH (page 685); CRH (page 717) and GnRH (page 779).

(iii) ***Ultrashort Loop Feedback.*** The *hypophysiotropic* hormones may inhibit their own synthesis and secretion via a control system referred to as ultrashort loop feedback.

CONTROL VERSUS REGULATION

Stability of an internal environmental variable depends upon the balance between opposing inputs and outputs. It is often possible to maintain one variable (parameter) constant only by moving others from their usual values. The mechanisms for maintaining a variable constant are: *Control* and *Regulation*. **(Table 70.2)**

Table 70.2: Control versus regulation

Control	Regulation
1. The control mechanisms operate to achieve (or maintain) any variation of a variable. However, they cannot ever succeed in bringing the variable all the way back to normal. Thus, it is the management of the rate of function.	1. The regulatory mechanisms operate to achieve (or maintain) a variable within a normal narrow range. Thus, a variable is preserved relatively constant under several conditions.
2. It is generally a conscious mechanism.	2. It is an involuntary action.
3. It partially involves a closed *feedback loop*.	3. It involves a closed feedback loop *i.e.* feedback mechanisms are involved.
4. Examples: (i) Control of food intake; (ii) Control of water intake; (iii) Control of HR and stroke volume; (iv) Control of peripheral blood flow; (v) Control of work output; (vi) Control of heat production and heat loss.	4. Examples: (i) Regulation of BP; (ii) Regulation of body temperature; (iii) Regulation of hormonal levels in the blood; (iv) Regulation of energy balance.

Note

There cannot be regulation without control *i.e.* controls are required to obtain regulation. For example:

1. Work output and food intake are controlled to regulate energy balance in the blood.
2. 'HR', stroke volume and peripheral blood flow need to be controlled for the regulation of 'BP'.
3. Heat production and heat loss are controlled for the regulation of body temperature.

Study Questions

1. Define and give physiological significance:
   - (i) Endocrine glands, hormone and parahormone
   - (ii) Neurosecretion and Neuroendocrine transducers
   - (iii) Cascade of events
   - (iv) Stress proteins/Heat stress proteins
2. Write short notes on:
   - (i) Radio immunoassays
   - (ii) Hormone assays
   - (iii) Hypothalamo-adenohypophysial system as a cascade amplifier
   - (iv) Feedback control mechanisms
   - (v) Levels of regulation of secretion of hormones
   - (vi) Regulation of receptors
   - (vii) Control versus regulation mechanisms
3. Classify hormones. Give characteristic features of each class.
4. Illustrate with the help of a well labelled diagram
   - (i) difference between protein and steroid hormone action on target cell and
   - (ii) Negative feedback control of hormone secretion.
5. Justify the statement, "there cannot be any regulation without control".
6. How is neural control of endocrine glands brought about?
7. Describe briefly how does the hormone interact at their target cells?

MCQs

1. **Which of the following method is sensitive for easy assessment of hormonal activity?**
   (a) Chromatography (b) ELISA
   (c) Radioimmunoassay (d) Cytochemistry assay
2. **All of the following hormones mediate their major effects without actually entering the target cell *except*:**
   (a) Mineralocorticoids (b) Insulin
   (c) Growth hormone (d) Glucagon
3. **The cation essential for adenylyl cyclase activity to form cAMP is:**
   (a) Calcium (b) Sodium
   (c) Magnesium (d) Potassium
4. **The following hormones increase the level of intracellular cAMP *except*:**
   (a) Vasopressin (b) Glucagon
   (c) Parathyroid hormone (d) 1,25 DHCC
5. ***Not a true* statement with reference to negative feedback control of hormone secretion:**
   (a) The response is opposite to the original stimulus
   (b) The response is the same as that of the original stimulus
   (c) The target organ hormones act either on the anterior pituitary or hypothalamus
   (d) The anterior pituitary hormones can act on the hypothalamus
6. **Control mechanism differs from regulatory mechanism in all of the following *except*:**
   (a) Operate to maintain any variation of a variable
   (b) Generally a conscious mechanism
   (c) Partially involves a closed feedback loop
   (d) Examples include: control of B.P. and body temperature
7. **Thyroid hormones belong to which class of hormone?**
   (a) Steroids (b) Proteins
   (c) Polypeptides (d) Amino acid derivatives
8. **Which of the following hormones *does not* need a second messenger?**
   (a) FSH (b) LH
   (c) Glucagon (d) Oestrogen
9. **Overall regulating organ for neuroendocrinal system is:**
   (a) Hypothalamus (b) Pituitary
   (c) Thalamus (d) Pineal gland
10. ***Not* a hypophysiotropic hormone:**
    (a) Somatostatin (b) Growth hormone
    (c) Growth hormone releasing hormone (d) Prolactin inhibiting factor

Answers

1. (b) 2. (a) 3. (c) 4. (d) 5. (b) 6. (d) 7. (d) 8. (d) 9. (a) 10. (b)

Chapter 71

The Pituitary Gland

I. Physiological anatomy
II. Anterior pituitary – adenohypophysis
  A. Growth hormone: Actions; Control of secretion; Applied aspect (gigantism; acromegaly)
  B. Physiology of growth – Factors affecting
  C. Prolactin: Conrtol of secretion; actions
III. Posterior pituitary – neurohypophysis
  A. Antidiuretic hormone: Control of secretion; Action;
    Applied aspect: SIADH; Diabetes insipidus
  B. Oxytocin: Actions; Control of secretion – Milk let down reflex
IV. Intermediate lobe of pituitary: MSH
V. Effects of hypophysectomy: Pituitary insufficiency.

(1) PHYSIOLOGICAL ANATOMY

1. The pituitary gland is in close anatomic relation to median eminence, a part of the hypothalamus. *Pituitary-hypothalamus forms a single functional unit;* which is the most influential endocrine system in the body (Fig. 71.1). The pituitary gland consists of:
   (i) ***Adenohypophysis:*** Anterior Lobe or Anterior Pituitary.
   (ii) ***Neurohypophysis:*** Neural Lobe or Posterior Lobe or Posterior Pituitary.
2. The pituitary gland lies in the sella turnica of the sphenoid bone at the base of the skull. In humans it weighs approx. 0.5 gms; 75% weight is of anterior lobe and remaining 25% weight is of posterior lobe.
3. **Adenohypophysis** is divided into *three parts*:
   (i) *Pars Distalis* represents the bulk of anterior lobe and is highly vascular.
   (ii) *Pars Intermedia* lies between pars distalis and the neural lobe, it is relatively avascular and is almost non-existent in humans.
   (iii) *Pars Tuberalis* is an elongated collection of secretory cells, which superficially surrounds the neural stalk; it is most vascular.
4. **Neurohypophysis** consists of *three components*:
   (i) *Median eminence,* located beneath the third ventricle. It is a small, highly vascular protrusion

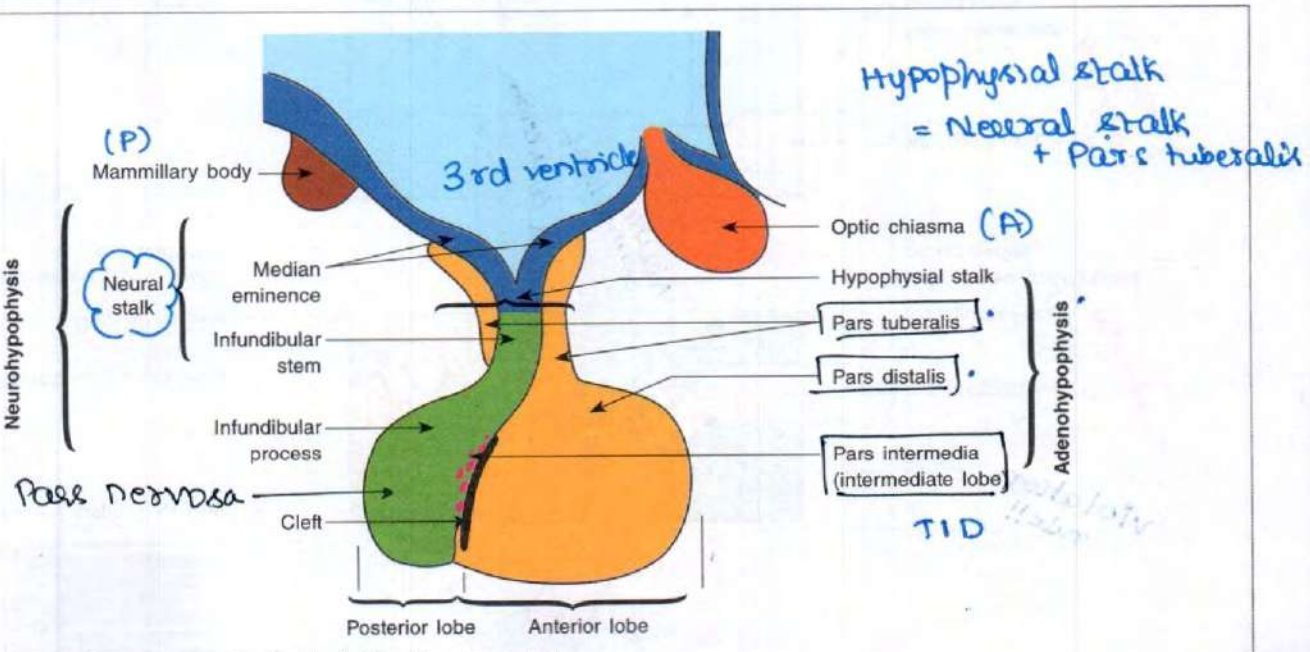


Fig. 71.1 Divisions of the pituitary gland and relationship to hypothalamus

of base of the hypothalamus (tuber cinereum). This is the region from which the portal vessel arise. It lies outside the blood brain brarrier.

(ii) *Infundibular stem*, a funnel shaped structure arises from the median eminence. The floor of the third ventricle is known as infundibulum (*i.e.* a funnel).

(iii) *Infundibular process (pars nervosa)*, a downward outgrowth that forms bulk of the posterior lobe. The *neural stalk* is composed of the median eminence and infundibular stem. It helps posterior pituitary to retain its neural connection with the hypothalamus. The *hypophysial stalk* (neural stalk plus pars tuberalis) attaches the pituitary gland with the hypothalamus.

5. Adenohypophysis is influenced by hormones which comes from the hypothalamus via the portal vessels *(hypothalamo-hypophyseal portal vessels, page 656)* and neurohypophysis by neurons *(hypothalamo-hypophyseal neural tract)* which convey hormones directly from hypothalamic nuclei for storage in the posterior lobe. These unmyelinated nerve tracts arise from the supraoptic and paraventricular nuclei within the hypothalamus **(Fig. 71.2)**.

6. **The Pituitary Hormones**

Anterior Lobe

(i) Thyroid stimulating hormone: (TSH, thyrotrophin).

Note

A portal system is a specialized region of the circulation consisting of two sets of capillaries directly connected by a set of large blood vessels. There are three portal systems in the body: one in the kidneys, one is the digestive system, and one in the brain. Thus hormones secreted into a portal system have a distinct **advantage**. A **much smaller** amount of hormone can be secreted to produce a given level of response, whereas a hormone secreted into general circulation is rapidly diluted by the total blood volume. In this way, a small number of neurosecretory neurons in the hypothalamus can effectively control the anterior pituitary.

(ii) Adrenocorticotrophic hormone (ACTH, corticotrophin).

(iii) Growth hormone (GH, somatotrophin-STH).

(iv) Follicle stimulating hormone (FSH).

(v) Luteinizing hormone (LH, interstitial cell stimulating hormone–ICSH).

(vi) Prolactin (Luteotropic hormone–LTH; luteotropin, lactogenic hormone, mammotrophin).

(vii) β-Lipotropin (β-LPH) obtained after breakdown of a large protein (page 676 and helps in enkephalins synthesis.

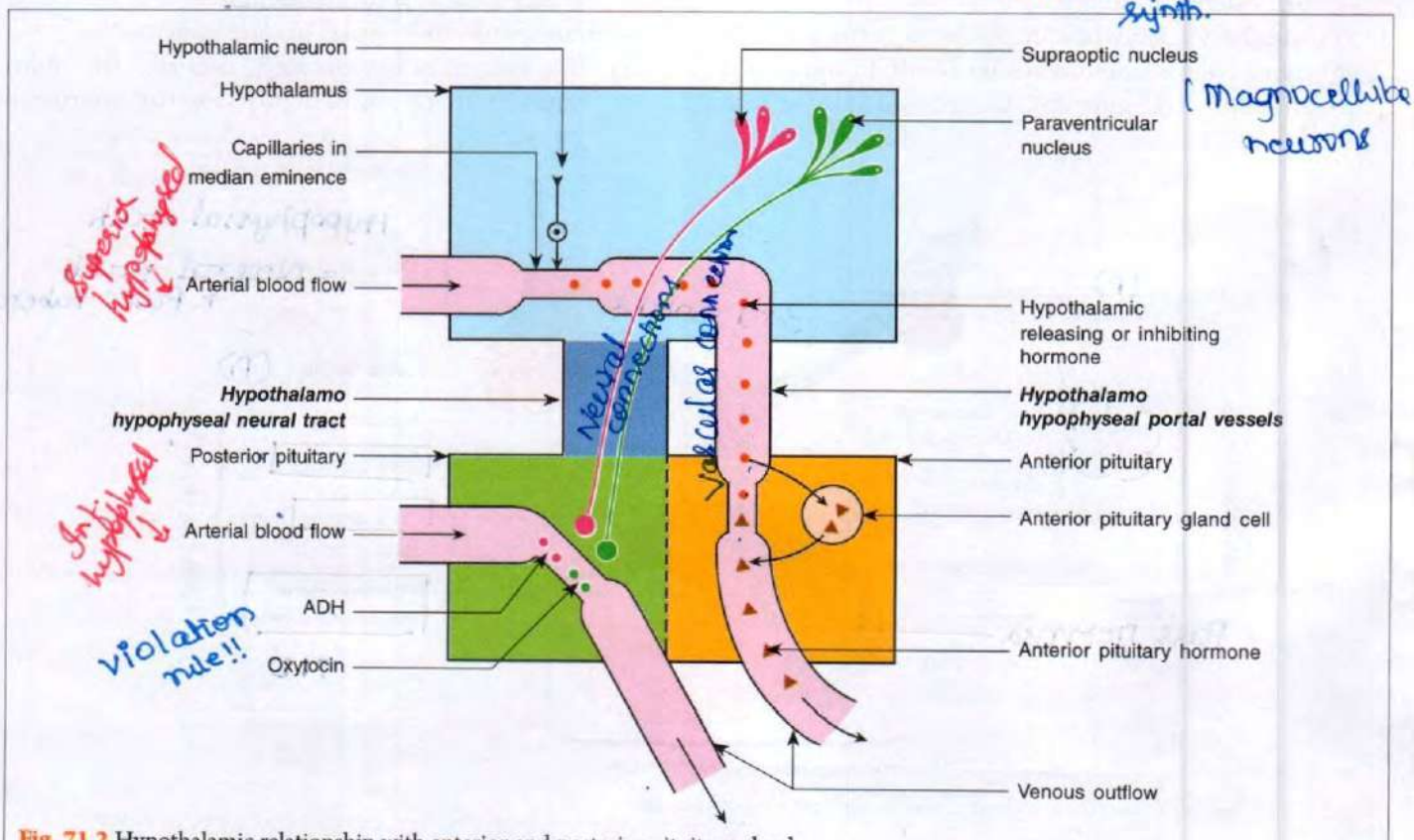


Fig. 71.2 Hypothalamic relationship with anterior and posterior pituitary gland

Important Note

The hormones of the anterior pituitary control many vital functions, viz., metabolism, growth and reproduction, all very complex processes, therefore, the anterior pituitary is often called the MASTER GLAND of the body.

(III) *Intermediate Lobe*

α and β melanocyte stimulating hormone (α, β MSH; melanotropin; intermedin).

(IV) *Posterior Lobe*

(i) Vasopressin (antidiuretic hormone, ADH).

(ii) Oxytocin.

7. Some of pituitary hormones are called ***Trophic (Tropic,*** which means pertaining to food or nourishment), *i.e.* they stimulate the secretion of other endocrine glands *e.g.* thyroid, adrenal cortex and gonads. In general, anterior pituitary hormones are all 'trophic' hormones.

(2) ANTERIOR PITUITARY (ADENOHYPHOPHYSIS)

Histology. *Two major cell* types are found in the anterior lobe: chromophils and chromophobes.

1. *75% – chromophils* (granular secretory cells) which exists in two forms:
   (i) *Acidophils* (Eosinophils) stain red or orange with acidic dyes; they account for approx. 80% of the chromophils and are of two types:
      (a) 'Somatotrophs' secrete growth hormone
      (b) 'Mammotrophs' secrete prolactin.
   (ii) *Basophils* stain blue or green with basic dyes; they account for 20% of the chromophils and are of *three types*:
      (a) 'Gonadotrophs' secrete LH and FSH.
      (b) 'Thyrotrophs' secrete TSH.
      (c) 'Corticotrophs' secrete ACTH and β-LPH.
2. *25%-chromophobes* (agranular cells) are small cells without any affinity for dyes. These cells are degranulated secretory cells.

The **Neurons** found in the anterior lobe are mainly the postganglionic sympathetic fibers that innervate the blood vessels. The blood supply to the anterior lobe is derived from *portal vessels* (page 660). This system begins and ends in capillaries without going through the heart and is therefore a *true portal system*. Branches of internal carotid artery divide to produce a dense network of capillary loop which drains into veins, the portal vessels. The venous drainage of the whole pituitary is via the cavernous sinuses into the jugular vein.

A. GROWTH HORMONE (GH) or HUMAN GROWTH HORMONE (HGH)

(I) General Characteristics

1. It is also called *somatotrophin* or *somatotrophic hormone* – STH.
2. It is synthesized by the acidophils of the anterior lobe and stored in very large amounts in the pituitary gland. It represents approx. 4-10% of the wet weight of the pituitary gland, which is equivalent to 5-15 mg. Daily GH output (adults/children) is 0.2 to 1 mg/day, with biological half life 6-20 minutes.
3. Human GH is a single unbranched polypeptide chain containing 191 amino acids with molecular weight of 21,500. It is bound to a protein in plasma and its concentration is an index of the number of growth hormone receptors in the tissues.
4. It varies considerably in structure from species to species, *i.e.* humans exhibit a *Species Specificity* for GH, and only human and monkey GH preparations have biologic activity in humans.

Note

Specificity means selectivity **i.e. the ability of a receptor to react with only one type or a limited number of structurally related types of molecules.**

5. It bears marked structural resemblance to prolactin and human chorionic somatomammotrophin (HCS), therefore, both have growth promoting activity.
6. GH is *secreted episodically* in periods of 20-30 minutes, with large diurnal fluctuations. A regular nocturnal peak in GH secretion occurs 1-2 hours after the onset of 'deep' sleep.
7. The plasma GH concentration (normal: 2-4 ng/mL) in the growing child is significantly higher by 5-8 ng/mL than that in the adult whose growth has ceased.
8. **Mode of action:** cAMP mediated hormone activity (page 653).

(II) Control of GH Secretion

The release of GH is primarily under the control of two hypothalamic (hypophysiotropic) hormones: *GH-releasing hormone (GHRH) and GH inhibiting hormone (GHIH)* **(Fig. 71.3)**.

(a) ***Stimuli that increases GH secretion.*** They do so by stimulating GHRH release; these are:

1. Relative or absolute **substrate deficiency** in the cell for the energy production which results in intracellular glucose deficiency. This is seen in:
   (i) Hypoglycemia (*most potent stimulus*, its effect is mediated by nor-adrenergic pathway);

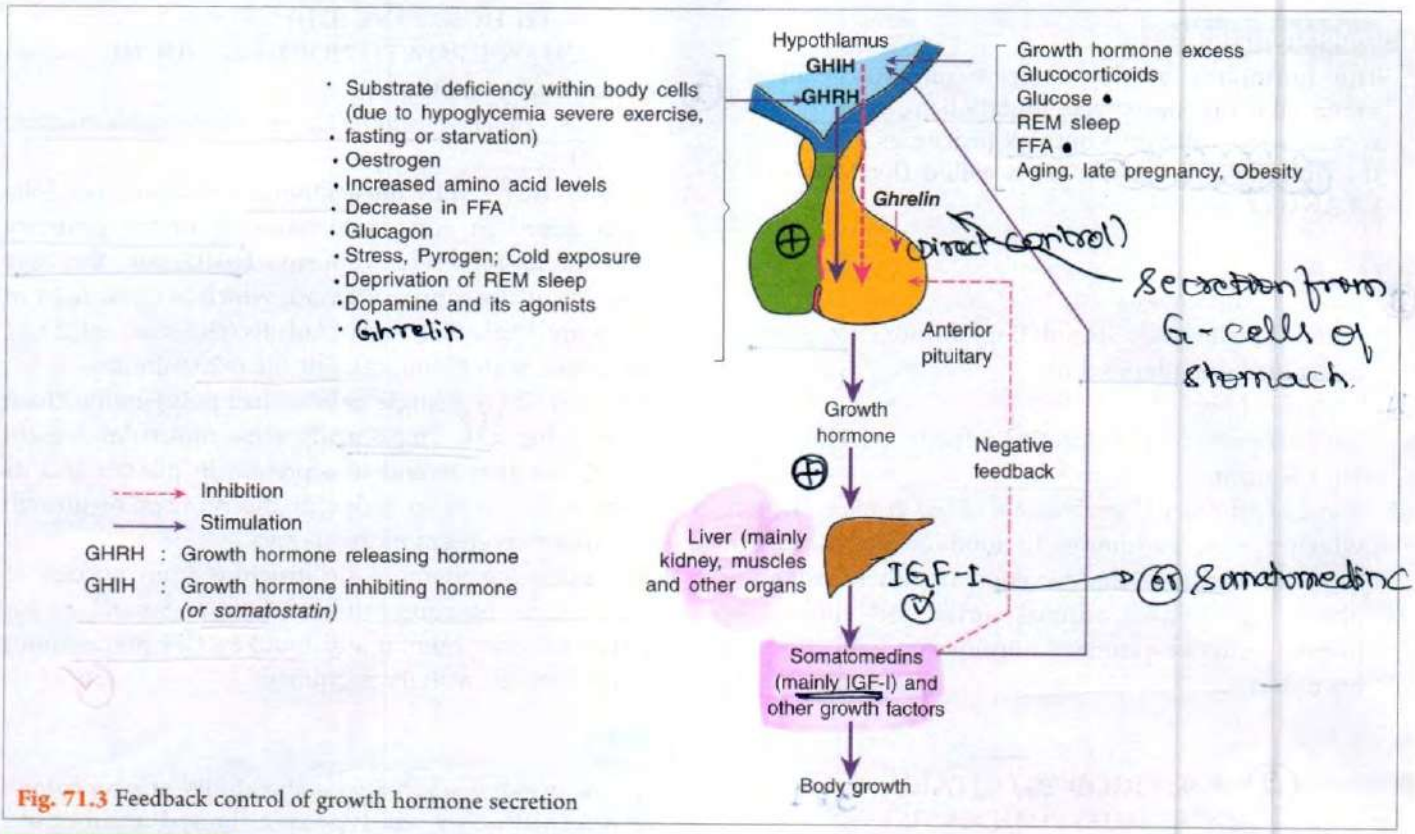


Fig. 71.3 Feedback control of growth hormone secretion

Important Note

GH increases circulating IGF-I (somatomedin C) which in turn exert a direct inhibitory action on GH secretion from the anterior pituitary. It also stimulates secretion of somatostatin of from the hypothalamus.

(ii) *2-Deoxy-glucose*, it produces systemic hyperglycemia but intracellular glycopenia.
(iii) Moderate to severe *exercise;*
(iv) *Fasting*, it increases GH level after 2 or 3 days. Less response in obese subjects – cause not known.

2. **Oestrogen, androgens** and decrease in FFA concentration.
3. Increase in circulating levels of **amino acids**; this is seen,
   (i) after protein meals, and
   (ii) I.V. infusion of amino acids specially Arginine.
4. **Glucagon**. It is an important stimulus, used as a test of GH secreting mechanism in patients with endocrine disorders.
5. **Emotional and stressful stimuli**, such as
   (i) Various psychological stresses, trauma, fears, etc.,
   (ii) Surgical operations,
   (iii) Pyrogens (fever producing agents),
   (iv) Exposure to cold.
6. In subjects **deprived of 'REM' sleep** (*i.e.* sleep associated with dreaming - page 986).
7. Increase in brain **Dopamine** and **Nor-epinephrine** content *e.g.* after administration of
   (i) L-dopa (in Parkinson patients, page 997), L-dopa is a precursor of dopamine and nor-epinephrine; and
   (ii) α-adrenergic agonists.
8. Stimulation of dopamine receptors in the brain or administration of dopamine receptors agonists like (i) Apomorphine and (ii) bromocriptine.

Note

GHRELIN (page 273), a polypeptide synthesized and secreted in the stomach and hypothalamus has marked GH stimulating activity.

(b) ***Stimuli that decrease GH secretion.*** They do so by causing release of GHIH, also called ***Somatostatin***. It is also found in nerve endings in the brain, cells of the antrum of stomach, and in δ-cells of pancreatic islets of Langerhans. It also blocks the secretion of insulin, glucagon and gastrin, and inhibits the intestinal absorption of glucose producing a state of hypoglycemia. GHIH inhibits the synthesis and release of GH. (Also see to page 1049).

Factors causing decrease in GH secretion are:

1. *GH*; it can inhibit its own secretion by increasing circulating IGF-I levels and IGF-I in turn exerts a direct inhibitory action on anterior pituitary via a short-feedback loop mechanism (page 681).
2. *Glucocorticoids* (cortisol);
3. *'REM' sleep*; GH is thus released in a pulsatile fashion during sleep, during which bursts of secretion occurs every 1-2 hours.
4. *Glucose*; its infusion decreases plasma GH level and inhibits the response to exercise;
5. *FFA*. (free fatty acids);
6. *Late pregnancy*; despite the presence of high oestrogen levels; therefore, medroxy progesterone decreases GH secretion.
7. *Old age* (see aging page 643).

Important Note

GH secretion is *pulsatile*, i.e. it shows marked and rapid spontaneous fluctuation throughout the day (increase or decrease) in response to specific stimuli. Its secretion shows a *circadian rhythm*, with the highest rates occurring during certian phases of sleep.

Actions of GH

1. *Stimulation of growth of bone, cartilage and connective tissue.*
   (i) The effects of GH on skeletal growth are mediated by a family of polypeptides called *somatomedins* (*i.e.* somatomedin and other growth factors). Somatomedins are synthesized in the liver (mainly), kidneys, muscles and other tissues in response to stimulation by the GH. Thyroid hormone and insulin are also necessary for normal 'osteogenesis'. In general, *GH increases the number of cells e.g. in muscle* and *bone* while insulin increases cytoplasmic growth. Thyroid hormones are required for the full effect of GH on DNA replication.
   (ii) Other growth factors include:
   (a) *Somatomedin A and B;*
   (b) *Insulin like growth factor I and II* (IGF-I and II); these are major circulating somatomedins and are synthesized mainly in the liver and cartilage (Details Table 71.1);
   (c) *Nerve growth factor* (NGF);
   (d) *Epidermal growth factor* (EGF);
   (e) *Ovarian growth factor* (OGF);
   (f) *Fibroblast growth factor* (FGF);
   (g) Thymosin;
   (h) *Multiplication stimulating activity* (MSA); and
   (i) *Platelet derived growth factor* (PDGF).
   (j) Relaxin

Table 71.1: Insulin like growth factor I and II

IGF-I (or somatomedin C)	IGF-II (or Multiplication Stimulating Activity)
1. Secretion: Independent of GH before birth but is stimulated by GH after birth; peak secretion at the time of puberty (13-17 years of age) and decreases in old age.	Independent of GH. Its secretions are constant throughout postnatal growth,
2. Plasma level: 10-700 ng/mL	300-800 ng/mL
3. Receptor: Similar to insulin receptor (page 749)	Mannose-6-phosphate receptor involved targeting proteins to intracellular organelles.
4. Major action (i) Growth stimulating activity; (ii) Control of skeletal and cartilage growth	Growth during foetal development

Important Note

Growth factors are polypeptides and proteins and are divided into three groups:

1. Factors responsible for the multiplication or development of various types of cells; for example: IGF-I and II, NGF, EGF, OGF, FGF etc.
2. Factors that regulate proliferation and maturation of blood cells; for example: Colony stimulating factors (CSF) and interlenkins (ILs)-page 66.
3. Factors produced by macrophages and lymphocytes and are important in regulation of immune system; for example: Cytokines (page 127).

(iii) 'Receptors' for somatomedins exist in chondrocytes, hepatocytes, adipocytes and muscle cells.
(iv) *Somatomedin has insulin like effect on tissues*, including lipolysis, increased glucose oxidation in fat, and increased glucose and amino-acid transport by muscle (page 748).
(v) *Before epiphysial closure*, GH through somatomedin, stimulates proliferation of chondrocytes, appearance of osteoblasts, incorporation of sulphates into cartilage; stimulation of DNA and RNA synthesis, and collagen formation in cartilage. The increase in the thickness of the epiphysial (cartilagenous) end-plate accounts for the increase in linear skeletal growth.
(vi) *After epiphysial closure* (fusion), bone length can no longer be increased by GH, but bone thickening can occur through periosteal growth. It is this

growth that accounts for the changes seen in hypersecretion of GH (*Acromegaly*) (page 665).

(vii) These reactions are the biochemical correlates of protein synthesis in 'general body growth' and also accounts for the hyperplasia and hypertrophy associated with increased tissue mass.

(viii) Somatomedin activity in plasma rises to the peak 16-20 hours after injection of GH. ***Somatomedin levels are better correlated with growth than plasma GH levels.***

(ix) Somatomedin activity is reduced by: glucocorticoids and protein deficiency.

2. ***Effect on Protein and Mineral Metabolism***

(i) **On protein metabolism:** GH is protein *anabolic* hormone. ***Mechanism of action:***

(a) It affects ribosomal attachment or translation (page 654).

(b) It increases transport of neutral and basic amino acids into the cells from the E.C.F. Therefore, plasma amino acid level decreases. This effect is unaffected by protein synthesis blocking drugs such as puromycin.

(a) and (b) result in 'positive' nitrogen and phosphorus balance *i.e.* increase in plasma phosphorus and decrease in blood urea nitrogen and amino-acid levels.

(c) It increases excretion of amino acids *i.e.* 4-hydroxyproline(mainly), which comes from collagen. Thus, hydroxyproline excretion is increased in:

- diseases associated with increased collagen destruction, and
- when synthesis of soluble collagen is increased. (GH stimulates synthesis of soluble collagen).

(d) It stimulates erythropoiesis.

(ii) **On mineral metabolism:**

(a) Increases Ca^{2+} absorption from GIT.

(b) Decreases Na^+, K^+, Ca^{2+} and phosphorus excretion from kidneys, because these minerals are diverted from kidneys to the growing tissues.

3. ***Effect on Carbohydrate and Fat Metabolism***

(i) **On carbohydrates** – GH is ***diabetogenic***, because it produces hyperglycemia by:

(a) increasing hepatic glucose output; and

(b) directly antagonizing the insulin effect on adipose tissue and skeletal muscle *i.e.* decreases glucose uptake by these tissues.

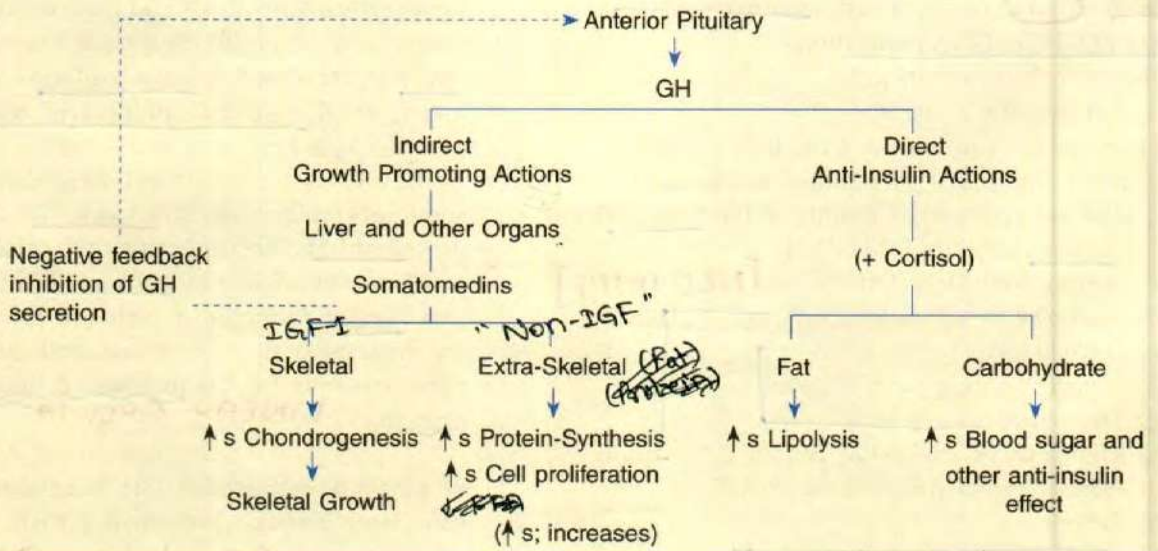
(ii) **On fat metabolism**

(a) GH has ***catabolic*** effect *i.e.* increases mobilization of fats from adipose tissues, increases circulating 'FFA' levels; stimulates gluconeogenesis (mainly in liver). This provides ready source of energy for the tissues during hypoglycemia, fasting and other stressful stimuli.

(b) GH is *ketogenic i.e.* increases hepatic oxidation of fatty acids to ketone bodies, acetoacetic and β-hydroxybutyric acid.

(iii) Increases ability of pancreas to respond to insulinogenic stimulation *i.e.* agents which increase insulin release from pancreas such as arginine, glucose etc. Therefore, by this way GH promotes growth, since insulin has a protein anabolic effect.

SUMMARY: *SOMATOMEDIN (SPECIALLY IGF I and II) MEDIATED AND DIRECT EFFECTS OF GROWTH HORMONE (GH)*



Important Note

In general, the effect of GH on metabolism is, *it increases body* proteins (by increasing protein synthesis); *uses up fats* stores for energy (by increasing mobilization of fatty acids from adipose tissue) and *conserve carbohydrates* (by decreasing rate of glucose utilization).

4. *On kidneys:* following removal of the anterior pituitary,
   (i) kidney size decreases
   (ii) GFR decreases
   (iii) Renal blood flow decreases, and
   (iv) Tubular secretion of PAH decreases.
   [Administration of GH and little thyroxine restores these effects.]
5. *On Thymus:* GH increases growth of thymus (which is often enlarged in acromegaly).
6. *Increases milk production in some lactating animals* (rodents, rabbits, etc.). GH can increase lactation in women also.

Applied Aspect

1. *Growth retardation* can occur when GH levels are increased and somatomedin levels are depressed *e.g.* in *Kwashiorkor* (page 635).
2. *African Pygmies.* They show lack of tissue response to the action of GH although both GH and somatomedin levels are normal. Their short stature is due to a decrease in cellular receptors. In addition, their plasma IGF-I concentration fails to increase at the time of puberty.
3. *Laron Dwarfism* or *GH insentivity syndrome.* In this syndrome there is congenital abnormality of the GH receptors, therefore, plasma concentration of GH binding protein decreases and IGF-I is not secreted in sufficient amounts.
4. *Giantism,* also called *Gigantism.* It is due to overproduction of GH during adolescence (*i.e.* before epiphysial closure) and is characterized by excessive growth of long bones (Fig. 71.4). Patients may grow to heights of as much as 250 cm (8 feet).

Characteristic features

1. Tall stature (excessive tallness as much as 2·5 mt or 8 ft.)
2. Bilateral gynaecomastia (enlargement of breast). It is due to increase in plasma oestrogen: androgen ratio in males.
3. Large hands and feet
4. Associated features:
   (i) coarse facial features
   (ii) loss of libido/impotence
5. *Acromegaly* It is usually due to acidophilic cell tumour of anterior pituitary which produces excessive secretion of GH during adulthood (*i.e.* after epiphysial closure). In 20–40% it is associated with hypersecretion of prolactin. It causes growth in those areas where cartilage persists. *Acromegaly means enlargement of the peripheral region* (Fig 71.5):

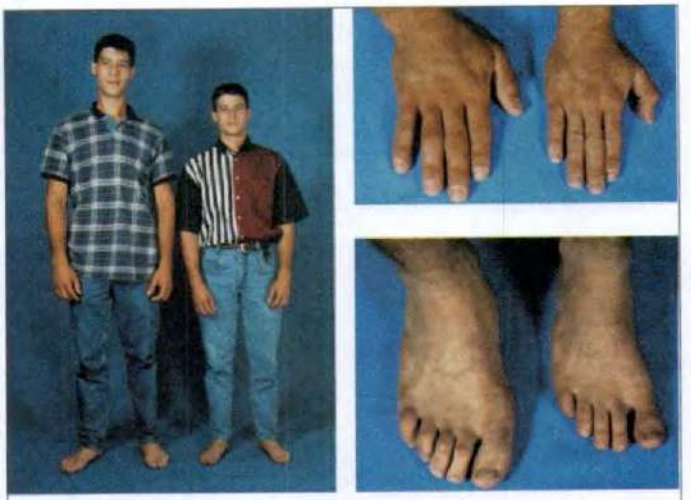


Fig. 71.4 Giantism (Gigantism), occurs during adolescence before epiphysial closure.
(**Note:** Excessive tallness more than 2 mts, i.e. 7 ft and hand compared with those of a normal subject)

Characteristic features

(i) Elongation and widening of the mandible ***(prognathism)***, resulting in an underbite and increased inter-dental spaces.
(ii) Enlargement of the frontal, mastoid, ethmoid and maxillary sinuses, causing a ***prominent brow.***
(iii) Thickening of the skin and coarsening of the facial features, which are due mainly to the proliferation of connective tissue and lead to oedema *i.e.* ***Acromegalic Facies*** (Fig 71.6).
(iv) Periosteal growth of vertebrae causes bowing of spine (*kyphosis*) and that of metacarpals and metatarsals leads to ***Acral Parts*** (Fig 71.6).
(v) Hypertrophy of the body soft tissues such as the heart (*cardiomegaly*), liver (*hepatomegaly*), kidney (*renomegaly*), intestine, spleen (*splenomegaly*), tongue and muscles. Therefore, causes increase in urinary excretion of creatinine.
(vi) Associated involvement of other endocrine organs, for example:
(a) Synergize with ACTH to increase the adrenal size.
(b) Synergize with androgens to increase size of accessory reproductive organs with increase in body hairs, increases protein content of the body, decreases fat content of the body and increases serum GH level more than 10 times the normal levels.
(c) Precipitation of osteoarthritis due to skeletal changes.
(d) In 25%, abnormal G.T.T. (page 753).

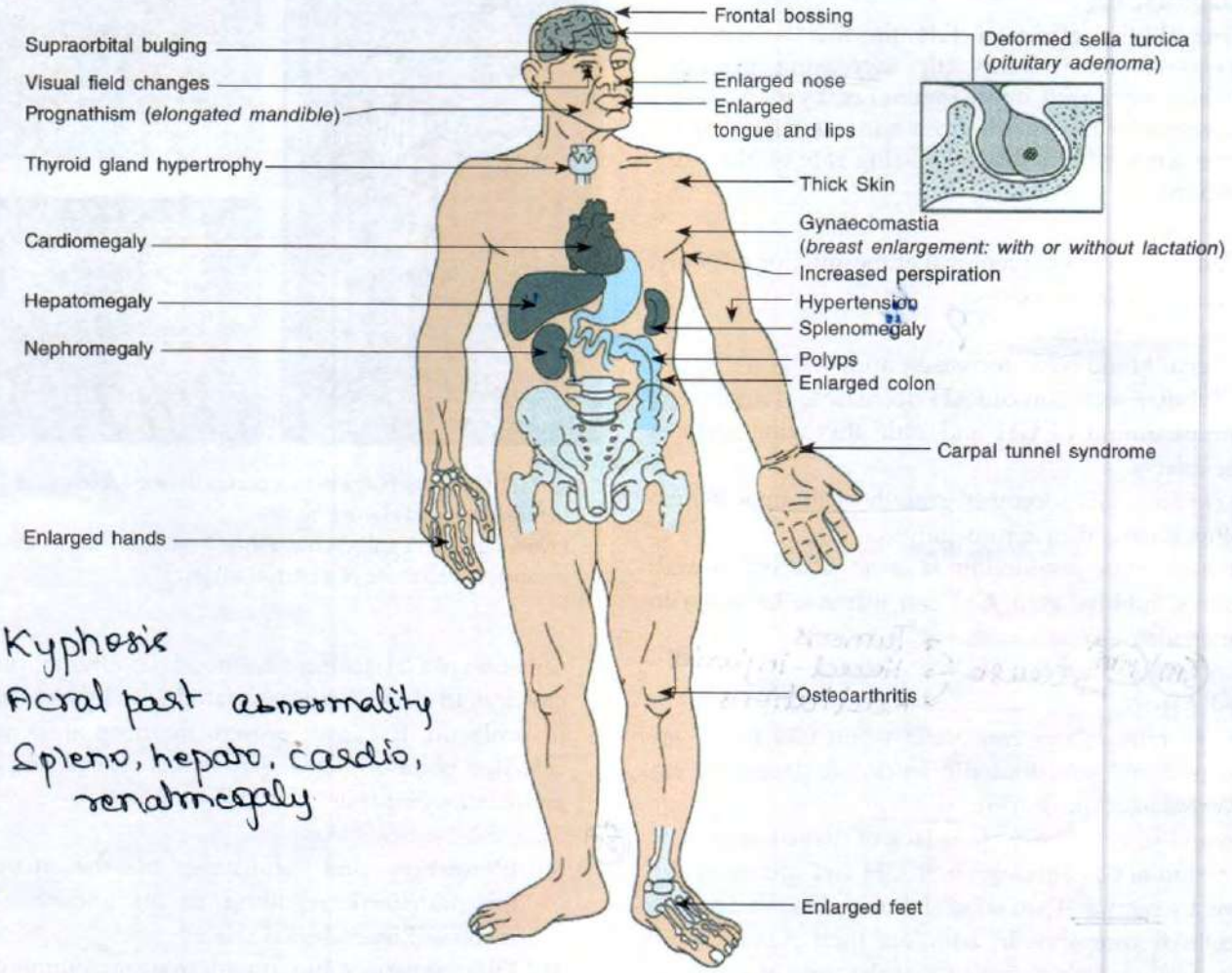


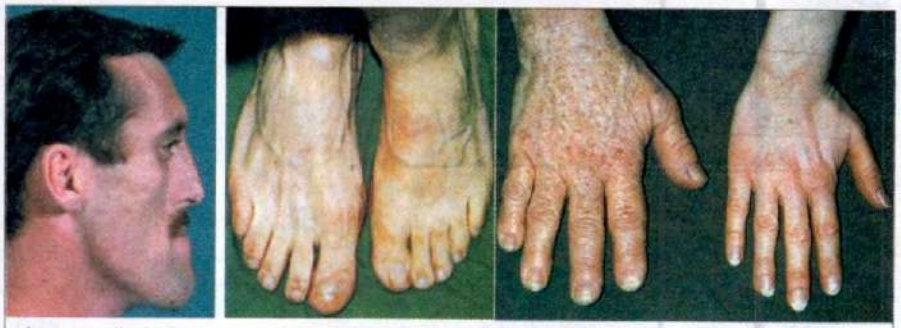
Fig. 71.5 Characteristic features - Acromegaly

(e) visual field changes *e.g.* bitemporal hemianopia (page 1095) etc.

(f) In 4%, ***Gynaecomastia*** (breast enlargement in males with or without lactation).

Note

Gynaecomastia can also occur in: newborn, at puberty in boys, men over 50 years of age, eunuchoidism (page 791), liver disorders and hyperthyroidism. In all cases there is an increase in the plasma oestrogen: androgen ratio.



Acromegalic facies and Prognathism

Acral parts: acromegalic foot and hand compared with those of a normal subject

→ Protruding Jaw

Fig. 71.6 Acromegaly, occurs during adulthood after epiphysial closure

6. Deficiency of GH secretion in immature individual leads to *stunted growth* or ***dwarfism***, which is accompanied by sexual immaturity, hypothyroidism and adrenal insufficiency. *Major causes* of dwarfism with accompanying features are summarized in **Fig. 71.7**.

7. Deficiency of GH may be due in part to the overall lack of anterior pituitary hormones ***(panhypopituitarism)*** or from an isolated genetic deficiency. In adults, in whom GH deficiency alone is rare, clinical manifestation may include impaired hair growth and a tendency towards fasting hypoglycemia.

I. **Familial** – Constitutional delay in growth, commonest cause: family history of shortness; body proportion according to the chronological age (Fig. 71.9B)

II. **Endocrine disorders**

*A. **Pituitary dwarf*** (due to growth hormone deficiency–secondary to decrease in GHRH)

Characteristic features (Fig. 71.7A)
1. Plumpness (fatness)
2. Immature facies
3. Small genitalia
4. Delicate extremities, body proportion according to the chronological age (Fig. 71.9B)
5. Delayed skeletal and dental development
6. Low circulating growth hormone level

*B. **Hypothyroid dwarf*** (due to thyroid hormone deficiency)

"CRETINISM"

Characteristic features (Fig. 72.8) - page 691
1. Gross retardation of 'mental' and 'physical' development
2. Body proportion remains infantile (Fig. 71.9B)
3. Bone age is retarded more than height
4. Associated hypothyroidism features
5. Earlier its onset, more severe is the delay in growth and skeletal maturation

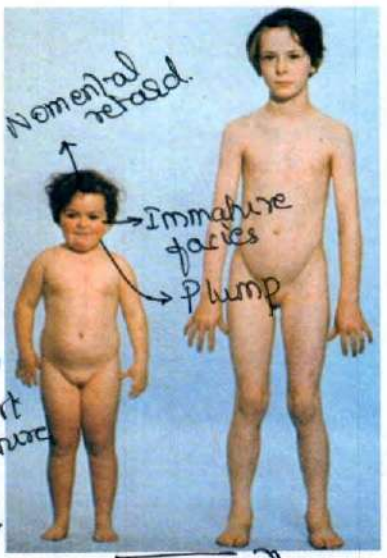
*C. **Cushing Syndrome*** (Fig. 74.8) - page 724
(due to excess of circulating glucocorticoids)

III. **Nutritional**
- A. ***Marasmus*** (Fig. 68.6 - page 635
- B. ***Rickets*** (Fig. 73.9) - page 709

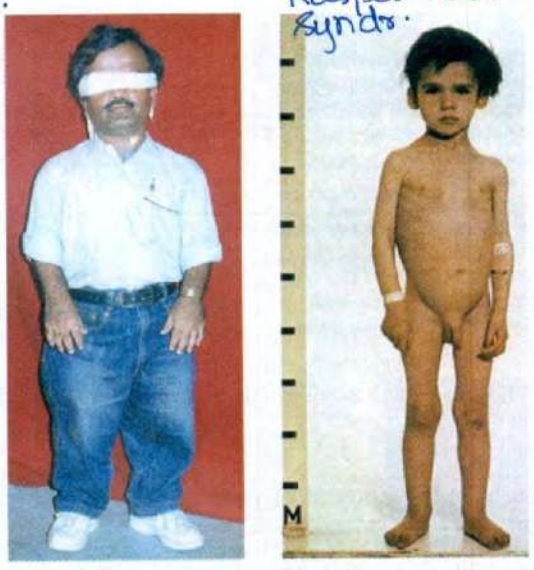
IV. **Miscellaneous**
- A. ***Systemic diseases*** *e.g.* prolonged anaemia; chronic renal failure, cyanotic congenital heart disease.
- B. ***Chromosomal abnormalities*** – Turner's Syndrome (Fig. 80.7) page 773
- C. ***Achondroplasia*** (Fig. 71.7B)

  Characteristic features
  1. Autosomal dominant disease of the skeleton in which there is faulty endochondral ossification (caused by fibroblast growth factor receptor 3 deficiency) resulting in dwarfism and is mentally sound.
  2. Abnormal body proportions – large head, short limbs with a normal trunk.
  3. The long bones are thickened and stout
- D. *Emotional deprivation – (Psycho-social Dwarfism or **Kaspar Hauser Syndrome**)* (Fig. 71.7C)

  Characteristic features
  1. The facial appearance, behaviour and intellect are immature
  2. Bone age is retarded in proportion to the reduced height
  3. Abdomen may be protuberant
  4. Responses to growth hormone and ACTH are deficient



(A) {A 9-year old pituitary dwarf (left) compared with age and sex matched control (right)}



(B) Achondroplasia

(C) Emotional deprivation

Fig. 71.7 *Major causes of Dwarfism*: short stature

B. PHYSIOLOGY OF GROWTH

(I) ***Growth*** is characteristic of living organisms. It includes increase in size and number of cells, leading to increased height and weight in human beings. It begins early in embryonic life and continues till old age; while (II) ***Development*** refers to maturation of functions.

Note

Hypertrophy may take place to compensate for a loss (page 115) or due to overuse (as in muscles).

After birth the ***General Growth Curve*** shows '4' distinct phases (Fig. 71.8). The general growth curve applies to the

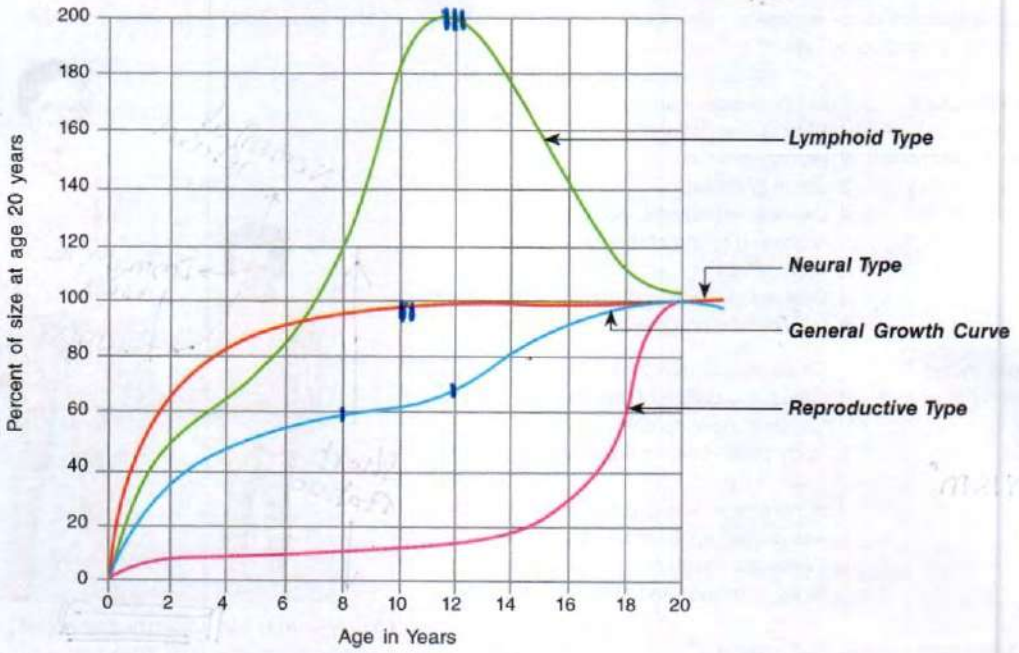


Fig. 71.8 Growth curves of various body organs after birth (growth at 20 years taken as 100% growth)

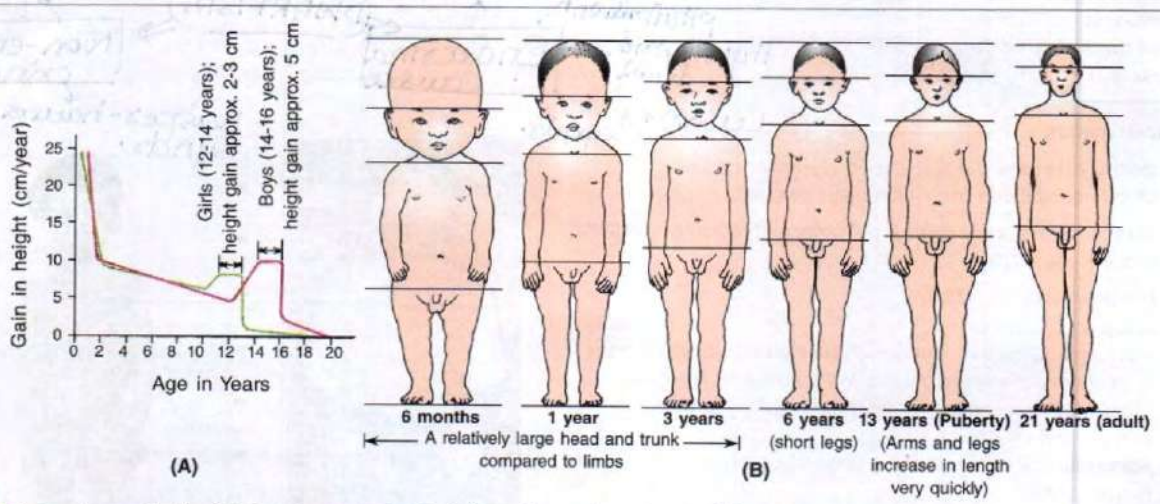


Fig. 71.9 Rate of growth after birth in boys and girls (A); and growth in height (B)

Note

The height of the body at 21 years has been taken as the standard

skeletal growth as a whole, the muscles and the thoracic and abdominal viscera.

1. A rapid increase during infancy *i.e.* specially during first year the weight increases from 3.5 to 10.5 kgm, an equivalent to about 30% of the growth.
2. A slow progressive growth from 3-12 years of age; during this period boys are slightly 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*. Growth spurt appears earlier in girls; therefore, girls mature earlier than the boys. Thus, rate of increase of height and weight is the greatest in girls at 12-14 years, and in boys at 14-16 years (Fig. 71.9).
   In girls, the increase in weight is mainly due to increased fat formation; in boys, it is mainly due to increased muscular growth.
   However, there are considerable individual variations in the age of onset of both puberty and its accompanying growth spurt.
4. Even when *pubertal growth* increase 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:*

(i) First, in infancy, it is partly a continuation of foetal growth period; and

(ii) Second is at the time of late puberty just before growth stops. It is due to the action of sex hormones, GH and IGF-I.

5. Certain parts of the body have distinctive growth curves. These are mainly of *three types:*

(i) *Neural Type.* There is a rapid initial increase in size of the brain, spinal cord and organs of special senses, together with the skull and they reach 60% and 90% of the adult size by approx. 2 and 6 years of age respectively.

Important Note

By 65-70 years of age, the brain has lost about 20% of the neurons present at birth.

(ii) *Lymphoid Type.* Lymphoid tissues including the thymus, tonsils and lymph nodes throughout the body grow rapidly in early childhood (40% of adult size by the age of 2 years.) and reach their maximum size at puberty. After this lymphoid tissue degenerates.

(iii) *Reproductive Type.* The gonads and the accessory organs of reproduction remain undeveloped until puberty (<10%) when very rapid growth begins and continues throughout adolescence. The reproductive system atrophies in women after the menopause.

(iv) Certain organs show different type of growth *e.g.* the adrenal glands and uterus are relatively large at birth, then they lose weight rapidly and regain their birth weights just before puberty.

(For growth and functional development of the foetus, refer to pages 831).

Factors affecting growth

1. *Genetic Factors.* Genetic factors are very important in relation to growth and stature. Children of tall, heavy parents are likely to have the same stature. Genetic factors are mainly responsible for certain racial differences in the height; for example, *Achondroplasia* (Fig. 71.7 B), a form of dwarfism which is due to failure of growth of long bones, is inherited as a Mendelian dominant. Although the differences between male and female pattern of growth are hormonally determined, the timing of the adolescent spurt appears to be genetically controlled via the hypothalamus.

2. *Nutritional Factors.* Diet deficient in quantity and energy, in proteins, minerals and vitamins, inhibits growth markedly and adversely; therefore

(i) If the lack of diet is sufficiently prolonged, the stunting of growth may be irreversible.

(ii) If the lack is less severe or for shorter period, restoration of normal diet leads to a compensatory increase in the rate of growth.

(iii) *Undernutrition* affects the growth of different organs and tissues unevenly. For example:

(a) Dietary deprivation has greater adverse effect on muscles and fats than on growth of bone. Moreover, teeth will be affected before the involvement of the bones.

(b) Skeletal maturation is less affected than skeletal growth and in the brain, the total brain growth is inhibited more than myelination.

(c) At puberty undernutrition affects the growth of genitalia less than that of other organs.

3. *Environmental Factors*

(i) Season and Growth: Growth in height is faster in the spring than in the autumn, whereas gain in weight is faster in the autumn than in the spring (cause – not known).

But these seasonal effects on growth are the greatest during the *adolescent spurt*, suggests a hormonal basis.

(ii) Diseases: Ill health causes temporary depression of growth, but during recovery the lost ground is regained, more or less completely. Thus, following illness in children, there is a period of ***catch-up-growth*** during which growth rate may be as much as 400% above normal. The acceleration continues until the previous growth curve is reached at which point growth slows to normal. How this is regulated precisely is not known.

(iii) Exercise: Repeated exercise of skeletal muscles can increase their mass by producing enlargement of individual fibers. This hypertrophy is favoured by anabolic steroids.

(iv) Emotional disturbances can cause decrease in rate of growth in children taking an adequate diet. Removal of cause leads to restoration of normal growth rate.

(v) Old age: Aging is characterized by:

(a) cellular degeneration due to degradative changes in the properties of multiplying cells, and

(b) impairment of various functions due to loss of non-multiplying cells.

Cause of degenerative changes is not known. It may be physiological or pathological in nature. However, it may predispose to fatal infections, malignant diseases and cardio-vascular changes, which accounts for the vast majority of deaths in old people.

Tests for GH: • Basal plasma GH level
• X-ray of skull
• Visual fields
• CT scan

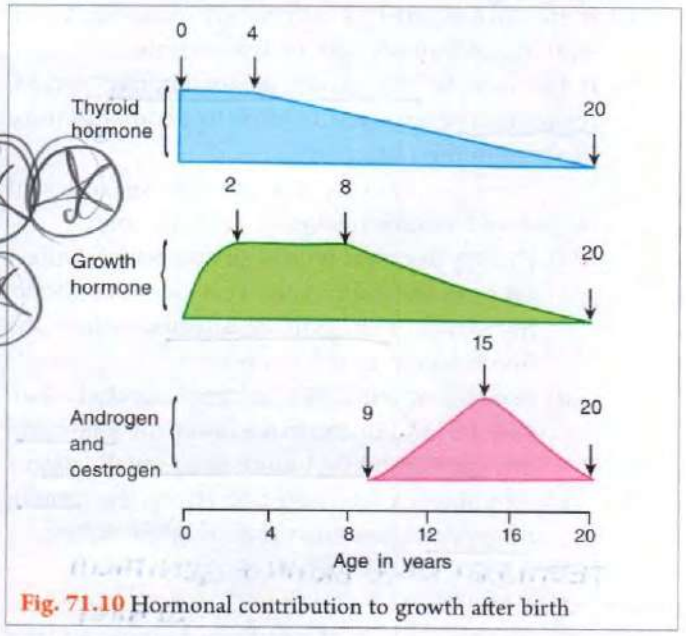


Fig. 71.10 Hormonal contribution to growth after birth

4. *Hormonal Factors*

(i) Contribution of hormones to growth after birth: **(Fig. 71.10)**

(a) Rapid growth during infancy is due to thyroid hormone and GH.

(b) Spurt growth at puberty is by androgens and GH.

(c) In between continuous growth is by thyroid hormone and GH.

(d) After attainment of puberty and rest of life is by thyroid hormone, GH and androgens.

(ii) *GH and thyroid hormone*

(a) Growth in utero and neonatal growth are independent of GH. Most of the dwarfed children have normal GH secretion. *Clinical features due to GH deficiency are:* normal birth weight; subsequent severe retardation of growth and tendency to obesity; low fasting blood sugar and delayed recovery from insulin hypoglycemia.

(b) *GH and thyroid hormone* show the *permissive action i.e.* either of the two cannot produce normal growth but when administered together they stimulate growth possibly via potentiation of the actions of somatomedins.

(c) *Role of thyroid hormone:*

– It is necessary for a completely normal rate of GH secretion. Hypothyroidism decreases the synthesis, storage and release of GH and retards growth.

– *It has widespread effects in tissue differentiation and maturation* (page 688) on the ossification of cartilage, the growth of teeth, the contours of the face and the *proportions of the body.* *Cretins* are, therefore, dwarfed and have infantile features (page 690). 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 adulthood.

(iii) **Androgen**. *Sources:* in males, testes (mainly) and adrenal cortex; in females, adrenal cortex (mainly) and ovaries.

(a) It is a protein anabolic hormone and is responsible for growth spurt; it produce an increase in GH secretion that increases IGF-I secretion. It causes increased ketosteroid excretion in urine in both sexes at puberty.

(b) Although androgen initially stimulates growth yet ultimately terminates growth by causing *epiphysial closure* thereby decreases linear growth.

Important Note

That is why *pituitary dwarfs* treated with testosterone first grow a few inches and then stop; similarly patients with *sexual precocity* tend to be dwarfed. Conversely, persons in whom testes are removed before puberty tend to be tall.

(c) *Oestrogen* have similar effects due to stimulation of androgen secretion by the adrenals. Sex steroids (oestrogen and androgen) stimulate both synthesis and release of GH which in turn increases IGF-I secretion to cause growth.

Note

Sex hormones fail to produce growth spurt that occurs at the time of puberty in individuals with GH deficiency. ∴ Permissive function

(iv) **Others**:

(a) *Adrenocortical hormones* exert permissive action on growth. *Proof:*

– Glucocorticoids are potent inhibitors of growth because of their direct action on cells and children treated with pharmacological dosage of glucocorticoids show decreased growth.

– Similarly, adrenalectomized animals fail to grow unless their BP and circulation are maintained by replacement therapy.

(b) *Insulin:* Diabetic children fail to grow because of increased breakdown of proteins and fats. However, growth is appreciated only when large amounts of carbohydrates and proteins are supplied with the insulin.

Treatment: BROMOCRIPTINE } Acromegaly.

C. PROLACTIN (PRL)

(I) General Characteristics

1. It is also called *Lactogenic or Mammotrophic or Galactopoetic Hormone.*
2. Prolactin is synthesized in the pituitary acidophil cells. During pregnancy or postpartum period prolactin cells may constitute over 50% of pituitary acidophils.
3. Prolactin is a single peptide chain containing 198 amino acids, MW 25,000, half life: 20 minutes. Its *receptors* resembles the GH receptors. Normal serum levels in adults:
   (i) Females : 6-50 ng/mL plasma
   (ii) Males : 6-25 ng/mL plasma

(II) Control of Prolactin Secretion

(A) ***Stimuli that increase prolactin secretion.*** They act via stimulating ***prolactin releasing factor (PRF);*** therefore,

1. Prolactin secretion increases 2-3 hours after the onset of *sleep* and continues throughout the sleep period.
2. *Exercise* and various *stresses* such as surgical operation, myocardial infarction etc.
3. *Pregnancy*; plasma prolactin levels begin to increase by 8th week of pregnancy and reaches peak concentration of 50-600 ng/mL at term. Oestrogen produce a slowly developing increase in prolactin secretion.
4. *Nursing* and breast stimulation raises the prolactin levels to 250 ng/mL due to:
   (i) stimulation of *prolactin releasing factor*
   (ii) direct inhibition of prolactin inhibiting factor (PIF)-secreting neurons
   (iii) inhibition of tonically discharging catecholaminergic neurons which synapse with PIF-secreting neurons.
5. *Primary hypothyroidism:* It is accompanied by high 'TRH' levels in hypophysial portal circulation which stimulates PRF. Since TRH is well absorbed when given orally, it could be widely used as a ***galactogogue*** (promoting lactation) (page 687).
6. *Dopamine antagonist* (phenothiazine and tranquilizers), adrenergic blockers and serotonin agonists; prolactin level may rise to 1000 ng/mL.
7. *Section of the pituitary stalk.*

(B) ***Stimuli that inhibit prolactin secretion***

Primarily, the control of prolactin secretion is mediated through an inhibitory peptide, ***prolactin inhibiting factor (PIF)***, which is released tonically by the hypothalamus into hypothalamo-hypophysial portal vessels. 'PIF' inhibits prolactin secretion by an action on the prolactin secreting cells of the anterior pituitary. *Dopamine* may be the main 'PIF', therefore, serotonin antagonists and *dopamine agonists* (bromocriptine, apomorphine) block the secretion of prolactin.

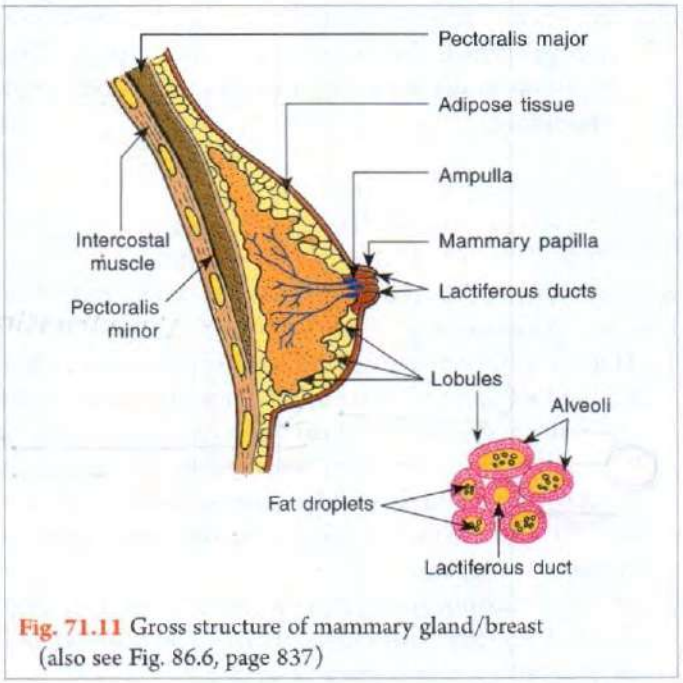


Fig. 71.11 Gross structure of mammary gland/breast (also see Fig. 86.6, page 837)

(III) Actions of prolactin

Prolactin plays an important role in the development of the mammary gland and in milk synthesis.

1. **During pregnancy**, the mammary duct gives rise to lobules of alveoli, which are secretory structures of this tissue **(Fig. 71.11)**. This differentiation requires prolactin, oestrogen and progesterone. Once lobuloalveolar system is developed, the role of prolactin and corticosteroids in milk production, although essential, becomes minimal. GH and thyroid hormone enhance milk secretion.
2. **Immediately following pregnancy**, prolactin stimulates galactosyltransferase activity, leading to the synthesis of lactose (details page 838).
3. In women, high serum levels of prolactin are associated with suppressed LH secretion and *anovulation*, which account for *amenorrhoea* (stoppage of periods) during post-partum lactation.
   (i) With continued nursing, FSH levels rise, but LH levels remain low.
   (ii) In early post-partum period, both FSH and LH levels are low and account for the *antireproductive* and *antigonadal* effects of prolactin.

(IV) Applied: *Hyperprolactinemia:*

The effects are due to associated decreased FSHs and LH levels.

1. In women, elevated serum prolactin manifests with galactorrhoea, infertility and menstrual abnormalities (amenorrhoea) (*Mechanism:* page 838).

2. In men, hyperprolactinemia is a cause of hypogonadism by decreasing GnRH (page 779) resulting in decreased spermatogenesis, libido and impotence.

POSTERIOR PITUITARY (NEUROHYPOPHYSIS)

A. ANTI-DIURETIC HORMONE (ADH) – VASOPRESSIN

General Characteristics

1. ADH is a hypothalamic hormone synthesized in the cells of the *supraoptic nucleus*. The hormones then pass down the axons bound to carrier protein, *Neurophysin II* and are stored in their endings in the posterior pituitary. From here ADH is subsequently released by nerve impulses arriving along the hypothalamo-hypophysial tract.
2. The hypothalamic nuclei that represent the main source of ADH are the supraoptic nuclei, which are called *magnocellular neurosecretory neurons*.
3. ADH is stored (but *not synthesized*) in the pars nervosa. *Evidences:*
   (i) Herring bodies (coarse large granules) can be visualized in hypothalamus and posterior pituitary by special staining technique. These bodies contain ADH and oxytocin. After section of hypothalamo-hypophysial tract, Herring bodies disappear below the section and pile up proximal to the point of section, showing that the granules are coming from the hypothalamus.
   (ii) Supraoptic nucleus destruction causes disappearance of Herring bodies with symptoms of ADH deficiency.
   (iii) In the absence of pars nervosa, the newly synthesized hormone still can be released into the circulation from the hypothalamus.
4. ADH is a polypeptide (nonapeptide); MW 1000; rapidly metabolized in the liver and kidneys; biological *half life* 16-20 minutes. It acts via three types of ***receptors*** (V_{1A}, V_{1B} and V_2), all are coupled to G-proteins (page 23).
5. The ***neurophysin II*** is the physiologic *carrier protein* for the intraneuronal transport of ADH and is released into the circulation with the neurosecretory products (ADH and oxytocin) without being bound to the hormone (Also see to page 373).

Control of ADH Secretion (Fig. 71.12)

(a) Osmotic Stimuli

1. *Hyperosmolality* is the *prime determinant* of ADH secretion. The most common physiologic factor altering the osmolality of the blood is water depletion or water excess. *As little as 1% change in plasma osmolality cause significant changes in ADH secretion.*

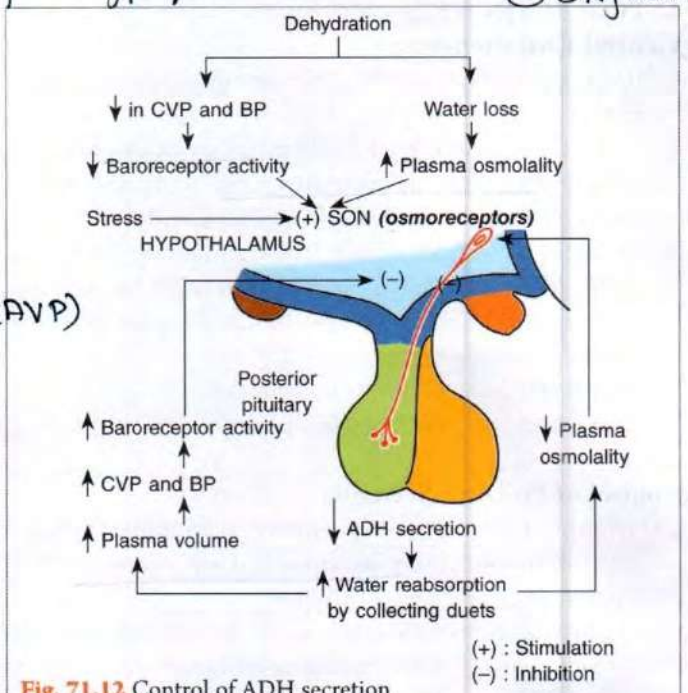


Fig. 71.12 Control of ADH secretion
(SON: supraoptic nucleus; CVP: central venous pressure; BP: arterial blood pressure

(i) The stimulation of the ***osmoreceptors*** located in the anterior hypothalamus (in the circumventricular organs, primarily OVLT - page 373) causes the reflex secretion of ADH. Increase in effective osmotic pressure of plasma stimulates *osmoreceptors* by their shrinkage; impulses travel via hypothalamo–hypophysial tract to reach posterior pituitary and increase ADH secretion.

(ii) However, *not* all the solutes (*e.g.* urea, glucose) stimulate the osmoreceptors, despite increasing plasma osmolality. Only those solutes to which cells are relatively impermeable make up the effective osmotic pressure, in response to which ADH is secreted; therefore,

(a) Na^+, sucrose and mannitol, which cross the BBB relatively slowly, are *potent stimulators* of ADH release. Since the plasma [Na^+] accounts for 95% of the effective osmotic pressure, the *osmoreceptor normally function as plasma Na^+ receptors*.

(b) Hyperglycemia or uremia is a *less potent* stimulator for ADH production and secretion than hypernatremia for the same level of osmolality as the glucose and urea get metabolized. Moreover, these substances can cross the BBB freely.

2. The control of ADH secretion by osmolality can be overridden by volume disturbances; for example, marked hyponatremia will be tolerated in order to maintain circulating blood volume.

(b) Osmotic Inhibitors

Hyposmolality of ECF (excessive water ingestion) causes expansion of intracellular volume of osmoreceptors, and thus decreases ADH secretion.

(c) Non-osmotic Stimuli

1. *Hypovolemia* is a more potent stimulus to ADH release than is hyperosmolality. A 10-25% decrease in blood volume, increases ADH release. A 10% decrease in blood volume is sufficient to cause release of enough ADH to participate in the immediate regulation of B.P. Contraction of blood volume without an alteration in the tonicity of body fluids may cause ADH release.

   Proof:

   (i) A lower osmotic threshold is required to cause ADH secretion in volume-depleted individuals.

   (ii) There exists inverse relationship between the discharge of *volume receptors* and the discharge of supraoptic nucleus; therefore, ↑ BV → ↑ stretch → stimulate volume receptors, via vagus nerve, send inhibitory impulses to supraoptic nucleus → ↓ ADH secretion. Conversely, a decrease in the stretch of the volume receptors causes an increase in ADH secretion.

   Volume receptors (or *baroreceptors*) are of two types: *venous* and *arterial* (details on pages 329 and 309).

   (a) Venous or ***low pressure baroreceptors***: these are located in the right and left atrium, vena cava, great pulmonary veins. These receptors monitor fullness of the vascular system.

   (b) Arterial or *high pressure baroreceptors*: these are located in the carotid sinus and aortic arch.

   (iii) Any reduction in intrathoracic blood volume (*e.g.* due to blood loss, quiet standing, upright body position and positive-pressure breathing) increases the ADH secretion. *Mechanism:* upon standing → marked ↓ in LA pressure → ↑ ADH release → antidiuresis.

2. Pain, nausea and vomiting, post-operative state, emotional stress (exercise, fear, anger) and drugs (*e.g.* nicotine, morphine, barbiturates, A-ch, chlorpropamide and β-adrenergic agonist) → ↑ ADH release by their direct action on supraoptic nucleus.
3. Variety of pulmonary and CNS disorders *e.g.* pneumonia, TB, stroke, meningitis, subdural hematoma → ↑ s ADH secretion.
4. Geriatric hyponatremic patients → ↑ ADH secretion → water retention. The condition is also associated with decreased aldosterone secretion, depression, confusion, lethargy and weakness.
5. Cirrhosis of liver and nephrosis increase ADH secretion because ADH is mainly inactivated by the liver and kidney.

(d) Non-osmotic Inhibitors

1. ↑ arterial B.P. or ↑ ECFV decreases ADH release because:
   (i) Hypervolemia, negative pressure breathing, water immersion upto the neck increases intrathoracic blood volume → ↑ tension in 'LA' or great veins or pulmonary veins → ↓ ADH release.
   (ii) In lying down position → ↑ in central blood volume → ↑ s 'LA' pressure → ↓ ADH release.
   (iii) Sleep → ↓ B.P. → ↑ ADH release.
2. Drugs – anticholinergic agents (atropine), ethanol, phenytoin, lithium and caffeine decrease ADH release by their direct action on supraoptic nucleus.
3. CO_2 inhalation decreases ADH release.

Actions of ADH

1. *In physiological dose ADH* →
   (i) increases permeability of distal tubules (mild action) and collecting ducts (mainly) to water (by increasing the pore size thorugh *aquaporin*-2, page 530) → increases water reabsorption (upto 12%) → urine volume decreases and its osmolality increases. It acts via V_2 *(vasopressin) receptors* stimulating increased cAMP formation intracellularly; (details page 653).
   (ii) decreases medullary blood flow;
   (iii) via V_{1A} *receptors* causes glycogenolysis in the liver;
   (iv) via V_{1B} *(or V_3) receptors* stimulates the release of ACTH from anterior pituitary thereby control aldosterone secretion.
2. *In pharmacological (i.e. high) dose* via V_{1A} *receptors*, it produces: peripheral vasoconstriction → ↑ B.P., because of this reason ADH is also called ***vasopressin***.

Important Notes

1. Because of its actions, ADH play an important role in the regulation of BP (page 351)
2. A synthetic peptide: I-deamino-8-D-arginine vasopressin *(DDAVP-desmopressin)* has very high anti-diuretic activity with little pressor activity and is very useful in the management of Diabetes insipidus (see below).

Applied Aspect

(a) Syndrome of Inappropriate ADH secretion (SIADH)

1. *Cause:* An excessive or inappropriate secretion of ADH from
   (i) the posterior lobe of pituitary gland, or

(ii) an ectopic (nonhypothalamic) sources *e.g.* a malignant tumour – bronchogenic carcinoma. (It may also cause destruction of inhibitory vagal afferents from the volume receptors

2. *Characteristic features:* Excessive ADH secretion has the following effect when water is ingested:
   (i) Water retention occurs with increase in blood volume and ECFV.
   (ii) Decreases aldosterone secretion → ↑ urinary excretion of Na^+ → hypernatriuria and hyponatremia.
   (i) and (ii) → hyposmolality; it is the increased ADH secretion despite the presence of hyposmolality which is ***inappropriate*** that is, the individual escapes from the renal effect of ADH (***Vasopressin Escape***)
   (iii) Decreases urinary excretion of water and continued excretion of Na^+ → ↑s urine osmolality → U_{osm} becomes higher than P_{osm} and urinary $[Na^+]$ exceeds 20 mEq/ L.
   (iv) The retained water in 'SIADH' first enters the plasma → ↓s P_{osm} → shift of water into interstitial space (*Oedema*) → ↓s its osmolality → further shift of water into 'ICF'. Therefore, 'SIADH' → water intoxication, called ***overhydration*** or a ***dilution syndrome***. .

(b) Diabetes Insipidus (DI)

1. *Causes*
   (i) ***Central or neurogenic DI*** *i.e.* complete or partial failure of ADH secretion.
   (ii) ***Nephrogenic DI*** *i.e.* complete or partial failure of the collecting tubules to respond to ADH. This may be due to either *V_2 receptor* unresponsiveness or mutation of aquaporin-2.
2. *Features*
   (i) Decrease in renal water reabsorption by collecting ducts → *Polyuria i.e.* diuresis of dilute urine (upto a volume 3-20 L day) → stimulate thirst and increased water intake *i.e. Polydipsia.*
   (ii) In ***Nephrogenic DI,*** urine output is directly proportional to the water delivered to the collecting ducts.

B. OXYTOCIN

Oxytocin is an nonapeptide and is synthesized within the cell bodies of the peptidergic neurons of the *magnocellular neurosecretory system* or the hypothalamo hypophysial neural tract. It is mainly synthesized in the *paraventricular nuclei* of the hypothalamus and stored in the posterior lobe of pituitary gland. It is transported bound to a carrier protein, *Neurophysin I,* from the hypothalamus to the posterior pituitary.

Actions of Oxytocin

1. (i) Oxytocin stimulates contraction of the smooth muscle cell (myoepithelium) lining the duct of mammary glands; therefore, causes **milk ejection** from lactating breasts.
   (ii) Stimulates the release of lactogenic and galactopoietic factors from anterior pituitary (also see to page 838).

Important Note

Oxytocin has proved useful clinically in women with engorged painful breasts and a poor flow of milk.

2. **Stimulates contraction of the smooth muscle of the uterus** (myometrium).
   (i) The sensitivity of the myometrium to exogenous oxytocin *during pregnancy* increases as pregnancy advances.
   (ii) Oxytocin plays a role *in labour* and has been shown to be a useful therapeutic agent in the induction of labour (page 824).
   (iii) It may facilitate the transport of sperm to the uterus by uterine contraction (page 818).
3. In high dosage it causes **relaxation of blood vessels** producing fall in B.P.
4. In males, *oxytocin receptors* are found in the testis, epididymus and prostate gland. Thus at the time of ejaculation, oxytocin **facilitates the transport of sperms** towards urethra by causing increased contraction of the smooth muscle of the vas deferens, and in the addition of seminal fluid to the sperms.
5. It plays an important role in social behaviour, such as intimacy, love or mother-child bonding (maternal care). Thus it has been also called ***love hormone***. *Oxytocin - responsible brain cells* found in the prefrontal lobe may play a role.

Control of Oxytocin Secretion

(A) Stimuli which increase oxytocin release

1. Oxytocin secretion is brought about by stimulation of cholinergic nerve fibers.
2. ***Milk Let-Down Reflex or Milk Ejection Reflex*** **(Fig. 71.13)**. Suckling → stimulation of the tactile (touch) receptors in the areolar region of the breast → activates somatoasthetic neural pathways → which transmit signal to the paraventricular nuclei in hypothalamus → Reflex secretion of oxytocin into blood stream. The oxytocin is carried to the mammary gland where it causes milk release following a latent period of 30-60 secs.
   (i) Oxytocin causes milk release in lactating women by contraction of the myoepithelial cells, which cover

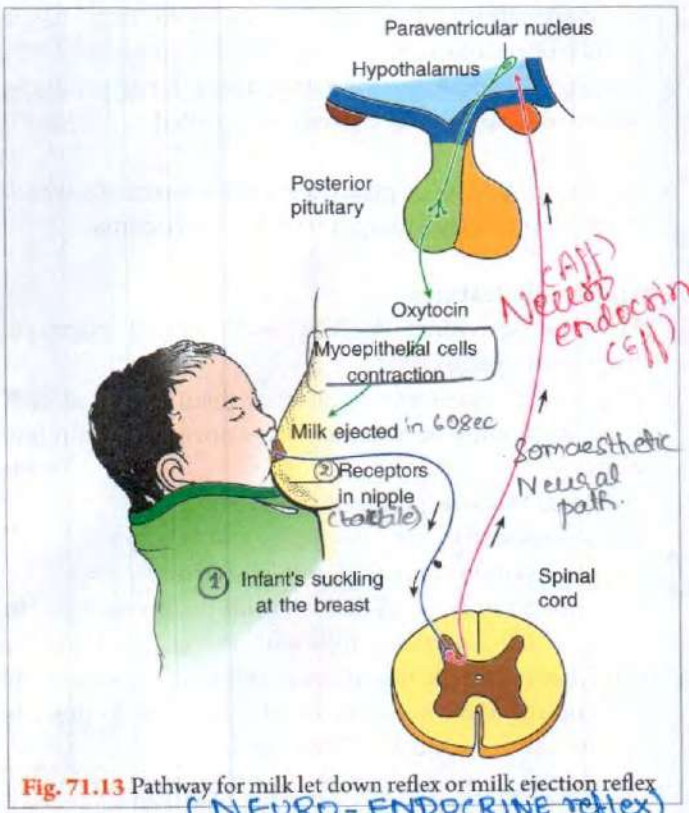


Fig. 71.13 Pathway for milk let down reflex or milk ejection reflex

the stromal surface of the epithelium of the alveoli, ducts and cisternae of the mammary glands. Thus expelling their contained milk into the duct.

Important Note

Suckling at the breast also promotes secretion of prolactin by inhibiting the release of PIF from the hypothalamus (page 671). Thus suckling causes both secretion and ejection of milk. This also explains the interaction of nervous and psychological factors, acting via the hypothalamus to influence lactation.

(ii) Oxytocin secretion can be *conditioned*, therefore, the physical stimulation of the nipples no longer is required. Thus, lactating women can experience milk release in response to the sight and sound of a baby.

(iii) Oxytocin is *not* required for successful nursing in humans.

3. Genital tract stimulation *e.g.* during coitus or parturition increases oxytocin release.

Mechanism

Dilatation of cervix
↓ *Afferent impulses*
Stimulate paraventricular nucleus in the hypothalamus
↓
Oxytocin release

(b) Factors which decrease oxytocin release

1. Emotional stress and psychic factor (*e.g.* fright) → decreases milk let down.
2. Activation of sympathetic neurons → release of epinephrine and nor-epinephrine → excitation of adrenergic fibers to hypothalamus → decreases oxytocin release.
3. Drugs *e.g.* ethanol and enkephalins.

Important Notes

1. In general, any stimulus, which increases ADH secretion, also increase oxytocin secretion and vice versa; but in smaller amounts. These stimuli cause increase in discharge of cells in supraoptic and paraventricular nuclei.
2. Both ADH and oxytocin are nonapeptides, but different at position of 3 and 8 amino acid.

INTERMEDIATE LOBE OF PITUITARY

Characteristic Features

1. It is rudimentary in humans and secretes nothing.
2. In animals it secretes ***Melanocyte Stimulating Hormone (MSH)*** *or Melanotropin*.
3. Skin of fish, reptiles and amphibians (frogs) contains two types of pigment cells:
   (i) *Melanophore*, which contains melanin pigment, and
   (ii) *Iridophore*, which contains reflecting type of platelets. Aggregation of reflecting platelets around the nucleus of iridophores and dispersion of melanin pigment to the periphery of melanophore produces *darkening* of the skin. Opposite occurs during *lightening* of the skin.
4. In humans there are *no pigment cells* but there are melanin containing cells called ***Melanocytes*** and their pituitary contains MSH. Repeated injection of MSH, either in lower animals or human beings, increases the synthesis of melanin, causing dark skin (specially of exposed parts).
5. MSH is of two types:
   (i) *α-MSH* – its structure is same in many species, and
   (ii) *β-MSH* (larger polypeptide), it differs from species to species.
6. *ACTH has 1/200 α-MSH activity and 1/100 β-MSH activity*, because, first few amino acid sequences in MSH are identical with ACTH. Therefore, diseases in which there is hypersecretion of ACTH, produce hyperpigmentation of skin.

Note

ACTH binds to melanotropin-1 receptors present on the melanocytes cell membrane.

For example, Addison disease, tumours of anterior pituitary. In contrast, hypofunction of pituitary decreases ACTH secretion producing 'pallor'.

7. ***Control of MSH secretion.*** In lower animals (fish, reptiles, amphibians etc.), skin colour change is under hypothalamus which secretes:
   (i) *MSH releasing hormone (MRH);* and
   (ii) *MSH-release inhibiting hormone (MRIH).*
   Therefore, animals against a dark background → stimulate MRH → dark skin, while on a light background → stimulate MRIH and animal colour lightens. The effect is *mediated by*: Retina →optic tract → brain stem →deep cervical ganglia →sympathetic nerve pathway to pineal gland which secretes melatonin *i.e.* an indol derivative (**Fig. 78.1**, page 759). This produces lightening of skin by stimulating MRIH secretion.
8. In humans, cells in anterior and intermediate lobe of pituitary contain a large protein, ***pro-opiomelanocortin*** which splits into ACTH and β-***lipotropin*** and these two hormones are secreted as such. In the intermediate lobe it is further hydrolysed to α-MSH, β-MSH, β-endorphin and ***'CLIP'*** *(corticotropin like intermediate lobe peptide).* Function of 'CLIP' is not known.

Applied: (1) ***Albinos*** are the individuals in whom there is congenitally a marked deficiency of melanin pigment in eyes, hair and skin.

(2) ***Piebaldism,*** a hereditary disorder characterized by white patches of skin that lack melanin. The defect is due to non-migration of pigment cell precursors to the skin from the neural crest during embryonic development. If the defect occurs after birth and is progressive, it is called ***vitiligo.***

EFFECTS OF HYPOPHYSECTOMY (Removal of the whole pituitary gland)

The anterior pituitary has a large reserve, and much of it can be destroyed or removed without producing detectable endocrine abnormalities.

1. With progressive loss of pituitary tissue, 'GH' secretion is first function to be impaired.
2. 70-90% destruction of anterior pituitary, decreases gonadotropin secretion also.
3. 90-95% destruction of anterior pituitary, leads to impairment of thyroid function also.
4. 100% destruction of anterior pituitary, produces marked degree of adrenal insufficiency. Therefore,
   (i) *signs of hypopituitarism are seen when more than 90% of anterior pituitary is destroyed;* and
   (ii) hypophysectomy is not fatal provided that glucocorticoids are given.

Causes of Pituitary Insufficiency

1. Cyst or tumour of anterior pituitary causes compression or destruction of whole of the pituitary tissue (panhypopituitarism).
2. Severe haemorrhage following child birth produces extensive pituitary necrosis, called ***Sheehan's syndrome.***
3. Haemorrhagic fever produces diffuse vasculitis which leads to pituitary enlargement due to oedema.

Characteristic features

1. Features secondary to GH and thyroid hormone deficiency (page 686).
2. **Signs and symptoms** of adrenal insufficiency which occur secondary to adrenal cortex atrophy within few days.
   (i) ↓ ACTH → pallor of the skin.
   (ii) ↓ glucocorticoids →
      (a) patient is sensitive to stress; and
      (b) urinary 17-ketosteroids decrease to 0.5-2 mg/day (Normal: 15 mg per day).
   (iii) Mineralocorticoids do *not* decrease because their control is by Renin secreted from JGA so there is no salt loss and no shock occurs.
3. Gonadal hypoplasia *decreases sex hormones* causing:
   (i) loss of spermatogenesis and impotency in males;
   (ii) abolition of ovulation and menstrual cycle in females results in sterility;
   (iii) loss of some secondary sexual characters specially loss of axillary and pubic hairs; and
   (iv) stoppage of urinary gonadotrophin excretion within 2 weeks to 2 months.
4. Depressed thyroid functions result in ***Myxoedema*** within 1-6 months (Details page 690).
5. There is increased sensitivity to insulin due to lack of anti-insulin action secondary to deficiency of 'GH'. Therefore, hypoglycemic effect of insulin increases.
6. On water metabolism
   (i) ↓ ACTH → ↓ s rate of protein catabolism
   (ii) ↓ TSH → ↓ BMR
   (iii) ↓ GH → ↓ GFR
   (iv) Glucocorticoids → defective water excretion.

   Finally,

   fewer osmotically active products of catabolism are filtered
   ↓
   ↓ in osmotic load presented for excretion
   ↓
   ↓ *Urine volume*

Note

Hypophysectomy thus causes only a *transient polyuria* even in the absence of ADH.

Study Questions

1. **Draw well labelled diagrams to show:**
   (i) feedback control of growth hormone secretion
   (ii) growth curves of different types of organs after birth
   (iii) milk let down reflex pathway.
   (iv) Hypothalamic relationship with pituitary gland.
   (v) Control of ADH secretion.
2. **Write briefly about:**
   (i) somatomedins and effects of growth hormone on skeletal growth
   (ii) Giantism (gigantism) and acromegaly
   (iii) growth spurt
   (iv) general growth curve and factors affecting growth
   (v) control of prolactin secretion
   (vi) actions of prolactin
   (vii) control of ADH secretion
   (viii) syndrome of inappropriate ADH secretion
   (ix) dilution syndrome
   (x) actions of oxytocin and control of its secretion
   (xi) Sheehans syndrome.
   (xii) Diabetes insipidius
   (xiii) Trophic hormones
   (xiv) Growth and development
   (xv) Low and high volume receptors
   (xvi) Gynaecomastia
   (xvii) Catch-up growth
   (xviii) Somatostatin
   (xix) Galactogogue
   (xx) Osmoreceptors
   (xxi) Ghrelin
   (xxii) Growth factors
3. **What will happen and why if:**
   (i) overproduction of growth hormone occurs
   (a) during adolescence and (b) during adulthood?
   (ii) GH deficiency occurs in
   (a) children and (b) adults?
   (iii) pituitary dwarf is treated with testosterone?
   (iv) prolactin secretion increases?
   (v) whole pituitary gland is removed in a person?
   (vi) if ADH secretion decreases?
4. **Give physiological basis of:**
   (i) acromegaly
   (ii) GH is diabetogenic
   (iii) GH is ketogenic
   (iv) African pygmies
   (v) sexual precocity individuals are dwarf
   (vi) hypothyroidism retards the growth
   (vii) diabetic children fail to grow
   (viii) amenorrhoea during post partum lactation
   (ix) milk ejection in a lactating mother in response to cry of the baby.
   (x) trophic hormones
   (xi) actions of somastostatin
   (xii) pituitary gland is regarded as master gland of the body
   (xiii) Portal system
5. **Name the hormones secreted by the anterior pituitary gland. Give one major action of each hormone.**
6. **Explain: somatomedin levels are better correlated with growth than plasma GH levels.**

7. Name growth promoting hormones. Give contribution of each to growth after birth.
8. List major hormonal causes of dwarfism. Give their characteristic features.
9. The osmoreceptors normally function as plasma sodium receptors. Explain.
10. Name the stimuli which increase the ADH secretion. Which is the most potent stimulus and why?
11. Give the major action of ADH. What percentage of water gets reabsorbed under its effect?
12. List posterior pituitary hormones. Describe briefly the action and control of secretion of any one of them.
13. Describe the actions and control of secretion of hormone(s) of intermediate lobe of pituitary gland.

MCQs

1. Trophic hormones refer to:
   (a) Hormones secreted from hypothalamus
   (b) Pituitary gland hormones
   (c) Hormones that stimulate the secretion of other endocrine glands
   (d) Hormones of posterior pituitary
2. Growth hormone secretion is primarily increased by:
   (a) Glucocorticoids (b) Glucose
   (c) Somatomedins (d) Deficiency of substrate in the cell
3. Somatomedins is synthesized in the following *except*:
   (a) Liver (b) Kidney (c) Muscle (d) Lungs
4. Growth hormone increases all of the following *except*:
   (a) Blood glucose concentration (b) Blood free fatty acid concentration
   (c) Protein synthesis (d) Metabolism of carbohydrates
5. Deficiency of somatomedin is seen in:
   (a) Laron dwarf (b) African pygmies
   (c) Pituitary dwarf (d) Hypothyroid dwarf
6. *Not* a feature of pituitary dwarf:
   (a) Gross retardation of mental and physical development (b) Plumpness (fatness)
   (c) Immature facies (d) Delicate extremities
7. 100% growth of different body parts ia attained at:
   (a) 12-14 years (b) 20 years (c) 25 years (d) 40 years
8. Which of the following hormones *does not* contribute to body growth after birth?
   (a) Thyroid hormone (b) Growth hormone (c) Androgens (d) ADH
9. Pituitary dwarfs treated with testosterone first growth a few centimeters and then stop, because:
   (a) It stimulates synthesis and release of GH
   (b) It initially stimulates growth but ultimately terminates linear growth by causing epiphyseal closure
   (c) It exerts permissive action on growth
   (d) Initially exerts anabolic effect followed by catabolic action
10. Urine output in diabetes insipidus may increase upto ..... litres/day:
    (a) 1-1.5 (b) 1.5-3 (c) 3-10 (d) 20
11. Prolactin plays an important role in all of the followings *except*:
    (a) Development of mammary glands (b) Milk secretion
    (c) Amenorrhoea (d) Milk ejection
12. Antidiuretic hormone may result in all *except*:
    (a) Reduces glomerular filtration rate
    (b) Secretion determined by plasma osmolality
    (c) Increases permeability of renal collecting duct cells to water
    (d) Secreted by nerve cells with their cell bodies in hypothalamus
13. Milk ejection reflex is mediated by hormone:
    (a) Oxytocin (b) Vasopressin (c) Prolactin (d) Oestrogen

14. **Panhypopituitarism causes all *except*:**
    (a) Pigmentation of skin (b) Infertility
    (c) Loss of secondary sexual characters (d) Cold intolerance
15. **All of the following are stimuli for growth hormone release *except*:**
    (a) Hypoglycemia (b) Stress (c) Obesity (d) Exercise
16. **Which of the following hormones is synthesized by neurosecretory neurons?**
    (a) Somatostatin (GHIH) (b) Somatomedin (c) Epinephrine (d) Nor-epinephrine
17. **Giantism (gigantism) is characterised by all of the following *except*:**
    (a) Occurs during adolescence (b) Excessive tallness upto 2.5 mt (8 feet)
    (c) Breast enlargement (d) Acral parts
18. **By the end of 6 years of age, ...% growth in nervous system is completed:**
    (a) 40 (b) 50 (c) 75 (d) 90
19. **Lymphoid tissues reach their maximum size:**
    (a) In early childhood (b) During adolescence
    (c) At puberty (d) At 20 years of age
20. **Hormones that may cause negative nitrogen balance include all of the following *except*:**
    (a) Excess of thyroid hormone (b) Cortisol
    (c) Growth hormone (d) Glucagon
21. **Factor *not* responsible for increased prolactin secretion:**
    (a) Exercise (b) Sleep
    (c) Dopamine (d) Breast stimulation
22. **Hyperprolactinemia effects are due to:**
    (a) High FSH and low LH levels (b) Both FSH and LH levels are low
    (c) Both FSH and LH levels are high (d) Suppressed LH secretion
23. **Non-osmotic stimuli for ADH secretion is:**
    (a) Uremia (b) Hyperglycemia
    (c) Haemorrhage (d) Excessive water ingestion
24. **Following are changes seen in SIADH *except*:**
    (a) Low plasma osmolality (b) Low urine osmolality
    (c) Hyponatremia (d) Oedema
25. **Albino is due to:**
    (a) Marked deficiency of melanin pigment (b) Thymus disorder
    (c) Tumour of pineal gland (d) ACTH deficiency

Answers

1. (c)	2. (d)	3. (d)	4. (d)	5. (a)	6. (a)	7. (b)	8. (d)	9. (b)	10. (d)
11. (d)	12. (a)	13. (a)	14. (a)	15. (c)	16. (a)	17. (d)	18. (d)	19. (c)	20. (c)
21. (c)	22. (b)	23. (c)	24. (b)	25. (a)					

Chapter
72

The Thyroid Gland

I. Physiological anatomy.
II. Formation and secretion of thyroid hormones.
III. Transport and metabolism of thyroid hormones.
IV. Regulation of thyroid secretion.
V. Actions of thyroid hormones.
VI. Applied: Goiter, Myxoedema; Cretinism; Grave's disease
VII. Antithyroid drugs.
VIII. Thyroid function tests.

COLLOID = Thyroglobulin + Iodine

PHYSIOLOGICAL ANATOMY

1. The word 'thyroid' is derived from Greek word *Thyreos*, means *'A Shield'*. Normal adult thyroid gland is the ***largest endocrine gland***, weighing 15-25 gms and it is highly vascular. It is situated in front of the larynx, bilobed (right and left lobes), connected by a bridge of tissue, called *Thyroid Isthmus*. There is sometimes a pyramidal lobe (3rd lobe) arising from the isthmus **(Fig. 72.1-A)**.
2. *Histology*
   (i) Thyroid is made up of multiple *acini or follicles*, 50-500 µm diameter. Approximately 40 follicles are grouped together to form a *lobule*. The follicular epithelium consists of a single layer of cuboidal cells **(Fig. 72.1-B)**. The cell height of the follicular epithelium varies with the activity of the gland *i.e.* degree of stimulation of TSH, cells becoming columnar when active and flat when inactive.
   (ii) The lumen of the follicle is filled with a clear, gelatinous pink material, called *colloid*, *i.e. thyroglobulin* containing iodine. Thyroglobulin is a glycoprotein, MW 6,60,000, synthesized in the thyroid cells and is secreted into the colloid by exocytosis of granules. Normal serum thyroglobulin concentration is 6 ng/mL.
   (iii) ***Thyroid cells:*** Highly vascular cells (blood supply: 5 mL/gm/min). The microvilli from the apexes of these cell project into the colloid. ***Functions:***
      (a) Collection of iodine from blood and transporting it to the colloid for hormone synthesis.
      (b) Synthesize the glycoprotein-thyroglobulin, which is stored as colloid in the follicles.

lobule = 40× follicle

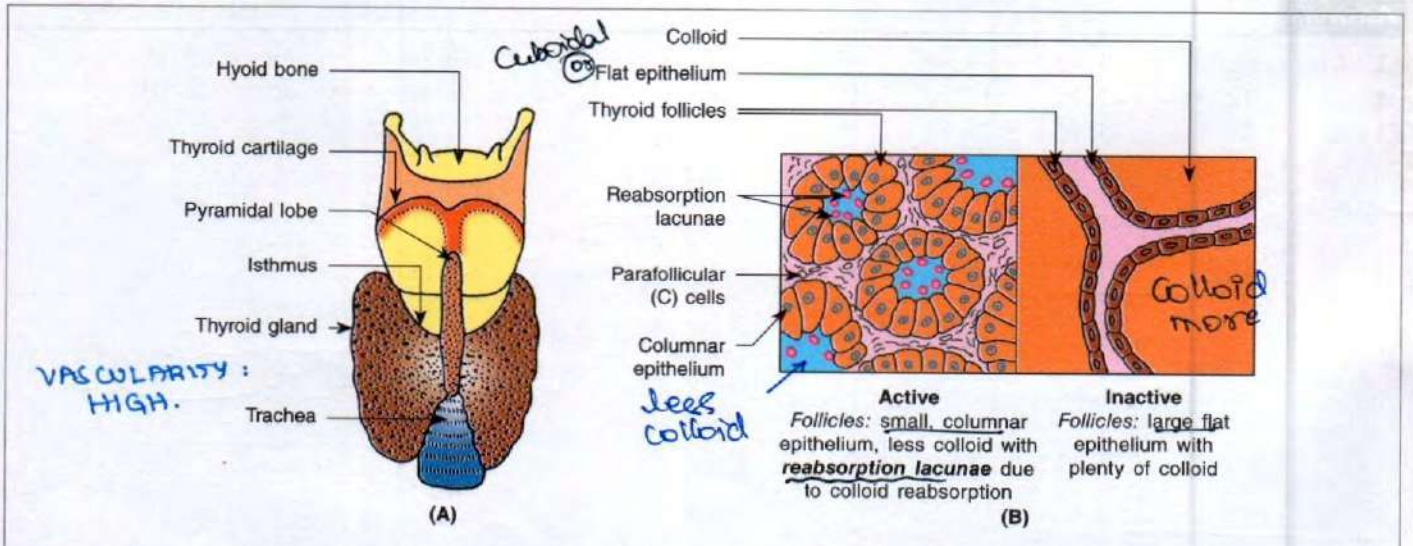


Fig. 72.1 Thyroid gland: Gross anatomy (A) and histology (B)

VASCULARITY : HIGH.

less colloid

Colloid more

Inactive follicular cells ; FLAT & High colloid.

Active follicular cells ; COLUMNAR

(c) Remove the thyroid hormones from thyroglobulin and secrete them into the circulation.

3. *Thyroid hormone* are:
   (i) ***Thyroxine*** (T_4)
   (ii) ***Tri-iodo-thyronine*** (T_3), and
   (iii) ***Calcitonin***.

   T_3 and T_4 are iodine containing amino acids, secreted by the follicular cells. They are synthesized in the colloid by iodination and condensation of *Tyrosine* molecules and bound by peptide linkage in thyroglobulin. These hormones remain bound to thyroglobulin until secreted. When they are secreted, colloid is ingested by thyroid cells and peptide bonds are hydrolyzed, discharging free T_3 and T_4 into the capillaries.

   Calcitonin (calcium-lowering hormone) is secreted by parafollicular cells or 'C' cells which lie in between the follicular cells.

4. *Functions of Thyroid gland.* Thyroid hormones are required particularly for normal foetal bone maturation and for normal development of the CNS.
   (i) It maintains the level of oxidative metabolism *i.e.* stimulate oxygen consumption of most of the body tissues, that is optimal for their normal function.
   (ii) It helps to regulate fat and carbohydrate metabolism.
   (iii) It is necessary for the tissue differentiation, normal growth and maturation.

   Thyroid is not absolutely essential for life, but its removal in adults leads to poor resistance to cold with mental and physical slowing; and, in children, mental retardation and dwarfism.

FORMATION AND SECRETION OF THYROID HORMONES

A. IODINE METABOLISM

Iodine (I_2) is the raw material essential for thyroid hormone synthesis. *I_2 sources:* sea fish (richest), bread, milk and vegetables.

1. *Daily average intake* of I_2 is 500 µgm.
2. *Daily requirement* of I_2 is 100-200 µgm for normal thyroid functions.
3. *Normal plasma iodide (I^-) level* is: 0.15-0.3 µgm/dL.
4. Thyroid contains 5-8 mg of I_2, *i.e.* 95% of total I_2 content of the body. The thyroid gland stores enough thyroid hormones to maintain a euthyroid state for 3 months without hormone synthesis.
5. Ingested Iodine (I_2) gets converted to Iodide (I^-) and is completely and rapidly absorbed into the blood to get distributed in ECF.
   (i) Principal organs that take up I^- are: (a) thyroid – to make thyroid hormones, and (b) kidneys – to excrete in urine.
   (ii) Approx. 120 µgm/day I^- enters the thyroid at normal rate of thyroid hormone synthesis and secretion. The thyroid secretes 80 µgm/day I^- in the form of T_4 and T_3, the remaining 40 µgm/day I^- diffuses into ECF. The secreted T_4 and T_3 are metabolized in liver and other tissues, with the release of 60 µgm/day I^- into the ECF.
   (iii) Some thyroid derivatives are excreted in bile. Some of I^- in them is reabsorbed via enterohepatic circulation, with a net loss of approx. 20 µgm/day I^- in stools.
   (iv) *Summary:* Total I^- entering ECF is 600 µgm per day (500 + 40 + 60) of which, 120 µgm/ day (20%) enters the thyroid and 480 µg/day (80%) is excreted in urine (Fig. 72.2).

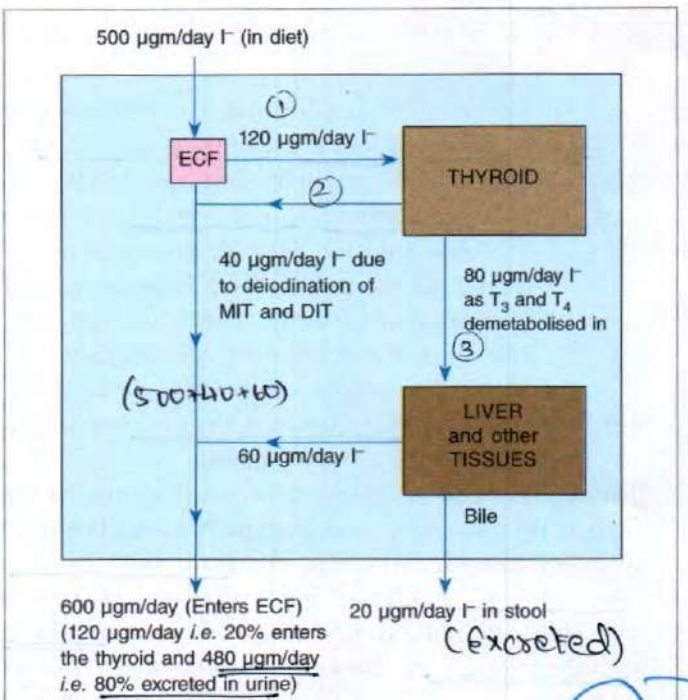


Fig. 72.2 Iodine (I_2) metabolism (I^- : iodide)

B. IODIDE TRAPPING MECHANISM (IODIDE PUMP)

1. Thyroid cells RMP is –50 mV *i.e.* inside cell is 50 mV negative as compared to interstitial fluid and luminal colloid. Therefore, I^- is reabsorbed into thyroid cells against the electrical gradient actively by *Iodide Pump (or Na^+/I^- symporter)* (Fig. 72.3).
2. The working of I^- pump depends on the activity of Na^+ – K^+ dependent ATPase system (which gets inhibited by *ouabain*) and the energy is provided by oxidative metabolism taking place in the cells. (An example of secondary active transport, page 19.)
3. ***Iodide (I^-) pump***
   (i) ***Inhibited by***

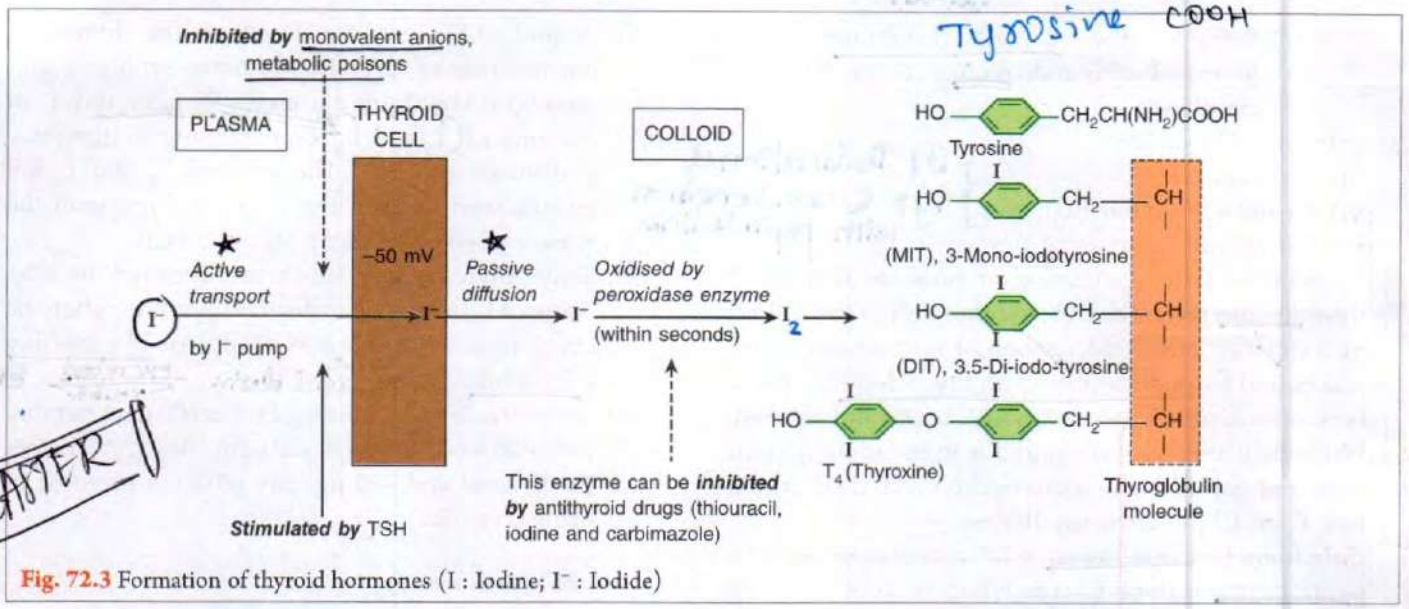


Fig. 72.3 Formation of thyroid hormones (I : Iodine; I⁻ : Iodide)

(a) **Competitive inhibition** – number of monovalent anions (chlorate, perchlorate, thiocyanate, pertechnetate, periodate, bi-iodate and nitrate) compete with I⁻ for active transport into the thyroid; this decreases I⁻ uptake to the point where ratio of thyroid I⁻ to plasma or serum free I⁻ *i.e.* T/S ratio become 1 (the ***normal T/S ratio*** is 25-50 : 1).

(b) Metabolic poisons *e.g.* dinitrite, cyanide etc.

(ii) ***Stimulated by*** TSH from anterior pituitary which increases I⁻ transport into the cell.

4. The salivary glands, gastric mucosa, placenta, ciliary body of eye, choroid plexus, mammary gland, posterior pituitary and adrenal cortex also transport I⁻ against concentration gradient but their concentration mechanism is not known; moreover, their uptake is not affected by TSH. These organs cannot form thyroid hormones.

C. TRANSPORT INTO THE COLLOID

1. I⁻ gets diffused passively into the colloid down the electrical gradient. Within the colloid I⁻ immediately gets oxidised within seconds by thyroid *Peroxidase* enzyme into I_2. I_2 then gets bound to '3' position of glycoprotein molecule *i.e. Tyrosine* (a large protein present in the colloid attached to thyroglobulin) forming *Mono-iodo-tyrosine (MIT)*. MIT is next iodinated in '5' position to form *Di-iodo-tyrosine (DIT)*.

2. DIT + DIT $\xrightarrow[\text{Oxidative condensation}]{\text{Undergo}}$ Thyroxine (T_4) + Alanine

This reaction is catalysed by thyroid peroxidase.

MIT+DIT $\xrightarrow[\text{Oxidative condensation}]{\text{Undergo}}$ Tri-iodo-thyronine (T_3) i.e. 3,5,3' T_3

$T_4 - I^- \xrightarrow{\text{Deiodination}}$ Tri-iodo-thyronine *(formed in small amounts)*

DIT + MIT ⟶ *Reverse* T_3 *i.e.* 3,3',5' T_3 (inactive)

3. Thyroid peroxidase and coupling enzymes which form T_4 and T_3 are competitively inhibited by **anti-thyroid drugs** Thiourylenes *e.g.* Thiouracil and Carbimazole.

4. MIT, DIT, T_3 and T_4 are all in peptide linkage with thyroglobulin which occurs as a colloidal aggregate within the follicles. This colloid is ingested by the thyroid cells by pinocytosis with formation of ***reabsorption lacunae*** **(Fig. 72.1B)**.

5. The **thyroid differs from other endocrine glands** in storing its active principles in the cavity of a vesicle rather than in the secreting cells themselves.

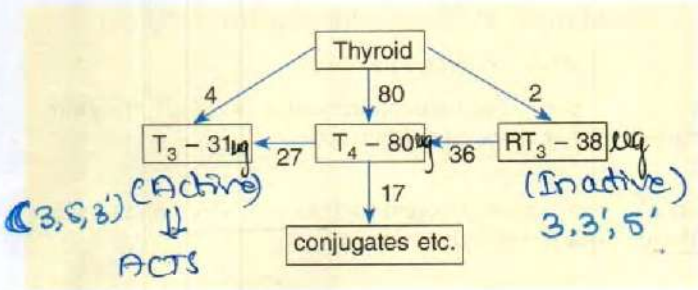
D. AVERAGE DISTRIBUTION OF IODINATED COMPOUNDS

1. MIT : 23% | DIT : 35%
   T_3 : 7% | T_4 : 35%

   T_3 and T_4 are secreted in plasma, T_3 : 4 μgm/day and T_4 : 80 μgm/day; remaining are traces of reverse T_3 and other components.

2. In thyroid cells are *lysosomes*, whose proteases break down the peptide bond to cause liberation of T_4, T_3, DIT and MIT into the cytoplasm. Iodinated T_3 and T_4 are deiodinated by a cell enzyme *Iodotyrosine Dehalogenase* and the I⁻ liberated is re-utilized. As this enzyme does attack MIT or DIT, therefore, they do not appear in circulation.

E. SECRETION AND INTERCONVERSION OF THYROID HORMONES (values in µgm/day)



Therefore, thyroid secretes approx. 90% T_4 and 10% T_3.

TRANSPORT AND METABOLISM OF THYROID HORMONES

A. TRANSPORT

1. Transport of thyroid hormones is by thyroid binding proteins viz. *thyroid binding globulin* (TBG), transthyretin or *thyroid binding pre-albumin* (TBPA) and *albumin*.
2. Albumin has by far the *greatest* capacity to bind thyroid hormones and TBG the *least*. However, affinities of the proteins for T_4 are such that most of the circulating T_4 is bound to TBG; only small amounts of T_4 are bound to *transthyretin* and practically none to albumin (Table 72.1).
3. The free thyroid hormones in plasma are in equilibrium with the protein-bound thyroid hormones in plasma and in the tissues (Fig. 72.4). Free T_4 and T_3 are added to the circulating pool by the thyroid. Free T_4 and T_3 in plasma are *Physiologically Active*, and it is this fraction which inhibits the pituitary secretion of TSH.
4. Because of the equilibrium, the entry of thyroid hormone in the tissues is increased whenever the concentration of free thyroid hormone in the plasma is elevated. The hormones are metabolized in the tissues, and consequently their rate of metabolism is increased.

Conversely, when the free thyroid hormone level in the plasma is decreased, the tissue uptake and rate of hormone metabolism are reduced.

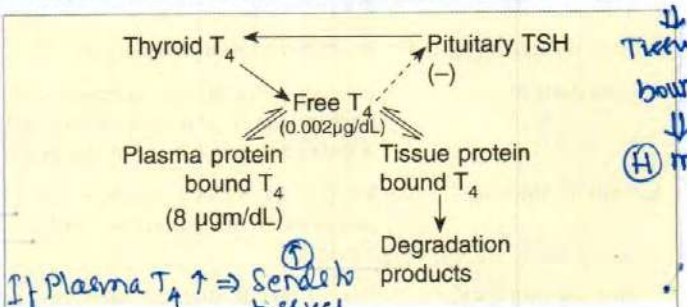


Fig. 72.4 T_4 distribution in the body. (– –): inhibition

5. Fluctuations in binding proteins: sudden, sustained rise or fall in the concentration of thyroid binding proteins in plasma can cause increase or decrease in concentration of free T_4 and T_3; but practically it is not seen, because there is a corresponding increase or decrease in the rate of entry of free T_4 and T_3 into tissues. This results in normal plasma concentration of free T_4 and T_3.
   Moreover, increase or decrease in concentration of free T_4 and T_3 via anterior pituitary causes alteration in TSH secretion and normal concentration of free T_4 and T_3 is restored.

Important Note

This is the reason why the patients with elevated or decreased concentration of thyroid binding proteins are neither hyper nor hypothyroid *i.e.* they are *euthyroid* (normal clinical thyroid state). Thyroid binding proteins levels are increased in oestrogen treated patients and during pregnancy; whereas its levels are decreased by glucocorticoids and androgens.

6. Differences between T_4 and T_3 (refer to Table 72.2).

Table 72.1: Thyroid hormones binding capacity of plasma proteins

Thyroid binding proteins	Biologic half life	Plasma level (mg/dL)	T_4 binding capacity (µgm/dL)	Affinity for*		Amount of thyroid hormone bound to normal plasma (µgm/dL)	
				T_4	T_3	T_4	T_3
1. Thyroxine binding globulin (TBG); MW 60,000	5 days	1.0–2.0	Low; 20	67%	46%	5.4	0.07
2. Transthyretin or Thyroxine binding pre-albumin (TBPA) MW 50,000	2 days	15–30	Moderate; 250	20%	1%	1.6	0.001
3. Albumin; MW 69,000	13 days	3500	High; 1000	13%	53%	1.0	0.08
Total protein bound thyroid hormone in plasma	–	–	–	–	–	8.0	0.15

* That is, Avidity with which binding proteins bind thyroid hormones under physiological conditions.

Table 72.2: T_4 and T_3 compared

	Thyroxine (T_4)	Tri-iodo-thyronine (T_3)
1. Total plasma level	3-8 µgm/dL	0.15 µgm/dL (50 times less than that of T_4).
2. Secretion into plasma	In large amounts 80 µg/day	In small amounts 4 µg/day.
3. Distribution	It is an extracellular hormone and acts as a *prohormone i.e.* stable precursor of T_3, because it gets converted to T_3 in the body.	T_3 penetrates tissue fluids and cells readily, therefore, it is an intracellular hormone.
4. Protein binding	99.95% to 99.98%; mainly to TBG, small amounts to transthyretin and very little to albumin.	99.8%; mainly bound to TBG and Albumin and very little to trans-thyretin.
5. Free plasma level	Less; 2 ng/dL (0.05%), therefore, more stable in the body. Biological half life 6-7 days.	More; 0.3 ng/dL (0.2%), that is 4 times more free; therefore comparatively less stable in the body, *i.e.* it has a shorter half life than T_4.
6. Duration of action	Longer but onset of action on tissues is slow.	Much shorter but more rapid onset of action on tissues. As free level is more and is more rapidly absorbed than T_4, therefore, *more potent* and *more active* than T_4 (approx. 3 to 5 times the biological activity of T_4).

B. METABOLISM

Thyroid hormones are deaminated and decarboxylated in many body tissues. As most of T_4 get deiodinated (removal of I^-) to T_3 and then it produces its physiological action, therefore, T_4 may be metabolically inert until it is deiodinated to T_3. Thus T_4 is a *Prohormone*.

Some of

$T_4 \xrightarrow{\text{Deiodinated}} RT_3$ (inactive)

$T_4 \xrightarrow[\text{i.e. removal of } (NH_2) \text{ COOH group}]{\text{Decarboxylation}}$ TETRAC (Tetraiodo-thyroacetic acid)

Similarly,

$T_3 \xrightarrow[\text{i.e. removal of } (NH_2) \text{ COOH group}]{\text{Decarboxylation}}$ TRIAC (Tri-iodo-thyroacetic acid)

In the liver, T_4 and T_3 are conjugated to form sulphates and glucuronides. These conjugates enter the bile and pass into the intestine. The thyroid conjugates are hydrolyzed, whereas free hormone to some extent are reabsorbed (*enterohepatic circulation*), but mainly they are excreted in stools. The I^- lost in this way amounts to approx. 4-5% of the total daily I^- loss.

Note

In fasted individuals or during starvation, plasma T_3 is reduced with a corresponding rise in RT_3, however, free and bound T_4 levels remain normal. The decline in T_3 conserves calories and protein. Conversely, overfeeding increases T_3 and reduces RT_3.

REGULATION OF THYROID SECRETION

The regulating factors which help to keep the thyroid secretion rates and serum levels of T_4 and T_3 are:

(A) *TSH – thyroid stimulating hormones*; and
(B) *thyroid autoregulation.*

A. TSH: THYROID STIMULATING HORMONE or THYROTROPHIN

1. It is a glycoprotein, secreted by the anterior pituitary, containing 211 amino acids, MW 31,000; biological *half life* 60 min; *degraded* mainly in the kidneys and to a lesser extent in the liver. TSH is made up of two subunits – α and β. TSH-α is identical to the α-subunit of LH, FSH and hCG-α; however, β unit is functionally specific. The *normal secretion rate* is 110 µgm/day with average *plasma level* 2.3 µIU/mL (range: 0.2–5.0 µIU/mL). Its secretion is under the control of the hypothalamus through secretion of *Thyrotrophin releasing hormone (TRH).*

Note

The secretion is *pulsatile* in nature in that it starts rising towards the late evening, peak is achieved at midnight and the secretion decreases during the daytime.effects on cardiac sphincter.

2. ***Mechanism of action*** – TSH acts via ***thyroid receptors*** resulting in activation of adenylyl cyclase through G_S in thyroid cell membrane to increase intracellular cAMP (page 653). It also activates phosphorylase C.

Note

Thyroid cells also contain receptors for IFG-I and other growth factors.

3. ***Effects of TSH on thyroid gland***
   (i) increases I^- trapping mechanism
   (ii) increases organic binding of I to tyrosine
   (i) and (ii) increase synthesis of T_4 and T_3.

(iii) increases pinocytosis
(iv) increases proteolysis of thyroglobulin *i.e.* increased release of stored T_4 and T_3
(v) increases synthesis of thyroglobulin into the colloid
(vi) increases number and size of thyroid cells resulting in hyperplasia with hypertrophy of the thyroid gland; therefore,
  (a) increased TSH secretion or prolonged administration of TSH produces *Goiter* (*enlargement of the thyroid gland*); and
  (b) removal of anterior pituitary causes atrophy of the thyroid gland.
(vii) increases blood flow to the thyroid gland.

Summary: Thus, TSH not only stimulates the secretion of stored thyroid hormones from follicular colloid but it also promotes synthesis of fresh thyroid hormones.

4. *Control of TSH secretion*

The release of TSH by the anterior lobe of the pituitary gland is regulated by the hypothalamus and via feedback mechanism (Fig. 72.5).

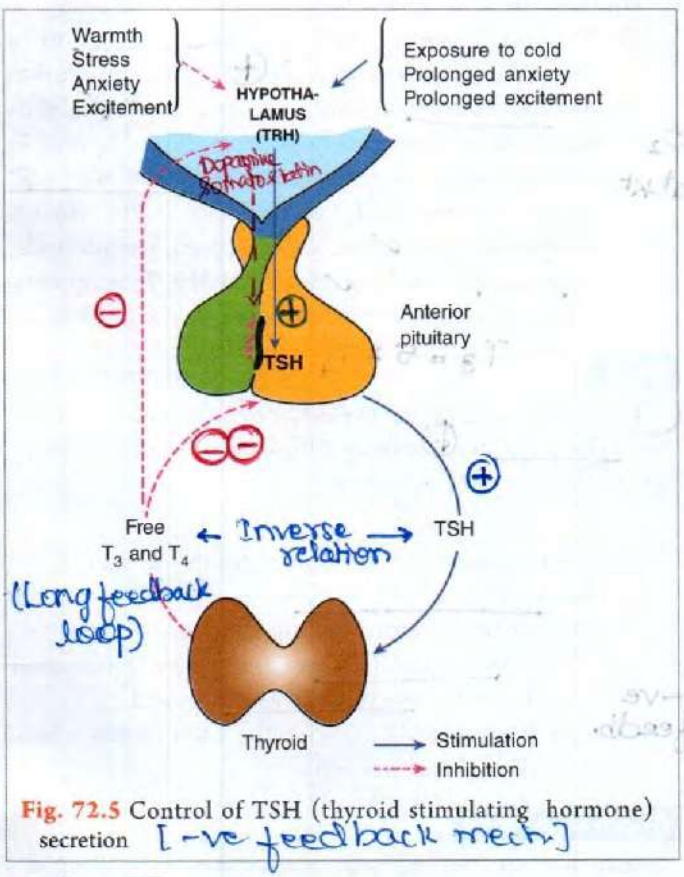


Fig. 72.5 Control of TSH (thyroid stimulating hormone) secretion

(i) *Hypothalamic control of TSH secretion:* Hypothalamus acts by secreting a tripeptide called *Thyrotrophin Releasing Factor/Hormone (TRF/TRH).* It is synthesized in the TRH secreting neurons in the anterior hypothalamus. TRH is transported to the median eminence, where it is stored. From there, TRH is released into the hypothalamo-hypophysial portal vessels to stimulate the secretion of TSH by the 'thyrotroph' cells of the anterior pituitary. TRH acts on anterior pituitary to release TSH via the adenylyl cyclase-cAMP system and Ca^{2+} within the thyrotrophs.

(ii) *Feedback control of TSH secretion*
  (a) *Fall in free T_4 (or T_3)* via negative feedback mechanism stimulates TSH secretion to cause rise in free T_4 (or T_3) from the anterior pituitary;
  (b) Conversely, *Rise in free T_4 (or T_3)* via negative feedback mechanism inhibits TSH secretion and causes fall in free T_4 (or T_3). (How? See below)

Important Note

There exists a marked inverse relationship between plasma free thyroid hormones (T_3 and T_4) and plasma TSH, therefore, *measurement of plasma TSH levels is one of the best tests of assessing thyroid functions.* Free T_3 is the principal feedback regulator of TSH secretion. For details, refer to page 695.

(iii) **TRH and thyroid hormones** (T_4 and T_3) *act competitively* on 'thyrotrophs' of the anterior pituitary. The stimulant action of TRH on pituitary 'thyrotrophs' is competitively inhibited by thyroid hormones (T_4 or T_3). This is the *basis for the negative feedback control* exerted by thyroid hormones on the secretion of TSH by the anterior pituitary.

(iv) Thus, free T_4 and T_3 decrease TSH secretion partly by an action on the hypothalamus and partly by a direct action on the anterior pituitary. However, *anterior pituitary is the main site of negative feedback mechanism,* since free T_4 and T_3 block the increase in TSH secretion produced by TRH. *Evidences:*
  (a) If we implant small amounts of *free* T_4 at anterior pituitary in one animal, it causes marked decrease in TSH secretion, whereas similar implant at the level of hypothalamus in second animal causes only slight decrease in TSH secretion.
  (b) If we isolate the anterior pituitary from hypothalamus by cutting hypothalamo-hypophysial tract, now anterior pituitary can regulate secretion of T_4 without the hypothalamus.

(v) The *deiodination of T_4* to T_3 occurs in many tissues but is the greatest in the pituitary. This shows that T_3 is the main hormone producing this 'negative feedback'.

Important Note

The *day-to-day* maintenance of thyroid secretion depends on the feedback interplay between thyroid hormones and TSH; while hypothalamus adjusts TSH secretion in certain *special situations* such as exposure to cold, warmth stress, anxiety, excitement etc.

(vi) **Other factors** regulating TSH secretion (by acting at the pituitary level):

(a) **Oestrogen** increases TSH secretion.

(b) **Large dosage of I^-** decreases release of thyroid hormone thereby decreases serum T_4 and T_3 concentration; thus TSH secretion increases.

(c) **Somatostatin** inhibits TSH secretion and the response to TRH.

(d) **Dopa and Dopamine** decrease the basal TSH secretion.

(e) **Glucocorticoids** also decrease TSH secretion.

B. THYROID AUTOREGULATION
(INTRINSIC AUTOREGULATORY PROCESSES)

1. Thyroid functions are also regulated by *Intrinsic Control System* within the thyroid which modify the responsiveness to TSH and thus maintain the constancy of stored hormone in the thyroid in spite of wide variation in iodine intake.
2. ***Role of Iodine in the diet***
   Iodine is the raw material for thyroid hormone synthesis and has ***paradoxical effects*** on thyroid functions in that:
   (i) in **small dose** it is necessary for normal thyroid functions, while
   (ii) in **high dosage**, it decreases the thyroid gland functions.
   Therefore, excessive ingestion of Iodine decreases I^- transport into follicular cells, wheres I_2 deficiency leads to the enlargement of thyroid gland. Thus, resulting in normal thyroid hormone secretion without altering the TSH secretion.
   This is possible due to the effect of organic *iodine affecting sensitivity of thyroid response to TSH;* iodine deficiency increases this sensitivity and iodine excess decreases the sensitivity.
3. ***Mode of action of Iodine***
   High dose of iodide (I^-) decreases the formation and release of thyroid hormone called *Wolff-Chaikoff effect*.
   The effect is brought by:
   (i) preventing oxidation of iodide (I^-) into iodine (I)
   (ii) preventing incorporation of I to tyrosine
   (iii) decreasing the proteolysis of thyroglobulin thereby leading to the accumulation of colloid.
   (iv) decreasing the blood flow to thyroid gland probably due to decreased energy metabolism
   (v) decreasing TSH effect on thyroid gland by decreasing cAMP response to this hormone.
4. These inhibitory effects due to I^- excess last for only 1-2 weeks and then wears off in spite of continued therapy.

Important Note

I^- has little, if any, effect on thyroid function in *normal* individuals, that is why in doubtful cases of thyrotoxicosis (where *Wolff-Chaikoff effect* is greater), the clinical response to I^- therapy can be used as a diagnostic test. However, *Goiter* sometimes develops in euthyroid patients taking large amounts of iodide in cough syrups.

ACTIONS OF THYROID HORMONES

Mechanism of action, refer to page 653.

1. ***Calorigenic (heat production) action: Thyroid Hormone Thermogenesis***
   (i) Thyroid hormones stimulate heat production in the body, an action seen secondary to stimulation of O_2 consumption which increases the BMR, thus resulting in increased heat production. T_3 and T_4 *increase the O_2 consumption and activity of $Na^+ - K^+$ pump of almost all metabolically active tissues, exception:* adult brain, testes, spleen, lymph node, ovary, uterus and anterior pituitary. T_3 is approx. 3 to 5 times more effective than T_4 (page 684).

Note

T_4 actually decreases the O_2 consumption of the anterior pituitary and thus inhibits the TSH secretion, page 685.

   (ii) The magnitude of calorigenic action depends upon the level of catecholamine secretion and on the level of BMR before the injection. Therefore,
   (a) if initial BMR is less, then after injection of T_3 or T_4, rise in BMR is more; and
   (b) if initial BMR is more, the rise in BMR is less. (Why? Not known).

Important Note

Because of decreased heat production, hypothyroid patients are hypersensitive to cold; while hyperthyroid patients are hypersensitive to warm temperature, as they cannot damp down heat production.

Most of the effects of thyroid hormones in the body are secondary to calorigenesis and are given as under.

A. ON PROTEIN METABOLISM

(i) T_4 *in physiological dose* is *Anabolic*, *i.e.* increases protein synthesis resulting in positive N_2 balance. In hypothyroid patients, thyroid hormones increase growth only when secretion of GH is normal, thus, protein synthesis needed for growth *requires both the thyroid hormone and GH.*

(ii) T_4 *in pharmacological doses* causes:

(a) Protein catabolism due to increase in BMR which leads to: negative N_2 balance, increases K^+ excretion in urine and increases hexosamine and uric acid excretion in urine. Therefore, if food intake is not increased, body weight is lost.

(b) Sometimes *catabolic effect* in skeletal muscle is so severe that it produces:

- marked muscle weakness with undue fatiguability (*Thyrotoxic Myopathy*)
- marked creatinuria (as creatinine phosphate is required to convert ADP to ATP, its reduction decreases the efficiency of muscular contraction).

(c) Mobilization of bone protein decreases bone mass (*Osteoporosis*) which leads to hypercalcemia with increased Ca^{2+} loss in urine (*Hypercalciuria*).

(d) Hypothyroidism is also associated with muscle weakness, cramps and stiffness.

(iii) Normally skin contains variety of proteins combined with mucopoly-saccharides, hyaluronic acid and chondroitin sulphuric acid. *In hypothyroidism*, because of decreased catabolism, these complexes deposited under the skin and subcutaneous tissues exert osmotic pressure which causes retention of water and sodium chloride. Eventually it produces dry, coarse, puffy appearance of skin, called *Myxoedema*. It is a *non-pitting* oedema and commonly seen around the eyes, hands, supra-paraocular fossa.

B. ON CARDIOVASCULAR SYSTEM

(i) Combined effect of T_4 and catecholamines on the heart causes, increase in HR (*sleeping pulse rate also increases*), increase in force of myocardial contraction and decrease in circulation time. The effects are due to:

(a) increased sympathetic activity on β-receptors via adenylyl cyclase-cAMP and

(b) increased expression of genes for α-myosin receptors, sarcoplasmic reticulum Ca^{2+} ATPase, β-adrenergic receptors, G-proteins, $Na^+ - K^+$ ATPase. So *increase in cardiac output* increases the systolic BP.

(ii) T_4 also increases the body temperature and produces *vasodilatation*, therefore

(a) increase in blood flow through skin produces warm, moist skin and

(b) decrease in peripheral resistance decreases diastolic BP.

(iii) Increase in systolic and fall in diastolic BP causes

(a) mild decrease in Mean BP; and

(b) increase in pulse pressure.

(iv) Decrease in circulation time increases the velocity of blood flow, causing inadequate tissue perfusion. Eventually there occurs inadequate tissue perfusion in spite of high cardiac output called *High Output Cardiac Failure*. This is clinically manifested as shortness of breath on exertion.

(v) Increase in myocardial O_2 utilization is more than the increase in coronary blood flow, which may *precipitate cardiac arrhythmias*.

C. ON BONE MARROW METABOLISM

(i) T_4 deficiency leads to anaemia due to:

(a) decreased bone marrow metabolism which decreases the erythropoiesis producing normocytic normochromic anaemia;

(b) (less common) decreased absorption of vitamin B_{12} from GIT may lead to megaloblastic anaemia.

(ii) T_4 excess stimulates erythropoiesis, increases production of 2,3 DPG in the RBCs, shifts O_2-dissociation curve to the right, thus more O_2 is released to the tissues.

D. ON VITAMINS

(i) Thyroid hormones, by stimulating metabolic processes, increase the demand for Co-enzymes and the vitamins from which they are formed. This produces vitamin deficiencies in hyperthyroid patients, specially of water soluble vitamins B-complex and C.

(ii) T_4 is necessary for hepatic conversion of β-carotene to vitamin A and for the conversion of vitamin A to retinene. Thus in T_4 deficiency, blood carotene level rises (*carotenemia*), which gives a *yellowish colour to the skin only*. As contrast to jaundice, in which sclera also gets stained yellow, it remains unstained in carotenemia.

E. ON LACTATION

T_4 is essential for maintenance of galactopoiesis *i.e.* lactation. If T_4 decreases, lactation decreases. Conversely,

if T_4 increases lactation increases and fat content in milk also increases (Also see to page 671).

F. ON GONADS

(i) *Cretins* show poor gonadal development with absence of secondary sexual characters.

(ii) In *hypothyroid* women there is an increase in menstrual bleeding, with occurrence of intermenstrual bleeding. The endometrium remains in the proliferative phase with marked hyperplasia. Conversely, in hyperthyroidism menstrual bleeding is scanty or absent due to effects of thyroid hormones on the hypothalamus.

(iii) T_4 does not stimulate the metabolism of uterus but it is essential for normal menstrual cycles and fertility. Alteration of thyroid activity impairs fertility in women largely as a result of disordered cyclic ovarian activity.

2. *On Carbohydrate Metabolism*

In physiological dosage thyroid hormones produce *two opposite effects* which balance each other.

(i) T_4 increases peripheral utilization of glucose (insulin like action) and thus can cause hypoglycemia;

(ii) T_4 can cause hyperglycemia as it:

(a) increases glucose absorption from intestine

(b) increases glycogenolysis in the liver, heart and skeletal muscle

(c) increases gluconeogenesis from pyruvate in the liver

(d) increases the breakdown of insulin

(e) decreases the rate of secretion of insulin.

In pharmacological doses or in hyperthyroid patients, thyroid hormones precipitate the *diabetes mellitus*.

3. *On Lipid Metabolism*

A. *On cholesterol:* T_4 has *two opposing effects:*

(i) increases synthesis of cholesterol in the liver;

(ii) (a) increases breakdown of cholesterol in the liver, and (b) increases the excretion of cholesterol in bile. These effects are due to increased formation of LDL receptors in the liver.

Effect (ii) is always greater than effect (i), therefore, T_4 decreases serum cholesterol (*normal:* 120-200 mg/dL).

The plasma cholesterol level drops before BMR increases, showing that this action is independent of stimulation of O_2 consumption.

B. *On Lipids*

In general, T_4 stimulates

(i) synthesis of lipids, and

(ii) mobilization and degradation of lipids by increased activity of lipase *i.e.* increases lipolysis.

Effect (ii) being greater than (i), T_4 decreases the stores of triglycerides and phospholipids. The naturally occurring form of T_4 is L–T_4; D–T_4 has only a small fraction of the activity of L–T_4. (Table 72.3)

D–T_4 and 'TETRAC' (page 684) have greater cholesterol lowering activity than naturally occurring L–T_4, whereas they have less of the other activities of the thyroid hormone (Table 72.3). Therefore, D-T_4 and TETRAC are used clinically as serum cholesterol lowering agents in atherosclerosis.

Table 72.3: BMR increasing and cholesterol lowering effects of thyroid hormones and its derivatives

	BMR rising effect	Cholesterol lowering effect
T_3	+ + +	–
L–T_4 (Natural)	+ +	+
TETRAC (Artif.)	+	+ +
D-T_4 (Artif.)	–	+ + +
RT_3	–	–

4. *On Growth and Development*

(i) T_4 is important for normal body growth and skeletal maturation; because it increases protein synthesis and can cause increased release and action of GH (page 670). Therefore, in Cretins, bone growth is slowed with delay in epiphysial closure of limbs as a result, limbs are short as compared to trunk.

(ii) T_4 helps in tissue differentiation and maturation. *Evidence:* In tadpole, T_4 causes early metamorphosis of tadpole into adult dwarf frog which is not more than the size of the housefly. Moreover, hypothyroid tadpoles can never become adult frogs.

5. *Effect on Nervous System*

A. *On CNS:* T_4 is necessary for normal development and activity of the CNS.

(i) *T_4 deficiency after birth* upto 2 years of age or in foetus causes:

(a) defective myelination in axons of cortical neurons;

(b) branching and development of dendrites decreases and synapses develop abnormally; and

(c) marked reduction in the vascular bed to the brain.

All these changes result in *infantile brain i.e.* anatomically brain is small and physiologically underdeveloped, thus producing mental retardation (*Idiot Child*).

Critical period is upto *1 year* of life, after 1 year even excessive administration of T_4 cannot restore the normal mental functions *i.e.* irreversible mental retardation develops. If deficiency occurs after 2 years of age, CNS manifestation can be reversed by adequate doses of T_4, therefore, early diagnosis of cretinism is vital.

Important Note

The parts of the CNS most affected are the cerebral cortex, basal ganglia and cochlea, therefore, T_4 deficiency during development causes mental retardation and motor rigidity and deafness.

(ii) *T_4 deficiency in adults* causes:
- (a) loss of all intellectual functions
- (b) memory loss
- (c) slow speech due to hoarse (husky) and slow voice (which can be diagnosed on phone)
- (d) mental and physical lethargy
- (e) electrical activity of brain decreases or not recordable (specially α-wave in EEG; normally α-wave frequency is 8-12/sec with an amplitude 50 mV).

Eventually, it leads to *Madness (or Psychosis)* known as ***Myxoedema Madness***.

(iii) *T_4 excess in adults* causes increased responsiveness to catecholamines which stimulate the reticular activating system producing:
- (a) emotional instability, anxiety, nervousness;
- (b) overexcitability and restlessness;
- (c) irritability;
- (d) insomnia, and
- (e) fatigue with fine rhythmic tremors in hands, tongue or eyeballs.

(iv) In adults, cerebral blood flow, glucose and oxygen consumption of brain are normal in hypo and hyperthyroidism and only traces of thyroid hormones pass the BBB. In infants thyroid hormone may stimulate O_2 consumption of brain and can produce other actions on CNS, as BBB is not developed.

B. *On peripheral nervous system*

(i) T_4 stimulates muscle spindle and causes contraction of muscles. In myxoedema, knee jerk 'reaction time' increases (*normal*: 20 msec) and in thyrotoxicosis, decreases;

(ii) T_4 deficiency
- (a) decreases the rate of conduction of impulse in nerve-fibers, and
- (b) decreases rate of muscle contraction and relaxation causing prolonged reaction time, this may be probably due to accumulation of myxoedematous fluid.

6. *Relation to Catecholamines*

Thyroid hormones and catecholamines both *potentiate* the action of each other. How? Refer to Table 72.4.

7. *On GIT*

T_4 causes modification of intestinal motility, therefore,

(i) T_4 deficiency decreases the intestinal motility and decrease in food intake produces constipation.

(ii) Conversely, T_4 excess produces diarrhoea due to:
- (a) increase in intestinal motility and food intake;
- (b) increase in gastric emptying, and
- (c) increase in intestinal transit time.

8. *On Water and Mineral Metabolism*

T_4 administration:

(i) In myxoedematous patients causes marked diuresis with excretion of NaCl;

Table 72.4: Relation of catecholamines to thyroid hormones

Catecholamines	T_4
(i) Epinephrine and nor-epinephrine increase BMR, stimulates CNS and increase HR and force of contraction of heart; their action is brief and rapid. (Also refer to page 738)	(i) Thyroid hormones also has the same action, but its action is prolonged and slow (page 686).
(ii) They cannot increase BMR in the absence of T_4.	(ii) Thyroid hormones can potentiate the action of epinephrine and nor-epinephrine and in their presence increase in BMR by T_4 is more.
(iii) They cause stimultion of reticular activating system.	(iii) Same effect since the thyroid hormone by increasing the expression of **catecholamine receptors** increases the catecholamines at the tissue level. Therefore, their actions on CNS and CVS can be: (a) *decreased* after sympathectomy or injection of β-blocking agents (*propranolol*) or reserpine (*i.e.* decrease in catecholamine stores). (b) *increased* due to increased adrenergic activity, by increasing catecholamines release.

(ii) In normal persons causes mild diuresis with loss of K^+ due to cellular breakdown;

(iii) In hyperthyroidism causes mild diuresis with K^+ and Ca^{2+} excretion in urine.

APPLIED

A. GOITER

1. Any enlargement of the thyroid gland is called ***Goiter*** and *anti-thyroid substances* that cause thyroid enlargement are called ***Goitrogens***.
   (i) Goitrogens are the substances that block one or more reactions in the synthesis of thyroid hormone.
   (ii) **A goiter *does not* denote the functional state of the thyroid gland.**
2. If the goitrogen reduces thyroid hormone synthesis to subnormal levels, TSH secretion is increased.
3. Goitrogens lead to increased synthesis of endogenous TSH, which is responsible for the formation of a hypertropic thyroid gland (*Goiter*).
4. ***Goitrogenic agents*** include:
   (i) **Iodide deficiency** – if daily intake of iodine falls below 50 µg (normal: 100-200 µg/day), it decreases the synthesis and secretion of thyroid hormone; so secretion of TSH increases, producing *Goiter* (swelling in the neck) called ***Iodine Deficiency Goiter*** or ***Endemic Goiter***. Most adult patients are clinically ***Euthyroid***. The addition of small amount of iodine (100-200 µg daily) in the form of iodized table salt will prevent its development. **(Fig. 72.6)**
   (ii) **Excess iodide** (page 686).
   (iii) **Monovalent ions** such as perchlorate and thiocyanate etc. (page 682) which block the I^- trapping mechanism (I^- pump).
   (iv) Thiocarbamides (propylthiouracil and methimazole, page 682), which block the coupling of iodine with tyrosine and MIT; also prevent conversion of T_4 to T_3 in extrathyroidal tissue.
   (v) Aminobenzenes (para-aminobenzoic acid-PABA; sulphonamide) which inhibit the conversion of I^- to I.
   (vi) **Vegetables of Brassicaceae family** *e.g.* cabbage, rutabagas, turnip etc. They contain (a) ***Progoitrin*** and (b) ***Progoitrin Activator*** (a heat labile substance), which converts progoitrin into goitrin. ***Goitrin*** is an active anti-thyroid agent, which prevents incorporation of iodine with tyrosine. However, goitrin intake on a normal mixed diet is usually not great enough to be harmful.

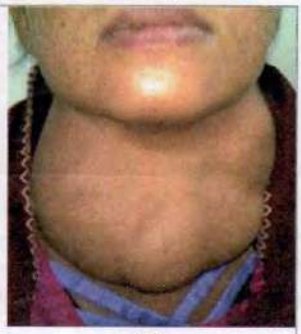
B. HYPOTHYROIDISM

Hypothyroidism is the condition resulting from *reduced* circulating levels of *free* T_4 *and* T_3.

It appears in two forms: *myxoedema* and *cretinism*.

1. ***Myxoedema*** – It is advanced hypothyroidism in adults characterized by swelling of skin and subcutaneous tissues.
   Characteristic features **(Table 72.5 and Fig. 72.7)**
   (i) Goiter, *i.e.*, enlargement of the thyroid gland
   (ii) Puffiness of face with periorbital swelling (page 687) **(Fig. 72.7 A)**
   (iii) Coarsening and loss of scalp hair **(Fig. 72.7 B)**
   (iv) Ptosis, *i.e.*, drooping of upper eyelid **(Fig. 72.7 A)**
   (v) Dry, thickened, rough and yellow skin (page 687) **(Fig. 72.7 C)**
   (vi) Associated features – low BMR, hypersensitive to cold (page 686), low voltage ECG, hoarseness of voice, psychosis (*myxoedematous madness*), memory loss (page 689), increase in S.cholesterol, decreased lactation, impaired fertility and menstrual disturbances page 688).
2. ***Cretinism*** – Children or infants who are hypothyroid from birth are called *Cretins*. It is due to *maternal iodine deficiency* (mainly), and congenital abnormalities of the *foetal hypothalamo-pituitary-thyroid axis*.
   Characteristic features **(Fig. 72.8)**
   (i) gross retardation of mental development;

(A)

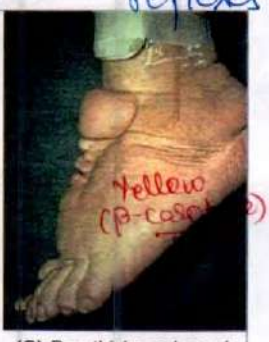


(B)

Fig. 72.6 Iodine Deficiency goiter or Endemic goiter (→)

(A) Ptosis, puffiness of face with periorbital swelling

(B) Coarsening and loss of scalp hair



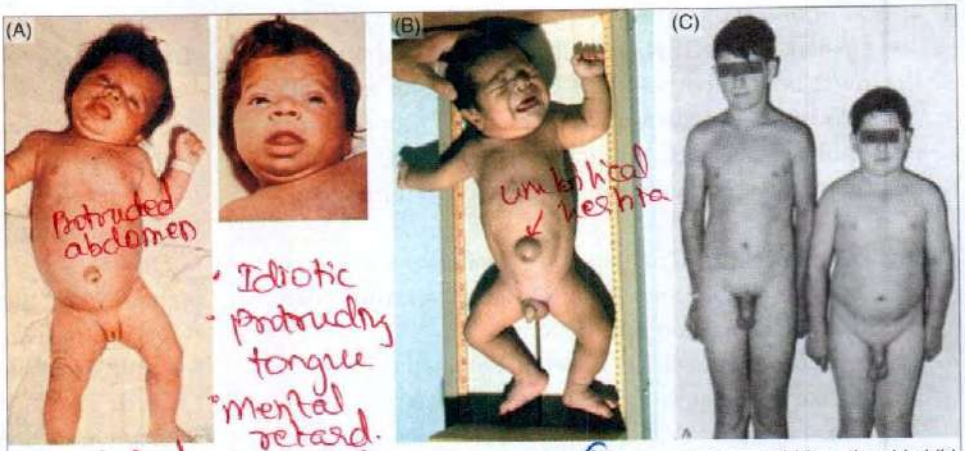
(C) Dry, thickened rough and yellow skin

Fig. 72.7 Myxoedema, hypothyroidism in adults

(ii) dwarfism and stunted growth, due to failure of skeletal and muscular growth;
(iii) protruded abdomen with enlarged protruded tongue;
(iv) failure of sexual development (page 688); and
(v) other characteristic features of hypothyroidism.

Note

Administration of iodine to the mother during the pregnancy can prevent cretinism in the offspring, by providing the foetus with sufficient iodine to synthesize its own thyroid hormones.



{A 8 year old hypothyroid child with growth retardation (right) for comparison with age and sex matched control (left).}

Fig. 72.8 Cretinism, hypothyroidism in neonates (A), in an infant (B) and in a child (C).

C. HYPERTHYROIDISM

It is the condition resulting from *increased* circulating levels of *free* T_4 *and* T_3. The commonest cause is *Grave's Disease* (*Exophthalmic Goiter* or *Thyrotoxicosis*).

Pathogenesis

1. It is an **auto-immune disorder**, as a result plasma cells derived from B-lymphocytes activated by antigens produce:
   (i) *Thyroid stimulation antibodies* – TSA (also called *Long Acting Thyroid Stimulator* – LATS or *Thyroid Stimulating Immunoglobulins* – TSI) – it has the same action as that of TSH; and
   (ii) *LATS protectors* – which prevent inactivation of LATS.
2. **LATS and LATS-protectors** are immunoglobulin of IgG class.
3. 'LATS' combine with receptors on thyroid cell plasma membranes and displace TSH from its binding sites and then act via stimulating cAMP to cause prolonged action (Fig. 72.9). This leads to:
   (i) increased formation and release of T_4 and T_3 from thyroid gland; and
   (ii) increased growth of thyroid gland.
   (i) and (ii) cause diffuse enlargement and hyperplasia of thyroid gland.

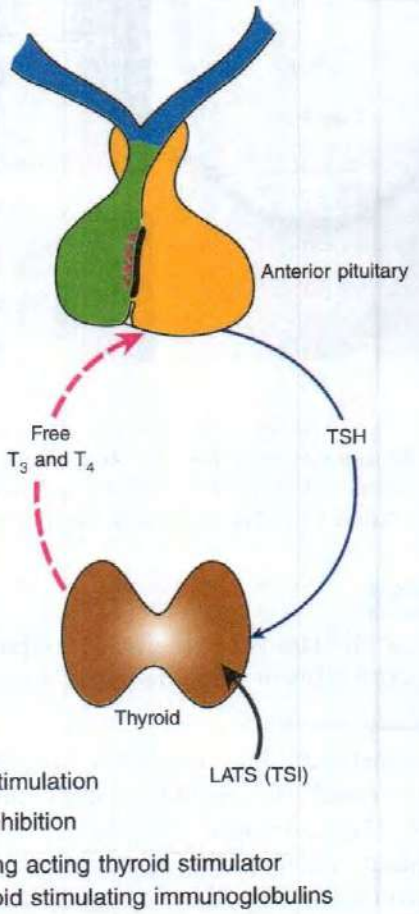


Fig. 72.9 Control of T_3, T_4 and TSH secretion in Grave's disease (size type arrows)

Important Note

Some of the antibodies damage the thyroid gland producing *Hashimoto's thyroiditis* (page 757) which can finally result in hypothyroidism.

Characteristic features (Fig. 72.10)

1. Features of hyperthyroidism (Table 72.5).
2. *Serum TSH* level is normal or decreases.

3. *Exophthalmos i.e.* protrusion of the eye balls (eye balls are pushed forward) with visibility of sclera between the lower lid and cornea. This is due to increased bulk of the orbital content following increased amount of mucopolysaccharides, water, increase in fat, muscle enlargement which gets infiltrated with lymphocytes **(Fig. 72.10 B)**.
   It is postulated that *TSH receptor-stimulating antibodies (TSA)* in the circulation cause release of *cytokines* that promote inflammation and oedema.
4. *Lid retraction* (*i.e.* visibility of sclera between the upper lid and cornea) due to *symphathetic* overactivity **(Fig. 72.10 C)**.
   (3) and (4) result in staring look of the patient (wide open eyes) with periorbital swelling.

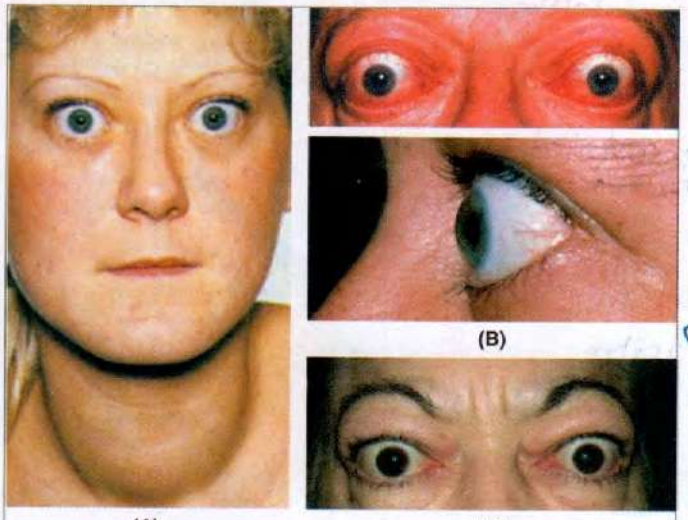


Fig. 72.10 (A) Hyperthyroidism, results from increased circulating levels of "free" thyroid hormones (T_4 and T_3); (B) Exophthalmos (*eye ball pushed forward*); and (C) Lid retraction —**Note:** Visibility of sclera between upper lid and cornea

Note

Exophthalamos occurs in 50% of patients and often precedes the development of frank hyperthyroidism.

Sometimes this condition develops due to the increased T_3 secretion with normal T_4, called ***T_3 Thyrotoxicosis***.
Main differentiating characteristic features between hypothroidism and hyperthyroidism: refer to **Table 72.5**.

ANTITHYROID DRUGS

Reduction of the hypersecretion of thyroid hormones in hyperthyroidism can be achieved by drugs which act in different ways on hormone synthesis and release.

1. **Drugs which inhibit trapping of iodide** (I^-) by the thyroid (page 681).
2. *Thiourylenes i.e.* drugs which inhibit oxidation and organic binding of iodine and also the coupling of iodotyrosines to form T_3 and T_4 (page 681).
3. *Iodine or Iodide:* acts mainly by reducing release of thyroid hormones (page 686).
4. **β-adrenergic blocking drugs** like propranolol, atenolol etc. reduce the CVS, CNS symptoms of hyperthyroidism. Thus are used in preparing patients for thyroidectomy.
5. **Radioactive iodine (^{131}I)**: It is given to destroy the overactive thyroid tissue.

THYROID FUNCTION TESTS

A. BASED ON METABOLIC EFFECTS OF T_4

1. *BMR i.e.* O_2 consumption of the subject under physical and mental rest (Details page 629).
   Normal: ± 20%
   Causes of increase: Hyperthyroidism (increase upto +100%); exercise, fever, pregnancy, anxiety, congestive cardiac failure, etc.
   Causes of decrease: Hypothyroidism (decreases to –30 to –40%); nephrotic syndrome, etc.
2. *Blood Sugar.* Normal (fasting) 70-90 mg/dL, increases in hyperthyroidism and decreases in hypothyroidism.
3. *S. Cholesterol.* Normal: 150-240 mg/dL, increases in hypothyroidism and decreases in hyperthyroidism.
4. *S. Creatinine.* Normal: 0.6 mg/dL, increases in hyperthyroidism and decreases in hypothyrodism.

B. BASED ON HANDLING OF IODINE

1. *Protein Bound Iodine (PBI)*
   Normal: 3.5–7.5 µgm/dL.
   (i) It reflects the index of circulating level of T_4 and T_3. Amount of T_3 is so low as compared to T_4, that T_3 does not contribute practically to PBI.
   (ii) It is the only **single reliable test** to diagnose thyroid functions if done under full precautions.
   (iii) *Disadvantage:* it also measures I_2 containing dyes which do not bind to TBG, therefore,
      (a) **false low** values are due to mercurial diuretics which block the catalytic reaction of estimation; and
      (b) **false high** values are seen in I_2 contamination *e.g.* I_2 containing expectorants or creams, drugs (enterovioform) and radiotherapy.
   (iv) PBI decreases in hypothyroidism, pregnancy and acute thyroiditis and increases in hyperthyroidism and patients on oral contraceptives.
2. *Butanol Extractable Iodine (BEI)*
   Normal: 3–5 µgm/dL; same basis as of PBI; increases in hyperthyroidism and decreases in hypothyroidism.

Table 72.5: Main differentiating features of hypothyroidism and hyperthyroidism

	Hypothyroidism	Hyperthyroidism
1. Definition	Reduced secretion of thyroid hormones, therefore, S. free T_4 and T_3 level decreases; normal: 2 ng/dL and 0.3 ng/dL respectively.	Increased secretion of thyroid hormones, therefore, S. free T_4 and T_3 level increases.
2. Causes: (a) Primary, (b) Secondary	(i) Thyroid removal	(i) Grave's disease *i.e.* exophthalmic goiter;
	(ii) I_2 deficiency in diet	(ii) Thyroid tumours
	(iii) Hashimoto's disease (autoimmune thyroid disease)	(iii) TSH secreting pituitary tumour
	(iv) Pituitary failure resulting in pituitary hypothyroidism	
	(v) Hypothalamus failure leads to hypothalamic hypothyroidism	
3. Based on calorigenic action (*Normal* BMR ±10%)	(i) BMR decreases to –30 to –40%	(i) BMR increases from +10% to +100%
	(ii) Hypersensitive (intolerance) to cold	(ii) Hypersensitive to heat (heat intolerance)
	(iii) Protein metabolism (page 687)	(iii) ***Thyrotoxic myopathy***; weight loss; creatinuria
	(a) ***Myxoedema*** leads to puffy face; weight gain	(a) Undue fatiguability; osteoporosis
	(b) Skin – dry, cold, thickened and rough	(b) Skin: warm, moist and soft
	(iv) CVS (page 687) bradycardia, ↓ SV, ↓ CO, low voltage ECG	(iv) Tachycardia (sleeping pulse rate >90 bpm), ***high output cardiac failure;*** exertional dyspnoea
	(v) Bone marrow (page 687) – normocytic normochromic anaemia	(v) Shift of O_2 dissociation curve to right.
	(vi) Vitamins (page 687) – carotenemia which gives rise to yellow skin	(vi) Vitamin B and C deficiency symptoms
	(vii) Lactation (page 687) – decreases.	(vii) Increases
	(viii) Gonads (page 688) – Menstrual irregularities	(viii) Scanty periods
4. On carbohydrate metabolism (page 688)	Low blood sugar	Precipitates diabetes mellitus (***thyroid diabetes***)
5. On lipids (page 688)	Serum cholesterol, triglycerides and phospholipids increase.	All these lipid levels decrease
6. CNS (page 688)	(i) ***Myxoedematous madness*** (psychosis)	(i) Overexcitability, tremors, irritability, nervousness, etc.
	(ii) Knee jerk: reaction time increases	(ii) decreases
	(iii) Memory loss	
	(iv) Hoarseness of voice	
7. Growth & development	Slow	Rapid
8. GIT (page 689)	Constipation and anorexia	Diarrhoea and hyperphagia (increased food intake)

3. ***Radioactive Iodine Uptake*** → Graphs enough
Radioactive studies **(Fig. 72.11)**.
(i) Normal thyroid can concentrate I_2 10,000 times more than the other tissues. Half life of ^{123}I, ^{125}I, ^{131}I and ^{132}I is 12 hours, 60 days, 8 days and 2–3 hours respectively.
(ii) Radioactive iodine uptake values must be interpreted with the physiology of I_2 metabolism.

Therefore,

(a) **On diet high in I_2** content, ^{123}I uptake is low, even though thyroid functions may be normal, because I^- pool is so large that the traces of radioactivity are excessively diluted. Conversely,

(b) ^{123}I uptake is high without hyperthyroidism, in individuals whose daily I_2 intake is adequate to prevent I_2 deficiency goiter but chronically lower than the average intake.

(iii) Patient should not be given any I_2 medication for one month, then 25 μ curies of radioactive iodine (^{123}I) is given orally in 100 mL water; thyroid uptake is determined by placing a γ-ray counter over the neck. An area over the thigh is also counted and count in this region is substracted from the neck count to correct for non-thyroidal radio-activity in the neck.

(iv) *Normal* radioactive iodine (RAI_2) uptake by thyroid is 20-40% and rest is excreted.

(a) In *hyperthyroidism* I^- is rapidly incorporated into T_4 and T_3 and these are released at an accelerated rate, therefore, amount of RAI_2 in thyroid gland rises rapidly, >60%, but it then levels off and may start to decrease within 24 hours (at a time when the I_2 uptake in normal subject is still rising). RAI_2 uptake at 3 hours is more likely to be abnormal than the 24 hours uptake in hyperthyroid patients.

(b) In *hypothyroidism* – RAI_2 uptake is low, <20%. Large amounts of RAI_2 destroy thyroid tissue, because the radiation kills the thyroid cells; therefore, useful in some cases of thyroid cancer.

Important Note

Diagnostic use of RAI_2 uptakes has become rare because of availability of methods for accurate measurement of $S.T_4$, $S.T_3$ and S.TSH. Also large amounts of RAI_2 destroy thyroid tissue because of radiation effects.

4. ***T_3 Suppression Test***

It is useful in suspected cases of thyrotoxicosis. Thyroxine (T_4) is given orally for two days; in euthyroids (normal functioning thyroid) radioactive iodine uptake should decrease because of T_3 suppression, while in thyrotoxicosis it does not decrease.

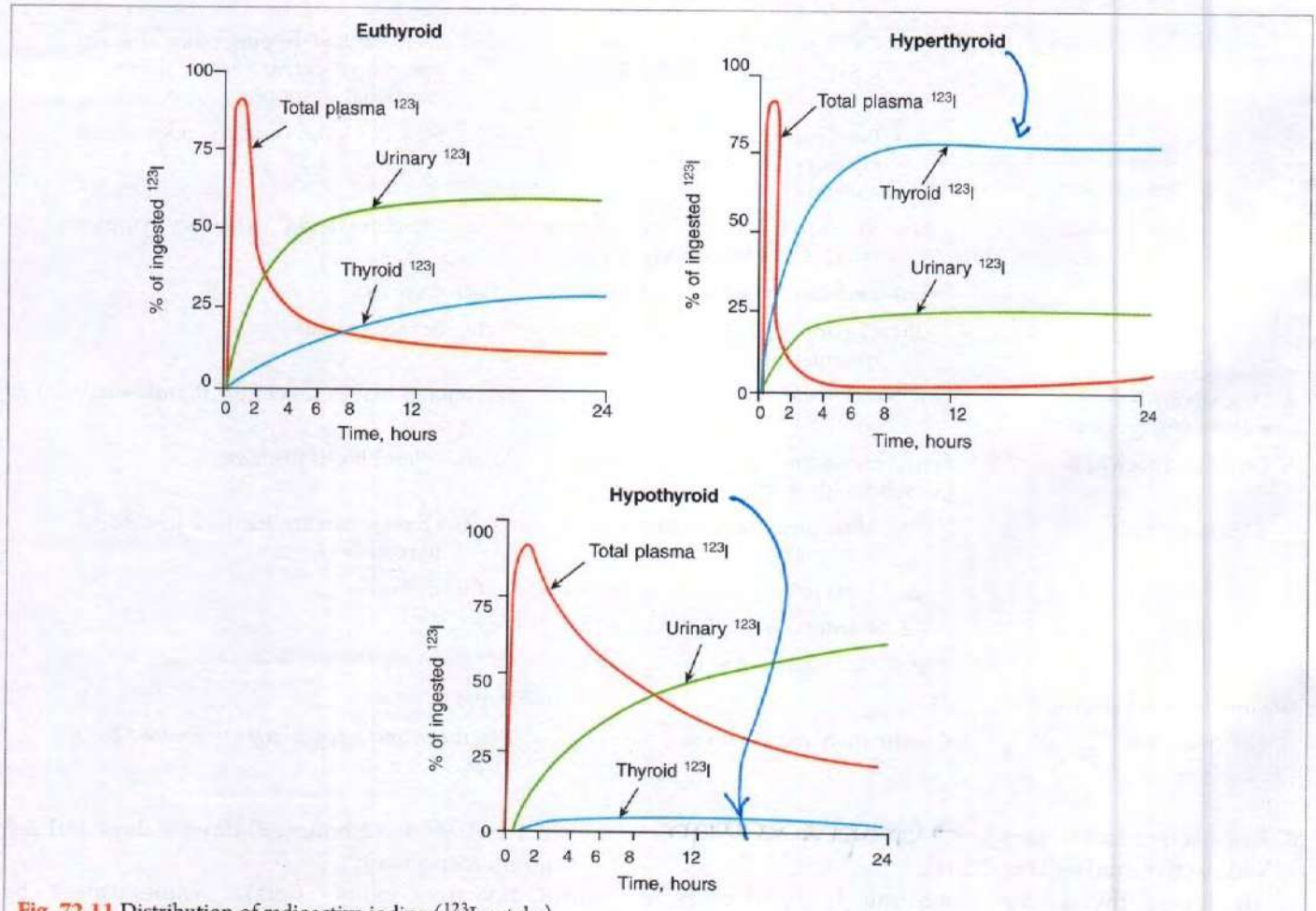


Fig. 72.11 Distribution of radioactive iodine (^{123}I uptake)

5. *Serum Thyroid Hormone and TSH Levels*
These are regarded as one of the **best tests to assess thyroid functions** (page 685) and can be accurately measured by radio-immunoassays. Normally, there is marked inverse relationship between serum free thyroid hormone and TSH levels.

Important Notes

(i) In *primary hypothyroidism* the S.TSH is abnormally high and is further raised by administration of TRH.
(ii) In *secondary hypothyroidism* due to pituitary deficiency, S.TSH level is reduced with normal response by TRH administration.
(iii) In *secondary hypothyroidism* due to hypothalamic hypothyroidism, S.TSH level is reduced but get raised following a test dose of TRH.
(iv) In hyperthyroidism, S.TSH levels are often undetectable and do not increase after administration of TRH.

See Biochem. Organfunc. tests.

C. OTHER INVESTIGATIONS

1. *Radiography*. It is done for:
(i) determining position of the trachea;
(ii) diagnosis of retro-sternal goiter, and
(iii) any evidence of bony metastasis of thyroid cancer.
2. *Indirect Laryngoscopy*. It is done to:
(i) confirm diagnosis of involvement of recurrent laryngeal nerve;
(ii) confirm whether vocal cords are paralysed or not.
3. *Biopsy* from thyroid gland for histo-cytological examination.
4. *Urinary Calcium Loss* – Normal: 100 mg per day, decreases in hypothyroidism and increases in hyperthyroidism.

* Isotopic Scan

	Normal	Hyperthyroidism	Hypothyroidism
Total $S.T_4$	3-8 µg/dL	↑s	↓s
Total $S.T_3$	0.15 µg/dL	↑s	↓s
Free $S.T_4$	2 ng/dL	↑s	↓s
Free $S.T_3$	0.3 ng/dL	↑s	↓s
S.TSH	0.2–5 µIU/mL	↓s	↑s

Summary: Thyroid function tests : Salient features

Test	Hypothyroidism	Hyperthyroidism
A. Based on metabolic functions		
1. BMR (normal: ±10%)	decreases to –30% to –40%	increases from +10% to +100%
2. S. Creatinine (*normal*: 0.2-0.6 mg/dL)	decreases	increases
3. Fasting blood sugar (*normal*: 50-90 mg/dL)	decreases	increases
4. S. Cholesterol (*normal*: 120-200 mg/dL)	increases	decreases
B. Based on handling of Iodine		
1. Total $S.T_4$ (3-8 µg/dL); $S.T_3$ (0.15 µg/dL)	decreases	increases
2. Free $S.T_4$ (2 ng/dL); free $S.T_3$ (0.3 ng/dL)	decreases	increases
3. Protein Bound Iodine (PBI) (*normal*: 3.5-7.5 µg/dL)	decreases	increases
4. Butanol Extractable Iodine (BEI) *normal*: 3-5 µg/dL	decreases	increases
5. RAI^{123} uptake (*normal*: 20-40%)	decreases <20%	increases >60%
6. Serum TSH level (*normal* 2.3 µU/mL)	(i) primary hypothyroidism: increases by 10 folds (ii) secondary hypothyroidism: decreases	decreases or undetectable
C. Others		
1. Urine Ca^{2+} loss (normal 100 mg/day)	decreases	increases

Study Questions

1. **Describe the critical role of iodine in the thyroid gland. How its transport is controlled?**
2. **Give the role of the hypothalamus and pituitary in regulating thyroid functions.**
3. **What will happen and why?**
   (i) If thyroid gland is removed in an adult individual?
   (ii) If I^- pump gets inhibited?
   (iii) To protein metabolism if T_4 is administered to an individual suffering from hypothyroidism?
   (iv) To serum cholesterol levels in myxoedema?
   (v) If one year old child suffers from hypothyroidism?
   (vi) If T_4 is administered to a normal person?
   (vii) If TSH is administered in an individual with I_2 deficiency?
   (viii) To T_4 secretion if I_2 is ingested in large amounts?
   (ix) To functional state of thyroid gland if intake of vegetables of Brassicaceae family is increased?
   (x) To T_3, T_4 and TSH levels in Grave's disease?
4. **Write short notes on:**
   (i) functions of thyroid cells and thyroid gland
   (ii) formation of thyroid hormones
   (iii) Myxoedema and cretinism
   (iv) high output cardiac failure
   (v) relation of catecholamine to T_4
   (vi) role of T_4 in growth and development
   (vii) effects of TSH on thyroid gland
   (viii) role of iodine on thyroid functions
   (ix) endemic goiter
   (x) characteristic features of Grave's disease
   (xi) LATS
   (xii) antithyroid drugs.
   (xiii) Differences between T_3 and T_4
   (xiv) Goitrogens
5. **Give physiological basis of:**
   (i) mechanism of action of antithyroid drugs
   (ii) calorigenic actions of T_4
   (iii) thyrotoxic myopathy
   (iv) carotenemia in hypothyroidism
   (v) non-pitting oedema of myxoedema
   (vi) high sleeping pulse rate in hyperthyroidism
   (vii) muscle weakness in both hypo and hyperthyroidism
   (viii) diabetes mellitus in hyperthyroid patients
   (ix) exophthalmos and lid retraction
   (x) myxoedema madness
   (xi) use of T_4 metabolites as cholesterol lowering agents
   (xii) alteration of thyroid activity impairs fertility in women
   (xiii) administration of I_2 preparation to individual prior to thyroid surgery
   (xiv) a person suffering from hypothyroidism is advised to avoid cabbage in his diet
   (xv) functional thyroid state during pregnancy in which concentration of thyroid binding protein is increased
   (xvi) Use of RAI in treatment of thyroid abnormalities
   (xvii) Primary and secondary hypothyroidism
   (xviii) Endemic goiter
6. **Is thyroid gland absolutely essential for life? Justify.**
7. **Describe briefly the role of T_4 on the development activity of the nervous system.**
8. **Early diagnosis and treatment of cretinism is vital. Explain.**
9. **A person suffering from hypothyroidism can be diagnosed on phone. Explain.**
10. **Justify: cretin is an idiot child.**
11. **How is T_4 secretion maintained on day-to-day basis?**
12. **Which is the main site of negative feedback mechanism in controlling TSH secretion? Explain.**
13. **List the various tests to assess the thyroid functions. Which test is most reliable and why?**
14. **Can T_4 be used to promote weight loss? Explain.**
15. **Describe the role of thyroid hormones in homeostasis and development.**
16. **Draw well labelled diagram:**
   (i) Iodine metabolism
   (ii) Control of TSH secretion
   (iii) Control of T_3, T_4 and TSH secretion in Grave's disease
   (iv) Radio-active iodine uptake

MCQs

1. **Colloid is:**
   (a) A glycoprotein
   (b) Thyroglobulin
   (c) Thyroglobulin containing iodine
   (d) Tyrosine molecule

2. **Total removal of thyroid gland in adults produces:**
   (a) Poor resistance to cold
   (b) Mental retardation
   (c) Dwarfism
   (d) All of the above

3. **The normal storage of thyroid hormones in thyroid gland is for:**
   (a) 1 week (b) 1 month (c) 2 months (d) 3 months

4. **Iodide (I^-) pump is inhibited by all of the following *except*:**
   (a) Metabolic poisons
   (b) Monovalent anions
   (c) TSH
   (d) Inhibition of Na^+–K^+ pump

5. **Euthyroid refers to:**
   (a) Hyperfunctioning thyroid state
   (b) Hypofunctioning thyroid state
   (c) Normal clinical thyroid state
   (d) High thyroid binding protein levels

6. **TSH is secreted at a higher rate:**
   (a) After removal of one lobe of thyroid
   (b) in warm adapted than in cold adapted persons
   (c) When BMR falls
   (d) During emotional stress

7. **Main hormone producing negative feed-back control of TSH secretion is:**
   (a) Free T_3 (b) Free T_4 (c) Iodine (in high doses) (d) All of the above

8. **Administration of exogenous thyroid hormone would likely lead to all of the following *except*:**
   (a) Increased O_2 consumption by brain
   (b) Decreased secretion of T_3
   (c) Decreased iodide uptake by thyroid gland
   (d) Inhibition of TSH secretion
   (e) Low blood sugar

9. **Yellowish tint of skin in myxoedema is due to:**
   (a) Anaemia (b) Increased bilirubin level (c) Decreased cholesterol (d) Carotenemia

10. ***False* statement regarding goiter:**
    (a) It is simply the enlargement of thyroid gland
    (b) Does not denote functional status of thyroid gland
    (c) Prolonged TSH secretion may produce it
    (d) Associated with increased thyroid hormones secretion

11. ***True* statement regarding endemic goiter:**
    (a) Also called iodine deficiency goiter
    (b) Occurs if intake of iodine falls below 100-200 µgm/day
    (c) Associated with normal thyroid hormone secretion
    (d) Associated with decreased TSH secretion

12. ***False* statement regarding LATS:**
    (a) Are thyroid stimulating immunoglobulins
    (b) It has same action as that of TSH
    (c) Displaces TSH from its binding sites
    (d) Cause enlargement of thyroid gland by increasing TSH secretion

13. **T_3 thyrotoxicosis:**
    (a) Also called Grave's disease
    (b) Develops due to increased T_3 secretion with normal T_4
    (c) Serum TSH level is increased
    (d) Iodine excess (major factor in its development)

14. **Best tests to assess thyroid functions is:**
    (a) Assessment of BMR
    (b) PBI estimation
    (c) Radioactive iodine uptake
    (d) Serum TSH and free thyroid hormone levels

15. **Thyroid perioxidase is required for all of the following steps in thyroid hormone synthesis *except*:**
    (a) Iodide uptake
    (b) Oxidation of iodide
    (c) Iodination of active iodide
    (d) Synthesis of iodothyronines

16. **Thyroid secretes approx. ....% T_4 and ....% T_3:**
    (a) 20; 80 (b) 10; 90 (c) 80; 20 (d) 90; 10

17. **Reverse T_3 is:**
    (a) Secreted from T_4 having no hormonal action
    (b) Secreted from T_4 having hormonal action
    (c) Principal hormone secreted by thyroid
    (d) More active than T_3

18. **Inhibitory effects due to I^- excess last for:**
    (a) As long as therapy is continued
    (b) 1-2 weeks
    (c) 1-2 months
    (d) 1-2 years

19. *Not* an action of thyroid hormone:
(a) Raises BMR (b) Increases cardiac output (c) Decreases cholesterol (d) Loss of libido

20. Regarding Myxoedema the following are *true except*:
(a) Swollen oedematous look of the face (b) Impotency, amenorrhoea etc.
(c) Increased BMR (d) Dullness, loss of memory

21. A patient with hypothyrodism is likely to have:
(a) Subnormal body temperature (b) Lid retraction
(c) Exophthalmos (d) Moist hands and feet

22. Hyperthyroidism is associated with:
(a) Positive nitrogen balance (b) A decreased urinary excretion of calcium
(c) A rise in level of plasma protein which binds thyroxine (d) Certain feature due to excessive beta adrenergic stimulation

23. *Not a true* statement regarding the lid retraction:
(a) Indicated by visibility of sclera between the upper lid and cornea
(b) Occurs due to sympathetic over-activity
(c) Same as exophthalmos
(d) A common finding in Grave's disease

24. Removal of thyroid gland leads to:
(a) High blood cholesterol level (b) Prolongation of reaction time for stretch reflexes
(c) Fine tremor of finger (d) Flattening of oral glucose tolerance curve

25. BMR is decreased in:
(a) Hyperthyroidism (b) Increased body temperature
(c) Cushing's syndrome (d) Nephrotic syndrome

Answers

1. (c)	2. (a)	3. (d)	4. (c)	5. (c)	6. (a)	7. (a)	8. (a)	9. (d)	10. (d)
11. (a)	12. (d)	13. (b)	14. (d)	15. (a)	16. (d)	17. (a)	18. (b)	19. (d)	20. (c)
21. (a)	22. (d)	23. (c)	24. (c)	25. (d)					

Chapter 73

The Parathyroids, Calcitonin and Vitamin D

I. Calcium metabolism

II. Phosphate metabolism

III. Physiology of bone

IV. Hormones regulating calcium metabolism: Vitamin D; Parathormone; Calcitonin

V. Applied: Rickets, Osteomalacia, hypo and hyperparathyroidism

PHYSIOLOGICAL ANATOMY

A. Role of Calcium (Ca) in Physiological Processes

1. *Hemostasis.* Ca is necessary for the activation of clotting enzymes in the plasma as well as the enzymes involved in producing inflammatory response.
2. Ca controls membrane excitation and Ca^{2+} influx occurs during the excitatory process of nerve and muscle. Excitable membrane contains specific Ca^{2+} channels. Ca^{2+} entry does not require an active transport process since *Ca concentration gradient on outside to inside the cell is 12,000 to 1.*

   $[Ca^{2+}]$ in ICF: 10^{-7} mol/L; and
   ECF: 1.2×10^{-3} mol/L.
3. Ca is bound to cell surface and has a role in *stabilization of the membrane* and intercellular adhesion.
4. Ca is necessary for *muscular contraction* (excitation-contraction coupling).
5. Ca is essential in all *excitation-secretion processes e.g.* the release of hormone by endocrine cells and release of other products by exocrine cells. It is also essential for *neurotransmitter release.*
6. Hormone action as 2° messenger.

B. Distribution, Absorption and Fate of Calcium in the Body

1. Total body calcium is approx. 1100–1200 gms (1.5% of body weight); out of this:
   (i) More than 99% is in the skeleton (bones),
   (ii) 4-5 gms in soft tissues (mainly muscles), and
   (iii) 1 gm in the ECF.
2. *Normal serum Ca* is 9-11 mg/dL (average: 10 mg/dL).
3. *Plasma calcium* occurs in *two forms:*
   (i) *Diffusible:* 5.36 mg/dL, *i.e.* 54-55%. It is of two types:
   (a) Ionized Ca^{2+} or *free* Ca^{2+} in body fluids (4.72 mg/dL or 47%). It is ***physiologically active.*** Its level depends on Ca absorption from the GIT.
   (b) Non-ionized Ca^{2+} *i.e.* Complexed Ca^{2+} combined with HCO_3^-, citrate and phosphate (0.64 mg/dL or 5%). It is physiologically inactive.
   (ii) *Non-diffusible:* 4.64 mg/dL or 45-46%. It is protein bound, specially to albumin; non-ionized, *physiologically inactive.* It constitutes a reserve of Ca to help maintain the constancy of $[Ca^{2+}]$. Its concentration decreases when plasma albumin concentration decreases, such as in nephrosis; its concentration increases in diseases in which abnormal plasma protein occurs.
4. **Daily dietary Ca intake** is approx. 1 gm. It is absorbed largely in the duodenum, jejunum and also from ileum by active transport process (mainly) and to some extent by passive diffusion. After oral administration Ca^{2+} absorption is completed within 4 hours.
   (Factors affecting Calcium absorption from GIT - Refer to **Table 73.1**).
5. In the intestine daily dietary Ca intake of 1000 mg is supplemented by 600 mg of Ca which enters the gut in various secretions. Of the total 1600 mg (1000 + 600 mg), 900 mg is excreted in the faeces and 700 mg is absorbed into the body *i.e.* a net gain of 100 mg of Ca which enters the ECF Ca pool **(Fig. 73.1)**. Ca in this pool is constantly being exchanged with:
   (i) by absorption from and excretion into the intestine,
   (ii) by glomerular filtration and reabsorption by the kidney,

Table 73.1: Factors affecting calcium absorption from GIT

Increased by	Decreased by
(i) Acidity in the stomach.	(i) Presence of alkalies which form insoluble Ca soaps.
(ii) Bile and bile salts – increase the solubility of Ca salts.	(ii) Reduced secretion of bile and bile salts – this leads to excess of unabsorbed fatty acids in the GIT which forms insoluble Ca soaps.
(iii) Presence of phosphate in adequate amounts in the diet.	(iii) Excess of inorganic phosphate, oxalate or phytic acid – convert Ca^{2+} into insoluble unabsorbable form.
(iv) Hypocalcemia – seen during pregnancy and lactation; following low Ca intake.	(iv) Hypercalcemia – seen following high Ca intake which decreases the Ca absorption from the GIT by inhibiting 1,25 DHCC.
(v) Vitamin D_3-1,25 Dihydroxychole-calciferol (1,25 DHCC).	
(vi) Parathormone (PTH).	
(vii) Growth hormone (GH).	
(viii) High protein diet.	

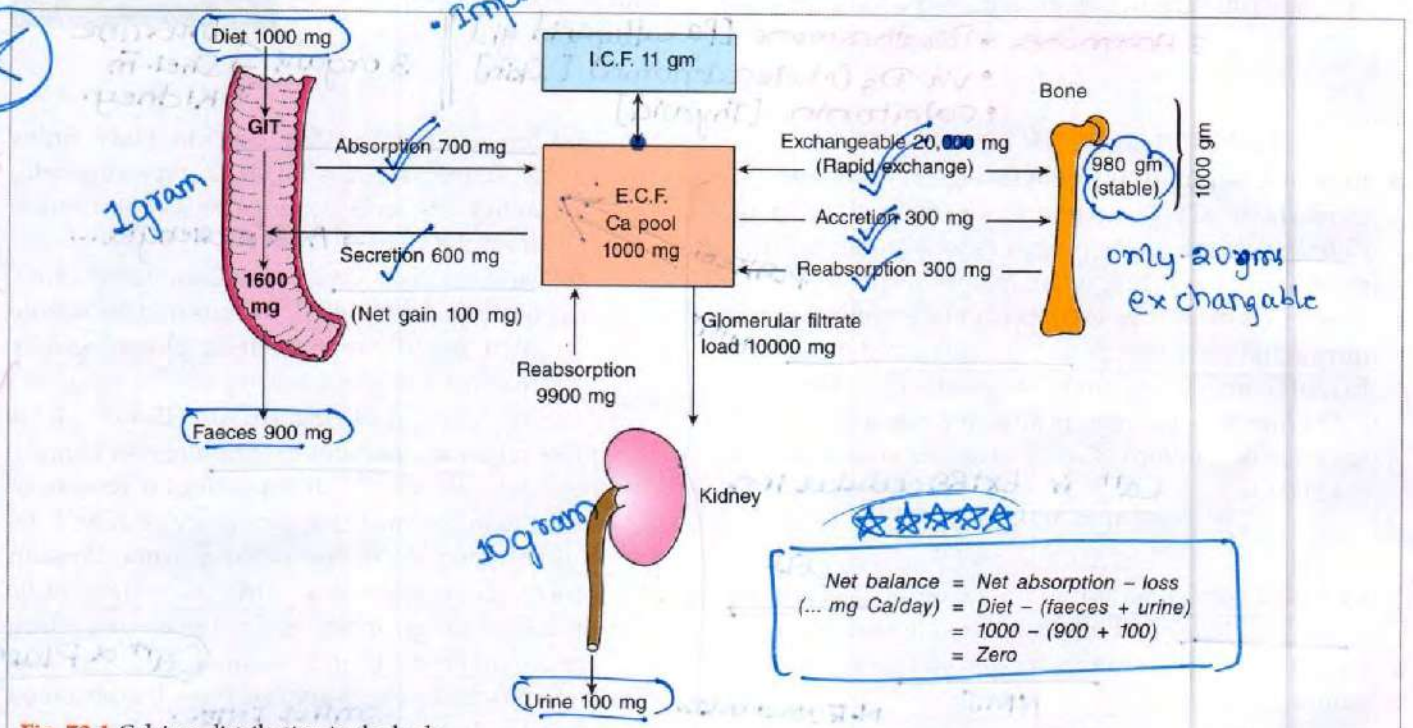


Fig. 73.1 Calcium distribution in the body

(iii) by ICF Ca, and
(iv) by ion exchange Ca in bone crystals.

(A) **In GIT**

Ca absorption undergoes adaptation *i.e.* it is high when Ca intake is low and it is low, when Ca intake is high.

(B) **In kidneys,**

(i) A large amount approx. 10 gms of Ca is filtered each day, of which 98-99% (9.9 gms) gets reabsorbed (60% in PCT, 38-39% in ascending limb of loop of henle and DCT). This Ca reabsorption is increased by parathyroid hormone, and decreased by cortisol and excess of thyroid hormone.

(ii) Thus, only 100 mg/day Ca is excreted in urine, thereby maintaining the balance.

(iii) Urinary excretion of Ca is largely independent of diet and is controlled mainly by serum Ca level; that is, when it is >11 mg/dL, its excretion in urine increases and when it is <7-8 mg/dL, it decreases.

(C) **Bone** contains approx. 1000 gms of Ca, which is of *two types*:

(i) A readily exchangeable reservoir, of which 20 gms is exchanged daily. Serum Ca is in equilibrium with this type of Ca.

(ii) A large pool of 980 gms constitute *stable* calcium, which is only slowly exchangeable. Only the process of mineral accretion and bone resorption

involve net movement of Ca into or out of this pool. This amounts to only 300 mg/day.

PHOSPHATE METABOLISM

1. It is found in ATP, cAMP, 2,3 DPG (diphosphoglyceric acid).
2. **Total body phosphate** (inorganic phosphorus) is 500-800 gms, approx. 80-85% of this is in the skeleton and remaining in the intracellular phosphate pool.
3. S. inorganic phosphate level (mostly occurs as HPO_4^{2-}):
   (i) in adults 2.5-4 mg/dL
   (ii) in children 5-6 mg/dL.
4. *Functions*
   (i) Gives rigidity to bones and teeth.
   (ii) Helps in the regulation of pH of blood and urine.
   (iii) Important in the regulation of glycolysis and energy metabolism.
   (iv) Forms a part of essential organic molecules *e.g.* nucleic acids (DNA, RNA); phospholipids and nucleotides.
5. *Distribution and Fate*
   (i) Approx. 3 mg/kg/day of phosphorus enters the bone with an equal amount leaving via reabsorption.
   (ii) Inorganic phosphorus in plasma is filtered in glomeruli of which 85-95% gets reabsorbed *actively* in PCT. Its excretion in urine is:
      (a) *increased by:* vitamin D excess; hyperparathyroidism; a high phosphate diet;
      (b) *decreased by:* GH, during lactation; hypoparathyroidism; a low phosphate diet.
   (iii) Inorganic phosphorus is absorbed in duodenum and other parts of small intestine by active transport and passive diffusion. Its absorption is directly related to the dietary intake and is increased by 1,25 DHCC, GH, parathormone, acids and by a low-calcium diet.
6. *Relation between plasma Ca and phosphate (PO_4^{3-})*
   (i) Serum Ca^{2+} varies inversely with the S. inorganic PO_4^{3-} level. However the product $[Ca^{2+}] \times [PO_4^{3-}]$ remains constant, called the **Solubility Product**. In rickets, in which absorption of Ca and phosphate is reduced, solubility product falls (page 709).
   (ii) The calcium to phosphorus ratio in bone is about 1.7 : 1.
7. Plasma **phosphate deficiency** leads to a fall in 2, 3 DPG and ATP concentration within the RBCs, and hence decreased release of O_2 from the haemoglobin to the tissues.

PHYSIOLOGY OF BONE

1. *Structure* – Bone is a living connective tissue and consists of:
   (i) 20% – collagenous protein 'matrix' (or *osteoid*) which comprises of protein collagen fibers (mainly) and ground substance *i.e.* an amorphous gel of mucopolysaccharides. Collagen is a fibrous protein rich in glycine, proline and hydroxyproline. The organic material gives the bone its *toughness and resilience (elasticity)*.
   (ii) 35% – *mineral salts* chiefly of phosphates with Ca^{2+} (mainly); Na^+, Mg^{2+} and CO_3^{2-}. The minerals give the bone its *rigidity and hardness*.
   (iii) 45% is water.
   For the maintenance of normal bone structure adequate amounts of both organic matrix and mineral salts must be available.
2. Bone is a cellular and well vascularized organ. **Total bone blood flow**: 200-400 mL/min. Bone is constantly being reabsorbed and reformed which is under the cellular control viz. *osteoblasts, osteocytes and osteoclasts.*
   (i) *Osteoblasts* – They are nuclear cells, *i.e.* highly differentiated cells that are non-mitotic in their differentiated state. These are ***bone forming cells*** and are located on the bone forming surface (*endosteum*). They synthesize and secrete collagen, forming a matrix around themselves which then calcify. They contain ***abundant alkaline phosphatase activity***. Therefore, osteoblasts form bone matrix and when they become surrounded by new bone, they become *osteocytes*.
   (ii) *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 a functional syncytium. Osteocytes provide rapid and transient movement of Ca from bone into the ECF space (***osteolytic activity*** *i.e. bone resorption*). Their activity is *stimulated by* parathyroid hormone; ↓ by calcitonin.
   (iii) *Osteoclasts* – They are large multinuclear giant cells containing numerous lysosomes. They erode and resorb previously formed bone. They have slow but sustained action. These cells ***contain acid phosphatase*** and appear to phagocytose bone, digesting it in their cytoplasm. The collagen breakdown products (pyridinolines) can be measured in the urine as an index of the rate of bone resorption.
3. *Mechanism of bone formation* **(Fig. 73.2)**
   (i) **Osteoblasts** in bone form 'microfibrils' (a collagen membrane), few cm in length and 15-30 nm in

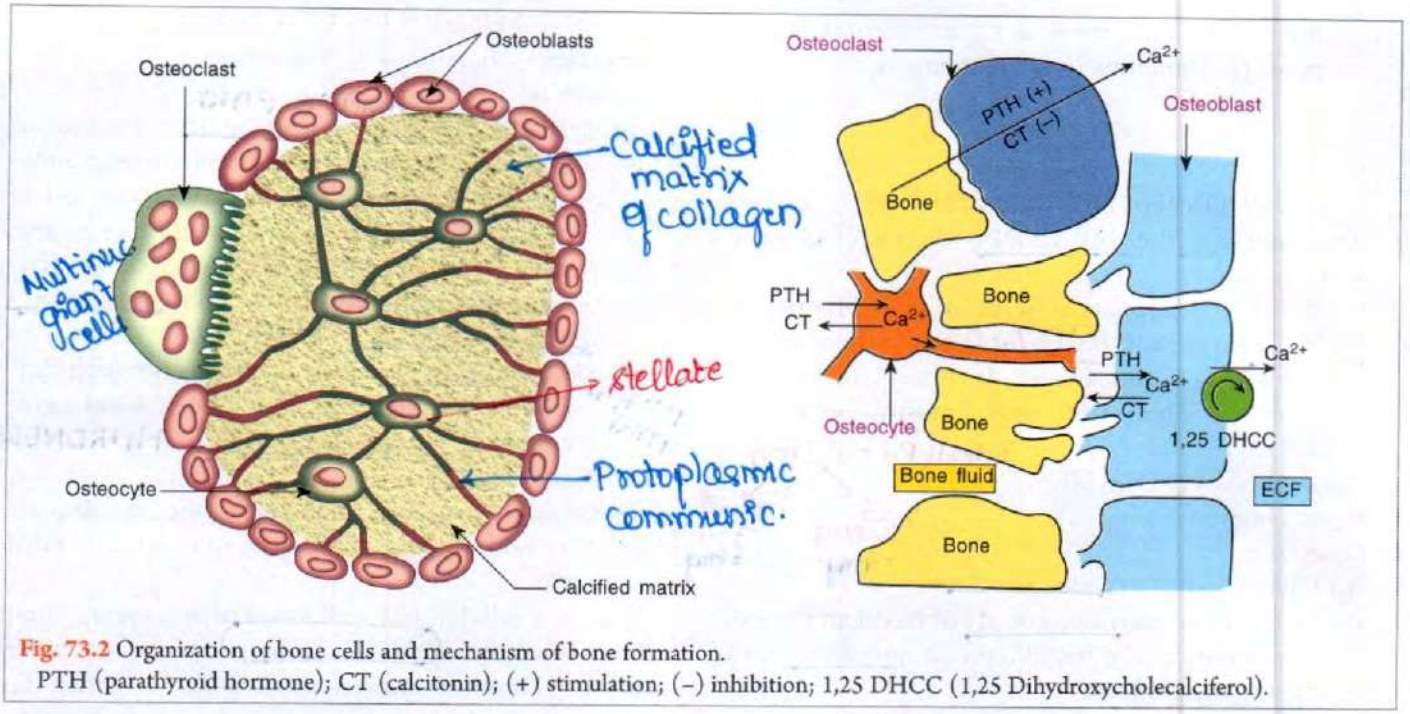


Fig. 73.2 Organization of bone cells and mechanism of bone formation.
PTH (parathyroid hormone); CT (calcitonin); (+) stimulation; (–) inhibition; 1,25 DHCC (1,25 Dihydroxycholecalciferol).

diameter. They separate the bone fluid from ECF and connect via protoplasmic processes to osteocyte deep in the bone.

(ii) During the normal process of mineralization, the mineral ions accumulate within membrane-bound vesicles. The *process of mineralization* is controlled mainly by parathyroid hormone (PTH), calcitonin (CT) and 1,25 DHCC.

(iii) PTH increases 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 can be carefully regulated. T_4, GH, adrenal glucocorticoids and gonadal hormones also participate in these processes.

(iv) Whether calcium phosphate precipitates out of solution depends upon the product of concentration of calcium and phosphate, *i.e.* the ***Solubility Product*** (page 709). For a certain value of this product, the solution is saturated. Whenever $[Ca^{2+}] \times [PO_4^{3-}]$ exceeds solubility product, calcium-phosphate precipitates.

(v) Associated with osteoblast in new bone is an *alkaline phosphatase* that hydrolyzes phosphate esters. The phosphate liberated by ester hydrolysis increases the concentration of phosphate in the neighbourhood of the osteoblast to a point where the solubility product is exceeded and calcium phosphate precipitates.

(vi) Bone formation is of ***three types***:

(a) ***Endochondral*** *i.e.* bone formation takes place after preliminary formation of cartilage. During foetal development, most of the bones are formed in this way.

(b) ***Membranous***, in which bone formation occurs without a cartilaginous phase. Examples: clavicles, mandibles.

(c) ***Endosteal***, in which bone formation occurs as a part of a constant process of remodelling. (see below)

4. ***Resorption (or absorption) of bone.*** It is brought about by osteoclasts and osteocytes, both of which along with osteoblasts increase their Ca permeability in response to PTH and draw Ca out of the bone fluid. The relationship between inorganic and organic phases of bone is so intimate that resorption of bone must involve the destruction of both matrix and mineral.

Important Notes

1. The bone formation and bone destruction go on continuously and simultaneously throughout the life. This cycle takes about 3 months, though their rates change with age and vary in different parts of the skeleton.
2. Obesity protects against bone loss and it has been observed that there is a neuroendocrine control of bone mass via *leptin* (page 1007).

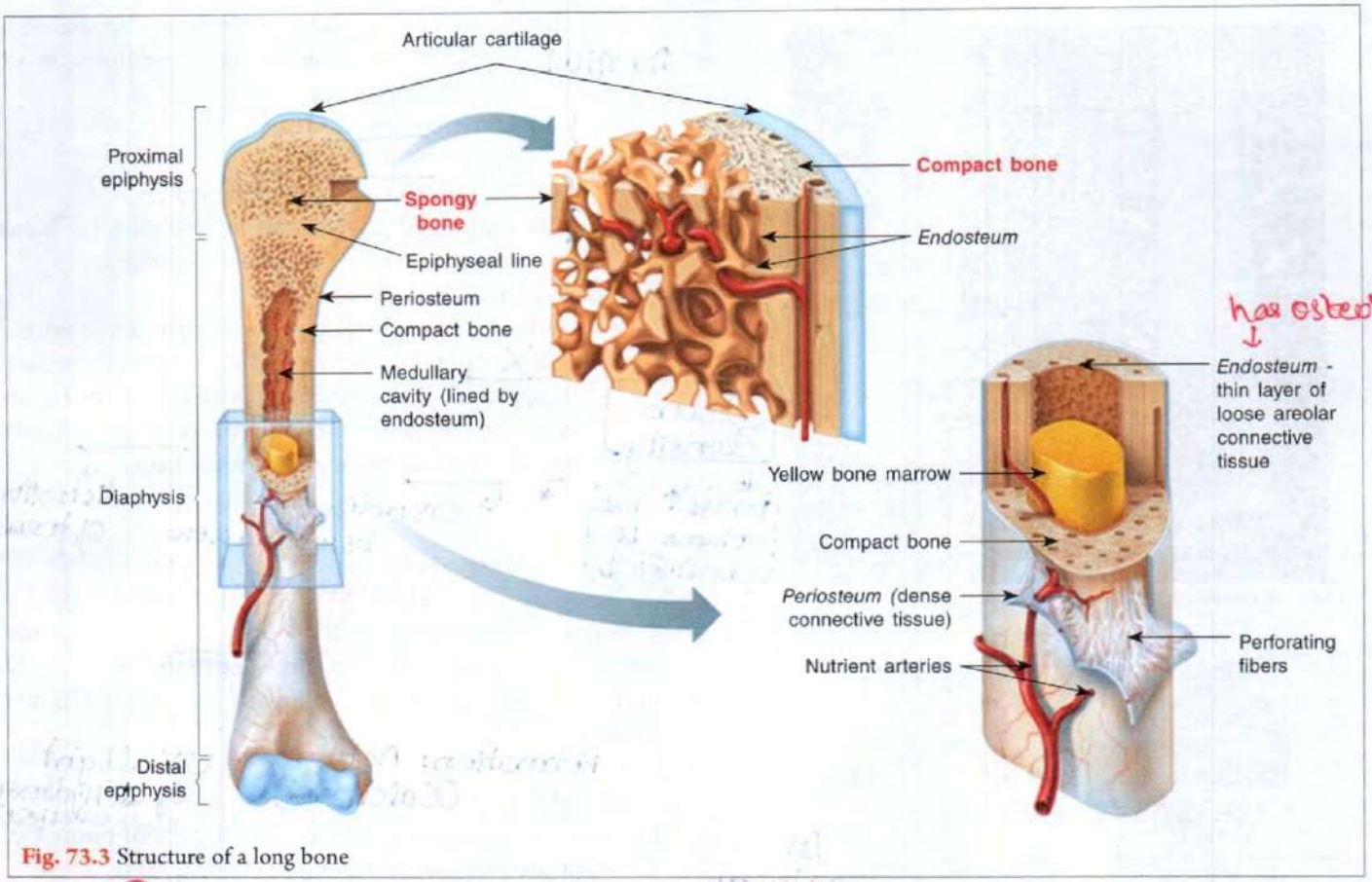


Fig. 73.3 Structure of a long bone

5. ***Bone Growth***

(i) During bone growth, specific areas at the end of each long bone (*epiphyses*) are separated from the shaft of the bone by a plate of actively proliferating cartilage (***epiphyseal plate***) **(Fig. 73.3)**. Growth in bone length occurs as this plate lays down new bone on the end of the shaft. The width of epiphyseal plate is proportionate to the rate of growth. Width is affected by number of hormones but markedly by GH via somatomedin and IGF-I (page 663).

(ii) Changes in the width of the tibial epiphyseal plate are used as the end point in the ***Tibia Test***.

(iii) Linear bone growth can occur as long as the epiphyses are separate from the shaft of the bone, but such growth ceases after the epiphyses unite with the shaft (***Epiphyseal Closure***). The last epiphyses closes after puberty. The normal age at which each of the epiphyses closes is known, and the ***Bone Age*** of an individual can be determined by X-raying the skeleton and noting which epiphyses are open or closed.

(iv) **Morphologically, bone is of two types:**

(a) ***Compact*** or ***cortical bone*** which makes up of the outer layer of bone with a low surface to volume ratio.

(b) ***Trabecular*** or ***Spongy bone*** which lies inside the compact bone with a high surface to volume ratio.

6. ***General terms***

(i) **Osteosclerosis** *i.e.* presence of *increased amount of calcified bone*; it occurs in patients with metastatic tumours, lead poisoning, hypothyroidism **(Fig. 73.4 A)**.

(ii) **Osteoporosis**. In this condition, there is *decrease in all constituents of bone*, which leads to decrease in bone mass *with preservation of normal ratio of mineral to matrix*. It occurs due to a relative excess of osteoclastic function resulting in increase in bone resorption and decrease in bone formation **(Fig. 73.4 B)**.

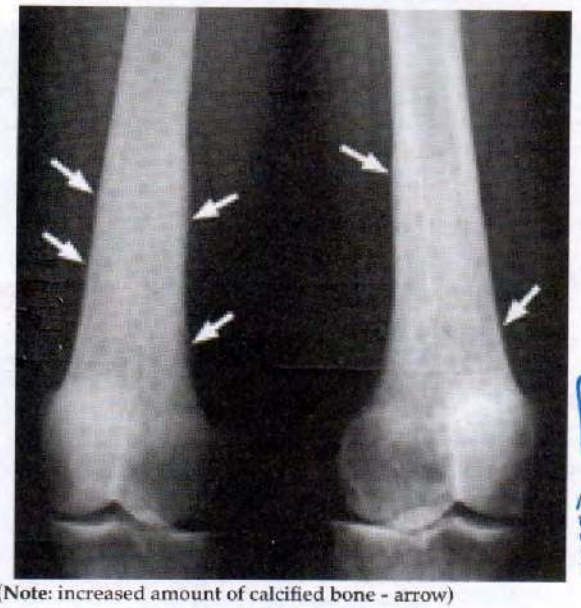
Usually after 40 years of age, there is normally a progressive loss of skeletal mass, leading to 'senile' osteoporosis with predisposition to fractures.

Causes

(a) In post menopausal women, decreased oestrogen concentration leads to increased sensitivity of bone to PTH.

Note

Oestrogen prevents osteoporosis by inhibiting effects of cytokines (IL-1, IL-6 and TNF - page 127) on osteoclasts.



(Note: increased amount of calcified bone - arrow)

(A)

Normal Osteoporosis

(Note: decrease in the bone mass - arrow)

(B)

Fig. 73.4 (A) Osteosclerosis and (B) Osteoporosis

(b) Cushing syndrome patients (page 723), corticosteroid therapy or hyperfunction of adrenal cortex.

(c) Hyperparathyroidism

(d) Hyperthyroidism

(e) Prolonged calcium deficiency

(f) Prolonged physical immobilization (as bone resorption exceeds bone formation).

(iii) **Osteomalacia** (refer to page 709).

(iv) **Osteopetrosis**, a rare severe bone disorder in which osteoclasts are defective so the osteoblasts operate unopposed. This results in a steady increase in bone density accompanied with neurological and haematological defects within the bone.

HORMONES REGULATING CALCIUM METABOLISM

Calcium concentration in the body fluids and in the cells is maintained within narrow limits by the activity of 3 hormones: *vitamin D, parathyroid hormone (PTH) and calcitonin.*

A. VITAMIN D (Calcitriol)

In the body it is converted to a more important hormone, 1,25-dihydroxycholecalciferol (1,25 DHCC) **(Fig. 73.5)**.

1. **1,25 DHCC is *physiologically active*** hormone and contains 27 carbon atoms; 100 times more potent than 25 HCC; **normal plasma levels:** 0.03 ngm/mL.
2. 1,25 DHCC *increases serum calcium and phosphate* by its *actions* on GIT, bones and kidney.
   (i) ***On GIT:*** It acts on nuclei of the intestinal epithelial cells to increase the production of mRNA (page 654). This, in turn, causes increased synthesis of a specific protein, that binds Ca^{2+} to increase its

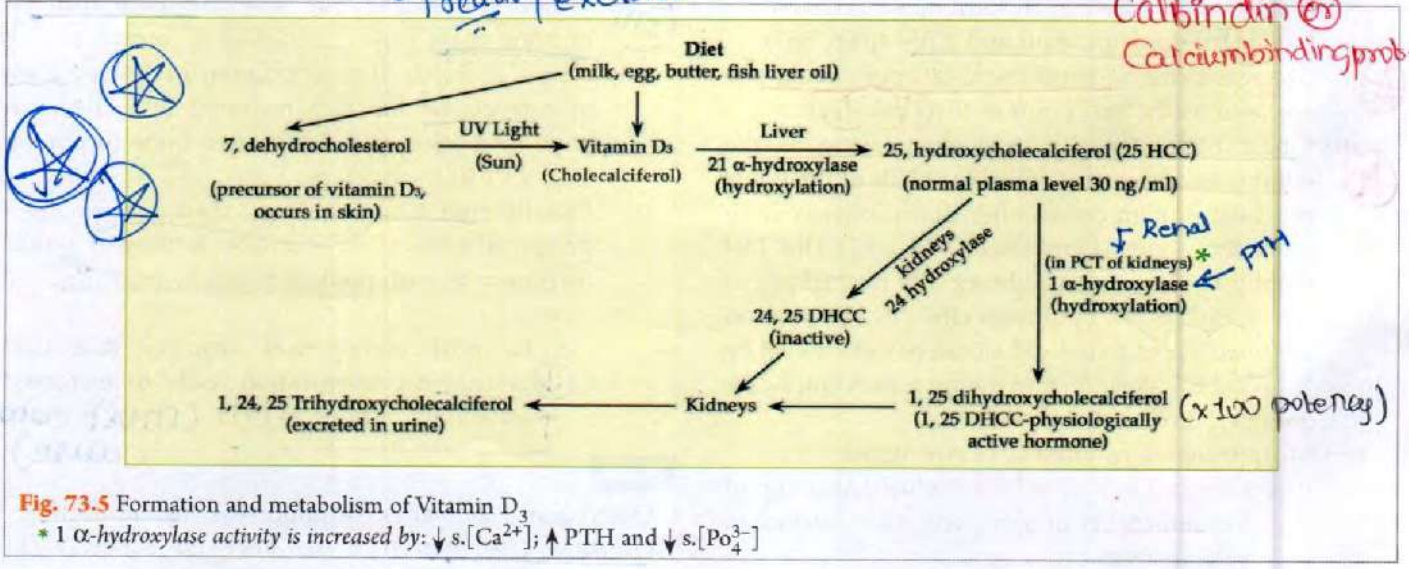


Fig. 73.5 Formation and metabolism of Vitamin D_3

* 1 α-*hydroxylase activity is increased by:* ↓ s.$[Ca^{2+}]$; ↑ PTH and ↓ s.$[Po_4^{3-}]$

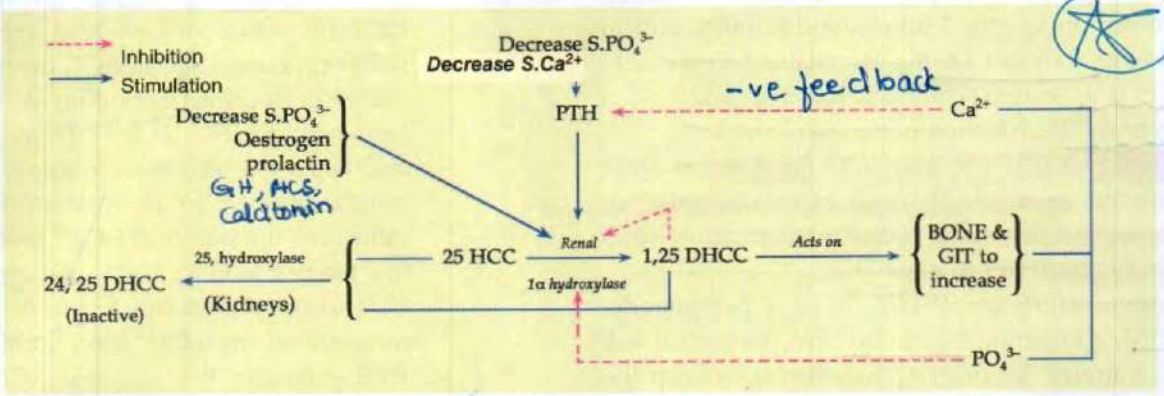


Fig. 73.6 Feedback control of formation of 1,25 DHCC (Abbreviations as given in the text)

absorption. Similarly, PO_4^{3-} absorption is also increased but the action is less marked.

(ii) *On bones:* It acts directly on bones to stimulate activity of oestoblasts which in turn causes proliferation of osteoclasts. Osteoclasts mobilize Ca from the bones by increasing the active transport of Ca out of osteoblast into ECF. Similar action is seen on PO_4^{3-}.

(iii) *On kidneys:*

(a) it increases reabsorption of Ca^{2+} from DCT, and

(b) increases reabsorption of HPO_4^{2-} from PCT; however, in *pharmacological dose* it leads to increased PO_4^{3-} excretion in urine.

Note

1,25 DHCC receptors are also found in the skin, lymphocytes, monocytes, breast and anterior pituitary gland. Therefore, *1,25 DHCC is also involved in* differentiation of immune cells and keratinocytes in the skin; regulation of growth and production of growth factors.

3. ***Regulation of 1,25 DHCC.*** It occurs in a *feedback* fashion by plasma Ca^{2+} and PO_4^{3-} levels **(Fig. 73.6)**.

(i) (a) **Low plasma Ca^{2+}**, *by increasing parathormone secretion* stimulates the renal 1 α-hydroxylase which increases the formation of 1,25 DHCC.

(b) **High plasma Ca^{2+}** by decreasing parathormone secretion inhibits the renal 1 α-hydroxylase which causes formation of inactive 24, 25 DHCC.

Similarly,

(ii) **Low plasma phosphate** increases 1,25 DHCC production and **high plasma phosphate** decreases 1,25 DHCC production. Increased PO_4^{3-} acts directly by inhibiting renal 1 α-hydroxylase activity.

(iii) (a) By direct *negative* feedback effect of 1, 25 DHCC on renal 1 α-hydroxylase.

(b) By direct *positive* feedback effect on the formation of 24,25 DHCC.

(iv) **During lactation,** prolactin increases the activity of renal 1 α-hydroxylase to increase 1,25 DHCC formation.

(v) *Oestrogen* also increases the activity of renal 1 α-hydroxylase to increase 1,25 DHCC formation.

(vi) 1,25 DHCC production is decreased by *T_4 and metabolic acidosis* while its production is increased by *GH, calcitonin* and *HCS*.

B. PARATHYROID HORMONE (Parathormone – PTH)

1. In humans there are *4 parathyroid glands,* two embedded in the superior pole and two embedded in the inferior pole of thyroid gland on the posterior surface. **(Fig. 73.7)**

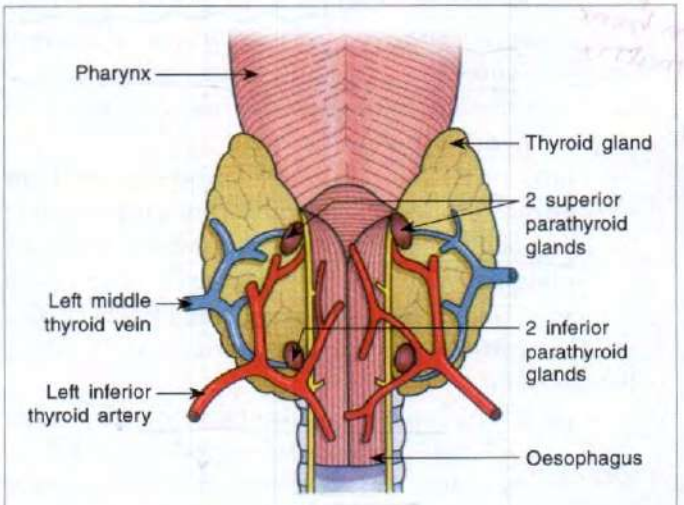


Fig. 73.7 The positions of the parathyroid glands (viewed from behind)

2. Parathyroid glands are highly vascular, each measuring about 6 mm in length, 3 mm in width and 2 mm in thickness; total weight 120 mg. It contains *2 types of cells*:
   (i) chief cells secrete *parathyroid hormone;* and
   (ii) oxyphil cells, function not known.
3. Parathyroid glands are ***Essential for Life,*** as their removal can cause death from asphyxia, resulting from spasm of laryngeal muscles, thoracic muscles and diaphragm (refer to page 710).
4. ***Parathyroid Hormone (PTH).*** It is a polypeptide, MW 9500, containing 84 amino acid, biological *half life* <20 minutes. Its primary function is to keep the Ca concentration in ECF and ICF constant, in spite of large variations in Ca intake and excretion. This is brought about by its action on both bone and kidney via ***PTH receptors*** (*serpentine receptors* - page 24) coupled to G-protien causing activation of adenylyl cyclase which increases the formation of intracellular cAMP (page 653).
5. ***Actions of PTH***
   (i) ***On Bones.*** PTH *increases plasma Ca^{2+} and decreases plasma PO_4^{3-}* by promoting bone resorption (*osteolytic effect*) which occurs in two phases; early and late.
      (a) **Early phase** is seen within few minutes of administration of PTH. Plasma $[Ca^{2+}]$ is raised by increased permeability of osteoclasts, osteocytes and osteoblasts to Ca^{2+} in bone fluid which causes osteoblasts to pump Ca^{2+} into ECF.
      (b) **Late phase** occurs hours or days after PTH administration. There occurs increased 'osteoclastic' activity and increased osteoclast formation with stimulation of osteoblast formation which promotes collagen synthesis and fresh bone formation. Increased collagen synthesis as well as its destruction is reflected by increased urinary excretion of hydroxyproline.

   Thus, physiologically these processes of bone destruction and bone formation are harmonized to bring about remodelling of bone which continues throughout the life in response to mechanical stress. This process is also regulated by 1,25 DHCC, glucocorticoids and thyroid hormones.

   (ii) ***On Kidneys***
      (a) PTH decreases reabsorption of PO_4^{3-} from PCT and increases its excretion in DCT, so increased PO_4^{3-} excretion in urine decreases $S.PO_4^{3-}$ (***phosphaturic action***). However, $[Ca^{2+}] \times [PO_4^{3-}]$ product in plasma remains constant because if one increases the other decreases.
      (b) **Initially**, increases Ca^{2+} reabsorption in DCT by active process and inhibition of reabsorption of Ca^{2+} in PCT, decreases Ca^{2+} excretion in urine (*hypocalciuria*). This initial response raises $S.Ca^{2+}$ (*Hypercalcaemia*), and when this rise is **later** amplified by the outpouring of Ca^{2+} from bone (under PTH influence), the very high $S.Ca^{2+}$ level increases the filtered load of Ca^{2+}, and excretion of Ca^{2+} in urine increases (*hypercalciuria*), thus maintaining the $S.Ca^{2+}$ level normal.
      (c) PTH promotes the *conversion of 25HCC to 1,25DHCC in the kidneys by* activating 1 α-hydroxylase via cAMP. (see above)
      (d) Increases urinary excretion of Na^+, K^+ and HCO_3^- and decreases excretion of NH_4^+ and H^+. This effect accounts for metabolic acidosis that occurs in hyperparathyroid states.
   (iii) ***On GIT,*** PTH produces *indirect effect*. Decreased $S.PO_4^{3-}$ increases the production of 1,25 DHCC which increases Ca^{2+} and PO_4^{3-} absorption from GIT, both by active and passive transport.
   (iv) ***On lactating mammary glands,*** PTH decreases the amount of Ca^{2+} secreted into the milk, thus conserves Ca^{2+} in body fluids.

Summary

The main PTH effects are:

(i) Hypercalcaemia and hypophosphataemia.
(ii) Hyperphosphaturia, hypocalciuria followed by hypercalciuria.
(iii) Increased urinary hydroxyproline excretion.
(iv) Increased resorption of bone; increase in number of osteoclasts and osteoblasts on bone surface.
(v) *Increased conversion of 25-HCC to 1,25 DHCC in the kidney.*
(vi) Activation of adenylyl cyclase in target tissues.

6. ***Regulation of Secretion of PTH***
   (i) ***Directly by $S.Ca^{2+}$ levels*** (***Calcium Feedback Loop***)
   ↓ $S.Ca^{2+}$ → stimulate parathyroid gland → ↑ PTH production → mobilization of Ca^{2+} from bones → normal $S.Ca^{2+}$; and vice versa.

Note

There is a cell membrane *Ca^{2+} receptor* coupled via G protein, its activation inhibits PTH secretion.

Evidence

(a) Size of parathyroid glands is inversely proportional to Ca^{2+} content of the diet.
(b) *Normal serum PTH is* 1 ngm/mL; if $S.Ca^{2+}$ is >12 mg/dL, PTH secretion is nil.

(ii) ***Indirectly by $S.PO_4^{3-}$***

$\uparrow S.PO_4^{3-} \rightarrow \downarrow S.Ca^{2+}$ and inhibit 1,25 DHCC $\rightarrow$ $\uparrow$ PTH.

Calcium Feedback Loop: From the reciprocal relationship between Ca^{2+} and PO_4^{3}, decrease in $S.PO_4^{3-}$ leads to increase in plasma Ca^{2+} activity; this in turn, decreases parathyroid secretion to its normal rate **(Fig. 73.6)**.Increased $S.PO_4^{3-}$ also stimulate PTH secretion by inhibiting 1, 25 DHCC formation. (1,25 DHCC acts directly on parathyroid glands to decrease prepro PTH mRNA). The action of parathyroid hormone on kidneys provides a rapid and sensitive means of correcting for minor fluctuations in the amount of parathyroid secretion, whereas the action of the PTH on bone is a slow, less sensitive response but of enormous capacity.

Chronic Renal disease
Rickets
↓
Prolonged ↓ in $S.Ca^{2+}$ because of decrease formation of 1,25 DHCC formation from diseased kidney
↓ *via feedback stimulation*
Compensatory parathyroid hypertrophy ***(secondary hyperparathyroidism)*** (page 710)

Important Note

A protein with PTH activity called *parathyroid hormone related protein (PTHrP)* is produced by many body tissues such as breast (main site), kidneys and the brain. It appears to act locally as a growth factor for the development of skin, hair follicles, cartilage, teeth and breasts. In its absence teeth will fail to erupt. Hypersecretion of PTHrP, a common complication of cancer of breast, kidney, ovary, skin result in hypercalcemia (*Humoral hypercalcemia of malignany*). Clinically it is associated with symptoms of hypercalcemia (page 711).

C. CALCITONIN (CT) – Calcium lowering hormone

1. It is a 32 amino acid polypeptide, secreted from clear cells (*C-cells*) or *parafollicular cells* of thyroid gland (page 681), therefore, also known as *Thyrocalcitonin*. However, total thyroid removal does not decrease circulating levels of calcitonin to zero, because C-cells are also present in the thymus, thus original name calcitonin is appropriate.
2. **Normal secretion** is 0.5 mg/day; half life less than 15 min; MW 3000. *Normal plasma level* 0.2 ngm/mL.
   Its secretion is increased by:
   (i) Increased $S.Ca^{2+}$ (*most potent stimulus*)
   (ii) CCK-PZ
   (iii) Glucagon
   (iv) Secretin
   (v) Oestrogen
   (vi) Dopamine, and
   (vii) Gastrin. (also a potent stimulus)
3. It is not secreted until the plasma Ca^{2+} exceeds 9.5 mg/dL **(Fig. 73.8)**. Plasma calcitonin is a direct function of plasma Ca^{2+} level and its regulation of secretion occurs by cAMP.

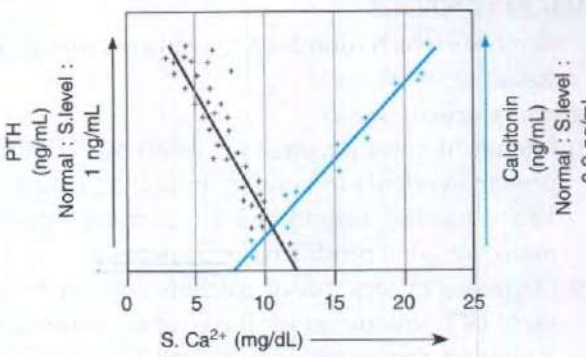


Fig. 73.8 Serum parathyroid hormone (PTH) and calcitonin concentrations against serum [Ca^{2+}]

4. ***Actions***

On bones

(i) It exerts its **Ca lowering effect** by inhibiting *osteoclastic* activity *i.e.* bone resorption due to a direct action of the hormone on the bone and can occur in the absence of parathyroid gland, GIT or kidneys.

(ii) It inhibits the Ca^{2+} permeability of osteoclasts and osteoblasts; acts by inhibiting the active transport of Ca^{2+} from bone cells into the ECF. It does not affect cAMP or the genetic mechanism regulating protein synthesis.

(iii) Also decreases osteoclast activity and its number.

(iv) Calcitonin activity is *associated with an increase in alkaline phosphatase* synthesis from the osteoblasts.

On kidneys

(i) Decreases renal formation of 1,25 DHCC which in turn decreases $S.Ca^{2+}$ and PO_4^{3-} by inhibiting renal 1-α-hydroxylase activity.

(ii) Increases Na^+, Ca^{2+}, Cl^- and PO_4^{3-} excretion in urine.

(iii) Reduces urinary excretion of hydroxyproline derived from bone.

On GIT

(i) Increases intestinal secretion of water and electrolytes.

(ii) Decreases gastric motility and acid secretion.

(iii) Inhibits intestinal (jejunal) absorption of Ca^{2+} and PO_4^{3-}.

5. *Physiological significance*
   (i) The CT hormone is more active in young individuals and may play a role in skeletal development by promoting Ca^{2+} storage in bones.
   (ii) Protects against post-prandial hypercalcaemia⊗
   (iii) Protects the bones of the mother from excess Ca^{2+} loss during pregnancy. Bone formation in infants and lactation are major drains on Ca^{2+} stores, and plasma concentration of 1,25 DHCC and calcitonin are both elevated in pregnancy.

D. MISCELLANEOUS

Other hormones which contribute to regulation of calcium metabolism:

1. *Adrenal glucocorticoids*
   (i) It tends to lower plasma Ca^{2+} levels by decreasing protein synthesis in bone by inhibiting osteoblast and osteoclast activity which decreases protein matrix of bone producing ***osteoporosis***.
   (ii) Decreases absorption of calcium and phosphate from GIT and increases their renal excretion by inhibiting the action of 1,25 DHCC on GIT and kidneys. *This is how glucocorticoids depress the hypercalcemia of vitamin D intoxication.*
   (iii) *Prostaglandin* (PG) of E-series secreted by certain tumours, increases plasma Ca^{2+}; *glucocorticoids* are reported to inhibit PG synthesis.
2. *GH* increases S.Ca^{2+} and increases Ca excretion in urine but also markedly increases intestinal absorption of Ca, thus resulting in positive Ca balance.
3. *Thyroid hormone* produces hypercalcaemia and hypercalciuria (*mechanism:* page 687). ↑Ca^{++} in urine, plasma
4. *Oestrogen* prevent osteoporosis by inhibiting effects of *cytokines* (IL-1 and 6) on osteoclasts (page 703).
5. *Insulin* increases bone formation; this is why uncontrolled diabetes mellitus patients show significant bone loss. ∴ DM → BoneLoss

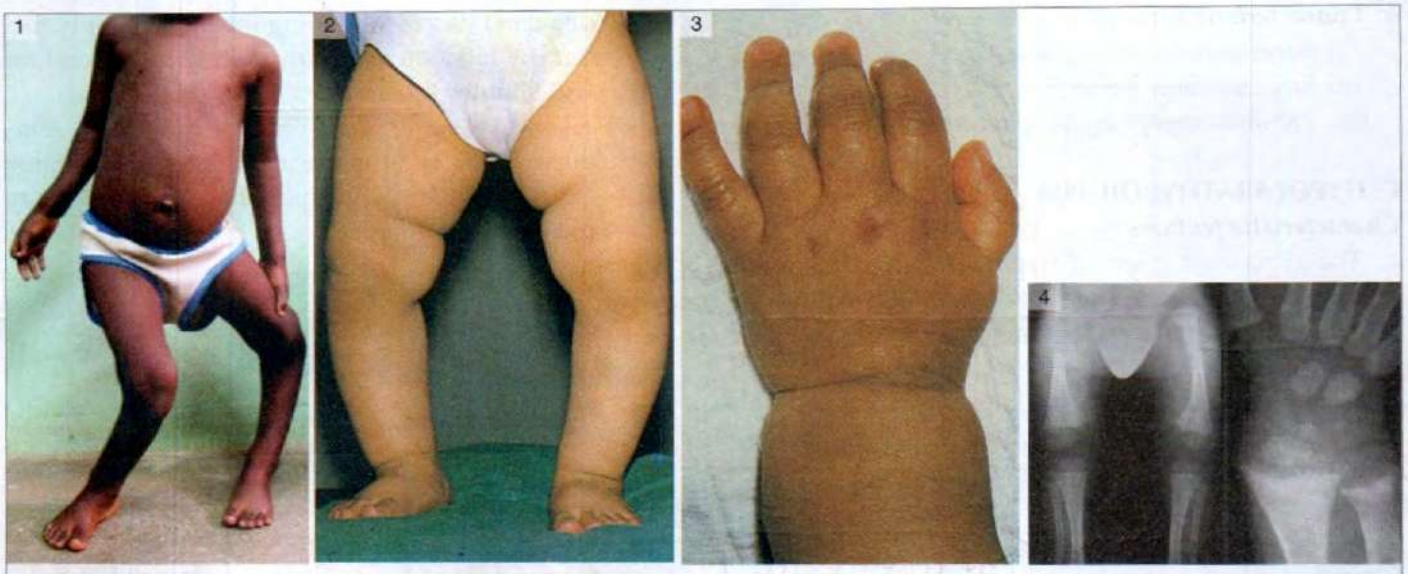
APPLIED

A. RICKETS → vit·D_3 deficiency

1. Rickets is the result of Vitamin D deficiency. It is a disease characterized mainly by bone deformities in young children. Vitamin D deficiency leads to poor absorption of Ca, therefore, protein of new bones fails to mineralize producing *Rickets* in children **(Fig. 73.9)**.
2. *Causes*
   (i) Inadequate intake of provitamins 7, dehydrocholesterol and vitamin D_3 – prevents vitamin D_3 formation.
   (ii) Inadequate exposure to sun.
   (iii) Kidney failure, prevents 1,25 DHCC formation.
   (iv) Liver dysfunction prevents 25, DHCC formation.
   (v) Defects in target cells receptors that fail to bind 1,25 DHCC.
3. The disease of children sets in about 6th month of life, and its intensity is directly related to the rapidity of bodily growth. It is **characterized by** bones which are soft due to deficient deposition of Ca salts. Therefore, bones get easily bent under the weight of the body and ***deformed bones*** develop.
4. *Pathology*
   (i) Process of ossification at the epiphyseal line takes place in an abnormal manner. Normally the epiphyseal line is a well defined narrow strip of cartilage 2 mm deep, behind which regular ossification is proceeding. In rickets, the *epiphysial line forms a wide, irregular band*, which can be felt as a marked projection on the surface.

Summary: Actions of three major hormones that regulate serum calcium and phosphate levels.

	Parathyroid Hormone	1,25 DHCC	Calcitonin
On Bone	↑s bone resorption (mobilizes calcium) (*osteolytic effect*)	Mobilizes calcium and phosphate	Inhibits bone resorption
On GIT	↑s calcium and phosphate absorption (Indirect effect)	↑s calcium and phosphate absorption	↓s calcium and phosphate absorption
On Kidney	(i) ↓ phosphate absorption from PCT and ↑ excretion in DCT (ii) ↑ calcium reabsorption from DCT	↑s reabsorption of calcium from DCT and that of HPO_4^{2-} from PCT	(i) Inhibits renal formation of 1,25 DHCC (ii) ↑s excretion of calcium and phosphate
Effect on S.Ca^{2+}	↑s	↑s	↓s
Effect on S.PO_4^{3-}	↓s	↑s	↓s
Stimulus for secretion	↓S.[Ca^{2+}]	↓S.[Ca^{2+}] ↑PTH ↓S.[Po_4^{3-}]	↑S.[Ca^{2+}]



Characteristic features

1. Deformed bones: bow legs (or knock knees), bones bent under body weight (bowing of weight bearing bones)
2. Thickening of wrists and ankles
3. Retarded growth, shortness of stature
4. Delayed dentition
5. Widening and cupping of epiphyseal cartilagenous plate
6. Other associated features: hypocalcemia, hypotonia, myopathy, prominence of the costochondral junction, frontal bossing

* frontal bossing
* Pigeon chest
* Rickety rosary
* Hypotonia, myop
* Hypocalcemia
* Thick wrists

Fig. 73.9 Rickets

* POOR REABS. of Ca^{++}
* Epiphyseal plate widening.

(ii) Normally the older cartilage cells degenerate and disappear, leaving many spaces into which the blood vessels and osteoblasts of the shaft can penetrate. In rickets, this apparently essential preliminary degeneration does not occur and so ossification is retarded. The cartilage cells persist and go on multiplying and give rise to ***broad irregular cartilagenous zone***. The matrix betweeen the cartilage cells and that of new bone itself does not become adequately impregnated with lime salts which results in ***'softness' of the bones***.

(iii) $S.Ca^{2+}$ and $S.PO_4^{3-}$ levels decrease; in active rickets the *solubility product, i.e.* product of $S.Ca^{2+}$ and $S.PO_4^{3-}$ (both expressed in mg/dL) is decreased to 30 (*normal is 60*).

(iv) Tetany may occur as a complication of rickets due to lowered $S.Ca^{2+}$.

(v) *S. alkaline phosphatase is commonly raised.*

Important Note

Vitamin D resistant rickets. It is caused by inactivating mutations of the genes either for renal 1α-hydroxylase or for 1, 25 DHCC receptor. In the former there is no response to vitamin D but a normal response to 1, 25 DHCC; whereas in the latter there is deficient response to both vitamin D and 1, 25 DHCC.

B. OSTEOMALACIA or ADULT RICKETS

1. Here the **amount of mineral accretion in bone per unit of bone matrix is deficient**. This is due to inadequate absorption of Ca owing to the deficiency of Vitamin D and Ca in the diet.
2. The disease is *limited to females*, usually appears after multiple pregnancies and lactation. Sometimes first manifestation occurs at puberty. The bones, specially pelvic girdle, ribs and femur become soft, painful and deformed **(Fig. 73.10)**. Symptoms usually recur with each succeeding pregnancy, but tend to clear up after lactation is completed.

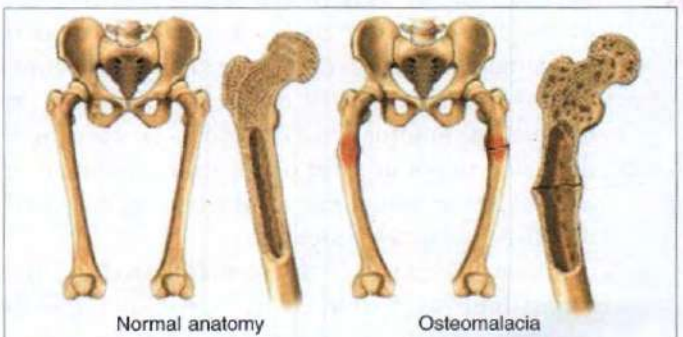


Fig. 73.10 Osteomalacia (Adult ricket): Deformed femur

3. S. Ca^{2+} is low, 6-7 mg/dL; S. inorganic PO_4^{3-} is low, and S. alkaline phosphatase is raised.

* Osteoporosis ⊕ Occurence ?

4. *Characteristic features*
   (i) Bone pain and tenderness
   (ii) Fractures may occur
   (iii) Proximal myopathy is common

C. HYPOPARATHYROIDISM

Characteristic features

1. The *commonest cause* of hypoparathyroidism is the removal of or damage to the parathyroid glands during thyroidectomy. The symptoms produced are due to decrease in ionized plasma Ca^{2+} level. As calcium exerts a stabilizing effect on the cell membranes of excitable tissues (page 143), therefore, hypocalcaemia increase the excitability of muscle and nerve membranes, which get potentiated by ischemia.

Note

The decrease in serum [Ca^{2+}] cause nerve fibers to respond to stimuli which are subthreshold for normal fibers and they may respond to a single stimulus with a repetitive discharge. The excitability of CNS is also increased by hypocalcemia.

2. *Total S.Ca^{2+} is decreased* to 4-8 mg/dL and the ionized Ca^{2+} to 3 mg/dL (decreased by 50%), resulting in ***Tetany***. Simultaneously, S. inorganic PO_4^{3-} increases to 6-16 mg/dL
3. ***Tetany*** – *Features:*
   (i) ***Neuromuscular Hyperexcitability*** Decrease in ionized Ca^{2+} (<50% of normal), increases membrane permeability to Na^+ producing numbness, tingling of extremities, and feeling of stiffness with cramps in extremities due to extensive spasm of skeletal muscle. If laryngeal muscles get involved, it leads to ***Laryngeal Stridor***; the associated *airway obstruction produces asphyxia*, convulsions and even death may occur.
   (ii) ***Facial Irritability.*** A nerve stimulus which normally cannot cause muscle contraction, here can cause contraction of muscles or even may respond to a single stimulus with a repetitive contractions. This is due to increased excitability of nerves to mechanical stimulation. Therefore, tapping over the facial nerve in front of ear or at the angle of jaw results in ipsilateral contraction of the facial muscles (***Chvostek's Sign***).
   (iii) ***Carpopedal Spasm*** – It is manifested in the upper limb as flexion at the wrist and thumb with hyperextension of remaining fingers, called ***Obstetric Hand or Carpopedal Spasm***. In the lower limbs toes are plantar-flexed and feet are drawn up. It may occur spontaneously or can be demonstrated by occluding the blood supply to a limb by inflation of a sphygmomanometer cuff for few minutes (***Trousseau's Sign***). **(Fig. 73.11)**
   (iv) ***Visceral manifestation*** include intestinal colic, biliary colic or bronchospasm, profuse sweating etc. All these effects are due to increased excitability of autonomic ganglia.

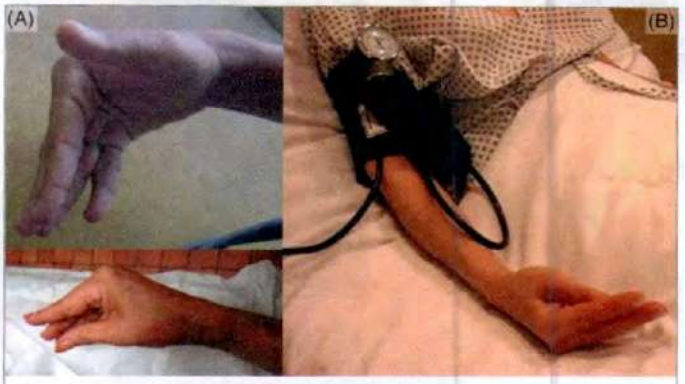


Fig. 73.11 Carpopedal Spasm or obstetric hand in tetany (A) and Trousseau's sign (B)

   (v) ***ECG changes*** – ST segment is prolonged with abnormal T-wave.
   (vi) Precipitate cataract formation, as Ca content of the lens is increased.
   (vii) S.Ca^{2+} level at which tetany occurs, is well above the level at which clotting defects would occur.

Important Notes

1. Hyperventilation, profuse vomiting or the excessive ingestion of sodium bicarbonate may cause *Alkalaemic Tetany*. This is because alkalosis (decrease in plasma H^+) in these states causes more ionization of plasma proteins, providing more protein anions to bind with Ca^{2+}.
2. *Pseudohypoparathyroidism, a receptor disease* in which tissues fails to respond to the PTH. It is characterized by hypoparathyroidism in spite of normal or increased level of serum PTH.

D. HYPERPARATHYROIDISM

1. ***Causes***
   (i) Diffuse hyperplasia of parathyroids, and
   (ii) Localized tumour (Adenoma or Carcinoma of parathyroid glands).
   (iii) Secondary hyperparathyroidism. Refer to page 707.
2. ***Characteristic features***
   (i) **A rise in S.Ca^{2+}** above 12.5 mg/dL produces weakness, lassitude, loss of muscle tone, thirst, polyuria, anorexia, nausea, vomiting, constipation and mental symptoms. Polyuria is due to DCT

damage so reabsorption of water decreases producing dehydration and thirst.

(ii) Kidney stones of calcium phosphate or oxalate usually occur due to calcium deposition in renal parenchyma (*Nephrocalcinosis*).

(iii) Demineralization of bones produces painful bones; there is radiological rarefaction and spontaneous fractures occur with multiple bone cysts, called *Osteitis Fibrosa*.

(iv) **Blood examination** shows:

(a) increase in S.Ca^{2+} (upto 22 mg/dL); ionized Ca^{2+} is raised;

(b) decrease in S.PO_4^{3-} below 2.5 mg/ dL (*normal*: 2.5-4.5 mg/dL);

(c) increase in S.alkaline phosphatase (*normal*: 5-13 KÅ).

(v) **Urine examination** shows: *Hypercalciuria* – normal Ca excretion is 100 mg/day, here it may increase to 400 mg/day secondary to hypercalcaemia. Similarly, there is increased PO_4^{3-} excretion in the urine.

E. FAMILIAL BENIGN HYPOCALCIURIC HYPERCALCEMIA

A genetic disorder due to mutation in the genes for Ca^{2+} receptor causing chronic increase in S.Ca^{2+} because the feedback inhibition of PTH secretion by Ca^{2+} is reduced **(Fig. 73.6)**

Study Questions

1. **Differentiate between:**
   (i) Osteosclerosis and osteoporosis
   (ii) Osteocytes and osteoclasts
   (iii) Action ot PTH on bone and kidney in maintaining serum calcium levels
   (iv) Parathormone and PTHrP
   (v) Rickets and adult rickets
   (vi) Tetany and alkalaemic tetany.
2. **Write short notes on:**
   (i) Role of calcium in physiological processes
   (ii) Factors affecting calcium absorption from GIT
   (iii) Solubility product and its significance
   (iv) Tibia test
   (v) Actions of PTH on bone and kidney
   (vi) Calcium feedback loop
   (vii) Role of calcitonin in regulation of S. calcium
   (viii) Features of hypoparathyroidism
   (ix) Signs of tetany
   (x) Salient features of hyperparathyroidism
   (xi) Bone growth
3. **Give physiological basis of:**
   (i) Bile increases calcium absorption from the GIT
   (ii) Higher incidences of fractures after 40 years of age
   (iii) Metabolic acidosis that occur in hyperparathyroid states
   (iv) Chronic renal disease may produce secondary hyperparathyroidism
   (v) Renal rickets
   (vi) Rickets associated with softness of bones
   (vii) Osteomalacia
   (viii) Neuromuscular hyperexcitability in tetany
   (ix) Hyperventilation may precipitate tetany
   (x) Carpopedal spasm.
4. **What determines the urinary excretion of calcium?**
5. **Give the relation between plasma calcium and phosphate. How their bodily concentration are achieved?**
6. **Depict diagrammatically :**
   (i) Calcium distribution in the body
   (ii) Feedback control of formation of 1, 25 DHCC.
   (iii) Serum PTH and calcitonim concentration against serum [Ca^{2+}]

7. Give physiological significance of epiphyseal closure.
8. Mention major causes of osteoporosis.
9. Name the hormones that maintain normal serum calcium and phosphate homeostosis. Briefly give their interaction.
10. Name the most potent stimulus for secretion of calcitonin. How is its level maintained in the plasma?
11. What will happen and why if parathyroid glands are removed in an individual?

MCQs

1. The largest amount of calcium is present in the plasma in what form?
   (a) Calcium-lipid combination (b) Calcium protein complex
   (c) Calcium carbohydrate complex (d) As ionized (free) calcium
2. The tensile strength of bone is due to:
   (a) Calcium salts (b) Collagen fibers (c) Proteoglycans (d) Ground substance
3. For calcium metabolism, all of the following are required *except*:
   (a) Vitamin D (b) Parathyroid hormone (c) Calcitonin (d) Thyroxine
4. *Not* an effect of parathormone:
   (a) Increases plasma Ca^{2+} and decreases plasma PO_4^{3-} (b) Increases both plasma Ca^{2+} and plasma PO_4^{3-}
   (c) Increases Ca^{2+} and PO_4^{3-} absorption from GIT (d) Increases Ca^{2+} reabsorption from DCT
5. Regarding parathyroid the following statements are *true except*:
   (a) It regulates calcium and phosphorus (b) Controls the balance of inorganic ions in blood
   (c) It is not essential for life (d) Its cellular effects are mediated through cyclic AMP
6. Physiological hyperplasia of parathyroid gland is due to:
   (a) Old age (b) Exercise
   (c) Chronic dietary vitamin D deficiency (d) Pregnancy
7. Thyrocalcitonin:
   (a) Lowers BMR
   (b) Reduces blood calcium level in absence of parathyroid glands
   (c) Released when blood phosphate level rises
   (d) Increases renal formation of 1,25 DHCC
8. Which of the following might *not* be expected in a patient with rickets due to vitamin D deficiency?
   (a) Elevated S. alkaline phosphate (b) Increased plasma Ca^{2+} concentration
   (c) Low plasma concentration of 1,25 DHCC (d) Decreased plasma phosphate concentration
9. Accidental removal of parathyroid glands during thyroidectomy results in:
   (a) Hypercalcemia (b) Tremors and muscle spasm
   (c) Myxoedema (d) Fall in BMR
10. Tetany features include all of the following *except*:
    (a) Neuromuscular hyperexcitability (b) Corpopedal spasm
    (c) Trousseau's sign (d) Clotting defects
11. Hyperparathyroidism is characterised by:
    (a) Hypocalcemia (b) Hyperphosphatemia
    (c) Multiple bone cysts (d) Increased bone formation
12. Which fraction of plasma calcium is maximum?
    (a) Free or ionized (b) Non-ionized (c) Bound to albumin (d) Bound to globulin
13. Which of the following is *not true* about calcium metabolism?
    (a) Phytates in diet increase absorption (b) Dihydroxycholecalciferol increases absorption
    (c) High protein diet increases absorption (d) 47% of total calcium is in ionized form
14. The amount of ionized calcium in blood falls in all of the following conditions *except*:
    (a) When sodium citrate is added to it
    (b) In hyperventilation
    (c) When blood phosphate level falls
    (d) When thyroid gland is perfused with calcium rich solution

15. **An increase in plasma parathormone level would lead to increase in which of the following?**
    (a) Number of active osteoblasts
    (b) Plasma inorganic phosphate concen-tration
    (c) Renal synthesis of 1,25 DHCC
    (d) Collagen synthesis
16. **Calcium metabolism is mainly dependent on:**
    (a) Calcitonin
    (b) Parathormone
    (c) Thyroxine
    (d) Growth hormone
17. **Active vitamin D_3 differs from parathormone in which of the following physiological effects?**
    (a) Increased renal phosphate reabsorption
    (b) Increased renal Ca^{2+} reabsorption
    (c) Increased intestinal Ca^{2+} absorption
    (d) Increased plasma Ca^{2+} concentration
18. ***Not* a correct statement for calcitonin:**
    (a) A calcium lowering hormone
    (b) Normal plasma level is: 0.2 ng/mL
    (c) Its secretion is increased by increased S.Ca^{2+}
    (d) Circulating level become zero following total thyroidectomy
19. **Rickets may be associated by all of the following *except*:**
    (a) Vitamin D deficiency
    (b) Bone deformities in young children
    (c) Liver dysfunction
    (d) Solubility product is normal
20. **The likelihood of developing tetany is increased when:**
    (a) Plasma HCO_3^- rises
    (b) Plasma magnesium rises
    (c) Respiratory failure develops
    (d) Anterior pituitary removed
21. **Metastatic calcification occurs when calcium is in:**
    (a) Acidic pH
    (b) Alkaline pH
    (c) Neutral pH
    (d) Ionic equilibrium

Answers

1. (d)	2. (b)	3. (d)	4. (b)	5. (c)	6. (c)	7. (b)	8. (b)	9. (b)	10. (d)
11. (c)	12. (a)	13. (a)	14. (c)	15. (c)	16. (b)	17. (a)	18. (d)	19. (d)	20. (a)
21. (b)									

Chapter
74

The Adrenal Cortex

I. Physiological anatomy
II. Biosynthesis, transport, metabolism and excretion of adrenocortical hormones
III. Regulation of glucocorticoids secretion – Role of ACTH
IV. Actions of glucocorticoids: Cushing's syndrome
V. Mineralocorticoids: Aldosterone actions and regulation of secretion
VI. Applied aspect: Primary and secondary hyperaldosteronism – Conn's disease
Primary and secondary Adrenocortical insufficiency – Addison's disease
VII. Sex hormones: Adrenal virilism

PHYSIOLOGICAL ANATOMY

ADRENAL (or SUPRA RENAL) GLANDS

1. There are two adrenal glands, one at the top of each kidney; in adults, each adrenal gland weighs 4-5 gms and consists of two distinct parts: the outer *adrenal cortex* and the inner *adrenal medulla*. **Adrenal cortex is essential to life** (why? page 722 and 724) and its mass is much more, approx. 80% of the total gland.
2. Adrenal cortex has **no** nerve supply but has a rich blood supply; right adrenal vein drains into inferior vena cava and left adrenal vein into the left renal vein. Therefore, adrenal hormones enter the systemic circulation directly (In contrast, pancreatic and GIT hormones are conveyed by portal vein to the liver before they can enter the systemic circulation).
3. The *adrenal medulla secretes* catecholamines: epinephrine, nor-epinephrine and dopamine; whereas the adrenal cortex secretes steroid hormones.
4. Adrenal cortex is divisible into *three zones* **(Fig. 74.1)**; these zones from outer to inner are:
   (i) ***Zona Glomerulosa***: (15% of the mass of the adrenal gland)
      (a) secretes *mineralocorticoids*, and
      (b) forms new cortical cells.
   (ii) ***Zona Fasciculata:*** (15% of the mass of the adrenal gland). It secretes *glucocorticoids*.
   (iii) ***Zona Reticularis***: (7% of the mass of the adrenal gland). It secretes *sex steroids*.

   In humans, zona fasciculata and reticularis act as a single functional unit, where mainly cortisol (glucocorticoid) and androgens are synthesized.
5. ***Adrenocortical hormones***
   (i) ***Mineralocorticoids***
   They contain 21-C atoms, therefore, called $C_{(21)}$ steroids. They have *more effect on mineral metabolism*, so promote sodium retention and potassium excretion from kidneys, therefore, essential for maintenance of sodium balance and ECFV. *Examples:*
      (a) *Aldosterone*
      (b) *Deoxycorticosterone (DOC)* – normally it is secreted in same amounts as the aldosterone. Its effect on mineral metabolism is negligible (3% of aldosterone); but diseases in which its secretion increases, it leads to appreciable effects.

   (ii) ***Glucocorticoids***-$C_{(21)}$ steroid
   They have more effect on carbohydrate (glucose) and protein metabolism. Its mineralocorticoid activity is 1/3rd of aldosterone. *Examples:*
      (a) *Cortisol or hydrocortisone.*
      (b) *Corticosterone* – It has a weak glucocorticoid and a slight mineralocorticoid activity. Its concentration in plasma is 1/10–1/15 that of cortisol.

Note

Corticosteroids means mineralocorticoids and glucocorticoids.

   (iii) ***Sex steroids***. They are $C_{(19)}$ steroids, having *minor effects on reproductive functions*. *Examples:*
      (a) Androgen (mainly), *i.e.* Dehydroepiandrosterone (DEA/DHEA); its activity is <20% of testosterone activity. *Normal* plasma level of DHEA is 150-200 µg/dL at 25 years of age in both sexes.
      (b) Oestrogen and progesterone, in very small amounts.

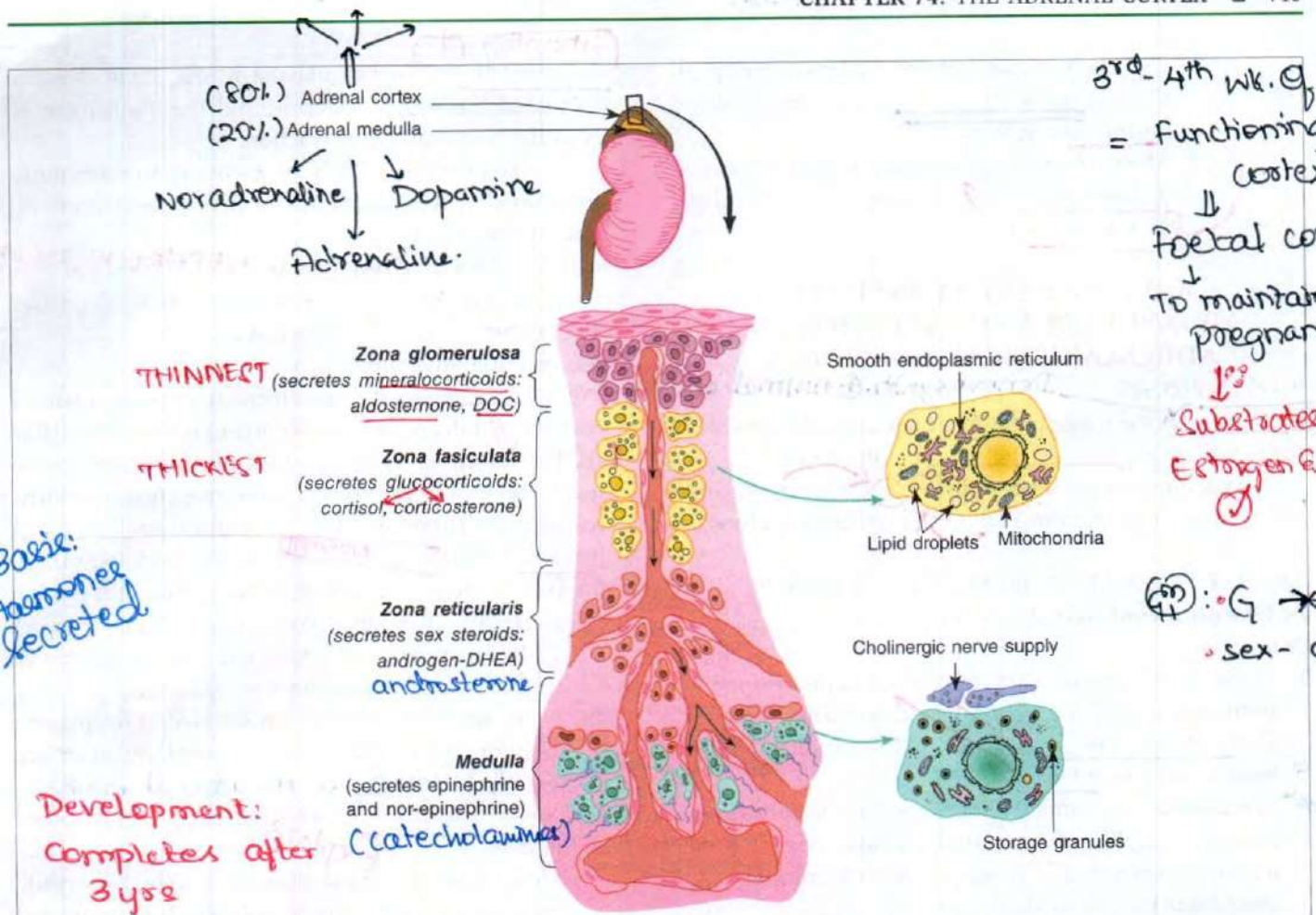


Fig. 74.1 Section through an adrenal gland showing both adrenal medulla and adrenal cortex (DOC: deoxycorticosterone; DHEA: dehydro-epiandrosterone)

6. ***Characteristic features*** of adrenal cortex and adrenocortical hormones

(i) **In foetus**, during 3rd-4th month of intra uterine life, *adrenals are larger than the kidney*. A major function of foetal adrenal is secretion of (DHEA) sulphate conjugate of androgen which is converted in the placenta to androgen and oestrogen and enters the maternal circulation. After birth, foetal adrenal cortex degenerates and secretion of cortisone increases rapidly. The *three differentiated zones are not formed until the third year of life.*

DHEA → placenta → Oestrogen + Androgen + Progesterone Substrates

(ii) Adrenal cortical cells contain very large amount of smooth endoplasmic reticulum, the site of hormone synthesis. Its all the three layers contain high amount of:

HARMONE SYNTHESIZERS

(a) Lipids specially cholesterol in ester form which is the precursor of all adrenal cortical hormones, and

(b) Vitamin C (ascorbic acid).

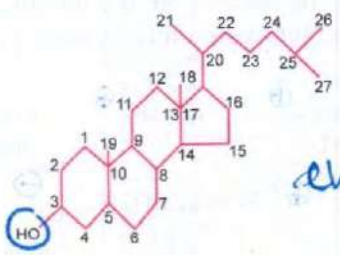
(iii) Zona glomerulosa can form the other two layers (zona fasciculata and reticularis). *Proof:* if we remove these two layers, they will regenerate.

1 → 2+3

LIPOPHILIC + STEROIDS

(iv) All its hormones are steroid hormones and lipid soluble, therefore, diffuse freely across the cell membranes into non-target as well as target organs; they are derived from cholesterol and have the same structural unit.

(a) $C_{(21)}$ steroids *i.e.* ***CPPP ring*** plus 2C side chain at $C_{(17)}$ position. *Examples:* mineralocorticoids and glucocorticoids.



Ring: Cyclo pentano perhydro phenanthrene nucleus (CPPP)

(b) Most of the $C_{(21)}$ steroids which have hydroxyl group at $C_{(17)}$ position in addition to side chain are called *17 hydroxy corticoids or 17 hydroxy corticosteroids (17-OHCS).*

addral 17-OH

(c) $C_{(19)}$ steroids *i.e.* keto or hydroxyl group at $C_{(17)}$, contain 19 C atoms; usually produce androgenic activity.

(d) Most of the $C_{(19)}$ steroids which have got a keto-group at 17 positions are called *17 ketosteroids*.

BIOSYNTHESIS, TRANSPORT, METABOLISM AND EXCRETION OF ADRENOCORTICAL HORMONES

BIOSYNTHESIS

Cholesterol is the major precursor of all steroid hormones. There is always plenty of cholesterol in the adrenal cortex. Adrenal cortex can synthesize cholesterol from acetyl CoA and can also take it from LDL in the circulating blood.

TRANSPORT, METABOLISM AND EXCRETION

A. Glucocorticoids (GCs)

Transport

1. In the blood stream >90% of cortisol binds reversibly with α-globulin, a glycoprotein called *Transcortin* or *Corticosteroid Binding Globulin* (CBG); small amounts bind loosely to *Albumin*.
   Corticosterone is similarly bound, but to a lesser degree, *i.e.* why half life of cortisol is slightly longer (60-90 minutes) compared to corticosterone (50 minutes).
   Plasma and urine concentration of glucocorticoids are given in **Table 74.1**.

Table 74.1: Glucocorticoids in blood and urine

	Cortisol	Corticosterone
1. Plasma conc. (free & bound) Average	10-25 µg/dL 14 µg/dL	0.2-1.0 µg/dL 0.4 µg/dL
2. Amount secreted	5-30 mg/day	1.5-4.0 mg/day
3. Biological half life	60-100 min	50 min

2. *Inter-relationship of free and bound cortisol* **(Fig. 74.2)**.
   At normal levels of total plasma cortisol, there is very little cortisol in plasma, but the binding sites on CBG become saturated when total plasma cortisol exceeds 20 µgm/dL. At higher plasma levels, there is some increased binding to albumin, but the main increase is in the unbound (free) fraction.

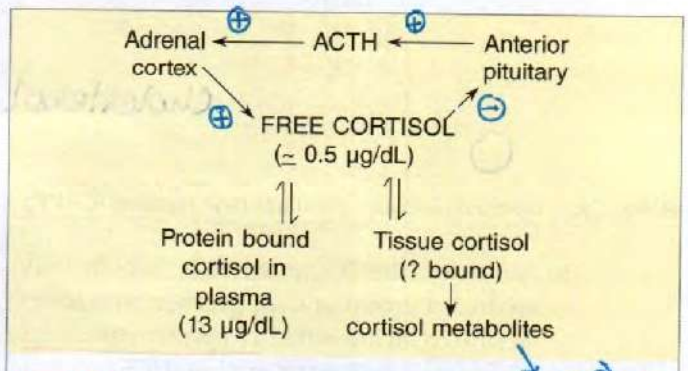


Fig. 74.2 Cortisol distribution in the body

3. *CBG:* Site of synthesis is liver; increases to three times the normal by injection of oestrogen (*e.g.* contraceptives) and in pregnancy.
   CBG decreases in:
   (i) cirrhosis of liver, CBG synthesis decreases
   (ii) nephrosis, more CBG is lost in urine
   (iii) multiple myeloma.
   When CBG increases it causes increase in protein bound cortisol and decrease in free cortisol which stimulates ACTH secretion. This increases plasma cortisol to a level which saturates the CBG and free cortisol returns to normal. Therefore, bound cortisol level remains increased, but ACTH secretion comes back to normal; opposite is seen when CBG level decreases. This is why:
   (i) pregnant women have high total plasma 17-hydroxycorticoid levels without symptoms of glucocorticoid excess; and
   (ii) some patients with nephrosis have low plasma 17-hydroxycorticoids without adrenal insufficiency.

Metabolism and Excretion: GCs are mainly metabolished in the liver.

(1) Most of the cortisol is reduced to 'dihydrocortisol' and then to 'tetrahydrocortisol', which is conjugated to form *tetrahydrocortisol glucuronide*... (a).
(2) Some of the cortisol in liver is converted to cortisone (an active GC-used clinically in synthetic form) which also forms *tetrahydrocortisone glucuronide* ... (b). (a) and (b) are physiologically inactive, highly water soluble, enter the circulation and are rapidly excreted in urine.
(3) Approx. 10% of secreted cortisol is converted in liver to 17-ketosteroid derivatives which are conjugated to sulphates and are excreted in urine.
(4) There is enterohepatic circulation of GC and approx. 15% of secreted cortisol is excreted in stools.
(5) The metabolism of corticosterone is similar to that of cortisol except that it does not form 17-ketosteroid derivatives.
(6) **Average amount of derivatives excreted in urine for 24 hours:**

(i) Free cortisol	: 0.03 mg
(ii) Tetrahydrocortisol glucuronide	: 5.0 mg
(iii) Tetrahydro cortisone glucuronide	: 3.0 mg
(iv) 20-hydroxy derivatives of (ii) & (iii)	: 6.0 mg
(v) 17-keto steroids derived from cortisol and cortisone (mostly sulphate conjugate)	: 1.0 mg
(vi) Unidentified metabolites	: 7.0 mg
TOTAL: 22 mg/day	

The rate of hepatic inactivation of GC is depressed in liver disease and during surgery or other stresses. Therefore, in stressed human, the plasma free cortisol level rises higher than it does with maximum ACTH stimulation in the absence of stress.

Normal 24 hours urine keto-steroids concentration:

In males: 15 mg
(i) 2/3 derived from adrenal cortex (*Source:* DHEA, Cortisol and Cortisone)
(ii) 1/3 derived from Testis (testosterone)
***In females*: 10 mg**

B. Aldosterone

1. It occurs in plasma in a very small concentration, 60% being bound to protein mainly to albumin and some to CBG; half life: 20 min.

	Aldosterone	DOC
Total plasma concentration (bound plus free)	0.007 µgm/dL	0.006 µg/dL
Average amount secreted	0.15 mg/day	0.2 mg/day

2. *Metabolism:*
   (i) Mostly in the liver, where it is conjugated with glucuronic acid to form tetra hydroglucuronide derivative.
   (ii) Some are conjugated in the kidney to form 18 glucuronide, which is hydrolyzed at pH 1.0 to free aldosterone; therefore called ***Acid Labile conjugate.***
3. *Excretion:* Aldosterone is excreted mainly in urine
   (i) 40% as tetrahydroglucuronide
   (ii) 5% as acid labile conjugate, and
   (iii) <1% as free form.

REGULATION OF GLUCOCORTICOIDS SECRETION

This is brought about by *two mechanisms*:
(A) by regulation of ACTH and
(B) by glucocorticoids feedback mechanism.

A. REGULATION OF ACTH SECRETION

(ACTH – Adrenocorticotrophic hormone or corticotrophin)

1. ACTH contains 39 amino acids, straight polypeptide chain, MW 4600; first 24 amino acids have been synthesized which have the same activity as that of ACTH. The sequence of 4-11 amino acids of ACTH is identical with β-MSH, therefore ACTH also possesses some MSH (melanocyte stimulating hormone) activity, it is *1/100 as potent as MSH*. ACTH biological *half life* is 10 minutes and it probably gets inactivated in blood and kidneys.

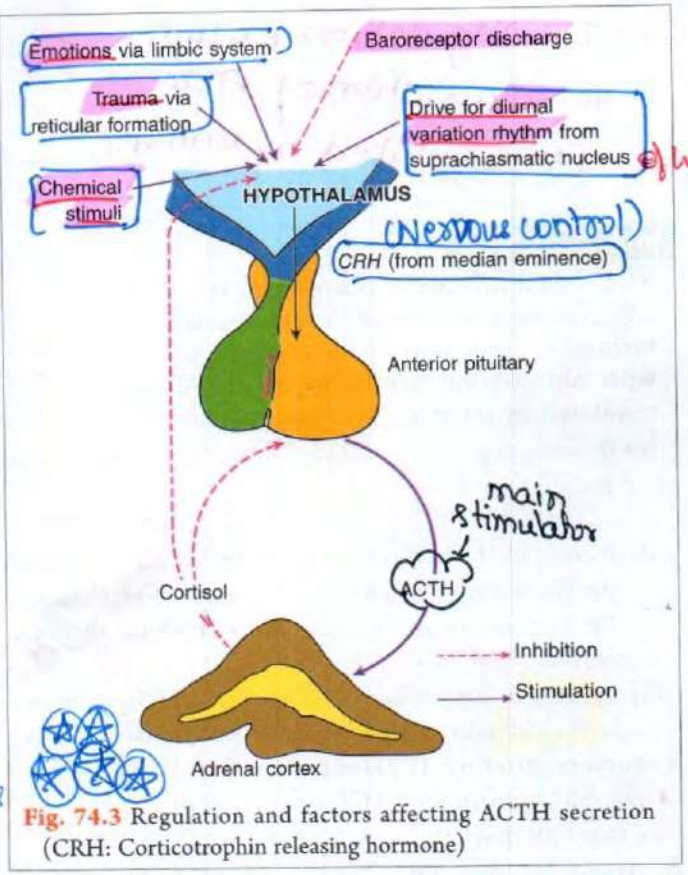


Fig. 74.3 Regulation and factors affecting ACTH secretion (CRH: Corticotrophin releasing hormone)

2. The secretion of ACTH is *mainly under nervous control.* The peptidergic neurons in median eminence of the hypothalamus release ***Corticotrophin Releasing Hormone (CRH)***, which stimulate the secretion of ACTH from anterior pituitary via hypothalamo-hypophysial portal system **(Fig. 74.3)**.
   CRH is a polypeptide consisting of 41 amino acids residue. Hypothalamic secretion of CRH is stimulated by cholinergic neurons. Serotonin (5 HT) also stimulates CRH secretion. Adrenergic neuron activity and GABA (gama amino butyric acid) inhibit release of CRH.
3. Both basal secretion of GC and the increased secretion provoked by stress are dependent upon *ACTH* from anterior pituitary.
   Evidence: Repeated injections of ACTH produce hypertrophy and hyperplasia of zona fasciculata and zona reticularis, associated with increased vascularity.

Mechanism of action of ACTH

ACTH binds to specific receptors on the cell membrane of adrenocortical cells to activate adenylyl cyclase via G_S. The resultant increase in intracellular cAMP activate protein kinase A which causes: **(Fig. 74.4)**

(i) increased conversion of cholesterol esters into free cholesterol;

ACTH regulation excludes the regulation of Aldo (∵ Regulated by RAAS)

Important Note

ACTH controls only those reactions which cause cortisol and corticosterone formation and not those concerned with aldosterone synthesis which is regulated by renin-angiotensin system (page 726).

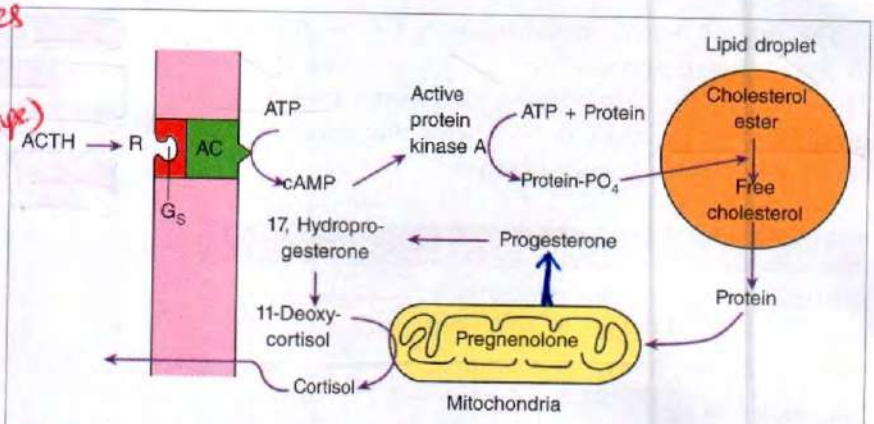


Fig. 74.4 Mechanism of action of ACTH (R: receptor; AC: adenylyl cyclase)

(ii) increased formation of protein which increases pregnenolone synthesis from cholesterol. Pregnenolone enters the mitochondria to form cortisol; and

(iii) increased formation of NADPH which increases hydroxylation at 11, 17 and 21 positions.

4. ***Factors affecting ACTH secretion*** **(Fig. 74.3)**

* ***Diurnal variation of ACTH secretion or Circadian rhythm***

(i) ACTH is secreted from anterior pituitary in irregular bursts throughout the day via release of CRH from the hypothalamus; therefore, plasma cortisol varies (increases or decreases) in response to these bursts. In normal persons GC secretion is maximum between 6 a.m. to 9 a.m. (before awakening from sleep **(Fig. 74.5)**; in night workers rhythm is reversed. The value falls steadily during the evening to reach its minimum between 6 to 9 p.m. to approx. 5 µgm/dL. Likewise is the secretion of ACTH; *maximum between 6–9 a.m. and minimum in the evening.*

morning = MAX.
midnight = min

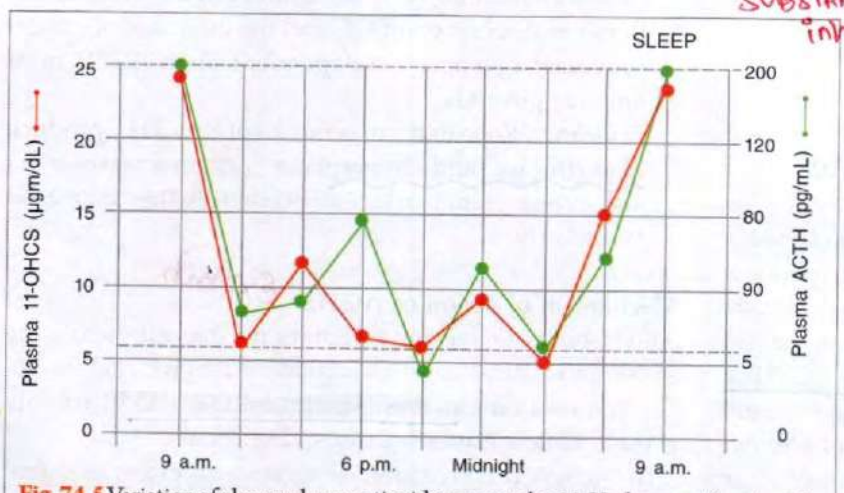


Fig. 74.5 Variation of plasma glucocorticoids measured as 11-Hydroxycorticosteroid (11 OHCS) and ACTH levels in 24 hours

Note

The morning plasma ACTH concentration in a healthy resting men is about 25 pg/mL.

(ii) This diurnal variation of ACTH secretion control is via a ***biological clock*** located either in limbic system or suprachiasmatic nucleus of hypothalamus, because destruction of any one or both of them abolishes the circadian rhythm (page 1003).

* ***Response to Stress***

During severe stress, the amount of ACTH secretion exceeds the amount necessary to produce maximal GC output **(Fig. 74.6)**.

B. GLUCOCORTICOID FEEDBACK MECHANISM

1. *Free* circulating GCs act via anterior pituitary and hypothalamus; increase in free GC inhibits ACTH secretion. Inhibition is apparently a linear function of free circulating GC level. Inhibition is rapid in onset but relatively prolonged, it probably represents persistent hormone action on the tissues.

SUBSTRATE (GC) inhibition

2. The level of free GC in plasma is normally very low, therefore, there is a little pituitary inhibition in the absence of stress. This is why an acute drop in circulating GC level is **not** a potent stimulus to ACTH secretion. Thus, the *rate of ACTH secretion is determined by two opposing forces:*

(i) the sum of the neural and other stimuli converging through the median eminence of hypothalamus to increase ACTH secretion; and

(ii) the magnitude of the braking action of GC on ACTH secretion, which

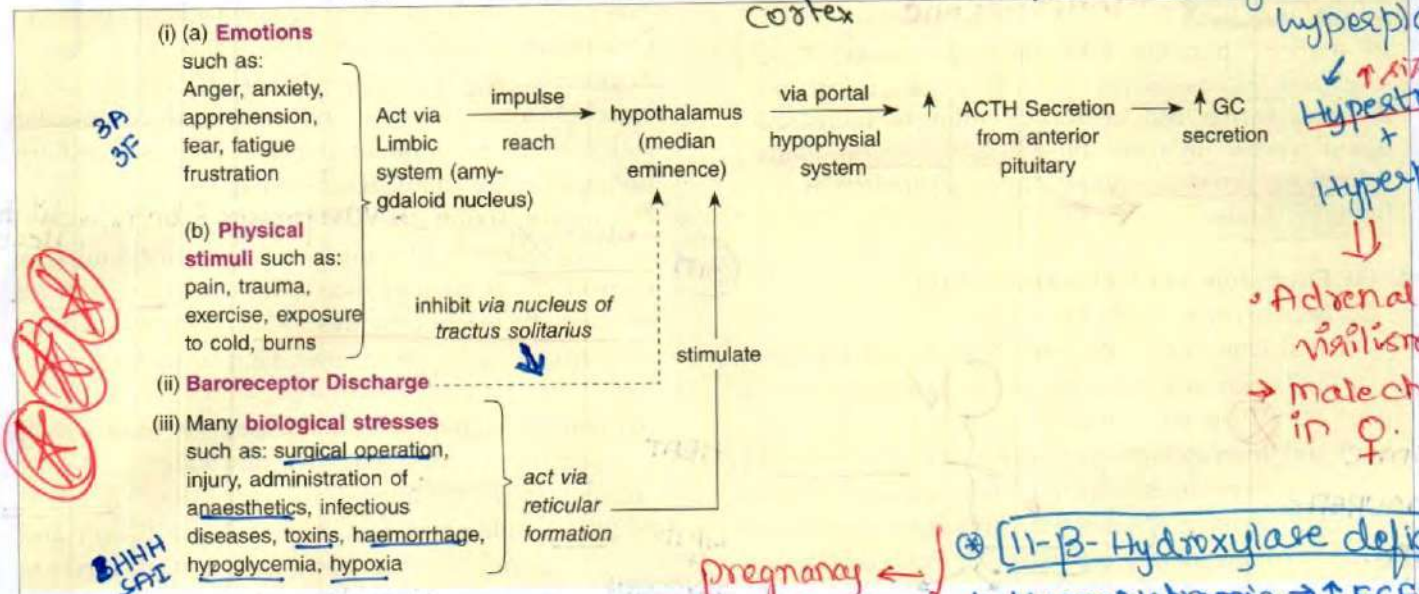


Fig. 74.6 Role of stress in ACTH secretion

is proportionate to their level in the circulating blood.

Important Note

Prolonged treatment with GC decreases ACTH synthesis and produces adrenocortical atrophy. Sudden stoppage of such therapy is lethal and person may die of *adrenal crisis* (page 727). This complication can be avoided by slowly decreasing the GC dose over a long period.

ACTIONS OF GLUCOCORTICOIDS

Mechanism of action: GC being a steroid hormone acts by stimulating DNA dependent mRNA synthesis in the nuclei of their target cells which leads to enzyme formation that modifies or alters cell function of the target organ (page 653).

1. ***On protein metabolism*** → catabolism (lysis)
   (i) GC causes protein ***breakdown***, specially in skeletal muscles; in normal individuals this effect is counter-balanced by anabolic processes. However, GC excess produces marked muscular weakness which leads to negative nitrogen balance.
   (ii) Protein breakdown increases the amino acids in plasma which are taken up by the liver to form new proteins.
   (iii) GC activates hepatic transaminase enzyme which increases deamination (*i.e.* removal of amino group – helps in glucose formation) and transamination (*i.e.* transfer of amino group helps in amino acids synthesis).
   (ii) and (iii) thus *increase 'gluconeogenesis'* in the liver. For example:

Alanine —*deamination*→ Pyruvic acid → glucose formation

Conversion of amino-nitrogen to urea increases urea production and increases nitrogen excretion in urine.

2. ***On carbohydrate metabolism*** → Imp. in STARVATION
   (i) Increases liver glucose-6-phosphatase activity to increase glucose formation (page 600) and stimulate gluconeogenesis in liver (see above).
   (ii) Prevents peripheral utilization of glucose by inhibiting phosphorylation and exerting anti-insulin action on peripheral tissues. Thus increases blood glucose.
   (i) and (ii) lead to *Hyperglycemia*.
   (iii) Increases glycogen synthesis by increasing glycogen synthetase, and indirect inhibition of glycolysis in the liver.

Note

Normally increased glucose synthesis is associated with glycogen breakdown, but here increased glucose formation does not occur at the cost of glycogen.

3. ***On fat metabolism*** → catabolism
   (i) Increases lipase activity by potentiating actions of other hormones *e.g.* GH, catecholamines, glucagon and thyroid hormone (***'lipolytic' action***).
   (ii) Favours mobilization of fatty acids from adipose tissue to liver where metabolism of fatty acids inhibits glycolytic enzymes and increases gluconeogenesis.

Important Note

In diabetic patients, GC increases plasma lipid level and *increases ketone bodies formation* and makes diabetes worse. But in normal subjects, increased blood glucose increases the insulin secretion which decreases lipase activity and counterbalances hyperglycemia.

4. ***On Electrolyte and Water Metabolism***

GC has two opposing effects:

(i) (a) Due to its mild mineralocorticoid activity it increases retention of Na^+ and excretion of K^+ by the kidney.

(b) Increases the synthesis of angiotensinogen from liver which in turn causes *increased secretion of aldosterone*. Increased aldosterone secretion causes excessive retention of Na^+ and water leading to oedema and hypertension.

(ii) Provides adequate GFR, antagonises the action of ADH on renal tubules and enhances ADH destruction by the liver, thus *promotes diuresis*.

In health, (i) and (ii) essentially balance each other and most important physiological function of GCs is the control of the distribution of body water and electrolytes.

Applied: In ***adrenal cortex insufficiency*** because of GC deficiency, there is a deficient 'diuretic response' (as GFR decreases and plasma ADH level increases), so that the 'water load' is not disposed of and this may lead to *Water Intoxication*. Because of hypotonic media, water enters the brain cells and produces convulsions, unconsciousness and death.

Important Note

In adrenal cortex insufficiency patients who present with circulatory collapse, glucose infusion may cause high fever (*glucose fever*) followed by collapse and death. This is probably due to the glucose being metabolized and water is retained further which dilutes the plasma (hypo-osmolar plasma) producing:

(i) water intoxication; and

(ii) swelling of thermoregulatory cells in hypothalamus and fever develops.

5. ***Vascular Reactivity***

(i) GC sensitizes arterioles to the constrictor action of catecholamines (specially NE).

(ii) GC inhibits COMT which causes breakdown of catecholamines (page 733).

(iii) GC enhances catecholamine synthesis via its activation of the epinephrine forming enzyme PNMT (page 733).

Thus, GC helps in maintaining normal blood pressure by restoring vascular reactivity.

Therefore, in the absence of GC, circulating catecholamines decrease and may produce vascular collapse due to vasodilatation and increase capillary permeability to colloidal substances.

6. ***Permissive Action***

Small amounts of GCs must be present for a number of metabolic reactions to occur, although they may not produce the reaction by themselves; this is called the *Permissive Action. For example:* GCs must be present for:

(i) glucagon and catecholamines to exert their calorigenic action (page 737 and 742);

(ii) for catecholamines to exert their lipolytic effect (release of FFA from adipose tissue) and glycogenolytic effect (breakdown of glycogen to glucose); and

(iii) for catecholamines to produce pressor response and bronchodilatation.

7. ***On Bone Metabolism***

GC excess:

(i) retards the development of cartilage and causes thinning of epiphyseal plate which inhibits new bone formation;

(ii) breaks down bone matrix due to protein catabolism;

(iii) decreases deposition of Ca^{2+}

(iv) increases Ca excretion in urine, as GFR increases.

(v) decreases Ca absorption from GIT by inhibiting action of 1,25 DHCC on GIT.

All these changes eventually produce:

(a) ***Osteoporosis*** which results in skeletal deformity and collapse of the vertebrae;

(b) ***Tetany*** due to decrease in $S.Ca^{2+}$.

8. ***On Blood Cells and Lymphatic Organs***

GC excess produces:

(i) *Eosinopenia* because it

(a) increases sequestration of eosinophils in lungs and spleen

(b) increases eosinophil destruction.

The changes in eosinophil levels have been used as an index of change in ACTH secretion.

(ii) *Lymphopenia*, due to:

(a) decrease in lymphocyte mitotic activity by interfering with DNA synthesis, and

(b) increased lymphocyte destruction in the circulation (directly); thus increased uric acid excretion in the urine;

(a) and (b) decrease size of lymph node, lymphoid tissue, spleen and thymus.

(c) decreased secretion of cytokine IL-2 results in reduced proliferation of lymphocytes, and these cells undergo apoptosis.

(iii) *Basopenia* due to similar action as on eosinophils.
(iv) *Neutrophilia*
(a) due to their increased release from the bone marrow
(b) prevents neurophil migration from vascular spaces into tissues, and
(c) inhibits ability of neutrophils to adhere or marginate to vessel wall.
(v) Polycythaemia by stimulating erythropoiesis.
(vi) Increases the platelet count.
(vii) Decreases clotting time.
That is why chronic adrenal insufficiency leads to moderate anaemia.

9. *On CNS*
(i) *Excess of GC* decreases the threshold of electrical excitation of the brain *i.e.* stimulates activity of brain excitability producing convulsions. This is the reason why corticosteroids are not given in epilepsy as they decrease convulsive threshold. Conversely, mineralocorticoids have opposite effect on CNS, and, therefore, are given to epileptic patients.
(ii) *In adrenocortical insufficiency*, patients are hypersensitive to:
(a) Taste and smell *e.g.* sucrose concentration of <12 millimole causes no sucrose sensation in normal subjects; here even sucrose concentration of 0.1 millimole produces sucrose sensation.
(b) Slowing of electrical activity of brain causes slowing of α-wave in EEG and personality changes, such as irritability, apprehension, restlessness, insomnia, loss of concentration, mental fatigue etc.

10. *On GIT*
(i) Increases gastric acid and pepsin secretion; and
(ii) Decreases gastric mucosal cell proliferation
Thus promotes peptic ulcer formation.
(iii) Increases absorption of fats from the intestine into the lymph.

11. *Resistance to Stress*
Any change in the environment that alters the optimal steady state in the body is called ***stress***. It is a normal physiological response to maintain life against adverse conditions *i.e.* variety of noxious or potentially noxious stimuli, which may be physical, mental, internal or external. These stimuli increase ACTH secretion which increases GC secretion. Most of the stressful stimuli also activate the sympathetic nervous system, including the *sympatho-adrenal medullary system*. General manifestation of stress is called *General Adaptation Syndrome* (page 734) which occurs in two stages:
(i) *Stage of Alarm* – No adaptation.
(ii) *Stage of Resistance* – Adaptation is optimum. This is brought about by interaction of adrenal cortex and adrenal medulla. For example: after removal of adrenal cortex, animals treated with maintenance dose of GC die immediately even when exposed to same noxious stimulus; that is why ***Adrenal Cortex is essential for life.***

Mechanism of action:
(i) GC interacts with catecholamines and causes activation of sympatho-adrenal medullary system;
(ii) GC enhances the action of catecholamines to maintain vascular reactivity (page 720);
(iii) GC is necessary for the catecholamines to exert their full FFA mobilizing action and the FFA are important during emergency for the energy supply.

Important Note
Long standing stress may precipitate abnormalities of Cushing syndrome (see below) by chronically elevating the levels of ACTH.

12. *Anti-Inflammatory and Anti-Allergic Action*
These effects are not seen with normal **physiological output** of GCs (25 mg/day); however, in **pharmacological doses** (50-75 mg/day) it causes:
(i) Inhibition of the inflammatory response to tissue injury by inhibiting ACTH secretion and can lead to severe adrenal insufficiency when treatment is stopped.
(ii) Suppression of the clinical manifestation of allergy.

Mechanism of production of inflammation **(Fig. 74.7)**
(i) Infection produces *local reaction* by causing:
(a) Swelling due to increased vascularization and increased capillary permeability secondary to increased kinin release; and
(b) Redness (hypererythmia).
(ii) Leucocyte lysosomal granules contain protease and hydrolase enzymes which lead to *tissue damage*.

Treatment of inflammation or allergy with high dosage of GCs causes:
(i) *decreased local reaction by:*
(a) decreasing hyperaemia, exudation, migration and infiltration of leucocytes at the site of injury;
(b) preventing release of kinins;
(c) inhibiting collagen synthesis;
(d) inhibiting phospholipase A_2 (page 93).
(ii) *prevents tissue damage* by stabilizing lysosomal membrane, thereby preventing escape of protease and hydrolase enzymes into the tissue fluid. Thus

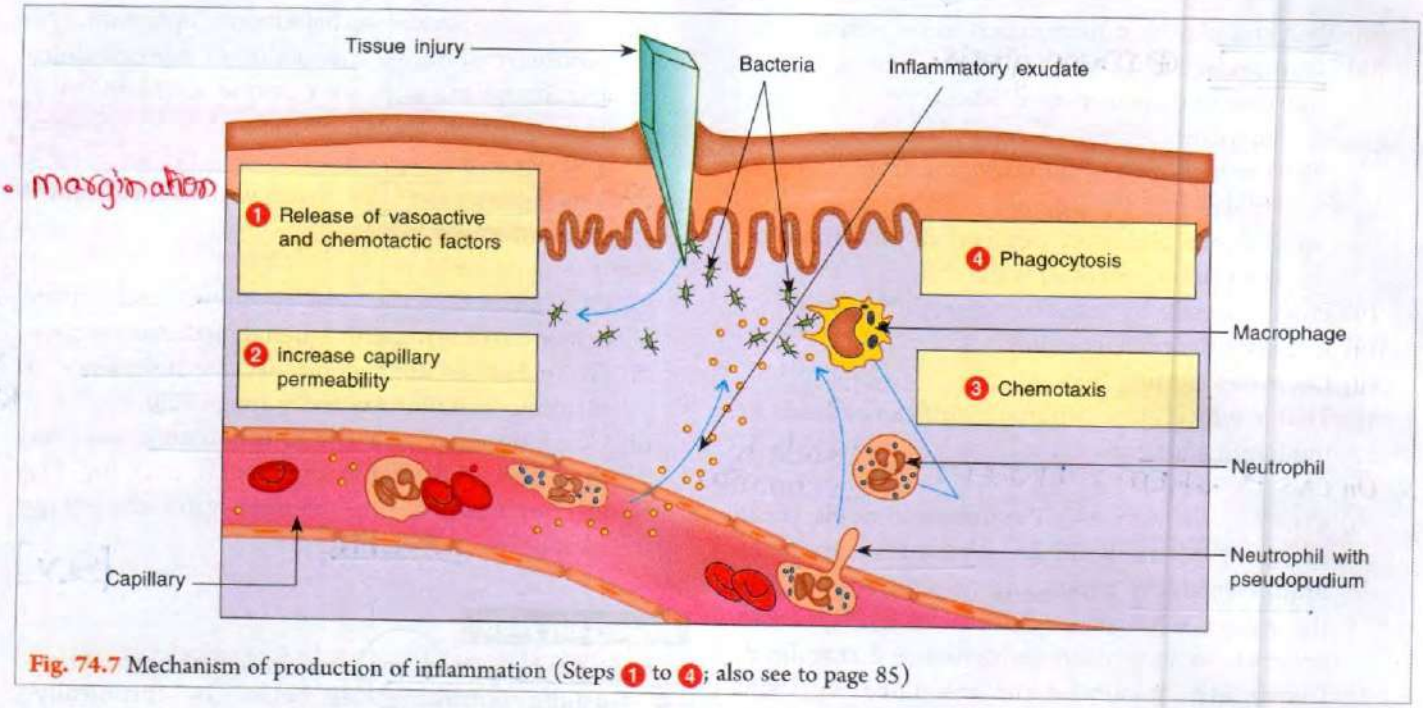


Fig. 74.7 Mechanism of production of inflammation (Steps 1 to 4; also see to page 85)

blocks the systemic effects of bacterial toxins by preventing damage to neighbouring tissues.

(iii) (a) *decreased fibroblastic activity*, which allows:
- spread of infection; and
- delays wound healing.

(b) decreased production of ground substance by collagen producing cells. This prevents tissue adhesion (GCs are, therefore, given after abdominal surgery).

(iv) *decreases release of endogenous pyrogens* from granulocytes, thus decreases fever.

(v) In late stages, *decreases antibody formation* by its destructive effect on fixed lymphoid tissues (the effect seen secondary to protein catabolism).

Note

GCs are used in prevention or reduction of immune response of the recipient to an organ transplant.

(vi) Slows the degrading effect of collagenase on joint tissues in rheumatoid arthritis. This is why GCs are injected intra articularly in arthritis.

(vii) Reduces histamine induced features of allergy or hypersensitivity response to antigen-antibody reaction by inhibiting release of histamine (as GCs decrease basophils). GCs do not affect the combination of antigen with antibody and have no influence on the effect of histamine once it is released, but it inhibits the intracellular synthesis of histamine.

Thus GCs act like *an asbestos suit against fire*, *i.e.* protecting the tissue from damage and preventing their normal response to injurious agents, but not extinguishing the fire.

Important Notes

1. GCs when used in patients with bacterial infections must be used along with antibiotics; otherwise signs and symptoms get masked by GC treatment; thus there may be serious and even fatal delays in diagnosis and institution of antibiotic treatment.
2. Prednisone and prednisolone are 'synthetic derivatives' of cortisone and cortisol respectively. Their anti-inflammatory potency is about five times that of their parent compound, without any increase of mineralocorticoid activity.

13. Other actions

(i) During foetal life, GCs *increase maturation of surfactant in lungs*.

(ii) In large doses GCs inhibit growth by decreasing GH and TSH secretion.

(iii) GCs inhibit the secretion of ACTH (page 719).

Applied: CUSHING'S SYNDROME

It is a clinical disorder which results from the exposure of body tissues to sustained high blood levels of glucocorticoids.

Causes:

(1) *Independent of ACTH* *i.e.* GC excess with low ACTH levels

(i) Iatrogenic: Prolonged treatment with high dosage of GCs (*most common cause*).

(ii) Adrenal cortex tumours: it causes atrophy of opposite adrenal due to suppression of ACTH secretion by high plasma cortisol levels.

(2) *ACTH dependent i.e.* GCs excess with increased ACTH levels

(i) Ectopic ACTH production by non-pituitary tumours *e.g.* cancer of the lung.

(ii) Basophilic tumours of pituitary.

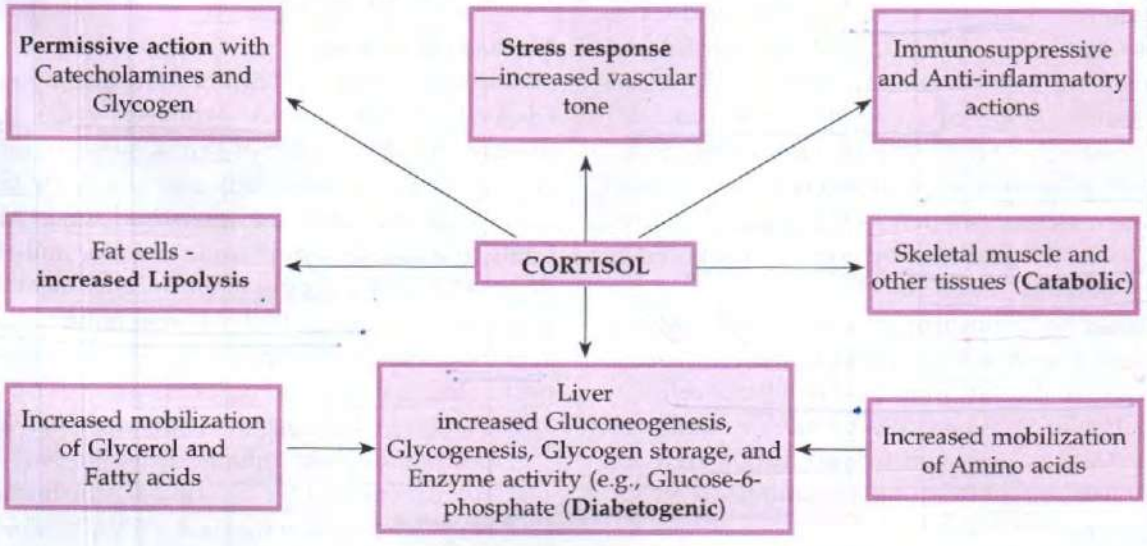
(iii) Iatrogenic: Treatment with ACTH.

Characteristic features

(As described by Harvey Cushing)

1. ***Protein metabolism:*** Increase in protein catabolism causes:
   (i) Negative nitrogen balance and retardation of growth.
   (ii) Thinning of the skin and subcutaneous tissues; skin becomes paper like and transparent.
   (iii) Muscles to get wasted and poorly developed, called *Steroid Myopathy*. This along with associated hypokalemia produces marked *muscular weakness*.
   (iv) Poor wound healing and minor injuries to produce bruises and ecchymoses, which get aggravated by precipitation of diabetes and decreased fibroblastic activity.
   (v) Hair to become thin and rough resulting in loss of scalp hair.
   (vi) Reduction in lymphoid tissue and dissolution of lymphocytes increases uric acid excretion in the urine.
   (vii) Breakdown of muscle which increases creatine excretion.
2. ***Carbohydrate metabolism.*** GCs excess produces hyperglycemia, glycosuria (due to hyperglycemia and increase in GFR), increased resistance to insulin and increase in liver glycogen, thus precipitate *insulin resistant diabetes mellitus*, specially in patients genetically predisposed to diabetes called *Steroid (adrenal) Diabetes*. It is associated with hyperlipidemia and ketosis.
3. ***Fat metabolism.*** GCs cause redistribution of fat at the expense of fat in the extremities, called *'Centripetal' distribution of fat*, **(Fig. 74.8)** therefore,
   (i) extremities are thin;
   (ii) deposition of fat
      (a) over abdominal wall leads to 'pendular' abdomen and rupture of thin skin due to stretching causes prominent ***reddish-purple striae*** (due to increased RBC count)
      (b) over face leads to ***moon like face*** with narrow eye slit and fish like mouth (because GCs also have mild mineralocorticoid activity)
      (c) on upper back causes ***buffalo hump***;
   (iii) increase in FFA level, blood lipids and cholesterol leads to *Atherosclerosis*.
4. **Electrolyte and water metabolism and vascular reactivity**: oedema and hypertension page 720).
5. **Bone metabolism**: osteoporosis and precipitate tetany (page 720).
6. **Blood**: Eosinopenia, lymphopenia, basopenia, neutrophilia, polycythaemia, increase in platelet count and decrease in clotting time (page 720).
7. **CNS**: frank toxic psychosis, euphoria, restlessness, excitability etc. (page 721).
8. **GIT**: predisposes to peptic ulcer formation (page 721).
9. **Anti-inflammatory action**: increased susceptibility to infection (page 721).
10. **Sexual changes**:
    (i) Increase in facial hair *(Hirsutism)* and 'acne' due to increased secretion of adrenal androgen.

Summary: The Principal actions of Glucocorticoids



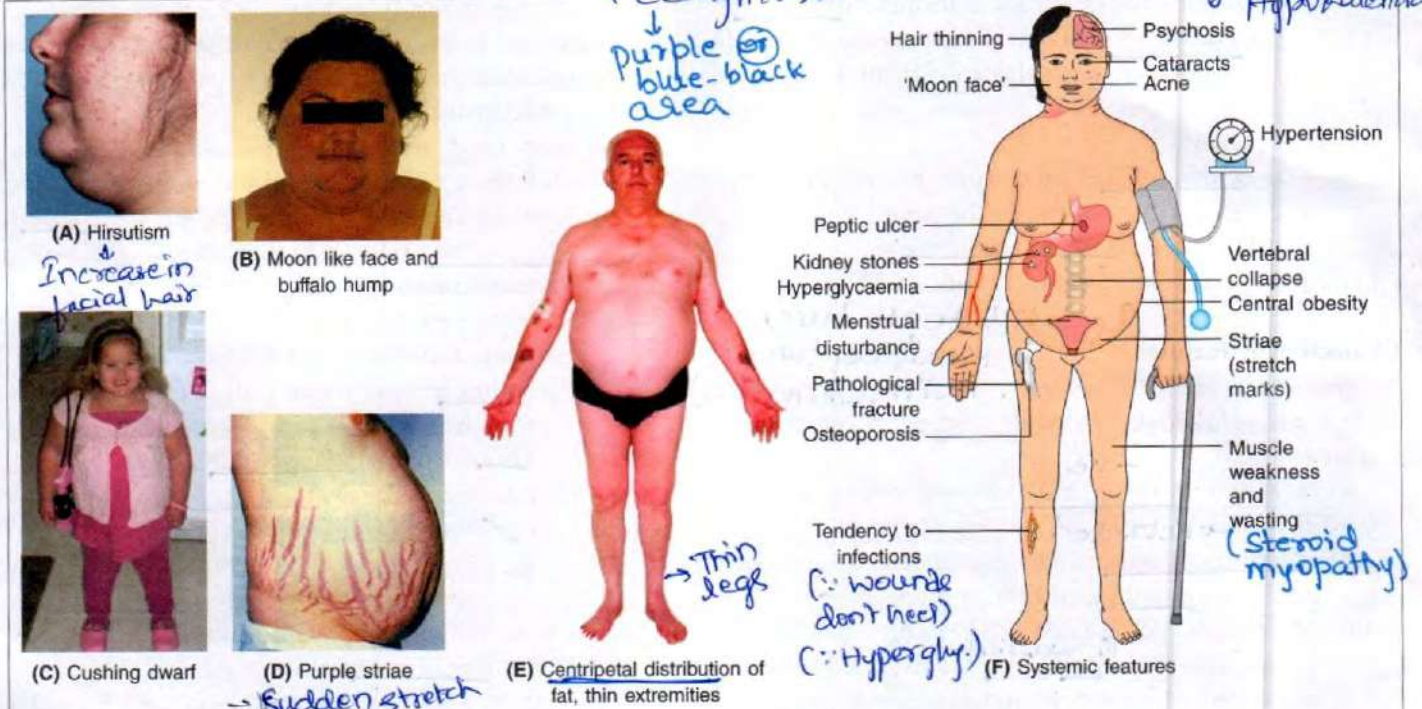


Fig. 74.8 Cushing's Syndrome, characteristic features results from an excess of circulating glucocorticoids.

(ii) Impotency and hypogonadism in males and amenorrhoea in females.

11. Diagnosis: free cortisol level in urine increases to three-fold (normal: 0.03 mg/ day).

MINERALOCORTICOIDS: ALDOSTERONE

Biosynthesis, transport, metabolism and excretion: page 716.

ACTIONS OF ALDOSTERONE

(1) Conservation of Sodium and Excretion of Potassium

Aldosterone causes retention of sodium from the kidney and increased urinary excretion of potassium; it has little effect on water excretion.

(i) It acts on the *principal (P) cells* of DCT and CT to increase Na^+ reabsorption in exchange for K^+ and H^+ which are then excreted in urine. (Aldosterone increases the number of *active epithelial Na^+ channels* – ENaC : see below). Of the total amount of filtered Na^+, only 1-2% is actively reabsorbed via the aldosterone dependent mechanism in the DCT (page 524). More than 75% of K^+ excreted in urine is attributed to K^+ secretion into the DCT.

(ii) It increases Na^+ reabsorption from the GIT, salivary and sweat glands. It may also lead to increase in K^+ and decrease the Na^+ in muscle and brain cells.

(iii) Stimulation of K^+ excretion is greatly dependent on dietary Na^+, as indicated by lack of K^+ excretion after aldosterone administration in animals with Na^+ deficient diet.

(iv) *Excess of Aldosterone* leads to:
   (a) increased plasma Na^+/K^+ concentration ratio (*normal:* 30) due to increased excretion of K^+;
   (b) decline in urine Na^+/K^+ concentration ratio (*normal:* 2) due to decreased Na^+ and increased K^+ excretion.

(v) *Removal of adrenal cortex results in:*
   (a) Na^+ and water loss, but Na^+ loss is more than water loss (as posterior pituitary is intact); however, decrease in ECFV produces hypotension, dehydration, circulatory collapse and finally death;
   (b) retention of K^+ produces hyperkalemia, dehydration and circulatory collapse.

Therefore *Aldosterone is essential for life.*

Mechanism of action

Aldosterone being steroid hormone acts by stimulating DNA-dependent mRNA synthesis (page 653). Na^+ diffuses out of the urine or saliva, sweat or GIT into the surrounding epithelium cells and is actively transported from these cells into the interstitial fluid. Aldosterone binds to a specific cytoplasmic receptor and the *Steroid-Receptor Complex* migrates to the nucleus, increases mRNA formation and promotes *Aldosterone Induced Protein (AIP)* synthesis. 'AIP' is responsible for Na^+ transport via three postulated hypothesis **(Fig. 74.9)**.

(i) ***Permease hypothesis*** – AIP increases membrane permeability of tubular cells to Na^+ from the tubular lumen (*due to increased activity and synthesis of epithelial sodium channels – ENaCs*). This increases

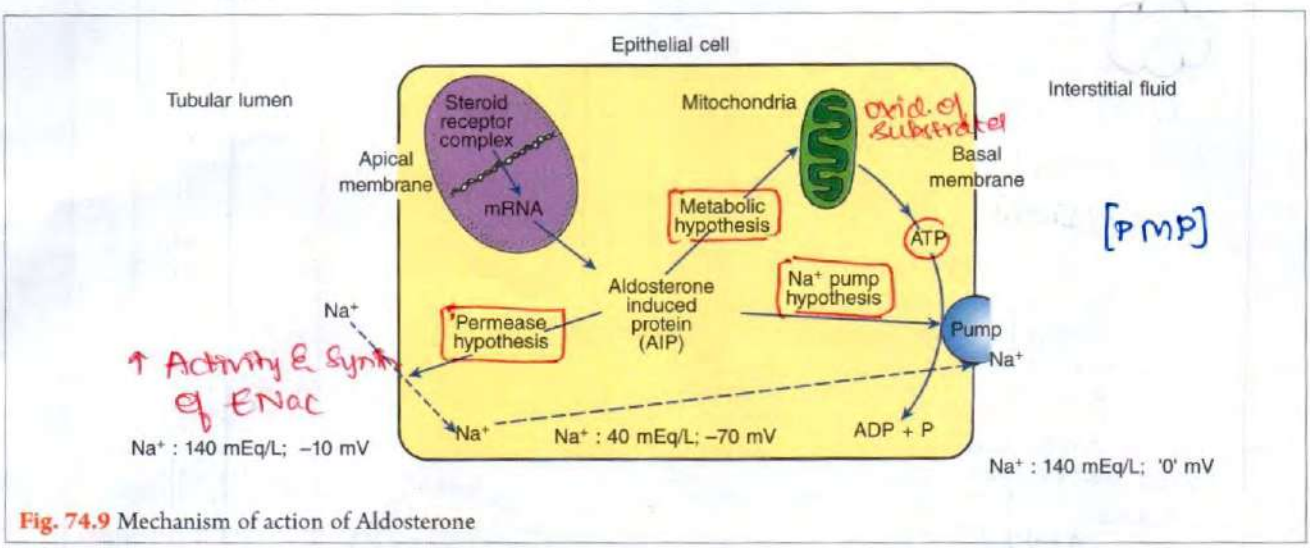


Fig. 74.9 Mechanism of action of Aldosterone

Na^+ reabsorption *passively* along the electrical and concentration gradients.

(ii) ***Metabolic hypothesis*** – AIP promotes oxidation of substrate to provide increased ATP. ATP causes more energy release for increased *active* transport of Na^+.

(iii) ***Sodium Pump hypothesis*** – AIP acts directly to increase the activity of Na^+ pump (increase activity of membrane Na^+–K^+ exchangers).

The net effect is increased transport of Na^+ from tubular lumen into the interstitium and thence into the blood stream.

(2) Water Excretion and ECF Volume Regulation

(i) Aldosterone has no direct effect on GFR, renal plasma flow (RPF) or renin production; however, by stimulating Na^+ reabsorption it causes water retention. The resultant *expansion of ECFV* then leads to an increase in GFR and RPF and a decrease in renin production.

(ii) A high circulating aldosterone level is a common finding in oedematous states such as cirrhosis of liver, nephrosis, congestive heart failure, etc. It is primarily due to the increased aldosterone secretion caused by reduction in the effective circulating blood volume.

(3) Relationship with Acid-Base Balance

Aldosterone affects acid base balance through its control of K^+ and H^+ secretion. Under the influence of aldosterone, increased amounts of Na^+ are in effect exchanged for K^+ and H^+ in the DCT (K^+ competes with H^+ for Na^+). Therefore,

(i) *Excessive secretion of aldosterone produces* hypokalemia which is characterized by increase in intracellular $[H^+]$. This promotes secretion of H^+ over K^+ in DCT and results in *Metabolic Alkalosis*.

(ii) *Conversely*, lack of secretion of aldosterone produces hyperkalemia, which is characterized by increase in intracellular $[K^+]$. This favours secretion of K^+ over H^+ from DCT and results in *Metabolic Acidosis*.

(4) Secondary Effects of Excess of Aldosterone

These are secondary to Na^+ reabsorption and its exchange with H^+ and K^+ in the DCT.

(i) Aldosterone excess produces *hypernatremia* which leads to increase in ECFV and hypertension due to Na^+ and water retention.

(ii) Increased secretion of K^+ in DCT increases its excretion in urine causing marked ***hypokalemia*** *which is characterized by:*

(a) muscular weakness;

(b) increased H^+ secretion (because K^+ and H^+ compete with Na^+) produces:
- acidic urine; and
- increase HCO_3^- reabsorption;

Increased HCO_3^- reabsorption → metabolic alkalosis (***hypokalemic alkalosis***) → decreases free ionized Ca^{2+} which may precipitate ***Tetany;***

(c) interferes with insulin secretion which decreases glucose tolerance (as Ca^{2+} and K^+ are necessary for insulin secretion);

(d) if prolonged, it causes renal tubular damage (***hypokalemic nephropathy***) producing polyuria, polydipsia, interferes with concentrating ability of kidneys.

(iii) *Escape Phenomenon* – In patients with hyperaldosteronism or when aldosterone is administered for several days to normal individuals, the kidney *escapes* from the Na^+ retaining effect, called *escape phenomenon.*

Mechanism: oversecretion of aldosterone produces hypernatremia with increase in ECFV. When the ECFV expansion reaches a certain limit, Na^+ excretion is usually increased in spite of continued action of aldosterone on the DCT. It is probably due to increased secretion of ANP (page 559).

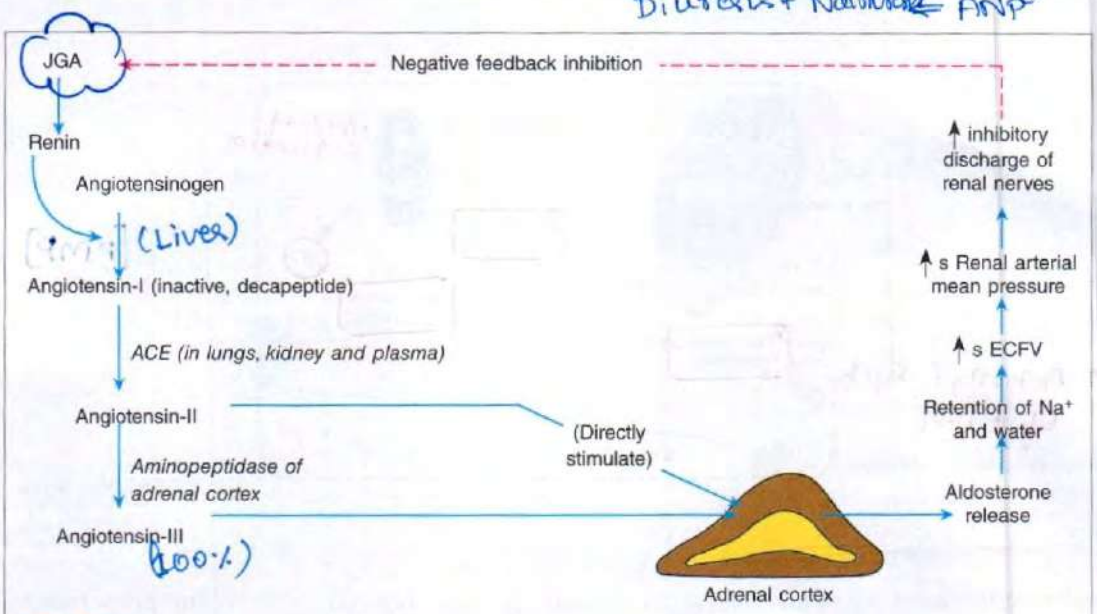


Fig. 74.10 Renin-angiotensin system (ACE: angiotensin converting enzyme; JGA: Juxtaglomerular apparatus) (Also refer to page 559)

Important Note

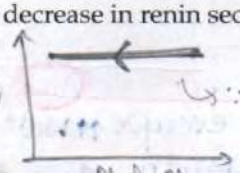
The escape phenomenon may not occur in patients with oedematous states such as congestive heart failure, nephrosis, cirrhosis of liver, toxaemia of pregnancy, etc. This is because of reduction in the amount of Na^+ reaching the DCT due to decreased renal blood flow (page 511)

REGULATION OF ALDOSTERONE SECRETION

Regulation of secretion of aldosterone is brought about by *extra renal* and *intra renal*, control mechanisms.

A. Extra Renal Control Mechanism

1. ***Hyponatremia:*** Decrease in plasma Na^+ increases aldosterone secretion via:
   (i) *Renin-angiotensin system* (see below); and
   (ii) *direct stimulation of adrenal cortex;*
2. ***Hyperkalemia:*** Increase in plasma K^+ increases aldosterone secretion by direct stimulation of adrenal cortex. It acts in similar fashion as angiotensin II acts *i.e.* by depolarizing the cells, which opens voltage gated Ca^{2+} channels, thus increasing the intracellular Ca^{2+}.
3. ***Circadian rhythm*** of aldosterone and renin secretion is same as seen with ACTH and GC secretion (page 718).
4. ***ACTH:*** Role of ACTH in secretion of aldosterone is minimal. *Proof:* Injection of large doses of ACTH increases aldosterone secretion which falls in 1-2 days even with increasing dose of ACTH injection. This is because of decrease in renin secretion secondary to fall in ECFV.



5. Factors which increase GC secretion (page 718) increase aldosterone secretion by increasing ACTH secretion.
6. Atrial Natriuretic Peptide (ANP): It inhibits renin secretion and decreases effect of angiotensin II on the adrenal cortex (page 559).

B. Intra Renal Control Mechanism

Aldosterone secretion is regulated by ***Renin-Angiotensin System*** **(Fig. 74.10)**, the major component of which is juxtaglomerular apparatus – JGA (page 504). The angiotensin II formed by release of renin binds to *angiotensin II receptors* (AT_1) coupled by G-protein in the zona glomerulosa to activate phospholipase resulting in increase in protein kinase C. Initially it causes increased conversion of cholesterol to pregnenolone and later increases conversion of corticosterone to aldosterone.

1. ***Role of sympathetic nervous system.*** It plays an important role in the control of renin release via the renal nerves.
   (i) JG cells and afferent arterioles are innervated directly by sympathetic unmyelinated post-ganglionic fibers. In the absence of renal nerves, the renal response to Na^+ depletion is decreased.
   (ii) Catecholamines and stimulation of renal nerves by vasoconstriction of afferent arterioles decrease renal perfusion pressure which increases renin release. This response is mediated via β-adrenergic receptors, therefore, β-agonists (sympathomimetic *e.g.* isoproternol) increase renin release while β-blockers (*e.g.* propranolol) or cutting of renal nerve decrease renin.

(iii) Sympathetic nervous system, by modulating the secretion of renin has an indirect effect on aldosterone secretion. Thus, *any stimulus which increases renin release increases aldosterone secretion and vice versa.*

2. ***Role of Renin.*** Renin circulatory half life is 40-120 minutes. **Renin release is increased by** decrease in effective circulating blood volume, which is induced by:
   (i) Acute hypovolemia due to haemorrhage, diuretic administration, or salt depletion (specially sodium).
   (ii) Acute hypotension due to ganglion blockade, or change in posture (postural hypotension).
   (iii) Chronic disorders associated with oedema *e.g.* cirrhosis of liver, CCF, nephrotic syndrome.
   (iv) Increased sympathetic activity caused by:
      (a) Upright posture (standing). This also decreases ANP secretion (page 580).
      (b) Exercise
      (c) Catecholamine administration, and
      (d) K^+ depletion.

Renin release is decreased by:
(i) Angiotensin II and III
(ii) ADH
(iii) Hypernatremia
(iv) Hyperkalemia (it also stimulates zona glomerulosa to secrete aldosterone) (page 725), and
(v) Prostaglandins specially PGE_2
(Also refer to page 506)

APPLIED ASPECT

A. CONN'S SYNDROME:
Primary Hyperaldosteronism

It refers to a condition in which there is prolonged excessive secretion of aldosterone from the adrenal cortex (*cause* – adenoma, tumour of zona glomerulosa). It is **characterized by:**

1. Elevated plasma and urinary aldosterone levels.
2. Rise in plasma sodium and marked fall in plasma potassium; decrease in sodium content of sweat, saliva and GIT secretions.
3. Prolonged hypokalemia which is associated with:
   (i) marked muscular weakness,
   (ii) kidney damage resulting in loss of its concentrating power and polyuria, called *hypokalemic nephropathy* (page 725),
   (iii) metabolic alkalosis, which may precipitate *tetany* (page 710).
4. Hypertension due to Na^+ and water retention. Increase in ECFV usually does not occur because of polyuria of hypokalemic nephropathy.
5. *Absence of peripheral oedema because of escape phenomenon* (page 725).
6. Muscle weakness

B. SECONDARY HYPERALDOSTERONISM
It is a condition in which aldosterone oversecretion occurs due to extra-adrenal factors. It occurs in patients with oedematous states *e.g.* congestive heart failure, nephrosis, cirrhosis of liver, and toxaemia of pregnancy.

Characteristic features
1. Increase in circulating levels of angiotensin II and renin; urinary aldosterone also increases.
2. Urinary K^+ excretion is not increased because there is a reduced flow of fluid into and through the distal segment of the nephron, which reduces K^+ secretion and offsets the stimulating effect of aldosterone. Also, decreased Na^+ and water delivery to DCT, the quantity of K^+ (and H^+) secreted in urine is limited. Hypokalemia may be precipitated by diuretics.
3. Hypertension with 'oedema'; this occurs due to Na^+ retention and water accumulation in the interstitial fluid compartment.

~~Muscle weakness~~ No much m weakness.

C. ADDISONIAN CRISIS: Adrenal Crisis
This is an 'acute' form of adrenal cortex insufficiency which occurs:
(i) after adrenalectomy (removal of adrenal cortex);
(ii) after abrupt withdrawal of therapeutically administered glucocorticoids inhibits ACTH synthesis resulting in adrenocortical atrophy; or
(iii) in patients with reduced basal secretion of cortisol when they are exposed to a sudden stress or infection.

It abolishes all secretions and is lethal, death occurs immediately due to circulatory collapse (page 724).

D. ADDISON'S DISEASE:
Primary Adrenocortical Insufficiency = Chronic

It is the 'chronic' form of adrenal cortex insufficiency in which 'slow destruction of the adrenal cortex' reduces secretion of glucocorticoids (cortisol) and mineralocorticoids (aldosterone).

Causes
1. Auto-immune disorders (*most common*) Grave's,
2. Tuberculosis (TB)
3. Carcinoma

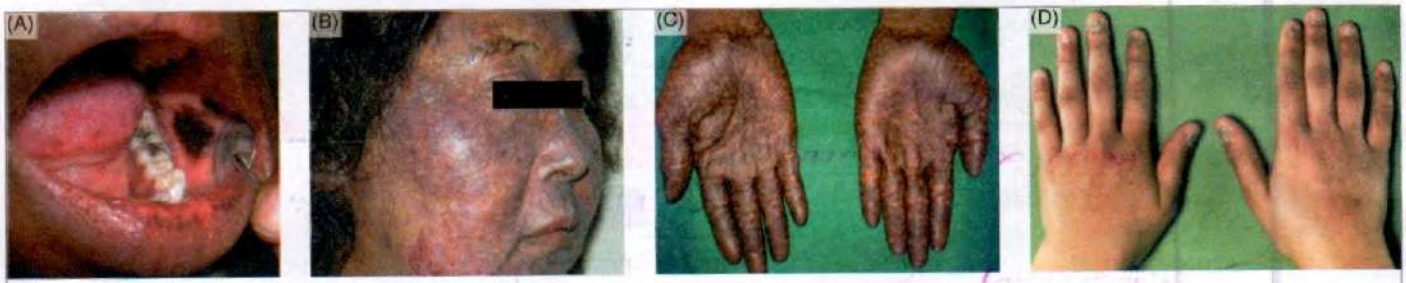


Fig. 74.11 Hyperpigmentation: (A) Gums, (B) Face and (C & D) Hands

4. *Water-house Friderichsen syndrome i.e.* haemorrhage of adrenal cortex due to severe infection.

Characteristic features

The features of relative adrenocortical insufficiency are mainly due to deficiency of GCs and some due to aldosterone lack also. These include:

1. Hypotension and water intoxication (page 720).
2. Anorexia, nausea, vomiting and diarrhoea, leading to dehydration and loss of weight.
3. Muscular weakness, mental confusion etc. (page 719).
4. Increased ACTH secretion for long time increases β-MSH activity (as ACTH has 1/100 β-MSH activity). This leads to generalized *pigmentation of skin* mucous membrane, gums, pressure points, folds and creases and darkening of areolas **(Fig. 74.11)**.
5. Decrease ability to withstand stress due to trauma, infection, etc.; if untreated, produces Addisonian Crisis (see above).
6. The morning plasma cortisol level is reduced sometimes to 'zero'.
7. Blood: Eosinophilia, lymphocytosis, neutropenia and anaemia (page 720).
8. Hypersensitive to taste and smell and slowing of α-activity in E.E.G. (page 721)

E. SECONDARY AND TERTIARY ADRENOCORTICAL INSUFFICIENCY

In diseases of anterior pituitary or hypothalamic disoders, there is deficient secretion of ACTH *or* CRH respectively and hence decreased secretion of GCs only (as secretion of aldosterone from the zona glomerulosa is not controlled either by the anterior pituitary *or* the hypothalamus).

Characteristic features

In addition to features of GC deficiency (see above), it shows:

1. Electrolyte balance is normal.
2. There are features of associated deficiency of other endocrine glands controlled by the anterior pituitary.
3. Mild or no skin pigmentation as plasma ACTH level is low.

Note

Patients with kidney disorder, and low circulating renin levels may present with isolated aldosterone deficiency, called *Hyporeninemic hypoaldosteronism*.

SEX STEROIDS

1. During foetal life, adrenals are hyperplastic and produce DHEA (page 714) which serves as the main precursor of oestrogen formation by the placenta. After birth adrenal cortex regresses and secretes less sex hormones.
2. At puberty in both sexes, adrenal androgen (DHEA) secretion again increases. It shows less than 20% of the activity of testosterone; therefore, exert very little masculinizing effect when secreted in physiological amounts. It contributes to increase in muscle mass, sexual hair and seborrhoea. Its secretion is controlled by ACTH by AASH (page 775) and not by gonadotrophins.

Important Notes

(i) The development of libido in women depends primarily on the action of adrenal androgens. *Proof:* libido persists after ovariectomy but not after adrenalectomy even with GC administration.

(ii) In males adrenal androgens are weak and cannot prevent the hormonal effects of castration.

Applied: Adrenogenital Syndrome

This syndrome is due to tumour of adrenal cortex which causes excessive secretion of sex steroids. How? Congenital deficiency of the enzymes 21 β-hydroxylase and 11β-hydroxylase leads to deficient secretion of aldosterone, cortisol and the syndrome of *congenital adrenal hyperplasia*. The hyperplasia is due to increased secretion of ACTH. The characteristic pattern that develops is called *adrenogenital syndrome*. Therefore,

1. Pre-pubertal boys develop secondary sexual characters without the testicular growth, called *Precocious Pseudo Puberty* (page 778).

Characteristic features

A. Prepubertal females develop:
   1. Primary amenorrhoea
   2. Partial masculinisation (diamond shape pubic hair)
   3. Increase serum testosterone with normal female 46XX chromosome constitution resulting in increased androgen production
   4. Female pseudohermaphroditism

B. Prepubertal boys develop secondary sexual characters without the testicular growth called *pseudo precocious puberty*

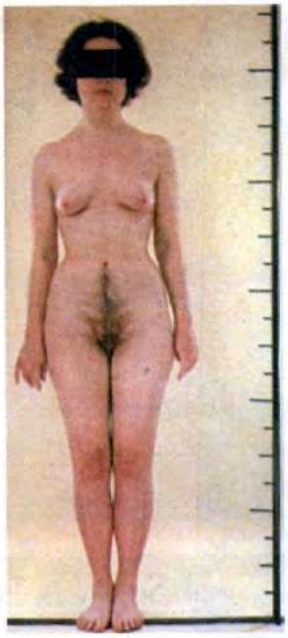


Fig. 74.12 Congenital virilizing adrenal hyperplasia, results from excessive production of androgen caused by 21 β-hydroxylase deficiency mainly.

2. In adult males, enhancement in existing secondary sexual male characters.
3. In genetically female foetus before 12 weeks of gestation it leads to development of male type external genitalia with ovaries, called *Pseudo Hermaphroditism* (page 774).
4. Prepubertal and adult females develop male secondary sexual characters (*Adrenal Virilism*, see **Fig. 74.12**). The features include: deepening of the voice, amenorrhoea, enlargement of clitoris, growth of hair in masculine distribution (diamond shaped pubic hair) and marked increase in muscular growth towards the male type.
5. In majority of cases, associated aldosterone deficiency causes loss of Na^+ (***Salt losing form*** of adrenal hypeplasia) resulting in hypovolemia. In some cases excessive secretion of 11-deoxycortisole produces hypertension (***hypertensive form*** of congenital adrenal hyperplasia).

Important Note

Rarely adrenal tumours secrete oestrogen to produce feminization in males, with enlargement of the breasts, atrophy of the testes and impotency.

Study Questions

1. **Give physiological basis of:**
   (i) Pregnant women have high total plasma 17-hydroxycorticoids levels without symptoms of GC excess.
   (ii) ACTH also possesses some MSH activity.
   (iii) The plasma free cortisol level rises high during stress than it does with maximum ACTH stimulation in the absence of stress.
   (iv) Sudden drop in circulating GC level is not a potent stimulus to ACTH secretion.
   (v) Mechanism of production of inflammation and its management with GC.
   (vi) GCs are used in prevention of rejection of a tissue transplant.
   (vii) Adrenal diabetes.
   (viii) Hyperglycemic effect of GC.
   (ix) Water intoxication in adrenal cortex insufficiency.
   (x) Glucose fever
   (xi) Osteoporosis associated with GC excess.
   (xii) Anaemia in persons suffering with chronic adrenal insufficiency.
   (xiii) Centripetal distribution of fat in Cushing's syndrome.
   (xiv) Escape phenomenon.
   (xv) Diurnal variation of ACTH secretion.
   (xvi) General adaptation syndrome.
   (xvii) GC acts like an asbestos suit against fire
   (xviii) Blood levels of GC are increased independent of ACTH
   (xix) Permissive action of GC.
   (xx) The changes in eosinophil levels are used as index of ACTH secretion
   (xxi) Adrenal cortex is essential for life
2. **What will happen and why:**
   (i) To various body functions in GC deficiencies?
   (ii) To blood cells and lymphatic organs during GC excess?
   (iii) If corticosteroids are given in an individual suffering from epilepsy?
   (iv) If prolonged treatment with GC is stopped suddenly?

3. **Write short notes on:**
   (i) Regulation and secretion of ACTH in response to stress.
   (ii) Steroid myopathy and steroid diabetes.
   (iii) Centripetal fat distribution in Cushing's syndrome.
   (iv) Escape phenomenon.
   (v) Conn's syndrome.
   (vi) Physiological and pharmacological effects of glucocorticords
   (vii) Addisonian crisis and Addison's disease.
   (viii) Adrenogenital syndrome.
   (ix) Congenital virilizing adrenal hyperplasia.
   (x) Regulation of ACTH secretion.
   (xi) General adaptation syndrome
   (xii) Actions of aldosterone
   (xiii) Sex steroids
4. **Describe the physiological role of plasma proteins that bind adrenocortical hormones.**
5. **Describe the mechanism by which mineralocorticoid and glucocorticoid produce changes in cellular function**
6. **Name the various layers of adrenal cortex and hormones they secrete.**
7. **Mention the functions of adrenal gland during foetal life.**
8. **Name the factors which affect ACTH secretion. What determines the rate of ACTH secretion?**
9. **Give the characteristic pattern which results from exposure of body tissues to sustain high blood levels of GC.**
10. **Differentiate between:**
    (i) Purple and white striae
    (ii) Primary and secondary adrenocortical insufficiency
    (iii) Primary and secondary hyperaldo-steronism.
    (iv) Physiological and pharmacological effects of adrenal androgens
11. **Explain briefly the role of GC in control of distribution of body water and electrolytes.**
12. **Mention effects of alteration in aldosterone secretion on acid base balance.**
13. **Give the secondary effects of excess of aldosterone in the body.**
14. **How is regulation of aldosterone secretion brought about?**
15. **Describe the action of aldosterone and the mechanism that regulate its secretion.**
16. **Draw labelled diagram:**
    (i) Costisol distribution in the body
    (ii) Regulation and factors affecting ACTH secretion
    (iii) Mechanism of action of ACTH
    (iv) Variations in glucocorticoids and ACTH levels in 24 hours
    (v) Mechanism of action of aldosterone
    (vi) Renin-Angiotensin system

MCQs

1. **The major steroid hormone secreted by the inner zone of the foetal adrenal cortex is:**
   (a) Cortisol (b) Dehydroepiandrosterone (DHEA)
   (c) Corticosterone (d) Oestrogen
2. **Normal 24 hours glucocorticoids derivatives excreted in urine:**
   (a) 0.3 mg (b) 3 mg (c) 15 mg (d) 22 mg
3. **ACTH is most effective in stimulating the secretion of:**
   (a) Hydrocortisone (cortisol) (b) Corticosterone
   (c) Adrenal androgenic hormones (d) Aldosterone
4. **ACTH secretion gets inhibited by:**
   (a) Baroreceptor discharge (b) Emotional stimuli (anger, anxiety, fear, frustration)
   (c) Stress (surgical operation, haemorrhage, hypoxia etc.) (d) Trauma, exercise, exposure to cold
5. **Glucocorticoids:**
   (a) Secretion increases following injury (b) Favours protein synthesis
   (c) Enhances effects of antigen-antibody reactions (d) Tends to lower blood pressure

6. **Cortisol can cause all of the following *except*:**
   (a) Inflammation to be suppressed
   (b) Fat to be used for energy
   (c) Lysosomal membranes to become unstable
   (d) The blood glucose concentration to increase
7. **All are seen in Cushing's syndrome *except*:**
   (a) Truncal obesity (b) Hypertension (c) Hypoglycemia (d) Hirsutism
8. **During aldosterone deficiency there is likely to be a fall in:**
   (a) Urine volume (b) Plasma potassium level (c) Blood volume (d) Blood viscosity
9. **Excessive secretion of aldosterone results in:**
   (a) Metabolic acidosis (b) Metabolic alkalosis (c) Respiratory acidosis (d) Respiratory alkalosis
10. **The least important factor in regulation of aldosterone secretion is:**
    (a) ACTH (b) Na^+ (c) K^+ (d) Renin-angiotensin
11. **Stimulation of both glucocorticoid (GC) and mineralocorticoid secretion is seen with:**
    (a) Anxiety (b) Exercise (c) Hyperkalemia (d) Low sodium diet
12. **Conn's syndrome is characterized by all of the following *except*:**
    (a) Marked muscular weakness
    (b) Hypokalemic nephropathy
    (c) Tetany
    (d) Oedema
13. **In Addison's disease the following is seen:**
    (a) Hyperkalemia (b) increase in ECFV (c) Hyperglycemia (d) High blood pressure
14. **Pregnant women have high total plasma 17-hydroxycorticords levels without symptoms of glucocorticoid excess because:**
    (a) ACTH secretion increases
    (b) Glucocorticoids demand increases during pregnancy
    (c) Most of glucocorticoids are rapidly metabolised to inactive form
    (d) Free cortisol level is normal whereas bound levels remain increased
15. **The diurnal variation of ACTH secretion control is:**
    (a) Cerebral cortex alone
    (b) Limbic system and hypothalamus
    (c) Hypothalamus and cerebral cortex
    (d) Hypothalamus alone
16. **Excessive glucocorticoids (GC) production is characterized by all *except*:**
    (a) Thick skin
    (b) Hypertension
    (c) Demineralisation of bone
    (d) Delayed healing of wounds
17. **What is *not true* for aldosterone?**
    (a) Secreted in increased amounts when blood volume falls
    (b) Is a polypeptide
    (c) Secretion tends to increase renal arterial pressure
    (d) Secretion results in a reduction in urinary volume
18. **Addisonian (or adrenal) crisis is:**
    (a) Acute form of adrenal cortex insufficiency
    (b) Seen after adrenal cortex removal
    (c) Seen after abrupt withdrawal of glucocorticoids
    (d) All of the above are true
19. **Loss of libido in women is due to:**
    (a) Ovariectomy
    (b) Adrenalectomy
    (c) Deficiency of gonadotrophins
    (d) All of the above

Answers

1. (b)	2. (d)	3. (a)	4. (a)	5. (a)	6. (c)	7. (c)	8. (c)	9. (b)	10. (a)
11. (a)	12. (d)	13. (a)	14. (d)	15. (b)	16. (a)	17. (b)	18. (d)	19. (b)	

Innervation path: (RETICULAR Formation) Medulla ob. & Hypothalamus → T_5 T_6 T_7 T_8 T_9 horn of Gray matter → Splanchnic n (Type B) (myelinated) → Medullary cells

Chapter 75

The Adrenal Medulla

I. Physiological anatomy
II. Biosynthesis, metabolism and excretion of catecholamines
III. Regulation of catecholamine secretion
IV. Actions of catecholamines
V. Applied aspect: Hypo and Hypersecretion (Phaeochromocytoma)

PHYSIOLOGICAL ANATOMY

1. *Adrenal medulla* consists of cords of densely innervated granules containing cells which are attached to venous sinuses. These cells are of two types:
   (i) *Epinephrine secreting cells*; they have large, less dense granules; and LARGE + SPARSE
   (ii) *Nor-epinephrine secreting cells*; they have small and more dense granules. SMALL + DENSE
   Both types of cells are stained brown with chrome salts, therefore, called ***Chromaffin Cells*** (or ***Phaeochromocytes***) **(Fig. 75.1)**. This chromaffin reaction is due to oxidation of catecholamines (epinephrine, nor-epinephrine and dopamine) in the granules.
2. In humans, approximately 80 to 90% of chromaffin granules in adrenal medulla synthesize epinephrine (adrenaline), the remaining 10 to 20% synthesize nor-epinephrine (nor-adrenaline).

Chromaffin ↓ Taken up Chromium salts

80-90%

$T_{1/2}$ = 1-2 min

mainly in medulla

10% → mainly in nerves

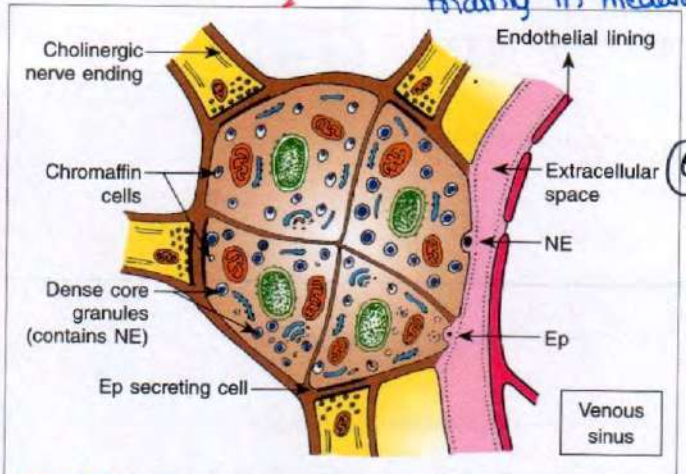


Fig. 75.1 Chromaffin cells (phaeochromocytes): Epinephrine (Ep) and nor-epinephrine (NE) secreting adrenal medullary cells

Note

The type of cell that secretes dopamine is not recognized. Dopamine is also synthesized from the sympathetic ganglia. (50%) - In adrenal medulla (50%) - In sympath. n end.

3. *In early foetal life*, adrenal medulla contains only nor-epinephrine (NE); the proportion of epinephrine (Ep) increases steadily after birth.
4. In the granulated vesicles Ep and NE are bound to ATP and a binding protein, called *Chromogranin*. The granules contents are released by exocytosis into the blood stream.
5. *Innervation:* Adrenal medulla is innervated entirely by splanchnic nerves, whose fibers end round the medullary cells, called pre-ganglionic fibers. These are myelinated (type B) secretomotor fibers which come out from the lower thoracic segments (T_5 to T_9) of the ipsilateral intermediolateral grey column of the spinal cord. ORIGIN

   Thus, adrenal medulla is in effect a ***sympathetic ganglion*** in which the post-ganglionic neurons have lost their axons and become secretory cells. The cells secrete when stimulated by the pre-ganglionic nerve fibers, that reach the gland via the splanchnic nerves.
6. *Mechanism of release of catecholamines*
   Stimulation of pre-ganglionic splanchnic fibers → release of A-ch → stimulate medullary chromaffin cells, by promoting inward movement of Ca^{2+} → secretion of Ep and NE into blood by exocytosis.

* Enkephalins, Neuropeptide Y

Ca^{++} / calmodulin pathway

āa ⇒ must be through cAMP mediated.

BIOSYNTHESIS, METABOLISM AND EXCRETION OF CATECHOLAMINES

A. BIOSYNTHESIS

Adrenal medulla synthesizes and secretes *catecholamines* (Ep, NE and dopamine).

1. Ep is produced almost exclusively in the adrenal medulla, with small amounts synthesized in the brain. Essentially all of the circulating Ep is derived from the adrenal medulla.
2. NE is synthesized in peripheral and central adrenergic neurons and in the adrenal medulla. It is widely distributed in neural tissues, including the adrenal medulla, sympathetic post-ganglionic fibers and the CNS. In brain, its concentration is the highest in the hypothalamus. The NE content of a tissue reflects the extent (or density) of its sympathetic innervation.

The chemical reactions involved in the catecholamine synthesis are shown in Fig. 75.2.

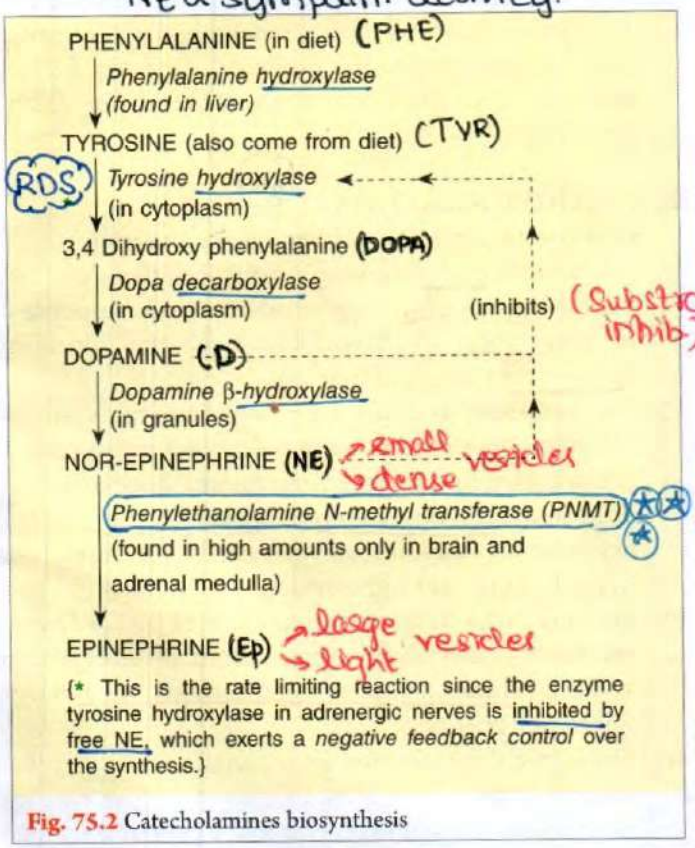


Fig. 75.2 Catecholamines biosynthesis

Applied: *Phenyl Pyruvic Oligophrenia or phenylketonuria*, an inborn error of metabolism due to inheritance of particular mutant gene leads to the deficiency of phenylalanine hydroxylase. This increases phenylalanine and its derivatives specially keto derivatives in the blood. As a result, protein synthesis in brain decreases producing *severe mental retardation* with associated decrease in muscle tone, learning and memory. These may be due to the deficiency of brain catecholamines and 5 HT level.

B. METABOLISM: REMOVAL AND INACTIVATION

The plasma *half-life* of catecholamines is 1-3 minutes. The biological effects of circulating catecholamines are terminated rapidly by two uptake processes: (Fig. 75.3)

(1) *Neuronal Uptake:* Adrenergic nerve endings have the capacity to take up catecholamines actively from the circulation into presynaptic terminals (*non-enzymatic inactivation*). This specific uptake accounts for inactivation of about 85% of released NE. It is less specific for Ep than for NE.

(2) *Extraneuronal Uptake:* It accounts for removing the remaining 15% of NE released from adrenergic nerve endings. It is mediated by postsynaptic cells and is followed by intracellular metabolic inactivation (*enzymatic inactivation*) by the enzymes monoamine oxidase (MAO) and catechol-o-methyl transferase (COMT).

(i) *Catechol-o-methyltransferase (COMT).* It is an extraneuronal (extracellular) enzyme, widely distributed with the highest levels in liver and kidney. It is also found in post-synaptic membranes. It metabolizes circulating catecholamines in kidney and liver and metabolizes locally released NE in the effector tissue. The action of COMT produces nor-metanephrine from NE; metanephrine from Ep, and VMA (vanillyl mandelic acid)

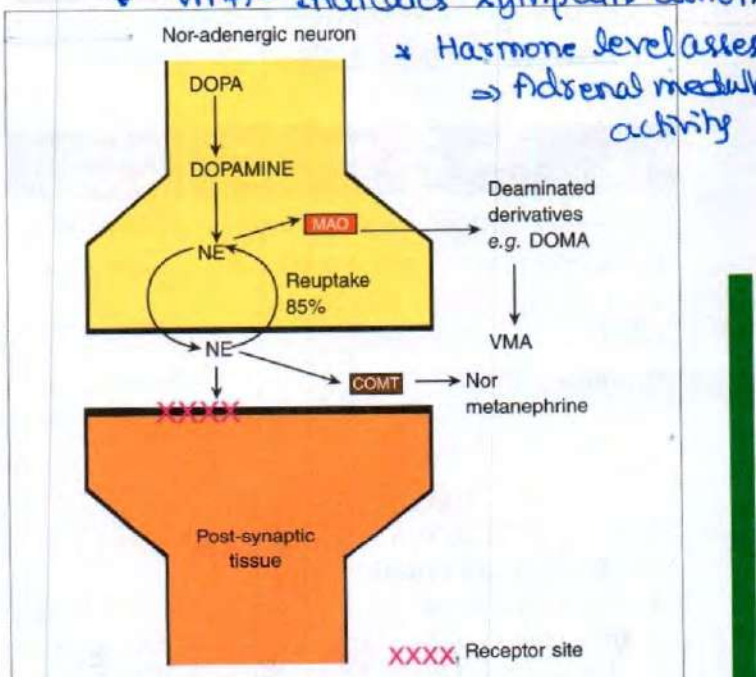


Fig. 75.3 Metabolism of catecholamines (abbreviation as in the text)

from 3,4-dihydroxymandelic acid (DOMA) by 3-O-methylation.

(ii) *Monoamine oxidase (MAO).* It is found in very high concentrations in the mitochondria of adrenergic nerve endings, liver, kidney, stomach and intestine.

Actions of MAO

(i) Catalyzes the oxidative deamination of Ep and NE to produce DOMA.

(ii) On the meta-O-methylated metabolites of Ep and NE (*i.e.* metanephrine and nor-metanephrine respectively), it produces 3methoxy 4-hydroxy mandelic acid (also called VMA) by oxidative deamination.

(iii) It also destroys 5-HT.

C. EXCRETION

(1) Normally, only 2-3% of catecholamine released into the body, escapes destruction; this amount is excreted in urine as:

(i) 50% in conjugation with sulphuric or glucuronic acid.

(ii) 35% as the deaminated metabolites – VMA (vanillyl mandelic acid); and

(iii) 15%, unchanged (Ep and NE in free form) or as metanephrines.

(2) Under normal circumstances Ep accounts for a very small proportion of urinary VMA because the majority of VMA is derived from NE. Therefore, *urinary VMA reflects the activity of the nerve terminals of the sympathetic nervous system rather than that of adrenal medulla.*

(3) *Normal Values*

	Normal urine excretion	Normal 'free' plasma level
Nor-epinephrine (NE)	30 µgm/day	300 pg/mL.
Epinephrine (Ep)	6 µgm/day	30 pg/mL.
Vanillyl mandelic acid (VMA)	700 µgm/day	–
Dopamine	–	35-40 pg/mL.

REGULATION OF CATECHOLAMINE SECRETION

A. NERVOUS CONTROL

(1) A-ch provides the major physiological stimulus for the secretion of the adrenomedullary hormones. In addition, angiotensin II, histamine and bradykinin stimulate catecholamine secretion.

(2) The secretion of catecholamine from the adrenal medulla is entirely controlled by the splanchnic nerves. These fibers are preganglionic and release A-ch as their transmitter.

(3) Mechanism of release of catecholamines (page 733).

(4) Splanchnic nerve activity is controlled by centres in the reticular formation in the medulla and hypothalamus ('higher control of catecholamine secretion'). The activity of these centres may be modified by afferent impulses from many parts of the body.

Important Note

Secretion from the adrenal medulla ceases after splanchnic nerve section.

(5) Secretion of glucocorticoids (GCs) by the adrenal increases the synthesis of PNMT in the adrenal medulla and thereby promotes the conversion of NE to Ep.

(6) As catecholamine synthesis is dependent on GCs, the functional integrity of the adrenal medulla indirectly depends on a functional pituitary gland for ACTH secretion and functional hypothalamus for CRH secretion.

B. SELECTIVE SECRETION:

Secretion in conditions of emergency or stress

(1) The adrenal medulla and sympathetic nervous system are both involved in the immediate bodily responses to emergency situations, but they can function independent of each other.

(2) The conditions in which sympathetic nervous system, including the *sympatho-adrenal medullary system* is activated are: fear, anxiety, pain, trauma, haemorrhage, fluid loss, asphyxia, hypoxia, changes in blood pH, exposure to extreme cold or heat, severe exercise, hypoglycemia and hypotension.

(3) The adrenal medulla contributes to the *Fight or Flight reactions* which occur in conditions of emergency and is a function of the sympathoadrenal medullary system (Details page 721).

(4) The secreted catecholamines, specially *Ep, help in the following ways:*

(i) letting more light to enter into the eyes by relaxing accommodation and producing pupillary dilatation (mydriasis);

(ii) providing better perfusion of vital organs and muscles

(a) by increasing HR and BP which also increase venous return; and

(b) by stimulation of sympathetic vasodilator system in skeletal muscles;

(iii) limiting the bleeding if wounded, by constricting blood vessels;

(iv) reinforcing the alert and aroused states by decreasing threshold in reticular formation;

(v) increasing glycogenolysis in the liver and lipolysis in adipose tissues, thus supply more energy for skeletal and cardiac muscles by raising blood glucose and FFA levels.

(5) In humans, Ep and NE appear to be released independently by specific stimuli, *e.g.*

(i) Anger and active aggressive states or situations, which are challenging and which allow active and appropriate anticipatory behavioural responses to the challenge *i.e.* ***situations with which the individual is familiar – are associated with increased 'NE' secretion.***

(ii) States of anxiety; tension but passive emotional displays or threatening situations of an unpredictable nature, in which active coping behaviour may be required but has not been achieved *i.e.* ***situations in which the individual does not know what to expect – are associated with increased 'Ep' secretion.***

Important Note

The sympathetic nerves, through their liberated NE, are mostly concerned with regulation of vascular tone, blood flow and BP; while the adrenal medulla through its predominant secretion of Ep, has its most important action on metabolism.

C. ADRENAL CORTEX AND SYMPATHOADRENAL MEDULLARY SYSTEM

(1) The environmental and emotional disturbances which stimulate adrenocortical secretion also usually activate the sympathoadrenal medullary system. The response in both cases being mediated by the hypothalamus. GC potentiates some of the actions of catecholamines (page 720).

(2) The activation of the *hypothalamus-pituitary-adrenal cortex system* is nearly as rapid as that of the sympathoadrenal medullary system so interactions between hormones secreted by the two systems can readily occur.

D. REGULATION OF ADRENERGIC RECEPTORS

A reciprocal relationship exists between catecholamine concentration and the number and function of adrenergic (adrenotropic) receptors.

A sustained decrease in catecholamine secretion is associated with an increased number of adrenergic receptors in the target cells and an increased responsiveness to catecholamine. Conversely, increased catecholamine secretion is associated with decreased responsiveness to it. *This phenomenon may account for the phenomenon of denervation hypersensitivity* (pages 171 and 189).

ACTIONS OF CATECHOLAMINES

The effect of adrenomedullary stimulation and sympathetic nerve stimulation are similar. In some tissues, however, Ep and NE produce different effects due to the existence of two types of *adrenergic receptors:* α *and* β. They have different sensitivities for the various catecholamines and, therefore, produce different responses via G-proteins (Details page 23).

1. *The* ***α-adrenergic receptors*** *are sensitive to both Ep and NE.* These receptors are associated with most of the *excitatory* functions of the body with at least one inhibitory function *i.e.* inhibition of intestinal motility.
2. **α-receptors are of two kinds α_1 and α_2:**
   (i) ***α_1-receptors*** are located on post synaptic membranes and are mainly *excitatory, e.g.* in blood vessels and the non-pregnant uterus; and
   (ii) ***α_2-receptors*** are located on presynaptic nerve terminals of cholinergic and adrenergic nerves. Activation of neuronal α_2-receptors is *inhibitory.*
3. *The* ***β-adrenergic receptors*** *respond to Ep* and in general are relatively insensitive to NE. These receptors are associated with most of the *inhibitory* function of the body with one important excitatory function *i.e.* excitation of myocardium.
4. **β-receptors are also of two kinds, β_1 and β_2,** both are located mostly on postsynaptic membrane sites. (β_3 receptors also exists)
   (i) ***β_1 receptors*** occur in cardiac muscle and their activation produces tachycardia and increases myocardial contractility; and
   (ii) ***β_2-receptors*** are typically those associated with relaxation of smooth muscle, *e.g.* in skeletal muscular blood vessels, GIT and bronchioles.
5. *Ep acts equally on both* α *and* β*-receptors, while NE acts on* α*-receptors.* NE also acts an β_1-receptors but has no action on β_2-receptors.
6. ***In humans, β-adrenergic mechanism predominates.***
7. α-receptor activation increases intracellular $[Ca^{2+}]$ and β-receptors activation decreases intracellular $[Ca^{2+}]$.

Responses of adrenergically innervated organs are shown in **Table 75.1**. These are mediated mainly by NE releases at adrenergic nerve endings, but in certain conditions release of Ep from adrenal medulla may modify the effect of adrenergic nerve activity.

Note

Also refer to pages 923-926.

Table 75.1: Effect of catecholamines and types of adrenergic receptors involved

	Effector organ	Receptor type	Response
1.	Eye		
	Iris radial muscle	α_1	Contraction (pupillary dilatation).
	Ciliary muscle	β_2	relaxation for far vision.
2.	Heart		
	SAN	β_1, β_2	Tahycardia; increase in conduction velocity.
	AVN	β_1, β_2	Increase in conduction velocity.
	Atria	β_1, β_2	Increase in contractility and conduction velocity.
	Ventricles	β_1, β_2	Increase in contractility and conduction velocity, and rate of idioventricular pacemakers; Extrasystoles.
3.	Blood vessels		
	In general (including skin and cerebral)	α_1, α_2	Constriction (arterioles and veins).
	Skeletal muscle and coronaries	α_1, α_2	Constriction. [VASO CONSTRICTION]
		β_2	Dilatation. [VASODILATATION]
4.	Lungs		
	Bronchial muscle	β_2	Relaxation (bronchodilatation).
	Glands	α_1	Decreased secretion.
		β_2	Increased secretion.
5.	GIT		
	Stomach and intestine (motility and tone)	$\alpha_1, \alpha_2, \beta_2$	Decrease in motility.
	(sphincters)	α_1	Contraction.
6.	Urinary bladder		
	Detrusor muscle	β_2	Relaxation.
	Trigone and sphincter	α_1	Contraction. No micturition
	Ureter (motility and tone)	α_1	Increases.
7.	Skin		
	Pilomotor muscle	α_1	Piloerection.
	Sweat glands	α_1	Selective stimulation results in localised sweating (*adrenergic sweating*).
8.	Uterus	α_1	Contraction.
		β_2	Relaxation.
9.	Liver	α_1, β_2	Glycogenolysis.
10.	Skeletal muscle	β_2	Increased contractility and glycogenolysis.
11.	Pancreatic islets	α_2	Inhibition of insulin and glucagon secretion.
		β_2	Stimulation of insulin and glucagon secretion.
12.	Spleen capsule	α_1	Contraction.
		β_2	Relaxation.
13.	Salivary glands (except parotid)	α_1	Thick viscous secretion.
14.	Adipose tissue	$\alpha_1, \beta_1, \beta_3$	Lipolysis causing release of FFA.
15.	Kidney – JGA	β_1	Renin secretion.
16.	Sex organs (male)	α_1	Ejaculation.
17.	Posterior pituitary	β_1	ADH secretion.

Colour body for receptors

ACTIONS

1. On CVS

(A) *On isolated heart*

Both Ep and NE stimulate β_1-receptors and produce:

(i) Increase in heart rate by:

(a) increasing slope of pacemaker potential which occurs due to increase in membrane permeability to Ca^{2+} and decrease in permeability to K^+;

↑ H.R → ↑ slope of pacemaker poten. → ↑ contrac.

(b) increasing conductivity through atria, AV Node and bundle of His.

(ii) Increase in force of contraction via cAMP system (page 653).

Thus, *catecholamines in high dose* result in generation of multiple pacemaker activity, specially in purkinje fibers and can produce fibrillation. *That is why Ep and NE should never be given I.V.*

causes vasoconstriction all over body ⇒ DBP & SBP ↑

(B) *On intact heart i.e.* heart and blood vessels.

(i) NE by its *direct* action: Reflex bradycardia

(a) on heart via β_1-receptors increases heart rate and force of myocardial contraction, which increases SBP;

(b) on blood vessels via α_1-receptors produces vasoconstriction to increase peripheral resistance which increases DBP.

(a) and (b) cause marked increase in MBP which *reflexly* by stimulation of baroreceptors (aortic and carotid sinus) decreases heart rate and myocardial contractility, and thus cardiac output decreases. Therefore, ***direct*** action of NE on CVS which increases heart rate and cardiac output is overcome by marked increase in MBP (*reflex action*) and eventually it produces bradycardia and decrease in cardiac output.

(ii) Ep by its direct action Tachycardia; CO↑

(a) on heart via β_1-receptors increases HR and force of myocardial contraction which increases SBP;

vasoconstric. of Splanchnic & Renal, Cutaneous

(b) on blood vessels via α-receptors produces vasoconstriction in skin and splanchnic area and via β_2-receptors produces skeletal muscle and liver blood vessels dilatation. The net effect is fall in peripheral resistance which decreases DBP.

vasodilat. in skel. m. B_2

↓↓ PP ↑↑ Increase in SBP and fall in DBP causes:

(a) widening of pulse pressure, and

(b) no change or slight rise in MBP; thus *reflex* effect on baroreceptors, is very mild.

Therefore, ***direct*** action of Ep on CVS will overcome its *reflex* action producing tachycardia and increase in cardiac output.

2. On Carbohydrate Metabolism = DIABETOGENIC

(i) Catecholamines *increase blood sugar*. How?

(a) Via β-receptors activate cAMP system (page 653) thereby increase phosphorylase activity in the liver, adipose tissues and skeletal muscles which increase glycogenolysis to raise blood sugar; and

LIVER glycogenolysis

(b) Via α-receptors increase 'glycogenolysis' (specially in muscles) by increasing intracellular Ca^{2+} which also increases blood sugar.

MUSCLE glycogenolysis

Important Note Ep = 3×NE

Epinephrine is *three times* more potent than NE to produce hyperglycemia as β-adrenergic mechanism predominates. In addition, in skeletal muscle, epinephrine increases glycogenolysis as in the liver but since muscle lacks glucose 6-phosphatase, more lactic acid is formed, which is converted to glucose by the liver (*gluconeogenic action*).

(ii) Catecholamines – Via β-receptors *increase the secretion of insulin and glucagon* and inhibit the secretion of these hormones via α-receptors.

(iii) Thus Ep injection produces:

(a) increase in blood glucose (more than that seen after NE injection)

(b) increase in lactic acid

(c) decrease in liver glycogen but after some time it starts increasing because oxidation of lactic acid in liver increases glycogen synthesis; this effect is responsible for calorigenic action (increase O_2 consumption) of Ep. **(Fig. 75.4)**

(d) decrease in muscle glycogen.

Gluconeogenic, Acidotic, Glycogenolytic

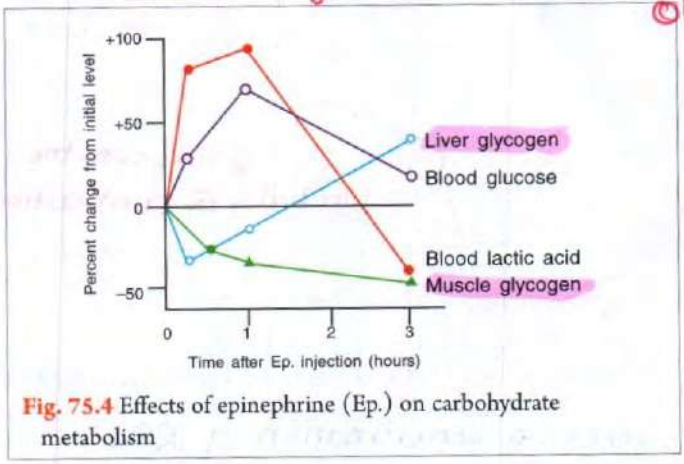


Fig. 75.4 Effects of epinephrine (Ep.) on carbohydrate metabolism

3. On Lipid Metabolism = KETOGENIC

(i) Catecholamines via β-receptors activate cAMP system which stimulates hormone sensitive lipase in adipose tissue and muscles. This breaks down stored triglycerides to FFA and glycerol (**Fig. 66.1**, page 611). The 'lipolytic' action of Ep is brief and that of NE prolonged.

(ii) In the liver some of the excess FFA are converted into ketone bodies which are transported from liver to peripheral tissues where they are important as energy source.

(iii) Cardiac muscle and renal cortex use fatty acids and ketone bodies in preference to glucose; whereas resting skeletal muscle uses fatty acids as the major source of energy. During extreme conditions, such as starvation and diabetes mellitus, the brain adapts to the use of ketoacids. Ketoacids are also oxidised by skeletal muscle during starvation.

β-oxidation of FFA ⇒ Keto genesis

Important Note

Ep. has predominant effect on the carbohydrate metabolism, whereas NE has more potent action on the lipid metabolism.

SBP → Stroke vol. } Dependance } Dopamine → vasoconstric. in Splanchnic & Renal

4. On BMR

Catecholamines increase the BMR (*calorigenic action*), only in the presence of T_4 and adrenal cortex. Ep shows slightly more calorigenic effect than NE. Ep. injection produces *biphasic* response *i.e.*

(i) ***Initial rapid rise in BMR*** **(Fig. 75.5)** occurs due to cutaneous vasoconstriction which decreases heat loss; and increase in muscular activity which increases heat production.

(ii) ***Slow and delayed rise in BMR*** which coincides with increased lactic acid level and can be abolished after removal of liver. Thus, it may be due to oxidation of lactic acid in the liver.

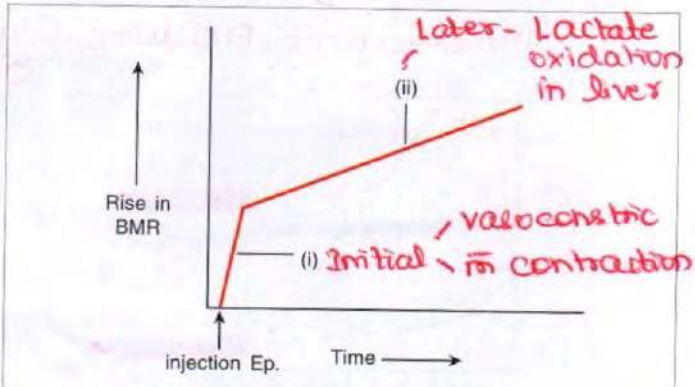


Fig. 75.5 Calorigenic effect of epinephrine (Ep.)
(i) initial rapid rise in BMR; (ii) slow and delayed rise in BMR

5. On CNS

(i) Catecholamines show stimulatory effect on CNS and produce: anxiety, apprehension, hyperventilation and coarse tremors of extremities.

(ii) It may inhibit release of ADH.

(iii) In Parkinsonian patients, it can increase rigidity and tremors.

NE is much less active in this respect.

Mechanism of action: Catecholamines activate reticular activating system (RAS) by lowering its threshold and then lead to arousal and alerting responses.

6. On Eyes

Ep.

(i) via α-receptors causes contraction of radial muscle of eye producing mydriasis;

(ii) via β-receptors relaxation of ciliary muscles for far vision and increases tone of eye muscles.

(i) and (ii) result in *wide open eyes* **(Fig. 75.6)**.

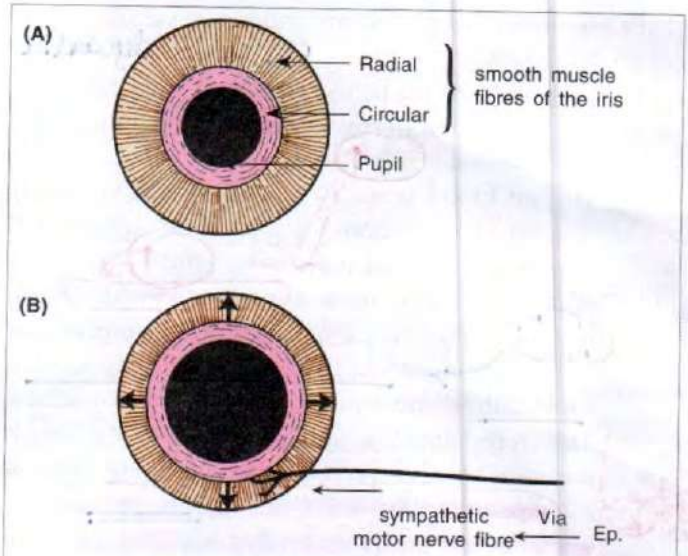


Fig. 75.6 Effect of Epinephrine (Ep.) on eye, before (A) and after (B) its administration.

7. On GIT

Ep. via β-receptors decreases tone and motility, and via α-receptors causes sphincteric constriction; thus Ep produces constipation.

8. On Urinary Bladder

Ep. via β-receptors causes relaxation of detrusor muscle, and via α-receptors causes contraction of trigone and sphincters; finally produces *Retention of Urine.*

9. On Skin

Catecholamines via α-receptors cause:

(i) Contraction of pilomotor muscles to produce piloerection of hair.

(ii) On sweat glands produce localized sweating on palm and sole called *Adrenergic Sweating.*

Note

Generalized sweating is cholinergic.

10. On Skeletal Muscles

Ep. via β_2-receptors:

(i) improve skeletal muscle blood supply; and

(ii) increases force of contraction of both normal and fatigue muscle in response to a stimulus.

At rest, sympathetic tone with continuous release of NE, produces a relatively small blood flow through skeletal muscles.

11. On Bronchial Muscles

Ep. via β_2-receptors relaxes bronchial musculature producing bronchodilatation.

12. On Blood

Ep.

(i) decreases CT (clotting time) due to increase in activity of factor V;

(ii) increases RBC count, PCV, haemoglobin concentration (due to mobilization of RBC from its depots specially the spleen);

(iii) increases plasma protein concentration due to movement of fluid out of the circulation;

(iv) marked increase in neutrophils (sequestrated neutrophils come into the circulation) and decreases eosinophils.

13. Miscellaneous

Catecholamines initially cause hyperkalemia (because of release of K^+ from the liver) followed by hypokalemia due to increased K^+ influx into skeletal muscle. The latter effect is mediated by β_2-adrenergic receptors.

ACTIONS OF DOPAMINE

1. It produces generalised vasoconstriction by releasing NE.
2. By an action on β_1-receptors it has a positive inotropic effect on the heart. The net effect is an increase in SBP and no change in DBP.
3. On kidneys:
   (a) via specific dopaminergic receptors produces vasodilation;
   (b) by inhibiting $Na^+ - K^+$ ATPase produces natriuresis.
   Therefore, it is useful in the treatment of shock.

APPLIED ASPECT

A. HYPOSECRETION OF CATECHOLAMINES

Common causes:

1. Tuberculosis (TB) of adrenal medulla.
2. Destruction of adrenal medulla by malignancy.
3. Adrenalectomy.
   It usually produces no clinical signs and symptoms because catecholamine production from sympathetic nerve endings appears to satisfy the normal biological requirements. Therefore, *adrenal medulla is **not** essential for life.*

B. HYPERSECRETION OF CATECHOLAMINES

This is seen in tumours of chromaffin tissue, called ***Phaeochromocytoma***. These tumours are usually benign and contain large amounts of both Ep. and NE.

Characteristic features

1. Sustained or paroxysmal hypertension; BP rises upto 300/200 mmHg.
2. Headache, sweating (*adrenergic sweating*); severe palpitation, substernal pain, anxiety, weakness, dizziness, pale cold and moist skin; blurred vision due to dilated pupils.
3. Increased body temperature, hyperglycemia, glycosuria and increase in BMR.
4. Increase in urinary excretion of catecholamines, metanephrines and VMA.

Important Note

All these features can be produced by infusion of large doses of Ep. or NE, showing that these tumours contain varying proportions of Ep. and NE in large amounts.

Study Questions

1. **Give physiological basis of:**
   (i) Denervation hypersensitivity
   (ii) Epinephrine and NE are never given I.V.
   (iii) Adrenergic sweating
   (iv) Use of dopamine in management of shock.
   (v) Adrenal medulla is a sympathetic ganglion
   (vi) Adrenal medulla is not essential for life
   (vii) Urinary VMA reflects the activity of sympathetic nerve terminals.
2. **Differentiate between effects of Ep and NE on**
   (i) intact heart
   (ii) metabolism.
3. **Write short notes on:**
   (i) Fight or Flight reactions
   (ii) Catecholamine secretion in conditions of stress
   (iii) Effect of Ep on carbohydrate metabolism
   (iv) Characteristic features of phaeochromo-cytoma.
   (v) Regulation of catecholamine secretion
   (vi) Effects of catecholamine
4. **Give situations in which specifically either Epinephrine or NE is released.**
5. **Give a general overview of distribution of α and β receptors in the body. How do these receptors respond to catecholamines?**
6. **Summarize biosynthesis, metabolism and functions of hormones secreted by the adrenal medulla.**
7. **Draw well labelled diagram:**
   (i) Metabolism of catecholamine
   (ii) Effect of Epinephrine an carbohydrate metabolism
   (iii) Calorigenic effect of Epinephrine
   (iv) Effect of Epinephrine on eye

MCQs

1. **Which of the following decreases markedly after bilateral adrenalectomy?**
   (a) Epinephrine (b) Nor-epinephrine (c) Dopamine (d) Serotonin
2. **Which is the rate limiting enzyme in biosynthesis of catecholamine?**
   (a) Phenylamine hydroxylase (b) Tyrosine hydroxylase
   (c) Dopa decarboxylase (d) PNMT (Phenylethanolamine N-methyl-transferase)
3. **Sympatho-adrenal medullary system gets activated in all of the following conditions *except*:**
   (a) Emotional stimuli (b) Trauma
   (c) Thermal and physical stress (d) Sleep
4. **In the typical reaction of fight or flight there is:**
   (a) Slowing of the heart rate (b) Fall of blood pressure
   (c) Dilatation of the pupils (d) Relaxation of anal and urethral sphincters
5. ***Not* a correct statement for the β-adrenergic receptors:**
   (a) Respond mainly to Ep
   (b) Associated with most of inhibitory functions of the body
   (c) β_1-receptors activation produces increased HR and myocardial contractility
   (d) β_2-receptors are typically those associated with constriction of smooth muscles
6. **Epinephrine increases all of the following in heart *except*:**
   (a) Automaticity (b) Conduction velocity (c) Refractory period (d) Contractility
7. **CVS response of catecholamines *in vivo* is:**
   (a) Tachycardia
   (b) Reflex bradycardia in case of Ep and tachycardia in case of NE
   (c) Reflex tachycardia in case of Ep and bradycardia in case of NE
   (d) Reflex bradycardia in case of NE and tachycardia in case of Ep
8. **Catecholamine insufficiency causes:**
   (a) A rise in plasma sodium/potassium ratio (b) Low blood pressure
   (c) Increased breakdown of protein (d) Usually produces no clinical symptoms
9. ***Not a correct* statement about phenyl pyruvic oligophrenia (or phenylketonuria):**
   (a) Occurs due to congenital deficiency of enzyme PNMT (b) Associated with increase phenylalamine and its derivatives in blood
   (c) Characterized by severe mental retardation (d) Protein synthesis in brain decreases
10. ***False* statement regarding fight or flight reactions:**
    (a) Situations with which the individual is *familiar* are associated with increased NE release
    (b) Situations in which the individual does not know *what to expect*, are associated with increased 'EP' release
    (c) 'Ep' is mostly concerned with regulation of BP
    (d) 'NE' is mainly concerned with regulation of vascular tone and blood flow
11. **What determines whether norepinephrine circulating in the body fluids will be excitatory or inhibitory in a particular organ?**
    (a) The nature of the receptor in the cells of the organ
    (b) The intensity of nerve stimulation of the organ
    (c) The chemical changes that occur in the norepinephrine before it excites the cells
    (d) The position on the cells where norepinephrine is secreted by the nerve endings
12. ***False* statement regarding actions of catecholamines:**
    (a) Ep acts equally on both α and β-receptors
    (b) NE mainly acts on α-receptors
    (c) In humans, β-adrenergic mechanism predominates
    (d) Responses of adrenergically inner-vated organs are mediated by Ep.
13. **The most important response to the stimulation of beta adrenergic receptors is:**
    (a) Cerebral vasodilation (b) Splanchnic vasoconstriction
    (c) Decresed blood sugar (d) Increased cardiac activity
14. **Which of the following is *true* about epinephrine?**
    (a) Converted to norepinephrine by methylation (b) Increases glycogen breakdown in liver and muscles
    (c) Is a polypeptide (d) Increases triglyceride deposition in adipose tissue
15. **Pheochromocytomas predominantly secrete:**
    (a) Epinephrine (b) Norepinephrine (c) Serotonine (d) Dopamine

Answers

1. (a) 2. (b) 3. (d) 4. (c) 5. (d) 6. (c) 7. (d) 8. (d) 9. (a) 10. (c) 11. (a) 12. (d) 13. (d) 14. (b) 15. (a)

Chapter
76

The Pancreas

I. Physiological anatomy
II. Glucagon, actions and regulation of secretion
III. Insulin (A) Structure and species specificity (B) Regulation of insulin secretion
(C) Actions of insulin (D) Mechanism of action of insulin
IV. Applied aspect (A) Diabetes mellitus, Glucose tolerance test
(B) Clinical types
(C) Hypoglycemia
(D) Hyperglycemic vs hypoglycemic coma

PHYSIOLOGICAL ANATOMY

1. The ***Exocrine*** secretion of pancreas *i.e.* pancreatic juice enzymes promote the digestion of carbohydrates, proteins and fats. The digested end products get absorbed by the intestinal mucosa and pass mainly by the portal vein to the liver.
2. The ***Endocrine*** secretion of pancreas *i.e. insulin and glucagon*, also enter the portal vein and are transported directly to the liver where they exert very important actions regulating the metabolism of carbohydrates, proteins and fats.
   Thus, exocrine and endocrine functions of pancreas are closely interrelated.
3. In normal adults, pancreas weighs 50-75 gm of which 1 gm (*i.e.* 1-2% of pancreatic weight) is the *islet tissue*, which are *plentiful in the tail of the pancreas*.
4. There are approximately 0.5 to 1.5 million ***Islets of Langerhans***, each being 75 to 175 µm in diameter. Histologically, depending upon the type and staining properties of the granules, there are four types of cells **(Fig. 76.1)**:
   (i) 15-20%, ***α-cells*** (or *A cells*), *i.e.* cells with small rounded or ovoid granules, which are stained red with mallory aniline blue dye. These cells synthesize and secrete ***Glucagon***. Identical cells have also been found in gastric antrum and duodenum.
   (ii) 70-80%, ***β-cells*** (or *B cells*), *i.e.* cells with large rhomboid granules which are stained bluish purple with mallory aniline blue dye. These cells synthesize and secrete ***Insulin***. Insulin content of the pancreas is directly proportional to the number of granules of β-cells, therefore, increased insulin secretion produces β-cell degranulation.
   (iii) 1-8%. ***δ-cells*** (or *D cells*). These are smaller than α and β cells. They synthesize and secrete ***Somatostatin*** *(GHIH)* and ***Gastrin*** (in small amounts) (for details, refer to pages 283 and 686).
   (iv) 1-2% ***F-cells***. These cells secrete ***pancreatic polypeptide*** which decreases the absorption of food from the GIT. Its secretion is under cholinergic control, therefore,
   - *increased by* a high protein diet; by fasting, exercise and acute hypoglycemia; and
   - *decreased by* somatostatin.
5. The islet cells are innervated by unmyelinated fibers from both parasympathetic (vagal) and sympathetic nerves whose endings are in close contact with α and β cells and can readily influence their secretory activity.
6. The α, β and δ cells are in close proximity with one another and appear to constitute a *functional syncytium*,

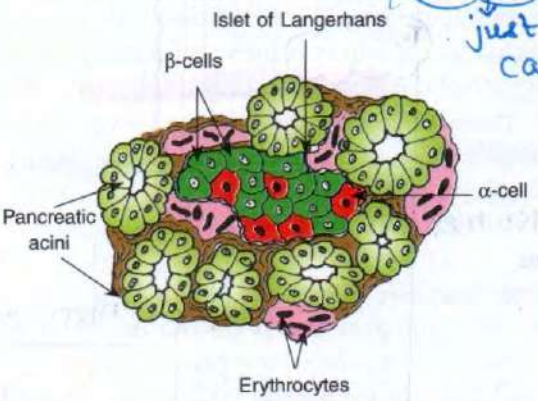


Fig. 76.1 Islets of Langerhans, the endocrine tissue of the pancreas

which forms a *paracrine control system* for the coordinated secretion of pancreatic polypeptides (Fig. 76.2).

(i) Insulin inhibits α-cell (glucagon) secretion, which increases peripheral glucose uptake and opposes glucagon-mediated glucose production.

(ii) Glucagon stimulates β-cell (insulin) and δ-cells (somatostatin) secretion, which increases hepatic glucose production and opposes hepatic glucose storage.

(iii) Somatostatin inhibits α-cell (glucagon) and β-cell (insulin) secretion, which produces hypoglycemia and inhibition of intestinal glucose absorption.

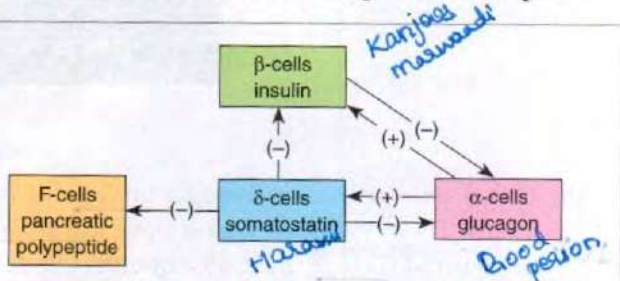


Fig. 76.2 Interrelationship between α, β and δ and F-cells of islets of Langerhans. [(+): stimulation; (−): inhibition]

GLUCAGON

1. Glucagon, *mobilizer of glucose*, is a straight chain polypeptide with 29 amino acids, MW 3485. Normal fasting glucagon concentration is 100-150 pg/mL. An increase in blood glucose level decreases plasma concentration of glucagon.
2. It is *synthesized from* precursor ***Proglucagon*** (contains 179 amino acids) in α-cells of pancreas and L-cells in the GIT.
3. Glucagon enters the portal vein in relatively high concentration and approx. 50% of which is removed by the liver in a single passage through this organ, that is why peripheral blood levels are relatively low. Its *half life* in circulation is 5-10 min, persists for much longer time in lymph and is *degraded* mainly by the liver. Therefore, in cirrhosis of liver peripheral blood level of glucagon increases. Also, degraded in tissues and plasma by an aminopeptidase.

Actions

Glucagon receptors have been identified in a variety of tissues. Glucagon acts mostly on the liver and adipose tissue where it *antagonises the actions of insulin*.

1. ***Stimulates Glycogenolysis*** – Glucagon increases the breakdown of liver glycogen to glucose, producing a rapid rise in blood glucose within a few minutes:
   (i) by inhibiting glycogen synthetase, and
   (ii) by activating cAMP formation via its action on G_S → activates protein kinase → activates phosphorylase enzyme, which converts glycogen to:

$$\text{Glucose-6-phosphate} \xrightarrow[\text{Phosphatase}]{\text{Liver}} \text{Glucose}$$

Glucagon also acts on the same liver cells to activate phospholipase C, and the resulting increase in intracellular Ca^{2+} also stimulates glycogenolysis.

Important Note

Epinephrine activates phosphorylase both in the liver and muscles to increase lactic acid formation which returns via blood to liver and is converted to glucose; while *glucagon activates phosphorylase only in the liver* to stimulate glycogenolysis but cannot increase lactic acid.

2. ***Promotes gluconeogenesis*** – Glucagon promotes formation of glucose from lactate, pyruvate, glycerol and amino acids, producing a slower but more sustained rise in blood glucose lasting for hours and days:
   (i) by increasing deamination of amino acids in the liver; and
   (ii) by increasing metabolic rate.
3. Glucagon is a powerful ***Lipolytic agent***. It acts via stimulating cAMP system to phosphorylate, a lipase in adipose tissue which releases FFA and glycerol into the circulation. In the liver, excess of FFAs are converted to 'ketone bodies' *i.e.* acetoacetic acid, acetone and β-hydroxybutyric acid (***ketogenic action***). (1), (2) and (3) cause release of glucose, amino-acid and FFAs into the circulation, therefore, glucagon is ***Catabolic in Actions*** *i.e. Hormone of Energy Release.*
4. ***Calorigenic action*** – This is not due to hyperglycemia but this action requires the presence of glucocorticoids and T_4. It may be due to increased hepatic deamination of amino-acids.
5. In large doses, glucagon increases force of contraction of the heart by increasing cAMP.
6. It stimulates the secretion of GH, insulin and pancreatic somatostatin.

Summary: Glucagon is glycogenolytic, gluconeogenic, lipolytic and ketogenic (catabolic action). It thus favours breakdown of stored nutrients and is a ***hormone of energy release.***

Regulation of Glucagon Secretion

The main factors which affect the glucagon secretion are given in Table 76.1.

Table 76.1: Major stimuli affecting glucagon secretion

Increased by	Decreased by
(1) *Hypoglycemia*. It is the *most important* stimulus for glucagon secretion, that is why its secretion increases during starvation to reach a peak on the 3rd day of a fast (time of maximal gluconeogenesis).	(1) *Hyperglycemia*. It causes increase release of insulin and GABA from β-cells. GABA via $GABA_A$ receptors decreases glucagon secretion by its direct action on α-cells thereby showing that these cells are insulin dependent.
(2) Following a *protein meal* or after infusion of glucogenic amino-acids (such as arginine, alanine, glycine, cysteine, threonine, serine etc.). These are converted to glucose in the liver under the influence of glucagon.	(2) Free fatty acids (FFR), *ketone bodies* etc.
(3) *GIT hormones:* CCK-PZ, gastrin (page 216), GIP.	(3) *Secretin*.
(4) *Sympathetic nerve stimulation* to pancreas. The effect is mediated via β-adrenergic receptors and cAMP. Various *stresses, fasting, exercise* and *infection*, increase the glucagon secretion in part by their stimulatory effect on sympathetic nervous system and partly by release of glucocorticoids.	(4) *α-adrenergic receptor stimulation*.
(5) *Others:* Drugs such as theophylline, cortisol, A-ch.	(5) *Insulin*, phenytoin, somatostatin (GHIH).

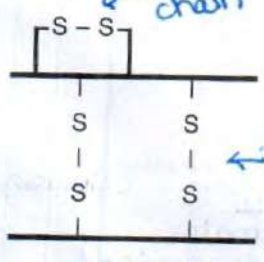
Important Note

The secretion of glucagon is more after oral administration of amino-acids than after their I.V. injection because oral administration also increases release of CCK-PZ, gastrin and other GIT hormones which further increase the glucagon secretion.

INSULIN

A. STRUCTURE AND SPECIES SPECIFICITY

1. Insulin was discovered by *Banting and Best* in 1921. It is a soluble small protein or large polypeptide containing 51 amino acids with MW 6000. It contains two chains of amino-acids, an *acidic* A-chain containing 21 amino-acids and a *basic* B-chain containing 30 amino-acids. A and B chains are connected by two disulphide (S-S) bridges and third disulphide bridge is located on the A-chain.



2. The 51 amino-acids arrangement varies from animal to animal without altering its biological activity, but if insulin of one animal is injected for prolonged period into another animal it may lead to antigenic properties by producing antibodies. As antibody titre is not high, therefore, it causes no problem; if increases, it inhibits endogenously secreted insulin (***Insulin Resistant***) but is usually responsive to insulin from other species. The insulin from cattle or sheep is liable to evoke the formation of antibodies in man which cause allergic reactions whereas pig insulin, which more closely resembles human insulin is much better tolerated.

3. ***Biosynthesis and Excretion***

(i) Insulin is synthesized on ribosomes in the rough endoplasmic reticulum as *pro-insulin* which gets translocated to the golgi apparatus to form *insulin*. Here formation of insulin continues within the storage granules which, therefore, contain pro-insulin, 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 **(Fig. 76.3)**.

(ii) Insulin is 10-20 times more active than *pro-insulin* on responsive tissues. *C peptide* has 10% biological activity of insulin and enters the blood along with the insulin when the granule contents are released by exocytosis. It can be measured by radio-immuno assay and its level provides an index of β-cell function in patients receiving exogenous insulin.

(iii) The process by which insulin is secreted normally requires glucose metabolism, possibly for the formation of ATP. It also depends on cAMP and requires the presence of Ca^{2+} and K^+. Ca^{2+} helps in contraction of microtubules and in discharging the granules content **(Fig. 76.4)**.

(iv) In non-obese humans ***normal fasting insulin concentration*** is 10-50 μU/mL. (7-350 pmol per dL) which increases to 8-10 times after I.V. injection of 20 gms of glucose.

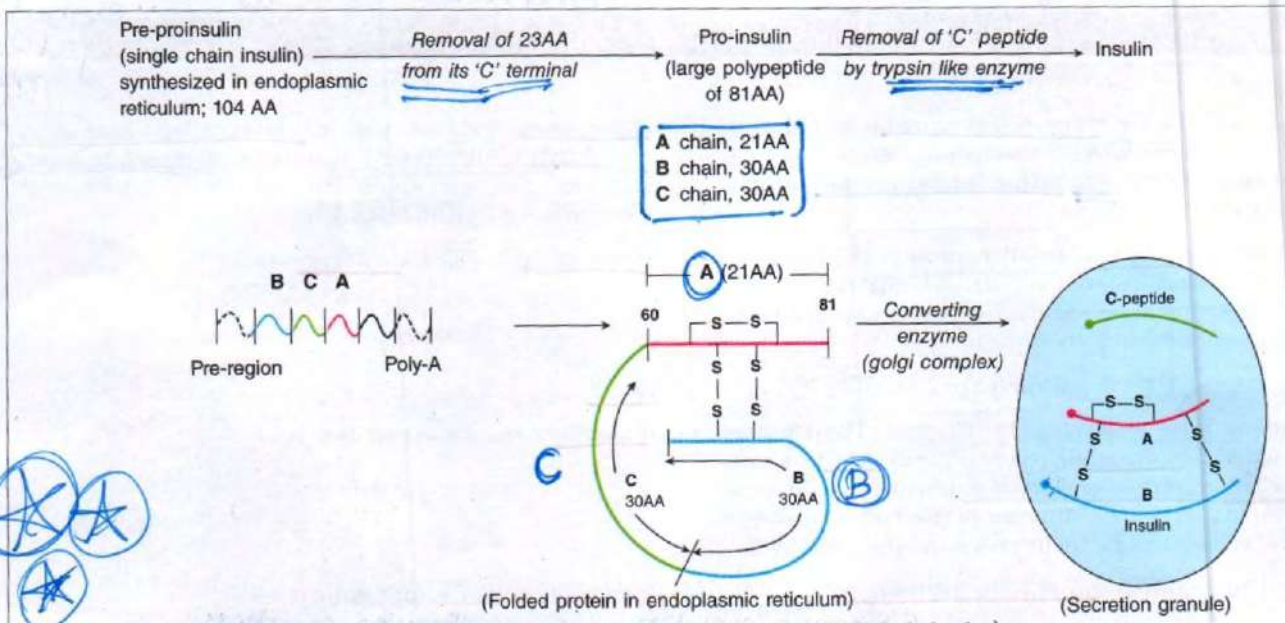


Fig. 76.3 Biosynthesis of Insulin (AA: amino-acids; C: connecting peptide; S-S: disulphide bridge)

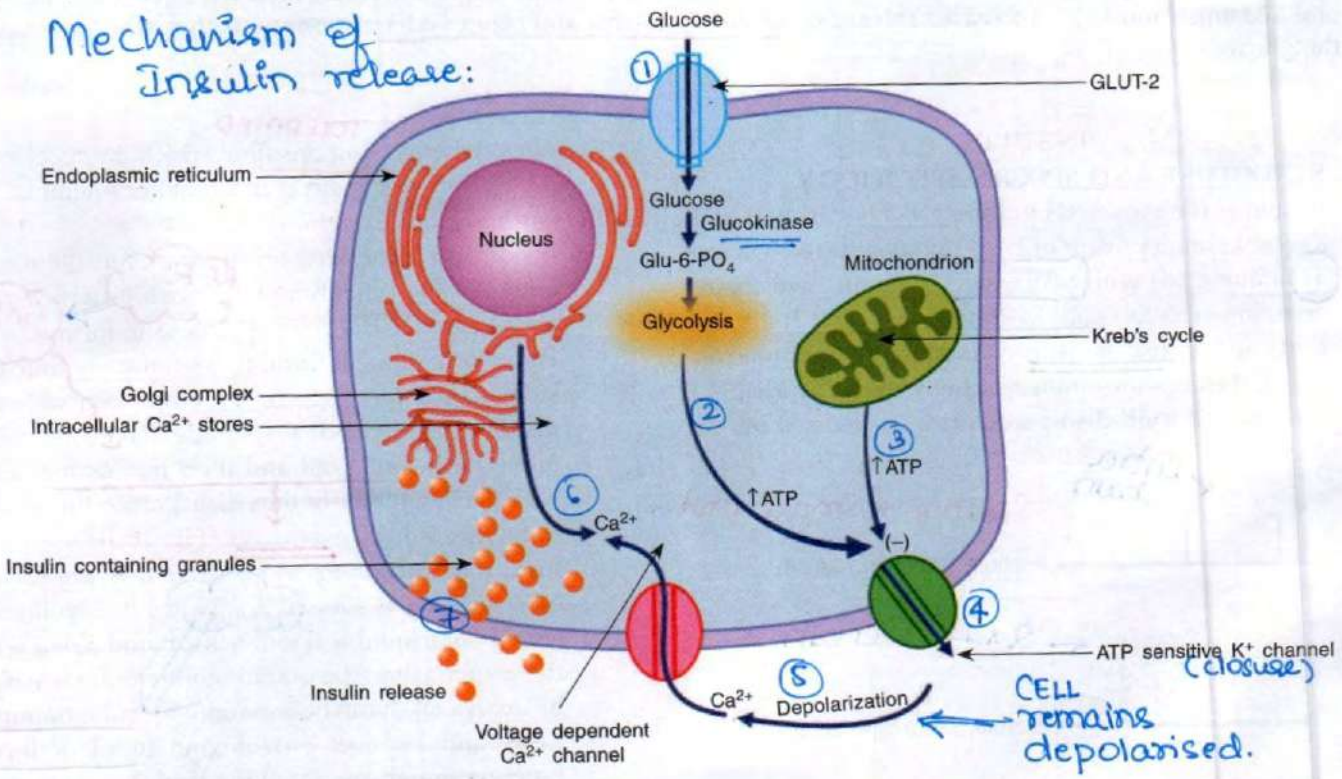


Fig. 76.4 Control of insulin secretion by carbohydrates. Glucose enters β-cells via GLUT-2 (independent of insulin) and is metabolized by enzyme glucokinase to pyruvic acid (page 600). ATP is generated and closes ATP-sensitive K^+ channels, the resultant decrease in K^+ efflux depolarizes the cell membrane. This opens voltage-sensitive Ca^{2+} channels, the increase in intracellular Ca^{2+} causes release of insulin by exocytosis. (*Metabolism of pyruvic* acid via citric acid cycle also increases the intracellular *glutamic acid*. This primes secretory granules for secretion.)

Note

Note: K^+ depletion decreases insulin secretion; that is why patients with primary hyper-aldosteronism (page 727) develop diabetic GTT.

(v) *Normal basal rate of insulin release* from β-cells is 1-2 U/hour. Its daily release is about 50 U out of a pancreatic store of 200-250 U of insulin.

Note

Plasma also contains a number of substances notably IGF-I and IGF-II (page 663) with insulin like activity. However, their activities are weak compared to that of insulin and cannot compensate for the insulin deficiency.

4. ***Transport and distribution***
   (i) Insulin binds with plasma protein, probably with a circulating protein with anti-insulin activity called ***Synalbumin***.
   (ii) *Half life* of insulin in circulation is 5-10 min.
   (iii) Insulin is fixed to many tissues but *RBC and most of brain cells do not bind it;* large amounts are bound in the liver and kidneys. The ***insulin receptor*** on the cell membrane is a glycoprotein. The insulin exerts its effect without entering the cell on which it acts.
5. ***Metabolism*** – Same as that of glucagon (page 742).
   (i) 80% gets metabolised by the liver and kidneys by ***hepatic glutathione insulin transhydrogenase (HGIT)***, which breaks the disulphide (S-S) bridge to SH groups with separation of A and B chains. Once the disulphide bridge is removed, its biological activity is lost.
   (ii) 20% gets metabolised by rest of the body tissues and destroyed by enzyme, ***insulin protease*** in various organs as it is made up of peptides and amino-acids.

B. REGULATION OF INSULIN SECRETION

A normal non-obese man secretes approx. 50 U insulin per day with the basal plasma insulin concentration of 10-50 μU/mL. It gets influenced by variety of stimulating and inhibiting factors. Mainly these factors are either substances related to glucose metabolism or agents that affect cAMP. (Refer summary on page 750)

1. ***Substrate Control*** – It is the ***most important*** factor in the control of insulin secretion.
   (i) *Control by carbohydrates:* Carbohydrates promote insulin secretion after their degradation during digestion to glucose. Increase in blood glucose increases insulin secretion by its direct action on β-cells (How? Refer **Fig. 76.4**). *Proof:* I.V. injection of 20 gms of glucose causes increase in insulin secretion, which is a ***biphasic*** response **(Fig. 76.5)**.
      (a) *First phase or primary response:* Immediate release of insulin which occurs within 0.5-1 min of glucose infusion, reaching a peak at 3-5 min and then declines but remains above the basal level. It is due to release of insulin from a ***Labile Pool*** of insulin within the β-cells and comprises approx. 2% of the total pancreatic store of insulin.
      (b) *Second phase or secondary response:* Slow, maintained and prolonged release of insulin which occurs on 2-3 hours of continued glucose infusion. The delayed response is due to release of insulin from a ***Stable Pool*** which comprises the remaining 98% of pancreatic store of insulin. (The glutamic acid appear to be responsible for release of insulin during the second phase - see **Fig. 76.4**)

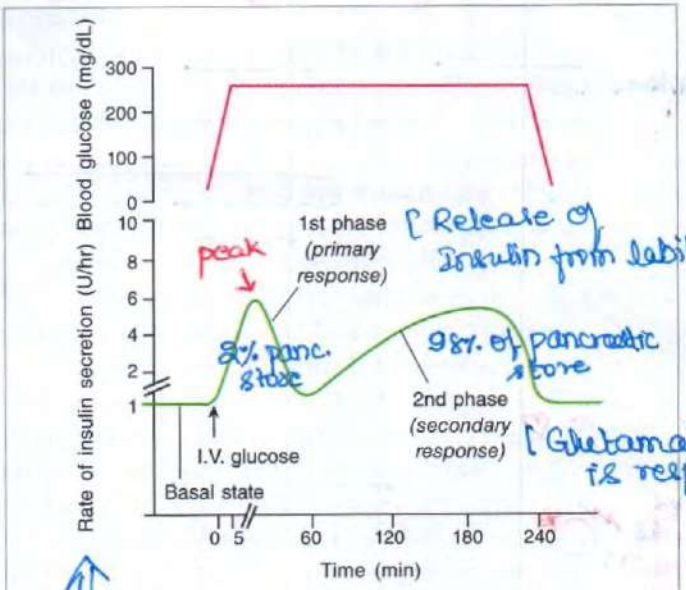


Fig. 76.5 Effect of constant glucose infusion on insulin secretion

The higher the basal level of insulin secretion, the greater is the secretion produced by glucose stimulation.

Important Notes

1. Insulin secretion relationship to glucose metabolism.
   (i) Any sugar such as mannose and fructose which gets metabolized in β-cells increases the insulin secretion.
   (ii) Sugars like galactose, D-xylose, L-arabinose which are not metabolized in β-cells cannot increase the insulin secretion.
   (iii) Sugars like 2-Deoxyglucose and manno-heptulose by inhibiting phosphorylation prevent glucose from being metabolized and thus decrease the insulin secretion.
2. Glucose not only promotes release of insulin stored in β-cells but also increases the synthesis of proinsulin, which is then converted to insulin.

(ii) *Control by protein and fat derivatives:* Mixture of essential amino acids or basic amino acids (arginine, leucine and lysine) stimulates β-cells to increase the insulin secretion from isolated islets in the absence of glucose, but the presence of glucose potentiates its effect. Similarly fat derivatives, β-keto acid *e.g.* acetoacetic acid; and nitric oxide (derived from L-arginine) also increase the insulin secretion.

Like glucose, these compounds generate ATP when metabolized and thus closes ATP-sensitive K^+ channels in the β-cells **(Fig. 76.4)**

2. *cAMP and various cAMP generating substances*

(i) *β-adrenergic receptor stimulation* increases intracellular cAMP that increases the insulin secretion by increasing intracellular Ca^{2+}. Conversely, *α-adrenergic receptor stimulation* decreases cAMP and thus insulin secretion decreases (similar action is seen on glucagon secretion). Thus *catecholamines* have a *double effect* on insulin secretion:

(a) Insulin secretion decreases because it directly acts on β-cells of islets which have more α-receptors; and

(b) Glucagon secretion increases because it directly acts on α-cells of islets which have more β_2-receptors.

The net effect of catecholamines is usually inhibition of insulin secretion.

(ii) cAMP is destroyed by phosphodiesterase enzyme. Therefore, theophylline and *oral hypoglycemic agents* such as biguanides (phenformin) and sulphonyl urea derivatives (tolbutamide, chlorpropamide), which inhibit phosphodiesterase increase the cAMP to increase the insulin secretion.

Note

Oral hypoglycemic agents also increase the insulin secretion by generation of ATP in the β-cells **(Fig. 76.4)**. This action is independent of increase in plasma glucose level.

3. *Neural Control*

(i) *by ANS:*

(a) ***Sympathetic*** – Stimulation of splanchnic or adrenergic nerves by causing release of catecholamines, stimulates α_2-adrenergic receptors and insulin secretion decreases.

(b) ***Parasympathetic*** – Stimulation of right vagus (which supplies β-islet cells) increases the insulin secretion via M_1 receptors (direct effect), which gets blocked by atropine; thus this effect mediated by release of A-ch at the vagal ending is due to increase in intracellular Ca^{2+}.

Important Note

Atropine prevents the increased insulin secretion produced by vagal stimulation but does alter the basal concentration of insulin in plasma. Therefore, effect of glucose on insulin secretion does not require the intact islet innervation; however, ANS maintains the normal islet sensitivity to glucose.

(ii) *by CNS* – Since ANS is under CNS control, therefore,

(a) during the periods *of feeding* and absorption of foodstuffs from GIT, vagal activity increases via hypothalamus which increases insulin secretion;

(b) during *starvation*, increased sympathetic activity via hypothalamus, decreases insulin secretion.

4. *Hormonal Control*

(i) **GIT hormones** released during digestion of food, for example: glucagon, secretin, CCK-PZ, gastrin, GIP (gastric inhibitory peptide) increase insulin secretion by:

(a) directly stimulating insulin release from β-cells;

(b) enhancing the stimulant effect of glucose and amino-acids on insulin secretion.

GIP alone in very small concentration can increase insulin secretion, therefore, it is known as ***Physiologic GUT factor****. This is why orally administered glucose produces the greater increase in plasma insulin concentration than I.V. glucose.*

Important Note

The release of GIT hormones causes a small increase in insulin which precedes the much greater subsequent insulin secretion in response to absorbed glucose and amino acids. **(Fig. 76.6)**

(ii) **Insulin:** Administration of exogenous insulin in normal individuals decreases endogenous secretion of insulin.

(iii) **GH** directly stimulates β-cells to increase insulin secretion.

(iv) *Somatostatin (GHIH)* directly inhibits β-cells to decrease insulin secretion.

(v) *Thyroid hormone, glucocorticoids, oral contraceptives* (oestrogen and progesterone preparations), in pharmacological doses increase blood glucose, which by producing *β-cells exhaustion* decrease insulin secretion and also depress glucose induced insulin secretion.

Important Note

The magnitude of insulin response to a given stimulus is determined by the secretory state of the β cells. When the stimulus is marked or prolonged, the β-cells become exhausted and stop secreting, called *β-cell exhaustion*. This explains why the individuals on high carbohydrate diet for several weeks have high fasting plasma insulin levels and also show a greater secretory response to glucose load. However, the pancreatic reserve is large, and it is difficult to produce β-cell exhaustion in normal individuals.

5. *Drugs*

(i) *Diazoxide* (antihypertensive), thiazide diuretics, phenytion directly inhibit β-cells and decreases insulin secretion.

Note

Thiazide also exert this effect because of loss of K^+ in the urine.

(ii) *Alloxan* by destroying β-cells decreases the insulin secretion.

(iii) *Oral hypoglycemic agents* - page 753

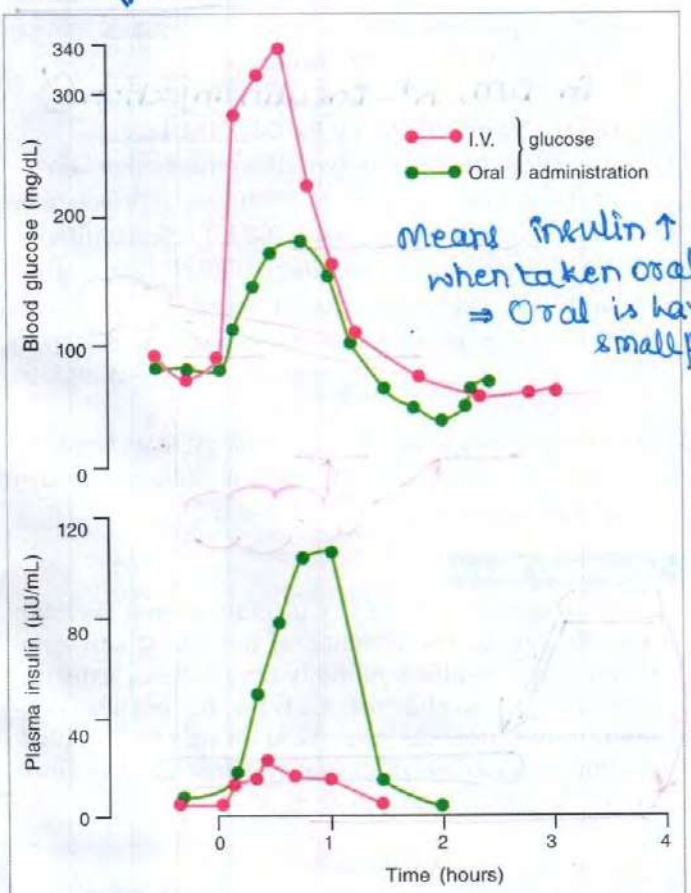


Fig. 76.6 Blood glucose and plasma insulin response to oral and I.V. glucose administration

C. ACTIONS OF INSULIN

1. *On Carbohydrate Metabolism*

(i) Insulin acts upon the plasma membrane of muscle and adipose tissue cell to facilitate the transport of glucose, amino acids, K^+, Mg^{2+} and inorganic phosphate into the cell. It also facilitates the transport of certain hexoses like galactose which are not metabolized in the muscle and adipose tissue cells.

(ii) Glucose itself can cross muscle cell membrane in the absence of insulin but only if the glucose concentration outside the cell is raised many times the normal level. In normal persons there is sufficient insulin in plasma to promote glucose uptake with a resting glucose 70-90 mg/dL.

(iii) Insulin *increases the glucose* entry into the tissues of skeletal muscle, cardiac and smooth muscles, adipose tissues, WBCs, eye lens, pituitary, fibroblast, mammary glands, aorta, liver and α-cell of pancreatic islet.

(iv) Glucose transport across the following cells does **not** require insulin:

(a) *Brain* - brain can metabolize glucose without insulin (*exception:* ventromedial nucleus of hypothalamus). Therefore, brain cannot withstand hypoglycemia.

(b) *Kidney tubules*, GIT and RBCs.

This is the reason, why in diabetic patients (insulin deficiency) glucose absorption from these tissues remains unaffected.

(v) Insulin ***produces hypoglycemia*** by the following mechanisms:

(a) insulin *promotes the glucose* uptake by most of the tissues of the body *i.e.* increases peripheral utilization of glucose, and

(b) insulin *increases glycolysis* in muscles, adipose tissue and liver:

- by stimulating activity of glycolytic enzymes, *e.g.*, it activates hexokinase enzyme to convert glucose to intracellular glucose-6-phosphate which cannot cross the cell membrane, and
- by inhibiting activity of enzymes favouring glucose synthesis, for example, it prevents gluconeogenesis by inhibiting enzyme pyruvic carboxylase and phosphoenol pyruvate carboxykinase (PEPCK) (Fig. 76.7);

(c) insulin *promotes synthesis of glycogen* by activating glycogen synthetase and simultaneously inhibiting enzyme of glycogen breakdown;

(d) insulin directly decreases the glucose output from the liver.

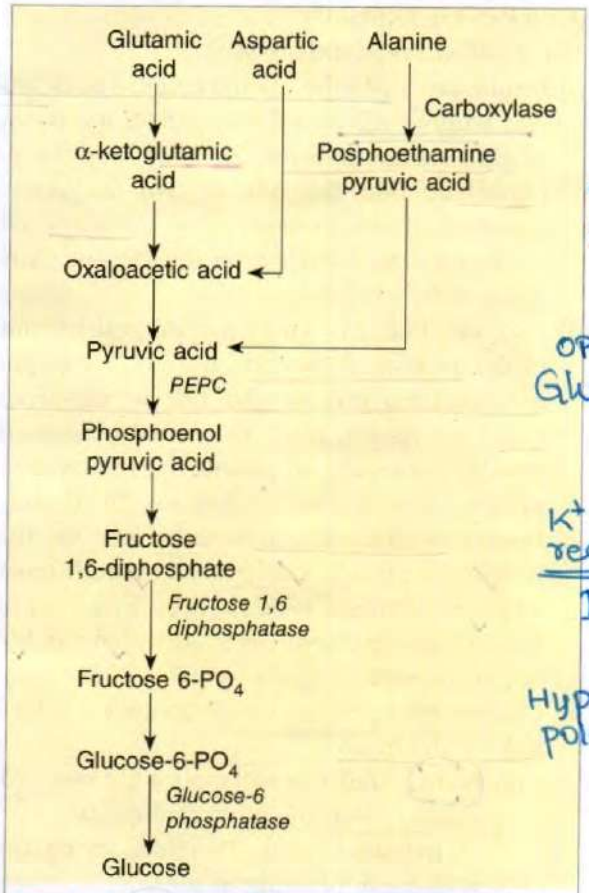


Fig. 76.7 Glucose formation from non-carohydrate sources (gluconeogenesis)

2. ***On Fat Metabolism*** → LIPOGENIC
   (i) Insulin *promotes the synthesis of FFA and triglycerides* in muscles, adipose tissue and liver. How?
   (a) Insulin *stimulates lipoprotein lipase* which breaks down circulating triglycerides (chylomicrons), thereby increases FFA in adipose tissue; and by providing Acetyl-CoA and NADPH from α-glycerophosphate (which comes from intracellular glucose) leading to the formation of triglycerides. Thus insulin increases the deposition of triglycerides.
   (b) Insulin *inhibits hormone sensitive lipase* in adipose tissue, so decreases the release of FFA from stored triglycerides. This action of insulin is secondary to decrease in cAMP production. (Also refer to page 611).
   (ii) Insulin can *increase the uptake of ketone bodies* in the muscle.
3. ***On Protein Metabolism***
   (i) Insulin *promotes amino-acids uptake* (specially into muscles), which is independent of protein synthesis, since increased entry of amino acids still occurs after inhibition of protein synthesis by puromycin.
   (ii) It *decreases protein breakdown* by decreasing the enzymes which induce gluconeogenesis.
   (iii) It *promotes protein synthesis* specially in muscles by a direct action on ribosomes to increase translational activity of mRNA. This action can still occur when RNA synthesis is decreased by actinomycin-D.

Summary: *Insulin is glycogenic, antigluconeo-genic, antilipolytic and antiketotic (anabolic actions). It thus favours storage of absorbed nutrients and is a* ***Hormone of Energy Storage or Hormone of Abundance*** (page 750).

4. ***Miscellaneous Actions***
   (i) Insulin directly *decreases the urea output* from the liver and increases uptake of K^+ and phosphate.
   (ii) Insulin increases K^+ entry into the cell thereby decreasing ECF [K^+]. How?

Insulin increases the RMP of skeletal muscle membrane and fat cells by increasing the activity of Na^+–K^+ pump, leading to hyperpolarization. This probably increases negativity within the cell which increases K^+ entry.

Clinical significance: In diabetic ketosis hyperkalemia often develops; therefore, when these patients are treated with insulin, it will produce severe hypokalemia which may be fatal. Hence, in such patients, K^+ should also be given along with insulin.

D. MECHANISM OF ACTION OF INSULIN

Glucose enters the cells by two different mechanisms:

(i) In most of body cells by *facilitated diffusion* (page 15) via ***glucose transporters*** (GLUT). Seven different GLUT have been identified (GLUT-1 through 7) and their affinity for glucose varies. GLUT-4 is the transporter in skeletal and cardiac muscle cells, adipose tissue and other tissues that are stimulated by insulin.

(ii) In the intestine and kidney cells by *secondary active transport with sodium* (page 19) via ***sodium dependent glucose transporters*** (SGLT 1 and 2).

Important Note

Exercise increases the entry of glucose into skeletal muscle cells in the absence of insulin. It can also increase the insulin sensitivity of muscle by causing increase in number of GLUT-4 in muscle cell membranes. Regular exercise training can produce prolonged increase in *insulin sensitivity* and is thus beneficial for diabetic patients.

1. All the actions of insulin are brought about by a reversible combination with specific glycoprotein

receptor (***insulin receptors***) on the surface of plasma membrane of many different cells in the body. Its biological activity is proportionate to the amount bound to the cell surface.

Insulin receptors

These are made of 2α and 2β glycoprotein subunits (*half life* : 7 hours). The α-subunits are extracellular whereas the β-subunits have tyrosine kinase activity and extend through the membrane **(Fig. 76.8)**. Binding of insulin → (+) tyrosin kinase activity of the β-subunit → its autophoshorylation → phosphorylation of intracellular proteins → insulin effect.

(Also see to important note page 651)

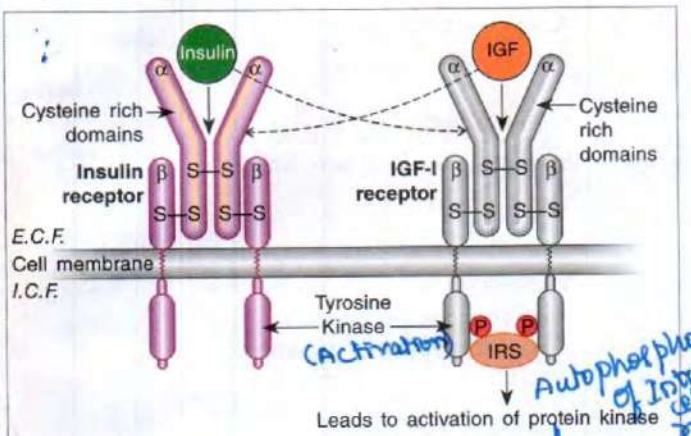


Fig. 76.8 Receptor for Insulin, IGF-I, and IGF-II (Also see page 663) [P-phosphate bond; IRS: Insulin receptor substrate)]

Note

Insulin receptors are very similar to receptors for IGF-I and other growth factors (page 663). Whereas the insulin binds to its own receptor and also to the IGF-I receptor; IGF-I and II bind to all three i.e. insulin, IGF-I and IGF-II receptors → Universal

2. Insulin does not penetrate into the cell, yet it exerts profound effect on the intracellular activities of muscle cell, adipose tissue and liver cells. How?
   (i) Insulin may *decrease cAMP formation* either by inhibiting the activity of *adenylyl cyclase* or by enhancing the activity of *phosphodiesterase*. (Both these enzymes are located on the inner surface of the membrane.)
   (ii) Insulin *facilitates the transport of ions* into insulin-responsive cells, which influences the intracellular enzyme activity. For example:
      (a) Change in intracellular [K^+] shifts the balance between glycogen synthesis and glycogen breakdown.
      (b) Presence of Ca^{2+} or Mg^{2+} intracellularly is must for protein synthesis.

3. The number or affinity or both of ***insulin receptors*** is affected by insulin, other hormones, exercise, food and other factors. How?
   (i) **Number of receptors** per cell may increase or decrease (details page 651):
      (a) *Increase* in starvation and during exercise. Exercise also increases glucose entry into the cells without insulin due to hypoxia; as glucose entry increases under anaerobic condition.
      (b) *Decreases* due to exposure to increased amount of insulin, obesity and acromegaly.
   (ii) **Affinity of receptors** for insulin may also increase or decrease:
      (a) *Increases* with exposure to decreased amount of insulin and in adrenal insufficiency.
      (b) *Decreases* due to excess of glucocorticoids.

Important Note

Because of opposing effects of insulin and glucagon, the blood level of these hormones in any given situation are important (*insulin-glucagon molar ratio*). This ratio on a balanced diet is about 2.3, it *decreases* when energy is needed during starvation or exercise, favouring glycogen breakdown and gluconeogenesis, whereas it *increases* when need for energy mobilization is low, thus favouring the deposition of glycogen, protein and fat.

APPLIED ASPECT

'Insulin' deficiency produces a clinical state called *Diabetes Mellitus*, while its excess leads to *Hypoglycemia*.

A. DIABETES MELLITUS

Diabetes means a 'siphon' or 'running through' and earlier it was used to describe the polyuria. ***Mellitus*** means sugar. Therefore, diabetes mellitus is a clinical state which is associated with *flow of sugar* in urine.

Causes

Diabetes mellitus is primarily a disease due to *Insulin deficiency*. It is usually associated with hormones which normally have antagonistic actions to insulin; for example, GH (page 664), glucagon (page 742) and glucocorticoids (page 719) and catecholamines (page 737).

Pituitary, Pancreas, Adrenal gl.

Important Note

Hormonal regulation of blood glucose concentration: refer to pages 605-607. The major cause of hyperglycemia in diabetes mellitus is derangement of glucostatic function of liver, secondary to insulin deficiency.

Insulin deficiency → Derangement of Glucostatic func.

Summary: Factors affecting insulin secretion and principal actions of insulin. (+): stimulaiton; (–): inhibition

↑Insulin

I Substrates
Carbohydrates – glucose, fructose
Proteins – amino acids
Fats – β-keto acids

II ↑ cAMP generation by
Theophylline
Oral hypoglycemics

III Neural
Vagal stimulation; A-ch
feeding

IV Hormonal
Glucagon; secretin
CCK-PZ; gastrin; GIP

V Drugs
Antidiabetics; oral hypoglycemic agents

β-cells

I Substrate
Carbohydrates – 2-deoxyglucose mannoheptulose

II ↓ cAMP generation by
β-blockers
Catecholamines

III Neural
Vagotomy; symphathetic. stimulation
Atropine; starvation

IV Hormonal
Insulin; thyroxine, glucocorticoids
stomatostatin

V Drugs
Antihypertensives; thiazides; anticonvulsants; K^+ - depletion, Fig. 76.4

INSULIN
(Hormone of Abundance/Energy storage)

Carbohydrates (page 747)	*Fats* (page 748)	*Proteins* (page 748)
↑ glucose uptake	↑ lipogenesis	Anabolic - ↑ protein synthesis and
↑ glycogenesis	↓ lipolysis	↓ protein breakdown
Antigluconeogenic	Antiketogenic	

In DM - effectiveness of Insulin action ⊗

Predisposing factors

1. *Hereditary.* The most typical form of diabetes is *hereditary iodiopathic diabetes mellitus* (*Evidence:* the very high incidence of the disease in identical twins and in children of parents who are both diabetic).
2. *Age.* The disease is common with increasing age.
3. *Obesity.* A reliable indicator for body fat is ***Body Mass Index (BMI)*** *i.e. body weight in kg/(height)*^{2} in metres. Individuals with values of 25–30 are overweight, and those with values > 30 are ***obese*** (Fig. 76.9). Adipose tissues in obese persons are more ***resistant to insulin*** actions than normal adipose tissue, *i.e.* a decrease ability of insulin to move glucose into the cells and to block the glucose release from the liver. Associated with obesity there is *hyperinsulinemia* and dyslipidemia (high circulating FFA and low HDL levels); alltogether it is called the ***Metabolic Syndrome*** or ***Syndrome-X***.

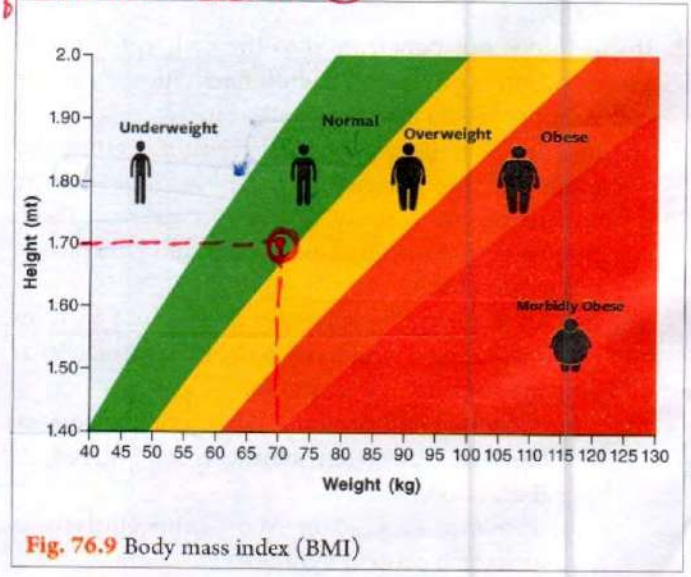


Fig. 76.9 Body mass index (BMI)

Insulin resistant → Hyperinsulinemia → dyslipidemia

It is postulated that circulating FFA level act on muscles and the liver to increase insulin resistance. Therefore, plasma insulin is increased in non-diabetic obese persons. The increased strain on β-islet cells activity in producing more insulin may lead to *Exhaustion of β-cells* (page 747) with onset of diabetes mellitus. Carbohydrate restriction decreases body weight and restores normal sensitivity of adipose tissues to insulin.

Signs and Symptoms of diabetes mellitus

These are mainly due to *hyperglycemia* with decreased utilization of glucose by cells; as a result, there is extracellular glucose excess and intracellular glucose deficiency, a situation called *Starvation in the midst of plenty.*

1. **Hyperglycemia** (raised blood glucose), it predisposes to infection like boils and urinary tract infection (a very common finding in diabetic patients).

Note

Glucose rich body fluids form a good culture medium for bacterial growth resulting in poor resistance to infections.

2. **Glycosuria** (presence of glucose in the urine).
3. **Polyuria** (loss of large amount of water in urine).
4. **Dehydration** (page 752).
5. **Polydipsia** *i.e.* increased thirst (secondary to dehydration).
6. **Polyphagia.** Low glucose utilization by *Glucostat cells* of ventromedial nucleus in hypothalamus (satiety centre) results in no inhibition of lateral nucleus in hypothalamus (feeding centre) which eventually produces increased hunger (polyphagia) (page 1007).
7. **Loss of weight.** In the absence of intracellular glucose which is a major source of energy there is mobilization of fats and breakdown of proteins specially in the muscles. The associated loss of fluids causes further weight loss. This is particularly seen in diabetes of more gradual onset like juvenile diabetes *[1 gm of glucose loss in urine causes loss of 4.1 kcals from the body].*
8. **Ketonuria.**
9. **Poor resistance to infections** due to protein depletion.

PATHOPHYSIOLOGY OF DIABETES MELLITUS

Metabolic and functional disturbances in diabetes mellitus are summarized in **Fig. 76.10.**

Once *diabetic ketoacidosis* developes, there is marked ***resistance to insulin.*** This might be due to:

(i) metabolic acidosis which can cause cellular dehydration (page 752);

(ii) presence of large amounts of FFA, or

(iii) relative or absolute increase in the activities of glucagon, GH or GC (peripheral circulatory failure by stimulating adrenal cortex increases the GC release).

Important Notes

1. Degree of ketoacidosis is directly proportional to the amount of fat stores, therefore, it is more severe in obese compared to thin individuals. Moreover, disturbances in fat metabolism is so prominent in diabetes mellitus, that it has been called more a *disease of lipids* than of carbohydrate metabolism.
2. FFA levels parallel the blood glucose level in diabetes mellitus, therefore in some way *FFA estimation is a better index to assess the severity of diabetes mellitus than the blood glucose.*
3. Acidosis is the *most common* cause of easy death in diabetes mellitus due to markedly decrease in total Na^+.
4. *Haemoglobin* A_{1c}: HbA_1 has an addition of glucose group attached to the terminal amino acid of β-chain of haemoglobin molecule (called *glycosylation*). This is a stable linkage and accumulates throughout the life span of RBCs (120 days) but its concentration at one time reflects the blood glucose of past 6–8 weaks. Thus glycosylated HbA concentration can be measured as an index of overall control of diabetes mellitus (DM). *Normal value* of HbA_{1c} is < 6% and value above 8% suggests poor control of DM, in between value suggests variable results: good control (7–8%); excellent control (< 7%).

Complications of diabetes mellitus

The *acute* complications of diabetes mellitus are based on metabolic and functional disturbances in the body and are summarized in **Fig. 76.10.** In addition, poor control of the disease predisposes to the development of the *chronic* complications which include:

(1) ***Atherosclerosis*** *i.e.* deposition of lipids underneath the tunica intima of blood vessels. The *common sites* are: coronary, cerebral and peripheral arteries. These are due to the long standing hyperlipidaemia and hypercholesterolaemia (due to increased hepatic production of VLDL or decreased removal of VLDL and LDL from the circulation). The result is *increased incidence of chronic* ulceration and gangrene (specially in the feet), MI and stroke (Also refer to page 615).

(2) ***Microangiopathy,*** a vascular lesion in which the capillary basement membrane is thicker than normal. This is ultimately responsible for:

(i) *Neuropathy i.e.* degeneration of sensory and motor nerves in the lower part of the body.

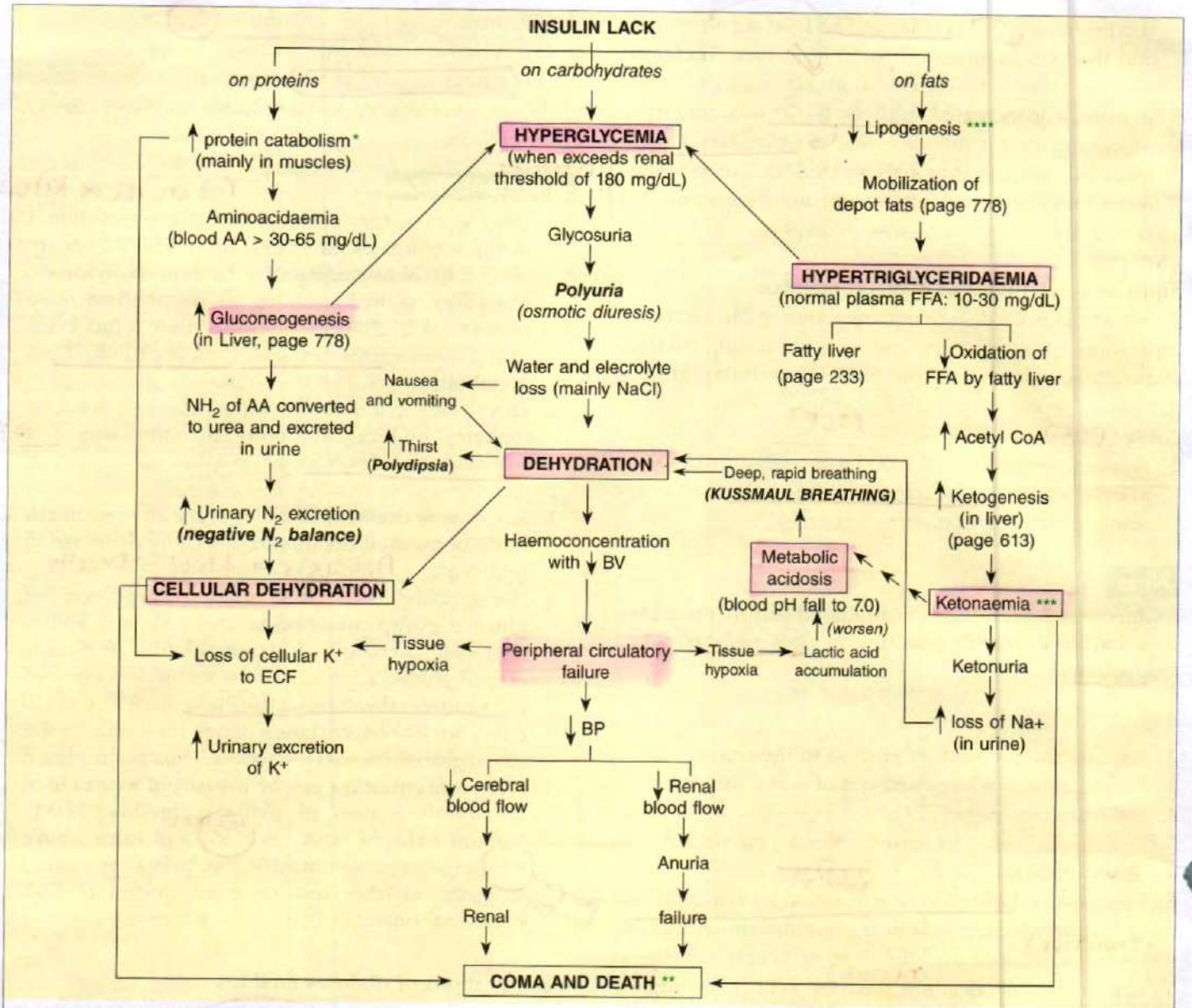


Fig. 76.10 Pathophysiology of diabetes mellitus

Important Notes

1. Increased protein catabolism (*) is associated with : muscular wasting and weight loss.
2. *Diabetic coma* (**) is due to: (i) metabolic acidosis, (ii) renal failure, (iii) cerebral ischaemia and (iv) severe dehydration.
   (ii), (iii) and (iv) by causing water to flow out of cells (cellular dehydration) produces hyperosmolality and cause coma, called *Hyperosmolar Coma* (page 18).
3. *Ketonaemia* (***) causes release of H^+ from Ketone bodies which result in acidosis (*Ketoacidosis*).
4. (****) Normally, 50% of the ingested glucose load burned to CO_2 and H_2O; 30-40% is converted to fat in the fat depots; and 5% is converted to glycogen. In DM less than 5% is converted to fat, therefore, glucose accumulates in blood producing hyperglycemia.

(ii) *Retinopathy i.e.* scarring of the retina leading to blindness, and

(iii) *Nephropathy i.e.* renal disease leading to renal failure.

B. CLINICAL TYPES

It is of two types: *juvenile* and *maturity onset*. (Refer **Table 76.2**).

Table 76.2: Differentiating features between two types of overt Diabetes Mellitus

Juvenile Onset (or Type I) Diabetes	Maturity Onset (or Type II) Diabetes
(i) It occurs before 14 years of age; patients are usually underweight.	(i) Most common type of diabetes. It occurs after 40 years of age; patients are normal or over weight.
(ii) Family history of diabetes mellitus – uncommon. However, a genetic factor may predispose to development of antibodies against β-cells of islet.	(ii) Family history of diabetes mellitus – strongly positive.
(iii) Develops ketosis and acidosis, if untreated.	(iii) Ketosis with infection (often absent; onset: slow
(iv) *Insulin secretion: low or absent* due to β-cell pathology (mainly *auto-immune disorder*). Thus producing severe diabetes mellitus.	(iv) Initially *insulin secretion is normal* or *increased*; later decreases. β-cells are usually normal but *main disturbance* is (a) less active insulin production, or (b) less cellular response to insulin due to deficiency of GLUT 4 insulin receptors in insulin sensitive cells (page 749), or (c) presence of antibodies against insulin.
(v) Patients are *sensitive to insulin.*	(v) Patients are *insulin resistant* (see below).
(vi) Treatment – injection of insulin; therefore, also called *insulin dependent diabetes mellitus (IDDM).*	(vi) Diet restriction; oral hypoglycemic agents, insulin is needed only during infections, therefore also called *non-insulin dependent diabetes mellitus (NIDDM).*

Glucose Tolerance Test (GTT)

This test is done to assess the glucose metabolic state of a person following administration of glucose orally with a dose of 75 gms glucose therefore, also called *oral GTT* **(Fig. 76.11).**

Conclusions

1. ***Normal GTT:*** When fasting venous blood glucose level is <115 mg/dL, and after 2 hours of glucose administration value is <140 mg/dL and no value is >200 mg/dL.
2. ***Diabetic GTT:*** When fasting venous blood glucose level is >126 mg/dL, and if the 2-hours post-prandial (PP) value and one other PP value are >200 mg/dL.
3. ***Impaired GTT:*** when the fasting and PP values are above the upper limits of normal but below the values diagnostic of diabetic GTT. (Also see to page 261, *Alimentary glycosuria.*)

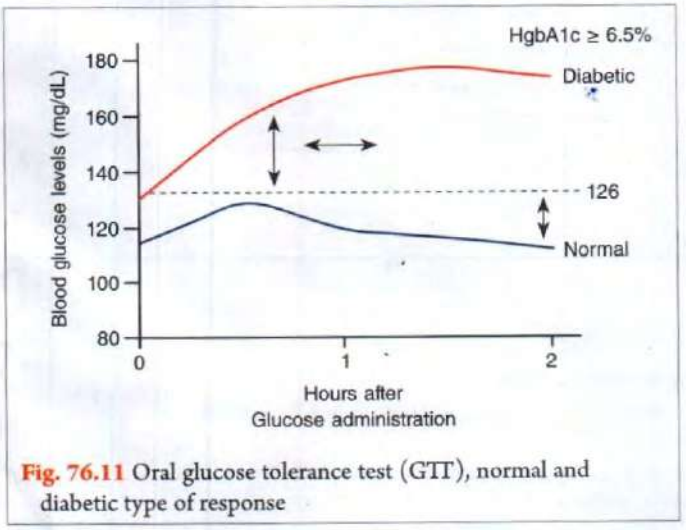


Fig. 76.11 Oral glucose tolerance test (GTT), normal and diabetic type of response

C. HYPOGLYCEMIA

Normal fasting blood glucose is 70-90 mg/dL. The blood glucose levels at which signs and symptoms of hypoglycemia appear are variable, why? Not known. For example: In normal person blood glucose <60 mg per dL leads to hypoglycemia whereas in diabetes mellitus patients signs and symptoms of hypoglycemia are produced when blood glucose level falls below 100 mg/dL.

Causes

1. Iatrogenic
   (i) insulin overdose, or
   (ii) overdose of oral hypoglycemic agents (page 747).
2. β-islet cell adenoma or hyperplasia (common in infants of diabetic mother).
3. Functional
   (i) delayed secretion of insulin after oral carbohydrate load, say after 2-4 hours of heavy carbohydrate meals,
   (ii) after severe exercise in diabetes mellitus patients.

Signs and Symptoms

These are mainly due to effect of hypoglycemia on CNS ***(neuroglycopenic symptoms)***. The carbohydrate reserve of neural tissues are very limited, and because of its high metabolic activity, normal functions depend on continuous glucose supply. As blood glucose falls, the cortex and other brain areas with high metabolic rates are affected first, followed by more slowly respiring vegetative centres in the medulla.

1. Derangement of cerebrum produces mental confusion, incoordination, slurred speech, irritability, feeling of

marked fatigue, difficulty in walking; convulsions and finally coma.

2. Low glucose utilization by hypothalamus leads to:
   (i) stimulation of ventromedial nucleus of the hypothalamus (satiety centre) produces *polyphagia i.e.* increased hunger (page 1007);
   (ii) stimulation of sympathetic activity increases catecholamine release from the adrenal medulla producing nervousness, pallor, palpitations, sweating, tremors, tachycardia, headache and anxiety.
3. Delayed changes are due to involvement of medulla leading to cardio-respiratory centre involvement/ failure which may be fatal.

Compensatory mechanisms

The natural recovery from hypoglycemia is brought about by secretion of hormones which increases the blood glucose level to normal. (Details, refer to page 605-607). The reactions involved are broadly divided into two: *early* and *late reactions*.

(A) Early reactions

(1) **Increased glucagon secretion** due to fall in blood glucose level and by sympathetic nerve stimulation.

(2) **Increased catecholamines** secretion by sympathetic stimulation.

(1) and (2) by promoting glycogenolysis and gluconeogenesis (page 737 and 742) increase the glucose output from the liver to raise blood sugar level to normal.

(B) Late reactions

The mechanisms which get activated later on are due to effect of hypoglycemia on the hypothalamus which results in:

(1) **Increase ACTH** secretion; this by increased glucocorticoids release
   (i) Increases gluconeogenesis, thus glucose output from the liver increases
   (ii) by its anti-insulin action, decreases peripheral utilization of glucose;

(2) **Increase GH** secretion results in:
   (i) increase glucose output from the liver
   (ii) decrease tissue binding of insulin

(3) **Increase TSH** secretion increases T_4 secretion which causes:
   (i) increased glucose absorption from GIT
   (ii) degradation of insulin
   (iii) increased epinephrine release.

(1), (2) and (3) raise the blood sugar level to normal.

D. HYPERGLYCEMIC COMA VERSUS HYPOGLYCEMIC COMA

	Hyperglycemic Coma	Hypoglycemic Coma
1. Cause	It is due to high blood glucose level, usually above 400 mg/dL.	It is due to fall in blood glucose level, usually below 40 mg/dL. It is a more serious medical emergency.
2. Rate of onset	Invariably slow, it takes hours or days to develop.	Rapid, it develops within minutes.
3. Precipitating factors	Insulin under dosage, infection, trauma.	Overdosage of insulin, missed meal, undue exercise.
4. Signs and symptoms		
(i) Breathing	Deep and rapid (air hunger), called ***kussmaul breathing***.	Laboured breathing,
(ii) Sweating	Absent	Usually marked.
(iii) Hydration	Marked dehydration	Normal, fairly hydrated.
(iv) CNS symptoms	Diminished reflexes	Various, often bilateral extensor plantar responses.
(v) Urine examination	Marked glycosuria and ketonuria.	No specific characteristic features seen.

Study Questions

1. Give physiological basis of:
   (i) Glucagon is a hormone of energy release.
   (ii) Insulin is a hormone of energy storage.
   (iii) Glucagon secretion is more after oral administration of amino acids than after its I.V. injection.
   (iv) Orally administered glucose produces the greater increase in plasma insulin concentration than I.V. glucose.
   (v) How glucose enters the brain cells during deficiency of insulin?
   (vi) Diabetic patient fails to gain weight inspite of polyphagia/failure to grow is a symptom of DM in children.
   (vii) Diabetic patients are given potassium supplements when treated with insulin.

(viii) Polyphagia of diabetes mellitus.
(ix) Diabetic ketoacidosis produces marked resistance to insulin.
(x) Ketoacidosis is more severe in obese compared to thin persons.
(xi) FFA estimation is a better index to assess the severity of DM than the blood sugar.

2. **Write short notes on:**
   (i) Actions of glucagon on body metabolism.
   (ii) List major stimuli affecting glucagon secretion.
   (iii) Insulin resistant.
   (iv) Regulations of insulin secretion.
   (v) Factors affecting insulin secretion.
   (vi) Physiological GUT factor.
   (vii) Mechanism of action of insulin.
   (viii) Kussmaul breathing.
   (ix) Complications of DM.
   (x) Hypoglycemia and hyperglycemia
   (xi) Exhaustion of β-cells
   (xii) Polyuria, polyphasia, hyperosmolar coma and polydipsia
3. **Give the insulin secretion relationship to glucose metabolism.**
4. **Name the body cells which do not require insulin to transport glucose across them.**
5. **Name the hormones that regulate blood glucose level.**
6. **Describe how insulin decreases blood glucose level.**
7. **Explain: metabolic and functional disturbances in diabetes mellitus.**
8. **Justify: "DM is more a disease due to disturbance of lipids than of carbohydrate metabolism."**
9. **Depict diagrammatically**
   (i) Effect of constant glucose infusion on insulin secretion
   (ii) Blood glucose and plasma insulin response to oral and I.V. glucose administration
   (iii) Normal and diabetic type of GTT response
10. **Mention compensatory mechanisms which operate to control hypoglycemia.**
11. **Differentiate between hyper and hypoglycemic coma.**
12. **Explain the cause of polyphagia and polydipsia in DM.**
13. **With the help of line diagram give "Pathophysiology of DM".**

MCQs

1 ***Not* an effect of glucagon in the body:**
(a) Mobilizer of glucose
(b) Stimulate glycogenolysis
(c) Promotes gluconeogenesis
(d) Hormone of abundance

2. **Glucagon secretion is more after oral administration of amino acids than after its I.V. injection because former also increases release of:**
(a) CCK-PZ (b) Gastrin (c) GIP (d) All of the above

3. ***Not* a correct statement regarding secretion of insulin:**
(a) GIP alone can cause its release
(b) Increase is more after oral administration of glucose than I.V. glucose
(c) Sugars which decrease glucose metabolism cause increase in insulin secretion
(d) Increased secretion occurs during feeding periods

4 **Insulin acts directly on all of the following tissues to cause glucose entry with the *exception* of:**
(a) Red blood cells (b) Skeletal muscle (c) Adipose tissue (d) Liver

5 **The primary physiologic effect of insulin seems to be:**
(a) Increased glycogen synthesis in the liver
(b) Increased glucose uptake by the brain
(c) Increased lipid synthesis in the liver
(d) Increased glucose uptake by many different tissues

6. **Insulin exerts all of the following effects *except*:**
(a) Promotion of lipogenesis
(b) Stimulation of glycogen synthase activity
(c) Increase in secondary active transport of glucose into muscle cells
(d) Increase in glucose transport in adipose

7. **Increase in insulin receptors is seen in:**
(a) Acromegaly (b) Starvation (c) Obesity (d) Diabetes

8. **Diabetes means:**
   (a) Disease due to insulin deficiency (b) Disease due to glucagon excess
   (c) Increased blood sugar levels (d) Siphon or running through

9. **Signs and symptoms of diabetes mellitus are mainly due to:**
   (a) Hyperglycemia (b) Glycosuria (c) Dehydration (d) All of the above

10. **Impaired glucose tolerance test (GTT) is one in which:**
   (a) Fasting venous blood glucose level is <80 mg/dL
   (b) After 2 hours of glucose administra-tion (post-prandial-PP), glucose level returns back to normal fasting level
   (c) Fasting venous blood glucose level is >126 mg/dL and one of the PP value is >200 mg/dL
   (d) Fasting and PP values are above the upper limits of normal but below the values of diabetic GTT

11. **Best index to assess the severity of diabetes mellitus is:**
   (a) Estimation of blood glucose (b) Ketone bodies estimation
   (c) FFA estimation (d) Haemoglobin A_{1C} concentration

12. **First body organ to manifest hypoglycemic symptom is:**
   (a) Cerebral cortex (b) Hypothalamus (c) Vasomotor centre (d) Medulla

13. **Hyperglycemic coma differs from hypoglycemic coma in all of the following *except*:**
   (a) Onset is invariably slow (b) Laboured breathing
   (c) Absence of sweating (d) Markedly dehydrated

14. **Islet cells of pancreas secrete all of the following *except*:**
   (a) GHIH (b) Gastrin (c) Glucagon (d) Pancreozymin

15. ***False* statement regarding glycogenolytic effect of glucagon:**
   (a) Inhibits glycogen synthetase in the liver (b) Activates phosphorylase both in liver and muscle
   (c) Activates liver phospholipase C (d) Activates cAMP formation in liver

16. **Glucagon secretion is increased by all of the following *except*:**
   (a) Hypoglycemia (b) Following a protein meal (c) Free fatty acids (FFA) (d) Gastrin

17. **Factor which is *not* responsible for increased insulin secretion:**
   (a) Glucose (b) Amino acids (c) Vagal stimulation (d) Catecholamines

18. **The relationship between plasma insulin and plasma glucose is:**
   (a) Linear (b) Exponential (c) Sigmoidal (d) Hyperbola

19. **Ingestion of a meal containing only protein would result in:**
   (a) Hyperglycemia (b) Increased insulin release
   (c) Decreased insulin release (d) Decreased hepatic glycogen

20. **Glucose transport occurs by insulin dependent facilitated diffusion in which of the following tissues?**
   (a) Cardiac muscle (b) Intestinal epithelium
   (c) Renal epithelium (d) Brain

21. **Insulin increases lipid synthesis in liver by all of the following mechanisms *except*:**
   (a) Activates lipoprotein lipase (b) Inhibits hormone sensitive lipase
   (c) Increases uptake of ketone bodies in the muscle (d) Increases glycogenolysis

22. **Juvenile onset (type I) diabetes differs from maturity onset (type II) diabetes in all of the following *except*:**
   (a) Occurs before 14 years of age (b) Family history of DM uncommon
   (c) Patients are sensitive to insulin (d) Also called non-insulin dependent DM (NIDDM)

23. **In a chronic diabetes patient, sudden disappearance of glycosuria with hyperglycemia is suggestive of:**
   (a) Increase renal tubular reabsorption of glucose (b) Marked decrease in GFR
   (c) Sudden fall in blood glucose level (d) All of the above

Answers

1. (d)	2. (d)	3. (c)	4. (a)	5. (d)	6. (c)	7. (b)	8. (d)	9. (a)	10. (d)
11. (c)	12. (a)	13. (b)	14. (d)	15. (b)	16. (c)	17. (d)	18. (c)	19. (b)	20. (a)
21. (d)	22. (d)	23. (b)							

Chapter 77

The Thymus

1. Thymus is located in the anterior part of the upper mediastinum (lower part of the neck). At birth it weighs 10-12 gms; during childhood and adolescence 20-30 gms, but during old age its growth decreases and it weighs 3-6 gms; because with increasing age, cortex and medulla are replaced by connective tissue and fat (Fig. 77.1).
2. Castration (removal of gonads) prolongs the period of persistence of the thymus. The sex glands therefore exert a depressant effect on the thymus.

HISTOLOGY

It is composed of a inner medulla and outer cortex:

(i) *Medulla* – it consists of reticular epithelial cells, a few lymphocytes and concentric corpuscles of Hassall.

(ii) *Cortex* – it is made up of actively multiplying, closely packed lymphocytes and contains no Hassall's corpuscles.

Thus, the thymus is essentially a lymphoid organ and like other lymphoid tissues it undergoes atrophy in response to glucocorticoids (page 720).

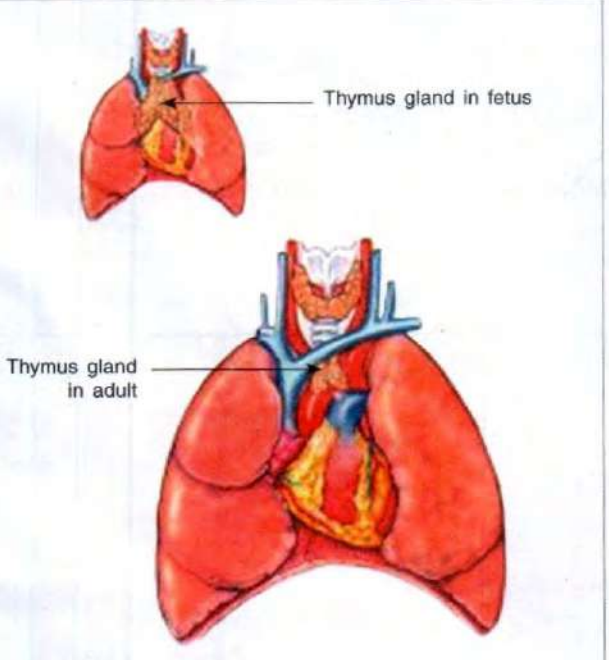


Fig. 77.1 Location of thymus gland

FUNCTIONS

1. **Removal of thymus in a newborn** animal produces:
   (i) lymphopenia and atrophy of all lymphoid tissue;
   (ii) failure to produce circulating antibodies to antigen of bacteria, viruses and red cells;
   (iii) a fatal wasting disease due to increased susceptibility to infections;
   (iv) suppression of delayed hypersensitivity reactions, and
   (v) failure to reject foreign tissue transplants.
2. **Thymectomy in adult animals** causes decline in immunological capacity but only after a few months during which the existing pool of competent lymphocytes becomes gradually depleted.

(1) and (2) show that thymus not only initiates the development of *immunologically competent T-lymphocytes* in early life but is also responsible for maintenance of an adequate pool of such cells in adult life (see also to page 115).

IMMUNOLOGICAL ROLE OF THE THYMUS

1. Thymus provides an environment favourable to lymphopoiesis. It receives precursors from the bone marrow which after development in the thymus pass on to the lymph nodes.
2. The Reticulo-epithelial tissue in thymus secretes a hormone, ***Thymosin***, which stimulates lymphopoiesis both within the thymus and in peripheral lymphoid tissue. Thus, the thymus promotes the development of immunologically competent T-lymphocytes.
3. Thymus also secretes a hormone, *Thymopoietin (Thymin)*, which inhibits A-ch release at motor nerve endings in *Myasthenia gravis* (page 158).

APPLIED

In the auto-immune disease *e.g.* *Myasthenia gravis, hemolytic anaemia* and *Hashimoto's thyroiditis* (page 691), there is hyperplasia of the thymus with the development of follicles with germinal centre like those which occur in normal lymph nodes. Normally lymphoid tissue within the thymus is not immunologically responsive, it lacks germinal centres and plasma cells. Moreover, lack of antibody formation may be due to a blood thymus barrier preventing access of antigen to thymic lymphocytes.

Study Questions

1. **Mention the effects of thymectomy in**
   (i) neonates
   (ii) adults.
2. **Write shorts notes on:**
   (i) immunologically competent lymphocytes.
   (ii) Immunological role of the thymus.
   (iii) Thymosin.
3. **How does the thymus differ from other lymphoid tissues?**

MCQs

1. **Thymosin, *not a correct* statement:**
   (a) Stimulates lymphopoiesis
   (b) Promotes the development of immuno-logically competent T-lymphocytes
   (c) Inhibits A-ch release at motor nerve endings
   (d) Secreted by tissue macrophage system in thymus
2. ***Not* a function of melatonin:**
   (a) Concerned with control of skin colour
   (b) Concerned with regulation of onset of puberty
   (c) Produces slowing of EEG rhythm
   (d) Produces sleep
3. **Pineal gland delay onset of puberty by the following mechanism:**
   (a) Secretes gonadotrophin inhibiting peptide
   (b) Inhibits gonadotrophin releasing hormone release from hypothalamus
   (c) Checks the secretion of FSH and LH
   (d) All of the above
4. ***Not* an action of histamine:**
   (a) Powerful stimulant for secretion of HCl by the stomach
   (b) Responsible for itch production
   (c) Dilates all smooth muscles of the body
   (d) Stimulate GIT secretions
5. **Prostaglandin secretion is maximum in:**
   (a) Urine (b) Semen (c) Amniotic fluid (d) Saliva
6. **Melatonin is secreted by:**
   (a) Hypothalamus (b) Pituitary gland (c) Pineal gland (d) Melanocytes
7. **The pineal gland contains high amounts of:**
   (a) Serotonin (b) Nor-epinephrine (c) Melatonin (d) All of the above

Answers

1. (c) 2. (a) 3. (d) 4. (c) 5. (b) 6. (c) 7. (d)

Chapter
78

The Pineal Gland

GENERAL FEATURES

1. It weighs approx. 120 mg. and lies between the superior colliculi *i.e.* roof of third ventricle at the posterior end of corpus callosum. It has a very rich blood supply.
2. It is connected by a stalk to the posterior commissure and habenular commissure.
3. It consists of parenchymal cells (*Pinealocytes*), glial cells (neuroglia), secretory cells and numerous post-ganglionic sympathetic nerve fibers from cells in the superior cervical ganglion.
4. The pineal gland is a ***Neuroendocrine Transducer*** as it forms and secretes a hormone called ***Melatonin*** in response to sympathetic nerve activity. Therefore, it is analogous to adrenal medulla, the posterior pituitary and the JG cells of the kidney; all of which secrete hormone in direct response to nervous activity. These organs do not function when transplanted.
5. The pineal gland resembles the neurohypophysis and the area postrema in lacking blood brain barrier, therefore, dyes and many drugs which normally penetrate the brain poorly, pass readily into the pineal gland.
6. Pineal is large in infants, begins to involute and calcifies during second decade of life but continues to form melatonin.
7. In adults, calcified (Ca^{2+}, Mg^{2+}, PO_4^{3-}, CO_3^{2-}) deposits appear radiopaque, which can be seen with X-ray as *Pineal Sand*. Displacement of a calcified pineal from its normal position indicates the presence of a space occupying lesion *e.g.* brain tumour.
8. It contains high amounts of 5 HT (serotonin), Norepinephrine and melatonin.
   Melatonin is synthesized from 5 HT and norepinephrine by the parenchymal cells (pinealocytes) **(Fig. 78.1)**.
9. ***Melatonin*** is secreted rapidly from pineal into the CSF and blood; being highly lipid soluble it penetrates into the cells in the hypothalamus and mid brain, into peripheral nerve fibers and into the gonads. The human pineal gland contains melatonin in concentration of 50-400 µgm/gm.
10. ***Diurnal variation in melatonin secretion.*** Melatonin synthesis and secretion are increased during the dark period of the day and maintained at a low level during the daylight hours (average daytime plasma concentration at all ages: 7 pg/mL),
11. **Melatonin plasma concentration** is much higher in children than adults, and it declines gradually with age:

(i)	in children (1-3 years)	250 pg/mL
(ii)	during adolescent (8-15 years)	120 pg/mL
(iii)	young adults (20-27 years)	70 pg/mL
(iv)	old age (above 65 years)	30 pg/mL

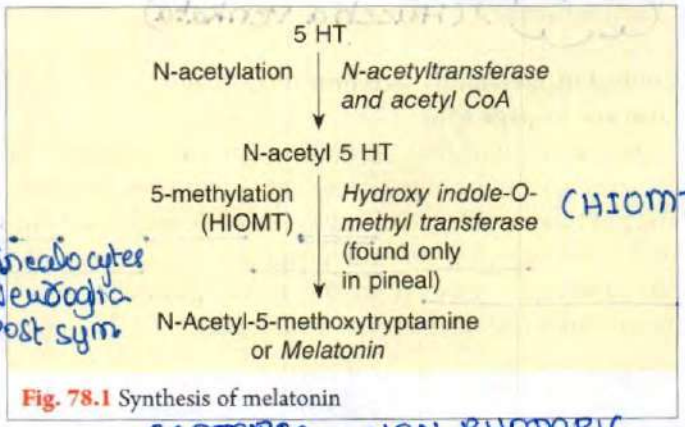


Fig. 78.1 Synthesis of melatonin

FUNCTIONS OF MELATONIN

1. It contracts the melanophores in amphibian skin and thus lightens its colour (page 676).
2. It is concerned with **regulation of onset of puberty**. The *pineal gland* may secrete some substance - *Gonadotrophin inhibiting peptide* which may delay onset of puberty (page 775).

Evidences

(i) Injection of melatonin or pineal gland extract, in mammals, inhibits oestrogen and causes atrophy of gonads (ovaries/testis) due to inhibition of hypothalamic gonadotrophin releasing hormone (GnRH) which decreases the secretion of FSH and LH from the anterior pituitary.

(ii) Removal of pineal gland in mammals causes stimulation of oestrous and hypertrophy of ovary

and uterus; increases weight of testis, seminal vesicles and prostate; increases secretion of male and female sex hormones; increases thyroid and adrenal cortical hormone secretion. This shows that melatonin also inhibits thyroid and adrenal cortical hormone secretion.

3. It produces *slowing of EEG rhythm*, sleep and rise in convulsive threshold.
4. It also secretes some substance which may cause *schizophrenia*.

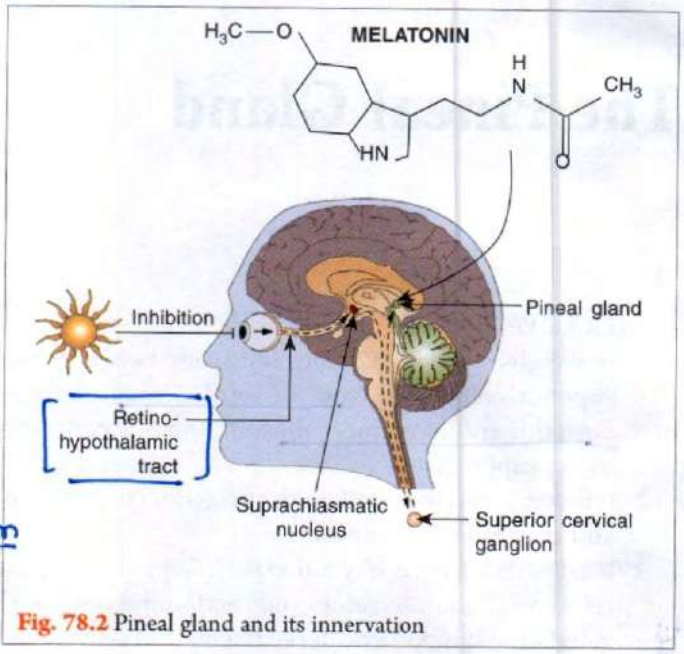


Fig. 78.2 Pineal gland and its innervation

Control of melatonin secretion (Fig. 78.2) (also see to page 676)

Exposure to darkness stimulates pineal secretion of melatonin; whereas exposure to light inhibits its secretion. The pathway involved is: Retina → optic tract → brain stem → superior cervical ganglion → sympathetic nor-adrenergic pathway to the pineal gland (increases intracellular cAMP to secrete melatonin).

Study Questions

1. **Define neuroendocrine transducer.**
2. **Give functions of melatonin.**
3. **Write shorts notes on:**
   (i) Pineal sand
   (ii) Diurnal variation in melatonin secretion
   (iii) Control of melatonin secretion
   (iv) Gonadotrophin inhibiting peptide.

Chapter 79

Local Hormones

Endocrine glands liberate their secretions into the blood stream to be carried to act on distant organs and tissues. Also, living tissues contain many substances which may be activated in certain circumstances to exert profound effects in their immediate neighbourhood. Such substances which act at the sites of their synthesis and release have been called ***Local Hormones***. Examples include:

1. Acetylcholine
2. Histamine
3. 5-hydroxytryptamine (serotonin)
4. Prostaglandins
5. Adenosine derivatives: AMP, ADP and ATP
6. Plasma polypeptides *e.g.* angiotensin, plasma kinins, etc.

ACETYL CHOLINE

Characteristic features

1. It acts as a peripheral cholinergic transmitter; in CNS cholinergic transmission is seen in Renshaw cells (page 856).
2. It is formed in non-nervous tissues which contain choline acetyltransferase and cholinesterase. (Details refer to page 1045)
3. The functions of locally formed A-ch are to promote rhythmic activity in nerve-free smooth muscle (*e.g.* amniotic membrane), in heart muscle and in cilia of epithelial cells (*e.g.* in oesophagus and trachea). All these effects are increased by an anticholinesterase (*e.g.* eserine).
4. A-ch is also synthesized in the placenta (nerve-free) where its function may be to dilate blood vessels.

HISTAMINE

Characteristic features

1. Histamine is widely distributed in body tissues, but the highest concentration occurs in skin, intestine and lungs, *i.e.* at surfaces in contact with the outside world.
2. Most of the histamine in the body occurs in:
   (i) the mast cells of the tissues – here it is associated with heparin,
   (ii) the basophil cells, and
   (iii) platelets.
3. *Actions*
   (i) *On CVS*
      (a) It produces arteriolar as well as pre-capillary sphincter dilatation.
      (b) Subcutaneous injection of 0.3 mg histamine causes: slight fall in SBP, marked fall in DBP, increase in HR, general flushing of the skin, dilates meningeal vessel and produces headache.
   (ii) **On smooth muscle:** It increases tone of most types of smooth muscles *e.g.* intestine and bronchioles.
   (iii) **Secretory action:**
      (a) It is a powerful stimulant for the secretion of HCl by the stomach and moderate stimulant for the secretion of pepsin.
      (b) It also stimulates salivary, pancreatic and intestinal secretions.
   (iv) **Itch and pain:** Histamine when injected in concentration ≥ 10 µg/mL, produces pain due to stimulation of nerve endings in deeper skin layers. However, in concentration ≤ 0.1 µg/mL produces itch only due to stimulation of nerve endings.

   Therefore, histamine might contribute to itching in urticaria and pain which occur with severe tissue damage.
4. **Release of histamine occurs in response to:**
   (i) **physical stimuli** *e.g.* firm pressure; application of heat or cold; and
   (ii) **chemical stimuli** *e.g.* morphine, allergy to foreign proteins.
      (a) Histamine release in the skin accounts for the 'triple' response (page 376).
      (b) Anaphylactic shock induced by foreign proteins is mainly due to release of histamine. ***Mechanism:*** Antigen reacts with tissue antibody and causes release of histamine which produces severe bronchoconstriction and profound fall in arterial BP. SRS-A *i.e.* slow reacting substance-A (*A means anaphylaxis*), a peptidolipid derived from arachidonic acid is also released. Its release in anaphylaxis is much more prolonged than that of histamine

and it produces long lasting bronchospasm. There are no known antagonists to SRS-A.

Important Note

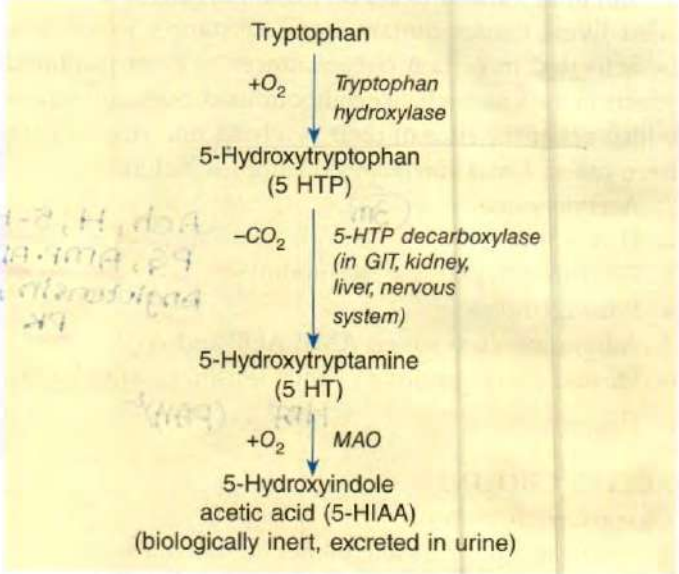
Certain allergic states like urticaria, allergic rhinitis, bronchial asthma might be described as local forms of anaphylaxis.

5. **Fate of histamine in the body**
   (i) Small amounts of histamine are excreted via kidneys partly as free and partly as conjugated histamine. Approx. 2-3 mg of histamine is released into the blood from the tissues every 24 hours, about 1% appearing unchanged in the urine.
   (ii) Most of the histamine is oxidised by enzyme *histaminase*. There is normally very little histaminase in plasma but in pregnancy it increases markedly, beginning at 2-3 months and reaching a peak at 6-7 months
   (*significance* – not known).
6. ***Anti-histamine drugs*** *i.e.* drugs which antagonise the action of histamine. These are:
   (i) Drugs acting in the opposite way to histamine *e.g.* β-adrenergic receptor agonist (isoprenaline, epinephrine etc.) to relax bronchiolar muscles thereby overcoming the effect of histamine.
   (ii) ***H_1-receptor antagonist*** *e.g.* mepyramine and promethazine combines with H_1-receptors and prevent histamine induced contraction of smooth muscles of intestine and bronchi. These drugs also relieve allergic states in which H_1-receptors are activated *e.g.* in urticaria and allergic rhinitis.
   (iii) ***H_2-receptor antagonist*** *e.g.* cimetidine, inhibits the gastric secretion of HCl evoked by histamine or pentagastrin. (Also refer to page 1046)

5-HYDROXYTRYPTAMINE (SEROTONIN or ENTERAMINE)

Characteristic features

1. 5-hydroxytryptamine (5 HT) is also called *serotonin* because when acting directly, it is a cardiac stimulant and a vasoconstrictor.
2. It is also called ***Enteramine*** as GIT contains 80-90% of all the 5 HT in the body. Platelets obtain their 5 HT while passing through the GIT (**Note:** ***platelets cannot synthesize 5 HT***).
3. **Distribution-***sites*
   (i) Blood – Normal serum 5 HT level is 0.1 µg/mL which is formed by 5 HT liberated from the platelets during clotting.
   (ii) Urine – Contains 0.1–1.0 mg/L of 5 HT.
   (iii) GIT.
   (iv) CNS, in sympathetic ganglia, brainstem and hypothalamus.
4. ***Sources***
   (i) Animal sources – venom of toad, wasp and scorpion.
   (ii) Plant sources – nettle stings, itch powder, bananas.
5. ***Formation and Metabolism***



6. ***Actions***
   (i) **CVS** – It produces pressor effect – raises HR, SBP, DBP, vaso and venoconstriction.
   (ii) **Respiration**
      (a) Reflex hypernoea is seen due to stimulation of carotid chemoreceptors.
      (b) Also produces bronchospasm (direct and reflex action), therefore, precipitates an acute attack of asthma in asthmatic subject.
   (iii) **Kidney** – antidiuretic effect due to:
      (a) afferent glomerular arteriolar constriction; and
      (b) ureteric spasm.
   (iv) **Smooth muscles**
      (a) 5 HT, increases the tone of smooth muscles *e.g.* arterioles, bronchioles, urinary bladder, intestine, uterus, pupil and nictitating membrane.
      (b) Reflexly stimulates intestinal peristalsis to cause evacuation of the bowels.
   (v) **Nerve endings** and fibers
      (a) 5 HT stimulates carotid chemoreceptors and produces effects on CVS and respiration.

(b) Stimulates cholinergic nerves in intestinal ganglia to produce effects on the GIT.
(c) Very potent stimulant of pain nerve endings in the skin. It potentiates the *algogenic* (pain producing) action of bradykinin.

(vi) CNS: 5 HT occurs in some nerve terminals in the brain (*serotoninergic nerves*) which have important physiological effects on mood, behaviour, sleep induction, analgesic action and regulation of body temperature. (Also refer to page 1045)

PROSTAGLANDINS

Characteristic features

1. The name *prostaglandins (PG)* was introduced by *Von Euler* in 1937 because they were first isolated from the semen and the active substance came from the prostate.
2. The immediate precursors of PGs in the body are 20-carbon essential unsaturated fatty acids *e.g.* Linoleic and arachidonic acids and linolenic acid.
3. The commonest PGs are PGA_1, PGA_2, PGE_1, PGE_2, $PGF_{1\alpha}$ and $PGF_{2\alpha}$. They are formed by various types of substitution and degrees of unsaturation in almost all organs of the body.

Biosynthesis: See **Fig. 79.1**.

Metabolism

1. PGs have short half life. PGEs and PGFs are very quickly destroyed in the lungs. It seems they are ***true 'local' hormones***, acting at the sites of their synthesis and release. PGAs are more stable.
2. Urinary metabolites of PGEs and PGFs give information about their biosynthesis and release. Increased urinary excretion of $PGF_{1\alpha}$ and $PGF_{2\alpha}$ is seen during pregnancy, which further increases at the time of labour.

Site of action

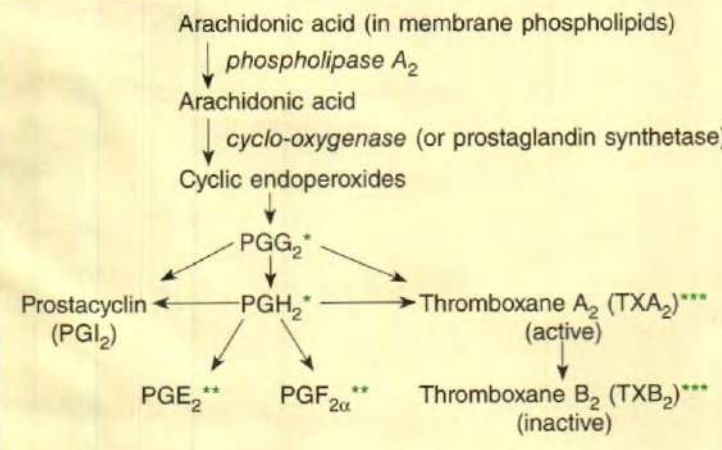
The receptors for PGs are located in the plasma membrane. ***Receptor-PGs interaction*** can affect the activity of adenylyl cyclase situated in the inner part of the plasma membrane.

Actions – PGs act on most organs and tissues of the body. The non-vascular actions of PGs are related to cAMP but vascular actions are independent of cAMP.

PGs have important biological actions but their physiological role is not clear.

1. *CVS*
   (i) PGA_1 and PGA_2 cause peripheral arteriolar dilatation, specially in splanchnic vascular bed.
   (ii) PGA_2 (also called ***Medullin***, as isolated from the renal medulla) has antihypertensive action, increases renal cortical blood flow and increases urinary excretion of sodium, potassium and water.
   (iii) PGE_2 produces local vasodilatation when given into an artery.

2. *Reproductive system*
   (i) Only PGEs and PGFs act on female reproductive system and,
      (a) stimulate contraction of gravid uterus;
      (b) promote secretion of hypothalamic gonadotrophin releasing hormone (GnRH).
   (ii) $PGF_{2\alpha}$
      (a) occurs in amniotic fluid, its concentration in this fluid and blood increases during labour, which shows it may initiate the onset of labour;
      (b) also found in menstrual fluid, where it may cause painful uterine contraction (Dysmenorrhoea).



Note

- PGH_2 is the precursor for various other PGs.
- TXA_2 is a potent inducer of platelet aggregation and a vasoconstrictor
- Prostacyclin is a potent inhibitor of platelet aggregation and a vasodilator.

Fig. 79.1 Biosynthesis and metabolism of prostaglandins (*, **, *** : unstable, stable and highly stable respectively)

3. *Blood platelets*
   (i) PGE_1 is a very active inhibitor of platelet aggregation. Its action is mediated through activation of adenylyl cyclase.
   (ii) PGE_2, PGG_2 and PGH_2 promote the aggregation of platelets. Aspirin and indomethacin inhibit aggregation of platelets by preventing formation of PGG_2 and PGH_2 from arachidonic acid.
   (iii) Platelets normally contain PGE_2 and $PGF_{2\alpha}$. Thrombin promotes PGE_2 synthesis and release and hence produces platelet aggregation.
4. *Inflammation*
   (i) *Local:*
      (a) PGE and PGA increase the histamine induced vascular permeability.
      (b) PGEs sensitize cutaneous nerve endings to the pain-producing action of bradykinin; however, in higher concentration they can produce pain directly.
      (c) many PGs, however, contribute to the production of itch, pain, vasodilation, increased vascular permeability and cellular infiltration.
   (ii) Systemic – PGs produce systemic effects of inflammation such as headache, fever, etc.
5. *Bronchial musculature* – PGEs relax the smooth muscle of bronchi and bronchioles but $PGF_{2\alpha}$ contracts them and may produce bronchial asthma.
6. *GIT*
   (i) PGE_1, PGE_2 or PGA_1 inhibit the secretion of gastric HCl induced by any stimuli.
   (ii) PGEs and $PGF_{2\alpha}$ inhibit the absorption of sodium and water to produce profuse, watery, cholera like diarrhoea. (Important: cholera toxin may act by releasing PGE_1).
   (iii) PGE and PGF increase intestinal motility.
7. *Metabolic action* – PGE_1, in vitro, inhibit lipolysis induced by ACTH, GH, glucagon and epinephrine by inhibiting adenylyl cyclase. However, in vivo the effects are variable.
8. *CNS:* Here PGs function as transmitters or modulators of neuron activity.
9. *ANS:*
   (i) PGEs inhibit neurally induced release of nor-epinephrine and the responses to nor-epinephrine.
   (ii) Also stimulate cholinergic neuroeffector junctions.
10. *Eye* – PGE_2 and $PGF_{2\alpha}$ occur in the iris and produce miosis.

ADENOSINE DERIVATIVES

1. Adenosine derivatives *e.g.* AMP, ADP and ATP occur in all cells and take part in the transfer and storage of energy. They relax smooth muscles, decrease HR, dilate blood vessels and produce pain.
2. ATP excites ganglion cells, and ADP promotes agglutination of platelets.

PLASMA POLYPEPTIDES

These are highly active polypeptides which can be formed from blood plasma, lymph and ECF.

1. Angiotensin (page 726).
2. Plasma kinin (page 323).

Study Questions

1. **Define and name the local hormones. Which one is a true local hormone?**
2. **Give the characteristic features of each of the following as a local hormone:**
   (i) Acetyl choline
   (ii) Histamine
   (iii) 5 HT
   (iv) Prostaglandins.
3. **How does histamine produces allergic reactions?**
4. **How do anti-histamine drugs act?**
5. **From where do the platelets obtain their 5 HT?**
6. **Explain why 5 HT is also called enteramine?**
7. **Mention the role of prostaglandins in inflammation.**
8. **Why are prostaglandins so called? Give their types.**
9. **Give main actions of prostaglandins.**

Unit X

THE REPRODUCTIVE SYSTEM

Chapter 80: Physiology of Reproduction

Sex determination and sex differentiation; Abnormalities of human sex development: Klinefelter's syndrome, Turner's syndrome, Hermaphroditism; Puberty: Control of the onset, stages, delayed and precocious puberty; Reproductive hormones: gonadotrophins (FSH, LH).

Chapter 81: Male Reproductive System

Testes: structure and function, spermatogenesis, structure of the sperm, seminal tracts and related glands, supporting structures; Seminal fluid (semen); Endocrine functions of testes: Testosterone; Control of testicular activity; Cryptorchidism and removal of testis (Eunuchoidism).

Chapter 82: Female Reproductive System

The female reproductive tract: the uterus and related structures, the ovaries, ovarian hormones (oestrogen, progesterone, relaxin), removal of ovaries and menopause; Female sexual cycles: changes in the ovaries, uterus (menstrual cycle), vagina and gonadotrophin secretion.

Chapter 83: Physiology of Coitus

Chapter 84: Contraceptive Measures

Chapter 85: Physiology of Pregnancy

Fertilization and implantation of ovum; Endocrinology of pregnancy: placental hormones, pregnancy diagnosis tests; Maternal physiology in pregnancy; Parturition.

Chapter 86: Physiology of Foetus and Newborn

The placenta; Growth and functional development of the foetus; Respiratory and cardiovascular adjustments of the infant to extra-uterine life; Nutrition of the newborn infant; the breast and lactation.

20.04.17	Introduction to Reproductive System Sex determination, differentiation
21.04.17	Puberty
22.04.17	Male reproductive system- I
24.04.17 (8-9)	Male reproductive system- II
25.04.17	Female reproductive system- I
26.04.17 (9-10)	Female reproductive system- II, Menopause
27.04.17	Fertilisation, Implantation, Functions of placenta, Tests for pregnancy.
28.04.17	Foeto-placental unit, Physiological changes during pregnancy, Nutritional needs of mother
02.05.17	Parturition, lactation, composition of breast milk.
03.05.17 (9-10)	Family planning

Chapter

80

Physiology of Reproduction

I. Sex determination and sex differentiation
II. Abnormalities of human sex development
(A) in males: Klinefelter's syndrome
(B) in females: Turner's syndrome; testicular feminization; superfemale
(C) combined: True and pseudohermaphroditism
III. Puberty: control of the onset; stages; delayed and precocious puberty
IV. Reproductive hormones: FSH, LH

An understanding of the physiology of reproduction is important for the:
(1) promotion of conception,
(2) foetal growth,
(3) foetal birth, and
(4) early development of healthy children.

SEX DETERMINATION AND SEX DIFFERENTIATION

Sexual development in the embryo involves two processes:
(A) *Sex determination*, and
(B) *Sex differentiation*.

A. SEX DETERMINATION

Characteristic features

1. It is a genetic phenomenon and depends on the constitution of the ***sex chromosomes***. The 'sex chromosomes' are called X and Y chromosomes, whereas the somatic chromo-somes are called *Autosomes*. Therefore, what is determined is the ***Sex Genotype*** or *Genetic Sex*.

Note

Phenotype sex is defined by the characteristics of the internal genital tract and external genitalia.

2. The primitive female germ cells *i.e.* *Oogonia* contain 46 chromosomes; 44 autosomes plus two identical sex chromosomes XX which carry female determining genes that code for the production of ovaries. During gametogenesis (production of germ cells), as a result of meiosis (reductional division), chromosomes become half in number, therefore, each ovum finally contains '22 + X' chromosomes **(Fig. 80.1)**.
3. The primitive male germ cells *i.e.* *Spermatogonia* also contain 46 chromosomes; 44 autosomes plus two sex chromosomes XY, where 'Y' carries male-determining genes that code for the production of *Testes*. The Testis determining gene product is a cell surface protein known as the *SRY* *i.e.* ***sex-determining region of the Y-chromosome***. During gametogenesis, as a result of meiosis, chromosomes become half in number, therefore, two kinds of spermatozoa (sperms) are formed; half the normal sperms contain '22 + X' chromosomes and other half contain '22 + Y' chromosomes.
4. The *ovum* may be fertilized by either kind of sperm with the following sex genotypes:

Sperm	*Ovum*	*Offspring*	*Sex genotype*
X	X	XX	Genetic female
Y	X	XY	Genetic male

Thus, ***genetic sex*** is determined entirely by the sperm. The sex-determining gene on the X and Y chromosomes acts on the primitive bipotential gonad to promote its development as a testis or an ovary.

5. ***Human chromosomes*** Fluorescent and other staining techniques make it possible to identify the individual chromosomes and study them in detail. Human cells are grown in tissue culture and treated with the drug colchicine, which arrests mitosis at the metaphase; then these are exposed to a hypotonic solution to make the chromosomes swell and disperse.

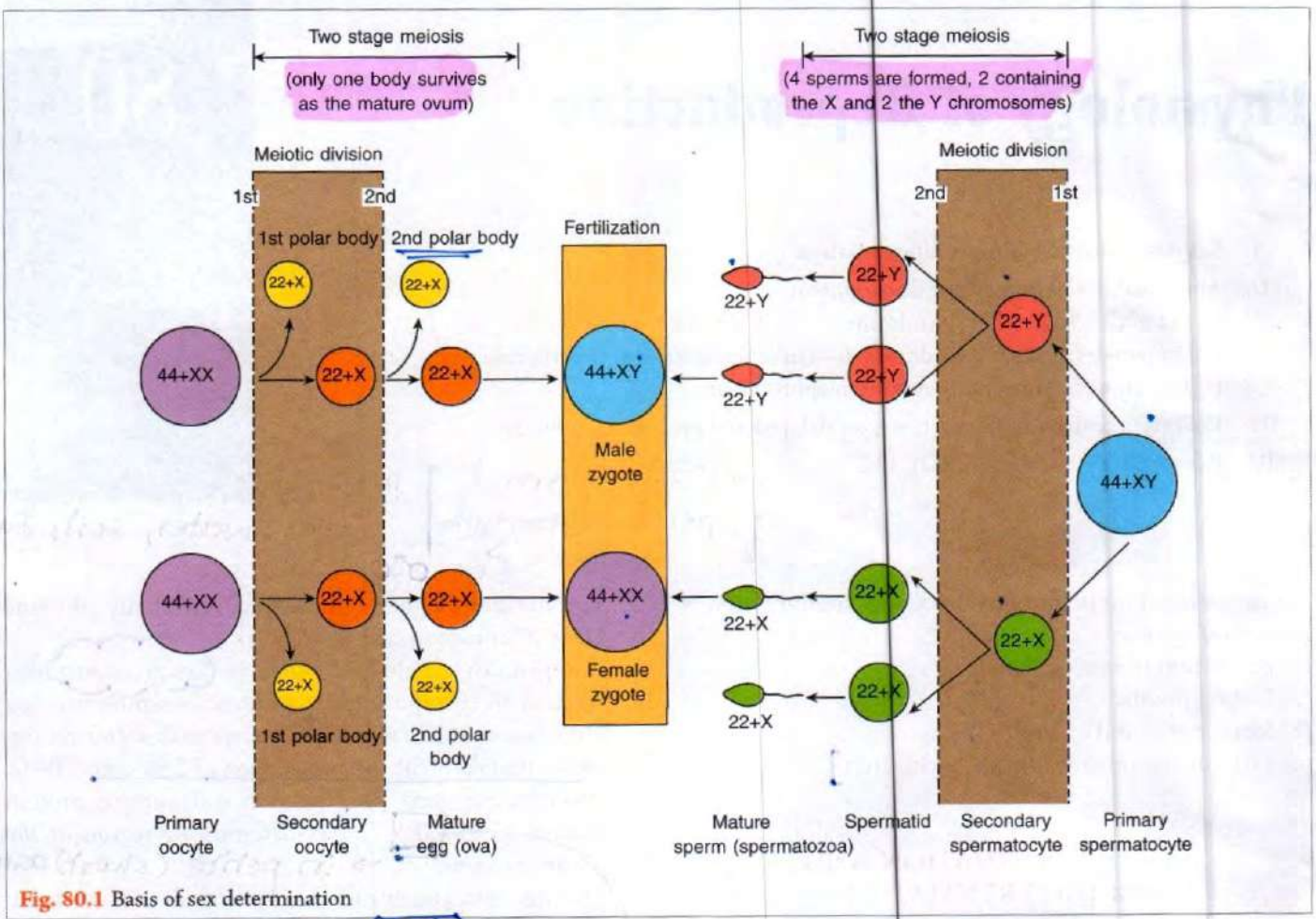


Fig. 80.1 Basis of sex determination

Because the human Y-chromosome is smaller than the X-chromosome, probably sperms containing the Y-chromosome are lighter and able to 'swim' faster up the female genital tract, thus reaching the ovum more rapidly. This may be the reason why the *number of males born is slightly greater* than the number of females.

6. *Sex Chromatin*

Soon after cell division has started during embryonic development, one or the other of the two X-chromosomes of the somatic cells in normal female *only* becomes functionally inactive. The choice of the X-chromosome which becomes inactive in any given cell is apparently random, so that one X-chromosome is inactivated in approximately half of the cells and the other X-chromosome in the other half. The selection persists through subsequent divisions of these cells, and consequently some of the somatic cells in adult females contain an active X-chromosome of paternal origin and some contain an active X-chromosome of maternal origin.

The inactivation of an X-chromosome forms *sex-chromatin*, also called *Barr Body* (Fig. 80.2). This barr body can be seen in the nuclei of somatic cells in the *female only* as a visible chromatin mass approximately 1 μm in diameter which lies against the inner surface of the nuclear membrane or it is also visible as a small "drumstick" of chromatin projecting from the nuclei of 1-15% of the polymorphonuclear leucocytes. Another form of sex chromatin is the *F-Body* i.e. a portion of the Y-chromosomes that can be stained with modern fluorescent technique. However, *usually the XY-chromosome pair of the male forms no detectable mass.* Thus the sex genotype can be identified by a cytological test, the most suitable cells being:

(i) the epithelial cells of the epidermal spinous layer
(ii) buccal mucosa
(iii) vagina or
(iv) blood leucocytes

B. SEX DIFFERENTIATION

Sex differentiation takes place in stages. The important *characteristic features* include:

1. The masculine characteristics of the body get influenced by the foetal testicular hormones against a basic feminine trend of the body. The development of the female organs results from the mere absence of testes.

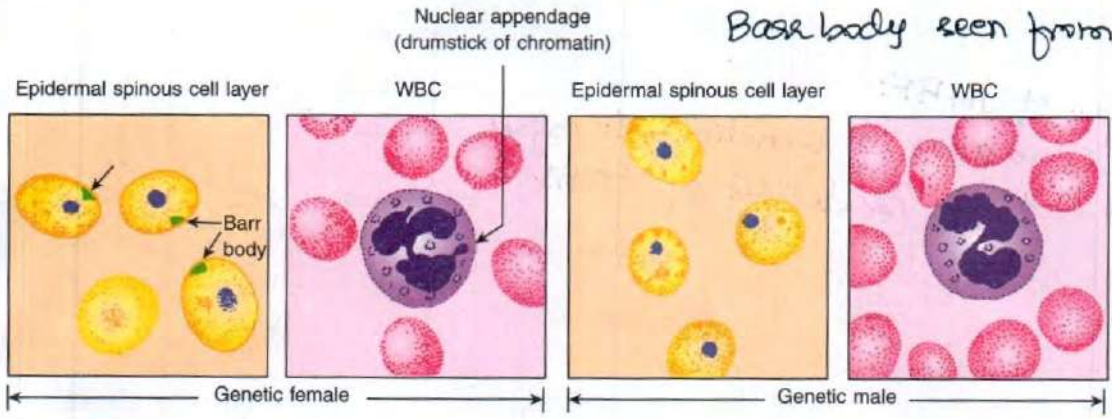


Fig. 80.2 Appearance of sex chromatin (barr body) in a genetic female and male

2. The males differentiate very early while the females quite late, because in the males the formation of testicular tissue occurs much earlier than ovarian tissue.

3. ***Gonadogenesis***
   (i) Primordial germ cells migrate into the urogenital ridge (*i.e.* a condensation of tissue near the adrenal gland) where proliferation of both non-germinal and germinal cells occurs. This leads to the formation of the ***Primitive Gonads*** which are identical in both sexes upto 6 weeks of gestation. The gonads develop a cortex and a medulla, called ***Bipotential Primordial Human Gonad*** **(Fig. 80.3)**.
   (ii) ***In the genetic males:***
      (a) *Testicular differentiation* begins as early as *seventh week* with the formation of primitive seminiferous tubules *in the medulla* and regression of cortex.
      (b) At about 8-9 weeks *Leydig cells* appear and proliferate rapidly in the interstitial spaces between the seminiferous tubules untill about 14 weeks.
      (c) The development of testis is controlled by the Y-chromosome, therefore, with 'XY' constitution the Y-chromosome causes early testicular development, which prevents subsequent ovarian formation.
   (iii) ***In the genetic females:***
      (a) The gonads continue to show proliferation of the coelomic epithelium and of the primordial germ cells which enlarge gradually and become *Oogonia in the cortex* whereas medulla regresses.
      (b) At about 11-12 weeks the oogonia undergo meiosis to form oocytes, which marks the point of ovarian differentiation from the undifferentiated gonad.
      (c) The development of an ovary requires the presence of XX chromosomes; therefore, with 'XO' chromosomal constitution there may be no ovarian tissue.

4. ***Genital Ducts and External Genitalia***
   At the eighth week of gestation, the embryo has both male and female primordial genital ducts (the *Wolffian Ducts* and *Mullerian Ducts*) as paired structures and the external genitalia have not yet become differentiated **(Fig. 80.4)**.
   (i) ***If the primitive gonads become an ovary*** or if there are no gonads at all,
      (a) the ***'mullerian ducts' form*** the fallopian tubes, uterus and upper part of the vagina,
      (b) the wolffian ducts disappear, and
      (c) the external genitalia assume their female form during the 3rd-4th months.
   (ii) ***If the primitive gonads become a testis:***
      (a) the ***'wolffian ducts' form*** the epididymis, vas deferens and seminal vesicles,
      (b) the mullerian ducts degenerate, and
      (c) the external genitalia acquire their male characteristics by the 5th month. However, the testes descend into the scrotum as late as 8th month.

Important Note

The development of female genitalia and female phenotype occurs in the presence or absence of a functional ovary, whereas the development of male genitalia and male phenotype only occurs in the presence of a functional testis. Thus, removal of the foetal testes (*castration*) at an early critical period prevents the formation of male genitalia and results in entirely female development of genitalia. However, castration of male foetuses at a late stage does not affect male sex differentiation.

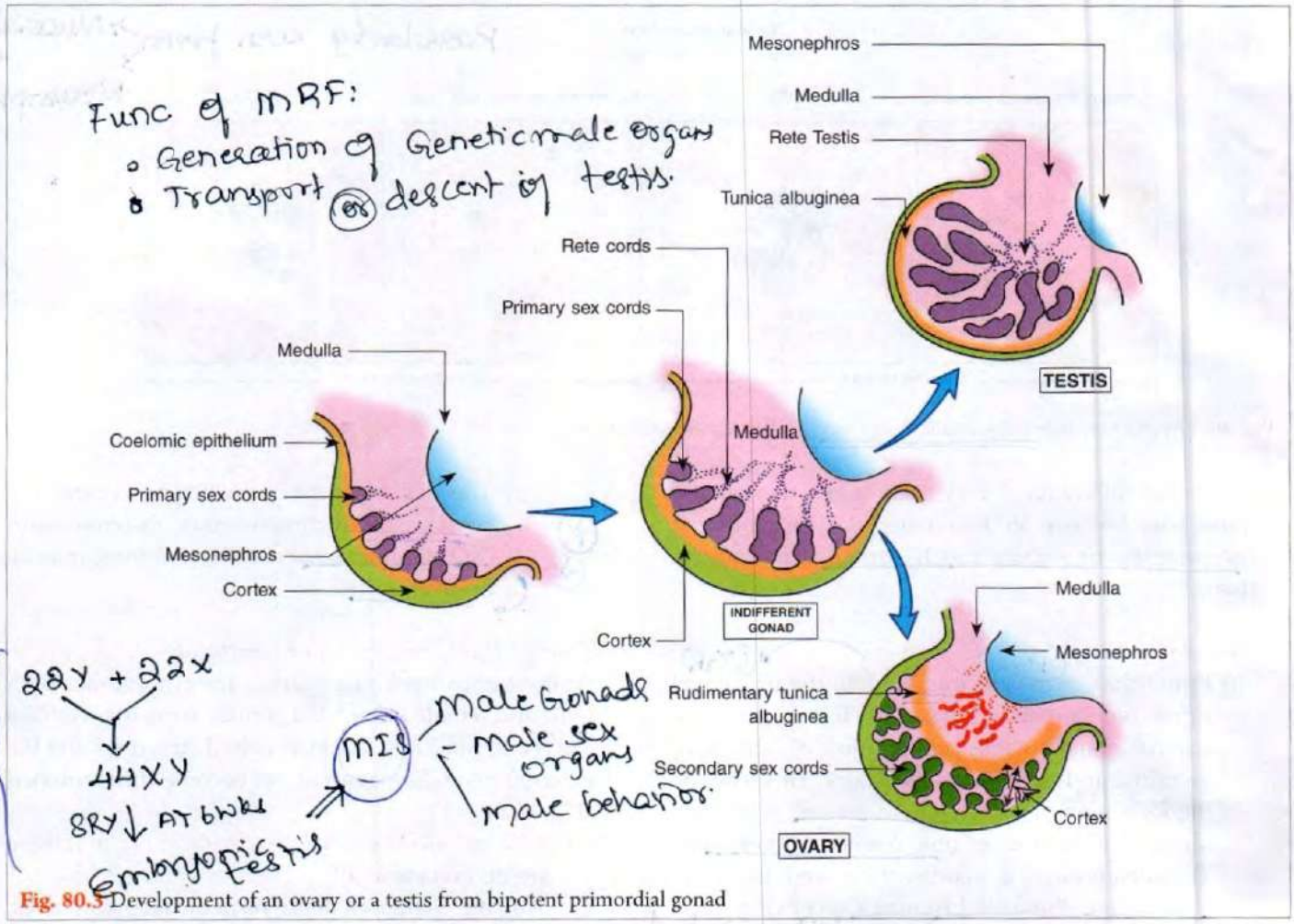


Fig. 80.3 Development of an ovary or a testis from bipotent primordial gonad

ROLE OF TESTIS IN SEX DIFFERENTIATION

The testis influences genital development in *three ways:*

1. It suppresses the growth of the mullerian ducts by a *local action i.e.* it causes involution of the mullerian ducts to which it is anatomically closely related. This is due to release from the foetal testis of a locally 'active' factor or hormone called ***Mullerian Regression Factor (MRF)*** (also called ***mullerian inhibiting substance – MIS***). This active agent is neither testosterone nor androgen; because, systemic or local administration of these agents does not suppress mullerian duct growth. This active agent is a polypeptide or nucleic acid and is derived from foetal seminiferous tubules, the Sertoli cells (page 784).

Important Note

MRF is also produced in small amounts by the granulosa cells of the ovarian follicles, but *MRF requires a high androgen to oestrogen ratio* to exert its effects on the mullerian ducts. MRF is involved in germ cells maturation in both sexes and in control of testicular descent in boys (page 791)

2. It causes the continued growth of the Wolffian ducts and its derived structures. How?
The Leydig cells of foetal testis secrete ***testosterone*** which becomes bound to a high affinity ***androgen-binding protein*** secreted by the Sertoli cells into the lumen of the seminiferous tubules. Synthesis of this protein is stimulated by FSH. The bound testosterone flows along the wolffian ducts and is released from its binding protein to produce high local concentrations which promote growth of the epididymis, vas deferens and seminal vesicles.
3. It is essential for differentiation and growth of male external genitalia, because male development of the external genitalia occurs only when there is adequate testosterone and androgenic stimulation of the target organs during the first 12 weeks of foetal life.

ABNORMALITIES OF HUMAN SEX DEVELOPMENT

Hormonal and/or environmental influences can lead to abnormalities of sex development. These can arise from changes in sex chromosomes or from abnormalities in sex

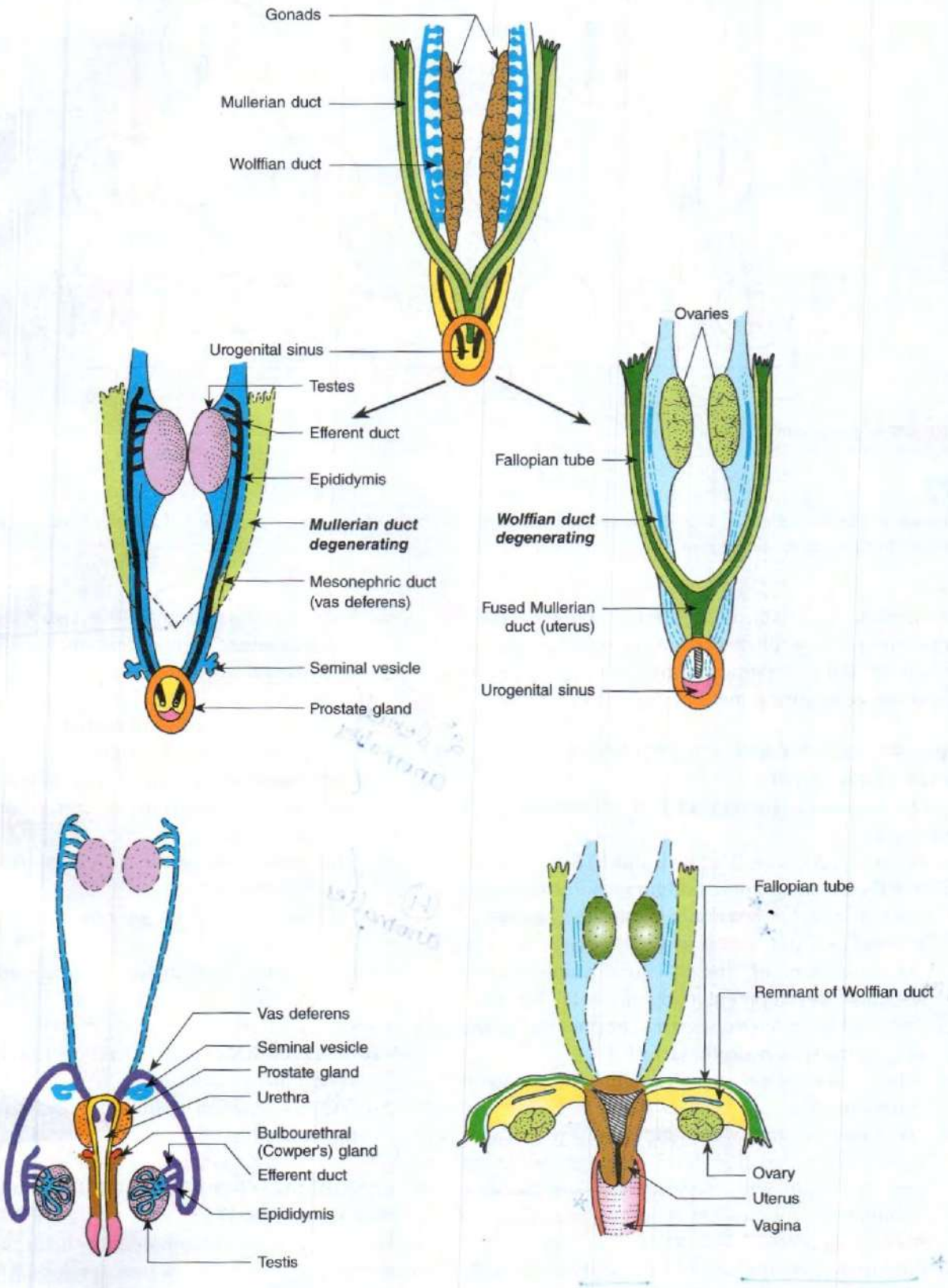


Fig. 80.4 Development of male and female internal reproductive systems from primordial genital ducts

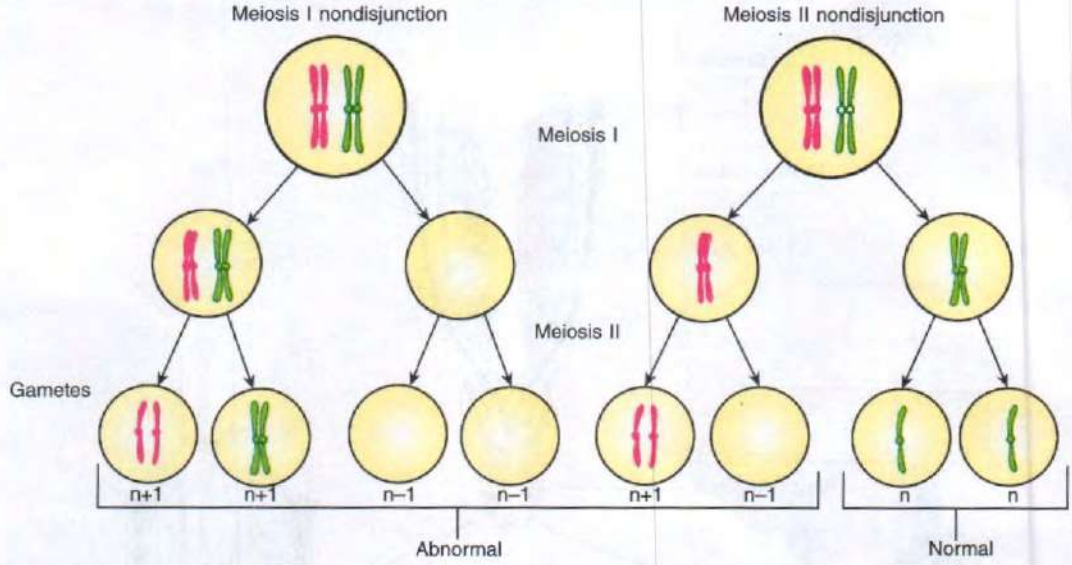


Fig. 80.5 Non-disjunction

Note

Meiosis is a two stage process, although non-disjunction occurs during first meiotic division but it can also occur in the second resulting in chromosomal abnormalities.

differentiation. An established defect in gametogenesis is ***non-disjunction***, a phenomenon in which a pair of chromosomes fail to separate, so that both go to one of the daughter cells during meiosis (**Fig. 80.5**).

A. ABNORMALITIES ASSOCIATED WITH MALE PHENOTYPE

1. ***Sex chromosome karyotype 47 XXY: Klinefelter's Syndrome***

Characteristic features (**Fig. 80.6** and **80.8**)

(i) It is the **most common** sex chromosome disorder; the individual is *genetically female with genitalia of a normal male* (the *sex-chromatin test is positive**). The presence of the Y-chromosome causes testicular development early in foetal life with sufficient testosterone secretion at puberty for the development of male characteristics.

(ii) Adult patients are usually tall with bilateral gynaecomastia.

(iii) The presence of *feminine stigmata* (physical and mental characteristics those of a female) in an apparent male with very small testes because seminiferous tubules are abnormal (*seminiferous tubule dysgenesis*).

(iv) Primary hypogonadism and infertility in the male which may be associated with mental retardation; because presence of more than two X-chromosomes leads to severe mental deficiency.

(v) *Sexual immaturity*
- (a) secondary sexual characters develop at puberty, pubic and body hair are sparse
- (b) penis tends to be small
- (c) testes are very small (pea size) and firm
- (d) patients are invariably sterile and impotent

(vi) *Associated features*
- (a) plasma testosterone levels are reduced or may be normal
- (b) serum LH levels are raised but S.FSH level is normal
- (c) Leydig cells in testes appear histologically normal

2. *Sex Chromosome Karyotypes*

(i) XXXY or XXXXY patterns are characterised by severe mental deficiency.

(ii) 'YO' combination is lethal and leads to intrauterine foetal death.

B. ABNORMALITIES ASSOCIATED WITH FEMALE PHENOTYPE

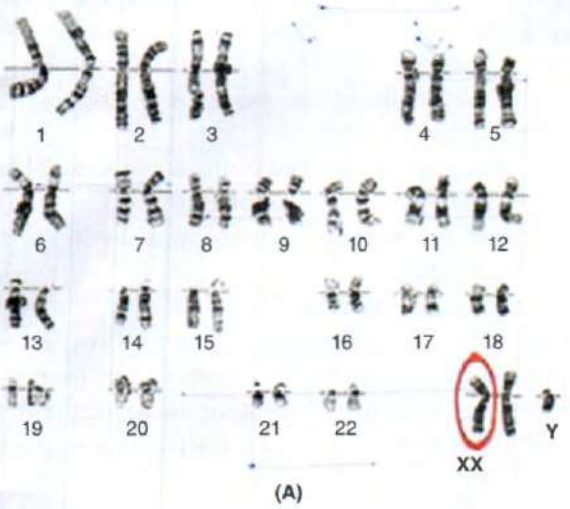
In the absence of the Y-chromosome testicular development does not occur and the sex organs develop on female lines.

1. *Ovarian (Gonadal) Dysgenesis: Turner's Syndrome*

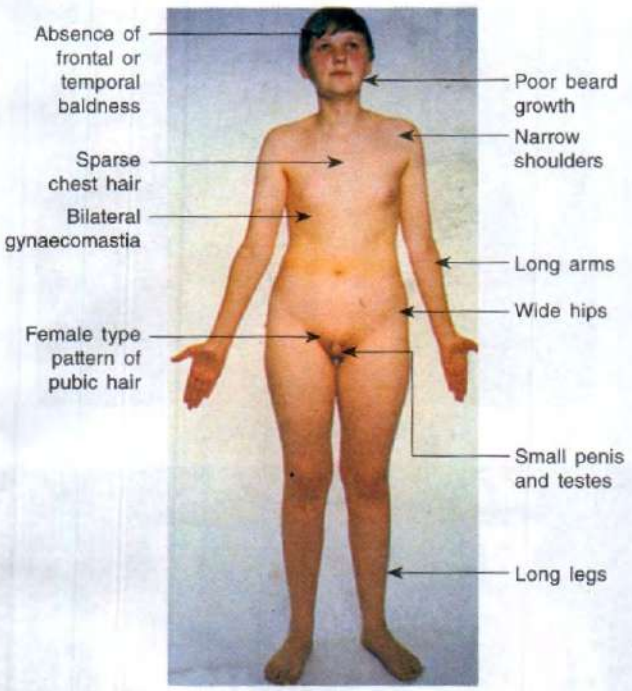
Characteristic features (**Fig. 80.7** and **80.8**)

(i) It is associated with absence of gonads and sex chromatin test is *negative*; karyotype pattern is

* **Note**: Two 'XX' chromosomes are required for a positive sex chromatin test.



(A)



(B)

Fig. 80.6 Klinefelter's Syndrome (*seminiferous tubule dysgenesis*)
(A) Karyotype - XXY; (B) Characteristic feature

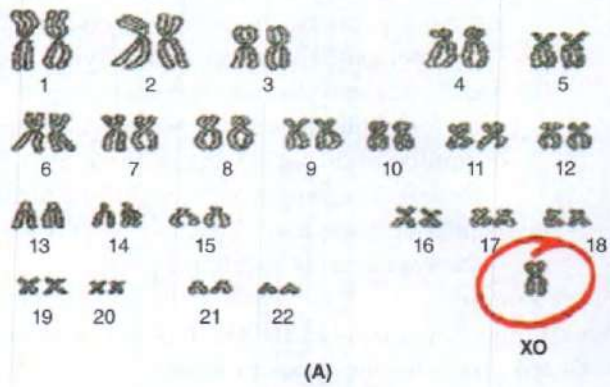
'XO' *i.e.* only one sex chromosome is present with 44 autosomes (45 chromosomes in all).

(ii) *Delayed puberty:* Diminished sexual development of female type, dwarfism and webbing of the neck.

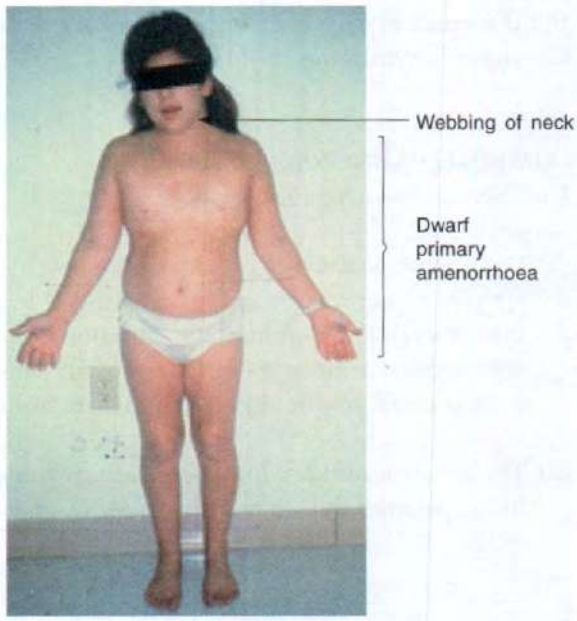
(iii) Commonest presenting complaint is *primary amenorrhoea* (non-appearance of the menses), therefore the condition is not recognized before puberty.

2. ***Testicular Feminization Syndrome or Complete Androgen Resistance Syndrome*** (TFS)

Sex chromosome karyotype XY.



(A)



(B)

Fig. 80.7 Turner's Syndrome (*ovarian/gonadal dysgenesis*)
(A) Karyotype - XO; (B) Characteristic features

Characteristic features

(i) The affected individuals are genetically males; sex chromatin test is negative with XY-karyotype.

(ii) The gonads are testes with immature seminiferous tubules and may be located in the abdomen or in the labia.

(iii) There is no spermotogenesis but leydig cells are abundant and secrete testosterone and oestrogen.

(iv) The abnormality lies in complete unresponsiveness of the male target organs to testosterone called *Androgen resistance* - page 775), as a result:

(a) The breast, nervous system, hypothalamus and external genitalia retain their responsiveness to oestrogen and individuals develop into normal females (physically as well as psychologically). However, after the normal age of puberty:

– breast development is normal

- pubic and axillary hair growth is scanty
- there is primary amenorrhoea, and
- external genitalia are of female type.

(b) Secretion of testicular non-steroidal hormone in early foetal life causes failure of development of mullerian duct derivatives, therefore,
- there is no uterus which results in primary amenorrhoea, and
- the vagina ends as a blind pouch.

3. ***Super Female***

Sex chromosome karyotype 'XXX'; it is not associated with any characteristic abnormalities **(Fig. 80.8)**. This pattern is **commonly found in the general population** and is second in frequency only to the XXY pattern of Klinefelter's syndrome.

C. COMBINED ABNORMALITIES

1. ***True Hermaphroditism (very rare)***

Features

(i) *Condition in which both ovarian and testicular tissues are present* (an ovary on one side and a testis on the other). Thus numerous variations in male and female differentiation can occur affecting both external and internal genital structures **(Fig. 80.9)**.

(ii) The *sex chromatin test* may be positive or negative (most patients show a mixture of 46 XX and 46 XY cells).

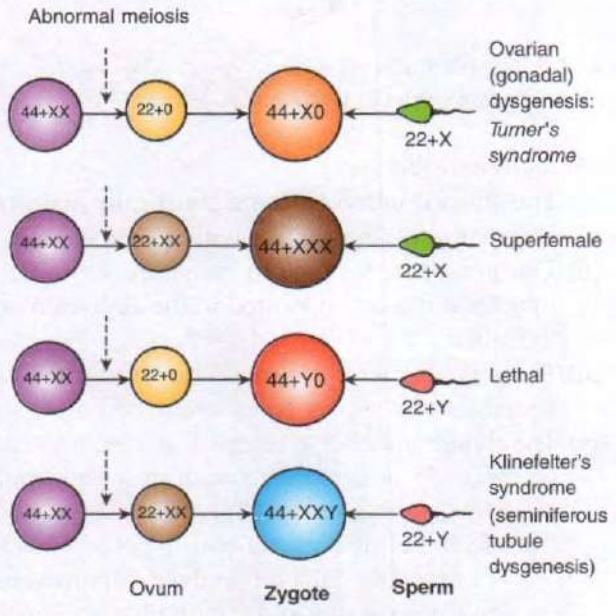


Fig. 80.8 Defects produced by maternal nondisjunction or simple loss of sex chromosome at the time of meiosis or during early mitotic division after fertilization

(iii) The external genitalia are variable and predominantly male and female forms are seen.

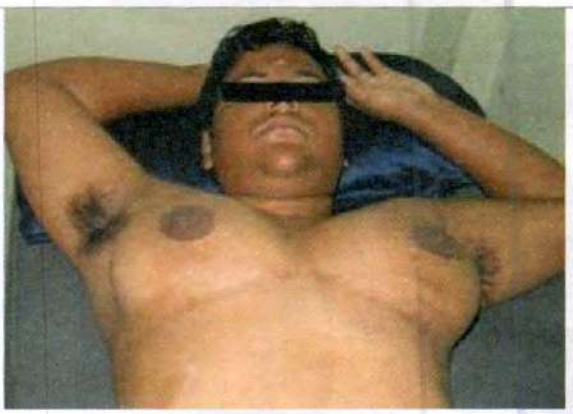
(iv) *Hypospadias* (*i.e.* external urethral opening is on the underside of the penis or in the vagina) is invariably present.

(v) Gonads may be located in the labiosacral folds, the inguinal canal or the abdomen.

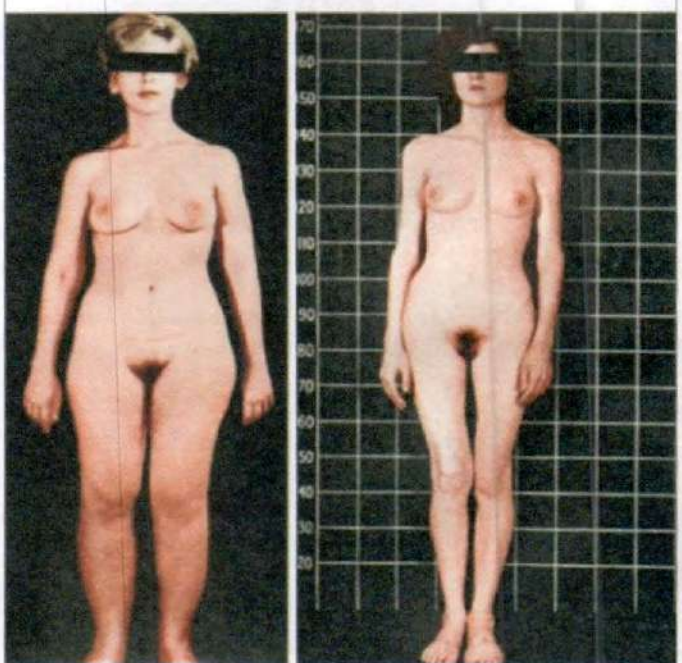
(vi) Breast development is present in about 60-70% of the patients

2. ***Pseudohermaphroditism***

Male and female pseudohermaphrodites are persons in whom normal gonadal development has occurred in accordance with their chromosomal sex but with later development of heterosexual (different sex genitalia)



(A)



(B)

Fig. 80.9 (A) True Hermaphroditism (a rare condition); (B) pseudohermaphrodite

characteristics. *Commonest types are*:

(i) *Female pseudohermaphrodite i.e.* an individual with feminine internal genitalia (ovaries, oviducts etc.) and masculine external genitalia (penis, testes etc.). The chromosomal sex is female. The syndrome is due to ***congenital virilizing adrenal hyperplasia*** (page 728).

(ii) *Male pseudohermaphrodite.* A male chromosomal sex individual (genetic male) with defective testes and has female internal and/or external genitalia.

Causes

(a) Embryonic testes are defective producing deficiency of MRF (page 770).

(b) ***Androgen resistance,*** in which male hormones cannot exert their full effects on the tissues either due to mutation in the *androgen receptor gene* or loss of receptor function. This result in ***Androgen resistance syndrome*** (page 773).

(c) Deficiency of adrenal androgens secondary to congenital deficiency of 17 α-hydroxylase.

(d) Congenital deficiency of 5α-reductase that converts testosterone to DHT in the target organs (page 790)

Testosterone → DHT

PUBERTY

INTRODUCTION

1. After birth, the gonads of both sexes remain silent until they are activated by gonadotrophins (FSH and LH) from the pituitary to bring about the final maturation of the reproductive system. This period of growth and maturation is known as ***puberty or adolescence***. Therefore, *it is the period when the endocrine and gametogenic functions of the gonads have first developed to the point where reproduction is possible.*
2. During childhood, before puberty:
   (i) Small amounts of gonadotrophins (FSH and LH) are secreted by anterior pituitary, and
   (ii) Hormonal secretion from gonads is too small to cause full development of reproductive organs but it keeps the secretion of hypothalamic gonadotrophin releasing hormone (GnRH) at a low level.
3. The age at the *time of puberty* is variable; puberty generally occurs between the ages of 8 and 13 years in girls, and 9 and 14 years in boys.

CONTROL OF THE ONSET OF PUBERTY

Different hypotheses:

1. Before puberty, the hypothalamus is more sensitive to the *inhibitory effects of gonadal steroids* and keeps the release of hypothalamic GnRH under check. (*Proof:* The hypothalamic extracts from immature animals do contain GnRH and following gonadal removal large amounts of gonadotrophins are secreted in immature as well as mature animals.) At puberty, the sensitivity of the hypothalamus to this negative feedback effect of gonadal steroids decreases (why? – not known), which increases GnRH release from the hypothalamus. This increases gonadotrophin (FSH and LH) secretion from the anterior pituitary to increase gonadal steroid secretion, which together with adrenal androgens produce the changes of puberty.
2. The release of hypothalamic GnRH is also inhibited by pineal gland hormone, ***melatonin***; therefore, the pineal gland also participates in regulating the onset of puberty (page 759).

Note

Adrenergic pathway may be involved in GnRH secretion.

3. At the time of puberty there is an increase in secretion of *adrenal androgens* without any change in the secretion of cortisol or ACTH. The onset of this increase is called *Adrenarche*, which may be due to:
   (i) a change in the enzyme systems in the adrenal so that more pregnenolone is diverted to the androgen pathway; and
   (ii) increased secretion of ***adrenal androgen stimulating hormone*** *(AASH)* from the pituitary gland.
4. *Role of Leptin* – Refer page 1007.

Important Note

Precocious puberty (see below) resulting from lesions of the hypothalamus shows that the critical factor involved in regulating the onset of puberty appears to be the release of GnRH by the hypothalamus.

↑↑ GnRH = mark for onset of puberty

Stages of puberty: changes during puberty

Time of development of the different physical manifestations of puberty in boys and girls are summarized in **Table 80.1** and **Fig. 80.10**.

APPLIED ASPECT

A. DELAYED or ABSENT PUBERTY

The age at which puberty sets in is variable, therefore, puberty cannot be considered to be pathologically delayed until the *menarche i.e.* first menstrual period has failed to occur by the age of 17 years (usual age 13-15 years) or testicular development by the age of 20 years (usual age 14-16 years).

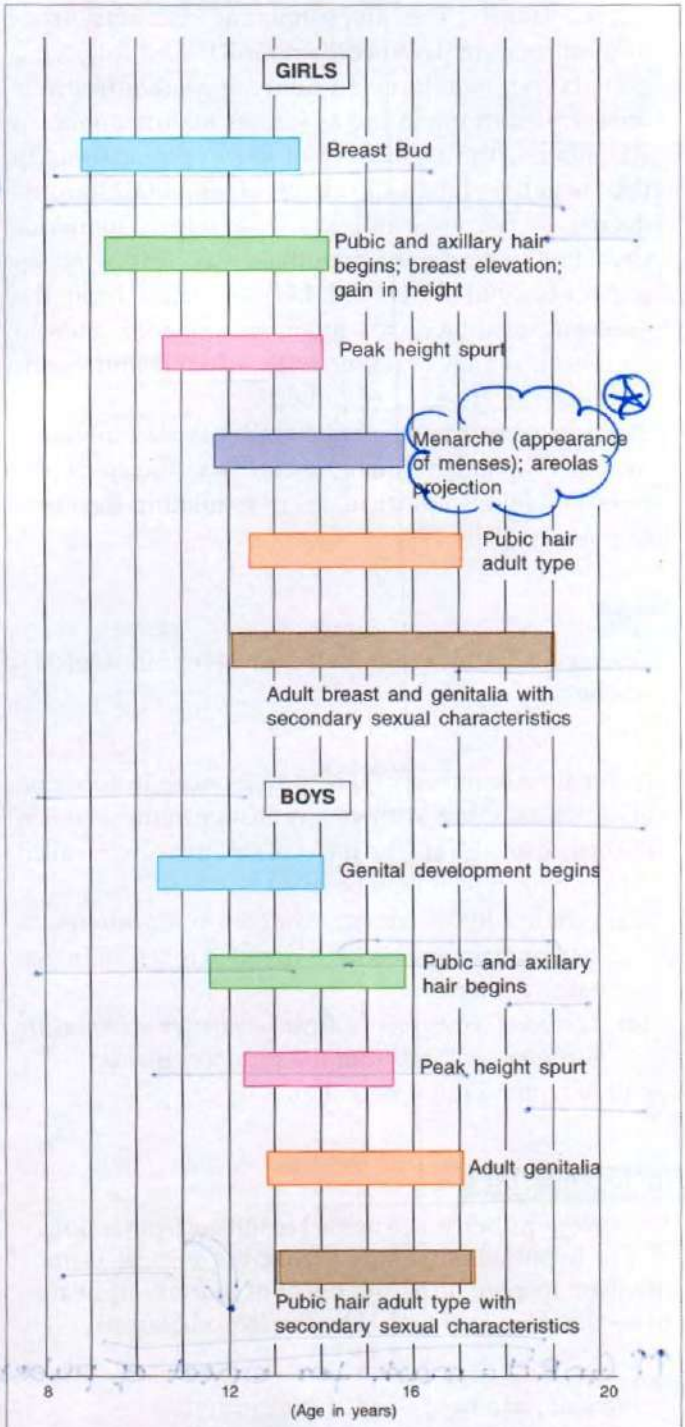


Fig. 80.10 Physical manifestations of puberty in girls and boys

Major causes

1. Constitutional
2. Gonadotrophin failure (hypothalamic or pituitary diseases)
3. Primary testicular disease

Characteristic features (Fig. 80.11)

1. Lack of pubertal development
2. Shortness of stature
3. Other associated features of endocrinal abnormalities
4. Low or normal gonadotrophin levels

Important Note

In some individuals puberty is delayed even though the gonads are present and other endocrine functions are normal. This clinical picture in males is called *Eunuchoidism* (page 791) and in females *Primary Amenorrhoea.*

B. *PRECOCIOUS PUBERTY*

Early development of secondary sexual characteristics is called precocious puberty. It is generally defined as the onset of secondary sexual characteristics before the age of 8 years. It is of two types: *true* and *pseudo* precocious puberty. The differences between the two types are given in Table 80.2.

REPRODUCTIVE HORMONES

The reproductive systems of both female and male are wholly dependent on hormones for their differentiation and full development. Among these are: polypeptide, glycoproteins and steroid hormones. Their characteristic features are given in Table 80.3.

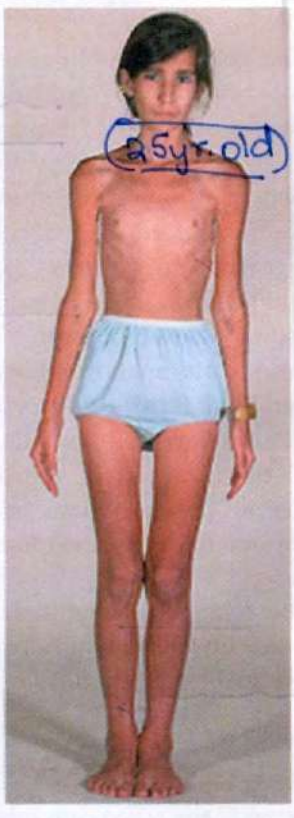


Fig. 80.11 Delayed or Absent puberty (puberty failure in a 16-year old girl due to gonadotrophin failure)

Table 80.1: Changes during puberty in boys and girls

Stage of puberty (bone age)	In Boys	In Girls
1. *Stage 1* (upto 7.5 years)	Preadolescent stage or stage of childhood.	Preadolescent stage.
2. *Stage 2* (12 years boys and 10.5 years girls)	Genital development begins by enlargement of the testes.	Appearance of 'breast bud' (***thelarche***) **Note:** Regular ovulation (page 802) usually appears about a year later.
3. *Stage 3* (14 years boys and 11.5 years girls)	Pubic and axillary hair begin, penis enlarges.	Pubic and axillary hair begin, (***pubarche***) elevation and enlargement of the breasts, gain in height (***height spurt***).
4. *Stage 4* (15.5 years boys and 13 years girls)	Further growth of external and internal genitalia occurs with peak gain in height (*height spurt*).	Projection of areolas, appearance of the menses (***menarche***).
5. *Stage 5* (16.5 years boys and 14 years girls)	Adult genitalia with secondary sexual characteristics which include:	Adult genitalia with secondary sexual characteristics which include:
(i) Body configuration	Broad shoulders, more muscular body.	Narrow shoulders, broad hips, thighs that converge and arms that diverge (*wide carrying angle*), female distribution of fat in the breast and hips giving the characteristic curves to the body.
(ii) Hair growth	Hair appears all over body in axilla, over the pubis, face and chest; hairline on scalp recedes anterolaterally; male pattern of pubic hair (triangle with base down).	Appearance of hair in the axilla and pubis; less body hair and more scalp hair; hair in pubic region concave upwards (female *flat-topped* pattern) of distribution of hair caused by local conversion of weak androgens from the ovary and adrenal cortex to testosterone).
(iii) Voice	Larynx enlarges, vocal cords increase in length and thickness, therefore, voice becomes deep and breaks.	Larynx does not enlarge to that extent as in males, therefore, voice becomes high pitch.
(iv) External genitalia	Penis increases in length and width, scrotal skin thickens, becomes pigmented and rugose.	Clitoris increases in length and width, labia majora and minora enlarge.
(v) Internal genitalia	Seminal vesicles, prostate and bulbourethral glands enlarge and secrete.	Ovaries, uterus and vaginal growth increases and their activity increases.
(vi) Skin changes	Acne (pimples) appears due to increased secretion from sebaceous glands by the action of androgens.	Acne and formation of comedones (*black heads*) is less as oestrogen antagonizes the action of androgen on sebaceous glands.
(vii) Psychological changes	Aggressive, active attitude, interest in opposite sex develops.	Changes in mental and emotional behaviour; shyness; interest in opposite sex develops.

PITUITARY GONADOTROPHINS: FSH AND LH

The gonadotrophic cells/gonadotrophs (page 661) in the anterior pituitary secrete gonadotrophins, FSH and LH. They are glycoproteins, each made up of an α and a β subunit with MW of about 30,000. The ***receptors*** for FSH and LH are coupled to adenylyl cyclase through G_S. Sialic acid is an important component of both FSH and LH. The *half life* of FSH is approximately three hours and that of LH is one hour.

Actions

A. Actions of FSH

(1) It helps to maintain the spermatogenic epithelium by stimulating Sertoli cells in the males (page 784).

(2) It is responsible for the early growth of ovarian follicles in the females (page 801).

B. Actions of LH

(1) *In males*: It is trophic to the leydig cells and causes increased secretion of testosterone (page 789); and

(2) *In females*

(a) it is responsible for final maturation of the ovarian follicles and oestrogen secretion from them;

(b) it is also responsible for *ovulation*; the initial formation of the corpus luteum and secretion of progesterone (page 802).

Table 80.2: Differences between two types of precocious puberty

True Precocious Puberty	Pseudo Precocious Puberty
1. *Definition:* Early development of secondary sexual characters *with* gametogenesis. It is due to an early but otherwise normal pubertal pattern of gonadotrophin secretion from the pituitary (Fig. 80.12).	1. *Definition:* Early development of secondary sexual characters *without* gametogenesis (no spermatogenesis or ovarian development). It is due to abnormal exposure of immature males to androgen or females to oestrogens.
2. *Causes*	2. *Causes*
(a) Constitutional – more common in females.	(a) Adrenal (i) congenital virilizing adrenal hyperplasia (page 728); (ii) androgen secreting tumours (in males); (iii) oestrogen secreting tumours (in females).
(b) Interruption of neural pathways that produce inhibition of GnRH due to: (i) cerebral disorders (infection, tumours, developmental abnormalities) involving posterior (ventral) hypothalamus near the infundibulum; (ii) pineal tumours which damage the hypothalamus;	(b) Gondal (i) Interstitial cell tumours of testis. (ii) Granulosa cell tumours of ovary.

Factors influencing gonadotrophin secretion

CNS is most intimately involved in the control of gonadotrophin secretion. The factors influencing gonadotrophin secretion which act through CNS are divided into hypothalamic and extrahypothalamic factors.

A. Hypothalamic factors

The hypothalamus, through its GnRH, is the final common nervous pathway through which various nervous and psychological factors influence the secretions of the pituitary gonadotrophins, FSH and LH. Examples of particular interest include:

1. *Stress.* Emotional disturbances and physical stress are known to cause irregularities in menstrual cycle and impair fertility.
   Evidence: Amenorrhoea (stoppage of menses) was general among women imprisoned in concentration camps.
2. *Lactation.* During lactation, cyclic ovarian function ceases in women resulting in amenorrhoea (***lactation amenorrhoea***). This is probably due to an effect on the hypothalamus of the afferent impulses originating from the nipple when the infant suckles.
3. *Altered lighting.* The cyclic pattern of gonadotrophin discharge is abolished and the normal menstrual cycle ceases by constant light stimulus for prolonged periods. It acts by inhibiting activity of the pineal glands (page 759).
   Evidence: The menstrual rhythm is frequently disturbed in nurses on night duty or air-hostesses travelling in intercontinental flights.
4. *Seasonal factors.* A variety of environmental factors may play a part but alteration in the relative length of daylight and darkness are of particular importance.
   Evidence: Many animals such as the cat and ferret (pole cat) breed only at certain times of the year.
5. *Mating.* Certain species ovulate only after coitus or other forms of sexual stimulation, called *reflex ovulators*.
   Examples: the rabbit, ferret and cat. Afferent impulses from the genitalia are responsible for initiating the discharge of LH which promotes ovulation in these animals.

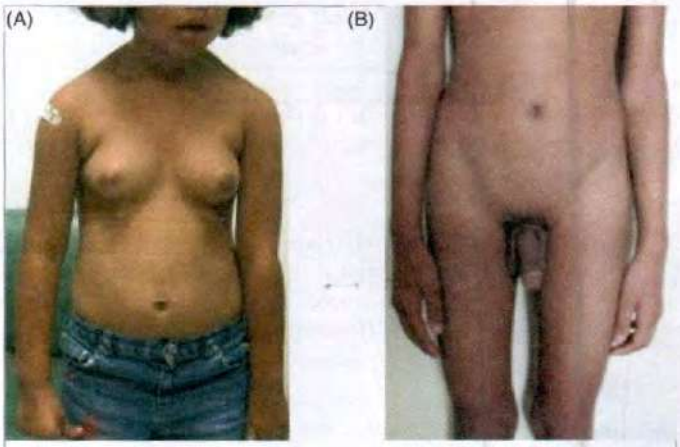


Fig. 80.12 True precocious puberty (**A**) In a 4-year old girl and (**B**) in a 3-year old boy

Note

Ovulation may occur in the pigeon simply in response to the sight of its own reflection in a mirror.

B. Extrahypothalamic factors

1. *Amygdala,* it also participates in the control of gonadotrophin secretion.
   Proof: The onset of puberty has been shown to be delayed by stimulation, and advanced by lesions, of the amygdala (page 1025).

Table 80.3: Reproductive hormones and their main functions

Reproductive Hormones	Main function
I. Polypeptide hormones	
1. Hypothalamic gonadotrophin releasing hormone (GnRH)	It acts on the anterior pituitary cells which synthesize and release FSH and LH.
2. Prolactin	It helps to promote breast development in pregnancy and lactation (page 671).
3. Oxytocin	It causes uterine contraction during labour and also promotes milk ejection during breast feeding (page 674).
II. Glycoprotein hormones	
1. Pituitary gonadotrophins	
(i) Follicle stimulating hormone (FSH)	Stimulates ovarian follicle growth in female and spermatogenesis in male.
(ii) Luteinizing hormone (LH) or interstitial cell stimulating hormone (ICSH).	Stimulates ovulation and luteinization of ovarian follicles in female and testosterone secretion in male.
2. Placental chorionic gonadotrophins	It helps to maintain corpus luteum and as a result ovulation and menstruation are prevented during pregnancy (page 820).
III. Steroid hormones	
1. Oestrogen	It is responsible for the maintenance of oogenesis, development of sex organs and secondary sexual characters in females at puberty (page 799).
2. Progesterone	It prepares the endometrium for implantation of the fertilized ovum and promotes the growth and development of the breasts (page 800).
3. Testosterone	It is responsible for the maintenance of spermatogenesis, development of sex organs and secondary sexual characters in males at puberty (page 789).
4. Adrenal androgens (DHEA)	At puberty in both sexes it contributes to increase in muscle mass, sexual hair and seborrhoea (page 728).

2. *Hippocampus*, it may inhibit spontaneous ovulation or ovulation induced by stimulation of the amygdala or preoptic region. This response is abolished by cutting the pathway from the hippocampus to the hypothalamus, suggesting that the hippocampus is also involved in the regulation of gonadotrophin secretion.

Control of Gonadotrophin Secretion

The release of gonadotrophins (FSH and LH) by the anterior lobe of the pituitary gland is regulated by a *gonadotrophin releasing hormone (GnRH)* derived from the preoptic region in the hypothalamus.

Note

There is a single hypothalamic GnRH which regulates the release of both FSH and LH from the anterior pituitary rather than the existence of two separate hypothalamic releasing hormones (RH) viz. LH-releasing hormone (LH-RH) and FSH-releasing hormone (FSH-RH).

GnRH is normally secreted in ***episodic bursts*** and fluctuations in the *frequency* and *amplitude* of the GnRH bursts are important in generating the other hormonal changes (viz LH and FSH) that are responsible for hormonal control of female sexual cycle (page 801). *Frequency* is increased by ostrogens and decreased by progesterone and testosterone. In general, epinephrine and nor-epinephrine in the hypothalamus increase GnRH pulse frequencies.

Mechanism of action of GnRH: GnRH accounts for the release of pituitary gonadotrophins (FSH and LH) by two mechanisms:

1. GnRH by increasing the membrane permeability of the cells (producing the gonadotrophin in the anterior pituitary) to Ca^{2+}, activates the release process.
2. GnRH combines with specific receptor site on the cell membrane and activates adenylyl cyclase leading to the generation of cAMP from ATP. The cAMP in turn activates release of the gonadotrophins.

3. *Supporting structures* are divided into:
   (i) Internal: a pair of spermatic cords; and
   (ii) External: scrotum and penis.

A. THE TESTIS

Structure

1. There are two testes, one being larger than the other; in adult each weighs 10-40 gms (average 25 gm), weight decreases in old age. It has rich sympathetic innervation.
2. ***Blood supply.*** It is highly vascular and capillaries of the testes are **not** fenestrated. The spermatic arteries to the testes are tortuous and blood in them runs parallel but in the opposite direction to blood in the pampiniform plexus of spermatic veins. This anatomic arrangement may permit ***countercurrent exchange*** (page 545) of heat and testosterone.
3. A white fibrous capsule, *Tunica Albuginea*, envelops each testis and sends partitions through its interior dividing it into ***Lobules***. **(Fig. 81.2A)**
   (i) Each lobule consists of three or four coiled *Seminiferous Tubules* (70-80 cm long) which open into the *Rete Testis*; from the rete testis arise *Ductuli Efferentes*, which drain into the *Epididymis*. The Epididymis is attached to the back of the testis and consists of a coiled tube, approximately 7 metres long which continues into the *Vas (Ductus) Deferens*. Seminiferous tubules and vas deferens contain smooth muscles.
   (ii) In addition, lobule also contains *collagen fibers* and *Leydig (interstitial) cells.*
4. *Leydig/interstitial cells:*
   (i) These are *endocrinal cells* which develop from the mesoderm of the embryo and are usually arranged round the blood vessels **(Fig. 81.2B)**. They are abundant in the 4th month of foetal life, fewer in the newborn and continue to diminish by the end of childhood; their number again increases at puberty. They remain constant in number during sexual life and finally diminish in old age.
   (ii) They *secrete androgenic hormone – testosterone* at about the time of puberty.
      (a) It helps in growth of the ***accessory organs of reproduction*** (epididymis, seminal vesicles, prostate, penis) and is responsible for the appearance of the secondary male sex characters (page 777).
      (b) Testosterone secretion is depressed by undernutrition, specially by vitamin, B deficiency.
5. The seminiferous epithelium contains *Sertoli Cells* whose features are **(Fig. 81.2B)**:
   (i) These are large columnar cells which extend from the basement membrane to the centre of the lumen of the seminiferous tubules.
   (ii) The cells are rich in glycogen which nourish the germ cells, the sperms.
   (iii) They secrete *androgen binding protein-ABP* (page 786), *inhibin B* (page 791) and *MRF* (page 770).
   (iv) They also secrete an enzyme ***aromatase (CYP 19)*** that converts androgens to oestrogen (page 790).
   (v) They provide *blood testis barrier* (see below) to chemicals and phagocytose defective sperms.
   (vi) They cause controlled release of mature sperms into the lumen of seminiferous tubules (***spermiation***).

Important Notes

1. Because of relatively tight connections between the Sertoli cells and other cells lining the seminiferous tubular wall (*Blood Testis Barrier*), proteins and other substances penetrate poorly into the area near the wall of the tubule. However, testosterone and other steroids penetrate this barrier with ease due to the fact that the Leydig cells are close to the tubules.
2. Blood testis barrier helps maintaining the composition of the fluid* in the lumen of the seminiferous tubules and also protects the germ cells from blood-borne noxious agents. It also prevents antigenic products of germ cell division from entering the circulation and generating an autoimmune response.
   *It contains high concentration of androgens, oestrogens, K^+, inositol, glutamic and aspartic acid with low content of protein and glucose.

Functions of Testis

1. Production and storage of viable sperms.
2. Synthesis and secretion of the androgenic hormone, testosterone.
   Both these functions are under anterior pituitary and hypothalamic control.

SPERMATOGENESIS

It is the process by which spermatozoa (sperms) are formed.

Characteristic features

1. It begins at puberty and continues throughout adult life to decline in the old age.
2. *Steps:* (Refer **Table 81.1** and **Fig. 81.2C**) Spermatozoa (sperms) contain 22 autosomes and 1 sex chromosome either X or Y which determines the genetic sex of the embryo.
3. Spermatogenesis takes on an average 64 days to form a mature sperm from a primitive germ cell.

Mature sperms are released from the Sertoli cells (*spermiation*) and become free in the lumen of the seminiferous tubules. The mature sperm in the seminiferous tubules are *non-motile* and rich in DNA.

Important Note

How non-motile sperms in seminiferous tubules reach the epididymis? Ciliary activity together with smooth muscle contraction of the seminiferous tubules, rete testes and ductus efferentes propels the sperms into the epididymis.

4. *Spermiogenesis* means conversion of spermatids to sperms (spermatozoa). This process takes place within the cytoplasm of the Sertoli cells and depends on the presence of androgen.
5. Spermatogenesis does not occur simultaneously in all parts of the testis; at any given moment some areas of seminiferous epithelium are active while others are at rest.
6. *Control:* FSH and androgen maintain the gametogenic function of the testis.
   (i) Anterior pituitary secretes *LH*, called *ICSH (interstitial cell stimulating hormone)* in the male, which stimulates Leydig cells to cause testosterone secretion. This via local lymphatics reaches the seminiferous tubules and stimulates spermatogenesis.

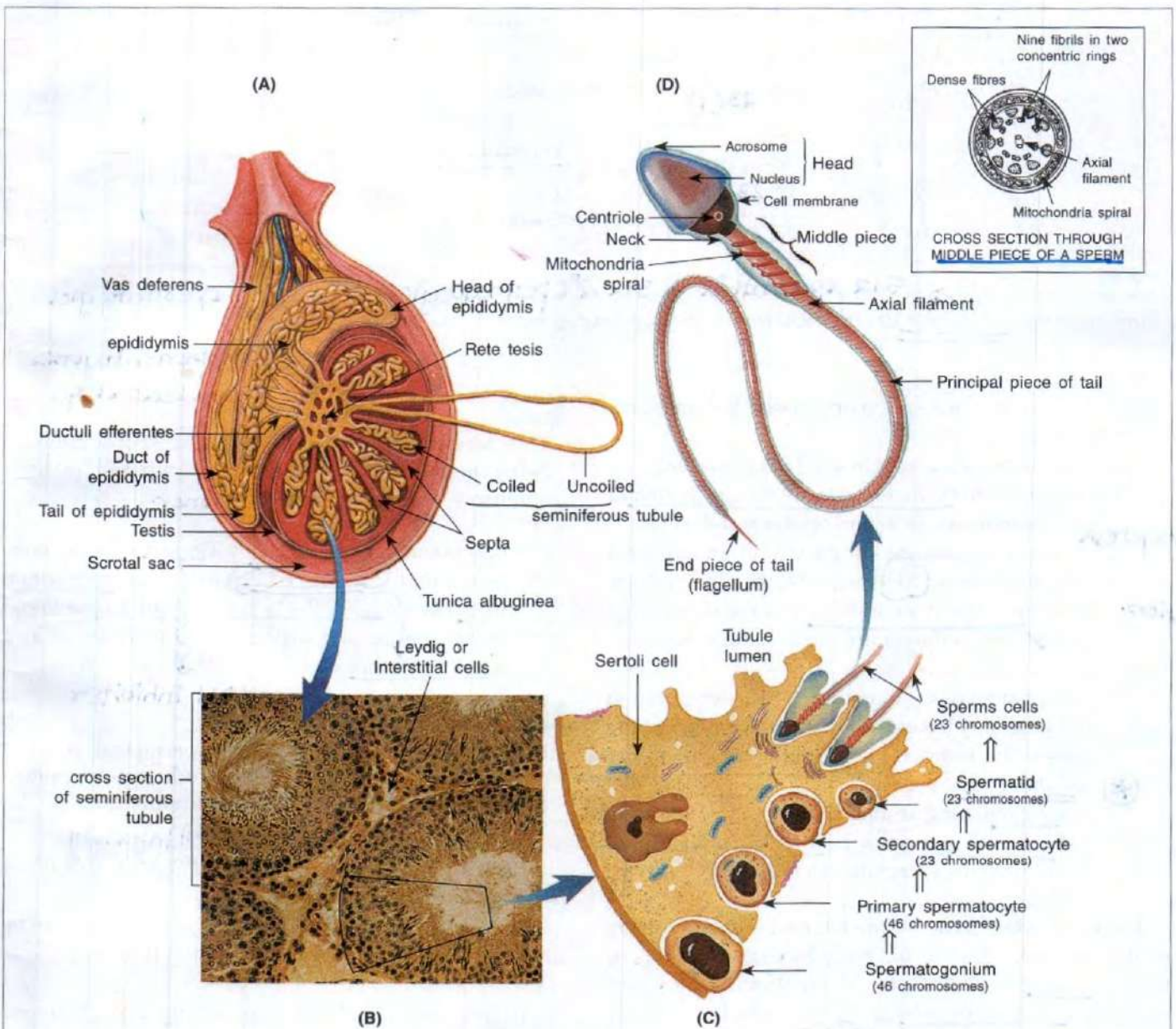
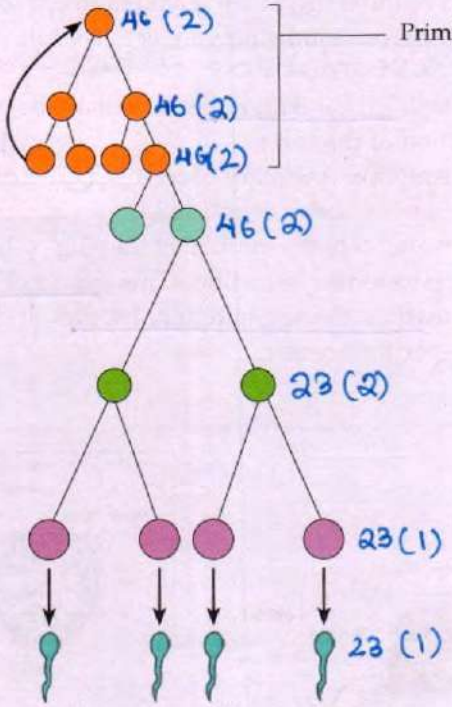


Fig. 81.2 (A) Parts of testis and epididymis; (B) Histology of testis; (C) Steps in spermatogenesis; and (D) Structure of a mature sperm

Table 81.1: Steps during spermatogenesis



	Choromosomes per cell	Chromatids per chromosome
Primitive germ cells or spermatogonia (lies along the sertoli cells)	46	2
↓ Mitosis division		
Primary Spermatocytes	46	2
↓ 1st meiotic division		
Secondary Spermatocytes	23	2
↓ 2nd meiotic division		
Spermatids	23	1
↓ Differentiation		
Sperms *or* Spermatozoa	23	1

Note

Approximately 512 spermatids are formed from a single spermatogonia.

512 spermatids → 512 2° spermatocytes → 256 1° spermatocytes → 128 Spermatogonia in the last stage

(ii) *Role of FSH* in spermatogenesis is uncertain. However,
(a) less androgen is required if FSH is present;
(b) it appears to facilitate the last stages of spermatid maturation via an action on the Sertoli cells;
(c) it also promotes the production of an ***androgen binding protein-ABP*** (page 784) thereby stabilizes the high supply of androgen to the developing germ cells in the seminiferous tubular lumen.

(iii) *Clinical significance:*
(a) Spermatogenesis requires a temperature considerably lower than that of the interior of the body. The testes are kept cool at a temperature of about 32°C by:
- air circulating around the scrotum, and
- heat exchange in a counter current fashion between the spermatic arteries and veins (page 784.

Therefore, when the testes are retained in the abdomen, or they are held close to the body by tight clothings or taking hot baths (43-45°C) for 30 minutes daily, or men working in hot surroundings (furnace workers, engine drivers, etc.), it may result in sterility.

Note

This may be the reason behind the sperm counts being higher in the winters as compared to the summers. Winter > Summer.

(b) Spermatids are attacked by ***Gossypol***, a phenolic compound (cotton seed oil) extracted from cotton plants that inhibits the lactate dehydrogenase found in the sperms and may prove to be of value as a male contraceptive.

LDH Inhibitor

Important Note

It is effective in producing azoospermia or severe oligospermia, but it is known to produce permanent azoospermia if taken for more than 6 months.

Persistency → permanent infertility

THE MATURE HUMAN SPERM or SPERMATOZOON
(sperms/spermatozoa – pleural)

The mature human sperm is 55-65 µm long and can be divided into *two parts*, a head and a tail (Fig. 81.2 D).

Head

(i) 4-5 µm length; 3 µm width and flattened anteriorly;

(ii) it consists of a nucleus capped by an *acrosome*.
   (a) Nucleus consists of densely staining chromatin material (DNA plus basic histones)
   (b) Acrosome contains mucopolysaccharides and acid phosphatase (involved in sperm penetration of the ovum and in fertilization; page 812).

Tail – it comprises:
(i) the neck,
(ii) the middle piece,
(iii) principal piece,
(iv) end piece.

The *axial filament* originates from the centrioles in the neck and consists of a central pair of fibril surrounded by two concentric rings of nine fibrils each.
(a) In the *middle piece*, the axial filament is surrounded by a spiral mitochondrial sheath which provides energy for motility of the sperm.
(b) The outer fibrils are the contractile components of the sperm.
(c) The *principal piece* of the tail contains a protein *CatSper* (a Ca^{2+} channel to permit Ca^{2+} influx), when gets activated causes movement of the sperm.

Important Note

It is not yet possible to separate the sperms bearing X and Y chromosomes in living semen by any methods available.

B. SEMINAL TRACT AND RELATED GLANDS

The seminal tract *consists of:*
1. The Epididymis.
2. The vas deferens.
3. Ejaculatory duct *i.e.* the terminal portion of vas deferens, which opens into the prostatic urethra.
4. The penile urethra which forms the common passage for urine and seminal fluid.

The *related glands* are:
1. Seminal vesicles, open into the ejaculatory duct,
2. Prostatic glands, open into the prostatic urethra,
3. Bulbo-urethral (Cowper's) glands, open into the penile urethra.

Epididymis

Features

1. Spermatozoa (sperms) in the seminiferous tubular lumen are moved along the tubules to the *Ductuli Efferentes* which lead to the epididymis.

Note

Oestrogen content of the fluid in the *rete testis* (page 784) is high. Here the fluid is reabsorbed and the sperms are concentrated. If the sperm directly enter the epididymis, they get diluted in the large volume of the fluid and infertility may occur.

2. The spermatozoa are then stored in the tail of epididymis, where they can remain viable for a month.
3. Its wall contains:
   (i) Smooth muscle, and
   (ii) Secretory columnar epithelium, its secretion *nourishes the spermatozoa* and helps them to mature. How? Epididymal secretions are:
      (a) rich in potassium and have a high K^+/Na^+ ratio;
      (b) high concentration of *glyceryl-phosphoryl-choline*, a potential source of energy;
      (c) contain testosterone which helps in the maturation of spermatozoa.
4. Here *non-motile spermatozoa become motile* when they are exposed to O_2.

Important Note

An enzyme which splits off choline and releases glycerophosphate is found in the endometrium, this could explain the enhanced sperm motility in utero.

Vas (Ductus) Deferens

The tail of the epididymis continues into the vas deferens.
1. It is a smooth muscular tube lined with a columnar epithelium, which transports spermatozoa into the dilated ampulla.
2. It serves as a *secondary storehouse for spermatozoa* which will be released at the time of ejaculation.
3. *Vasectomy*
   (i) A simple procedure for sterilization in males, in which vas deferens is ligated and sectioned.
   (ii) It may cause some degeneration of seminiferous tubules without affecting the testosterone secretion from the Leydig cells and secretions of other related glands *i.e.* seminal vesicles; prostate and Cowper's glands.

Important Note

For first two months after vasectomy viable spermatozoa may be released from the ampulla, therefore, during this period conventional methods should be used for contraception purposes (page 814).

Seminal Vesicles

1. These are two lobulated glands (about 7 cm in length), situated between the urinary bladder and rectum which secrete fluid into the ejaculatory duct.
2. Its secretion is thick and sticky (viscid) and rich in:
   (i) potassium,
   (ii) fructose, it is oxidised by the mitochondria of the middle piece of spermatozoa,
   (iii) phosphoryl choline,
   (iv) citric acid,
   (ii), (iii) (iv) *provide energy for movement of the spermatozoa.*
   (v) ascorbic acid, and
   (vi) hyaluronidase enzyme, splits mucopolysaccharides, therefore, sperms can penetrate through the cervical mucus plug.
3. It also synthesizes and secretes prostaglandins which increase formation of cAMP. This leads to the contraction of uterus during coitus and, therefore, sperms can be sucked into the uterus.
4. Its secretion *contributes to* 60% *of semen's total volume.*

Prostate

It is a fibro-musculoglandular structure with the following features:

1. It lies just below the urinary bladder and the urethra, passes through the small hole in the centre of the prostate.
2. It consists of many follicular spaces leading into ducts; between the follicles there is a good amount of muscular tissue.
3. The epithelium of the follicles secretes the prostatic fluid:
   (i) it is thin and opalescent and gives the semen its *characteristic odour*;
   (ii) slightly acidic in reaction, pH: 6.4;
   (iii) rich in calcium
   (iv) contains:
   - zinc, citric acid, cations (mainly Na^+),
   - serine protease or ***prostate specific antigen*** **(PSA)**
   - enzyme fibrinolysin (plasmin), and
   - acid phosphatase.
4. Its secretion *contributes to* 20% *of semen's total volume.*

Note

PSA hydrolyzes the sperm motility inhibitor *semenogelin* in semen. Elevated PSA levels occurs in: prostate cancer, prostatitis and benign hypertrophy of prostate (BHP).

Bulbo-urethral (Cowper's) Glands

(1) These are of pea size and shape, located below the prostate gland.
(2) They form a mucoid alkaline secretion which is discharged into the anterior (penile) urethra.
(3) **Functions**
   (i) Lubrication
   (ii) Its alkalinity helps to protect the sperms from the acid present in the male urethra and female vagina, thereby increases sperm motility.

C. SUPPORTING STRUCTURES

Internal

Spermatic cords – These are thick cord like structures located in the inguinal canal, one on each side. They consist of the vas deferens, lymphatics, blood vessels and nerves, enclosed in a white fibrous tissue.

External

1. *Scrotum* – It has two sacs, each containing a testis, epididymis and lower part of spermatic cord.
2. *Penis* – It has three bundles of cavernous (erectile) tissues: (**Fig. 83.1**, page 810)
   (i) two bundles of corpora cavernosa penis, and
   (ii) one smaller bundle which contains the urethra, called corpora cavernosa urethrae.

   Distal end of the penis has a slight bulge called *Glans Penis.*

Functions

(i) It contains urethra (terminal duct) which forms the common passage for both urine and semen.
(ii) It is the copulatory organ by means of which sperms are introduced into the female vagina.

SEMINAL FLUID (SEMEN)

It is the fluid that is ejaculated at the time of orgasm.

Characteristic features

1. It consists of the products of the seminiferous tubules (*i.e.* the sperms) and the secretions of the seminal tract and related glands (see above).

2. *Composition*

Colour	:	White, opalescent
Specific gravity	:	1028
pH	:	7.35 to 7.50
* Average volume	:	2.5 to 3.5 mL per ejaculate
Sperm Count	:	80-120 million/mL (average 100 million/mL); ***motile*** with more than 80% sperms having normal morphology.

Important Note

Volume of semen and sperm count decreases rapidly with repeated ejaculation. 50% of men with counts of 20-40 million/mL and essentially all of those with count less than 20 million/mL are sterile.

Other components:

From seminal vesicles (form 60% of semen's total volume:

- (i) Fructose (1.5-6.5 mg/mL)
- (ii) Phosphoryl-choline
- (iii) Ergothioneine
- (iv) Ascorbic acid
- (v) Flavins
- (vi) Prostaglandins.

From prostate (form 20% of semen's total volume)

- (vii) Spermine
- (viii) Citric Acid
- (ix) Cholesterol, phospholipids
- (x) Fibrinolysin, fibrinogenase
- (xi) Zinc
- (xii) Acid phosphatase
- (xiii) Phosphate
- (xiv) Bicarbonate } act as buffers
- (xv) Hyaluronidase.

3. *Reaction:* Alkaline fluid – *Importance:* Sperms get rapidly immobilized in an acid medium; acid prostatic fluid being neutralized by secretions of other related glands (page 819).
4. The fluid part of the semen is contributed chiefly by the prostate and seminal vesicles.
5. It is rich in fructose (fructose concentration exceeds that of glucose in blood): *significance* – spermatozoa have very little cytoplasm and use fructose as their metabolic fuel.
6. It is liquid when ejaculated but soon coagulates in vitro or in the vagina; however, after 15 minutes, it undergoes secondary liquefaction.

(i) Mechanism of coagulation of semen

Semen contains fibrinogen and thromboplastin, but no prothrombin or thrombin and rich in non-ionic calcium (excess citrate from the prostate removes the calcium from the ionic state). Semen coagulation involves the conversion of its fibrinogen into fibrin (exact mechanism is not known).

(ii) Mechanism of Liquefaction

The secondary liquefaction of the fibrin is due to the specific enzyme, fibrinolysin (plasmin), present in the prostatic fluid.

Note

2 mL of prostatic fluid at body temperature can liquify 100-1000 mL of clotted plasma in 18 hours.

7. Spermatozoa lose their fertilizing capacity before their mobility. The maximal duration of fertilizing capacity within the female reproductive tract (*e.g.* cervix) is 28-48 hours; whereas motility may persist for 48-60 hours.

ENDOCRINE FUNCTION OF THE TESTES

The testis secretes principal male sex hormone, the *Testosterone;* it also secretes *Oestrogen* in small amounts.

A. TESTOSTERONE

It is C_{19} steroid with an OH group in the 17 position (page 716).

(i) Biosynthesis

1. Testosterone is synthesized from cholesterol (page 716) in the Leydig cells of testis. Its secretion is under the LH control (page 790) which stimulates the Leydig cells via cAMP pathway coupled to G_s. cAMP,
   (i) It increases the formation of cholesterol from cholesterol esters, and
   (ii) increases conversion of cholesterol to pregnenolone via the activation of protein kinase A.
2. Testosterone is also formed by the adrenal cortex from zona reticularis layer (page 714).

Total (free and bound) plasma concentration

(i) In adult men: 300-1000 ng/dL = (1 µg/dL)
(this decreases with advancing age due to decreased secretion of FSH and LH, therefore, testes become smaller; spermatogenesis decreases and number of Leydig cells decreases)

(ii) In adult women: 30-70 ng/dL. (0.1 µg/dL)

Daily Secretion

- In adult males : 4-9 mg (average 7 mg)
  In adult females : 350 µgm (average)

(ii) Transport

1. 97-98% circulates in the blood bound to plasma proteins
   (i) 65% to sex hormone binding β-globulin called ***Gonadal steroid binding globulin*** **(GBG)** or *sex steroid binding globulin.*
   (ii) 35% to albumin; and
   (iii) remaining to other proteins.
2. 1-2% circulates in blood in free form which is *physiologically active.*

(iii) Mode of Action

In the target organs inside the cell it is converted by enzyme, 5α-reductase to more potent and stable

dihydrotestosterone (DHT), which is ***physiologically active*** rather than the testosterone. DHT is bound to nuclear chromatin and promotes mRNA activity which, in turn, stimulates the synthesis of proteins (page 653). Normal plasma level of DHT is approximately 10% of the plasma testosterone level.

Note

Congenital deficiency of 5α-reductase results in male pseudohermaphroditism (page 774).

(iv) Metabolism

1. It is inactivated in the liver by converting it into less potent androsterone and dehydroepiandrosterone – DEA (page 712), both of which appear in inactivated form in the urine conjugated with glucuronic or sulphuric acid as *17 ketosteroids.* This is why the natural androgens when given orally are ineffective, as they get inactivated while passing through the liver.
2. Approximately 2/3rd of the urinary 17 ketosteroids are of adrenal origin and remaining 1/3rd are of testicular origin (page 717).

(v) Actions

1. Along with FSH, testosterone is responsible for the maintenance of spermatogenesis (page 784). It also promotes and maintains the motility and fertilizing power of the sperms.
2. It is responsible for the development of accessory sex organs (page 784) and secondary sexual characters at puberty (page 777).
3. It exerts an inhibitory feedback effect on pituitary LH secretion (see below).
4. *General metabolic effects:* It produces protein anabolic and growth promoting effect; how?
   (i) It causes nitrogen retention in the body and increases synthesis and deposition of protein in certain tissues, specially skeletal muscles which result in increased muscular strength.
   (ii) It plays an important role in adolescent growth spurt (page 668) and may also increase the libido.
   (iii) It causes the epiphyses to fuse to the long bones, thus eventually stopping linear growth.
   (iv) It causes retention of calcium sulphate, phosphorus, sodium, potassium chloride and water.
   (v) It also increases the size of the kidneys and promotes erythropoiesis (page 69).

Important Notes

1.(i) Formation of the male external genitalia in the foetus, and
(ii) Enlargement of the prostate; appearance of the facial hair, the temporal recession of the hair line and acne at the time of puberty;
(These are dependent on the formation of DHT.)
2. On the other hand
(i) Formation of male internal genitalia in the foetus.
(ii) pubertal enlargement of the penis and scrotum; and
(iii) the increase in muscle mass, male sex drive and libido.
(These are mediated directly by testosterone.)

B. OESTROGEN

1. Normal plasma oestrogen level in adult male: 30 pg/mL (2-5 ng/dL).
2. Daily output: 0.05 mg (50 µgm).
3. *Sources:*
   (i) 70% of oestradiol is formed by conversion of circulating testosterone and androstenedione by an *enzyme aromatase* (page 784);
   (ii) small amount is produced by adrenal cortex (page 714), and
   (iii) 30% is secreted by testis: some comes from the Leydig cells and some from Sertoli cells.

CONTROL OF TESTICULAR ACTIVITY

The growth and functions of the testis are controlled by the hypothalamus and anterior pituitary **(Fig. 81.3)**.

1. The hypothalamus releases gonadotrophin releasing hormone (GnRH) which acts on anterior pituitary to increase the release of FSH and LH (in males LH is also called interstitial cell stimulating hormone – ICSH).
2. **ICSH** stimulates the Leydig/interstitial cells of testis and promotes the testosterone secretion which causes growth and development of the accessory organs of reproduction (page 784).
3. **FSH** controls spermatogenesis by its direct stimulating action on the seminiferous tubules. It is necessary for the maintenance of an optimal level of spermatogenic activity (FSH also stimulates the secretion of ABP and inhibin-B, page 784).
4. Testis in turn influences the activity of hypothalamus and anterior pituitary by two mechanisms:
   (i) *Direct effect:* The testis normally inhibits the secretion of gonadotrophins (FSH and LH) from the anterior pituitary via:

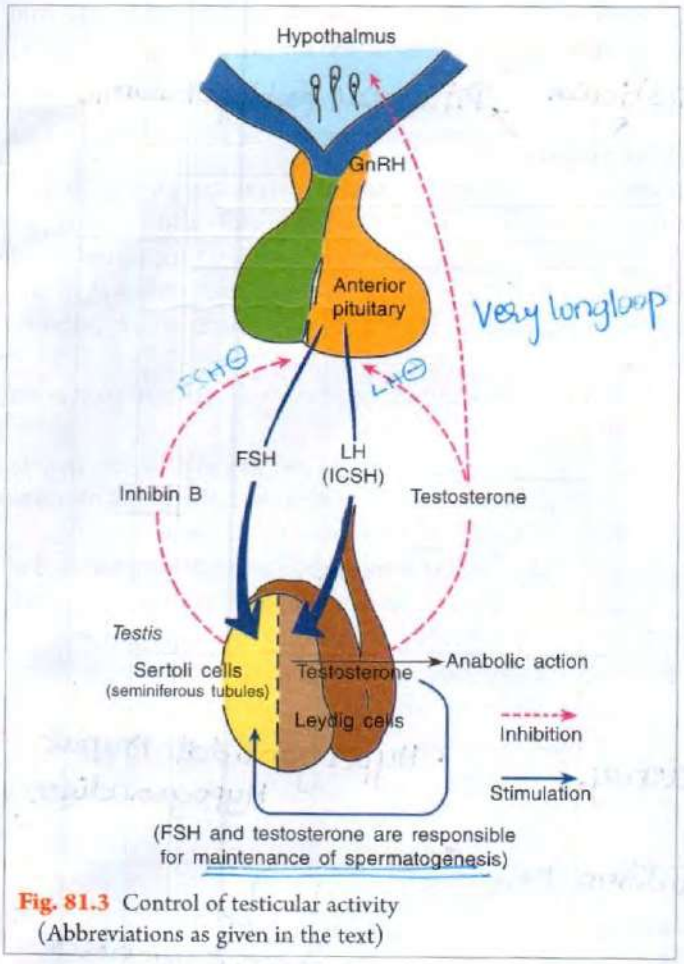


Fig. 81.3 Control of testicular activity (Abbreviations as given in the text)

(a) testosterone, which directly exerts an inhibitory feedback effect on pituitary LH (ICSH) secretion; and

(b) some unidentified testicular factor, ***inhibin B*** derived from the seminiferous tubules (Sertoli cells) feed backs to inhibit FSH secretion.

Proof: Patients who have atrophy of seminiferous tubules show elevated plasma FSH levels with normal levels of testosterone and LH secretion.

(ii) *Indirect effect:* Testosterone also exerts an inhibitory feedback effect on pituitary gonadotrophin (FSH and LH) secretion by inhibiting release of GnRH from the hypothalamus (page 779).

Proof: Implantation of minute amounts of testosterone in the hypothalamus but not in the pituitary causes testicular atrophy.

APPLIED ASPECTS

A. CRYPTORCHIDISM: UNDESCENDED TESTES

The testes develop in the abdominal cavity and normally migrate to the scrotum during foetal development under the influence of MRF (page 770). Incomplete descent

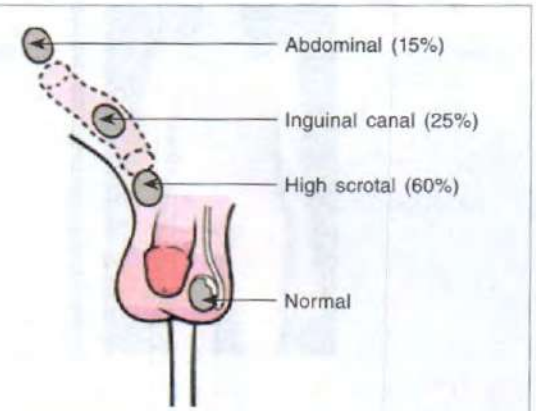


Fig. 81.4 Cryptorchidism (undescended testes): percentage incidences

of testes on one or both sides in newborn is called ***Cryptorchidism***, the testes remaining in the abdominal cavity or inguinal canal. Spontaneous descent of these testes is the rule; the percentage incidences of undescended testes are 2% at 1 year of age which falls to 0.3% after puberty **(Fig. 81.4)**.

Characteristic features

1. Seminiferous tubules remain infantile due to higher temperature to which the gland is exposed in the abdomen compared to the scrotum (page 786), therefore, spermatogenesis fails to occur resulting in sterility. Since Leydig cells are normal and continue to secrete testosterone, male secondary sexual characters develop normally.
2. The anterior pituitary may control the descent of testes.

   Proof: Patients with undescended testes when given treatment with gonadotrophin hormone, showed improvement.
3. Its treatment should be given before puberty, because of high incidence of sterility and malignant testicular tumours in these individuals.

B. REMOVAL OF TESTES: MALE HYPOGONADISM

Before puberty – Removal of testes before puberty produces permanent sterility due to absence of testosterone. The clinical picture which develops is called ***Eunuchoidism*** and shows the following ***characteristic features*** **(Fig. 81.5)**:

1. Usual pubertal changes do **not** occur; therefore,
   (i) there is no growth of hair on the face and trunk or axilla;
   (ii) pubic hair pattern is of female type (page 777) being concave upwards due to adrenocortical androgen secretion;
   (iii) growth of larynx arrested which results in high pitched voice;

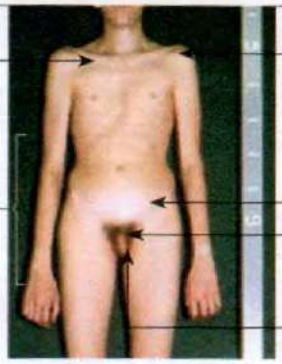


Fig. 81.5 Characteristic feature of Eunuchoidism (removal of testes before puberty)

(iv) body configuration resembling that of adult female due to abnormal deposition of fat on buttocks, hips, pubis and breasts, and

(v) muscles are soft and poorly developed.

2. Failure of development of accessory organs of reproduction, therefore, penis, scrotum, seminal vesicles and prostate remain small.

3. Some of the individuals are characteristically tall due to delay in the union of the epiphysis.

After puberty

Some of the secondary sexual characters and accessory organs depend on testesterone not only for their development but also for their maintenance. Thus these characters or organs are depressed after removal of the testes (castration). Therefore, castration after puberty results in:

(i) atrophy of seminal vesicles and prostate (common finding);

(ii) no alteration in voice as the growth of the larynx during adolescence is permanent; the penis remains normal size; beard remains unaffected;

(iii) sexual desire and penile erection is little impaired, if at all it is purely due to psychological changes; this may lead to hot flushes, irritability and depression.

(iv) other body functions including life span, senility, intelligence etc. are not affected.

Study Questions

1. **Write short notes on:**
   (i) blood testis barrier (ii) functions of testis
   (iii) control of spermatogenesis (iv) vasectomy
   (v) Prostate specific antigen (PSA) (vi) inhibin-B
   (vii) eunuchoidism (ix) Spermiogenesis
   (viii) Leydig and Sertoli cells (xi) Cryptorchidism
   (x) Action of Testosterone and DHT
   (xii) Inhibin-B
2. **Illustrate with the help of labelled diagram:**
   (i) Structure of a mature sperm
   (ii) Control of testicular activity.
3. **Give physiological basis of:**
   (i) Sterility in a man working in hot surroundings.
   (ii) Gossypol as male contraceptive.
   (iii) Use of conventional contraceptive measures for about 2 months after vasectomy.
   (iv) Androgen when given orally are ineffective.
   (v) Undescended testes.
   (vi) Sperm count tends to be greater in winters.
4. **What will happen and why?**
   (i) If testes fail to descend into the scrotum?
   (ii) If testes are removed in an individual
   (a) before puberty
   (b) after puberty?
   (iii) If congenital deficiency of 5 α-reductase occurs in an individual
5. **How do the non-motile sperms in seminiferous tubules reach the epididymis?**
6. **Give the functions of:**
   (i) epididymis (ii) vas deferens (iii) seminal vesicles
   (iv) prostate and (v) bulbo-urethral glands.
7. **In which portion of male genital tract do the sperms become motile? How do the sperms get energy for movement? How do the sperms penetrate through the cervical mucus plug?**

8. Give the sources and functions of oestrogen in males.
9. Why are so many sperms released per ejaculation when only one sperm is required to fertilize the ovum?
10. Give in detail composition and functions of seminal fluid.

MCQs

1. *Not* a feature of Sertoli cells:
   (a) Nourish sperms and control their release
   (b) Provide blood testis barrier
   (c) Secrete testosterone
   (d) Secrete inhibin B
2. Spermiation means:
   (a) Release of mature sperms from Sertoli cells
   (b) Conversion of spermatids to sperms
   (c) Conversion of non-motile to motile sperms
   (d) Process by which sperms are formed
3. *False* statement about spermatogenesis:
   (a) Continues throughout adult life
   (b) Takes about 74 days to form a mature sperm from primitive germ cell
   (c) Single spermatogonia forms four spermatids
   (d) Does not occur simultaneously in all parts of the testis
4. Primary spermatocytes to get converted into secondary spermatocytes require presence of:
   (a) FSH (b) LH (c) FSH & LH both (d) Testosterone
5. Optimal temperature for spermatogenesis is:
   (a) Normal body ltemperature, 37°C
   (b) 43-45°C
   (c) 39-40°C
   (d) 32°C
6. How long the sperm remains viable in the epididymis?
   (a) 1 week (b) 2 weeks (c) 3 weeks (d) 4 weeks
7. Vasectomy, *false* statement is:
   (a) A simple procedure for sterilization in males
   (b) Cause absolute degeneration of semiferous tubules
   (c) Testosterone secretion and other glandular secretions not affected
   (d) For first two months after vasectomy viable sperms may be released from the ampula
8. *Not a correct* statement about seminal vesicles:
   (a) Its secretion is thick and sticky
   (b) Its secretion provides energy for movement of sperms
   (c) Secretions are rich in enzyme hyaluronidase
   (d) Contributes to 20% of semen's total volume
9. Prostrate, *not a true* statement:
   (a) A fibro-musculoglandular structure
   (b) Secretion is thin, opalescent and gives the semen its characteristic odour
   (c) Its secretion contributes to 40% of semen's total volume
   (d) Secretion is slightly acidic (pH 6.4) and rich in acid phosphate
10. A person is said to be infertile when sperm count decreases beyond:
    (a) 20 million/mL (b) 40 million/mL (c) 60 million/mL (d) 80 million/mL
11. Maximum duration of sperm fertilizing capacity within female reproductive tract is:
    (a) 12-24 hours (b) 24-48 hours (c) 48-72 hours (d) 72-96 hours
12. Peak testosterone levels are seen about:
    (a) 7-8 p.m. (b) 2 a.m. (c) 7-8 a.m. (d) 12 p.m.
13. Following are the effects of testosterone *except*:
    (a) Increases haemopoiesis
    (b) Calcium retention
    (c) Increases total quantity of bone matrix
    (d) Increases BMR
14. Cryptorchidism refers to:
    (a) Male hypogonadism
    (b) Removal of testis before puberty
    (c) Removal of testis after puberty
    (d) Undescended testes
15. Castration after puberty produces all the following *except*:
    (a) Loss of sexual desire and impotency
    (b) Atrophy of seminal vesicles and prostate
    (c) No alteration in voice
    (d) Beard remains unaffected

16. *Not a true* statement about blood testis barrier:
(a) Formed by tight connections between sertoli cells and seminiferous tubular wall
(b) Testosterone can penetrate this barrier with ease
(c) Phagocytose defective sperms
(d) Protects the germ cells

17. Fluid in the lumen of seminiferous tubules is rich in all *except*:
(a) Potassium (b) Glucose (c) Androgens (d) Glutamic acid

18. Testosterone secretion from Leydig cell is under control of:
(a) FSH (b) LH (c) Androgen (d) Oestrogen

19. Daily sperm production in an adult is approx.:
(a) 1 million (b) 3 millions (c) 5 millions (d) 7 millions

20. *Not a correct* statement regarding acrosome:
(a) Envelops the sperm nucleus (b) Consists of DNA
(c) Contains acid phosphatase (d) Helps in sperm penetration to the ovum

21. Which of the following provides energy for motility of sperms?
(a) Tail (b) Axial filament (c) Mitochondria (d) Central pair of fibrils

22. *Not* a function of epididymus:
(a) Helps sperm transport (b) Helps sperm maturation
(c) Stores the sperms (d) Provides energy for movements of sperms

23. Following vasectomy, it is advisable to use conventional method for contraception for a period of:
(a) 15 days (b) 1 month (c) 2 months (d) 3 months

24. pH range of semen is:
(a) 6.2 - 6.5 (b) 7.0 - 7.3 (c) 7.35 - 7.5 (d) 7.5 - 7.9

25. Infertility is usually:
(a) Present when sperm count in ejaculate is <10,000,000/mL
(b) Present when there is loss of function in posterior pituitary in females
(c) Due to the defect of functions in female partners rather than in males
(d) Due to disorders of endocrine functions of both males and females

26. Sperm motility is decreased in:
(a) Alkaline pH (b) Neutral pH (c) Acidic pH (d) None of the above

27. Semen contains all *except*:
(a) Fructose (b) Thromboplastin (c) Fibrinogen (d) Prothrombin

28. Testes *does not* produce:
(a) Oestrogen (b) Testesterone (c) Fructose (d) Inhibin B

29. In the testis, the cells that secrete testosterone:
(a) Germinal epithelium (b) Leydig cells (c) Sertoli cells (d) Sperm cells

30. Natural androgens when given orally are ineffective because:
(a) Rapidly inactivated by HCl in the stomach (b) Gets hydrolysed by digestive juices
(c) Inactivated in the liver (d) Not absorbed by the GIT mucosa

31. A major source of urinary 17 ketosteroids is:
(a) Adrenal cortex (b) Testes (c) Thyroid gland (d) Pancreas

32. Control of testicular activity is brought about by:
(a) Direct inhibitory effect of testosterone on pituitary LH secretion
(b) Inhibition from sertoli cells directly inhibit pituitary FSH secretion
(c) Testosterone indirectly exerts an inhibitory feedback effect on pituitary gonadotrophins secretion by inhibiting release of GnRH from hypothalamus
(d) All of the above

Answers

1. (c) 2. (a) 3. (c) 4. (a) 5. (d) 6. (d) 7. (b) 8. (d) 9. (c) 10. (a) 11. (b) 12. (c) 13. (a) 14. (d) 15. (a)
16. (c) 17. (b) 18. (b) 19. (a) 20. (b) 21. (c) 22. (d) 23. (c) 24. (c) 25. (a) 26. (c) 27. (d) 28. (c) 29. (b) 30. (c)
31. (a) 32. (d)

Chapter

82

Female Reproductive System

I. The female reproductive tract
   (A) The uterus and related structures
   (B) The ovary: ovarian hormones (oestrogen, progesterone, relaxin); removal of ovaries, menopause.

II. Female sexual cycles
   (A) Changes in the ovaries
   (B) Changes in the uterus: the menstrual cycle
   (C) Changes in the vagina
   (D) Changes in the gonadotrophin secretion

THE FEMALE REPRODUCTIVE TRACT

It consists of a *uterus*, a pair of *ovaries*, a pair of *fallopian tubes (oviducts)* and a *vagina* (Fig. 82.1).

A. THE UTERUS

Characteristic features

1. The uterus consists of:
   (i) *Body* (corpus) with bulging upper surface, the *fundus*, and
   (ii) Neck called *cervix*.
2. The uterine cavity is small, triangular in shape with *three openings:*
   (i) two for fallopian tubes at its upper outer angles, and
   (ii) one directed downwards (*internal os*) which opens into the cervical canal and leads via *external os* into the vagina.
3. (i) The prepubertal uterus is a small organ weighing 10-15 gms.
   (ii) The post-pubertal uterus is pear shaped, grows

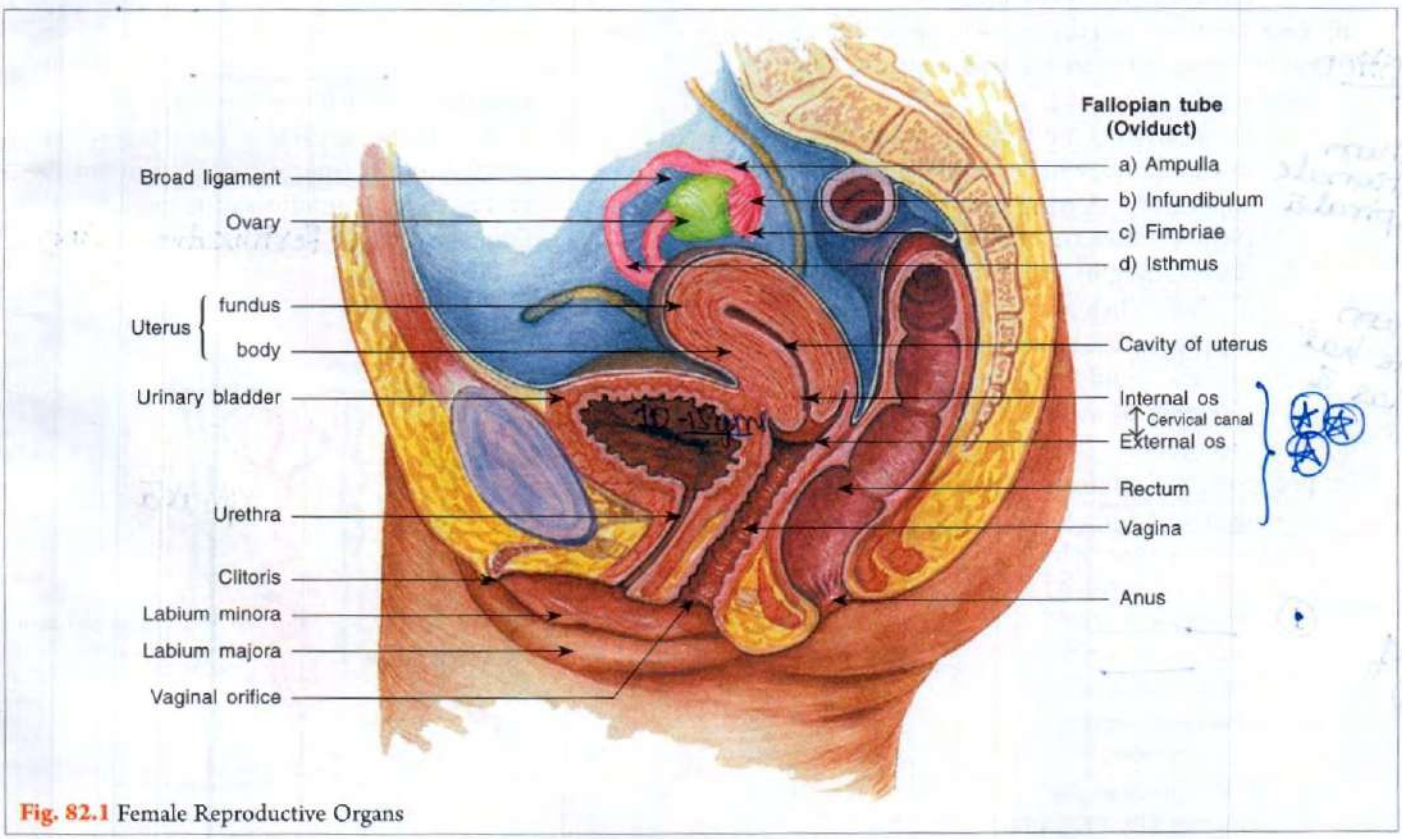


Fig. 82.1 Female Reproductive Organs

under the influence of oestrogen, measures 7.5 cm × 5 cm × 2.5 cm (3" × 2" × 1") and weighs 30-60 gms.

(iii) During late pregnancy the uterus enlarges considerably through stretching by the growing foetus and by hormonal action; the final weight being 800-1000 gms.

4. The *body of the uterus* consists of '3' coats:
   (i) Innermost coat is of mucous membrane called *Endometrium*.
   (ii) Middle thick coat is of smooth muscle called *Myometrium*, which gives strength to uterus. It is
      (a) thickest in the fundus which contracts forcefully, and
      (b) thinnest in the cervix which dilates during delivery.
   (iii) Outermost coat is a serous coat of parietal peritoneum which covers only upper 3/4th of the uterus. (Perimetrium)

5. *Endometrium. Salient features:*
   (i) It plays an important role in reproduction. How?
      (a) It undergoes characteristic changes during the *Menstrual Cycle i.e.* recurrent monthly discharge of blood from female genital tract.
      (b) It helps in implantation of fertilized ovum and supplying the nutrients essential for its growth and development.
   (ii) Two kinds of arterial vessels pass through the myometrium to enter the endometrium, *spiral* and *basal arteries*: **(Fig. 82.2)**
      (a) *Spiral* arteries are tortuous arteries and end in capillaries which supply the middle and superficial portion of the endometrium (***Stratum Functionale***). (2/3rd)
      (b) *Basal* (straight) arteries which run only for a short distance and supply the basal portion of the endometrium (***Stratum Basale***). (1/3rd)
   (iii) The secretions from the progestational endometrium (endometrium influenced by progesterone) are rich in:
      (a) Glucose – which provides energy and nourishes the blastocyst for a few days before implantation takes place in the hormonally prepared endometrium.
      (b) Enzymes and proteins which stimulate RNA and protein synthesis in the blastocyst.

6. *The Cervix*
   (i) It is much less muscular compared to the rest of the uterus, and contains more connective tissue. Its mucosa, called ***Endocervix*** contains columnar mucus secreting epithelium with some ciliated cells. Endocervix is **not** shed at the time of menstruation.
   (ii) Cervical secretion normally contains approximately 92% water, NaCl and glycoprotein (sialomucin type). Its composition and character changes in response to hormonal influences (page 799 and 803).
   (iii) *Functions*
      (a) Allows entry of spermatozoa (sperms) from the vagina into the uterus and to store viable sperms for 1-2 days;
      (b) Allows escape of menstrual wreckage;
      (c) Permits passage of the foetus at term;
      (d) Prevents entry of infectious microorganisms.

7. *The Fallopian Tubes (Oviducts)*
   (i) Each fallopian tube length is approx. 10 cm (4").
   (ii) It consists of same three coats as that in the uterus (page 827). Ampulla - Isthmus - Infundib.
   (iii) Its distal end gets expanded into a funnel like portion called *Infundibulum* which opens with finger-like projections known as *Fimbriae*.
   (iv) *Functions*
      (a) Serve as ducts for ovaries by providing passage by which ova can reach uterus.
      (b) Fertilization function. The union of a spermatozoon (sperm) with an ovum (egg) occurs here, normally in the *ampulla* of the fallopian tube. (Fertilization point)

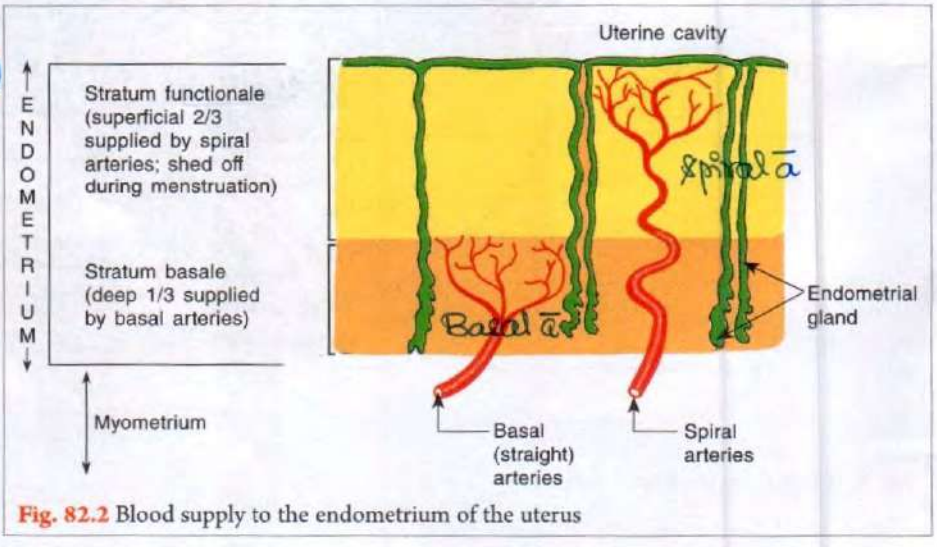


Fig. 82.2 Blood supply to the endometrium of the uterus

B. THE OVARY

Characteristic features

1. There are two ovaries, one on each side, behind and below the fallopian tubes.
2. Total weight of the adult ovaries is 10-20 gm, which decreases with increasing age.
3. *Primary functions:*
   (a) to produce and discharge *Ova* (eggs); and
   (b) to secrete female hormones called ovarian hormones (oestrogen and progesterone mainly).

(a) *Production and Discharge of Ova*

Process of formation of ova is called ***Oogenesis***. (Fig. 82.3 and Table 82.1)

(i) Ova are formed from approx. the 10th week of foetal life from *Oogonia* which multiply freely by mitosis and by 5th month of the intrauterine life the two ovaries contain 6-7 million germ cells.

(ii) Formation of *oogonia* ceases by the 7th month and at term all the **oogonia** have become *Primary Oocytes*. There are approx. 2 million 'oocytes' at birth, falling to 300,000 at 7 years. Completion of the first meiotic division does not occur until ovulation at puberty (page 802) when, after extrusion of the *First Polar Body*, *Secondary Oocytes* are formed. The second meiotic division begins immediately, but this division stops at metaphase and is completed only when a sperm penetrates the *oocyte* (page 819).

(iii) During the course of maturation the *primary oocyte* first becomes surrounded by a basal lamina to form a *Primordial Follicle*.

(iv) The spindle shaped cells inside the basal lamina become cuboidal forming *Primary Follicle*.

(v) Later, these cuboidal cells multiply to form *Granulosa Cells*, around which stromal cells outside the basal lamina differentiate to form the *Theca*. The "Theca" is vascularized but granulosa cells receive no blood supply.

(vi) The 'oocyte' is immediately surrounded by *Zona Pellucida* through which protoplasmic processes pass from the granulosa cells to make contact with the cell membrane of the oocyte and may provide nutrients and maternal proteins.

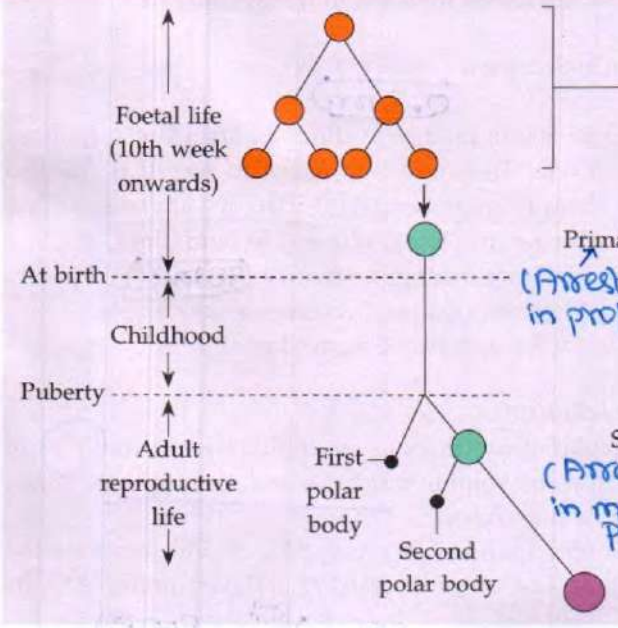
(vii) After the 7th month of intrauterine life some of the primary follicles show accumulation of fluid rich in oestrogen, which comes from the granulosa cells and thus form *Graafian Follicles* (also called ***secondary follicles***).

(viii) From birth onwards, degeneration (*i.e. Atresia*) of large number of primary and secondary follicles continues until by the menopause there are no follicles left.

Important Notes

1. After birth no new oocytes are formed. On the other hand, in the male, spermatogenesis begins at puberty and new sperms are continually being formed thereafter, to gradually cease in old age.
2. Only 300-400 follicles proceed to 'ovulation' (page 802) during the years of female fertile life from menarche to menopause.

Table 82.1: Steps during Oogenesis



	Choromosomes per cell	Chromatids per chromosome
Oogonia	46	2
Primary oocytes (2 million)	46	2
Secondary oocytes	23	2
Ovum (Egg)	23	1

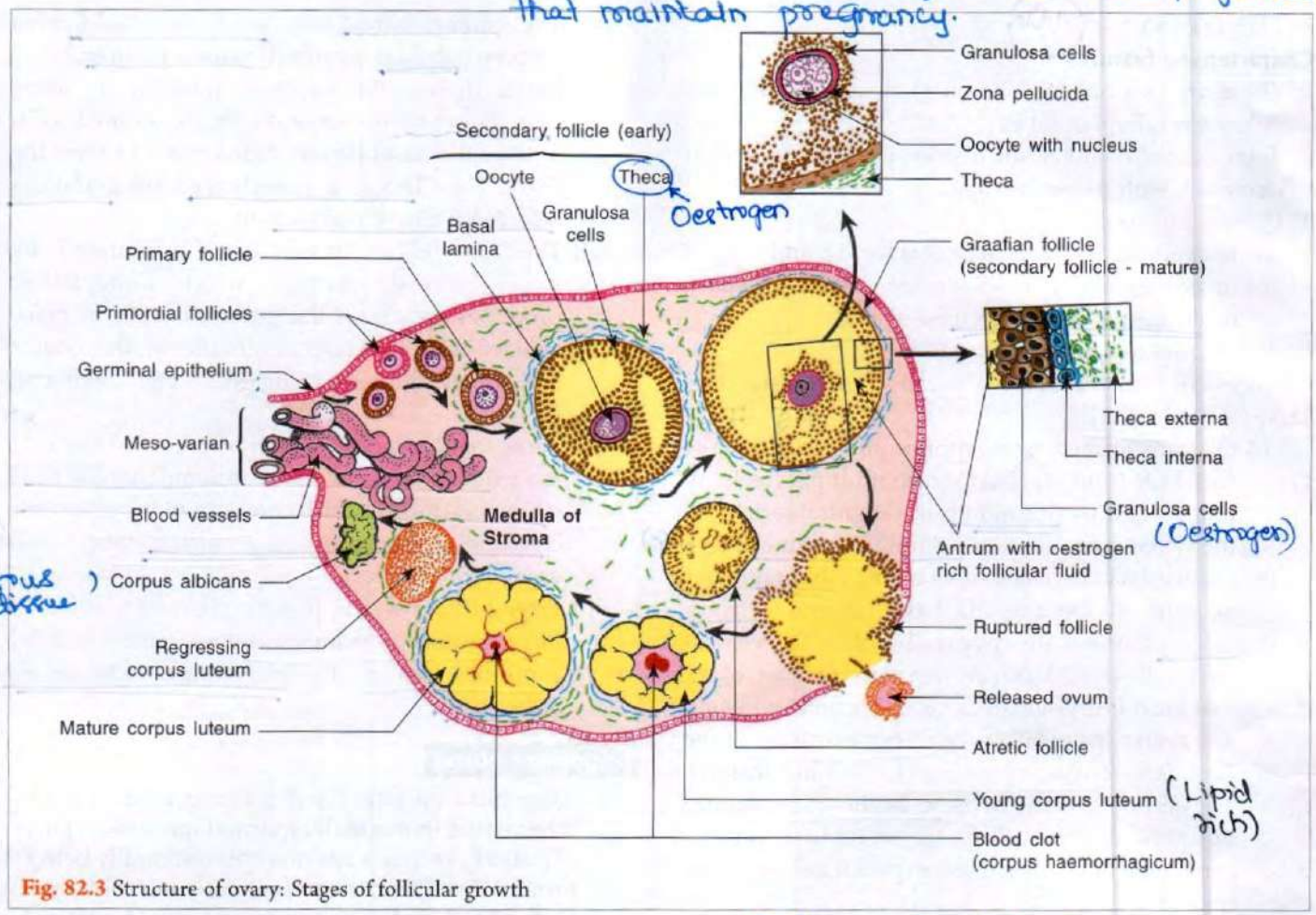


Fig. 82.3 Structure of ovary: Stages of follicular growth

(b) *Ovarian Hormones*

OESTROGENS

All oestrogens are steroid hormones with cholesterol as the main precursor (Biosynthesis, page 716). The physiological active natural oestrogens are:

1. *17 β-oestradiol (most potent);*
2. *oestrone*, intermediate precursor of (1), and
3. *oestriol* (least potent).

Sources

1. Theca interna cells of the graafian follicles (*major source*, **Fig. 82.3**). These cells have many LH receptors.
2. Granulosa cells of the graafian follicles

Note

Oestrogens from granulosa cells do not enter the circulation and remain in the follicular fluid.

3. Placenta (page 821),
4. ~~Adrenal cortex~~ – in small amounts,
5. Testis – in small amounts.

Transport

1. 97% circulates in blood bound to plasma proteins
   (i) 60% to albumin
   (ii) 37% bound firmly to *gonadal steroid binding globulin – GBG* (page 789).
   Total (free + bound) plasma oestradiol level is 50-300 pg/mL.
2. 3% circulates in blood in free form.

Daily Secretion

1. *In females:*
   (i) 35-500 µgm/day in different stages of menstrual cycle. There are two peaks of secretion: 1st just before ovulation (200-500 µgm/day), and 2nd during mid luteal phase (250 µgm/day).
   (ii) 15-45 mg during pregnancy.
   (iii) After menopause, decreases to low levels.
2. *In males:* approx. 50 µgm/day.

Metabolism

Circulating oestrogens are conjugated in the liver to form water soluble sulphates and glucuronides which are then excreted.

(i) 65% excreted in urine, 80% of which is excreted as *oestrone* and *oestriol*; and remaining 20% as *oestradiol*.

(ii) 10% excreted in faeces.
The fate of remaining 25% is not known.

Mechanism of Action

It is specifically and rapidly taken up by target organs, such as uterus, vagina, anterior hypothalamus and anterior pituitary, in which there is a specific binding protein in the cell cytoplasm or in lysosomes. The bound product rapidly enters the nucleus and via DNA and RNA initiates changes which enhance cell replication and/or protein synthesis (page 653).

Actions → "PUBERTAL SPURT"

Before puberty, oestradiol is secreted in very small amounts which has little physiological action. At puberty, oestradiol is secreted in large quantities and results in the following changes in the body.

A. *Promotes the growth of internal genitalia.* The growth of the ovaries, uterus and vagina increases and their activity also increases.

(1) *Changes in the ovaries:* It is responsible for completion of ovarian cycle (page 801) characterised by ovulation and corpus luteum formation.

(2) *Changes in the uterus*

(i) Promotes mitotic activity in the uterine muscle and endometrium; therefore,

(a) In the myometrium the uterine muscle fibers enlarge and become more excitable and active; also their sensitivity to oxytocin increases. These effects are due to action on calcium binding by the myometrial cell membrane.

(b) In the endometrium, oestrogen
- stimulates growth of glandular epithelium,
- causes hyperaemia probably by release of histamine, and
- increases the content of water, electrolytes, nucleotides, proteins and enzymes.

(ii) Cervical mucus secretion becomes *copious and watery.*

(iii) Fallopian tubes:

(a) stimulates the secretory activity of the cell lining, and

(b) increases the motility of the muscle coat and cilia.

(3) *Changes in the vagina*

(i) It promotes mitotic activity in the epithelium to increase it in height from 2-3 layers of low cuboidal cells to approximately 10 layers of cells; the most superficial of which shows cornification and desquamation.

(ii) It increases vaginal secretions and makes it acidic by promoting the breakdown of glycogen to lactic acid. This helps to protect the vagina against bacterial infection.

(iii) Oestrogens are necessary for the lubricating vaginal secretion associated with coitus.

B. *Promotes the growth of external genitalia,* therefore

(i) clitoris increases in length and width, and

(ii) enlargement of labia majora and minora.

C. *Responsible for the appearance of secondary sexual characters in females* (page 777) and breast enlargement at puberty (page 837).

D. *Influences the gonadotrophin secretion* by the anterior pituitary via feedback mechanism. How? The effects of oestrogen vary with the dose.

(i) *In small doses,* oestrogen acts directly upon the hypothalamus and anterior pituitary to inhibit the secretion of FSH and LH via a *negative* feedback mechanism (Fig. 82.6).

(ii) *In larger doses,* oestrogen produces *positive* feedback effect on LH secretion by promoting the responsiveness of the pituitary to GnRH. This causes a small rise in FSH concentration also (Fig. 82.5). CAUSES LH surge.

(iii) During luteal phase, elevated levels of oestrogen and progesterone (page 806), inhibit the secretion of FSH and LH via negative feedback effect in the hypothalamus (Fig. 82.6).

Important Note

Moderate and constant level of circulating oestrogen produces negative feedback effect on LH secretion; whereas an elevated oestrogen level produces positive feedback effect and stimulates LH secretion. (LH surge)

E. **Plays a role in pregnancy and parturition** (pages 821 and 824).

F. Increases the plasma levels of thyroxine (page 686) and cortisol binding globulin (page 714) and also causes increased secretion of angiotensinogen.

G. It **lowers plasma cholesterol** level and may, therefore, help to prevent the development of atherosclerosis. This may explain low incidences of MI in females. However, in pharmacological doses, oestrogen promotes thrombosis, thus, it is **not** used for prevention of coronary artery disease.

Important Note

Sexual activity in women is not related to oestrogen secretion, since libido is often well marked after the menopause; it is probably due to secretion of weak androgens from adrenal cortex and their conversion to testosterone in the skin.

H. Other: Oestrogen play an important role in body growth (page 670) and bone growth (page 703).

Uses

Artificial oestrogens, such as diethyl stilboestrol and ethinyloestradiol are relatively active when given orally. Therefore, these are used clinically:

(i) to control menopausal symptoms (page 801) which occur when ovarian function ceases;

(ii) in the oral contraceptive pills (page 816).

PROGESTERONE

1. It is a C_{21} steroid.
2. *Sources*
   (i) Corpus luteum and the placenta (*major source*).
   (ii) Testes and adrenal cortex (in small amounts).
3. It is non-hormone *i.e.* it has no action of its own.
4. *Plasma level*
   (i) in men – 0.3 ng/mL
   (ii) in women – 0.9 ng/mL during follicular phase of menstrual cycle which increases by 20 folds during the luteal phase (page 804).
5. *Transport:* 98% circulates in blood bund to plasma proteins; 80% is bound to albumin and 18% is bound to GBG (page 789); and approx. 2% circulates in blood in free form.
6. It has a short half life and is converted in the liver to pregnediol, which is conjugated to glucuronic acid and excreted in the urine.
7. *Mechanism of Action:* It acts by an action on DNA to initiate synthesis of new mRNA (page 654).
8. *Actions*
   (i) On the oestrogen-stimulated proliferated endometrium it produces the secretory changes which prepare the endometrium for implantation of the fertilized ovum (blastocyst) (page 805).
   (ii) On cervical secretion (page 803).
   (iii) Promotes the growth of lobules and alveolar tissue in the breasts (page 836).
   (iv) To some extent, it antagonizes the action of oestrogen; for example:
      (a) it decreases the excitability of myometrial cells;
      (b) reduces spontaneous electrical activity, raises the membrane potential and decreases the sensitivity of the myometrium to oxytocin. However, progesterone may induce slow uterine contractions of high altitude.
   (v) Decreases number of oestrogen receptors in the endometrium and increases the rate of conversion of 17 β-oestradiol to less active oestrogen.
   (vi) Increases *basal body temperature* (BBT) slightly due to formation of its derivatives, etiocholanolone and pregnendiol. This may explain why BBT increases by 0.5°C at the time of ovulation (page 801).
   (vii) Others:
      (a) *inhibits ovulation* probably by inhibiting release of LHRH (GnRH) from the hypothalamus which, in turn, decreases the release of LH and also potentiates the inhibitory effect of oestrogen on secretion of GnRH (Fig. 82.6);
      (b) stimulates respiration and thus decreases alveolar pCO_2; and
      (c) *in large doses,* produces natriuresis by blocking the action of aldosterone on the kidneys.
9. *Control of Secretion*
   LH from anterior pituitary activates adenylyl cyclase in the corpus luteum to increase cAMP formation. This by increasing the synthesis of a new protein increases the progesterone secretion.
10. *Uses*
    (i) Synthetic progesterone preparations (*i.e.* its orally absorbed derivatives) are incorporated in the contraceptive pills (page 816).
    (ii) It is of value in pregnant women who have had repeated abortion, either by promoting placental progesterone formation or by reducing uterine contractions.

RELAXIN

1. It is a polypeptide with MW 8000.
2. *Sources*
   (i) Corpus luteum (mainly); its concentration increases in tissues and blood during pregnancy.
   (ii) Also produced by the uterus and the placenta.
   (iii) In the prostate gland in males.
3. *Use*
   (i) Facilitates delivery by:
      (a) relaxation of the symphysis pubis and other pelvic joints;
      (b) inhibition of uterine contractility, and
      (c) softening and dilatation of the cervix.
   (ii) *In males,* it is found in semen, where it help to maintain sperm motility and aid in sperm penetration of the ovum.

REMOVAL OF OVARY

Characteristic features

Before puberty

1. Puberty does not set in.
2. The menstrual flow does not appear.
3. Secondary sexual characters do not develop.

Therefore, presence of ovary is essential for the onset of puberty.

In Adults

1. Atrophy of the whole genital tract *i.e.* the uterus, vagina and the external genitalia structure.
2. Menstruation ceases permanently.
3. Vasomotor changes are common, like:
   (i) flushing of skin of the face, neck and upper chest, called ***Hot Flushes*** *i.e.* sensation of warmth (cause not known). However, they coincide with LH surge (page 805); and
   (ii) feeling of suffocation and night sweats.
4. Effects on the breasts – variable
   (i) they may increase in size due to local accumulation of fat, or
   (ii) they may shrink due to atrophy of glandular tissue.
5. Obesity develops due to diffused deposition of fat.
6. Effect on sexual desire – variable, but often unaffected, because it is independent of sex hormones and largely determined by psychological factors.
7. Emotional disturbances of varying degree ranging from a certain amount of irritability or depression to insanity.

MENOPAUSE

It is the period of life when menstruation naturally ceases with *appearance of characteristic features as described above.* It usually occurs between the age of 45 and 55 years (Average 52 years).

Note

A period usually between the ages of 45 and 55 years called *perimenopausal* occurs before menopause, which may last upto 10 years. During this period the menses become irregular and level of inhibin-B (page 805) decreases.

It is associated with marked changes in the ovaries, therefore,

(i) ovaries become smaller, the graafian follicles disappear and replaced by fibrous tissue;
(ii) ova, corpus luteum and internal secretion of the ovary are no longer formed.

Cause: These ovarian changes are not due to lack of anterior pituitary gonadotrophins (FSH and LH) which actually increase, as negative feedback effect of oestrogen and progesterone is reduced. The changes are due to *senile* changes in the ovary which no longer reacts to the stimulatory effect of hormones (specially gonadotrophins); and finally, its function declines. Therefore, the ovaries no longer secrete 17 β-oestradiol, and oestrogen is only formed in small amounts by conversion of androstenedione in the circulation. Oestradiol (synthetic oestrogens) reduces the hot flushes and other symptoms of the menopause.

Important Note

Although the function of the testes gradually declines with advancing age, there is no evidence of male menopause (*climacteric or andropause*) similar to that occurring in women.

FEMALE SEXUAL CYCLES

The changes that occur periodically (*i.e.* repeatedly at fairly uniform intervals) in females during reproductive age constitute the female sex cycle. The rhythmic changes take place in the following organs:

A. Changes in the ovaries, called *The Ovarian Cycle;*
B. Changes in the uterus, called *The Menstrual Cycle;*
C. Changes in the vagina, and
D. Changes in the gonadotrophin secretion, it comprises *Hormonal Control of Female Sexual Cycles.*

A. CHANGES IN THE OVARIES: THE OVARIAN CYCLE

Premenarchal Ovary

1. From birth to menarche, ovarian weight increases steadily due to:
   (i) increased volume of developing follicles, and
   (ii) an increase in stroma.
2. After 8 years of age, oestrogen secretion by the ovary is sufficient to promote an increase in uterine weight.

Postmenarchal Ovary

1. At the menarche, hypothalamic maturation leads to onset of cyclic *ovulation* (*i.e.* release of ovum from the ovary at periodic interval, while atresia continues).
2. During each cycle, of approx. a month time, some 10-15 follicles enlarge to become *secondary follicles,* under the influence of FSH from the anterior pituitary (Fig. 82.5). Fluid accumulation occurs in these follicles but only **one** out of 15 enlarged follicles (why? not known, probably its ability to secrete more of oestrogen than the others) proceeds to the stage of *ovulation.*

Note

The first meiotic division is completed just before ovulation, page 797.

This ovum gets immediately surrounded by zona pellucida and granulosa cells, called *cumulus oophorus* which is shed into the abdominal cavity and is picked up by the fimbriated end of the fallopian tube (also refer to page 818). The rupture of follicle is due to:

(i) ischaemic necrosis of overlying cells;
(ii) proteolytic enzyme action, and
(iii) increased fluid pressure within the Graafian follicle.

3. Multiple ovulations occur in 1-2% of all cycles.

4. At the time of ovulation antral fluid escapes and the follicle wall collapses, leading to haemorrhage into the theca interna and this forms *Corpus Haemorrhagicum* (Fig. 82.3). Minor bleeding from the follicles into the abdominal cavity may cause peritoneal irritation and transient lower abdominal pain (*Mittelschmerz*).
5. After ovulation capillaries from the theca interna invade the rapidly dividing granulosa layer and the clotted blood is replaced with yellowish, lipid rich luteal cells, forming the *Corpus Luteum* (*yellow body*) (Fig. 82.3). This enlarges for 8 or 9 days during which the luteal cells secrete oestrogen and progesterone; and
   (i) if fertilization has *not* occurred, the corpus luteum regresses and eventually becomes *Corpus Albicans*;
   (ii) if pregnancy occurs the corpus luteum continues to grow for several months under the influence of *vascular endothelial growth factor* (page 311) and begins to degenerate at approx. the 6th month. There are usually no more periods occur until after delivery.
6. *Time of Ovulation* → 13-15th day of menstr.
   (i) *Ovulation* is the release of the ovum (egg) from the ovary at fairly fixed intervals. It can be determined by:
      (a) recording the *basal body temperature* (*BBT*) *i.e.* recording the body temperature (oral or rectal), before getting out of bed in the morning. In the preovulatory phase the oral *BBT* is 36.3–36.8°C, which increases by 0.3 to 0.5°C one-two days after ovulation. It is probably due to the increase in progesterone secretion, since progesterone is thermogenic (page 800);
      (b) examination of the *cervical mucus* which shows *'fern' like pattern* (Fig. 82.4); the mucus is thinnest at the time of ovulation and its elasticity (*spinnbarkeit*) increases so that a drop of it can be stretched into a thread, 8-12 cm in length.

Note

Presence of functioning corpus luteum is also an indicator of ovulation; this can be determined by *Endometrial biopsy* which shows a secretory pattern (page 803).

   (ii) The timing of ovulation is of value when it is desired to promote or avoid conception. How? The time of ovulation is the time of maximum fertility (page 805), therefore, for pregnancy to occur, the coitus (intercourse) should take place within a day or two on either side of the ovulation (*fertile period*).

(A) Proliferative or oestrogen phase: Cervical mucus dries in an arborizing 'fern like' pattern and spinnbarkeit phenomenon

(B) Secretory or progesterone phase: Cervical mucus thick and cellular that does not form a 'fern' pattern

Fig. 82.4 Fern test *i.e.* pattern formed when cervical mucus smear is made on a slide, permitted to dry and examined under microscope (low power, X40).

Because neither an ovum (egg) after discharge from the ovary nor the sperm after being introduced into the vagina are functionally active after an interval of 24-48 hours. The rest of the menstrual cycle constitutes a more or less *Safe Period* *i.e.* pregnancy is unlikely to occur even if no other methods of birth control are employed.

Important Note

This method will, however, fail in its purpose if ovulation in any month is premature or delayed, and such variations occur frequently.

B. CHANGES IN THE UTERUS: THE MENSTRUAL CYCLE

Menstrual cycle is recurrent monthly discharge of blood from the female genital canal.

Menstrual is a Latin word which means 'mensis', a month *i.e.* a lunar month of 28 days. However, the cycle is by no means as regular as the word suggests and menstrual cycles of 25 to 35 days are regarded as normal cycles.

Note

Sexual cycle in mammalian species that do not menstruate is named *oestrous cycle*. It is named oestrous *i.e. heat period*, the only time during which the sexual interest of the female is aroused.

It is related to ovulation and the secretion of ovarian hormones (oestrogen and progesterone), which influence the hypothalamo-pituitary activity to bring about cyclical changes in the endometrium during the female reproductive period *i.e.* between the menarche and the menopause.

The human menstrual cycle is counted from the day on which menstrual bleeding begins. It occurs in *'4' phases:*

1. ***Menstrual Phase (days 0–4)***
   (i) If the ovum shed at ovulation is not fertilized, ***menstruation*** (bleeding from the female genital canal) occurs, which on an average lasts for about 3-5 days. During this phase progesterone and oestrogen secretions fall rapidly secondary to degeneration of the corpus luteum **(Fig. 82.5)**.
   (ii) There is bleeding and shedding of the superficial 2/3rd of the endometrium which occurs sequentially in different parts of the endometrium due to spasm of the spiral arteries for several hours (produced by release of prostaglandins (specially $PGF_{2\alpha}$) from lysosomes) leading to the endometrial necrosis **(Fig. 82.2)**. When the vessels relax, shedding of necrotic endometrium, leakage of blood and release of mucus make up the 'debris' lost during menstruation.

Note

The cervical mucosa does not undergo cycle desquamation.

   (iii) Menstrual bleeding is ***predominantly arterial,*** only 25% of the blood in the flow being venous in origin. Menstrual blood clots promptly in the uterus but is liquified by fibrinolysin in the vagina. This is why the menstrual blood does not contain clots unless the bleeding is excessive. The total blood lost in normal women varies from 10 to 80 mL (average: 40 mL). Menstrual blood contains prostaglandins.

Important Note

During menstruation, tremendous numbers of WBCs are released along with the necrotic material and blood. As a result the uterus is highly resistant to infection even though the endometrial surface is eroded.

2. ***Proliferative or Oestrogenal Phase or pre-ovulatory phase (days 0–14)***
   It represents the restoration of the epithelium from the preceding menstruation. The oestrogen secreted from the developing ovarian follicles under the influence of FSH is responsible for this phase **(Fig. 82.5)**.
   (i) Immediately after bleeding has ended the endometrium is less than 2 mm thick and consists of a ciliated columnar epithelium dipping down into a loose stroma to form simple tubular glands.
   (ii) ***From day 5 to day 14*** the endometrium thickens and proliferates *i.e.* proliferation occurs in the glands, blood vessels, stroma and superficial epithelium until the endometrium becomes approx. 4 mm thick. The uterine glands increase in length but do not secrete to any degree.
   (iii) ***Cervical secretion:*** increases in volume, becomes *alkaline and watery* (water content increases to 98% from 92%). It promotes the survival and transport of sperms. It dries in an arborizing 'fern' like pattern when a thin layer is spread on a slide **(Fig. 82.4)**.

3. ***Ovulatory phase (day 14)***
   This occurs due to a sudden rise in LH secretion secondary to rise in oestrogen concentration **(Fig. 82.5)**.
   (i) ***At about day 14*** ovulation occurs and at this time cervical mucus increases in volume and becomes more watery, thus there may be a small vaginal discharge of watery cervical fluid.
   (ii) The ***cervical mucus is thinnest*** at the time of ovulation and thus can easily be penetrated by spermatazoa than any other time.

4. ***Secretory or Progestational or Luteal Phase or post-ovulatory phase (day 14–28)***
   It represents the preparation of the uterus for the implantation of the fertilized ovum. This phase is influenced by progesterone secreted by the luteal cells of the corpus luteum **(Fig. 82.5)** and its *length* is remarkably constant at about *14 days*.
   (i) About 36 hours after ovulation, when the corpus luteum is well formed within the ovary, the endometrium undergoes further development to become 6 mm thick which ends at about 28 days with the onset of menstruation.
   (ii) **Endometrial changes** are the following:
      (a) Endometrial glands increase in length and diameter and become more tortuous and filled with mucus (saw toothed appearance);
      (b) The stroma cells proliferate and enlarge;
      (c) The spiral arteries become more coiled and dilated and the veins become filled with blood. Finally there is exudation of clear and blood stained fluid from the congested vessels.
   (iii) ***Cervical secretion becomes thick, tenacious and cellular*** forming a viscous plug which constitutes

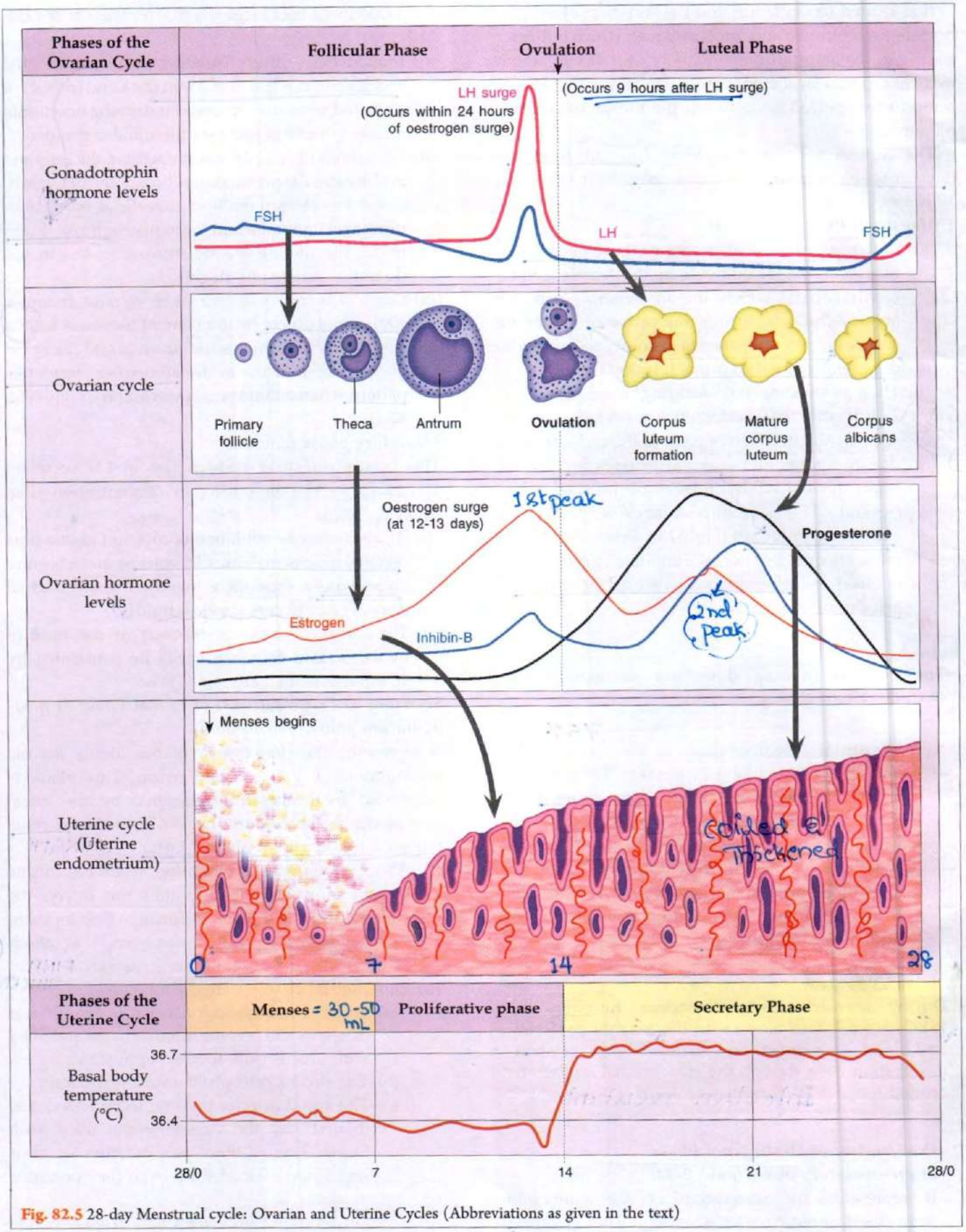


Fig. 82.5 28-day Menstrual cycle: Ovarian and Uterine Cycles (Abbreviations as given in the text)

a barrier against spermatozoa and infectious micro-organisms.

Important Notes

1. Sometimes ovulation fails to occur during the menstrual cycle, called *anovulatory cycle*. This is commonly seen for the first 1–1½ years after menarche and before the onset of menopause. When ovulation does not occur, no corpus luteum is formed and the *effect of progesterone on the endometrium is absent*; however, oestrogen continues to cause proliferative endometrium. The time it takes for bleeding to occur is variable and the flow is also variable, ranging from slight bleeding to profuse bleeding.
2. Cyclic changes normally occur *in the breasts* during the menstrual cycle under the influence of oestrogen and progesterone (Fig. 86.6, page 838). This results in pain, swelling and tenderness of the breasts during 10 days prior to menstruation. However, these changes are transient and disappear during menstruation.

C. CHANGES IN THE VAGINA

No clear cut cyclical vaginal changes can be identified.

(i) *During proliferative phase:* vaginal epithelium becomes cornified which can be identified in the vaginal smear.

(ii) *During secretory phase:* a thick mucus is secreted, vaginal epithelium proliferates and becomes infiltrated with leucocytes.

D. CHANGES IN THE GONADOTROPHIN SECRETION

(Hormonal Control of Female Sexual Cycle)

Main aim of gonadotrophins (FSH and LH) is to prepare the endometrium each month for a pregnancy. How?

1. In women with normal ovaries and anterior pituitary, the menstrual cycle depends on secretion of hypothalamic gonadotrophin releasing hormones – GnRH (page 779). *The hypothalamic control of the anterior pituitary is cyclic.* The hypothalamus by release of GnRH acts on the anterior pituitary which synthesizes and releases FSH and LH (Fig. 82.5). Therefore, serum concentrations of FSH and LH rise during menstruation.
2. **Rise in FSH concentration (Fig. 82.5):**
   (i) promotes development of ovarian follicles (page 801), and
   (ii) also increases secretion of oestradiol (oestrogen) from the theca interna cells (page 799). Increase in serum concentration of oestradiol leads to the 'proliferative' changes in endometrium (page 804).
3. Thus rise in FSH concentration increases the serum concentration of oestradiol to reach a 'peak' at 12-13 days, called *Oestrogen Surge.*
4. *Oestrogen Surge* has a *'positive' feedback effect i.e.* it increases the responsiveness of the pituitary to GnRH which induces within 24 hours a burst of LH secretion *(LH Surge)* (Figs. 82.5 and 82.6). This causes a sudden rise in LH serum concentration at the mid-cycle. *Ovulation occurs about 9 hours after the 'LH surge'. Therefore, LH is also called* ***Ovulating Hormone.*** However, the stimulus to ovulation may depend on both LH and FSH or on the ratio of LH to FSH (LH acts as synergist to FSH). Therefore, at the same time when LH peak occurs, FSH serum concentration also suddenly rises to a peak *(FSH Surge)*, though the rise is less than LH peak (Fig. 82.5). The timing of the LH-FSH peak is much more variable and it may occur at any time between day 11 and day 23 of the menstrual cycle.
   There occurs a drop in oestradiol secretion at the time of ovulation.
5. After ovulation, serum LH and FSH concentrations fall to very low values for the rest of the cycle, but as the corpus luteum is formed, serum progesterone concentration rises markedly and serum oestradiol also rises along with *inhibin-B* during the 2nd half of the cycle (Fig. 82.5). The elevated progesterone, oestrogen and inhibin-B levels inhibit FSH and LH secretions via *'negative' feedback effect* on the hypothalamus (Fig. 82.6).

Note

In females, *inhibin-B* is derived from the granulosa cells of the ovarian follicles.

6. Progesterone, acting on the endometrium primed by oestrogen produces the 'secretory' phase of the endometrial development (Fig. 82.5) which is progestational in character *i.e.* the endometrium is prepared for implantation of the *blastocyst* formed from the fertilized ovum. If pregnancy occurs, corpus luteum does not disappear but persists and continues to secrete progesterone and oestrogen, however, its function begins to decline after 8 weeks of pregnancy. If it fails to secrete these hormones during the early months of pregnancy, spontaneous abortion occurs.
7. If no fertilization takes place, corpus luteum regresses (***Luteolysis***), as a result progesterone and oestrogen secretions fall sharply, the spiral arteries go into spasm (by the action of $PGF_2\alpha$) and when they subsequently relax menstruation occurs (***withdrawl bleeding***).
   Once luteolysis begins, the oestrogen and progesterone levels fall and the secretion of FSH and LH increases and new cycle begins.

Chapter

83

Physiology of Coitus

I. Changes in males

II. Changes in females

III. Orgasm

IV. Fate of sperms in female genital tract

Coitus means the sexual intercourse. The changes occurring in coitus are described below.

CHANGES IN MALES

The introduction of sperms into the vagina involves two processes:

A. Erection of the penis, and

B. Ejaculation (emission) of the seminal fluid.

Both processes are fundamentally reflex in character occurring at spinal cord level.

A. ERECTION OF PENIS (Fig. 83.1)

1. *Afferent impulses* – originate from stimulation of the glans penis or the skin around the genitals, anterior abdominal wall or anterior and inner surface of the thighs. The response is long circuited through the brain and involves the activity of the highest cortical levels (psychological influences, specially of emotional states) which can modify the reaction either by way of reinforcement or inhibition (page 1024).
2. *Efferent pathway*

   (i) Erection is brought about by the *nervi erigentes*

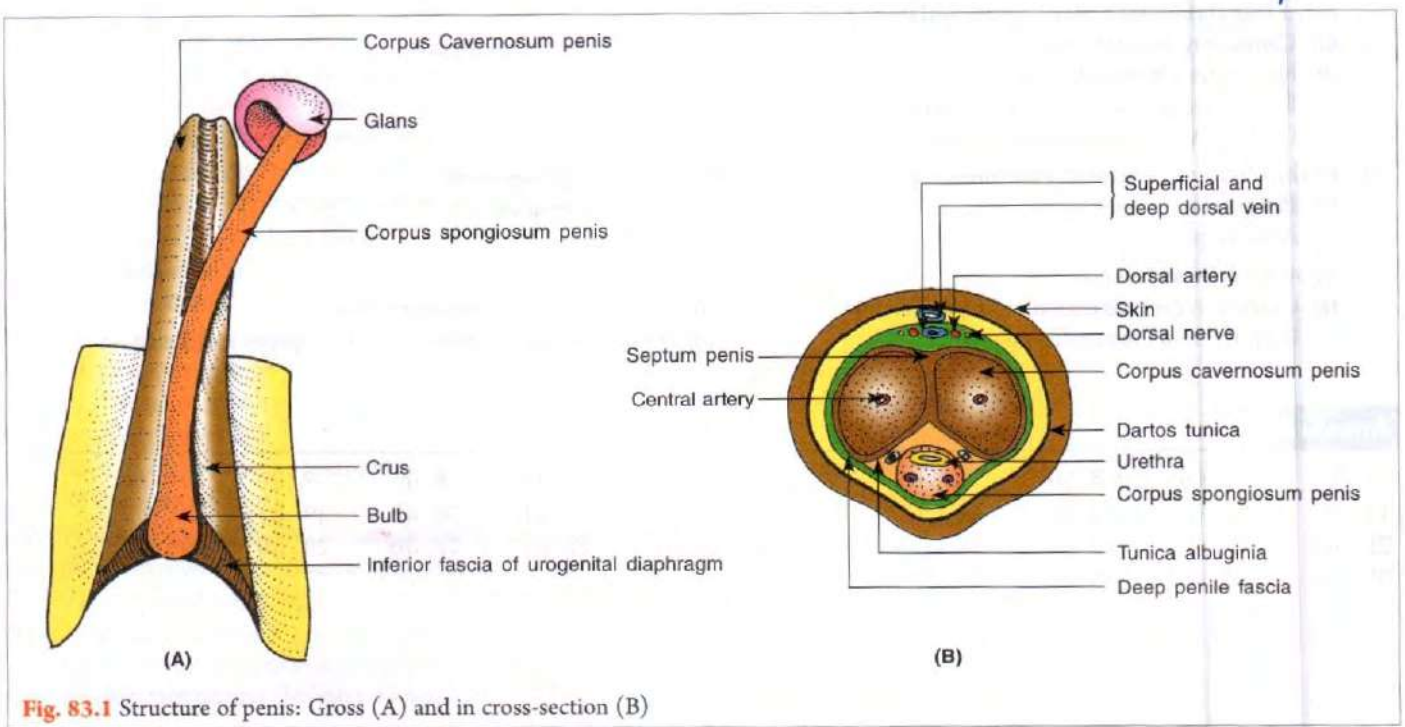


Fig. 83.1 Structure of penis: Gross (A) and in cross-section (B)

(*sacral parasympathetic vasodilator nerves*) which supply sexual erectile tissue. These fibers probably release A-ch and the vasodilator VIP as co-transmitters to cause:

(a) relaxation of the muscle coat of the arterioles of penis, and

(b) relaxation of spongy tissue of the corpora cavernosa and corpora spongiosa.

(a) and (b) lead to compression of dorsal vein of the penis, blocking the blood outflow and adding to the turgor (swelling) of the organ. Therefore, the penis, which in the resting state is small, flabby and covered with wrinkled skin, becomes thickened, elongated and rigid. The angle which the erect penis makes with the trunk follows closely that of the vagina. Its length is such that, when introduced into the vagina, the semen is deposited high up in the posterior part of the vagina.

(ii) Nervi erigentes also contain *non-adrenergic non-cholinergic fibres*. These fibres are rich in *NO synthase* that catalyses the formation of *nitric oxide (NO)*, a potent vasodilator (page 322). *Sildenafil (Viagra)* by inhibiting the breakdown of cGMP increases the production of NO and is widely used in the treatment of impotence.

(iii) Sympathetic vasoconstrictor impulses to the arterioles of penis terminate the erection.

B. EJACULATION (EMISSION) OF THE SEMINAL FLUID

1. *Afferent pathway*

(i) Friction between the glans penis and the vaginal mucosa stimulate touch receptors in the glans penis and impulses reach the spinal cord via internal pudendal nerves.

(ii) This gets reinforced by:

(a) afferent streams, and

(b) psychological influences.

2. *Efferent pathway*

(i) Afferent impulses integrated in the upper lumbar segments of the spinal cord causes a reflex discharge along the sympathetic (via hypogastric) nerves which are motor to seminal pathway. This results in:

(a) Contraction of muscle coats of epididymis and ductus deferens, seminal vesicles and prostate. Therefore, the seminal fluid (page 788) is discharged into the posterior urethra between the internal and external sphincters of urinary bladder, called *emission* (**Fig. 62.1**, page 574).

(b) Contraction of internal vesical sphincter prevents reflux of semen into the urinary bladder.

(c) Contraction of the sphincter vesicae and the associated inhibition of detrusor vesicae prevents a simultaneous discharge of urine.

(ii) The semen is thence *ejected* i.e. propelled out by the rhythmic contractions of the bulbo-cavernosus and ischio-cavernosus muscles due to increased somatic nerve activity in upper sacral and lowest lumbar segments of spinal cord; and motor pathways traversing the 1st to 3rd sacral roots and the internal pudendal nerves leading to rhythmic contraction of muscles causing semen ejaculation out of urethra.

(iii) Increased parasympathetic activity further increases the prostatic fluid secretion.

Applied Aspect

1. Stimulation of the hypogastric (sympathetic) nerves produces ejaculation of semen in man.
2. After sectioning of sympathetic nerve below L_2 or blocking it by drugs such as guanethidine and methyl dopa or sectioning of presacral nerve, penile erection and sensation remain normal but ejaculation can no longer occur.
3. **Ganglion blocking drug** (hexamethonium) which inhibits both sympathetic and parasympathetic nerve pathways, reduces both ejaculation and erection.
4. Section of all the sacral nerves below S_1 (sacral parasympathetic outflow section), abolishes erection and produces relative anaesthesia of the penis.

CHANGES IN FEMALES

A satisfactory intercourse is associated with appropriate psychological and reflex reactions in the female, consisting of:

1. Engorgement of vulva.
2. Relaxation of adductor muscles of the thighs and of the vaginal orifice.
3. Secretion of lubricating mucus by the vulvular glands because of release of VIP from vaginal nerves.
4. Erection of clitoris; afferent impulses (tactile) from the stimulated clitoris and labia minora may heighten the state of physical excitement. These stimuli are reinforced by tactile stimuli from the breast and by visual, auditory and olfactory stimuli and help to achieve a complete *orgasm*. This is accompanied by autonomically mediated rhythmic contraction of the vaginal wall.

As a result of all these changes, vagina becomes distensible, its lining is lubricated and it becomes easily penetrable by the penis.

Chapter 84

Contraceptive Measures

I. Changes in males

II. Changes in females

III. Orgasm

IV. Fate of sperms in female genital tract

Spacing & Terminal methods

Contraceptive measures mean methods used to prevent conception (pregnancy). They include all temporary and permanent measures to prevent pregnancy resulting from coitus (sexual intercourse). The contraceptive measures may be broadly divided into two groups:

I. *Measures in males*, and
II. *Measures in females.*

CONTRACEPTIVE MEASURES IN MALES

A. Conventional methods

It means those methods that require action at the time of sexual intercourse, such as use of *condom* (trade name ***Nirodh***, a Sanskrit word, meaning prevention). The aim of these methods is to prevent live sperm from meeting the ovum. They are effective only if used consistently and carefully.

Advantages

1. Easy to use;
2. Free from side-effects, and
3. Provide protection against sexually transmitted diseases (STD).

Generally NOT used.

Disadv: Tearing of condoms.

B. **Coitus interruptus** *i.e.* withdrawal of penis before ejaculation.

Disadvantage: Slightest mistake in timing the withdrawal or even a drop of semen is sufficient to cause pregnancy.

C. **Vasectomy** *i.e.* bilateral ligation of the vas deferens (page 787). (15).

Advantage: It is relatively safe and convenient method. ASTERILE ⊕ POTENT

Disadvantage: 50% of vasectomized patients develop antibodies against sperms, therefore, in case of those patients wishing to restore fertility at a later stage, success rate after restoration of patency of the vas is only about 50%.

Anti-sperm antibody.

D. **Drugs** which inhibit spermatogenesis, such as:

1. *Gossypol* (page 786). → Spermiogenesis ⊗ inhibitor (By LDH inhibition)
2. *Testosterone.* Administration of testosterone in high doses decreases the sperm count. Therefore, testosterone therapy has been suggested as a measure of male contraception. However, in such a high dose, it causes sodium and water retention.

Disadvantage: These drugs are too toxic to be used clinically.

Note

The use of inhibin B (page 790) as a potential male contraceptive measure is under way.

CONTRACEPTIVE MEASURES IN FEMALES

A. Conventional methods

1. Use of *diaphragm* on the cervix. (Female condom)

Disadvantages: NOT recommended by NFWP

(i) trained persons will be needed to demonstrate the technique of use;
(ii) it can cause local infection if left in the vagina.

2. Use of *douches, spermicidal jellies and creams.* For example, ***Today*** (trade name) is a small polyurethane foam sponge saturated with spermicide, monoxynol-9.

Disadvantage: Besides producing messiness it produces burning sensation and irritation locally.

3. *Rhythm method or calendar method.* This method involves confinement of sexual intercourse to *safe period* only (page 802). The method is not practical

→ Used along with Condoms.

and has not been satisfactory as a means of preventing pregnancy.

B. **Tubectomy** *i.e.* bilateral ligation of the fallopian tubes. This method is relatively safe, convenient and permanent means of preventing pregnancy.

C. **Intrauterine Device**

Implantation of a foreign body (a piece of metal or plastic) into the uterine cavity for contraceptive purposes is called *intrauterine device (IUD).*

Mechanism of action

1. It speeds the passage of the fertilized ovum through the uterus and prevents its implantation in the endometrium.
2. It disturbs the orderly sequential changes taking place in the endometrium during the menstrual cycle.

Types – IUDs are of three types:

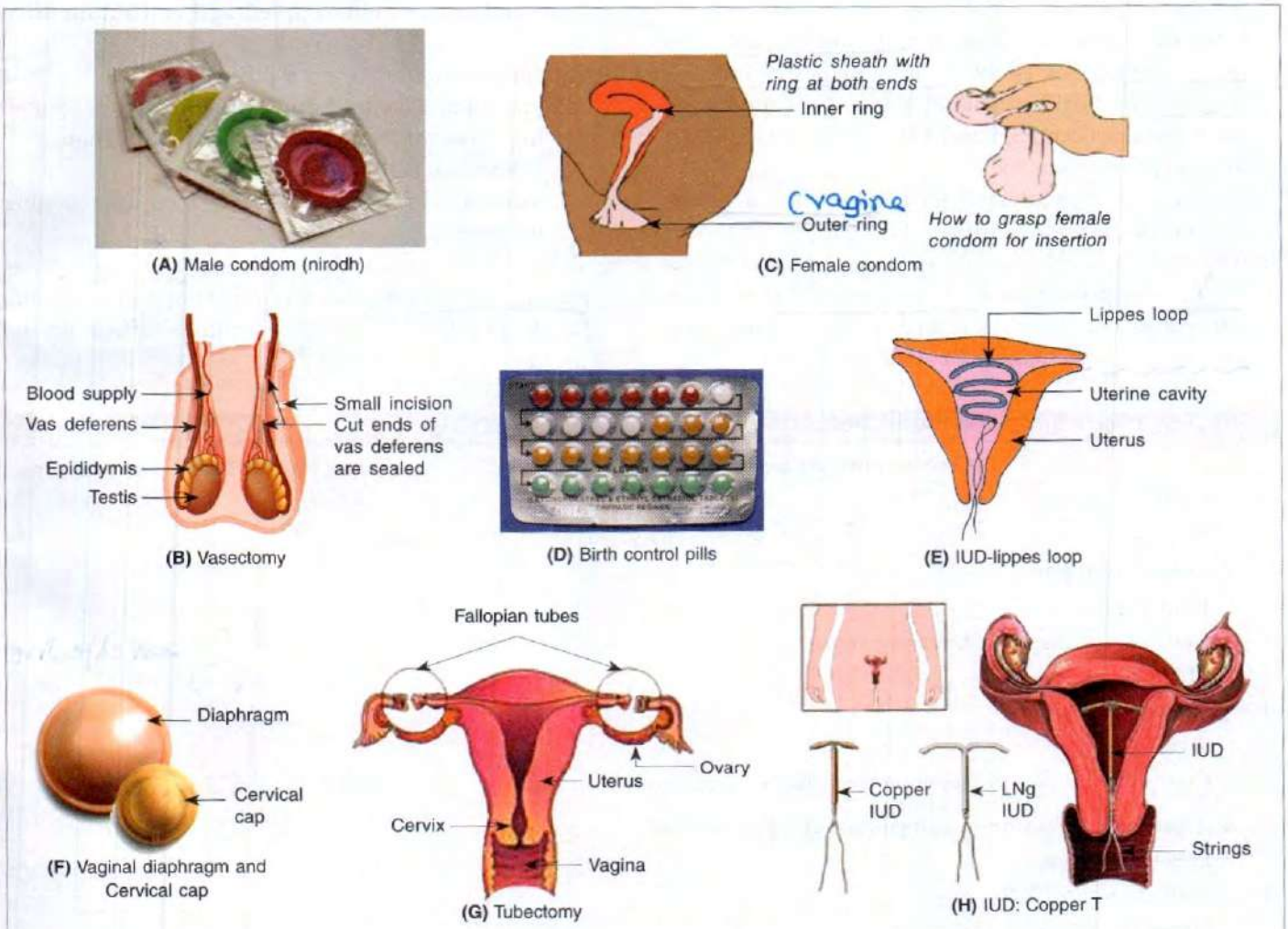
1. ***Non-medicated IUD*** *e.g.* Lippes loop. It is double S-shaped, made of polyethylene, a plastic which is non-toxic, non-tissue reactive. It has an attached thread or a tail made of fine nylon, which projects into the vagina after insertion.
2. ***Copper IUD*** *e.g.* Copper-T. It acts by altering the composition of cervical mucus and also decreases sperm motility.
3. ***Hormone releasing IUD.*** It is filled with progesterone and acts by increasing the viscosity of cervical mucus. It also makes the endometrium unfavourable for implantation of fertilized ovum.

Important Note

IUDs have to be replaced periodically at intervals of 2-4 years, otherwise they tend to lose their efficacy and may cause intrauterine infection.

D. **Contraceptive pills**

If correctly used contraceptive pills are 100% successful in preventing fertilization. The commonly employed contraceptive pills are:



(A) Male condom (nirodh)
(C) Female condom
(B) Vasectomy
(D) Birth control pills
(E) IUD-lippes loop
(F) Vaginal diaphragm and Cervical cap
(G) Tubectomy
(H) IUD: Copper T

Fig. 84.1 Various contraceptive measures: in males (A, B) and in females (C to H)

1. ***Classical pill or combined pill***
It contains orally active progesterone (nor-ethioesterone, norethynodrel, chromadinone etc.), combined with small amounts of oestrogens (ethinyloestradiol). The pill is given for 21 consecutive days beginning on the 5th day of the menstrual cycle (pill is given from the 5th to 25th day of the menstrual cycle).
When the bleeding occurs this is considered as the first day of the next cycle. The bleeding is from an incompletely formed endometrium caused by the withdrawal of exogenous hormones. Therefore, it is called *withdrawl bleeding* rather than menstruation.
Mode of action
(i) By an action or hypothalamus which inhibits the secretion of LH. This, in turn, *inhibits ovulation* (page 799).
(ii) It makes the cervical mucus thick which renders the cervical mucus hostile (unfriendly) to sperm penetration.
(iii) It induces endometrial changes which prevent implantation of the blastocyst.

2. ***Sequential pill***
It involves administration of high dose of oestrogen for 15 days followed by 5 days of oestrogen plus progesterone. This inhibits ovulation by suppressing the release of both FSH and LH (role of FSH and LH in conception, page 805).
Disadvantage: This increases the incidence of carcinoma (cancer) of the endometrium.

3. ***Administration of large doses of oestrogen*** decrease FSH level with multiple irregular bursts of LH secretion rather than a single mid-cycle peak thereby producing *anovulatory cycles* (page 805).

4. ***Mini pill or micropill***
It involves the administration of 'low dose of progesterone' through whole of the menstrual cycle. This prevents fertility without inhibiting ovulation. It may act on:
(i) cervical mucus, or
(ii) endometrium, or
(iii) decrease the motility of fallopian tubes.

Important Note NORPLANT:
Now-a-days implants of progesterone (progestins) are inserted under the skin which can prevent pregnancy for 5 years.

5. ***Post-coital pill or 'Morning after' pill***
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. It is advocated as an emergency method; for example, after unprotected intercourse, rape or contraceptive failure.
Disadvantages of contraceptive pills
Long use of oral contraceptives significantly produces:
1. high risks of thrombo-embolic phenomenon
2. precipitate diabetes mellitus
3. increases systemic arterial BP by their salt retaining properties.

6. ***Progesterone antagonist,*** such as 'Mifepristone', is helpful in producing abortion following the conception. It acts by inhibiting the progestational effects on the uterus.

Table 84.1: Commonly used contraceptive measures and their relative effectiveness

Contraceptive measures	Failure rate per 100 women per year
A. *Conventional methods*	
1. Condom	2-3
2. Coitus interruptus	6.7
3. Diaphragm	2
4. Douches, spermicidal jellies and creams	12
5. Rhythm	15.5
B. *Vasectomy/tubectomy*	0.05–0.1
C. *Oral contraceptives*	
1. Classical/combined pill (progesterone plus oestrogen in small amounts	0.25
2. Sequential pill (oestrogen in high dose plus progesterone)	0.32
3. Progesterone only	1.2
D. *Intrauterine Device (IUD)*	
1. Lippes loop	1.3
2. Copper T	1.5

Study Questions

1. **Give physiological basis of:**
   (i) Contraception
   (ii) Withdrawal bleeding
   (iii) Classical pill
   (iv) 'Morning after' pill, post-coital pill, mini pill and sequential pill.
2. **How safe is the safe period?**
3. **Write shorts notes on:**
   (i) Drugs which inhibit spermatogenesis
   (ii) Coitus interruptus
   (iii) IUD
   (iv) Progesterone antagonist
   (v) Rhythm method for contraception
   (vi) Contraceptive pills.
4. **Give conventional methods of contraception in either sex.**
5. **How far are recanalization procedures successful in an individual following a vasectomy or a tubectomy?**
6. **Why does IUD need to be replaced at periodic intervals?**
7. **Which contraceptive measure is almost completely successful and which one has the maximum failure rate? Justify.**

MCQs

1. **Best contraceptive measure in males is:**
   (a) Conventional methods (b) Coitus interruptus (c) Vasectomy (d) Drug gossypol
2. **Mechanism of action of intrauterine contraceptive device (IUCD) is based on:**
   (a) Prevents its implantation in endometrium
   (b) It inhibits ovulation
   (c) It blocks the entry of sperms in female genital tract
   (d) Promotes anovulatory cycles
3. **The mechanism of action of contraceptive pills is based on:**
   (a) By inhibiting ovulation
   (b) By increasing the motility of fallopian tubes
   (c) By decreasing motility of sperms
   (d) It blocks the entry of sperm into fallopian tubes
4. **Sequential pill involves administration of:**
   (a) High dose of oestrogen for 15 days, followed by 5 days of oestrogen and progesterone
   (b) Large doses of oestrogen
   (c) Double dose of combined pill followed by another two pills 12 hours later
   (d) Low dose of progesterone throughout whole of the menstrual cycle
5. **Testosterone as a measure of male contraceptive agent:**
   (a) In high doses decreases the sperm count
   (b) Relatively safe and convenient
   (c) Permanent means of preventing pregnancy
   (d) All of the above
6. **Conventional methods as contraceptive measures in females have low acceptability because:**
   (a) Trained persons are needed to demonstrate the technique
   (b) Risk of local infection
   (c) Produces burning sensation and irritation locally
   (d) All of the above
7. **Classical contraceptive pill, *not true* is:**
   (a) Contains orally active progesterone with small amounts of oestrogen
   (b) Given for 21 consecutive days beginning on 5th day of menstrual cycle
   (c) Bleeding is from an incompletely formed endometrium
   (d) Prevents fertility without inhibiting ovulation
8. **Implants of progesterone under the skin acts by:**
   (a) Preventing fertility without inhibiting ovulation
   (b) Decreasing motility of fallopian tubes
   (c) Make the cervical mucus thick and tenacious
   (d) All of the above

Answers

1. (c) 2. (a) 3. (a) 4. (a) 5. (a) 6. (d) 7. (d) 8. (d)

Chapter

85

Physiology of Pregnancy

I. Fertilization and implantation of the ovum

II. Endocrinology of pregnancy: placental hormones; pregnancy diagnostic tests

III. Maternal physiology in pregnancy

IV. Parturition

The physiology of pregnancy is important because it is concerned with:
(1) the nutrition to the growing foetus;
(2) the maternal changes needed to provide adequate nutrition to growing foetus; and
(3) the maternal changes required for child birth and lactation.

FERTILIZATION AND IMPLANTATION OF THE OVUM

A. EVENTS LEADING TO THE FERTILIZATION OF THE OVUM

1. *Transport of ovum from the ovary to the ampulla*

At the time of ovulation two changes take place:

(i) the fimbriae of fallopian tube encircle and rub the surface of the ovary as a result of contraction of its smooth muscle. The activity of this smooth muscle is:
  (a) increased by oestrogen; and
  (b) decreased by progesterone;

(ii) the ciliated cells in the mucosa of the infundibulum of the fallopian tube are maximally developed and most active, under the influence of oestradiol (oestrogen).

(i) and (ii) convey the ovum and its surrounding cumulus cells rapidly into the ampulla. The ovum is then held up at the *ampullary-isthmic* junction for 2 to 3 days. During this time:

(a) **if no fertilization occurs**, the ovum degenerates and dies; or

(b) **if fertilization takes place** (which usually occurs in the mid portion of the fallopian tube), cell divisions occur until the blastocyst is transported into the uterus. This is brought about by relaxation of the sympathetically innervated muscle of the isthmus assisted by ciliary action towards the uterus. The muscular relaxation is further favoured by progesterone and by PGE_1.

2. *Transport of spermatozoa (sperms) from the vagina to the ampulla*

(i) Cervical mucus is most easily penetrated by most of the *motile* spermatozoa at the time of ovulation. Spermatozoa may survive in the cervical glands for some time without undergoing phagocytosis which quickly destroys them in the uterus. The spermatozoa are then released from this reservoir and only small number reach the fallopian tube to produce fertilization.

(ii) The transport of spermatozoa from the cervix to the fallopian tube *takes 30-60 minutes*, and occurs due to:
  (a) *sperm motility* – sperm moves @ approx. 3 mm/min through the female genital tract,
  (b) the appropriate ciliary activities, and
  (c) muscular movements in the uterus.

3. *Environment for survival of ova and spermatozoa*

(i) The mucosa of the fallopian tube also contains secretory cells, which at the time of ovulation contain granules of glycogen. Breakdown of glycogen to glucose helps oviductal fluid to provide an environment in which ova and spermatozoa can survive for short periods.

(ii) The fluid also contains substances needed for cell division upto the stage of blastocyst. The substances are: plasma proteins, specific muco-proteins (from the secretory cells), lactate and pyruvate which:
  (a) provide energy

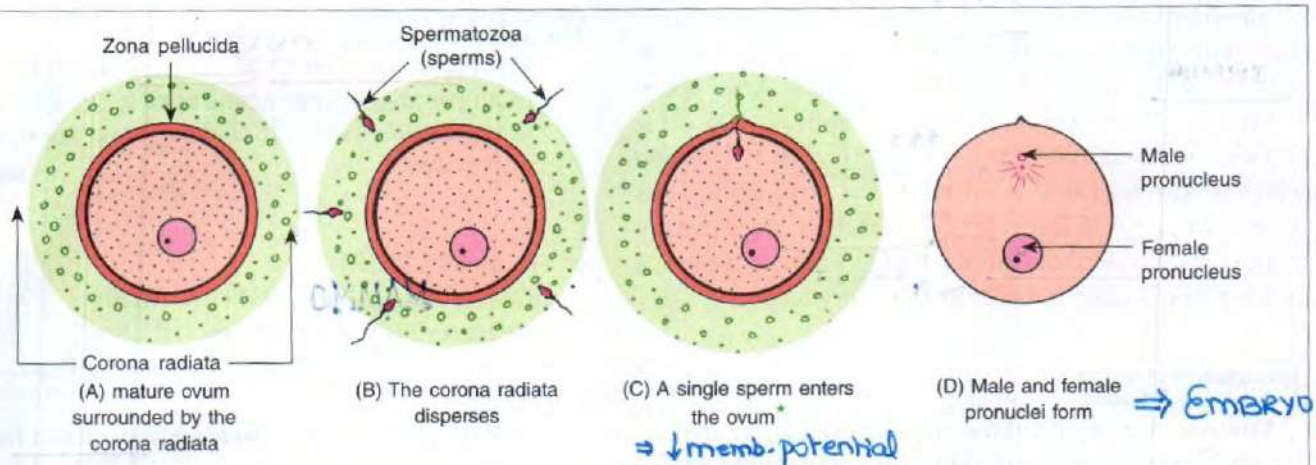


Fig. 85.1 Events leading to the fertilization of ovum
(*This is associated with completion of second meiotic division of the oocyte, page 797.)

(b) provide O_2 and HCO_3^- (which increases respiration)
(c) provide carbon for structural purposes, and
(d) helps to keep pH in the range of 7.5 to 7.8.

4. ***Fusion of ovum and sperm*** **(Fig. 85.1)**

(i) Many sperms attach to the *Zona pellucida*, a membranous structure that surrounds the ovum. The sperms then bind to the zona pellucida by a reaction between *sperm receptors* in the zona and a specific egg-binding protein (*Fertilin*) on the sperm plasma membrane. Binding is followed by the ***acrosomal reaction*** (page 812) which appears to be triggered by the sperm receptor. This reaction is the breakdown of the acrosome, a lysosome like organelle on the head of the sperm, with the release of various enzymes including the trypsin like protease ***acrosin***. Acrosin facilitates the penetration of the sperm through the zona pellucida.

(ii) When one sperm reaches the membrane of the ovum, it fuses to it, setting off a reduction in the membrane potential of the ovum that prevents *polyspermy i.e.* the fertilization of the ovum by more than one sperm. This transient potential change is followed by a structural change in the zona pellucida that provides protection against polyspermy on a more long-term basis. Fusion of the cell membranes of the sperm and the ovum activates the cell, and embryonic development begins.

B. IMPLANTATION OF FERTILIZED OVUM

Cell division begins at once in the fertilized ovum. The developing embryo, now called a *Blastocyst* (8 or 16 cell stage) at first floats freely in the fallopian tube and then enters the uterus **(Fig. 85.2)**. Once in contact with the endometrium, the blastocyst becomes surrounded

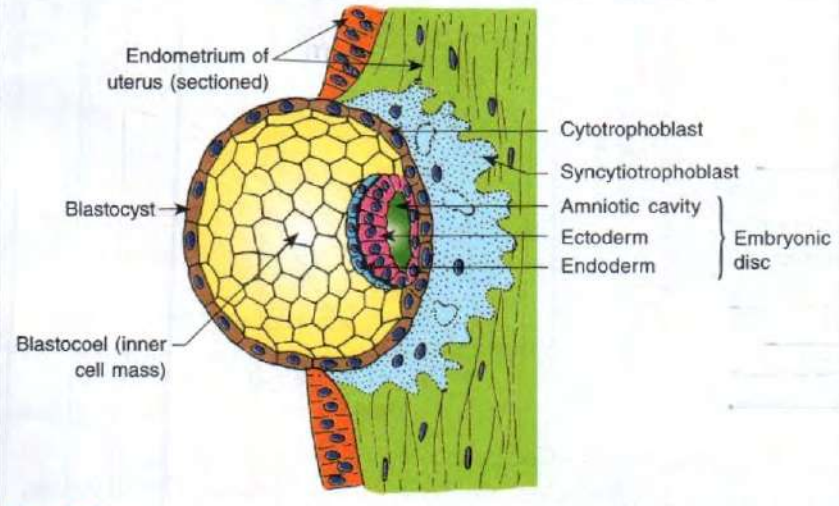


Fig. 85.2 Internal view of the blastocyst at implantation about 7 days after fertilization

Important Note

In some women who have been rendered infertile by fallopian tube obstruction, fertilization has been produced by adding spermatozoa to an isolated ovum *in vitro*; and after a few days the blastocyst so formed has been inserted into the progestational uterus (uterus primed with progesterone). The subsequent growth in uterus has led to the birth of apparently normal *test tube babies*. However, it has only 5–10% chance of producing a live birth.

by an outer layer of *Syncytiotrophoblast*, a multinucleated mass with no clear cell boundaries, and an inner layer of *Cytotrophoblast* made up of individual cells. After about 7 days the blastocyst, consisting of approx. 200 cells, becomes attached to the progestational endometrium into which it burrows (***implantation***) by the lytic action of its syncytiotrophoblast layer. The implantation site is usually on the dorsal wall of the uterus. A ***placenta*** then develops and the trophoblast remains associated with it.

Important Note

Maternal recognition of the onset of pregnancy arises from the secretion of chorionic gonadotrophin which causes the corpus luteum to persist.

ENDOCRINOLOGY OF PREGNANCY (PLACENTAL HORMONES)

The hormones synthesized and secreted by the placenta are:

(1) Human chorionic gonadotrophin (HCG),
(2) Human chorionic somatomammotrophin (HCS),
(3) Human chorionic thyrotrophin (HCT),
(4) Oestrogen and progesterone,
(5) Relaxin; and
(6) GnRH and inhibin.

1. HUMAN CHORIONIC GONADOTROPHIN (HCG)

(i) It is a glycoprotein formed by syncytiotrophoblastic cells of the placenta immediately after implantation of the fertilized ovum.

(ii) It is made up of α and β subunits. HCG-α is very similar to the α-subunit of LH, FSH and TSH. MW: HCG-α, 18,000; HCG-β, 28000.

(iii) HCG is primarily luteinizing and luteotrophic (*i.e.* it acts like LH, page 779) and has little FSH activity. It helps to maintain the corpus luteum which continues to secrete oestrogen and progesterone. As a result ovulation and menstruation are prevented. It can be ***detected in serum from about 10 days after ovulation*** (assuming fertilization has occurred), and in the urine as early as 14 days after conception. Then its concentration in serum and urine rises rapidly to reach a peak at 50-60 days after the LMP (1st day of last menstrual period). After this its concentration falls to a very lower level which is maintained till just before labour when it falls to "zero" (Fig. 85.3).

(iv) It is not absolutely specific for pregnancy. Small amounts are secreted by a variety of gastrointestinal and other tumours in both sexes.

Important Notes

1. The presence of HCG in the urine forms the basis of all pregnancy diagnostic tests (page 822).
2. If foetus dies early HCG disappears from serum and urine.

2. HUMAN CHORIONIC SOMATOMAMMOTROPHIN (HCS)
or Human Placental Lactogen (HPL)
or Human Chorionic Growth Hormone Prolactin (HCGP)

(i) It is synthesized by placental syncytiotrophoblastic cells.

(ii) It resembles GH in amino acids content and MW (page 661), therefore, it is lactogenic and has a small amount of growth stimulating activity.

(iii) Its concentration in serum rises steadily from 70 days to term. (Fig. 85.3)

(iv) *Functions:*

(a) It is *maternal GH of pregnancy* to bring about the nitrogen, potassium and calcium retention and decreased glucose utilization.

(b) It promotes the growth and development of the breasts during pregnancy. If foetal death occurs late in pregnancy HCS secretion falls.

(v) The amount of HCS secreted is directly proportional to the size of the placenta; therefore, low HCS levels are a sign of ***placental insufficiency***.

3. HUMAN CHORIONIC THYROTROPHIN (HCT)

(i) It is a placental substance with properties like those of TSH (page 684).

(ii) Its physiological function is not known.

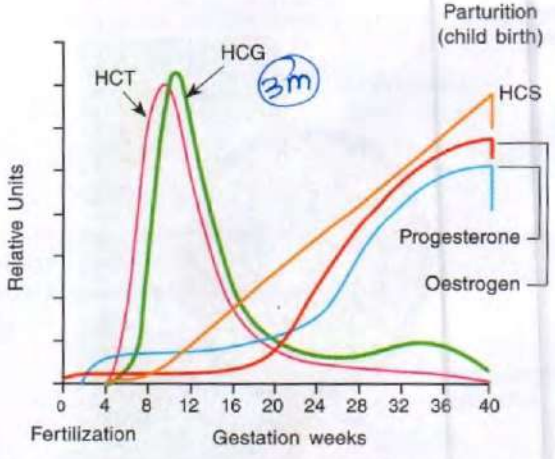


Fig. 85.3 Changes in serum level of placental hormones [HCG, HCS and HCT: Human Chorionic Gonadotrophin, Somatomammotrophin and Thyrotrophin respectively]

(iii) Its concentration in serum follows a curve like that for HCG. (Fig. 85.3)

4. OESTROGEN AND PROGESTERONE

The foetus and the placenta interact as a *functional unit*, called *Foeto-placental unit* in the formation of oestrogen and progesterone (Fig. 85.4).

OESTROGEN

(i) During pregnancy its secretion occurs at first from the corpus luteum (page 801) and later from the placenta. Oestrogen and oestradiol are synthesized in the placenta from dehydroepiandrosterone (DHEA) and 16-hydroxy DHEA respectively. Both of which enters the placenta from maternal and foetal circulations (Fig. 85.4).

Note

Oestradiol, the predominant oestrogen of pregnancy, originates from the foetal adrenal cortex which forms DHEA. Therefore, the urinary oestradiol excretion of the mother can be monitored as an index of the state of the foetus development.

(ii) Urine and plasma oestrogen concentrations rise steadily to reach a peak at the time of labour.

(iii) Urinary oestrogen consists mostly of oestriol with lesser amounts of oestrone and oestradiol, mainly as glucuronides (page 830). After delivery oestrogen excretion rapidly decreases.

PROGESTERONE

(i) Although the placenta cannot synthesize cholesterol from acetate both mother and foetus can do so and the cholesterol so formed diffuses into the placenta which possesses the enzymes needed to convert cholesterol to progesterone via pregnenolone.

Note

Some of the pregnenolone is also synthesized in the foetal liver.

The progesterone can diffuse back into:

(a) maternal circulation and exerts its physiological action, and

(b) foetal circulation for the formation of DHEA in the foetal adrenal gland (Fig. 85.4).

(ii) Its secretion rises in parallel with that of oestrogen. However, during last few weeks of pregnancy the plasma concentration of progesterone falls.

Important Note

Both oestrogen and progesterone are required for the initiation and maintenance of pregnancy. These hormones are produced mainly by the corpus luteum during the first 6 to 8 weeks of pregnancy. After this time ovariectomy does not interrupt pregnancy as the *Foeto-placental unit* takes over the formation of oestrogen and progesterone.

5. RELAXIN

It helps to maintain pregnancy by inhibiting uterine contraction (Also see to page 800).

6. GnRH AND INHIBIN

GnRH stimulates and *inhibin* inhibits HCG secretion, thus they act in a paracrine fashion to regulate HCG secretion.

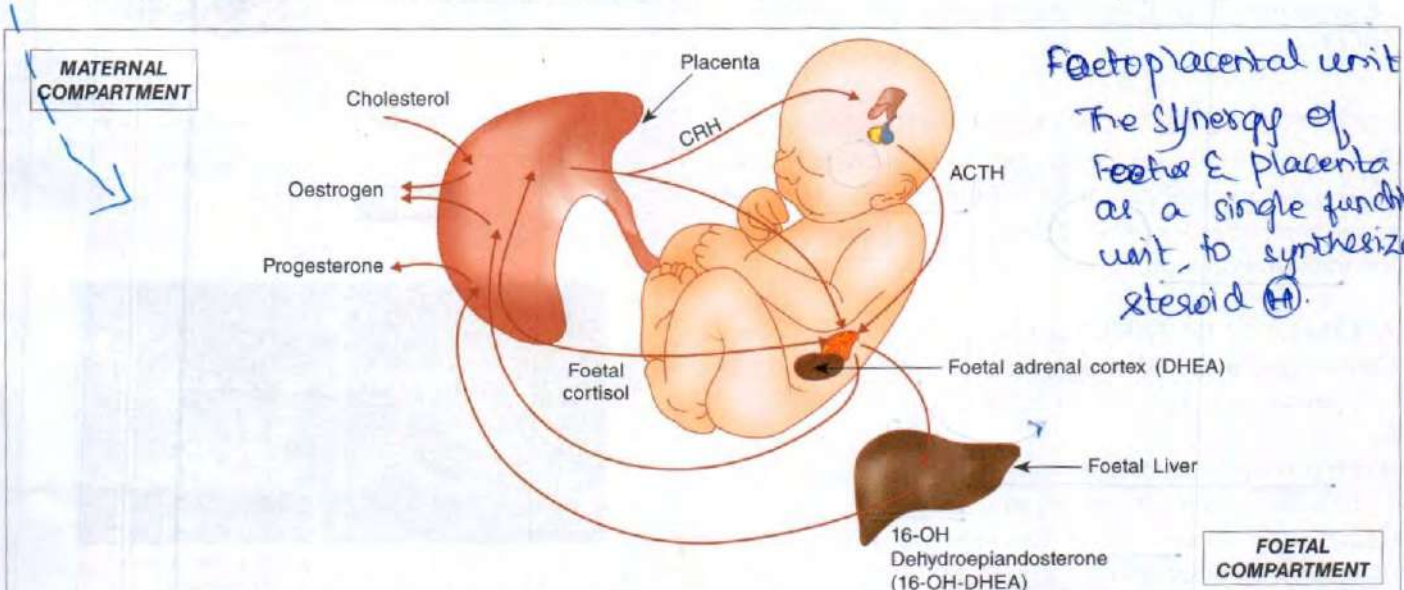


Fig. 85.4 Foeto-placental unit (*i.e.* barrier between the mother, placenta and foetus) showing formation of oestrogen and progesterone [CRH: Corticotrophin releasing hormone; ACTH: Adreno cortico trophic hormone]

* BIOLOGICAL TESTS:
• Friedman test
• Galli Mainini test

PREGNANCY DIAGNOSTIC TESTS

These are all based on the presence of human chorionic gonadotrophin *(HCG) in urine, which can be detected as early as 14 days after conception* with test accuracy of 99%. The sensitivity of these tests varies, but usually a HCG concentration of about 2500 IU/L of urine is required to obtain a positive result. This will normally occur about 10-12 days after the first missed period.

IMMUNOLOGICAL TESTS (GRAVIDEX test)

Principle: Antibodies to HCG can easily be induced in rabbits (by injecting HCG) and the antiserum so produced can be used to detect the presence of HCG in urine or serum from pregnant women by means of complement fixation, haemagglutination or precipitin tests.

Procedure: The presence of the HCG is demonstrated by an immunochemical reaction between HCG absorbed on to *latex particles* and HCG antiserum. The steps involved in the reaction are **(Fig. 85.5)**:

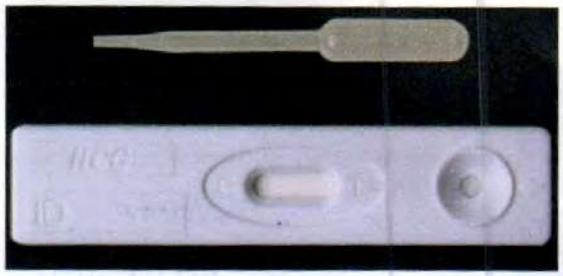
(1) A drop of urine of non-pregnant women (*contains no HCG*) + A drop of HCG antiserum (*contains HCG antibodies*) → No neutralization of HCG antiserum, therefore, it will produce *agglutination* when mixed with HCG-coated latex (which contains HCG).

(2) A drop of urine of pregnant women (*contains HCG*) + A drop of HCG antiserum → Neutralization of HCG antiserum, therefore, it will produce *no agglutination* when mixed with HCG-coated latex.

In this test the reaction is carried out on a glass slide with a black background.

Important Note

If the urinary HCG is low, a *false negative* result will occur; also *false positive* results can occur either at the menopause or ovulation due to increased secretion of LH.



1. Place one drop of water onto the green latex dot

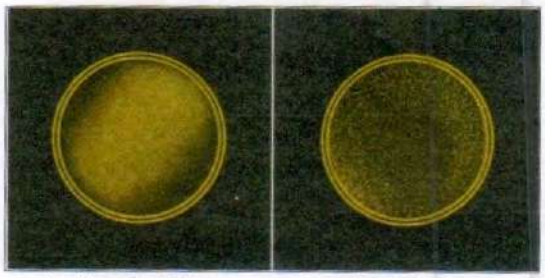
2. Draw up the urine sample.

3. Squeeze one free-falling drop of urine onto the colourless antiserum dot; mix the urine and antiserum thoroughly. Then rock the slide for 30 seonds.

4. After this 30-second period, using the same dispenstir mix the drop of dissolved antiserum and the drop of resuspended latex particles together.

5. Rock the slide (or slide holder) back and forth gently in a "figure 8" motion for two minutes so that the liquid slowly flows over the entire encircled area.

6. Read the result under a strong glare-free light at the end of two minutes while still gently rocking the slide.



Positive End Point – *No agglutination*

Negative End Point – *Agglutination*

Fig. 85.5 Gravindex test steps

MATERNAL PHYSIOLOGY IN PREGNANCY

The *average duration of human pregnancy* is 280 days (40 weeks), when calculated from the first day of LMP ***(last menstrual period)*** or 266-270 days, when calculated from the time of ovulation.

A. CHANGES IN THE UTERUS

Uterus increases in weight from 30-60 gm in the non-parous state to 800-1000 gm at full term. This is due to: (x 20)

(1) Hypertrophy of pre-existing muscle cells (mainly) both in width and length by approx. 5-9 times.
(2) formation of new fibers (hyperplasia) during early months of pregnancy.
(3) increase in the amount of connective tissue and elastic tissue between the muscle fibers.

All these effects are seen during the first two or three months of pregnancy due to oestrogen. Subsequent enlargement of uterus is due to growing foetus which causes uterine wall to become thinner (5 mm thick) and the foetus can be easily palpated through it.

B. CHANGES IN THE BODY SYSTEMS AND ORGANS

1. BLOOD

(i) *Blood volume:* it increases by approx. 30% from 4 litres to 5.4 litres mainly due to increase in plasma volume. Therefore, RBC count, haemoglobin concentration and PCV decrease producing anaemia called ***physiological anaemia of pregnancy***. Its characteristic features are that of iron deficiency anaemia (page 73) as iron demand markedly increases during pregnancy (page 824).

Advantages of increased blood volume

(a) to meet the demands of an enlarged uterus with its markedly increased blood supply; and

(b) to provide increased flow to the skin for the elimination of additional heat and to the kidneys for the excretion of the additional waste products from mother and foetus.

(ii) *Plasma proteins*

(a) total plasma protein concentration decreases;

(b) S.fibrinogen increases which increases the ESR;

(c) S.albumin is markedly decreased; and

(d) α and β globulins concentration increases (compensatory increase).

2. THE HEART AND THE CIRCULATION

(i) Heart enlarges due to pressure of the enlarging uterus on the diaphragm.

(ii) Cardiac output increases due to increase in stroke volume and 'HR' from 5L/min to 6L/min.

(iii) Systemic BP:

(a) both SBP and DBP decrease ⇒ MBP ↓; PP ↔

(b) Anticubital venous pressure is normal and

(c) Femoral venous pressure increases due to pressure of enlarged uterus on the pelvic veins.

(iv) Blood flow through the hand and forearm increases; this helps in loss of the excess heat produced by increased body metabolism.

3. RESPIRATION

(i) *Vital capacity (VC):* No change, because any decrease in VC due to upward displacement of the diaphragm gets compensated by increase in width of the pleural cavity which tends to increase it.

(ii) *Pulmonary ventilation* increases due to increase in 'TV' and frequency of breathing. This may be due to increased progesterone level which increases the sensitivity of the respiratory centre to CO_2 and causes fall in arterial pCO_2.

(iii) *Body O_2 consumption* increases by 15%, this helps:

(a) to meet the needs of the growing foetus, and

(b) to meet the extra body O_2 demand resulting from increased cardio-pulmonary work and from the added uterine muscles, breast tissues and the placenta.

4. GIT

(i) There is ***morning sickness*** (*i.e.* feeling of nausea and vomiting) in early months of pregnancy (cause not known).

(ii) Hypochlorhydria

(iii) Decrease in motility of the stomach and colon.

5. URINARY SYSTEM

(i) RBF and GFR increase in parallel with increase in cardiac output. CO ↑ ⇒ RBF & GFR ↑

(ii) Increased GFR increases the load of solutes presented for reabsorption. This may account for the glycosuria of pregnancy.

(iii) The ureters get dilated due to pressure effect of the growing foetus.

6. ENDOCRINE GLANDS

(i) *Thyroid gland* shows mild enlargement with hyperplasia and increased thyroxine output. However, oestrogen increases thyroxine binding protein in the plasma, therefore, there are **no** signs and symptoms of hyperthyroidism (page 683).

(ii) *Adrenal Cortex* shows enlargement of the zona fasciculata layer in particular, therefore, cortisol secretion increases, but **no** signs of Cushing's syndrome are seen due to corresponding increase in plasma protein 'transcortin' (page 716).

(iii) Placental hormones (page 820).

7. NERVOUS SYSTEM

Shows mild mental changes which vary from craving for unusual articles of diet to alteration in mood and behaviour. In some, a true *psychosis* may also develop (cause not known).

8. SKIN

shows pigmentation of the nipple, breast areolas and linea alba; brownish patches on the face and neck also develop. These changes may be due to oversecretion of ACTH or MSH (page 676) and disappear after delivery.

C. METABOLIC CHANGES

1. *During pregnancy* there is marked increase in body weight, on an average, 12.5 kg. The gain in weight during whole of pregnancy is as follows:

(i) Foetus, placenta and liquor amnii	:	4.5 kg
(ii) Uterus, breast	:	1.5 kg
(iii) Blood	:	1.5 kg
(iv) Tissue fluid	:	1.5 kg
(v) Maternal stores of fat	:	3.5 kg
Total	:	12.5 kg

2. *Water Metabolism.* During later months (5-6 months onwards) of pregnancy excess of water is retained in the foetus, placenta, amniotic fluid, breast, uterus and other tissues. Therefore, during the early days of the puerperium there is a marked diuresis, sweating and a weight loss of approx. 2.5 kg. The retention of water is due to:
   (i) Fall in plasma protein concentration, specially of albumin, as a result, colloidal osmotic pressure of the plasma decreases.
   (ii) Retention of sodium due to the steroidal sex hormones.
3. *Protein Metabolism.* There is positive nitrogen balance during pregnancy and lactation period, so that more nitrogen is retained than is needed for the foetus, uterus, placenta and milk.
4. *Carbohydrate Metabolism.* Renal threshold for glucose decreases during pregnancy producing glycosuria (see above).
5. *Fat Metabolism*
   (i) There occurs increase in blood concentration of cholesterol, phospholipids and neutral fats.
   (ii) Adipose tissue depot fat increases to supply energy in the later stages of pregnancy and during lactation.
6. *Mineral Metabolism.* During pregnancy, the mother stores approximately 50 gms of calcium and 35-40 gm of phosphorus. Only half the calcium goes to the foetus specially during the last month, the rest being stored in the maternal tissues to be utilized during lactation.
7. *Iron Metabolism*
   (i) The foetus at term contains 375 mg of iron which accumulates at a rate of approx. 0.4 mg/day in the first 6 months of pregnancy and at about 4 mg/day during last 3 months of pregnancy.
   (ii) A further 500-700 mg of iron is required by the mother for:
      (a) increased haemoglobin synthesis, and
      (b) myoglobin formation in the growing uterus.
   (iii) 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.

PARTURITION

Parturition means the process of giving birth to a young one (*i.e.* child birth). The uterine contractions which are painless and of mild intensity initially during the first trimester of pregnancy, gradually increase from the 30th week until during labour to become much greater, more frequent and painful.

Initiation and Control of Parturition

The processes which initiate and control parturition can be divided into: (1) nervous control and (2) hormonal control.

1. *Nervous Control.* Nervous mechanisms play a *little role* in direct control of parturition because parturition can still occur after mid-thoracic section of the spinal cord or after cutting sympathetic supply to the uterus.
2. *Hormonal Control.* The foetus initiates parturition by neurohormonal process. How?
   (i) Parturition is triggered off by release of *corticotrophin-releasing factor* (CRF) from the foetal hypothalamus and from the placenta. It promotes release of ACTH from the anterior pituitary in the foetus. This acts on large foetal adrenal cortex to increase the secretion of cortisol which passes from foetus into placenta and causes:
      (a) *increased oestrogen secretion* (which causes 100 fold increase in number of *oxytocin receptors* in the myometrium; this causes normal oxytocin levels to initiate uterine contractions, setting up a *positive feedback*) and
      (b) *decreased progesterone secretion*.

   Therefore, synthesis of $PGF_{2\alpha}$ in the placenta and myometrium increases which increases the sensitivity of the myometrium to the uterine stimulant action of oxytocin. (Normal prelabour plasma oxytocin concentration: 25 pg per mL.)
   (ii) Distended cervix and vagina during labour (later stages) *increase the oxytocin secretion* which results in expulsion of the foetus and placenta.

Note

Oxytocin also reduce postpartum bleeding.

Evidences

1. Destruction of the foetal hypothalamus, or hypophysectomy or in an anencephalic foetus (which has no hypothalamus), there is no secretion of ACTH or cortisol and hence the onset of labour is greatly delayed.
2. During the first stage of labour the amniotic fluid contains PGE_1 and $PGF_{2\alpha}$. Anti-inflammatory drugs,

such as aspirin and indomethacin which inhibit prostaglandin synthesis, may delay the onset of labour.

3. The sensitivity of the uterus to oxytocin increases during the latter part of pregnancy and is the greatest just before the onset of labour.
4. The concentration of plasma oestrogen increases and that of progesterone decreases during the last few weeks of pregnancy.

During labour, spinal reflexes and voluntary contractions of the abdominal muscles (***Bearing Down***) also aid in delivery.

Role of Oxytocin in Parturition: See Fig. 85.6. (For detailed actions, refer to page 675).

Important Note

The delivery can occur without *bearing down* and without a reflex increase in secretion of oxytocin since paraplegic women can go into labour and delivery.

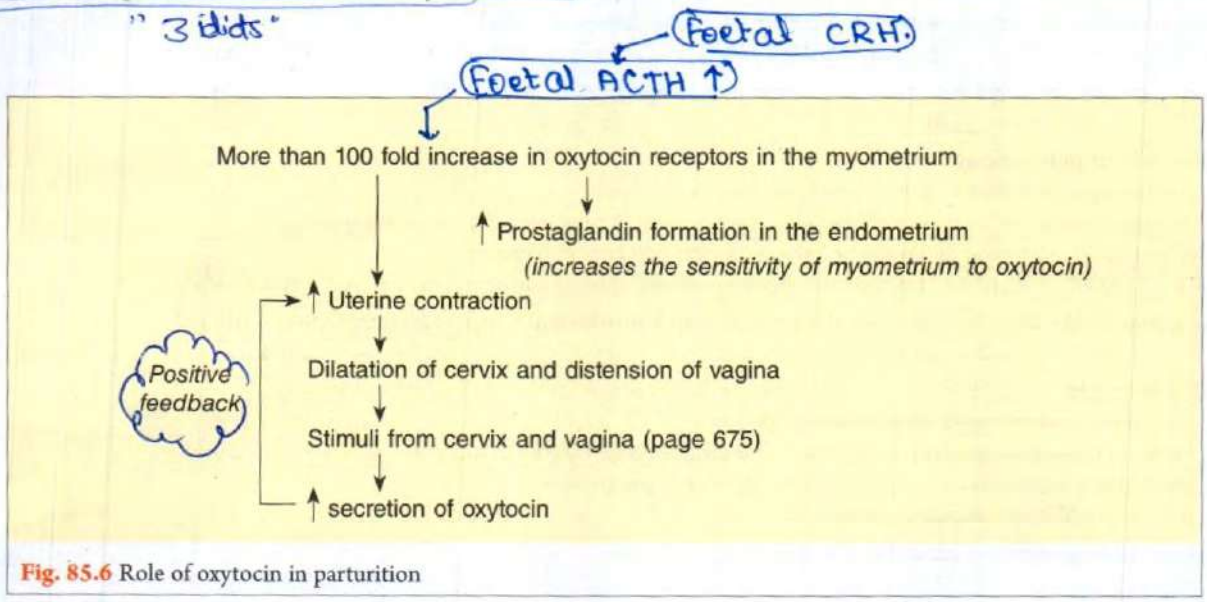


Fig. 85.6 Role of oxytocin in parturition

Study Questions

1. **Write short notes on:**
   - (i) transport of ovum from the ovary to the fallopian tube
   - (ii) transport of sperm from vagina to the ampulla
   - (iii) environment needed for survival of ova and sperm
   - (iv) implantation of fertilized ovum
   - (v) role of HCG and HCS during pregnancy
   - (vi) foeto-plancental unit
   - (vii) changes in the mother during pregnancy
   - (viii) iron metabolism during pregnancy
   - (ix) initiation and control of parturition
   - (x) implantation of fertilized ovum.
   - (xi) acrosomal reaction and polyspermy
   - (xii) Parturition
   - (xiii) Maternal growth hormone of pregnancy
2. **Give physiological basis of:**
   - (i) test tube babies
   - (ii) prevention of fertilization of ovum by more than one sperm
   - (iii) HCS levels are measured to assess the placental functions
   - (iv) pregnancy diagnostic tests
   - (v) anaemia of pregnancy
   - (vi) skin changes during pregnancy.

3. **Draw labelled diagram:**
   (i) Events leading to the fertilization of the ovum
   (ii) Foeto placental unit
   (iii) Implantation of fertilized ovum
   (iv) Changes in serum level of placental hormones
4. **List the hormones secreted by placenta.**
5. **What will happen if ovariectomy is done about 8 weeks of gestation?**

MCQs

1. **Ovum fertilization usually occurs in which part of the fallopian tube?**
   (a) Fimbrial end (b) Infundibulum (c) Ampulla (d) Isthmus
2. **Normal sperms move at the rate of ..... mm/min in the female genital tract:**
   (a) 0-1 (b) 1-3 (c) 5-10 (d) 11-20
3. ***Not true* about polyspermy:**
   (a) Polyspermy is fertilization of ovum by more than one sperm
   (b) Structural change in zona pellucida when a sperm fuses in the ovum, prevents polyspermy
   (c) Reduction in membrane potential of fertilized ovum prevents polysperm
   (d) Fusion of cell membranes of ovum and sperms prevents entry of further sperms across zona pellucida
4. **How many weeks after fertilization placenta provides nutritional support to developing embryo?**
   (a) 1 (b) 2 (c) 3 (d) 4
5. **HCG, *not true* is:**
   (a) Formed by syncytiotrophoblastic cells of placento
   (b) Helps to maintain secretion of oestrogen and progesterone by corpus luteum
   (c) Maximum production occurs during 2nd trimester of pregnancy
   (d) It is not absolutely specific for pregnancy
6. **The level of hormone indicating placental insufficiency is:**
   (a) HCS (b) HCG (c) Oestrogen (d) Progesterone
7. **In pregnancy:**
   (a) Plasma fibrinogen levels increased (b) Fibrinogen levels decreased
   (c) Thyroglobulins decreased (d) IgD markedly increased
8. **During later months of pregnancy there is tendency for:**
   (a) Respiratory acidosis (b) Respiratory alkalosis (c) Metabolic acidosis (d) Metabolic alkalosis
9. **Factors contributing to the initiation of parturition include:**
   (a) Increased stretch of the uterus (b) Increased secretion of oxytocin
   (c) Increased pressure on the cervix (d) All of the above
10. **Unfertilized ovum remains viable in the fallopian tube for ..... days:**
    (a) 1-2 (b) 2-3 (c) 3-4 (d) 4-5
11. **The transport of spermatozoa from the cervix to fallopian tube takes:**
    (a) 5-10 minutes (b) 10-30 minutes (c) 30-60 minutes (d) 60-90 minutes
12. **Transport of sperms from vagina to ampulla occurs due to:**
    (a) Sperm motility (b) Appropriate ciliary activities in the fallopian tube
    (c) Muscular movements in the uterus (d) All of the above
13. ***Not true* regarding test tube babies:**
    (a) Fertilization of ovum and subsequent foetal development is carried out in vitro
    (b) In vitro fertilization of ovum, and after few days the blastocyst inserted into the progestational uterus
    (c) A procedure carried out in women with blocked fallopian tubes
    (d) If carried out successfully, it leads to the birth of apparently normal baby
14. **After about ..... days, blastocyst implants on the wall of the uterus:**
    (a) 6 (b) 7 (c) 8 (d) 9
15. **Maximum production of HCG occurs during:**
    (a) 1st trimester (b) 2nd trimester (c) 3rd trimeters (d) Implantation
16. **The pregnancy test is based on detection of which hormone?**
    (a) Progesterone (b) Oestrogen (c) HCG (d) LH

17. *Not a correct* statement for human chorionic somatomammotrophin?
    (a) It is maternal growth hormone of pregnancy
    (b) Promotes the growth and development of breasts during pregnancy
    (c) Its plasma levels directly correlate with growth of placenta and the foetus
    (d) Secreted by cytotrophoblast cells of placenta
18. Secretion of oestriol during pregnancy:
    (a) Is dependent on both a viable foetus and a functioning placenta
    (b) Is largely produced by the maternal ovaries
    (c) Is not dependent on a viable fetus
    (d) Is lower than the secretion rate of oestriol in non-pregnant body
19. Physiological anaemia of pregnancy is due to decreased:
    (a) RBC count
    (b) Haemoglobin concentration
    (c) Haematocrit
    (d) All of the above
20. Uterine contractility during labour is increased by:
    (a) Altered oestrogen progesterone ratio
    (b) Oxytocin
    (c) Prostaglandins
    (d) All of the above

Answers

1. (c)	2. (b)	3. (d)	4. (b)	5. (c)	6. (a)	7. (a)	8. (b)	9. (d)	10. (b)
11. (c)	12. (d)	13. (a)	14. (b)	15. (a)	16. (c)	17. (d)	18. (a)	19. (d)	20. (d)

Chapter

86

Physiology of Foetus and Newborn

I. The Placenta
II. Growth and functional development of the foetus
III. Adjustments of the infant to extra-uterine life
(A) Respiratory adjustments at birth (B) Circulatory adjustments at birth
IV. Nutrition of the new born infant
V. The Breast and Lactation

THE PLACENTA

1. For the first few days after implantation nutritive material to the foetus comes from the:
   (i) plasma in the *decidua* (*i.e.* endometrium), and
   (ii) endometrial glandular secretion containing glycogen.
   Afterwards requirements for foetal growth come from maternal circulation through the ***placenta*** *(Foetal Lung)*.
2. Initially the rate of placental growth is much greater than that of the foetus but later placental growth slows down. By the 4th week of pregnancy, the placental growth is sufficient enough to allow diffusion of substances between mother and the foetus. At term placenta weighs 0.5 kg and the foetus weighs about 3.5 kg.
3. *Function:* For the foetus the placenta combines the functions of the alimentary tract, kidneys and lungs.
4. *Blood supply:* Blood supply of the placenta can be divided into *three heads*:
   (i) *Vascular arrangement within the placenta, i.e.* the relation between the maternal and foetal circulation within the placenta.
   The human placenta is ***Haemochorial*** *i.e.* the *chorionic villi* (small finger like projections from the outer layer of the blastocyst) dip directly into the maternal blood **(Fig. 86.1)**. The foetal and maternal circulations are thus separated only by 3 thin layers:
   (a) the foetal vascular endothelium;
   (b) the connective tissue of the villus, and
   (c) the trophoblast.
   (ii) *Uterine blood flow:* It supplies maternal blood to the placenta.
   (a) It is expressed in terms of weight of uterus plus its content *i.e.* foetus. *Normal:* 125-150 mL/min/kg or 600-750 mL/min (near term).
   (b) Approx. 80-85% of the total uterine blood flow goes to the maternal placenta, the remainder supplying the endometrium and myometrium.
   (c) Uterine blood flow increases as pregnancy advances, probably under the effect of oestrogen which produces uterine vasodilatation.
   (iii) *Umbilical blood flow:* It supplies the foetus; *Normal:* 170-240 mL/min/kg foetal weight.
   The increase in umbilical flow to satisfy the growing demands of the foetus is brought about by a rise in foetal arterial B.P. and cardiac output during later stages of pregnancy.
5. *Gaseous Exchange at the Placenta* **(Fig. 86.2)**
   (i) *Oxygen transport:* Foetal oxygen consumption is approximately 7 mL/min/kg *i.e.* 20-25 mL/min. The blood is supplied to the foetus by umbilical vein with pO_2, 30-35 mmHg, which is approximately 1/3rd of arterial pO_2 in adult. Moreover, the relatively well oxygenated blood derived from the placenta is progressively diluted as it traverses the foetal circulation **(Fig. 86.4)**. Therefore, foetal tissues are supplied with blood which is approximately 60% saturated with O_2. However, compensatory mechanisms in foetus for this reduced arterial pO_2 are:
   (a) There is a shift of the *O_2-haemoglobin dissociation curve* for foetal blood to the **left** as compared

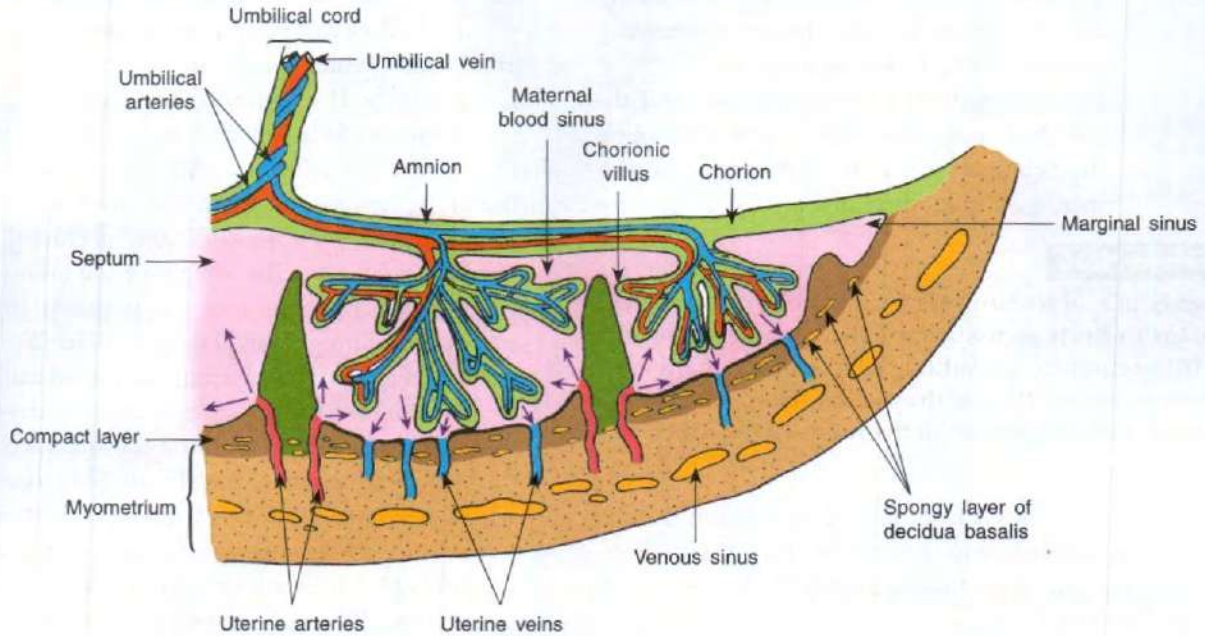


Fig. 86.1 Physiological anatomy of the mature placenta (two placental villi are shown). The direction of blood flow in the maternal blood sinuses is indicated by arrows.

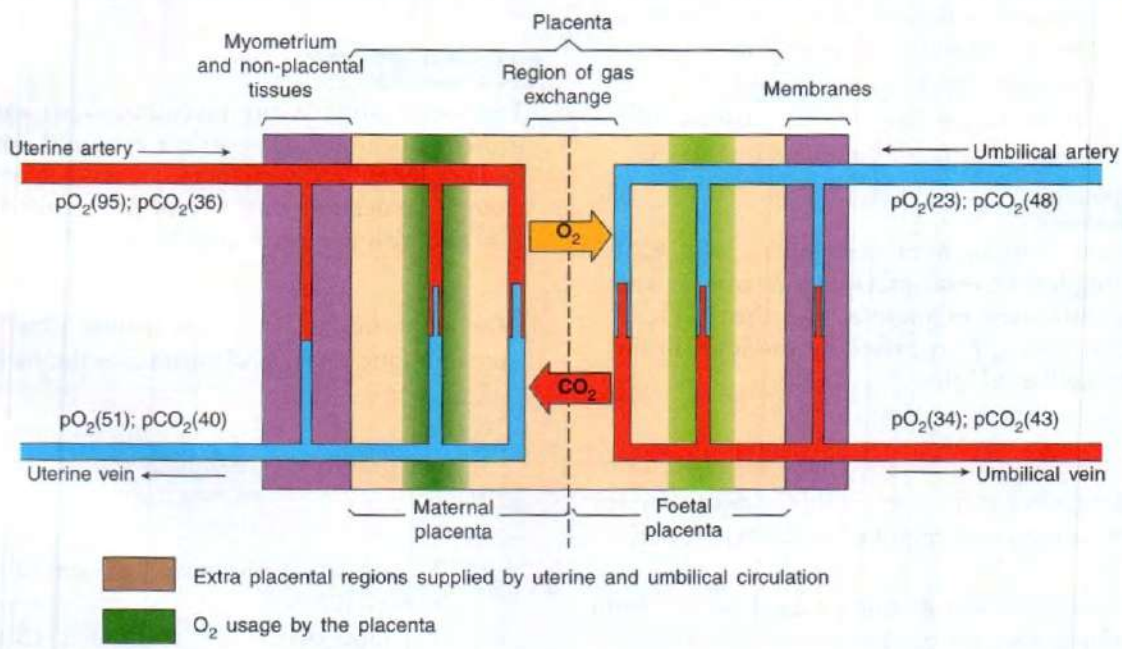


Fig. 86.2 Gaseous exchange at the Placenta (values in mmHg)

with that of adult blood (page 430), because, HbF has less affinity for 2,3 DPG compared to HbA (DPG competes with O_2 for the binding sites on haemoglobin molecule). Therefore, foetal blood can take up much larger volume of O_2 than adult blood at low pO_2. (P_{50} values: HbA, 27 mmHg; HbF, 19 mmHg (page 431).

(b) Greater concentration of haemoglobin in the foetus (18-20 gm/dL at term), increases O_2 carrying capacity of blood.

(c) Increased uptake of O_2 by foetal blood as it traverses the placenta due to the ***Double Bohr's Effect*** because, while flowing through the placenta:

– pCO_2 of foetal blood decreases and its

pH increases, this shifts O_2-haemoglobin dissociation curve to left to cause increased loading of O_2; whereas,

- pCO_2 of maternal blood increases and its pH decreases, this shifts O_2-haemoglobin dissociation curve to right and causes increased unloading of O_2.

Important Note

A higher pO_2 of 60-80 mmHg is undesirable because of: (i) toxic effects on tissue growth and development, and (ii) premature activation of circulatory changes; such as, (a) constriction of the ductus arteriosus (page 834); or (b) vasodilatation in the lungs (page 832).

(ii) *CO_2 output:* pCO_2 in umbilical vein blood is only slightly above that in uterine vein blood (Fig. 86.2), but placental membranes offer little hindrance to its passage, because:

(a) CO_2 is 20 times more diffusible than O_2; and

(b) there is a ***Double Haldane's Effect***, therefore,

- increased unloading of O_2 from the maternal blood passing through the placenta increases its ability to take up CO_2;
- increased loading of O_2 in the foetal blood helps to increase the unloading of CO_2.

Important Note

The pregnant woman hyperventilates (page 823), thus reducing her alveolar pCO_2 to ≤ 30 mmHg and this also contributes in maintaining the pCO_2 in the umbilical vein approximately at the level in the normal adult (40 mmHg).

6. *Placental transfer of foodstuffs.* The placenta performs the GIT function for the foetus; this is necessary for absorption of materials required for foetal growth.

Salient features

(i) The role of transfer of nutritive substances from maternal to foetal circulation increases throughout pregnancy specially during the last few weeks.

(ii) Passage of substances into the foetal circulation is inversely related to MW of the substances, therefore, substances with MW less than 1000 (water, Na^+, Mg^{2+}, Cl^-, urea and uric acid), cross the placenta readily by simple diffusion. Moreover, antibodies which are γ-globulins of MW above 1,00,000 can also cross the placenta. For example, antibodies to diphtheria and tetanus toxin can pass from mother to foetus to produce a short lasting passive immunity in the foetus. Even RBCs can pass from the foetus to the maternal circulation, thus Rh antibodies can pass in the opposite direction.

(iii) Plasma proteins cross the placenta only in minute amounts. The foetus synthesizes its proteins from amino acids transferred across the placenta.

7. *Drugs and the placenta.* All drugs are of low MW, therefore, majority of them can cross the placenta.

8. *Placenta and hormonal influence on foetal growth*

(i) *Placental size:* The weight of the infant is a direct function of weight of the placenta (in the later stages of pregnancy) because, placental size limits foetal growth by limiting the transfer of metabolic substances (O_2, CO_2), fats, carbohydrates, amino acids, or inadequate hormone production. *That is why foetal weight is less in multiple pregnancies.*

(ii) *Hormonal influence:* Foetal production of the hormones necessary for development after birth probably does not influence gross foetal weight, *i.e.* overall foetal birth weight; because birth weight is normal in infants who subsequently develop signs of congenital hypothyroidism or idiopathic hypopituitary dwarfism within a few months of birth.

Important Note

The foetal pituitary produces both TSH and human growth hormones. These are required for normal development of particular organs, specially the change associated with sexual differentiation (page 768) and also the development of the brain.

9. *The amniotic fluid.* It is a clear fluid which collects in the amniotic cavity and surrounds the foetus.

Composition

Volume	: 500-1000 mL (at term)
Specific gravity	: 1007-1025
Water	: 98-99%
Solids	: 1-2%

(i) 50% organic: proteins (0.5 gm/dL); glucose (20 mg/dL).

(ii) 50% inorganic: Ca^{2+}, Na^+, K^+, Cl^- (in small amounts).

Formation and removal

(i) mainly by transudation from maternal blood and/or active transport across the amniotic epithelium;

(ii) to a small extent from foetal pulmonary secretion and foetal urine.

The fluid is removed through drinking by the foetus and by return to the maternal circulation.

Functions

(1) to provide the foetus with fluid to drink;

(2) to keep the foetus at an even temperature;

(3) to protect the foetus against injury; and
(4) to provide a medium in which foetus can move easily.

GROWTH AND FUNCTIONAL DEVELOPMENT OF THE FOETUS

During the first, second or third weeks foetus remains microscopic in size but thereafter dimensions of foetus increases almost in proportion to age. (Fig. 86.3; Table 86.1)

Development of the Organ Systems

Within 1 month after ovum fertilization, all different organs get differentiated.

After 3-4 months of gestation: details of different organs established

After 4 months of gestation: organs of foetus are grossly the same as those of the newborn child

Between 4 to 9 months of gestation: required for complete cellular development of these structures

1. *CVS*

(i) Formation of heart begins during the 4th week following fertilization, contracting @ 65/min, which increases steadily as foetus grows, reaching 140 beats/min at birth.
(ii) Formation of blood cells (page 66).

2. *The respiratory system*

Respiration cannot occur during foetal life. However, respiratory movements do take place beginning at 12 weeks, following tactile stimuli or foetal asphyxia. After 20 to 24 weeks, respiratory movements get inhibited, possibly due to:

(i) special chemical conditions in the body fluids of the foetus; or
(ii) presence of fluid in foetal lungs; or
(iii) other unknown stimuli.

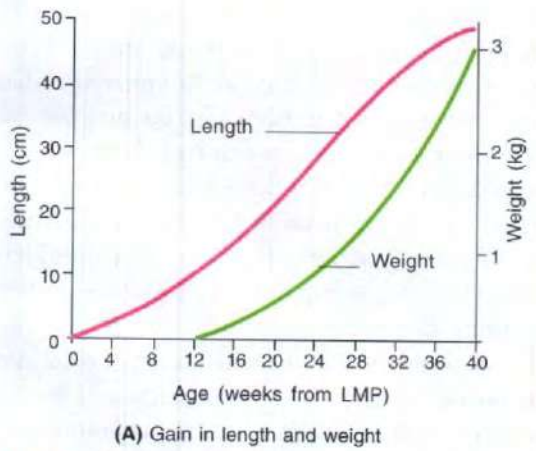
Advantage of inhibited respiratory movement: it prevents filling of the lungs with debris from the meconium excreted by GIT.

3. *CNS*

Most of skin reflexes are present in foetus by 12-16 weeks. However, most of higher functions which involve cerebral cortex are undeveloped even at birth. Indeed myelination of tracts of CNS complete only one year after the birth.

4. *GIT*

After 20 weeks, foetus ingests and absorbs large quantities of amniotic fluid (page 830) and at 24 weeks, GIT functions approach that of normal newborn infant. Small quantities of ***Meconium*** are continuously formed in the GIT and excreted from the bowels into the amniotic fluid. Meconium consists of: (i) unabsorbed residue of amniotic



(A) Gain in length and weight

(B) Dimensions

Fig. 86.3 Growth and development of the human foetus

Table 86.1: Growth and development of human foetus

Age of foetus (w.r.t. LMP)*	Length	Weight
12 weeks	10 cm	During 1st month: Nothing (as rate of placental growth is much greater initially)
20 weeks	25 cm	0.5 kg at 5½ months (maximum weight gain is after 20 weeks)
40 weeks (at term)	53 cm	2 kg at 36 weeks; 3-4 kg at birth.

*LMP: 1st day of last menstrual period

fluid; and (ii) excretory products from GIT mucosa and glands.

5. Kidneys

Foetal kidneys are capable of excreting urine after 20 weeks, and urination occurs normally in uterus. However, renal control system for regulation of ECF electrolyte balance and specific acid-base balance reaches full development only few months after birth.

6. Foetal Metabolism

Foetus utilizes mainly glucose for energy and it has a high rate of storage of fats and proteins. (Most of the fats being synthesized from glucose, rather than being absorbed from the mother's blood.)

(i) *Metabolism of calcium and phosphorus*
25 gm of calcium and 20 gm of phosphorus are accumulated in the foetus during gestation (page 824). Half of this accumulates after 24 weeks of gestation, which coincides with the period of rapid ossification of the foetal bones and with the period of rapid weight gain of the foetus.

(ii) *Accumulation of Iron.* Most of the iron is in the form of haemoglobin which begins to form at third week following fertilization of the ovum. Approximately 1/3rd of iron in a fully developed foetus is normally stored in the liver. This iron can be used for several months after birth by the newborn infants for the formation of additional haemoglobin.

(iii) *Utilization and storage of vitamins*
In general, vitamin functions are the same in the foetus as in adults and are required in the same amounts.

ADJUSTMENTS OF THE INFANT TO EXTRA-UTERINE LIFE

Features of the newborn infant:

1. Instability of various hormonal and neurogenic control system due to:
   (i) immature development of different organs of the body;
   (ii) control systems gradually adjusted to the completely new way of life.
2. Most obvious effect of birth on the baby is the loss of the placental connection with the mother *i.e.* loss of metabolic support, therefore, the immediate adjustment required of the infant is to begin breathing.

A. RESPIRATORY ADJUSTMENTS AT BIRTH

1. *Breathing at birth* occurs due to stimulation of respiratory centre by:
   (i) Impulse from a slightly asphyxiated state incident to the birth process.
   (ii) From sensory impulses originating in the suddenly cooled skin; handling and gravitational stimuli. (In utero, foetus weight is supported by the surrounding amniotic fluid and gravitational forces are not acting on it. This causes immediate spontaneous complete normal respiratory rhythm).

Important Note

If infant fails to breathe immediately after birth, body becomes progressively more hypoxic and hypercapnic which provides additional stimulus to the respiratory centre and breathing starts within a few seconds to a few minutes after birth.

2. *Degree of hypoxia that an infant can tolerate:* After birth, if breathing is delayed by more than 8-10 minutes, irreversible brain damage (specially motor system) begins; if it gets delayed beyond 10-15 minutes, death occurs because prolonged hypoxia causes depression of the respiratory center.
   Common causes of foetal hypoxia are:
   (i) compression of umbilical cord;
   (ii) premature separation of placenta;
   (iii) excessive contraction of uterus which cuts off the blood flow to placenta; and
   (iv) excessive anaesthesia of the mother.
3. *Expansion of the lungs at birth:* At birth, the walls of the alveoli are kept collapsed by the surface tension of the viscid fluid that fills them. Therefore, to open the alveoli for the first time, more than 25 mmHg of negative pressure is required to oppose the effects of this surface tension. But once the alveoli are open, further respiration can be effected with relatively weak respiratory movements. Fortunately, the first inspiration of the newborn infants are extremely powerful, which are usually capable of creating as much as 60 mmHg negative pressure in the intrapleural space. However, breathing does not become completely normal until 40 minutes after birth.
4. *Breathing following birth.* Establishment of maintained regular breathing after birth is the conjoint effect of:
   (i) Continuous stimulation of arterial chemoreceptors even by increased arterial pO_2 and decreased arterial pCO_2; because before birth the carotid body chemoreceptors are relatively inactive despite the low pO_2 of carotid artery blood. After birth, due to tying of umbilical cord, asphyxia occurs which leads to generalised increase in sympathetic nervous activity thus decreases carotid body blood flow and chemoreceptor activity increases;
   (ii) Gravitational stress;
   (iii) Change in temperature, and
   (iv) Mechanical stimuli.

Applied

In infants born prematurely, and some full term babies, are born without the capability of secreting *surfactant*. This results in development of ***respiratory distress syndrome*** (also called *Hyaline membrane disease*, page 416) due to collapse of alveoli. This finally leads to death due to severe pulmonary insufficiency.

5. ***Respiratory System of a Newborn***

Normal respiratory rate : 40 breaths/min
Tidal volume : 16 mL
Minute ventilation : 640 mL/min*
(*This is two times as great in relation to body weight as that of an adult.)

Functional residual capacity is only half that of an adult in relation to body weight. This allows cyclic changes in the blood gas concentration when the respiration becomes slowed, because it is the residual air in the lungs that smoothens the blood gas variation in the adult.

B. CIRCULATORY ADJUSTMENTS AT BIRTH

Physiological Anatomy of Foetal Circulation

(Refer Fig. 86.4)

1. Oxygeneted blood returning from the placenta via the umbilical vein (80% saturated with O_2) enters the liver. After giving off a branch which supplies blood to left 2/3rd of the liver, it joins the portal sinus (a branch

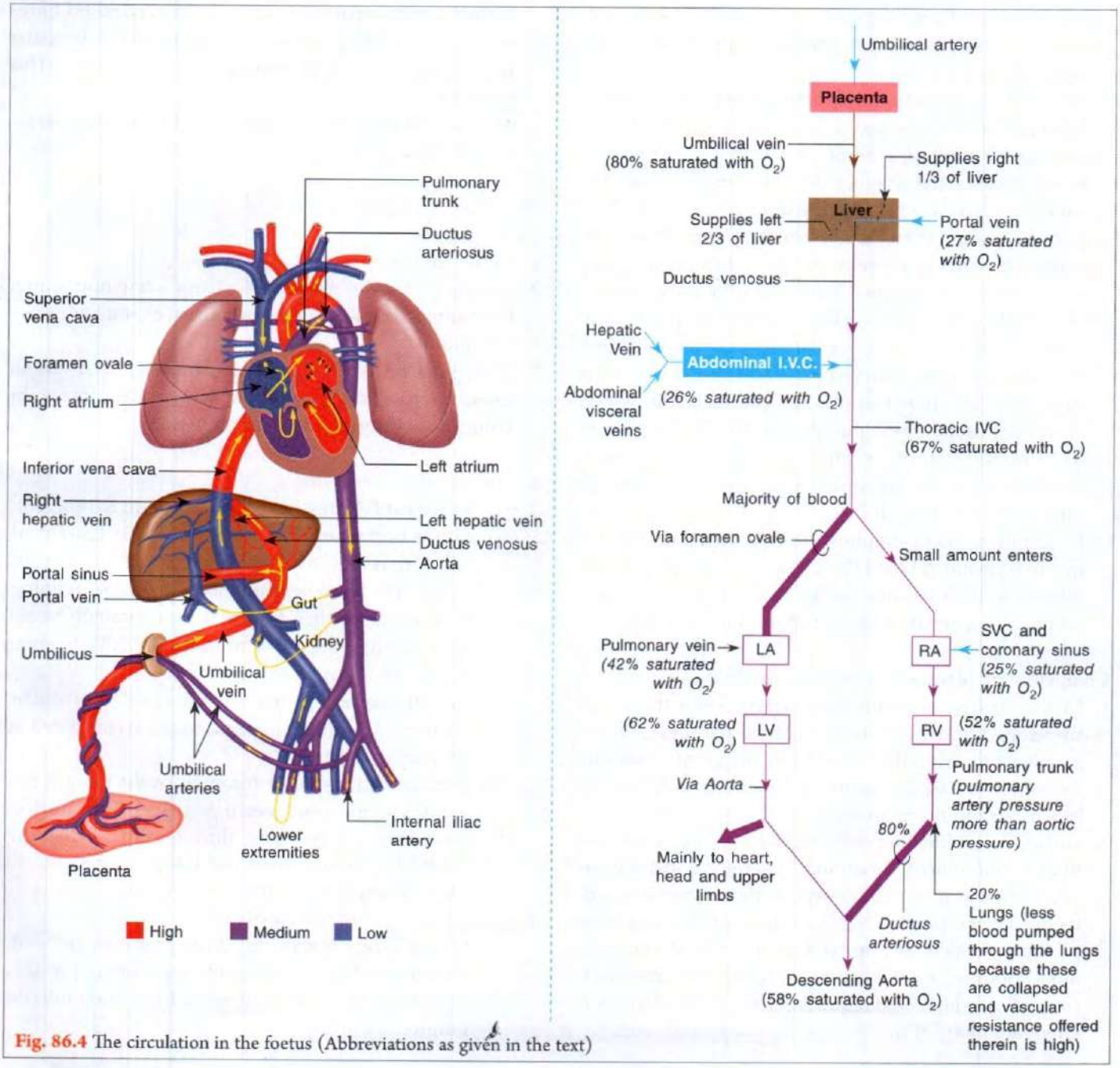


Fig. 86.4 The circulation in the foetus (Abbreviations as given in the text)

of portal vein) to form ***Ductus Venosus*** (it links the umbilical vein with the IVC). The right 1/3rd of liver is supplied by branches of the portal venous blood (27% saturated with O_2).

2. The *ductus venosus* runs on the undersurface of the liver to join the inferior vena cava (IVC) at its junction with the hepatic veins. As a result of the admixture of blood from umbilical vein (80% saturated with O_2) with hepatic and systemic venous blood (26% saturated with O_2), the blood in *Thoracic 'IVC'* becomes 67% saturated with O_2.
3. Majority of the thoracic 'IVC' blood passes through the ***foramen ovale*** (a gap in the inter atrial septum) and reaches the left atrium (LA) where it is joined by the blood coming from the pulmonary vein (42% saturated with O_2) and passes on to the left ventricle (LV) (62% saturated with O_2).
4. Blood in the LV is mainly pumped into the vessels of head and fore limbs and only small amount of blood goes to the ascending aorta.
5. Right atrium (RA) receives the blood mainly from the superior vena cava (SVC) (25% saturated with O_2) and in small amount from the thoracic IVC. This blood (52% saturated with O_2) passes onto the right ventricle (RV) from where it is pumped into the pulmonary artery.
6. Main bulk of blood (80% of RV output) in the pulmonary artery passes via ***ductus arteriosus*** *i.e.* a direct link between the pulmonary artery and the aorta (thus bypassing the lungs) to the descending aorta, which also receives the blood pumped by the LV. Less blood (20% of RV output) is pumped through the lungs, because these are collapsed and vascular resistance offered therein is high.
7. Descending Aorta supplies the blood to the body and the deoxygenated blood (58% saturated with O_2) finally returns to the placenta via the two umbilical arteries, where deoxygenated blood becomes oxygenated.

Characteristic feature of Foetal Circulation

1. In the foetus, as pulmonary artery joins the aorta, therefore, the two ventricles work in parallel (and not in series) to drive the blood from the great veins into the arteries. The LV ejects approximately 20% more blood per minute than the RV.
2. During foetal life, lungs are mainly non-functional and liver is only partly functional. Therefore, foetal heart need not pump much blood through either lungs or the liver but it pumps large quantities of blood through placenta, which is approximately 55% of the total blood pumped by the heart. Therefore, the immediate circulatory adjustment required by the infant is to allow adequate blood flow through the lungs and liver.

Changes in the circulation after birth

The circulatory changes/adjustments which occur at birth are divided into two: *primary* and *secondary changes* **(Fig. 86.5)**.

Primary changes

Tying of the umbilical cord stops the placental circulation producing the following changes:

1. Blood flow through umbilical vein ceases causing contraction of ductus venosus within 1-3 hours after the birth. (How? Not known).
2. Doubles the systemic vascular resistance. This increases the pressure in the LA, LV and aorta.
3. Marked decrease in volume of blood flowing up the IVC together with expansion of previously collapsed lungs produces five-fold decrease in pulmonary vascular resistance *i.e.* fall in pulmonary artery pressure. This leads to:
   (i) marked increase in pulmonary blood flow; and
   (ii) decrease in 'RA' and 'RV' pressures.

Secondary changes

These include:

1. *Closure of 'foramen ovale'.*
2. *Closure of 'Ductus Arteriosus'* within a few hours after birth (may take 1-8 days); permanent closure occurs at 1-4 months.
3. *Closure of Ductus venosus* which increases portal venous pressure from 'zero' mmHg to 6-10 mmHg, forces the blood flow through the liver sinuses.

1. Closure of foramen ovale

(i) Increased LA pressure and decrease in RA pressure causes backward flow from LA to RA. Thus small valve that lies over foramen ovale on the left side of the atrial septum closes over the opening, preventing further flow through foramen ovale. As a result, within few minutes of birth it causes closure of foramen ovale.
[As ductus arteriosus is still open this causes greater 'LV' output approx. by 20% compared to RV output at birth].

(ii) Permanent closure of foramen ovale takes a few months to one year. Even if permanent closure does not occur, LA pressure throughout life remains 2-4 mmHg greater than the RA pressure and the back pressure keeps the valve closed.

2. Closure of Ductus Arteriosus (DA)

(i) Within a few hours after birth, increase in aortic pressure and decrease in pulmonary artery pressure causes backward flow of blood from aorta into the pulmonary artery.

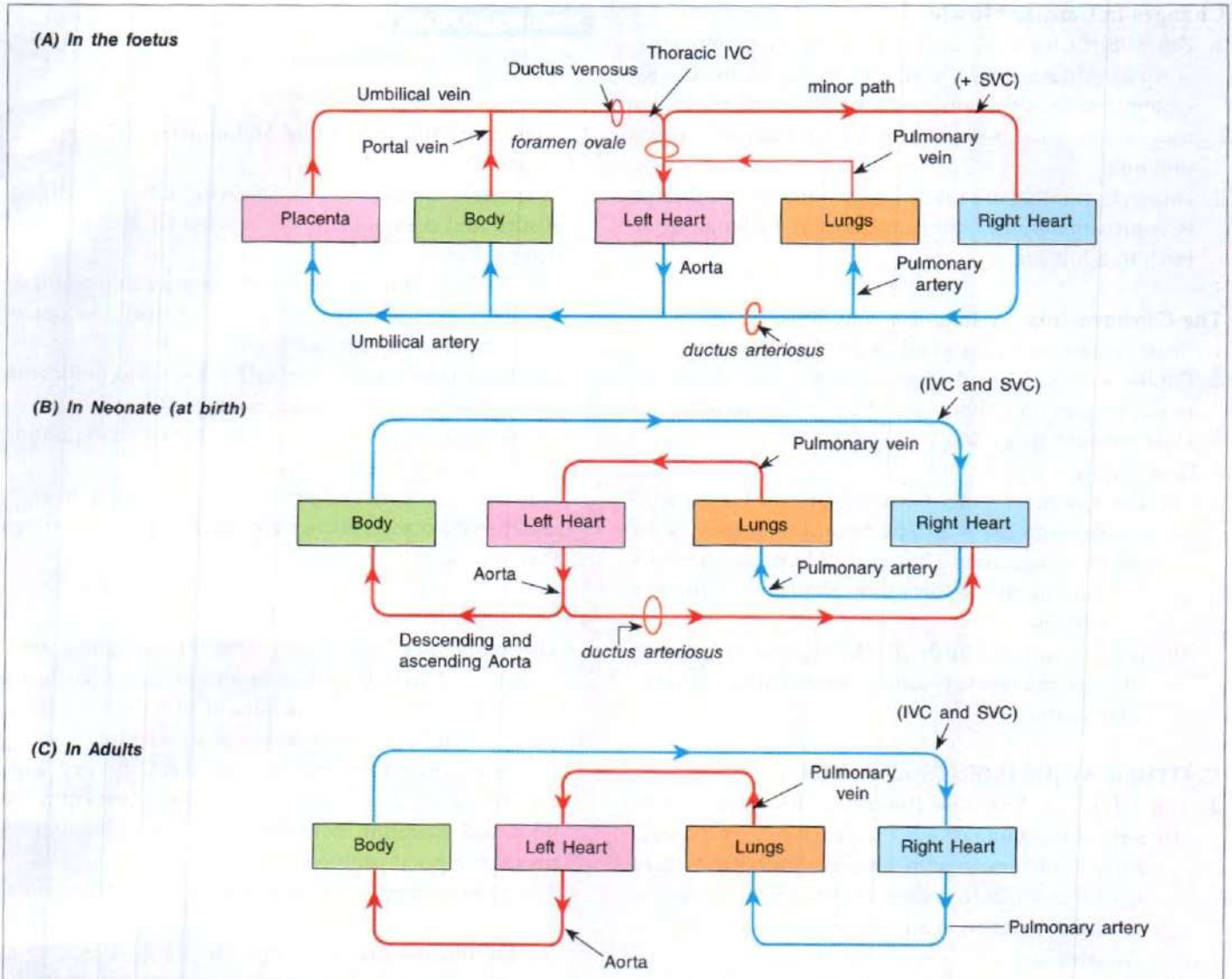


Fig. 86.5 Changes in the circulation after birth

(ii) Gradual constriction of DA occurs over next 1-8 days *(functional closure of DA)*; and finally ***permanent closure*** occurs at 2-3 weeks by growth of fibrous tissue into its lumen.

(iii) Other factors which causes closure of ductus arteriosus: During foetal life pO_2 of ductus blood is 15-20 mmHg which increases to 100 mmHg within a few hours after birth. This increased availability of O_2 is known to cause contraction of smooth muscle in the DA wall.

Mechanism

(a) By reduction in concentration of vasodilator, specially $PGF_2\alpha$, PGE_1 and PGE_2 and

(b) Release of catecholamines from adrenergic innervation of ductus itself or from adrenal medulla.

Important Note

This may explain higher incidences of patency of the 'DA' in children with history of foetal distress at birth or with history of delivery at high altitude.
After closure of 'DA', blood is pumped through lungs and body by the two ventricles operating in series.

3. *Closure of Ductus Venosus* (DV)

(i) In foetal life, portal blood from abdomen joins the blood from the umbilical vein, which via DV (bypassing liver) reaches IVC.

(ii) After birth: blood flow through umbilical vein ceases and within 1-3 hours, muscular wall of DV contracts (how? not known); as a result portal vein pressure increases from near 'zero' mmHg to 6-10 mmHg, which forces the blood flow through the liver sinuses.

Changes in Cardiac Muscle

1. Before birth the wall thickness of the two ventricles is equal. After birth, LV-wall rapidly grows thicker as systemic arterial pressure rises and RV wall thickness may not be great because of fall in pulmonary artery pressure.
2. However, number of muscle fibers in the two ventricles is approximately the same and does not change from birth to adult life.

The Cardiovascular system of a New Born

1. *Blood volume:* 300 mL (90 mL/kg)
2. *Cardiac output:* 550 mL/min (which is two times as much in relation to body weight as in the adult)
3. *Blood pressure:* (page 360)
4. *Blood picture*
   (i) RBC Count – average 6-7 × 10^6/μL which gradually decreases to 3-4 × 10^6/μL by approximately 8-10 weeks of age due to absence of hypoxic stimulus of foetal life, and returns to normal within another 2-3 months.
   (ii) WBC Count – At birth: 20,000/μL; count decreases after second week, reaching normal adult value at 5-10 years.

C. OTHER ADJUSTMENTS AT BIRTH

1. *Fluid Balance, Acid Base Balance and Renal Function*

(i) Rate of fluid intake and fluid excretion in infant is seven times more with reference to body weight as in the adult; therefore, even a slight alteration of fluid balance leads to rapidly developing abnormalities.
(ii) The rate of metabolism in infants is two times more in relation to body mass as in the adult, *i.e.* two times as much acid is normally formed which produces tendency towards acidosis in infants.
(iii) Functional development of kidneys is not complete till one month of age *i.e.* kidneys of newborn can concentrate urine to only 1.5 times the osmolality of the plasma instead of the normal 3-4 times in adults. Therefore, important problems of infancy are: acidosis, dehydration or overhydration.

2. *Liver Functions*

During first few days of life liver functions are quite deficient as liver of the new born:
(i) Conjugates bilirubin with glucuronic acid poorly causing less excretion of bilirubin.
(ii) Less plasma protiens are synthesized, therefore, total plasma protein concentration decreases producing Hypoprotinaemic oedema.
(iii) Gluconeogenic function is deficient, thus decreases blood glucose level to 30-40 mg/dL.
(iv) Less clotting factors are formed.

Important Note

Physiological jaundice, page 79.

3. *Digestion, Absorption and Metabolism of Energy Foods*

In general, ability of the newborn infant to digest, absorb and metabolize food is same as of older child except that:
(i) There is deficient secretion of pancreatic amylase, therefore, newborn utilizes starch less adequately compared to older children.
(ii) Absorption of fats from GIT is less, thus, milk with high fat content is inadequately utilized.
(iii) Because of poor liver function, glucose concentration in blood is unstable and also low.

However, neonates are capable of synthesizing proteins and thereby storing nitrogen in much higher percentage than in adults.

4. *Metabolic Rate and Body Temperature*

The basal metabolic rate (BMR) of a neonate with respect to body weight is approximately two times that of the adult which results in two times as great cardiac output and minute ventilation in infants.
However, since body surface area (BSA) is very large compared to body mass, heat is readily lost from the body and, therefore, maintenance of body temperature presents a great problem.
Temperature regulation in the newborn is maintained by:
(i) During the first 48 hours after birth, T_4 secretion increases, which increases heat production in the body.
(ii) Deposits of brown adipose tissue occurs at: intra scapular region, around the neck, behind the sternum, around the kidneys and adrenal glands.

Brown fat is highly vascular with rich sympathetic nerve supply, therefore, responsi-ble for increased oxygen consumption and heat production on exposure to cold.

Important Note

In infants, neutral zone temperature is from 32.5–33.5°C *i.e.* the temperature at which oxygen consumption at rest or when asleep is minimal (in adults it is 27 ± 2°C, page 581). Therefore, average oxygen consumption is more in newborn, being 4.6 mL/kg/min (compared to adult 3.7 mL/kg/min). That is why premature babies are kept at this temperature in the incubator.

NUTRITION OF THE NEW BORN INFANT

Foetus obtains all its energy from glucose obtained from the mother's blood. At birth, amount of glucose stored in the infant body as glycogen is sufficient to supply the infant's needs for only a few hours; thereafter, appropriate mechanisms are available for the infant to utilize stored fats and proteins for metabolism until mother's milk can be provided 2-3 days later.

1. *Need for calcium and vitamin D:* The newborn infant is in a stage of rapid ossification of its bones at birth, therefore, ready supply of calcium throughout infancy is needed which is adequate in usual diet of milk. However, vitamin D is required to absorb this calcium from the GIT.
2. *Need for iron in the diet:* If mother had adequate amount of iron in diet during pregnancy, the liver of the newborn usually has enough stored iron to keep forming the blood cells for 4-6 months after birth.
3. *Need for vitamin C:* Vitamin C is not stored in significant amounts in foetal tissues, yet it is required for proper formation of cartilage, bone and other intracellular structures of the infant. Moreover, milk is a poor source of vitamin C, therefore, citrus fruits should be given by the third week of life.
4. *Immunity:* Neonate does not form antibodies of its own to a significant extent. By the end of first month, baby's γ-globulin (which contains antibody) decreases to less than 50% of the original level with corresponding decrease in immunity. Thereafter, baby's own immunization process begins to form antibodies and γ-globulin concentration returns to normal by the age of 12-20 months.

   Antibodies inherited from the mother can protect the infant for approximately six months against most major childhood infectious diseases (specially diphtheria, polio, tetanus) except for whooping cough.

THE BREAST AND LACTATION

THE BREAST

A. Structure of the Breast

1. The breast arises from the surface epithelium as solid column of cells which gradually is hollowed out to become *ducts*. These ducts branch to give rise to *terminal ductules* which, in turn, lead to the *alveoli*. **(Fig. 86.6)**
2. Covering the external surface of the epithelium of the alveoli and ducts are numerous elongated, branching striated cells, called *myoepithelium*.

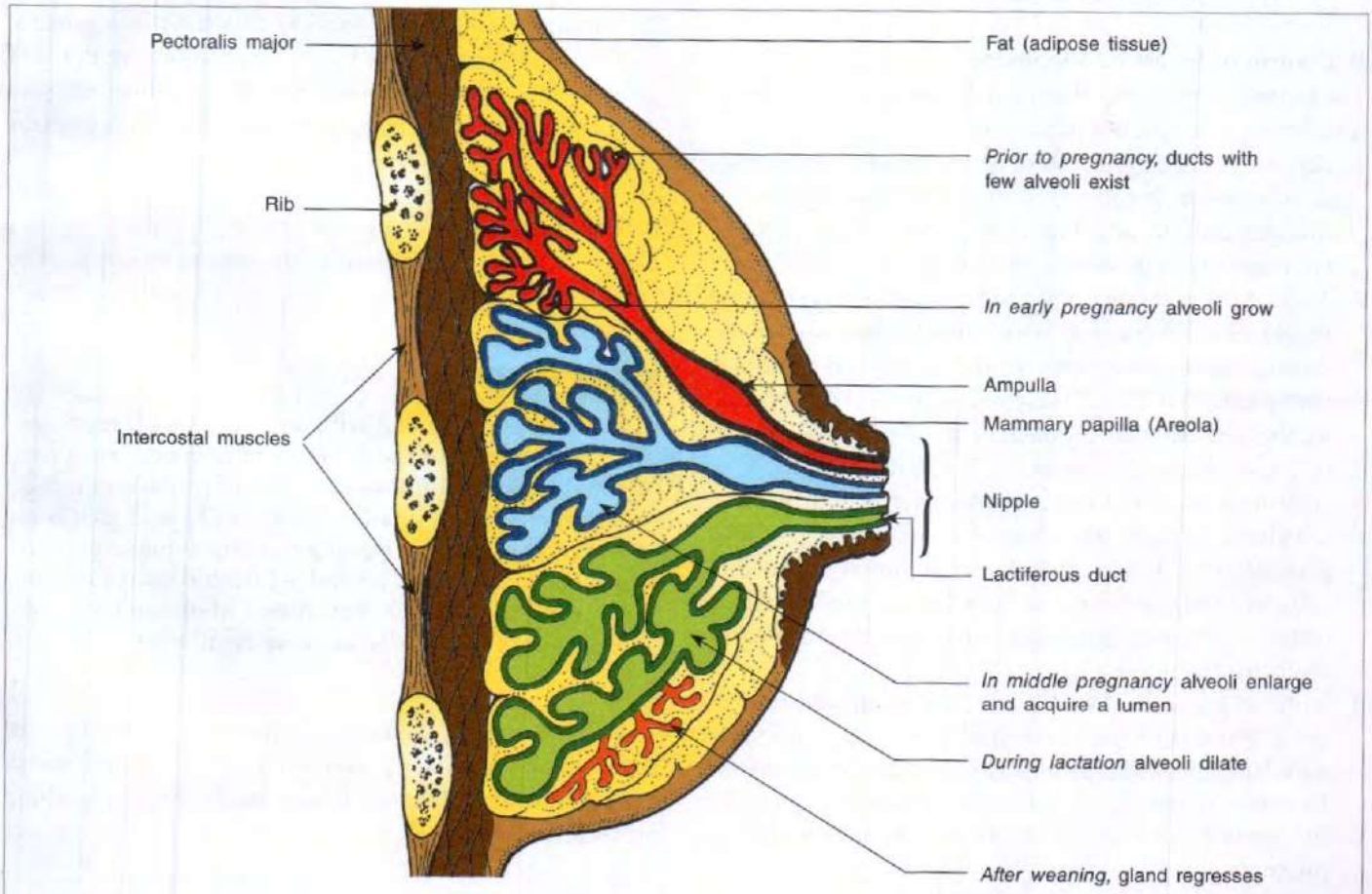


Fig. 86.6 Structure of the breast (also see to **Fig. 71.11**, page 671)

3. *At birth* the breast is rudimentary and consists of a tiny nipple from which radiate a few ducts. Little further development occurs until the time of puberty.
4. *At puberty* –
   (i) There occurs considerable growth and branching of the duct system which undergoes further proliferative changes with the recurrence of each menstrual cycle followed by regression. However, on the whole, progressive enlargement takes place due to increased deposition of fat.
   (ii) Between each menstrual period there is hyperaemia of the breasts, increase in interalveolar stroma with formation of new alveoli; however, these changes are transient.
5. *During pregnancy* the breasts enlarge greatly with marked change in structure.
   (i) During the first half of pregnancy there is further duct development accompanied by the appearance of many alveoli which form *lobules*. No milk is secreted by the breast gland cells at this stage.
   (ii) During the second half of pregnancy the epithelial cells swell with gradual initiation of secretory activity and slow accumulation of milk in the alveolar lumen. The further enlargement takes place due to distension of the breast with its secretion.

B. Control of breast development

The control of breast development depends on the complex interaction of a number of hormones.

1. *Role of oestrogen.* Oestrogen causes only *duct* development. It causes thickening of the nipple and marked growth and branching of the ducts. This is why oestrogen is called *growth hormone* of the breast.
2. *Role of progesterone.* Progesterone when given alone produces no changes in breast development; however, when given together with oestrogen, marked glandular development occurs. Thus progesterone is responsible for the *glandular* development *i.e.* it promotes the growth of the *lobules* and alveolar tissues in the breast.
3. *Role of prolactin.* Prolactin acts on a breast that has developed under the influence of oestrogen and progesterone. It acts directly on mammary epithelial cells to produce localized alveolar hyperplasia. This action is increased by *growth hormone, corticosteroids* and *thyroxine* (page 696).
4. *Role of placenta.* During pregnancy, in addition to oestrogen and progesterone the placenta also produces a prolactin growth hormone like factor, called ***placental lactogen*** (page 820). All these hormones promote the growth and development of the breast during pregnancy.

LACTATION

Lactation consists of two separate processes: *milk secretion* and *milk ejection*.

A. Milk secretion

It is the synthesis of milk by the alveolar epithelium and its passage into the lumen of the gland. It occurs in two phases: initiation and maintenance of secretion.

1. *Initiation of milk secretion* is called *Lactogenesis.*
   (i) Though some secretion is present in the breasts during the second half of pregnancy, a free flow of milk occurs only some days (1–3 days) after the child birth. The initiation of milk secretion is controlled by low circulating levels of oestrogen which activate the lactogenic function of the anterior pituitary mediated by prolactin. This effect is due to reduced secretion of prolactin inhibiting factor (PIF) by the hypothalamus (page 671).
   (ii) During pregnancy the lactogenic action of oestrogen is inhibited by progesterone. However, after child birth the rate of progesterone secretion decreases markedly before the decrease in oestrogen occurs, thus allowing the oestrogen to perform its lactogenic action.
2. *Maintenance of milk secretion* is called *Galactopoiesis.* This is also controlled by prolactin along with other hormones; these include growth hormone, thyroid hormones, insulin, adrenal cortical ovarian hormones (page 671).

B. Milk ejection

That is discharge of milk from the breast. *Mechanism of milk ejection*, page 674.

Important Note

Lactation is associated with amenorrhoea (stoppage of menstrual periods) and temporary sterility, probably due to inhibitory action of prolactin on the secretion of the gonadotrophins FSH and LH, but women can become pregnant again while nursing. *Lactation amenorrhoea* period is variable from 6 weeks (in women who do not nurse their infants) to 25–30 weeks (women who nurse regularly).

Chiari-Frommel Syndrome (rare) *i.e.* persistance of lactation and amenorrhoea in women who do not nurse their infants after delivery. It is probably due to persistant prolactin secretion.

Human Milk

Salient features

1. Milk is a natural balanced food and requires only the minimum of supplements to form a perfect diet.
2. It contains first class quality of protein, carbohydrates, fat, mineral salts (specially calcium and phosphorus) and vitamins.
3. *Colostrum*
   (i) it is the fluid secreted during the first three days after the child birth;
   (ii) it is deep yellow in colour and rich in protein (8.5 gm/dL) and salts;
   (iii) it is coagulated into solid mass spontaneously or by heat;
   (iv) it contains large granular bodies, called ***colostrum corpuscles***, which represent alveolar cells of the gland antibodies, leucocytes and macrophages loaded with fat; these corpuscles are abundant in the first two weeks.

Important Note

In the newborn, secretion of a fluid resembling colostrum may occur from nipple, probably stimulated by maternal hormones. It disappears after 1-2 days.

4. *'Transition' milk* or intermediate milk is formed during the first few weeks after parturition. *'Mature' milk* appears at the end of the first month.
5. Composition of colostrum, mature human milk and cow's milk is given in Table 86.2.
   (i) Proteins of milk come from the plasma amino-acids and proteins. Immunoglobulins can pass unchanged from maternal blood to milk. Two proteins are found in human milk, caseinogen and lactalbumin in the ratio of 1:2.
      (a) *Caseinogen:* it is converted by "rennin" into calcium caseinate which is insoluble in water, but is easily digested by gastric juice (page 215).
      (b) *Lactalbumin:* it resembles serum albumin.
   (ii) Fat of milk is in the form of minute globules; free fatty acids are found in minute amounts. Fat is formed partly from neutral fat of the blood and partly from acetate.
   (iii) The carbohydrate of milk is the disaccharide lactose (glucose-galactose). It is derived from the glucose of the plasma.
   (iv) The ***ash*** contains Ca^{2+}, K^{+}, Na^{+}, P^{3+} and Cl^{-}; iron is present in traces.
   (v) The vitamin content of milk depends on the maternal diet. It usually contains enough vitamins for the first few months of pregnancy. Vitamin supplements may be needed later.

Important Notes

(a) Milk is richer in younger women. It is unaffected by the return of menstruation but is adversely influenced by illness or by emotional disturbances.
(b) If the diet is inadequate, initially body tissues are used to form milk, therefore, it is not reduced much in amount. However, later milk production is reduced.

6. *The major differences between human and cow's milk are:*
   (i) The human milk contains considerable less proteins, less salts (0.03 gm/dL of calcium against 0.14 gm/dL in cow's milk) and more carbohydrates.
   (ii) Cow's milk contains about six times as much caseinogen as human milk which in the stomach forms large solid insoluble masses.
   (iii) Cow's milk contains considerable more fatty acids (eight times more than the human milk) and calcium.

Table 86.2: The differences between human and cow's milk (Values in gm/dL)

Content	Human colostrum	Mature human milk	Cow's milk
1. Protein	8.5	1.0 – 2.0	3.5
2. Carbohydrate (lactose)	3.5	6.5 – 8.0	4.7
3. Fat	2.5	3.0 – 5.0	3.5
4. Ash (Ca^{2+}, Na^{+}, K^{+}, P^{3+}, Cl^{-})	0.37	0.18 – 0.25	0.75
5. Calcium	–	0.03	0.14

3 1 2 – Caeboh.
3 1 2 – Fats
1 3 2 – Prot.

Study Questions

1. **Give physiological significance of:**
   (i) haemochorial and meconium
   (ii) foramen ovale, ductus arteriosus and ductus venosus
   (iii) lactogenesis and galactopoiesis
   (iv) colostrum and transition milk.
2. **Give physiological basis of:**
   (i) hyperventilation in pregnant women
   (ii) low foetal weight in multiple pregnancies
   (iii) closure of ductus arteriosus, foramen ovale and ductus venosus
   (iv) higher incidences of patent ductus arteriosus in children with history of foetal distress
   (v) a higher pO_2 of 60-80 mmHg is undesirable in a foetus
   (vi) impaired foetal development in females who smoke heavily
   (vii) Premature babies are kept in the incubator at neutral zone temperature.
3. **Write shorts notes on:**
   (i) double Bohr's effect and double Haldane's effect
   (ii) amniotic fluid
   (iii) growth and development of foetus
   (iv) respiratory system of a newborn
   (v) line diagram showing circulation in foetus
   (vi) temperature regulation in a newborn
   (vii) control of breast development
   (viii) milk secretion and milk ejection.
   (ix) Circulatory adjustment at birth
   (x) Respiratory adjustment at birth
4. **Differentiate between:**
   (i) milk secretion and milk ejection
   (ii) human and cow's milk
   (iii) lactogenesis and galactopoiesis.
5. **Give the compensatory mechanisms in foetus for decreased arterial pO_2.**
6. **How is expansion of lungs brought about at birth? How is regular breathing established in a newborn?**
7. **Mention the characteristic features of foetal circulation.**
8. **How can long inherited antibodies from the mother protect an infant against infectious diseases?**
9. **Draw labelled diagram:**
   (i) Gases exchange at placenta
   (ii) Gain in length and weight of a foetus
   (iii) Changes in circulation after birth
   (iv) Structure of breast in early, middle and late pregnancy

MCQs

1. **Umbilical vein pO_2 is:**
   (a) Same as that of arterial pO_2 in adult
   (b) 2/3rd of arterial pO_2 in adult
   (c) 50% of arterial pO_2 in adult
   (d) 1/3rd of arterial pO_2 in adult
2. **pCO_2 is maximum in:**
   (a) Umbilical artery (b) Umbilical vein (c) Uterine artery (d) Uterine vein
3. **Amniotic fluid, *not a true* statement:**
   (a) Volume at term is about 1 L
   (b) Protein and electrolyte content same as of plasma
   (c) Formed mainly by transudation from maternal blood
   (d) Removed through drinking by the foetus
4. **The details of different organs are established in foetus after ..... months of pregnancy:**
   (a) 2-3 months (b) 3-4 months (c) 4-5 months (d) 5-6 months

5. **A neonate can tolerate complete asphyxia upto:**
   (a) 4-5 minutes (b) 8-10 minutes (c) 10-15 minutes (d) 15-30 minutes
6. **In a newborn, breathing becomes completely normal only after ..... minutes of birth:**
   (a) 20 (b) 30 (c) 40 (d) 50
7. **Cardiovascular function in neonate is different from that in embryo in that in neonates:**
   (a) Left atrial pressure becomes lower than the right atrial pressure
   (b) Pressure in all cardiac chambers is same throughout the cardiac cycle
   (c) Pulmonary vascular resistance is higher than in embryo
   (d) Pulmonary vascular resistance is lower than in embryo
8. **A patent ductus arteriosus in the new-born is:**
   (a) A typical right-to-left shunt (b) Distinguished by poor oxygenation of the arterial blood
   (c) Usually associated with an intra-ventricular septal defect (d) An open vessel connecting the aorta to the pulmonary artery
9. **Lactogenesis differs from galactopoiesis in that:**
   (a) It is defined as initiation of milk secretion (b) Referred as maintenance of milk secretion
   (c) Controlled by prolactin (d) Influenced by growth hormone, thyroid hormone, insulin, etc.
10. **How foetal O_2 requirements are met when pO_2 of umbilical vein blood is only 30-35 mmHg?**
    (a) HbF has more affinity for O_2 as compared to HbA (b) Haemoglobin concentration in foetus is greater
    (c) Double Bohr's effect (d) All of the above
11. **Oxygen saturation of blood in umbilical artery is about ..... %:**
    (a) 40 (b) 60 (c) 80 (d) 90
12. **Following is *true* about umbilical vein:**
    (a) Paired structure carrying oxygenated blood (c) Unpaired structure carrying oxygenated blood
    (c) Paired structure carrying deoxygenated blood (d) Unpaired structure carrying deoxygenated blood
13. **CO_2 gradient in placenta is ..... mmHg:**
    (a) 2-3 (b) 4-5 (c) 5-10 (d) 10-15
14. **Substance which can easily and rapidly cross the placenta to enter the foetal circulation:**
    (a) Urea (b) Plasma proteins (c) Antibodies (d) RBCs
15. **Greatest growth of foetus occurs during:**
    (a) First trimester (b) Second trimester (c) Third trimester (d) Equal in all trimesters
16. **Formation of heart in a foetus begins during ..... week of pregnancy:**
    (a) 2nd (b) 3rd (c) 4th (d) 5th
17. **Which of the following organs first forms RBCs in a foetus?**
    (a) Liver (b) Bone marrow (c) Placenta (d) Spleen
18. **Respiratory movement in a foetus which appears at 12 weeks, gets inhibited after 20-24 weeks possible due to:**
    (a) Special chemical conditions in the body fluid of the foetus
    (b) Presence of fluid in foetal lungs
    (c) Other unknown stimuli
    (d) All of the above
19. **Meconium:**
    (a) Starts forming in foetal GIT at 20-24 weeks
    (b) Consists of unabsorbed residue of amniotic fluid
    (c) Contains excretory products from GIT mucosa and glands
    (d) All of the above
20. **How much negative pressure is required to open up the foetal alveoli for the first time?**
    (a) 10 mmHg (b) 15 mmHg (c) 20 mmHg (d) 25 mmHg
21. **During foetal life, less blood is pumped through the lungs because:**
    (a) Lungs are mainly non-functional (b) Lungs are collapsed
    (c) Vascular resistance offered by lungs is high (d) All of the above
22. **Foetal distress at birth results in higher incidences of patency of ductus arteriosus because:**
    (a) Birth hypoxia prevents contraction of smooth muscle in the wall of ductus arteriosus
    (b) Increased pulmonary artery pressure
    (c) Increased resistance in pulmonary vasculature
    (d) All of the above

23. **The cardiac output of neonate is:**
(a) 200 mL/min (b) 350 mL/min (c) 400 mL/min (d) 550 mL/min

24. **Which of the following breast change is not a function of oestrogen?**
(a) Acinar growth (b) Ductular growth (c) Stromal growth (d) Fat deposits

25. **Colostrum is:**
(a) Fluid secreted during the first three days after child birth (b) Rich in proteins and salts
(c) Contains leucocytes loaded with fat (d) All of the above

26. **Human milk differs from cow's milk as it:**
(a) Contains less proteins and salt (b) Contains more carbohydrates
(c) Contains less fat and calcium (d) All of the above

Answers

1. (d) 2. (a) 3. (b) 4. (b) 5. (b) 6. (c) 7. (d) 8. (d) 9. (a) 10. (d) 11. (b) 12. (b) 13. (a) 14. (a) 15. (c)
16. (c) 17. (a) 18. (d) 19. (d) 20. (d) 21. (d) 22. (a) 23. (d) 24. (a) 25. (d) 26. (d)

Unit XI

THE NERVOUS SYSTEM

- **Chapter 87: Organization of the Nervous System**

  Central nervous system: Brain and spinal cord; Peripheral nervous system: Somatic and autonomic nervous system

- **Chapter 88: The Synapse**

  Physiological anatomy, structure, types and classification of synapses; Electrical events at synapses; Inhibition of synapses; properties of synapses.

- **Chapter 89: Sensory Receptors**

  Definition, function and classification; Cutaneous receptors, electrical and ionic events in receptors; Properties of receptors.

- **Chapter 90: Reflexes**

  The Reflex arc, classification; Monosynaptic reflex (stretch reflex): muscle spindle, higher control,muscle tone and inhibition (inverse stretch reflex); Polysynaptic reflexes: the withdrawal reflex; General properties of reflexes.

- **Chapter 91: The Sensory System**

  Important terminology; Ascending (Sensory) tract in the spinal cord; Somatosensory cortex; Somatic sensations: touch-pressure, proprioception and kinesthesia, temperature, pain and others (itch, vibratory sense, two-point discrimination, stereognosis).

- **Chapter 92: The Motor Areas and Descending Tracts**

  Motor areas; Descending tracts: Pyramidal and extrapyramidal tracts; Applied: Lower versus upper motor neuron lesion; Lesions of the pyramidal tracts – hemiplegia.

Chapter 925 : CSF , BBB.

- **Chapter 93: The Autonomic Nervous System**

  Differences between somatic and autonomic nervous system; Organization of ANS: sympathetic and parasympathetic divisions; Chemical transmission at autonomic junction; Responses of effector organs to autonomic nerve impulse.

- **Chapter 94: Spinal Cord Lesions**

  Functions of the spinal cord; Transection of the spinal cord: complete, incomplete, hemisection (Brown-Sequard syndrome); Sensory disturbances.

- **Chapter 95: The Vestibular Apparatus (Labyrinth)**

  Physiological anatomy; the vestibular pathways; Functioning: Mode of action of semicircular canals and otolith organ (saccule and utricle); role in regulation of posture; Vestibular dysfunctions.

#: Cover CSF from Dr. Sudhakar.

Chapter 96: Control of Body Movement and Posture

Introduction; Control of body movement: Levels of motor control system; Control of body posture: Postural reflexes; mechanism of normal standing posture; Walking.

Chapter 97: The Reticular Formation

Ascending reticular system (reticular activating system); Descending reticular system: inhibitory and facilitatory projections; functions of reticular formation.

Chapter 98: The Cerebellum

Physiological anatomy: Divisions-lobes; the cerebellar cortex: structure, inputs, neural circuits; connections, functions and lesions of the cerebellum.

Chapter 99: The Thalamus

Introduction; Classification of thalamic nuclei; connections and functions; Thalamic syndrome.

Chapter 100: The Electroencephalogram and Sleep

Electroencephalogram (EEG): Normal EEG; physiological basis; Uses.

Sleep: factors affecting, physiological changes; types (NREM vs REM, sleep cycle); Genesis; Control of 'sleep-waking' cycle; Sleep disorders.

Chapter 101: The Basal Ganglia

Physiological anatomy; Connections and functions; Diseases of the basal ganglia: Parkinson's disease, chorea, athetosis.

Chapter 102: The Hypothalamus

Physiological anatomy: hypothalamic nuclei; connections and functions; Control of food and water intake.

Chapter 103: The Cerebral Hemisphere (Cerebrum)

Physiological anatomy; Structure, methods of study; Parietal, frontal, prefrontal, occipital and temporal lobes. (Kluver-Bucy Syndrome)

Chapter 104: The Limbic System: Emotion and Motivation

The limbic system: structure, connections, functions, unique features.

Emotions: fear and rage; Motivation: reward and punishment system. Sexual behaviour.

Chapter 105: Higher Functions of the Nervous system

Language (speech): dominant versus representational hemisphere, speech centres, speech pathways, speech disorders – aphasia. Learning: conditioned reflexes; Memory: Alzheimer's disease and senile dementia.

Chapter 106: Chemical Transmission in the Nervous system

Introduction: Neurotransmitter classification; A-ch; Biogenic amines: Catecholamines (epinephrine, nor-epinephrine, dopamine), Serotonin, histamine; Amino-acid neurotransmitters: excitatory and inhibitory; Polypeptides: Enkephalins, Endorphins and substance P, CGRP, Neuropeptide Y; Purinergic neurotransmitters: Adenosine, ATP; Others: Nitric oxide, prostaglandins.

Chapter

87

Organization of the Nervous System

I. Central nervous system: Brain and spinal cord

II. Peripheral nervous system
   A. Somatic nervous system
   B. Autonomic nervous system

Brain = KIMS

The basic structural and functional unit of the nervous system is the individual nerve cell, the *neuron* (for details, refer to page 135). Billions and trillions of such neurons constitute the *Nervous System*. The various parts of the nervous system are interconnected, but for convenience the nervous system can be broadly divided into two major parts: *central* and *peripheral* nervous system.

CENTRAL NERVOUS SYSTEM

part of the nervous system which occupies the central of the body is called central nervous system (CNS). mprises the *brain* and the *spinal cord*.

College Nimrah mosque rd

THE BRAIN (HOLLE)

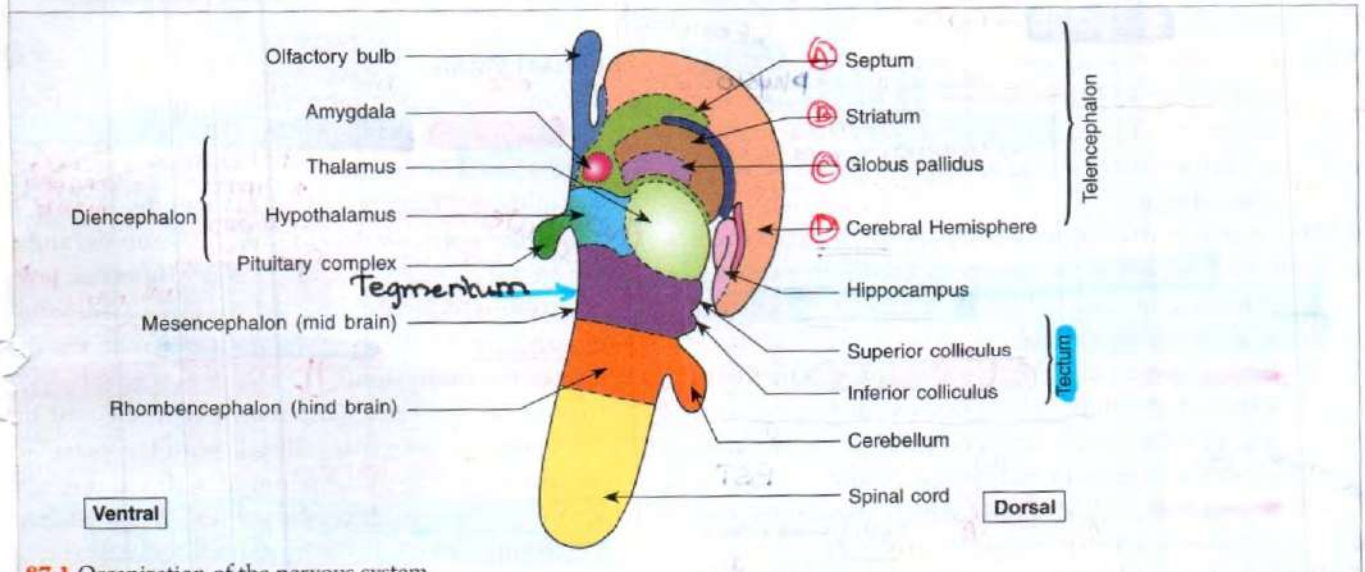
eighs about 1.5 kg in adults and comprises all the ctures which are intracranial i.e. located within a hard bony skull. It is divided into 3 parts: *fore* brain, *mid* brain and *hind* brain. The brain also contains 4 interconnected cavities, the *cerebral ventricles*, that contain cerebrospinal fluid (CSF). (4)

1. ***Fore brain:*** It is subdivided into: *telencephalon* and *diencephalon* **(Fig. 87.1)**.

   (i) ***Telencephalon*** – it consists of the two *cerebral hemispheres* (or *cerebrum*) and their interconnections.

   (a) The hemispheres, although separated by a longitudinal division, are connected to each other by bundles of nerve fibers known as commissures, the *corpus callosum* being the largest.

   (b) The cortex of each hemisphere is divided into 4 lobes, the *frontal, parietal, occipital* and *temporal* **(Fig. 87.2)**.



87.1 Organization of the nervous system

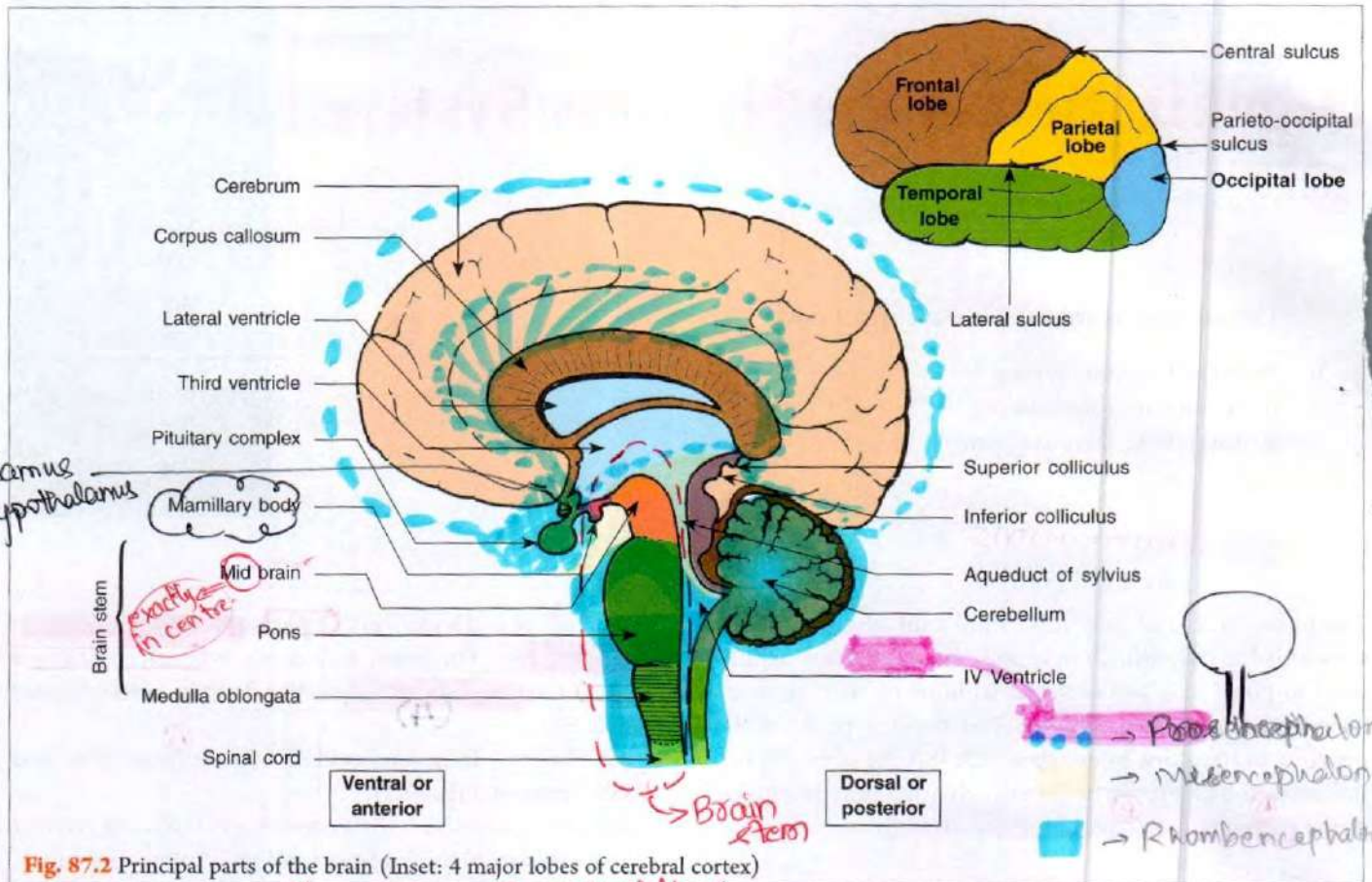


Fig. 87.2 Principal parts of the brain (Inset: 4 major lobes of cerebral cortex)

(c) The *cerebral cortex*, an area of grey matter, about 3 mm thick, is highly folded. This increases the area available for cortical neurons without increasing appreciably the volume of the brain.

(d) The *subcortical nuclei* form other areas of grey matter that lie deep within the cerebral hemispheres. Predominant among them are the *basal ganglia*.

(ii) *Diencephalon* – its upper 2/3rd comprises *thalamus* and lower 1/3rd comprises *hypothalamus* which connects with the *pituitary complex*. The thalamus is a large cluster of nuclei that serves as a synaptic relay station.

2. *Mid brain or Mesencephalon:* It is divided into two parts by *Aqueduct of Sylvius* (duct which connects the IIIrd ventricle in the midbrain, with the IVth ventricle in the pons and medulla) into:

(i) Ventral part called *cerebral peduncle*, chiefly of white matter, uniting the pons with the thalamic region of the cerebrum. It comprises the *tegmentum*, *substantia nigra* and *basis peduncle*; and

(ii) Dorsal part, called *tectum* which constitutes two elevations, *superior and inferior colliculi*.

3. *Hind brain or Rhombencephalon.* It comprises *pons*, *medulla oblongata* and *cerebellum*.

Important Note

An area of brain that includes both grey and white matter is the *Limbic System*. It is formed by an interconnected group of brain structures, including portions of frontal and temporal lobes, thalamus, hypothalamus, as well as the pathways that connect them (page 1024).

Important Points

1. The mid brain, pons and medulla together constitute the *brain stem*. All cranial nerves are situated in the brain stem. For example:
   (i) in the mid brain – III and IV nerves,
   (ii) in the pons – V, VI, VII and VIII nerves, and
   (iii) in the medulla – IX, X, XI and XII nerves.
2. The **cerebellum** is connected by three large bundles of nerve fibers, the *cerebellar peduncles* with the dorsal side of the brain stem:
   (i) via *superior cerebellar peduncle* with the mid brain,
   (ii) via *middle cerebellar peduncle* with the pons, and
   (iii) via *inferior cerebellar peduncle* with the medulla.
3. Running through the core of the brain stem and consisting largely of neuron cell bodies (*i.e.* grey matter), is the *reticular formation* (page 957).

FUNCTIONS OF THE BRAIN

Refer to Table 87.1.

Table 87.1: Functions of the brain

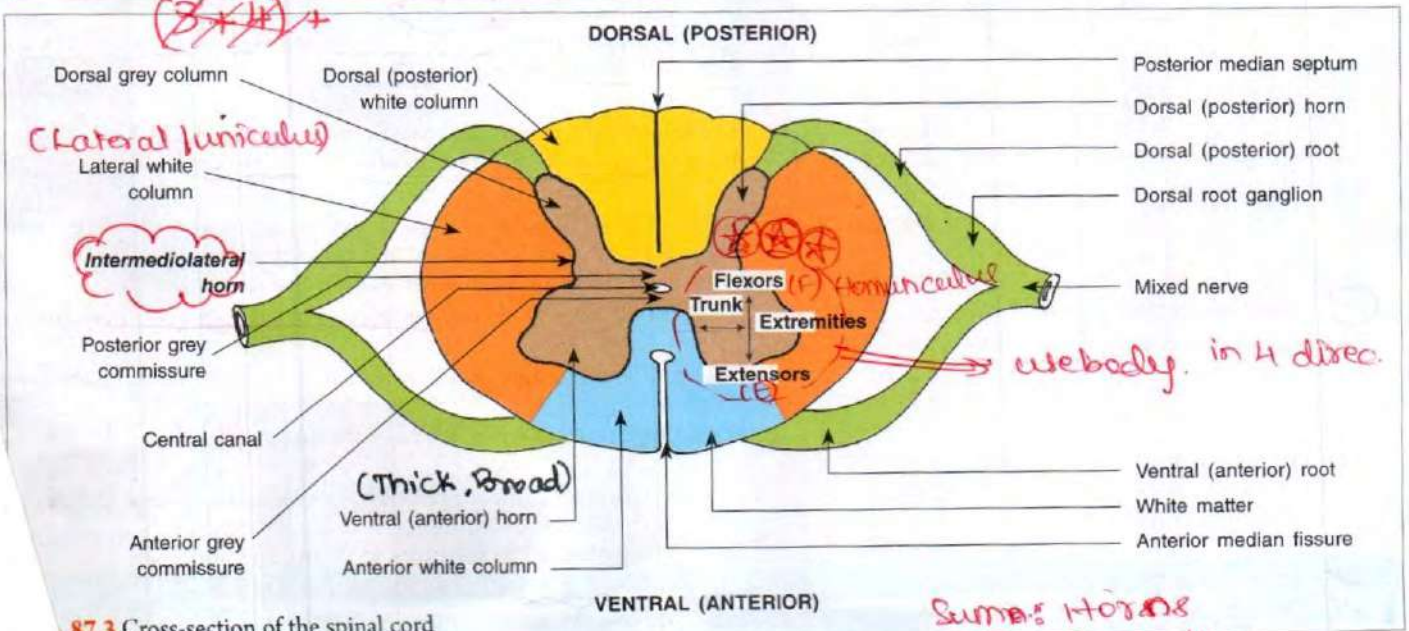
Region	Function
I. Cerebrum	
1. Cerebral cortex	
(i) Sensory fields	Perception
(ii) Motor areas	Skeletal muscle movement
(iii) Association areas	Integration of information and direction of voluntary movement
2. Basal gangila	Movement
3. Limbic system	
(i) Amygdala	Emotion and memory
(ii) Hippocampus	Learning and memory
II. Diencephalon	
1. Thalamus	Integrating center and relay station for sensory and motor information
2. Hypothalamus	Homeostasis and behavioural drives
3. Pituitary	Hormone secretion
4. Pineal gland	Melatonin secretion
III. Cerebellum	Muscular movement and coordination
IV. Brain stem	
1. Midbrain	Eye movement
2. Pons	Relay station between cerebrum and cerebellum; coordination of breathing
3. Medulla oblongata	Control of involuntary functions
4. Reticular formation	Arousal, sleep, muscle tone, pain modulation

B. THE SPINAL CORD

1. The spinal cord is a long (approx. 45-50 cm in length), narrow (about 2 cm in diameter) cylindrical structure. It lies outside the skull beginning from its base at the foramen magnum to terminate at the lower border of 1st lumbar vertebra. Below the 1st lumbar vertebra the spinal cord contains the lumbar and sacral roots in bands, known as the *cauda equina* (or horse tail).
2. A *cross-section* of the spinal cord shows the following structures (Fig. 87.3):
   (i) A prominent fissure anteriorly, called *anterior median fissure* and a less prominent fissure (or septum) posteriorly, called *posterior median fissure* (or septum); between these fissures lies the *central canal*.
   (ii) The grey matter consisting of nerve cells forms an H-shaped figure long and narrow *dorsal (posterior) horns;* and thick, broad *ventral (anterior) horns*. The horizontal stem of the H constitutes the *grey commissure* (anterior and posterior), which surrounds the central canal.
   (iii) The ventral or anterior horn contains the cell bodies of α, γ and Renshaw motor neurons; axons of α and γ motor neurons pass out in the ventral (or anterior) roots. These nerve fibers are *purely motor* in function.

Important Note

The ventral horn motor neurons show an orderly topographical arrangement within the spinal cord (Fig. 87.3). Motor neurons supplying the muscles of the proximal limb muscle and the trunk are situated medially, and those supplying the distal limb muscles are situated laterally. The muscles that flex the limbs (*flexors*) are represented more posteriorly (*dorsally*), while the muscles that extend the limbs (extensors) are represented anteriorly (*ventrally*).



87.3 Cross-section of the spinal cord

(iv) The **dorsal or posterior horn** receives the fibers of the posterior roots which are *purely sensory* in function. Their cell bodies are found in the dorsal (posterior) root ganglion which is a swelling on the posterior root. These ganglion cells are bipolar, their axons connect both with peripheral structures and with structures in the dorsal horn.

Important Note

In between the ventral and dorsal horns lies the *intermediolateral horn* which contains the cell bodies of *autonomic* neurons (sympathetic division). These sympathetic neuronal cell bodies extend only between T_1 to L_2 segment of the spinal cord.

(v) Surrounding the grey matter is the white matter, consisting of large numbers of ascending and descending axons cut across. The white matter is divided into three *white columns* (or funiculi):

(a) *anterior white column*, lying between the anterior median fissure and the anterior roots;

(b) *lateral white column*, lying between the anterior and posterior roots; and

(c) *dorsal white column*, lying between the posterior roots and the posterior median fissure.

(vi) The sensory and motor fibers join to form a *mixed nerve* which comes out from the vertebral canal as a *peripheral spinal nerve* via the intervertebral foramen.

Important Notes

1. In the brain stem and the spinal cord white matter surrounds the grey matter and consists mostly of myelinated nerve fibers; whereas in the cerebrum and cerebellum, grey matter surrounds the white matter and consists mainly of nerve cells and neuroglia.
2. The fatty 'myelin' in myelinated nerve fibers gives a white appearance to the white matter whereas the cell bodies of neurons provide the grey matter, a grey (ash colour) appearance.

Table 87.2: The cranial nerves: Fiber types and functions

	Name	Fiber types	Principal function
I.	Olfactory nerve	Afferent	Olfaction (smell)
II.	Optic nerve	Afferent	Vision
III.	Oculomotor nerve	Mixed (i) Efferent (ii) Afferent	 Innervate extrinsic muscles that move the eyeball and intrinsic muscles that constrict pupil and alter lens shape for accommodation. Bring sensation from proprioceptors in eye muscles.
IV.	Trochlear nerve	Mixed (i) Efferent (ii) Afferent	 Innervate extrinsic muscles that move the eyeball. Bring sensation from proprioceptors in eye muscles.
V.	Trigeminal nerve	Mixed (i) Efferent (ii) Afferent	 Innervate muscles of mastication. Bring sensations from receptors in skin and skeletal muscles of face, nose, and mouth and from teeth sockets.
VI.	Abducens nerve	Mixed (i) Efferent (ii) Afferent	 Innervate extrinsic muscles that move the eyeball. Bring sensations from proprioceptors in eye muscles.
VII.	Facial nerve	Mixed (i) Efferent (ii) Afferent	 Innervate skeletal muscles of facial expression and swallowing; also innervate nose, palate, lacrimal and salivary glands. Bring taste sensation from anterior 2/3rd of the tongue.
VIII.	Vestibulocochlear nerve	Afferent	Audition (hearing), and maintenance of balance and equilibrium.
IX.	Glossopharyngeal nerve	Mixed (i) Efferent (ii) Afferent	 Innervate muscles involved in swallowing and parotid salivary gland. Bring taste from posterior 1/3rd of the tongue.
X.	Vagus nerve	Mixed (i) Efferent (ii) Afferent	 Innervate muscles of heart, pharynx, larynx and GIT; and glands of thorax and abdomen. Bring information from receptors in thorax and abdomen.
XI.	Spinal accessory nerve	Efferent	Innervate neck muscles (sternomastoid and trapezius).
XII.	Hypoglossal nerve	Efferent	Innervate muscles of the tongue.

PERIPHERAL NERVOUS SYSTEM

This is the part of nervous system which lies outside the CNS. It consists of the nerves extending from the brain and spinal cord out to all parts of the body. It is divided into: *somatic* and *autonomic* nervous system.

A. THE SOMATIC NERVOUS SYSTEM

It is made up of all the nerve fibers going from the CNS to the skeletal muscles cells. It comprises the *spinal* and *cranial* nerves.

1. ***The spinal nerves:*** There are *31 pairs* of the spinal nerves. Each pair is attached to the spinal cord by two roots viz. dorsal root and ventral root. These include:
   (a) 8 pairs of *cervical* nerves,
   (b) 12 pairs of *thoracic* nerves,
   (c) 5 pairs of *lumbar* nerves,
   (d) 5 pairs of *sacral* nerves, and
   (e) 1 pair of *coccygeal* nerve.

   31 pairs

   S_2 S_3 S_4

2. ***The cranial nerves:*** These nerves have their cell bodies in the brain. There are 12 pairs of the cranial nerves. Some are *afferent (sensory)*, some are *efferent (motor)* and those containing both of these components are called *mixed* nerves **(Table 87.2)**.

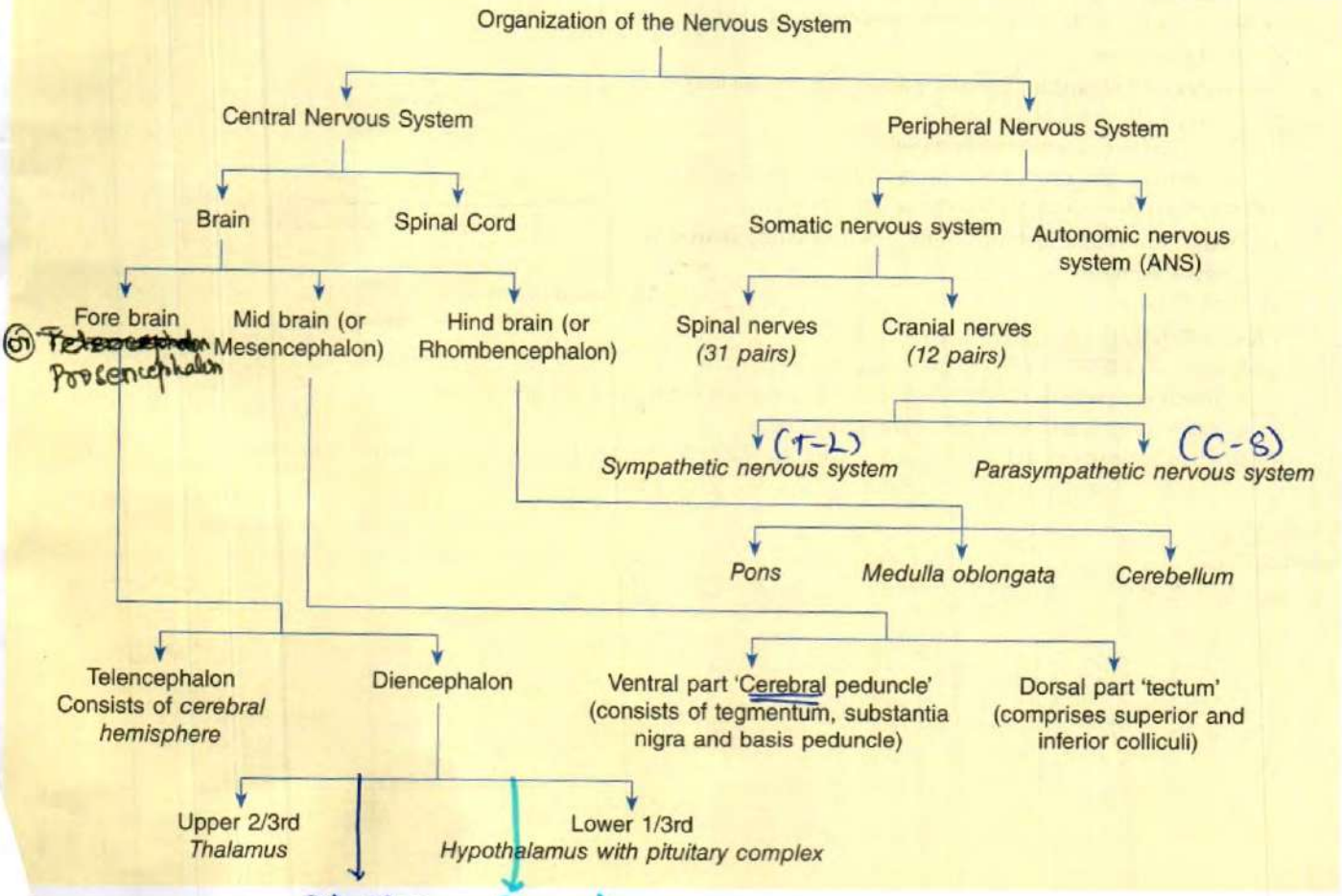
B. THE AUTONOMIC NERVOUS SYSTEM (ANS)

The innervation of all tissues *other than* skeletal muscle is by way of the ANS.

It is also called *vegetative or involuntary nervous system.* It is organised into two distinct regions along the CNS forming the *sympathetic* and *parasympathetic* systems. The ***sympathetic division*** consists of the thoracic and lumbar ganglia, therefore, also called *thoraco-lumbar division;* and ***parasympathetic division*** consists of the cranial ganglia (III, VII, IX and X cranial nerves) and sacral ganglia (2nd, 3rd and 4th sacral segments of the spinal nerves), therefore, also called *craniosacral division.* (For details refer to pages 919 - 928)

#: Cervical region doesn't have any ANS nuclei.

SUMMARY



Study Questions

1. Give functional organization of:
   (i) a neuron
   (ii) nervous system.
2. Draw a cross-section of the spinal cord and label the prominent structures.
3. Name the motor neurons located in the spinal cord.
4. How are the motor neurons arranged within the ventral horn of the spinal cord?
5. Give the fiber types and functions of the cranial nerves.

MCQs

1. *Not a true* statement regarding the brain stem:
   (a) It comprises of midbrain, pons and medulla
   (b) All cranial nerves originate from this place
   (c) Three large bundles of nerve fibers connects it with the cerebellum
   (d) Contains many of the areas concerned with regulation of heart rate, B.P. and respiration
2. Motor neuron *not* contained within the anterior horn of the spinal cord is:
   (a) Alpha
   (b) Delta
   (c) Gamma
   (d) Renshaw cell
3. *True* about topographical arrangement of motor neurons within the anterior horn of spinal cord is:
   (a) Motor neurons supplying the muscles of the trunk are situated medially
   (b) Those supplying the extremities are situated laterally
   (c) Flexors group of the muscles are represented posteriorly
   (d) All of the above
4. *False* statement regarding the autonomic nervous system:
   (a) Innervate all tissues of the body
   (b) Also called vegetative nervous system
   (c) Sympathetic division is called thoraco-lumbar division
   (d) Cranio-sacral division is parasympathetic division
5. An area of brain that includes both grey and white matter is the:
   (a) Cerebral cortex
   (b) Basal ganglia
   (c) Limbic system
   (d) Corpus callosum
6. Intermediolateral horn of the spinal cord:
   (a) Contains cell bodies of autonomic neurons
   (b) Contains sympathetic neuronal cell bodies that extends throughout the spinal cord
   (c) Contains only parasympathetic neuronal cell bodies
   (d) Contain sympathetic neuronal cell bodies that extend only between T_1 to L_2 segment of the spinal cord

Answers

1. (b) 2. (b) 3. (d) 4. (a) 5. (c) 6. (d)

Chapter

88

The Synapse

I. Physiological anatomy
   A. Structure of a synapse
   B. Types of synapses
   C. Classification of synapses
II. Electrical events at synapses: EPSP; IPSP
III. Inhibition at synapses
IV. Properties of synapses

PHYSIOLOGICAL ANATOMY

The term *synapse* was first introduced by *'Sherrington' C.S.* (1924) as the site of *contiguity* (contact without continuity). It is the junction where the axon (or some other portion) of one cell terminates on the dendrites or some other portion of another cell. The neuron which sends messages is called the *presynaptic cell* whereas the neuron which receive messages is called the *postsynaptic neuron*. Synapse is invariably used to describe the separation between the axon terminals of one nerve fiber and the dendritic processes of an adjacent neuron.

A. STRUCTURE OF A SYNAPSE

The structure of synapse varies considerably throughout the nervous system, however, general features at most of the synapses comprise the following structures: **(Fig. 88.1)**

1. *Synaptic knob.* It is the terminal bulbous (knob like) ending of the presynaptic axon which is devoid of neurofilaments and contains:
   (i) *Synaptic vesicles*
      (a) The presynaptic cytoplasm contains *vesicles*, approx. 50 nm in diameter gathered near the membrane. These vesicles contain small packets of chemical transmitter responsible for excitation (or inhibition) of the neuron next in the chain. The vesicles are transported down the axon along *microtubules* in the axon.
      (b) *Types of synaptic vesicles in the nervous system.*
      - Small clear type - contain A-ch, glycine, GABA or glutamic acid
      - Small dense type - contain catecholamine;
      - Large dense type - contain neuropeptides
      (c) Synaptic vesicles at excitatory synapses are circular whereas those at inhibitory synapses are flat or elongated.
      (d) *Mechanism of release of chemical transmitter* from the vesicles is same as seen at neuromuscular junction (page 155).
   (ii) Mitochondria containing plentiful of ATP.
   (iii) Microtubules.
   (iv) *Presynaptic membrane.* It is the nerve membrane which is in close approximation with the membrane of the postsynaptic cell.

Important Note

The number of synaptic knobs varies from one per postsynaptic cell (in the mid-brain) to a very large number, upto 10,000 (in the spinal cord).

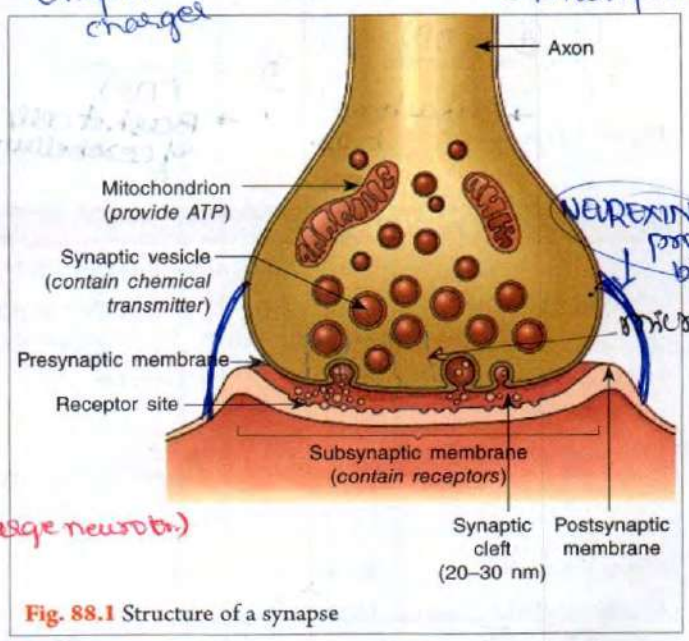


Fig. 88.1 Structure of a synapse

2. *Subsynaptic and postsynaptic membrane.* The surface of the cell membrane involved in the synapse is called the 'subsynaptic membrane' and the remainder of the motor neuron cell membrane is called the 'post synaptic membrane'. *Receptors* are usually located on the subsynaptic membrane.
3. *Synaptic cleft.* It is a gap of 20-30 nm that separates the pre and postsynaptic membranes.

Important Note

Orderly organization of the synapse depends on *Neurexins*, i.e. protein bind to the membrane of the presynaptic neurons. They bind to the *neurexin receptors* in the post-synaptic neurons and function as:

1. hold synapses together; and
2. provide a mechanism for the production of synaptic specificity.

B. TYPES OF SYNAPSES

The various types of synapses which commonly exist in the nervous system are given in Table 88.1 and Fig. 88.2.

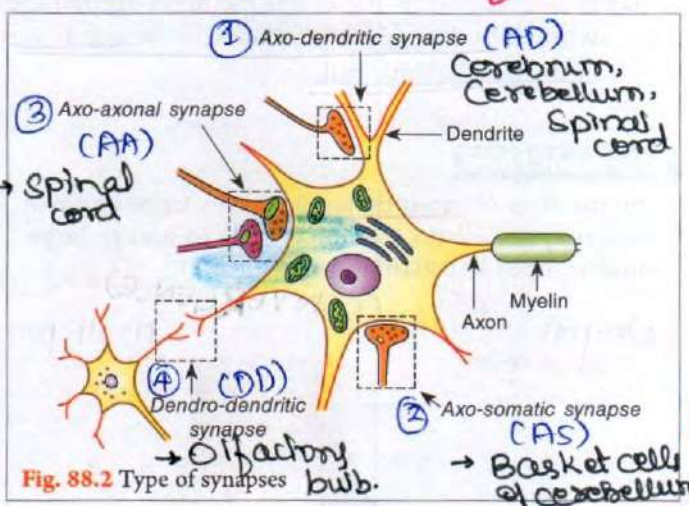


Fig. 88.2 Type of synapses

C. CLASSIFICATION OF SYNAPSES

1. *Anatomical classification.* Based on the type of synapses and their anatomic features the synapses are of two types: *type I and type II.* (Table 88.2)
2. *Physiological classification.* Based on functional transmission the synapses are divided into 3 types:
   (i) *Chemical synapses* – Synapses where impulse in the presynaptic cell causes secretion of chemical neurotransmitter. Transmission at most synaptic junction is chemical.
   (ii) *Electrical synapses* – Synapse where transmission is electrical.
   (iii) *Conjoint synapses* – Synapses where transmission is both chemical and electrical.

   Differentiating features between chemical and electrical synapses are given in Table 88.3.

Note

A neuron postsynaptic to one group of cells can be presynaptic to another.

ELECTRICAL EVENTS AT SYNAPSES

Single stimulus applied to the sensory nerves, does not lead to the formation of a propagated action potential in the post-synaptic neuron, rather it produces either a transient partial depolarization or a transient hyperpolarization.

A. EXCITATORY POSTSYNAPTIC POTENTIALS (EPSP)

1. The initial *depolarizing response* produced by a single stimulus to the sensory nerve begins about 0.5 msec after the afferent impulse enters the spinal cord. It rises to its peak 1–1.5 msec later, if it is not sufficient to cause the generation of a spike; and then declines slowly over the next 4 msec (Fig. 88.3). During this potential, the excitability of the neuron to other stimuli is increased, therefore, the potential is called an EPSP.

Table 88.1: Type of synapses and their location within the nervous system

Type of synapse	Site of contiguity (close proximity between)		Main location in the nervous system
	Part of pre-synaptic cell	Part of post-synpatic cell	
1. *Axo-dendritic* (most commonly seen)	Axon	Dendrite	(i) Motor neurons in the spinal cord. (ii) Excitatory synapse in the cerebral cortex. (iii) Climbing fibers in the cerebellum (page 964).
2. *Axo-somatic*	Axon	Soma or perikaryon	(i) Motor neurons in the spinal cord. (ii) Basket cells of the cerebellum (page 964). (iii) Autonomic ganglia.
3. *Axo-axonal*	Axon	Axon	(i) Spinal cord.
4. *Dendrodendritic* (rare)	Dendrite	Dendrite	(i) Synapse between mitral and granule cell in the olfactory bulb (page 1057).

Table 88.2: Anatomical classification of synapses

Type I	Type II
1. Example: Axodendritic synapses.	1. Axosomatic synapses
2. It shows marked thickening of the subsynaptic membrane.	2. Subsynaptic membrane shows slight thickening which is not continuous.
3. Synaptic cleft – wider (30 nm) and filled with dense extracellular material.	3. Synaptic cleft – narrow (20 nm) and no such dense material is found here.
4. Sites (Refer to Table 88.1)	

Table 88.3: Physiological classification of synapses

Chemical Synapses	Electrical Synapses
1. Here transmission of impulse from pre to post-synaptic site occurs due to liberation of chemical mediator (page 155).	1. Here pre and post-synaptic membranes come very close to form *gap junction* (pages 10 and 175). These junctions act as *low resistance bridges* through which ions can pass with relative ease.
2. These are seen at *most* of the synaptic junctions in the nervous system. They always transmit the signals in one direction, i.e. from presynaptic to postsynaptic neuron.	2. These are seen at *some* of the synaptic junctions in the nervous system and can transmit signals in either direction (e.g. in the lateral vestibular nucleus, hippocampus and cerebral cortex).
3. Synaptic cleft is present.	3. Synaptic cleft gets replaced by 'low resistance bridges'.
4. Synaptic delay (page 858) present.	4. Synaptic delay absent because of low resistance bridges.
5. They are sensitive to hypoxia.	5. They are insensitive to hypoxia.
6. It allows for large number of synapses per neuron and a large variety of neurotransmitters. This result in infinite processing of information. This is particularly of help in the processing of learning and memory.	6. There are not too many synapses on the same neuron. Therefore, transmission across it is rapid and efficient.

2. The current generating the EPSP passes in through the synaptic cleft and inward across the activated subsynaptic membrane, but outward across the remaining of the postsynaptic membrane. The area of inward current flow thus created is so small that it will not drain off enough charges to depolarize the whole membrane; instead, an EPSP is produced.
3. EPSP due to activity in one synaptic knob is small, but EPSPs produced by each of the active knobs *summate*. This summation may be *spatial* or *temporal*.

(i) ***Spatial summation*** – If we stimulate two afferent nerve fibers simultaneously, both of which make synaptic connections with the motor neuron, their EPSPs get summated to the critical level and thus may produce a 'spike' discharge from the motor neuron. This is called *spatial summation* **(Fig. 88.3)**. The excitation of either fiber alone does not produce a spike potential and activity in one synaptic knob is said to *facilitate* activity in another to approach the firing level. This is due to increased release of the chemical transmitter.

(ii) ***Temporal summation*** – If we stimulate one afferent nerve fiber for the second time before the decay of first stimulation, neither of which alone can generate 'spike' from the motor neuron; however, each produces some EPSP which may get summated

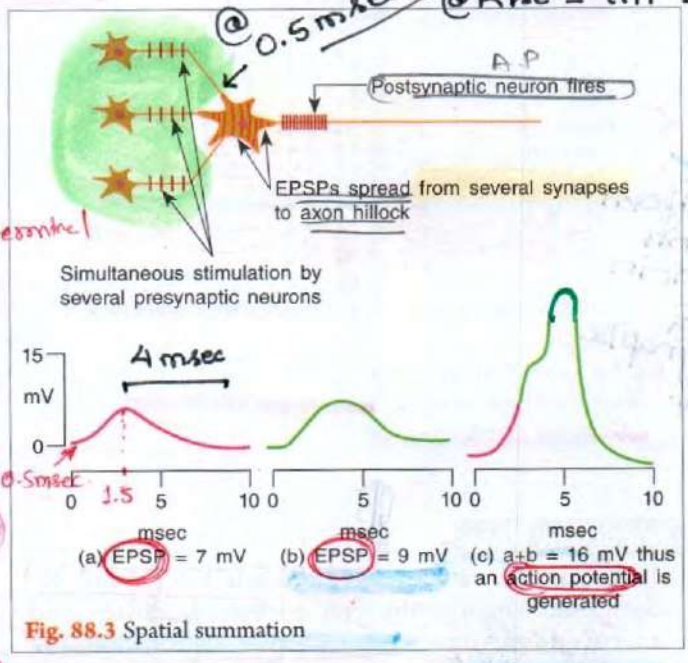


Fig. 88.3 Spatial summation

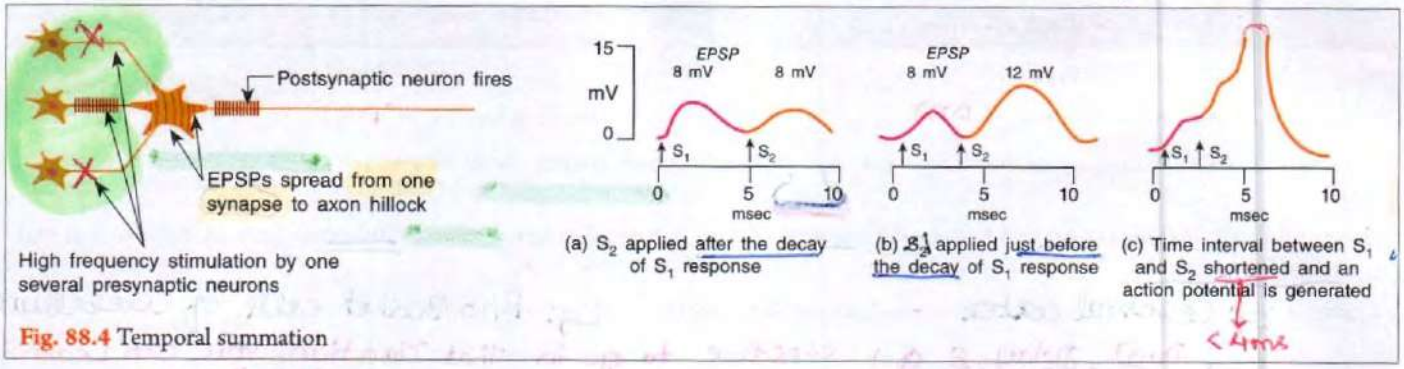


Fig. 88.4 Temporal summation

to the critical level necessary for the initiation of a 'spike' potential. This is called *temporal summation*. **(Fig. 88.4)**

(For difference between EPSP i.e. graded potential and action potential, refer page 43.)

4. *Ionic basis of EPSPs*

(i) The released excitatory transmitters bind to appropriate postsynaptic receptors and cause opening of 'chemically' gated (Na^+ or Ca^{2+}) ion channels in the subsynaptic membrane of the postsynaptic cell **(Fig. 88.5)**.

(ii) The production of 'end plate potential' by A-ch at the neuromuscular junction provides a good example of the operation of these mechanisms (page 156).

(iii) EPSP can also be produced by agents that close K^+ channels.

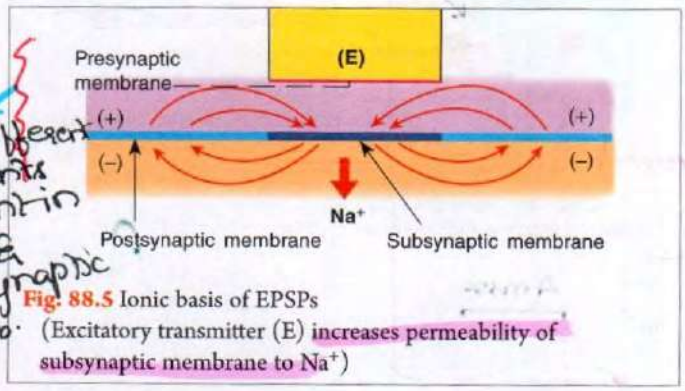


Fig. 88.5 Ionic basis of EPSPs
(Excitatory transmitter (E) increases permeability of subsynaptic membrane to Na^+)

Important Note

The axons have only voltage-gated Na^+ and K^+ channels, whereas the cell bodies, dendrites and axonal endings have many different kinds of chemical gated channels. Therefore, the type of postsynaptic response produced by a transmitter depends on the type of channel that is associated with the synapse.

B. INHIBITORY POSTSYNAPTIC POTENTIALS (IPSP)

1. IPSP is produced by stimulation of certain presynaptic fibers which regularly initiate a *hyperpolarizing response* in spinal motor neurons. It begins about 1–1.5 msec after the entry of afferent impulse into the spinal cord and rises to a peak in 1.5–2 msec after its onset and declines exponentially with a time constant of about 3 msec **(Fig. 88.6)**. During this potential, the excitability of the neuron to other stimuli is decreased, that is why it is called an IPSP.
2. 'Spatial' and 'temporal' summation of IPSP also occurs, as seen with EPSP (see above). This type of inhibition is called *postsynaptic* (or *direct*) inhibition.

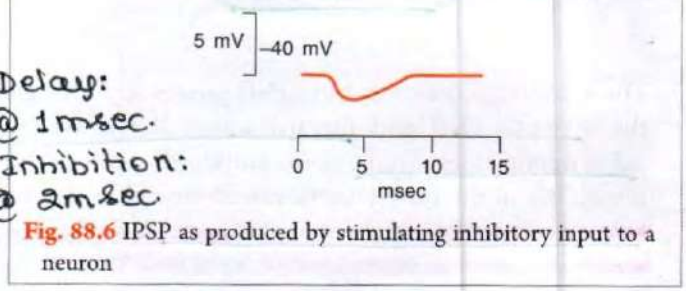


Fig. 88.6 IPSP as produced by stimulating inhibitory input to a neuron

3. *Ionic basis of IPSPs* **(Fig. 88.7)**

(i) IPSP is due to the liberated inhibitory chemical transmitter on the subsynaptic membrane, therefore, it becomes highly permeable to K^+ and Cl^- but retains a high degree of impermeability to

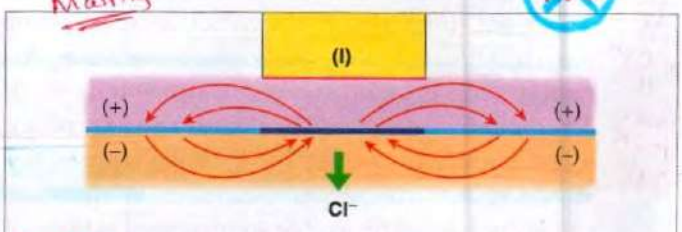


Fig. 88.7 Ionic basis of IPSPs (also see **Fig. 88.5**)
(Inhibitory transmitter (I) increases permeability of postsynaptic membrane to Cl^-.)

Na^+. This results in hyperpolarization of the whole postsynaptic membrane. However, the permeability change is short lived, and resting conditions are rapidly restored.

(ii) 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.

Important Note

Slow EPSPs and IPSPs have been described in autonomic ganglia (page 925), cardiac and smooth muscles, and cortical neurons. These postsynaptic potentials have a long latency of 100-500 msec and last several seconds.

C. GENESIS OF ACTION POTENTIAL IN POSTSYNAPTIC NEURON

1. The activity of the postsynaptic neuron when sufficient to reach the firing level, i.e., 10-15 mV of depolarization, a propagated 'spike' results. This threshold depolarization level is similar to the level achieved by EPSP during natural synaptic excitation.
2. A given afferent impulse becomes more effective in exciting the synaptic propagation of a spike potential if the motor neuron is submitted to progressive depolarization; conversely, hyperpolarization of the membrane makes the motor neuron less susceptible to synaptic activation.
3. When EPSP depolarization reaches the critical level it produces a spike potential 'first' in the initial segment (IS) of the axon and the axon-hillock, called *IS spike*. This potential is 30-40 mV in height and 'takes off' from a threshold depolarization of 10-15 mV which has previously been achieved by the EPSP.
4. The *IS spike* requires a relatively low degree of depolarization for its own production but, once initiated, itself produces a further depolarization of 30-40 mV. *This is why the portion of the cell with the lowest threshold for the production of a full-fledged action potential is the 'initial segment'.* (Also refer to page 137)

Important Note

The algebraic sum of all the excitatory (depolarizing) and inhibitory (hyperpolarizing) activity on postsynaptic neuron determines the membrane potential (Fig. 88.8). Thus, soma of the neuron acts as an *integrator* that permits the grading and adjustment of neural activity necessary for normal function.

INHIBITION AT SYNAPSES

It is of 2 types: *Postsynaptic* and *Presynaptic inhibition.*

A. POSTSYNAPTIC INHIBITION

It depends on the delivery of an inhibitory chemical by the incoming axons which hyperpolarizes the subsynaptic membrane. It is subdivided into *direct* and *indirect inhibition.*

1. Direct Inhibition or Afferent Inhibition

Inhibition which results due to stimulation of afferent nerve which passes *directly* to the motor neurons in the spinal cord; thus, *postsynaptic inhibition* during the course of an IPSP is called direct inhibition because it is not due to the effects of previous postsynaptic neuron discharge (page 854). For example:

(i) ***Postsynaptic inhibition in the spinal cord***

(a) If the muscle spindles (afferent nerve endings) of an extensor muscle are stimulated by stretching the muscle, this results in reflex contraction of the muscle itself and simultaneously reflex relaxation of its antagonist (flexor).

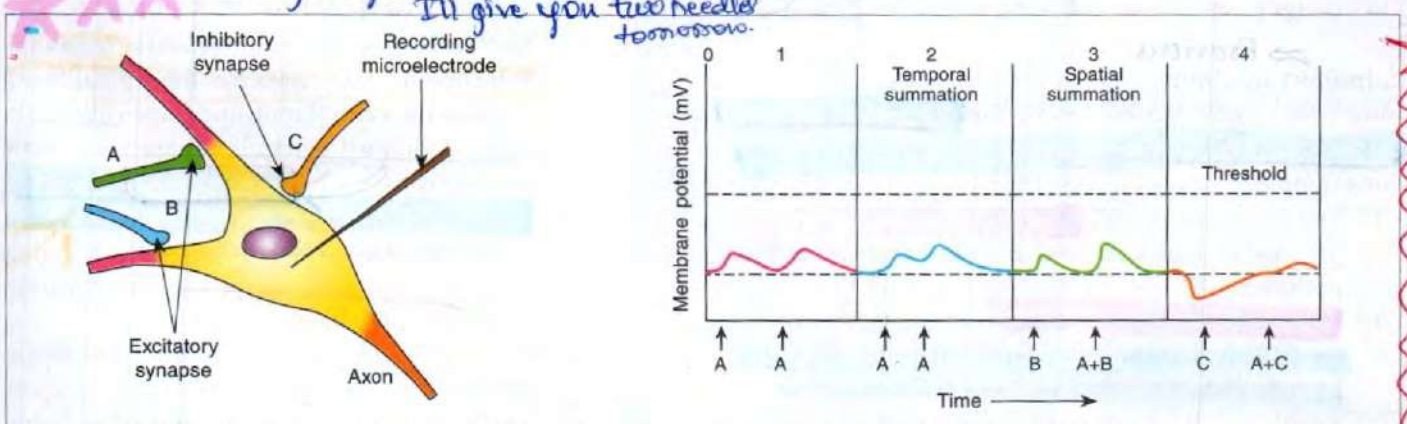


Fig. 88.8 Summary: Interaction of EPSPs and IPSPs at the postsynaptic neuron (arrows indicate time of stimulation)

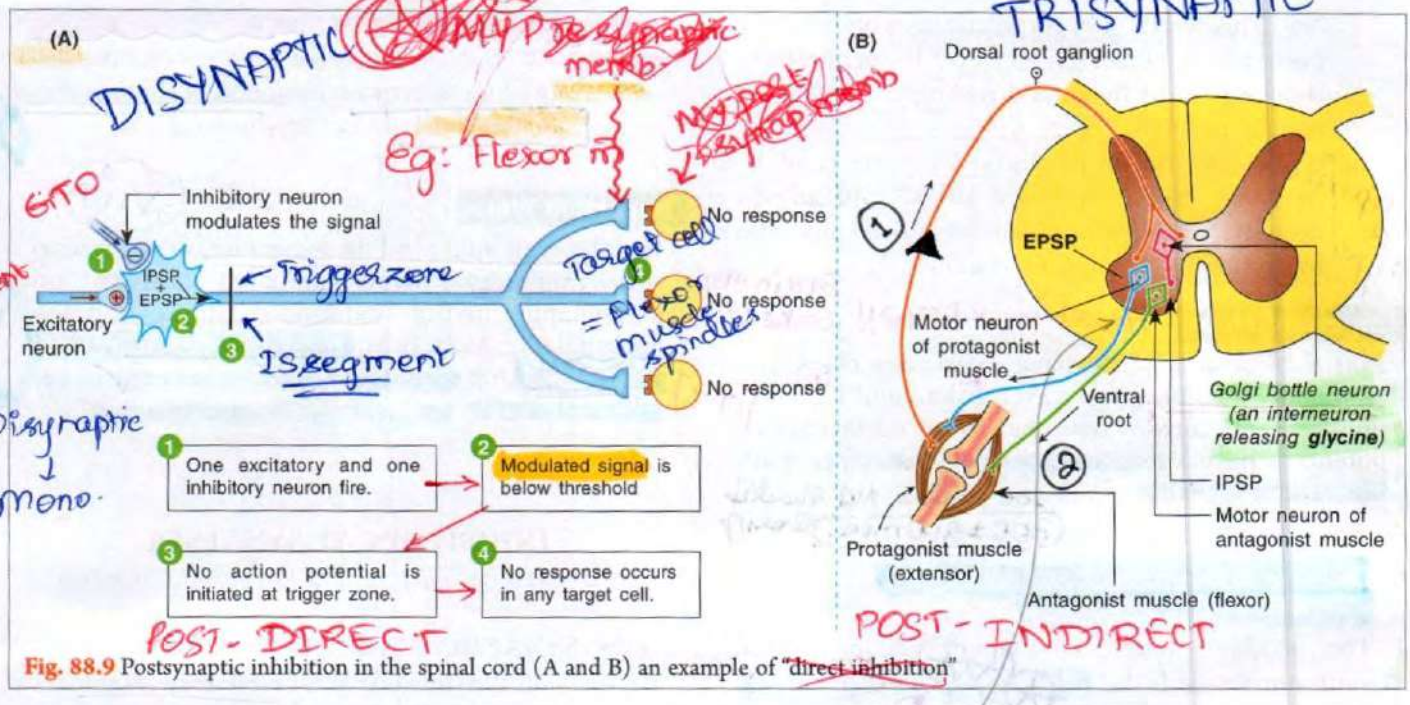


Fig. 88.9 Postsynaptic inhibition in the spinal cord (A and B) an example of "direct inhibition"

(b) *Mechanism:* The afferent impulses in the nerve fibers from the muscle spindles pass directly to the spinal motor neurons supplying the same muscle and cause EPSPs which summate to produce propagated responses in the postsynaptic motor neurons. At the same time these impulses also pass along interneurons (*Golgi Bottle Neurons*) which liberate an inhibitory transmitter ***glycine*** at their synaptic connections with motor neurons **(Fig. 88.9)** supplying the antagonist muscles.

(c) Thus when glycine is secreted from its synaptic knobs to the postsynaptic neuron, an IPSP is produced due to an increase in the permeability of the postsynaptic cell membrane to Cl^-. In this way, excitatory input is converted into inhibitory input.

(d) The pathway for direct inhibition is *disynaptic.*

(ii) *Golgi tendon organ inhibition:* Refer to page 879.

2. Indirect Inhibition

Inhibition which occurs due to the effects of previous postsynaptic neuron discharge is called *indirect inhibition.* For example:

(i) The postsynaptic cell can be refractory to excitation because it has just fired and is in its refractory period.

(ii) During *after-hyperpolarization* it is also less excitable. In spinal neurons, after repeated firing, this after hyperpolarization may be large and prolonged.

(iii) **Renshaw cell inhibition** or *Negative feedback inhibition* – In this type of inhibition, neurons may inhibit themselves in a 'negative feedback' fashion. How? **(Fig. 88.10)**

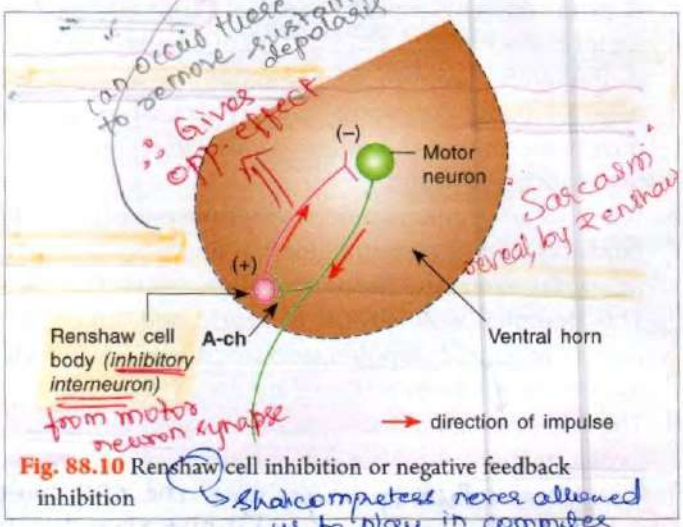


Fig. 88.10 Renshaw cell inhibition or negative feedback inhibition

(a) Motor nerve axons give off some collateral branches as they traverse the spinal cord towards the ventral root, and these collaterals make excitatory synaptic connections with interneurons, called *Renshaw cell* situated in the ventromedial part of the ventral horn. These Renshaw cells in turn send axons which make inhibitory synaptic connections with the motor neurons.

(b) These cells are activated when the motor neurons are excited synaptically and thereupon 'feedback' in a 'negative' fashion on the motor neurons, thus checking their discharge.

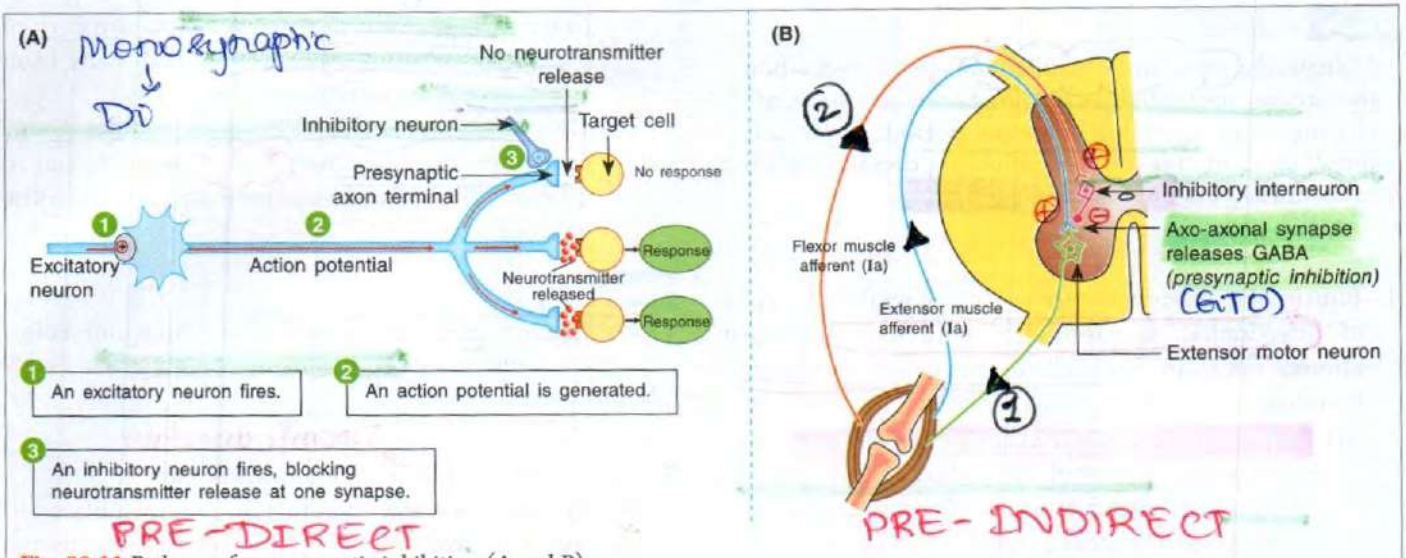


Fig. 88.11 Pathways for presynaptic inhibition (A and B)
(Convergence of flexor Ia fibers on to inhibitory interneuron which in turn makes contacts on the terminals of an afferent Ia fiber from extensor muscle.)

(c) The Renshaw cells are stimulated by *A-ch.*
(d) Similar inhibitions via recurrent collaterals are seen in the cerebral cortex and limbic system.

Important Notes

1. Any given afferent nerve release only one type of transmitter from its terminal branches. In case of the dorsal root ganglion cells with their primary afferent fibers, the nerve terminals liberate an *excitatory* transmitter.
2. The Renshaw cells and some intermediate neurons liberate an *inhibitory* transmitter.
3. Inhibitory cells are *short axon neurons* lying in the grey matter, while all transmission pathways, in and out of the cord and up and down the cord, are formed by the axons of excitatory cells.

B. PRESYNAPTIC INHIBITION

This type of inhibition often occurs at the ***presynaptic terminals*** before the signals ever reaches the synapse. It is usually caused by discharge of inhibitory interneurons.

1. It is induced by *axo-axonal synapses*. Here, afferent fibers can influence each other by means of collaterals which innervate interneurons. These then form synaptic contacts with the presynaptic terminals of the other afferent fibers (Fig. 88.11). The interneuron which cause presynaptic inhibition lie at the base of the dorsal horn.
2. *Mechanism:* Activation of presynaptic receptors
   (a) reduces the opening of Ca^{2+} channels directly; or
   (b) increases Cl^- and/or K^+ permeability, so that the size of the action potentials reaching the excitatory ending (i.e. distal to the synapse) is reduced (Fig. 88.12).
   (c) direct inhibition of neurotransmitter release (independent of Ca^{2+} influx into the excitory endings).

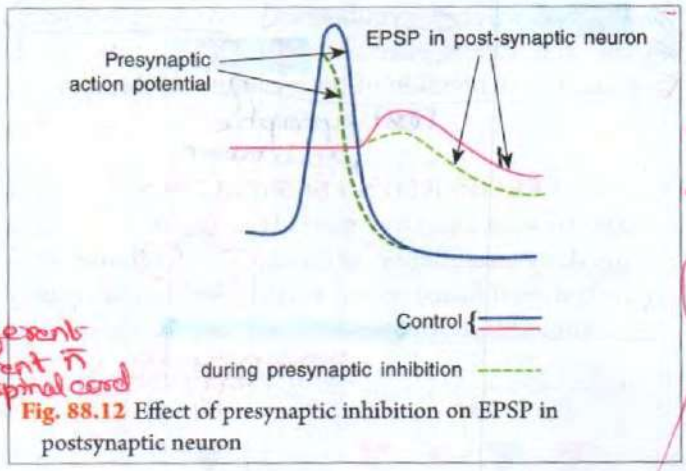


Fig. 88.12 Effect of presynaptic inhibition on EPSP in postsynaptic neuron

Note

The *'all or none'* law for action potential holds good only under a given set of experimental conditions (page 40).

3. The inhibitory transmitter at the axo-axonal synapse *is gamma-aminobutyric acid (GABA)*. Acting via $GABA_A$ receptors, it increases Cl^- permeability, whereas $GABA_B$ receptors via G-protein, produces an increase in K^+ permeability.

Note

Conversely, *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*.

4. *Physiological significance* – In general, all types of myelinated somaesthetic (conscious) primary afferent fibers are subjected to presynaptic inhibition; therefore,
   (i) Activity in myelinated cutaneous afferents are particularly powerful in inducing presynaptic inhibition of the cutaneous afferents themselves (page 899); (For details refer to lateral inhibition page 887)
   (ii) Muscle afferents receive predominantly presynaptic inhibitory influences from the other muscle afferents (Fig. 88.11).
   (iii) *Feed-forward inhibition* seen in the cerebellum (page 964)

Applied Aspect

(1) Presynaptic inhibition is antagonized by the convulsant drug picrotoxin.
(2) Barbiturates greatly pronounce presynaptic inhibition.
(3) The convulsant effect of strychnine is due to its profound depression of postsynaptic inhibition.

PROPERTIES OF SYNAPSES

1. **Convergence and Divergence (Fig. 88.13)**
   (i) Many presynaptic neurons converged (meet on a common focus) on any single postsynaptic neuron. For example, in spinal motor neurons, some inputs come directly from the dorsal root, some from the long descending spinal tracts, and many from interneurons (interconnecting neurons).
   (ii) The axons of most presynaptic neurons divide into many branches that diverge (separate out in different directions) to end on many post-synaptic neurons.

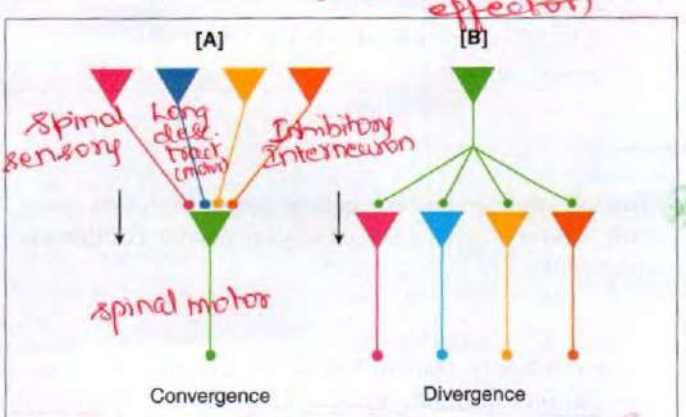


Fig. 88.13 'Convergence' of neural input from many neurons onto a single neuron (A); and 'divergence' of output from a single neuron onto many others (B)

Note

Convergence and divergence play important role in phenomenon of occlusion and facilitation (see below).

2. **Law of Forward (One Way) Conduction**
   (i) Synapses permit conduction of impulses in one direction only, from the presynaptic to the postsynaptic neuron. An impulse conducted *antidromically* up the axons of the ventral root dies out after depolarizing the cell bodies of the spinal motor neurons. This is because the chemical mediator at synaptic junction is located in the synaptic knob of the presynaptic fibers but not in the postsynaptic membrane.
   (ii) *Significance:* Since axons will conduct impulse in either direction with equal ease, the one-way 'gate' at the synapses determines the direction of an impulse. This is necessary for orderly neural function.
3. Synapses are more susceptible to hypoxia than the nerve fibers (axons).
4. *Fatigue* occurs at the synapse.
   (i) *Mechanism:* Repeated stimulation of presynaptic neuron leads to gradual decrease and finally disappearance of the postsynaptic response, a phenomenon called *synaptic fatigue* or *habituation*.
   (ii) This is due to exhaustion of chemical transmitter, as its synthesis is not as rapid as the release. The decreased release of neurotransmitter from the presynaptic terminal is due to a gradual inactivation of Ca^{2+} channels which decreases the intracellular Ca^{2+}.

Important Note

The CNS neurons cannot sustain an oxygen lack; this may explain why the first site of fatigue of the synaptic chain is located in the brain.

5. **Synaptic Delay**
   (i) 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.

(ii) *Significance:*

(a) Conduction along a chain of neurons is slow if there are many synapses in the chain.

(b) It is possible to determine whether a given reflex pathway is monosynaptic or polysynaptic by measuring the delay in transmission of impulse from the dorsal to the ventral root across the spinal cord.

6. **Summation** – page 853.

7. **Occlusion** – When two afferent excitatory nerves (a and b) 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 the tension produced by each afferent nerve stimulated separately. This phenomenon is called *occlusion* (Fig. 88.14-A). 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 and b are stimulated together. This decrease in response is due to presynaptic fibers sharing postsynaptic neurons. *Thus occlusion is due to afferent fibers overlapping in their central distribution.*

8. **Subliminal Fringe**

(i) *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 (not in the *discharging zone*) by activity in the presynaptic neurons but do have their excitability increased.

Note

The neurons that have few active knobs ending on them are in *subliminal fringe*, and those with many active knobs are in the *discharging zone*.

(ii) When two afferent excitatory nerves (a and b) 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 the tension produced by each afferent nerve stimulated separately (Fig. 88.14-B). 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* (page 853).

Important Note

Inhibitory impulses show similar temporal and spatial facilitation and subliminal fringe effects.

Physiological significance

(i) Because of summation, occlusion and subliminal fringe effects, the patterns in peripheral nerves are usually altered as they pass through synapses on the way to brain. One such effect is phenomenon of referred pain (page 897).

(ii) The interaction between excitatory and inhibitory influences at synapses play an important role in integrating and modulating activity of the nervous system.

9. **Synaptic Plasticity**

Plasticity implies 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 postsynpatic in location and play an important role in

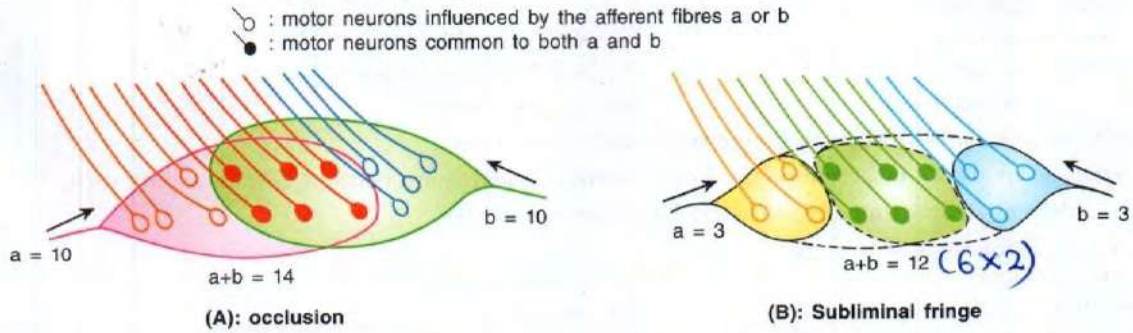


Fig. 88.14 (A) Occlusion: Stimulation of excitatory nerve a or b each excites 10 motor neurons; stimulation of a and b together excites only 14 motor neurons, because 6 are common to both afferents. **(B) Subliminal fringe**: Stimulation of excitatory nerve a or b each excites 3 motor neurons and produces a subliminal effect on another 6 motor neurons. Stimulation of a and b stimulates 12 motor neurons as the two subliminal fringes get summated.

learning (conditioned reflexes, page 1035) and memory (page 1037). (Also refer to pages 899 and 1073).

Forms of synaptic plasticity

(i) One form of plastic change is *post-tetanic potentiation* in which a brief tetanizing stimuli in the presynaptic neuron results in increased production of postsynaptic potentials lasting for minutes to hours. It occurs due to increased Ca^{2+} influx in the presynaptic neuron (Fig. 88.15). Hence, the response is potentiated. (It is a form of synaptic facilitation, page 858).

(ii) If post-tetanic potentiation gets much more prolonged and lasts for days, it is called *long term potentiation*. It is due to an increase in intracellular Ca^{2+} in the *postsynaptic neuron* rather than the presynaptic. This phenomenon occurs in many parts of the nervous system but commonly seen in the hippocampus.

(iii) *Long term depression*

It is opposite to long term potentiation and is characterized by slower stimulation of presynaptic neurons. It is associated with decrease in synaptic conduction following decreased Ca^{2+} influx. This phenomenon commonly occurs in the hippocampus and the cerebellum. It may be involved in mechanism by which learning occurs in the cerebellum.

(iv) *Fatigue or Habituation:* page 858.

(v) *Sensitization*

(a) Sensitization is the *presynaptic facilitation* of an impulse (page 858). It may occur as a transient response or if it is reinforced by additional pairing of the noxious (injurious) stimulus and the initial stimulus (page 1036). Thus sensitization involves prolonged occurrence of increased postsynaptic responses after a stimulus is paired once or several times with a noxious stimulus.

(b) It is due to a Ca^{2+} mediated changes in adenylate cyclase that results in greater production of cAMP.

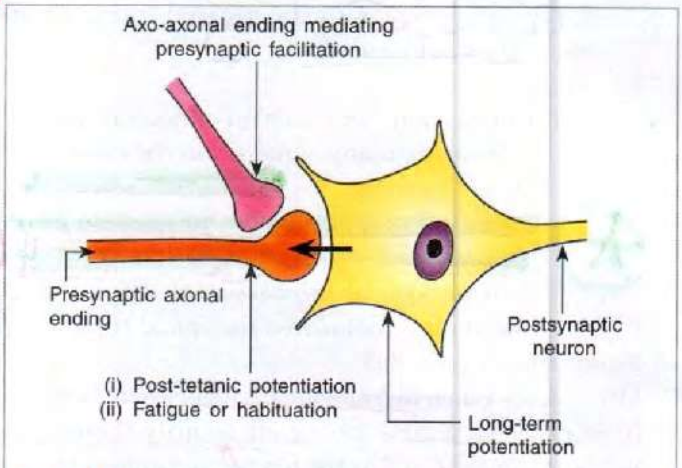


Fig. 88.15 Synaptic plasticity: Presynaptic and postsynaptic sites producing changes in the strength of synaptic transmission

Important Note

Sensitization may occur even if it is reinforced by pairing of non-noxious stimulus. For example, the mother who sleeps through many kinds of noise but wakes promptly when her baby cries.

Study Questions

1. Draw well labelled diagram:
   (i) Structure of a synapse
   (ii) types of synapses
   (iii) Spatial and temporal summation
   (iv) Ionic basis of EPSP and IPSP
   (v) Occlusion and subliminal fringe
   (vi) Synaptic plasticity
2. What are the types of synapses? Mention their characteristic differences.
3. How many synaptic knobs can be accommodated on to a single spinal motor neuron? Give its significance.
4. Give the main differentiating features between EPSP and action potential.
5. Give physiological significance of:
   (i) subsynaptic membrane
   (ii) electrical synapses
   (iii) EPSP and IPSP
   (iv) summation
   (v) IS spike
   (vi) Renshaw cell inhibition
6. How does grading and adjustment of neural activity is brought about?
7. With the help of suitable diagrams show how inhibition at synapses is achieved? Give its physiological significance.
8. Define the term 'synapse'. Describe its properties with the help of suitable examples.

9. Give the physiological basis of following synaptic properties:
   (i) fatigue
   (ii) summation, occlusion and subliminal fringe
   (iii) synaptic plasticity.
10. Which part of the motor neuron is excited first and how current flow due to depolarization spreads to different parts of a motor neuron?
11. What is the possible chemical transmitter for direct inhibition and presynaptic inhibition?
12. How does strychnine cause muscular hyperactivity?
13. How do you measure synaptic delay? Give its significance.
14. How does barbiturate control convulsions?
15. Write briefly and give physiological significance of:
   (i) Direct and indirect inhibition
   (ii) Presynaptic inhibition
   (iii) Synaptic plasticity
   (iv) Occlusion and subliminal fringe
   (v) Summation

MCQs

1. The number of synaptic knobs terminating over a post-synaptic cell in the spinal cord are upto:
   (a) 10 (b) 100 (c) 1000 (d) 10000
2. The type of synapse which most commonly exist in the nervous system is:
   (a) Dendodendritic (b) Axo-axonal (c) Axo-somatic (d) Axo-dendritic
3. Chemical synapses *differ* from electrical synapses in all of the following *except*:
   (a) Seen at most of the synaptic junctions in the nervous system
   (b) Synaptic cleft is present
   (c) Synaptic delay is present
   (d) Insensitive to hypoxia
4. EPSP (Excitatory postsynaptic potential):
   (a) Is the reversal of polarity which occurs when a presynaptic neuron is stimulated
   (b) May be recorded from an electrode in posterior root ganglion cell
   (c) Is not conducted
   (d) Due to electric field induced by electrical activity is presynaptic nerve terminal
5. When temporal summation occurs at the neuronal soma, which of the following will cause the greatest degree of summation?
   (a) Fiber stimulus frequency of 1,000 impulses per second
   (b) Fiber stimulus frequency of 100 impulses per second
   (c) Fiber stimulus frequency of 10 impulses per second
   (d) Fiber stimulus frequency of 1 impulse per second
6. What happens to the excitability of the neuron during a transient hyperpolarization of its membrane?
   (a) The neuron is facilitated
   (b) The neuron is inhibited
   (c) There is no change in degree of facilitation or inhibition
   (d) None of the above
7. Which part of a motor neuron has the lowest threshold for a propagated action potential?
   (a) Axon (b) Initial segment (c) Soma (d) Dendrite
8. Renshaw cell inhibition is a typical example of:
   (a) Presynaptic inhibition (b) Direct inhibition
   (c) Recurrent inhibition (d) All of the above
9. Which of the following transmitter substances almost always tend to inhibit the post-synaptic neuron?
   (a) Gamma-aminobutyric acid (GABA) (b) Dopamine
   (c) Glycine (d) Norepinephrine

10. *Not* a property at the synapse:
(a) All or none law
(b) Law of forward conduction
(c) Fatigue occurs at synapse
(d) More susceptible to hypoxia than nerve fibers

11. Occlusion at synapse occurs due to:
(a) Increased excitability of post-synaptic neurons
(b) Synaptic delay phenomenon
(c) Afferent fibers overlapping in their central distribution
(d) Release of inhibitory transmitter

12. Post-tetanic potentiation:
(a) Lasts for days
(b) Is increased post-synaptic potentials in response to stimulation
(c) Is due to increased intracellular Ca^{2+} in post-synaptic neurons
(d) Also called presynaptic facilitation

13. The EPSP which is likely to produce an action potential is:
(a) –20 mV
(b) –10 mV
(c) +10 mV
(d) +20 mV

14. When summation occurs, activity in one nerve fiber is said to facilitate activity in another to approach the firing level. This is due to:
(a) Increased release of chemical transmission
(b) Summation of stimuli
(c) Summation of effects
(d) All of the above

15. Excitatory synaptic transmitter substances cause which ions preferentially to move through the post-synaptic membrane?
(a) Magnesium ions
(b) Potassium ions
(c) Chloride ions
(d) Sodium ions

16. Magnitude of the IPSP is:
(a) –5 to –10 mV
(b) –10 to –20 mV
(c) 5 to 10 mV
(d) 10 to 20 mV

17. Post-synaptic inhibition in the spinal cord during the course of an IPSP is called:
(a) Direct inhibition
(b) Indirect inhibition
(c) Renshaw cell inhibition
(d) Negative feedback inhibition

18. Pathway for direct inhibition is:
(a) Monosynaptic
(b) Disynaptic
(c) Trisynaptic
(d) Variable

19. *Not true* of Renshaw cells:
(a) Liberate an inhibitory transmitter
(b) Are short axon neurons lying in the grey matter
(c) Stimulated by acetylcholine
(d) Inhibit themselves in a negative feedback fashion

20. Gamma-amino butyric acid (GABA), a major inhibitory transmitter in the CNS, acts by:
(a) Increasing the permeability of neuron to K^+
(b) Increasing the permeability of a neuron to Na^+
(c) Increasing the permeability of the cell to Ca^{2+}
(d) Decreasing the permeability of the cell to Ca^{2+}

21. In spinal reflex, following are seen *except*:
(a) Latency
(b) Fatiguability
(c) Summation
(d) Memory

Answers

1. (d) 2. (d) 3. (d) 4. (c) 5. (a) 6. (b) 7. (b) 8. (c) 9. (a) 10. (a) 11. (c)
12. (b) 13. (c) 14. (a) 15. (d) 16. (a) 17. (a) 18. (b) 19. (d) 20. (a) 21. (d)

Chapter 89

Sensory Receptors

I. Introduction
II. Classifications of receptors
III. Cutaneous receptors
A. Mechanoreceptors B. Thermoreceptors C. Pain receptors
IV. Electrical and Ionic events in receptors
V. Properties of Receptors

INTRODUCTION

Information of the outside world and changes occuring within the body itself are conveyed by sensory nerve impulses to the CNS via a variety of *sensory receptors* which are part of a neuron or of a specialized cell.

1. *Definition: Receptor* is a specialized modified sensory nerve-ending which undergoes *depolarization* (*i.e.* form nerve impulses) in response to a *specific* stimulus and in turn sends information to the CNS.
2. *Function:* It acts as a *transducer* that converts various forms of energy in the environment into electric energy (*i.e.* action potential) in the neuron.
3. The different forms of energy converted by receptors include: (A) Mechanical (touch, pressure); (B) Thermal (degrees of warmth); (C) Electromagnetic (light); and Chemical (smell, taste, O_2 and CO_2 content of blood).
4. The receptor along with the surrounding non-neuronal cells is called a *sense organ*.

Note

In general, the term receptor is also used in a very different meaning such as: to proteins that build neurotransmitters, hormones and other substances with great affinity and specificity.

CLASSIFICATIONS OF RECEPTORS

A. ACCORDING TO TYPE OF STIMULUS

(see box below)

Important Note

Different forms of energy when reach the consciousness, produce sensation of particular element and those which fail to reach the consciousness get utilized in regulation of BP, body temperature, etc.

B. GENERAL or ANATOMICAL CLASSIFICATION

1. *Special Senses.* They are located at one place (in the head) very close to the CNS and are specialised for one type of sensory stimulation. Information from them is carried by cranial nerve. *Examples:* vision, hearing, smell, taste, rotational and linear acceleration.
2. *Superficial or cutaneous (skin) senses.* The senses whose receptors are located in the skin are called cutaneous senses. Information in them is carried by cutaneous branches of the spinal nerves. *Examples:* touch, pain, pressure, thermal (cold/warm).
3. *Deep senses.* These senses are carried by the muscular branches of the spinal or cranial nerves from the deep

Receptor type	Stimulus receptor energy
1. Mechanoreceptors	Mechanical, *e.g.* touch, pressure (**baroreceptors**), vibration, acceleration
2. Chemoreceptors	Chemical (*i.e.* change in chemical composition of the environment in which receptors are located) *e.g.* receptors for taste, smell, osmoreceptors, glucoreceptors.
3. Thermoreceptors	Thermal (degree of warmth).
4. Nociceptors	Noxious *i.e.* stimuli which are damaging or injurious to the body tissues, *e.g.* pain.
5. Photoreceptors	Electromagnetic: Light *e.g.* rods and cones in retina.

body tissues. *Examples:* sensation of joints, muscles and tendons.

4. ***Visceral senses.*** These senses are concerned with perception of internal environment and are carried by the ANS. *Examples:* pain from visceral structures; concentration of glucose in blood.

Important Note

The major sensory modalities can further be classified as:

(i) *Conscious senses* which reach the consciousness. For example: all *special* and *superficial senses* (see above);

(ii) *Unconscious senses i.e.*, sensory receptors which relay information that does not reach consciousness. For example: the receptor which relay information about *muscle length, muscle tension, arterial blood pressure, central venous pressure, inflation of lungs, temperature of blood, arterial pO_2, pH of CSF, osmotic pressure of plasma, arteriovenous blood glucose difference etc.*

C. ACCORDING TO THE TYPE OF RECEPTORS

Sherrington's classification

1. ***Telereceptors.*** These are the receptors concerned with sensory perception at a distance. *Examples:* hearing, vision, smell.
2. ***Exteroceptors.*** These receptors are concerned with perception of external environment. *Examples:* touch, temperature, pain, pressure.
3. ***Interoceptors.*** These receptors respond to changes within the body itself and comprise the following:
   (i) *Proprioceptors.* These receptors give information about changes in position of the body in space specially the joints or tension of muscles at any given moment. These include:
      (a) Muscle spindles (page 874),
      (b) Joint receptors (page 865),
      (c) Golgi tendon organs (page 879),
      (d) Vestibular receptors (page 939),
   (ii) *Viscero*ceptors, *e.g.* baroreceptors (page 328), osmoreceptors (page 558) and glucoreceptors; and
   (iii) *Chemo*receptors (page 331).

CUTANEOUS RECEPTORS

The skin contains receptors called the ***cutaneous receptors***, that respond to touch, pressure, pain and temperature. Most of the sensory nerve fibers in the skin are unmyelinated, however, few large myelinated sensory fibers are also found that respond to touch, vibration and pressure. The temperature and pain sensations are conveyed by small myelinated (Aδ) fibers and unmyelinated 'C' fibers.

A. MECHANORECEPTORS

In general, mechanoreceptors (receptors concerned with sensations of touch and pressure) consist of a lamellated connective tissue capsule which surrounds an unmyelinated axon (Fig. 89.1). These include:

1. ***Merkel's discs and Meissner's corpuscles***
   (i) These are concerned with perception of *touch*, therefore called *tactile receptors*.
   (ii) Beside touch sensibility, these receptors also respond to changes in texture, slow vibrations and sustained pressure.
   (iii) They form the expanded tips and encapsulated endings respectively on the sensory nerve terminals of A fibers (β and δ group).
   (iv) They occur in groups in the cutaneous papillae with maximum density in the skin of finger tips, lips, nipples, orifices of the body and around the base of hair follicles.
   (v) They are *rapidly adapting* receptors. This is why we do not feel our clothes once they are put on.
2. ***Pacinian corpuscles***
   (i) These are nerve terminals of Aβ fibers mainly and concerned with perception of *pressure* (or sustained touch) and fast vibrations.
   (ii) They are large receptors, resemble an onion in shape and lamination.
   (iii) They are found in large numbers in the skin, subcutaneous tissues, mesentery and in the neighbourhood of tendons and joints.
   (iv) They respond to deformation caused by firm pressure and are *quickly adapting*. This is why we do not feel seat pressure when sitting.
3. ***Ruffini's end organs***
   (i) These are encapsulated expanded endings of myelinated Aδ or unmyelinated 'C' group of fibers. They are concerned with perception of degree of *warmth* and also act as mechanoreceptors (specially sustained pressure).
   (ii) They are found in the dermis and are supplied by large myelinated axons. They are slowly adapting receptors.
4. ***Krause's end bulbs***
   (i) They are spherical mechanoreceptors and their afferent fibers belong to the Aδ group.
   (ii) They occur in conjunctiva, in the papillae of the lips and tongue, in the skin of genitalia and in the sheath of nerves.

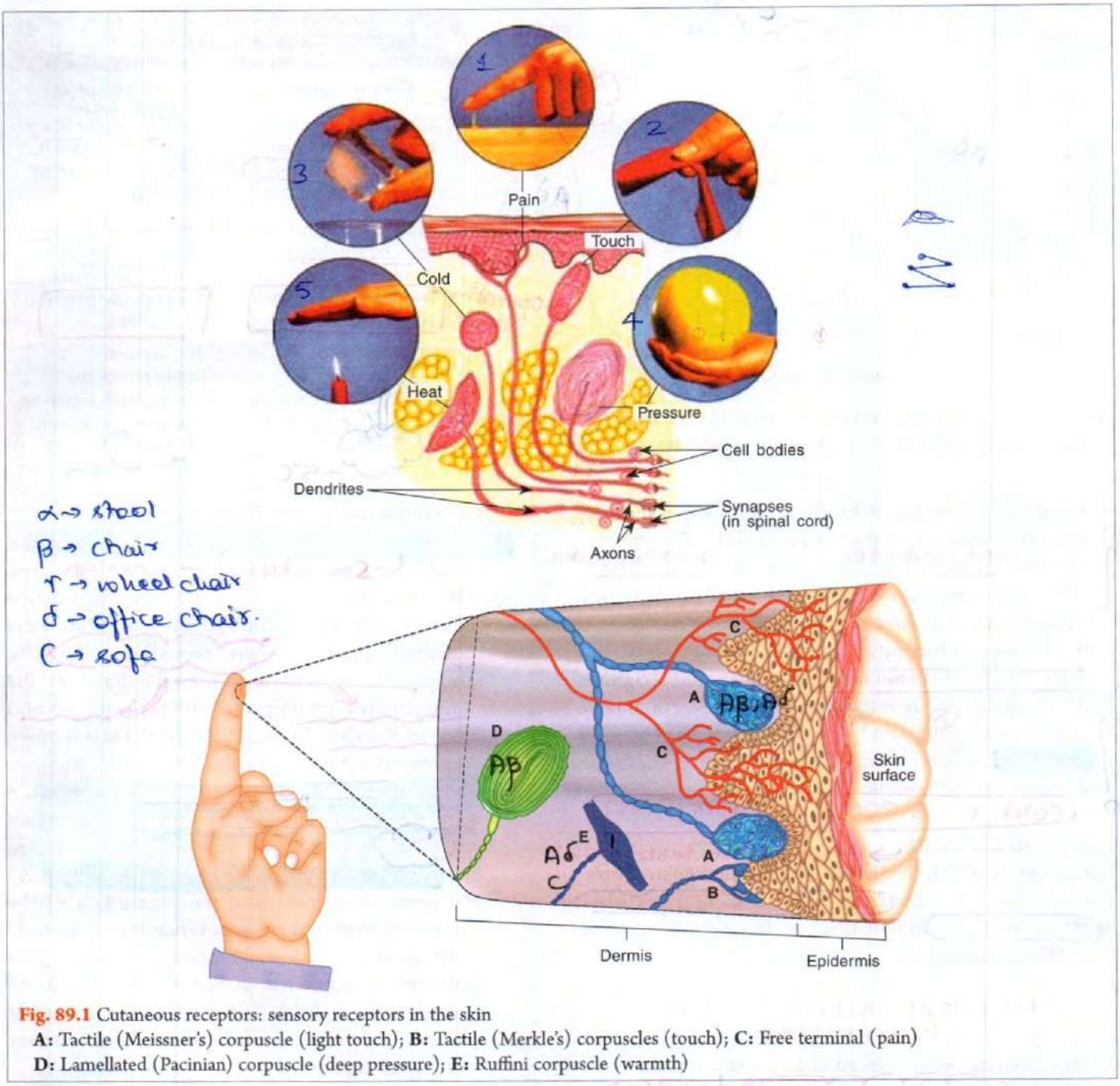


Fig. 89.1 Cutaneous receptors: sensory receptors in the skin
A: Tactile (Meissner's) corpuscle (light touch); **B:** Tactile (Merkle's) corpuscles (touch); **C:** Free terminal (pain)
D: Lamellated (Pacinian) corpuscle (deep pressure); **E:** Ruffini corpuscle (warmth)

5. ***Naked nerve endings***
   (i) These are the terminal branches of thin myelinated Aδ or unmyelinated 'C' fibers.
   (ii) They are concerned with perception of pain and injurious (noxious) stimuli. They can also convey sensations of touch and temperature.

Important Note

'Joint receptors' are mainly the Pacinian corpuscles, Golgi tendon organs and Ruffini's end organs which are situated in the ligaments of the joint. They are *quickly adapting* receptors and form the endings of afferent nerves of group I fibers.

B. THERMORECEPTORS

1. *Thermoreceptors* or temperature receptors are the terminal branches of thin myelinated Aδ and unmyelinated 'C' fibers. These are found on the chest, nose, nipples, anterior surface of the arm and forearm, and on the abdomen. There are 4-10 times more *cold receptors* than *warm receptors.*
2. Differences between cold and warm receptors (refer **Table 89.1** and **Fig. 89.2**).
3. Both the warm and cold receptors respond primarily to the temperature of the tissues which immediately surround them and not to the gradient of temperature between the deep subcutaneous tissue and the surface.

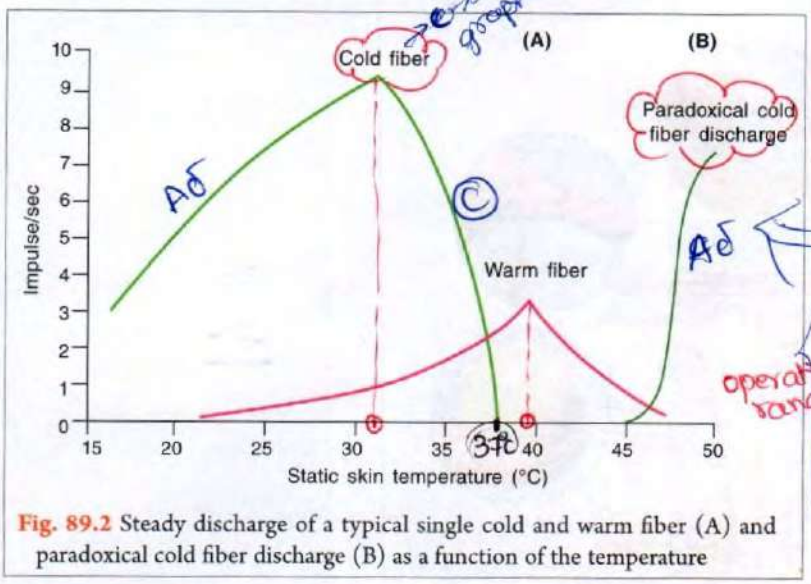


Fig. 89.2 Steady discharge of a typical single cold and warm fiber (A) and paradoxical cold fiber discharge (B) as a function of the temperature

Table 89.1: Main differentiating features between cold and warm receptors

Cold receptors	Warm receptors
1. Cold receptor fibers are mainly the thin myelinated (Aδ fibers, 2.5 μm in diameter.	1. Warm receptor fibers are unmyelinated 'C' fibers, 0.4–1.2 μm in diameter.
2. They fire with a 'steady' discharge at any one tissue temperature between 10 and 35°C.	2. They fire with a fairly steady discharge at any one tissue temperature between 35 and 45°C.
3. The maximal frequency of the steady discharge is at a tissue temperature of 25-30°C.	3. The maximal frequency of the steady discharge is at a tissue temperature of 38-43°C.

Therefore, a stimulus of 35°C will feel warm if the skin is at 30°C, and cool if the skin is at 40°C. *This explains why the cold metal objects feel colder than wooden objects of the same temperature because the metal conducts heat away from the skin more rapidly.*

4. If the tissue temperature is raised beyond 45°C the warm receptors do not respond but the cold receptors discharge at an increasing rate producing a mixed sensation of cold and pain (*paradoxical cold fiber discharge*). This is probably because above 45°C, tissue damage begins to occur.

C. PAIN RECEPTORS

The receptors which mediate pain are called *nociceptors*. They are located at the ends of small 'C' unmyelinated or myelinated Aδ afferent neurons (for details, refer to page 895).

ELECTRICAL AND IONIC EVENTS IN RECEPTORS

1. The electrical events in receptors can be studied by selecting *'pacinian corpuscles'* because:
   (i) they are relatively large in size,
   (ii) they are easily available in the mesentery of experimental animals,
   (iii) they can be isolated, subjected to microdissection and studied with microelectrodes.
2. The pacinian corpuscle consists of the following parts:
   (i) A straight, unmyelinated ending of a sensory nerve fiber (2μm in diameter) which is surrounded by concentric lamellas of connective tissue.
   (ii) The myelin sheath of the sensory nerve begins inside the corpuscle, therefore, the first node of Ranvier is located inside and the second node outside the corpuscle (usually near the point at which the nerve fiber leaves the corpuscle).
3. *Mechanism of natural excitation: Generator Potential* (Fig. 89.3)
   (i) The pacinian corpuscle can be stimulated mechanically by a rod which produces local potential changes. Two recording electrodes are placed on the sensory nerve (one on the unmyelinated ending and other on the second node of Ranvier), to record the electrical responses to pressure applied over the corpuscle.
   (ii) When a small amount of pressure is applied, a non-propagated depolarizing potential resembling an EPSP (page 852) is recorded. This is called the ***generator potential* or *receptor potential***. As the pressure is increased, the magnitude of the receptor potential increases. When the magnitude of the generator potential is about 10 mV, an action potential is generated in the sensory nerve. As the pressure is further increased, the generator potential becomes even larger and the sensory nerve fires repetitively.
4. *Source of the generator potential* – The source of the generator potential can be demonstrated from the study of experimental analysis as given below.
   (i) *After removal of the connective tissue lamellae* from the unmyelinated nerve endings in a *pacinian* corpuscle by microdissection, when pressure is applied to the naked nerve ending, a *generator potential* is still produced along with the action potential; but this generator potential decays more slowly.
   (ii) *Blockage of first node of Ranvier* by pressure or drug (*e.g.* narcotics), the generator potential response persists but no action potential can be recorded. This shows that conducted impulses are abolished by *blockage* of first node of Ranvier.

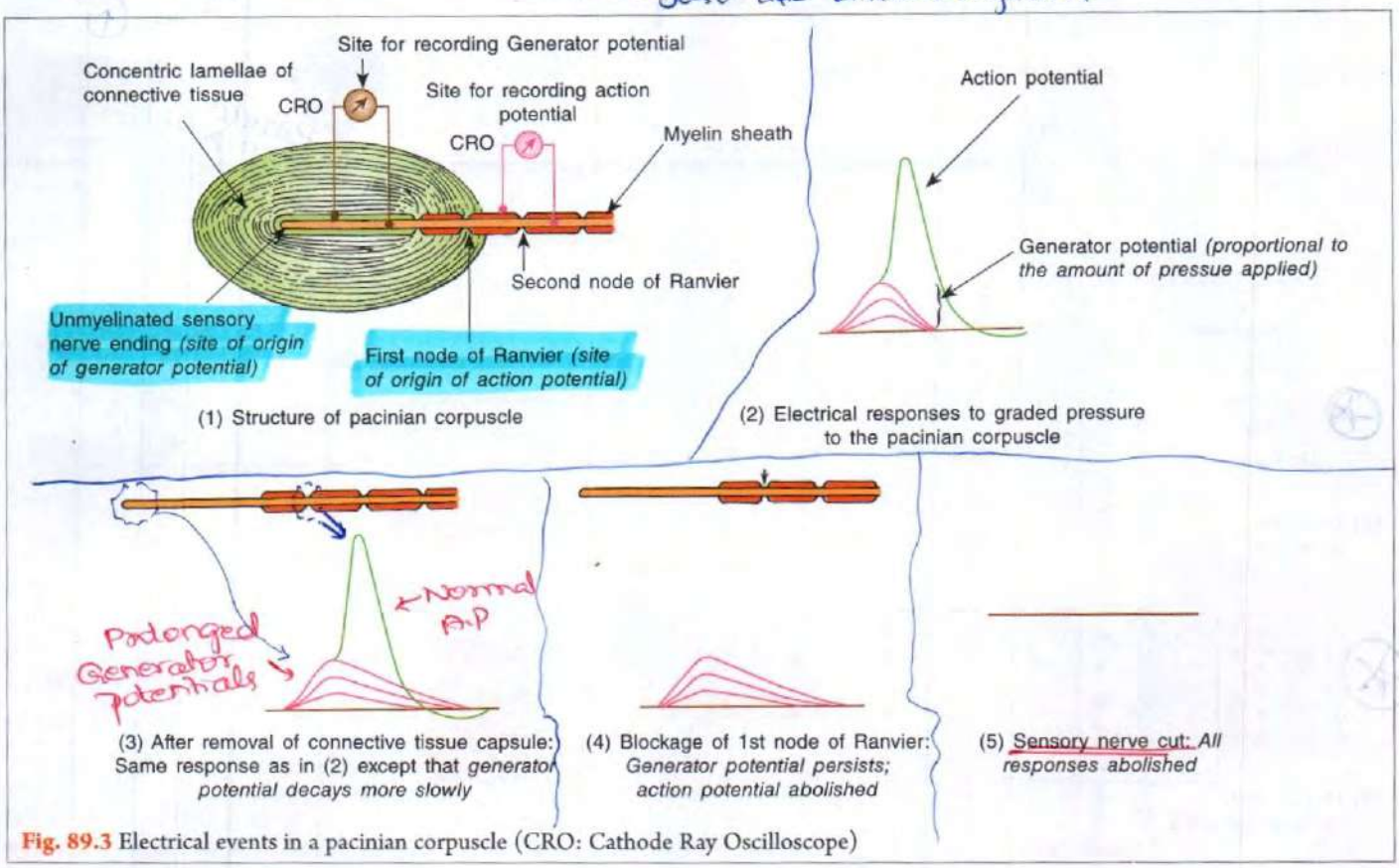


Fig. 89.3 Electrical events in a pacinian corpuscle (CRO: Cathode Ray Oscilloscope)

(iii) *When the sensory nerve is cut* and is allowed to degenerate, neither the generator potential nor the action potential can be recorded.

Conclusion – This shows that the generator potential originates from the unmyelinated nerve ending and not from the capsule or from first node of Ranvier. The generator potential so produced, electrotonically depolarizes the first node of Ranvier.

(For differences between the generator/receptor potential and action potential, refer to page 43)

5. ***How action potential is produced in the sensory nerve?***

(i) The generator potential, depolarizes the sensory nerve at the first node of Ranvier. Once the firing level is reached, an action potential is produced and the membrane repolarizes. If the generator potential is great enough, the neuron fires again as soon as it repolarizes, and it continues to fire as long as the generator potential is large enough to bring the membrane potential of the 1st node of Ranvier to the firing level. Thus the 1st node of Ranvier converts the graded response of the receptor into the action potential.

(ii) The receptor, therefore, converts the mechanical energy into an electric energy, the magnitude of which is proportional to the intensity of the stimulus.

6. ***Relationship between the intensity of stimulus, the size of generator potential and frequency of action potential in the afferent nerve.***

(i) The magnitude (size) of the generator potential is directly proportional to the intensity of stimulus, i.e. greater the intensity of the applied stimulus, larger will be the magnitude of the generator potential.

(ii) There also exists a relationship between the magnitude of generator potential and the frequency of action potential in the sensory nerve; i.e. frequency of action potential in a sensory nerve is also directly proportional to the magnitude of the generator potential **(Fig. 89.4)**.

From (i) and (ii), the frequency of action potential (S) a stimulus generates in a sensory nerve fiber is thus related to the intensity of the initiating stimulus (I) by a power function (a)

$$\text{Freq} \propto (\text{Inten})^a \quad \text{i.e.} \quad S \propto I^a$$

Based on these facts *Weber* and *Fechner* proposed two different laws.

1. **Weber's law:** The law states that the just noticeable difference between two stimuli is proportional to the magnitude of the stimuli.
2. **Fechner's law:** The law states that subjective sensation is proportional to the logarithm of the stimulus intensity. i.e., $P \propto \log I$

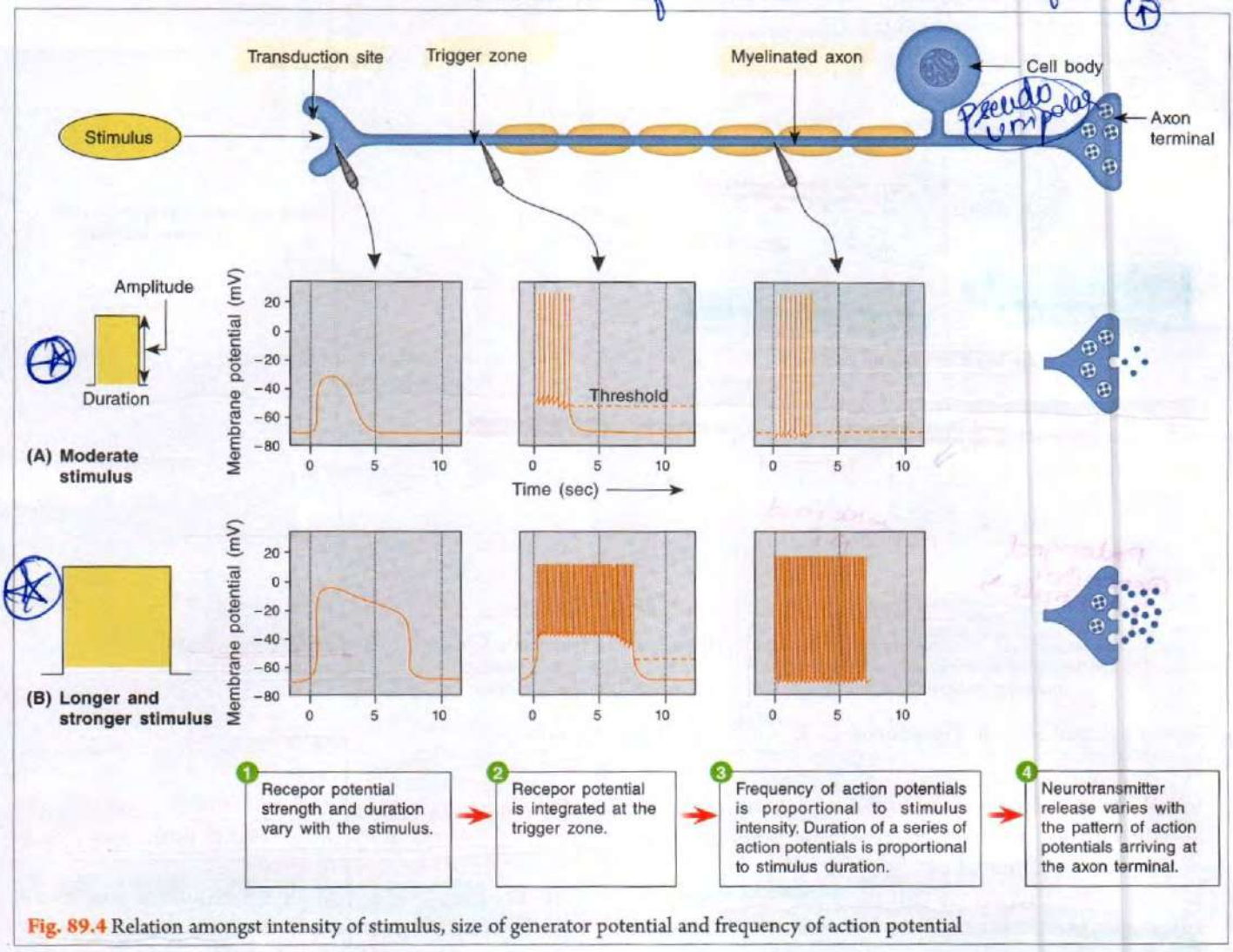


Fig. 89.4 Relation amongst intensity of stimulus, size of generator potential and frequency of action potential

Weber-Fechner law combines the above two different laws and this kinds of relationship can be described by a *differential equation* as:

$$dp = k\frac{ds}{S}$$

where, dp - differential change in perception
dS - differential increase in the stimulus
S - Stimulus at the instant
k - constant factor

Integration of above equation gives

$$p = k \log S + C$$ (C is the constant of integration)

Therefore, the relationship between stimulus and perception is *logarithmic*. This means that if a stimulus varies as a *geometric progression* (*i.e.* multiplied by a fixed factor), the corresponding perception is altered in *an arithmetic progression* (*i.e.* in additive constant amounts).

For example, If a stimulus is tripled in strength (*i.e.* 3×1), the corresponding perception may be two times as strong as its original value (*i.e.* 1+1). If the stimulus is again tripled in strength (*i.e.* 3×3×1), the corresponding perception will be three times as strong as its original value (*i.e.* 1 + 1 + 1). *Hence, for multiplications in stimulus strength, the strength of perception only adds.*

Thus, magnitude of the sensation felt is proportionate to the log of the intensity of the stimulus (details on page 870).

7. *Ionic basis of generator potential*

(i) The stimulus initiates an increase in the permeability of the membrane of the unmyelinated terminal to Na^+, the resultant influx of Na^+ causes development of generator potential. {*Proof:* Na^+ depletion diminishes and finally abolishes the generator potential in pacinian corpuscle.}

(ii) The magnitude of change in the perme-ability of the membrane is proportional to the intensity of the stimulus. How the mechanical stimulus brings about change in membrane permeability is not known; it is probably due to stretching or

distortion of the membrane or it could be due to the release of some chemical mediator.

PROPERTIES OF RECEPTORS

1. *Specificity of Response or Law of Adequate Stimulus* – The receptors respond maximally only when an appropriate *specific* stimulus is applied. The receptors in each of the sense organs are thus adapted to respond to one particular form of energy at much lower threshold than other receptors response to this form of energy. The particular form of energy to which a receptor is most sensitive is called its *adequate stimulus*. For example:
   (i) Warm water stimulates Ruffini's receptor at low intensity of stimulus producing a specific response. However, it also stimulates the naked nerve endings of pain at high stimulus and the response produced is not complete.
   (ii) The adequate stimulus for the rods and cones in the eye is light. Pressure on the eyeball will also stimulate these receptors, but the threshold of these receptors to pressure is much higher than the threshold of the pressure receptors in the skin.
   (iii) Likewise, the tactile receptors respond to deformation, the golgi tendon organs to stretch and the cochlea to vibrations of the basement membrane set up by sound at much lower threshold of stimulus.
2. *Adaptation* – When a stimulus of constant strength is applied to the receptor, the frequency of action potential in its sensory nerve decreases over a period of time, a phenomenon called *adaptation or desensitization* (page 143). This is due to accommodation of sensory nerve fiber to the generator potential. The degree to which adaptation occurs varies with the type of receptors. These receptors are of two types: *tonic* and *phasic* receptor **(Fig. 89.5)**.
   (i) *Tonic receptors:* They are poor, *slow and incompletely adapting* receptors, therefore, they can continue to transmit the informations for many hours even if the intensity of stimulus remains absolutely constant over many days. Thus the generator potential is prolonged and decays slowly. This is important for life because if these receptors get adapted, it will damage the body. How?
      (a) The muscle spindle adaptation is slow; the discharge continues as long as the muscle is stretched. This is particularly helpful in prolonged postural adjustments.
      (b) Sensation of pain and cold are initiated by potentially noxious stimuli and they would lose some of their warning values if their receptors showed marked adaptation.
      (c) Baroreceptors and chemoreceptors operate continuously in the regulation of BP; adaptation of these receptors would limit the precision with which the regulatory system operates.
   (ii) *Phasic (or rate) receptors:* These are *rapidly adapting* receptors and transmit signals only when the stimulus strength is changed. Therefore, number of impulses transmitted is directly proportional to the rate at which the change take place. Thus the generator potential in them is short and decays rapidly. Examples are touch, olfactory and pressure receptors.
3. *Muller's Doctrine of Specific Nerve Energies (Muller, 1835)* – In general, action potentials are similar in all nerves, then why stimulation of a touch receptor causes a sensation of touch and not of warmth. This is because the sensation produced by impulses

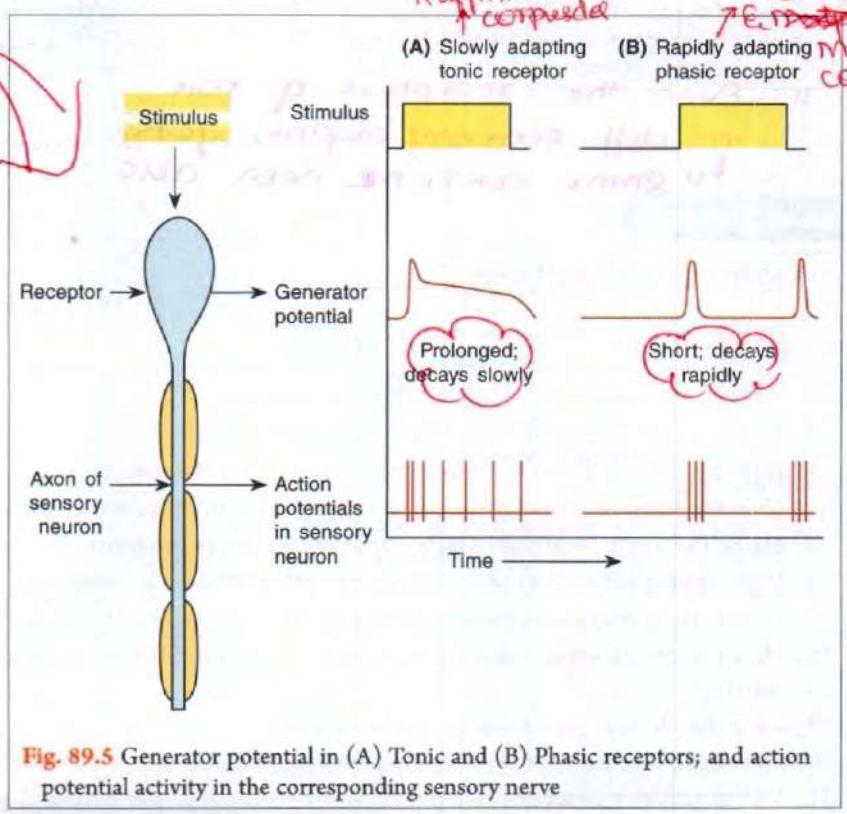
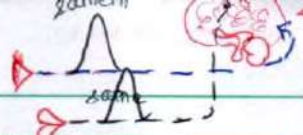


Fig. 89.5 Generator potential in (A) Tonic and (B) Phasic receptors; and action potential activity in the corresponding sensory nerve



#: For same sense stimulus (Eg: Pain), PERCEPTION for same intensity may be diff. [Eg: At lips - max.]

generated in a receptor depends upon the specific part of the brain they ultimately activate. In addition, the specific pathways are separate from sense organ to cortex and are achieved early during development of the C.N.S.. This principle was first established by Muller and is called *Muller's doctrine of specific nerve energies*. Therefore, when the nerve pathways from a particular sense organ are stimulated, the sensation produced is that for which the receptor is specialized no matter how or where along the pathway the activity is originated.

This explains why activation of the pain pathway by the pressure of a growth in the spinal column results in the perception of pain.

4. *Law of Projection* – No matter where a particular sensory pathway is stimulated along its course to the cortex, the conscious sensation produced is referred to the location of the receptor. This principle is called the *law of projection*.

For example: a limb that has been lost by accident or amputation, the patient usually experiences intolerable pain and proprioceptive sensations in the limb that is no longer there (called *Phantom limb; phantom* means non-existing or absent limb). These sensations are due to the irritation of the damaged nociceptive and proprioceptive afferents at the stump of the removed limb. This generates impulses in nerve fibers that previously came from the receptors in the removed limb, and the sensations produced are projected to where the receptors used to be located.

sensation here refers to receptor that was in cut off limb

#: Even the receptors of pain in diff sensory organs, going to SAME CORTICAL AREA also

Note

Phantom sensations may also occur after the removal of other body parts e.g. after amputation of the breast or extraction of a tooth etc.

5. *Law of Intensity Discrimination* – How the brain interprets different intensities of sensations? i.e., how it is possible to tell whether the touch is light or heavy; pain is mild, moderate or severe?

There are two ways in which informations about intensity of stimuli is transmitted to the brain:

(i) by variation in the frequency of the action potentials generated by the activity in a given receptor (Weber Fechner Law, page 867), and

(ii) by variation in the number of receptors activated. How?

As the strength of a stimulus is increased, it spreads over a large area activating more and more receptors in the neighbourhood, called *recruitment of sensory units* (page 886). In addition, with weak stimuli, only receptors with low threshold fire, whereas with stronger stimuli, receptors with higher threshold also fire. Thus more afferent pathways get activated which is interpreted in the brain as an increase in intensity of the sensation. (Law of Adeq. Stimuli)

Note

Intensity determination is determined primarily by the properties of the peripheral receptors.

Study Questions

1. Draw well labelled diagram:
   (i) Sensory receptors in the skin
   (ii) Discharge from thermal receptors
   (iii) Electrical events in a pacinian corpuscle
   (iv) Relationship amongst intensity of a stimules, size of generator potential and frequency of action potential
   (v) Generator potential in tonic and phasic receptors
2. How is the information 'coded' in the sensory nerves?
3. Define a 'receptor'. What are receptor 'types'? Give their properties.
4. Give the features of receptors which conveys sensation from the joints.
5. Name the nerve terminals which form the cutaneous receptors.
6. Differentiate between cold and warm receptors. What is a paradoxical cold fiber discharge?
7. Why is the pacinian corpuscle selected for the electrical events of receptor?
8. How is it possible that different nerve fibres transmit different modalities of sensation inspite of similar type of electrical activity?
9. Give the physiological basis of 'phantom limb'.
10. Give main differences between receptor potential and action potential.
11. Define receptor potential and give its source. How is action potential produced in the sensory nerve?

12. **Differentiate between tonic and phasic receptors with suitable examples. Give their physiological significance.**
13. **Give physiological significance:**
    (i) sensory unit
    (ii) proprioceptors
    (iii) sense organ
    (iv) nociceptors
    (v) poor, slow and incompletely adapting receptors.
14. **Differentiate between:**
    (i) Receptor and sense organ
    (ii) General and special senses
    (iii) Conscious and unconscious senses
    (iv) Cold and warm receptors
    (v) Generator potential and action potential.
15. **Write short notes on:**
    (i) Receptor types
    (ii) Cutaneous receptors
    (iii) Electrical and ionic events at receptor
    (iv) Paradoxical cold fiber discharge
    (v) Weber's Fechner law
    (vi) Properties of receptors
    (vii) Sensory unit
    (viii) Phantom limb

MCQs

1. *Not true* **about superficial senses is:**
   (a) Their receptors are located in skin, therefore, also called cutaneous senses
   (b) Informations in them is carried by cutaneous branches of spinal nerves
   (c) Examples include: touch, pain, pressure and thermal
   (d) Stimulus for all these senses is mechanical
2. *Not* **a feature of tactile receptors:**
   (a) They occur in groups in the skin papillae
   (b) Maximum density is seen in the skin of genitalia and tongue
   (c) They are rapidly adapting receptors
   (d) These are sensory nerve endings of A fiber (β and δ group)
3. **Meissner's corpuscle:**
   (a) Detects the degree of tension in the muscles
   (b) Detects the rate of change of muscle length
   (c) Detects very rapid changes in pressure
   (d) Responds specifically to light touch
4. **Nociceptive stimuli are transmitted by:**
   (a) Naked nerve ending
   (b) Pacinian corpuscles
   (c) Merkel's disc
   (d) Ruffini end organ
5. *Not true* **statement about cold receptors:**
   (a) Are unmyelinated 'C' fibers (Aδ)
   (b) 4-10 times more than warm receptors
   (c) Respond primarily to temperature of tissues which immediately surround them
   (d) Also get activated when tissue temperature is raised beyond 45°C [Paradoxical cold fibre discharge]
6. **Cold metal objects feel colder than wooden objects of the same temperature because:**
   (a) Number of cold receptors is more than warm receptors
   (b) Cold receptors are thin myelinated Aδ fibers
   (c) Metal conducts heat away from the skin rapidly
   (d) Cold receptors have low threshold of excitation
7. **Paradoxical cold fiber discharge:**
   (a) Occurs when warm receptors respond to raised tissue temperature
   (b) Cold receptor discharge at increasing rate when tissue temperature is raised beyond 45°C
   (c) So called because stimulation of cold receptors produces sensation of warmth
   (d) None of the above is true
8. **Weber's Fechner law deals with:**
   (a) Frequency discrimination
   (b) Receptive field organization
   (c) Intensity discrimination of Stimuli
   (d) Two point discrimination
9. **No matter where a particular sensory pathway is stimulated along its course to the cortex, the conscious sensation produced is referred to the location of the receptor. This is:**
   (a) Law of projection
   (b) Muller's Law
   (c) Weber's Fechner law
   (d) Bell Magendie's law
10. **As the strength of a stimulus is increased, it spreads over a large area activating more and more receptors. This is called:**
    (a) Specificity of response
    (b) Muller's doctrine of specific nerve energies
    (c) Recruitment of sensory unit
    (d) All of the above

11. **Meissner's corpuscles are believed to be sensitive to:**
(a) pH of interstitial fluid (b) Histamine
(c) Change of temperature (d) Mechanical deformation

12. **We *do not* feel our clothes once they are put on because:**
(a) Cutaneous receptors do not respond to this stimulus
(b) No receptors are present over the skin to sense their presence
(c) They fail to generate activity in any of the cutaneous receptors
(d) They activate the tactile receptors which are rapidly adapting receptors

13. ***False* statement about Pacinian corpuscles:**
(a) Respond maximum to sustain touch
(b) Are large receptors resemble an onion in shape and lamination
(c) Are found in large number in the skin, subcutaneous tissues and mesentery
(d) Slowly adapting receptors

14. **Ruffini end organ is mainly associated with sensation of:**
(a) Pressure (b) Cold (c) Pain (d) Touch

15. **Kinesthetic sensations are detected mainly by what type of receptors:**
(a) Muscle spindles (b) Golgi tendon organs (c) Skin receptors (d) Joint receptors

16. **What causes stimulation of the thermal receptors?**
(a) Change in the membrane structure caused by temperature
(b) Change in the metabolic rate of the nerve ending
(c) Increase in the concentration of sodium ions outside the neuron
(d) Change in viscosity of the fluid surrounding the neuron

17. **Source of generator potential in Pacinian corpuscle is:**
(a) Unmyelinated sensory nerve ending (b) Receptor capsule
(c) First node of Ranvier (d) Second node of Ranvier

18. **Phenomenon of adaptation is complete and occurs fastest in:**
(a) Pacinian corpuscles (b) Muscle spindles
(c) Joint capsule receptors (d) Hair base receptors

19. **Why does stimulation of touch receptors causes a sensation of touch and *not* of warmth *because*:**
(a) Differences in the action potential in nerves
(b) Specific part of the brain the sensation ultimately activates
(c) Law of projection
(d) Law of adequate stimulus

20. **Capacity to discriminate an increment in intensity of stimulus is:**
(a) Greater when amplitude of generator potential is smaller
(b) Greater in higher range of stimulation
(c) Greater in lower range of stimulation
(d) Greater if duration of latent period increases

21. **The intensity of sensory stimuli is determined by:**
(a) Duration of latent period (b) Amplitude of action potential
(c) Frequency of action potential (d) Amplitude of generator potential

Answers

1. (d) 2. (b) 3. (d) 4. (a) 5. (a) 6. (c) 7. (b) 8. (c) 9. (a) 10. (c) 11. (d) 12. (d) 13. (d) 14. (b) 15. (d)
16. (b) 17. (a) 18. (a) 19. (b) 20. (c) 21. (c)

Chapter 90

Reflexes

I. Introduction: the Reflex arc; classification of reflex
II. Monosynaptic reflexes: the stretch reflex
  A. Muscle spindle
  B. Higher control of stretch reflex
  C. Muscle tone
  D. Inhibition of stretch reflex: reciprocal inhibition, inverse stretch reflex
III. Polysynaptic reflexes: the withdrawal reflex
IV. General properties of reflexes

INTRODUCTION

Reflex is an *involuntary* (automatic) response to a stimulus which depends on integrity (completeness) of reflex pathway *i.e.* the *reflex arc.*

THE REFLEX ARC

1. It forms the functional unit of the nervous system and consists of *receptor,* an *afferent* neuron, an *efferent* neuron and an *effector* organ.

Note

A *stimulus* is a detectable change in the environment. A *receptor* detect the environmental change and sends the information to an integrating centre. The path travelled by the signal between the receptor and the integrating centre is called the *Afferent pathway* ('afferent' means 'to carry to'). The output of the integrating centre travels along a path known as the *Efferent pathway* ('efferent' means 'to bear away from') to an *Effector* (a device that constitutes the overall response of the system).

2. The number of *synapses* (connection between afferent and efferent neurons) varies from one to many hundred. These synapses are located in the brain or spinal cord.
3. The afferent neurons enter via the dorsal roots or cranial nerves and have their cell bodies in the dorsal root ganglia or in the homologous ganglia on the cranial nerves. The efferent fibers leave via the ventral root or corresponding motor cranial nerves.

Important Notes

1. In the spinal cord fact that the dorsal roots are sensory and the ventral roots are motor is called *Bell-Magendie Law.*
2. Since the connection between afferent and efferent neurons is usually present in the CNS, therefore, activity in the reflex arc is modified by the multiple inputs converging on the efferent neurons (page 882).

Classification of Reflexes

Reflexes can broadly be divided into two categories: *Mono and polysynaptic reflexes.*

1. *Monosynaptic reflexes.* Reflexes in which only one synapse is present between the afferent and efferent neurons. *Example:* All the stretch reflexes (biceps, triceps or knee jerks).
2. *Polysynaptic reflexes.* Reflexes in which one or more (upto 100) interneurons are present between the afferent and efferent neurons. *Examples:* Withdrawal reflexes, gross flexor reflex, gross extensor reflex and superficial reflexes.

MONOSYNAPTIC REFLEXES: THE STRETCH REFLEX

1. When a skeletal muscle with an intact nerve supply is stretched, it contracts. This response is called the *Stretch Reflex* (Fig. 90.1).
   (i) The *stimulus* that initiates the reflex is 'stretch' to the muscle.
   (ii) The *response* is contraction of the muscle being stretched.

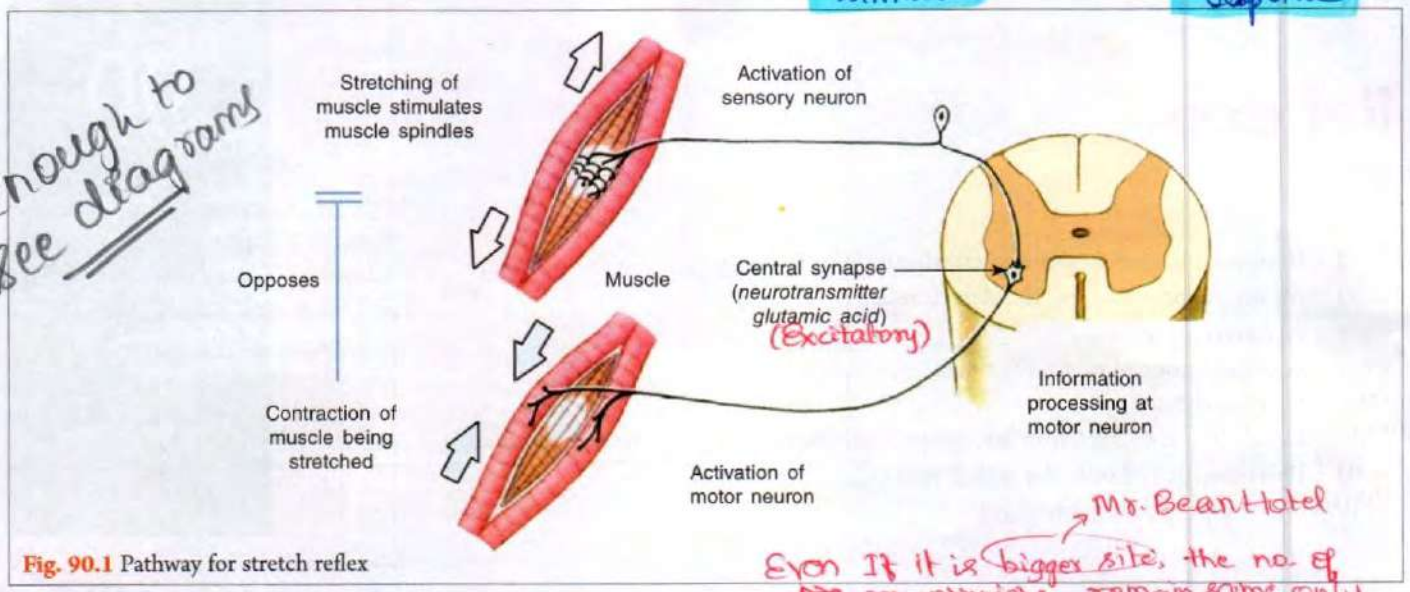


Fig. 90.1 Pathway for stretch reflex

(iii) The *receptor* is the *muscle spindle.*

(iv) The *neurotransmitter* at the central synapse is glutamic acid. (Glutamate)

For example: when the patellar tendon is tapped by a *patellar hammer,* it stretches the quadriceps muscle; the stretched muscle contracts reflexly, elevating the leg (called the *knee jerk* or *knee reflex*).

2. ***Reaction time.*** The time between the application of the stimulus and the response is called the reaction time; for a stretch reflex such as the knee jerk it is 19-24 msec. (NS)

3. ***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 msec (page 890), therefore, only one synapse could have been traversed for this reflex activity; stretch reflexes are thus called the *monosynaptic reflexes.*

Important Notes

1. The stretch reflex is the best known monosynaptic reflex in the body. It is the 'fundamental' reflex which plays an important role in control of body posture.
2. The most important characteristic of stretch reflex is that it is highly developed in *antigravity muscles i.e.,* the muscles which oppose the force of gravity. Examples: the extensor group of muscles of legs and the flexor group of muscles of arms (Details page 952).

A. THE MUSCLE SPINDLE

Structure

1. It is a macroscopic structure, 4 mm long, spindle shaped and is widely distributed within the muscle. Its number depends on the type of the muscle, such as small distal muscles which help in delicate control, contain more muscle spindle (150/gm); while large muscles contain lesser number (5/gm).
2. Each muscle spindle contains 8-12 muscle fibers enclosed in a connective tissue 'capsule', called the ***intrafusal muscle fibers***, while the regular contractile units of muscle are called the ***extrafusal muscle fibers*** **(Fig. 90.2)**. The intrafusal fibers are in parallel with rest of the muscle fibers because the ends of the 'capsule' of the spindle are attached to the tendons at either end of the muscle or to the sides of the extrafusal fibers.
3. The central area of the spindle is 80-120 µm wide and in this region the intrafusal ibers are surrounded by fluid contained in the capsule.
4. *Intrafusal muscle fibers: Features*
   (i) They are more embryonal in character, striations are less developed, 6-30 µm in diameter;
   (ii) Their ends are contractile while the centre is not;
   (iii) They are of 2 types:
   (a) *Nuclear bag fibers* – contain many nuclei in a dilated central area; These are two subtypes: *dynamic and static fibres;* and
   (b) *Nuclear chain fibers* are thinner and shorter, lack a definite bag and show only a single line of nuclei lying in a chain. Their ends are connected to the sides of nuclear bag fibers.

Note

Each muscle spindle has about 2 or 3 nuclear bag fibers and 5 nuclear chain fibers.

(Bag: Chain = 1 : 2)

Innervations

Muscle spindles are supplied by 2 types of nerve fibers: sensory and motor nerves.

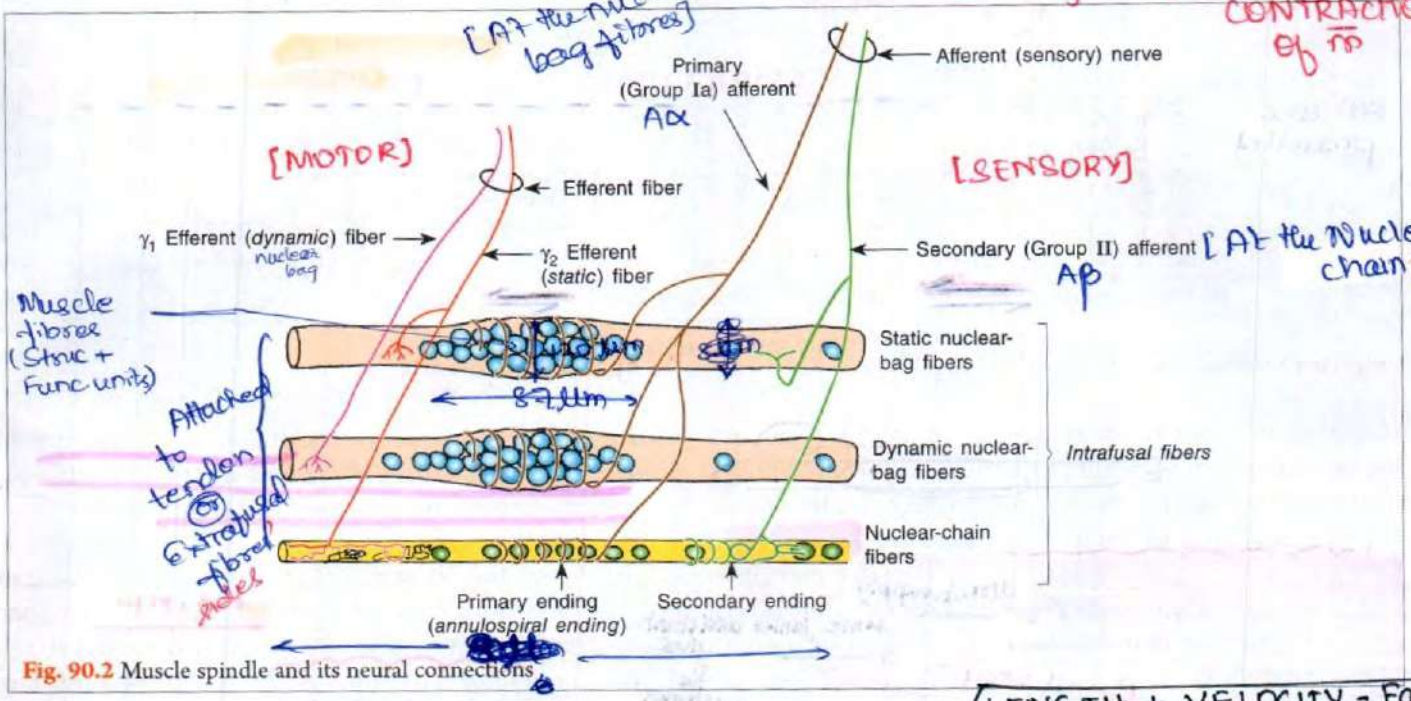


Fig. 90.2 Muscle spindle and its neural connections

1. ***Sensory supply.*** Each muscle spindle has 2 types of sensory endings:
   (i) A single ***primary (or annulospiral) ending.*** This is terminations of rapidly conducting group Ia (or Aα) afferent fibers, 12-20 μm diameter, that wrap around the centre of the nuclear bag and nuclear chain fibers. Both these primary endings get stimulated when the muscle spindle is stretched, but the pattern of response differs (Fig. 90.3).
   (a) The nerve from ending in the nuclear bag region discharge most rapidly while the muscle is being stretched and less rapidly during sustained stretch; (i.e. it respond to both changes in length of the muscle and velocity at which it is being stretched); this is called a *dynamic response.*
   (b) The nerves from the endings in the nuclear chain fibers discharges at an increased rate throughout the period of sustained stretch only (i.e. during steady state length of the muscle); this is called a *static response.*
   (ii) 6–8 ***secondary endings.*** These are terminations of group II (or Aβ) afferent fibers, 6-9 μm diameter, and are located near the polar ends of the nuclear chain fibers and static nuclear bag fibers (these fibers do not innervate dynamic nuclear bag fibers. These endings also respond mainly to sustained stretch, therefore, measure the muscle length.
   The fibers from the primary endings terminate directly on α-motor neurons supplying the extrafusal fibers of the same muscle.

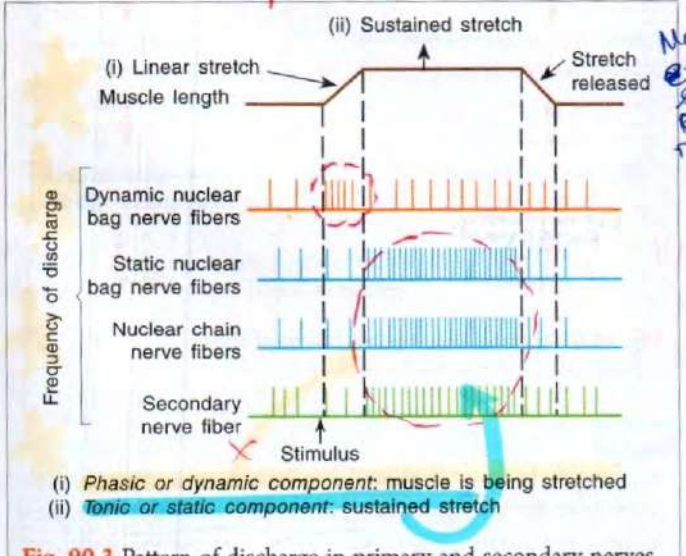


Fig. 90.3 Pattern of discharge in primary and secondary nerves of muscle spindle

2. ***Motor supply.*** Motor supply to the muscle spindle comes from the ventral horn cells in the spinal cord by *γ efferent fibers.*
   γ-efferent fibers (or fusiform fibers). These are group Aγ fibers (3-6 μm diameter) of 'γ-motor neurons' with high threshold of excitation. These fibers are further subdivided into: γ_1 and γ_2 fibers.
   (a) *γ_1-fibers.* They supply the ends of dynamic nuclear bag fibers, and
   (b) *γ_2-fibers.* They supply static nuclear bag fibers and the ends of nuclear chain fibers.

Stimulation of γ-efferent fibers produces no detectable contraction of the muscle, because intrafusal fibers are not strong enough or plentiful enough to cause shortening.

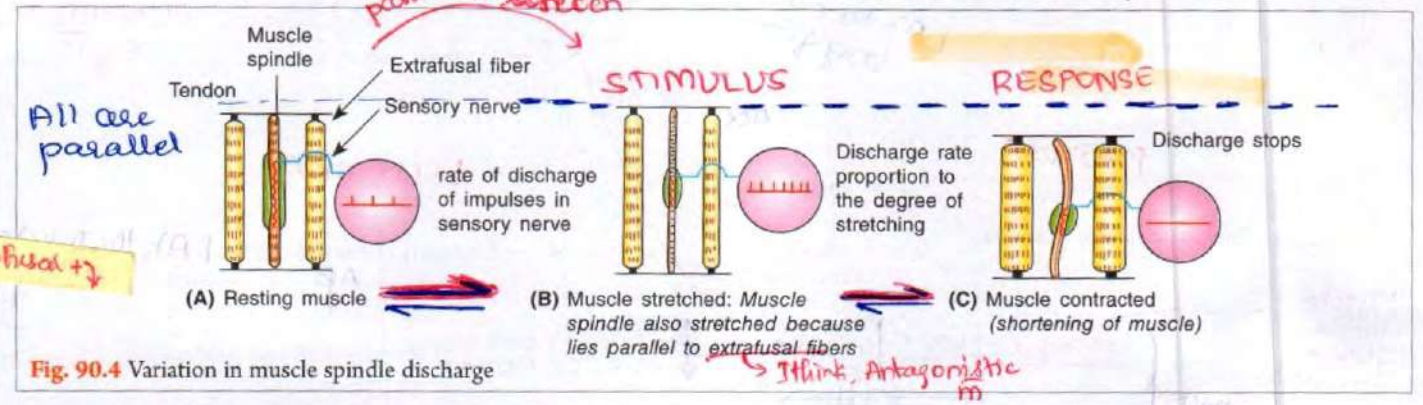


Fig. 90.4 Variation in muscle spindle discharge

However, it produces shortening of contractile ends of intrafusal fibers, this stretches the central portion of spindle to initiate impulse in sensory nerve which finally leads to *reflex contraction* of the muscle. Therefore, muscle can be made to contract via stimulation of α-motor neurons that innervate the extrafusal fibers *directly*, or stimulation of γ-motor neurons that initiate contraction *indirectly* via the stretch reflex.

Physiological significance

1. When the muscle is passively stretched the spindles are also stretched, these in turn, set up action potentials in the sensory fibers whose frequency is proportionate to the degree of stretching **(Fig. 90.4)**. Thus, harder a muscle is stretched, stronger is the reflex contraction.
2. If the whole muscle is stretched during stimulation of γ-efferents, additional action potentials are generated in the sensory nerve due to further stretch on central portion **(Fig. 90.6)**. Thus spindle sensitivity varies with the rate of γ-efferent discharge.
   (i) *Stimulation of γ_1-efferent fibers* increases the spindle sensitivity to rate of change of stretch (phasic or dynamic component), therefore, γ_1-fibers are also called the *dynamic γ-efferent fibers*.
   (ii) *Stimulation of γ_2-efferent fibers* increases the spindle sensitivity to steady, maintained stretch (tonic or static component) therefore, γ_2-fibers are also called *static γ-efferent fibers*.

   Thus it is possible to adjust the muscle spindle sensitivity to dynamic and static events.

Control of γ-efferent discharge

The rate of γ-efferent discharge is governed by higher centres, receiving both *excitatory and inhibitory impulses* (page 877).

Functions

Muscle spindle is the receptor of stretch reflexes which are fundamental reflexes to regulate the posture. How?

1. ***By Length Servo Mechanism.*** It is a system of *negative feedback* device that operates to maintain muscle length during body movements. The muscle spindle compares the length of extrafusal fibers with intrafusal fibers and thereby controls the length of extrafusal fibers.

   Mechanism

   (i) When the muscle spindle is stretched, action potentials are set up in the sensory nerve proportionate to the degree of stretching **(Fig. 90.4 B)**.

   (ii) The *motor control system* (page 947) in the brain initiates voluntary and involuntary muscle movements. Its neurons discharge simultaneously (*i.e.* almost at the same time) to activate both α and γ motor neurons in the spinal cord, called *α-γ coactivation*. Thus when a muscle contracts, its spindle remain active. This causes both the extrafusal and intrafusal fibers to contract at the same time. Therefore,

   (a) if at any moment altered length of the muscle is more than the required during movement, muscle spindle discharge increases and reflex shortening is produced **(Fig. 90.5)**;

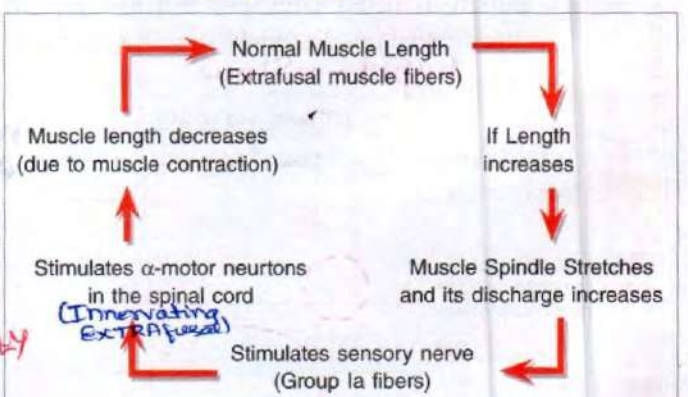


Fig. 90.5 Operation of length servo mechanism (system of negative feedback device)

Note

Changes in the muscle length are associated with changes in the joint angle. Thus muscle spindles provide information on position, i.e., proprioception - page 895.

(b) conversely, if the muscle is shortened without a change in γ-efferent discharge, muscle spindle discharge decreases and the muscle relaxes (Fig. 90.4 C).

Thus the muscle spindle and its reflex connections via α-γ *linkage* constitute a *negative feedback device* which operate to maintain muscle length during body movements.

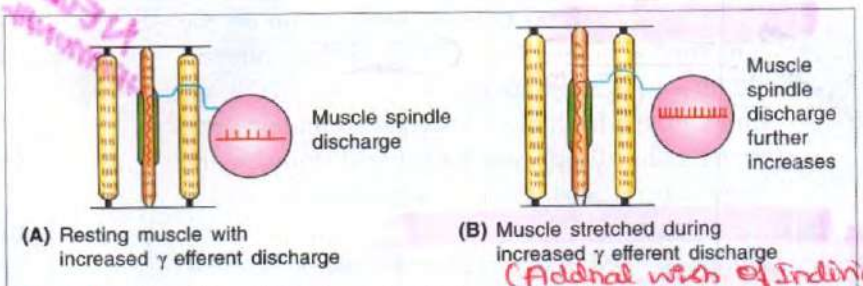


Fig. 90.6 Effect of stretching of muscle with increased γ-efferent activity on muscle spindle discharge (compare with Fig. 90.4)

2. *By 'Follow up Servo' Mechanism.* Muscle spindle also acts in regulation of posture by sustained contraction of the muscle. How? (Fig. 90.6)

There is increased γ-efferent discharge along with the increased discharge of the α-motor neurons (via α-γ *coactivator* see above). This increases the spindle sensitivity. Increase α-motor neuron discharge decreases pull on muscle spindles, but muscle spindles are contracting through γ-motor neuron discharge. This stimulates α-motor neurons and muscle contracts. Thus because of this *α-γ linkage* spindle shortens with the muscle, and spindle discharge may continue throughout the muscle contraction. This is how the spindle remains capable of responding to stretch and reflexly adjusting motor neuron discharge throughout the contraction.

Note

If an individual wish to perform any additional muscular activity against this stable background, additional action potential is generated in the sensory nerves (Fig. 90.6B). Thus it is possible to adjust the spindle sensitivity to dynamic and static events.

B. HIGHER CONTROL OF STRETCH REFLEX

1. Since the connection between the afferent and efferent neurons is in the CNS (brain or spinal cord), therefore, activity in the reflex arc can be modified (inhibited or facilitated) by higher centres. However the balance between the two will determine the normal reflex activity.
2. γ-motor neuron activity is regulated to a large degree by descending tracts from a number of areas in the brain. Thus, the sensitivity of the muscle spindle and hence the threshold of the stretch reflexes in various parts of the body can be adjusted and shifted to meet the needs of the postural control.
3. The brain areas that *facilitate and inhibit* the stretch reflexes are shown in Fig. 90.7. These areas generally act by increasing or decreasing muscle spindle sensitivity.
   (i) *Facilitatory reticular formation* area which is located in the brain stem discharges spontaneously in response to afferent input like reticular activating system (page 959). This increases discharge of γ-motor neurons and stretch reflex become hyperactive.

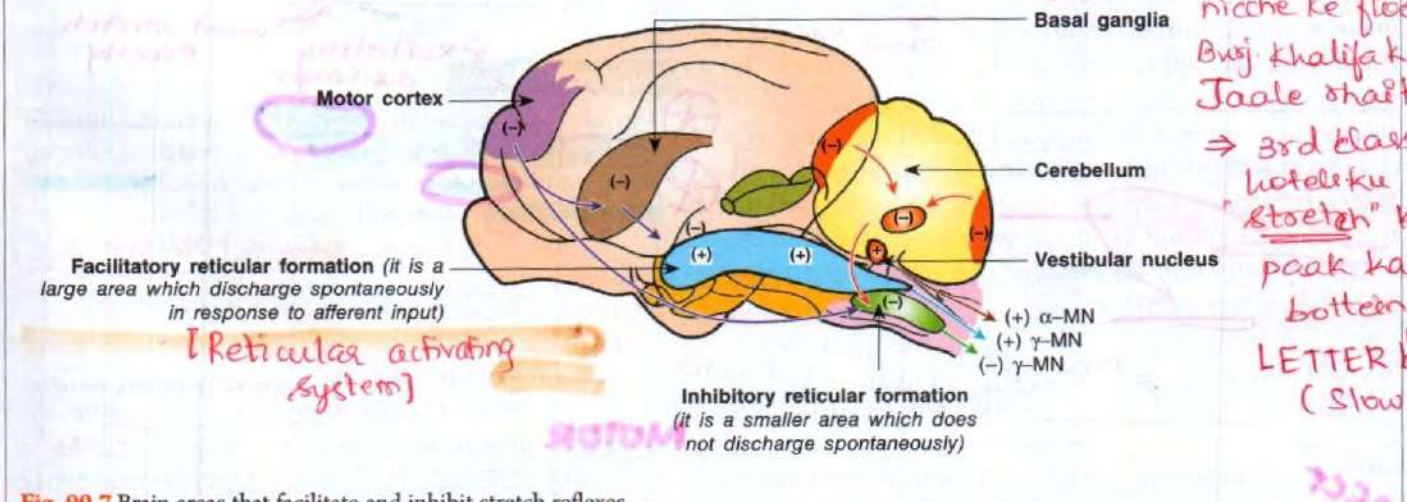


Fig. 90.7 Brain areas that facilitate and inhibit stretch reflexes
(Also refer Fig. 97.2, page 958) (+) and (–) facilitatory and inhibitory areas respectively. (MN: Motor Neurons)

(ii) *Vestibular nucleus* acts by a direct action on the α-motor neurons (*Proof:* After cutting afferent nerve) *i.e.*, deafferentation of the muscle, if we stimulate the facilitatory reticular formation area, stretch reflex disappears; however, if stimulate the vestibular nucleus, muscle contraction occurs.)

(iii) *Inhibitory reticular formation* area acts by inhibiting γ-efferent neuron discharge, thereby decreases the spindle sensitivity. It does not discharge spontaneously.

(iv) Fibers from the *cerebral cortex*, and *cerebellum* reflexly inhibit the stretch reflex, they act by stimulating the inhibitory reticular formation.

(v) Inhibitory area in the *Basal ganglia* may act through inhibiting facilitatory reticular formation or by stimulating the inhibitory area in the motor cortex.

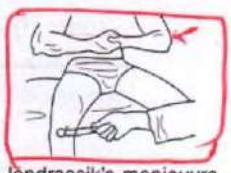
Important Note

In normal healthy individuals the balance of facilitatory and inhibitory impulses converging on the γ-efferent neurons shifts towards inhibition and stretch reflexes remain inhibited.

4. *Other factors* which increase the γ-efferent discharge.
   (i) *Anxiety.* This explains the hyperactive tendon reflexes in anxious patients.
   (ii) *Unexpected movements.*
   (iii) Stimulation of skin specially by *noxious agents.*

Physiological significance

Sometimes deep tendon reflexes (such as knee jerk reflex) cannot be elicited without applying *reinforcement (Jendrassik's manoeuvre).* This is done by asking the individual to make a strong voluntary muscular effort with the upper limb. For example, to hook the fingers of the two hands together and then to pull them against one another as hard as possible or to make a clench fist with the ipsilateral hand or clenching of teeth. Reinforcement acts by increasing the excitability of the α-motor neurons and by increasing the sensitivity of the muscle spindle primary sensory endings to stretch (by increased γ-efferent drive).



Jendrassik's manieuvre

5. ***SUMMARY***

(i) *Stretch reflex decreases i.e.* becomes *hypoactive* due to:
   (a) cutting or destruction of afferent or efferent nerve to the muscle,
   (b) stimulation of inhibitory areas in the brain,
   (c) inhibition of facilitatory areas in the brain,
   (d) hypothyroidism.

(ii) *Stretch reflex increases i.e.* becomes *hyperactive* due to:
   (a) destruction of any of the inhibitory areas in the brain,
   (b) stimulation of facilitatory areas in the brain,
   (c) any factor which increases the γ-efferent discharge (see above),
   (d) hyperthyroidism.

Applied Aspect

When the brain stem is transected at the level of the top of the pons, two of the 3 inhibitory areas that drive the reticular inhibitory centre are removed. Discharge of the facilitatory areas continue, but that of the inhibitory areas is decreased; as a result the balance of facilitatory and inhibitory impulses converging on the γ-efferent neurons shifts towards facilitation, and stretch reflexes become hyperactive.

C. MUSCLE TONE

1. *Definition.* Certain amount of tension present in the *resting muscle* due to *low frequency* and *asynchronous discharge* of γ-motor neurons which produces resistance of a muscle to stretch (or lengthening). *It is a state of partial tetanus.*

   The discharge is out of phase with each other which ultimately merges to produce smooth muscle contraction.

2. *Basis of muscle tone.* It depends on the stretch reflex which is under the control of higher centres (page 908).
   (i) *Hypotonic* or *flaccid* muscle is one which offers little or no resistance to stretching; and
   (ii) *Hypertonic* or *spastic* muscle is one in which resistance to stretch is high.

Important Note

Muscles are generally *hypotonic* when the rate of γ-efferent discharge is low *i.e.*, hypoactive stretch reflex; and *hypertonic* when it is high *i.e.* hyperactive stretch reflex (see above).

3. *Causes of hypotonia* (decrease in muscle tone)
   (i) Destruction of local reflex arc anywhere in its pathway. For example:
   (a) destruction of efferent (motor) nerve to a muscle by injury or poliomyelitis,
   (b) destruction of dorsal column (sensory) (page 888) as seen in syphilis. Syphilis frequently causes the constrictive fibrosis around the

dorsal nerve roots fibers where they enter the spinal cord. This condition is called *Tabes dorsalis*.

(ii) Stimulation of inhibitory areas in higher centre.

(iii) Inhibition or destruction of facilitatory areas in the brain (page 878).

(iv) During sleep.

(v) Certain drugs like barbiturates, tranquilizers in high doses.

Important Note

The influence of the cerebellum on the muscle tone is complex, however, its destruction produces hypotonia rather than hypertonia (page 968).

4. *Causes of hypertonia* (increase in muscle tone)

(i) Stimulation of facilitatory areas in the brain.

(ii) Destruction of inhibitory areas in the brain.

(iii) Any factor which increases the γ-motor neuron discharge (page 878).

Important Note

In brain diseases which cause increase in muscle tone, if hypertonia is confined to only one group of muscles, it is called *Spasticity*; however, when hypertonia involves both groups of muscles, extensors as well as flexors equally, it is referred to as *Rigidity*.

For example: lesion of internal capsule and UMNL (page 914) produces spasticity, whereas basal ganglia lesion leads to rigidity (page 995).

5. *Clinical assessment of muscle tone*

The clinician assesses the resistance offered by moving the muscle passively at their various joints. He uses his 'experience' in deciding whether such resistance is normal, low or high.

D. INHIBITION OF STRETCH REFLEXES

Because of its monosynaptic pathway, the inhibition of stretch reflexes is produced by pathways that end with inhibition of α-motor neurons. This is brought out by 2 mechanisms: *reciprocal innervation* and *inverse stretch reflex*.

1. *Reciprocal innervation or reciprocal inhibition*

When a stretch reflex occurs, 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, a phenomenon called *reciprocal innervation*. The pathway mediating this effect is ***bisynaptic***, *i.e.*, 2 synapses are involved. This is an example of postsynaptic inhibition and its mechanism is already discussed earlier (page 856, Fig. 88.9).

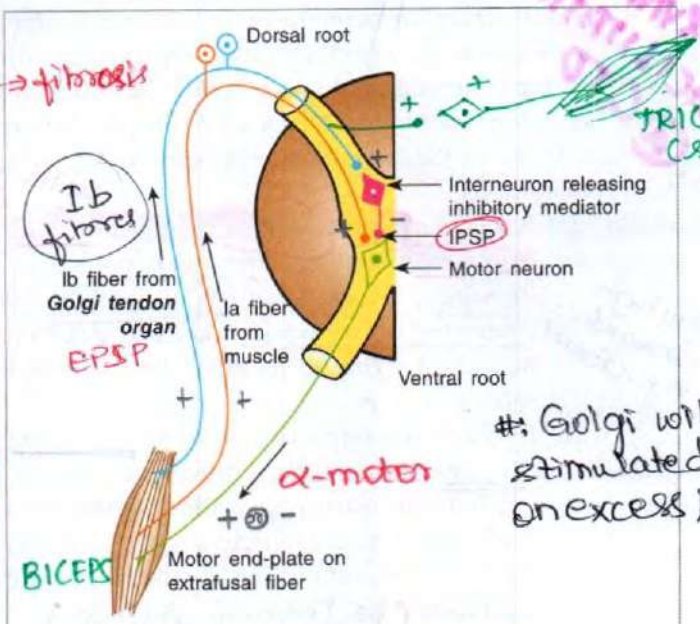


Fig. 90.8 Pathway responsible for the stretch reflex (——) and inverse stretch reflex (——)

Significance: Reciprocal innervation ensures that the movement of the 'agonist' muscle is not obstructed by contraction of the 'antagonist' muscles.

2. *Inverse stretch reflex* (Fig. 90.8)

(i) As noted earlier, the harder a muscle is stretched, the stronger is the reflex contraction (stretch reflex, page 873). This is seen only upto a certain point, however with further increase in stretch, contraction suddenly comes to an end and muscle relaxes. This relaxation in response to strong stretch is called the *inverse stretch reflex* or ***autogenic inhibition***. The receptors involved are the *Golgi tendon organs*.

(ii) *Golgi tendon organs*

(a) They are found at the musculotendon junction in *series* with the muscle fibers and there are 3-25 muscle fibers per tendon organ.

(b) The threshold of the Golgi tendon organs to their *natural stimulation* by active contraction of muscle fibers is very low.

(c) They also get stimulated *by passive stretch* to the muscle but the degree of stimulation is not great because the more elastic muscle fibers take up much of the stretch. Therefore, a strong stretch is required to produce relaxation.

(iii) *Pathways* – Afferent from the Golgi tendon organs form group Ib fibers; these fibers end in spinal cord on *inhibitory interneurons* which, in turn, terminate via short axonal pathway on the motor neurons that supply the muscle from which the Ib fiber arises. They also make excitatory connections with the motor neurons supplying the antagonists to the

muscle. Therefore, stimulation of the Golgi tendon organs produces excitatory postsynaptic potentials in the interneuronal cells which releases an inhibitory transmitter. This leads to the production of IPSPs on the 'agonist' motor neurons.

(iv) *Significance*

(a) It acts as a ***protective reflex*** to prevent tearing of muscles. How? A strong and potentially damaging muscle force *reflexly* inhibits the contraction of the muscle producing relaxation instead of trying to maintain the force and risking damage.

(b) It plays an important role in regulating 'tension' during normal muscle activity, *i.e.*, when the muscle contracts the force (tension) developed within a muscle acts as a stimulus for its own relaxation. This is called ***autogenic inhibition***.

Clinical Significance

1. *Lengthening Reaction or Clasp Knife effect*

It is the response of a *spastic* (muscle in which resting tone is high) to lengthening (*i.e.*, stretching) due to operation of *stretch reflex* and *inverse stretch reflex*. How? 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 (page 879), passive flexion of 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. Clinically, this sequence of resistance to flexion followed by relaxation when a limb is moved passively is known as ***clasp knife effect*** (because of its resemblance to the closing of a pocket knife). The physiological name for it is the *lengthening reaction* because it is the response of a 'spastic' muscle to lengthening.

2. *Clonus*

(i) It is a sign of increased reflex activity characterized by repetitive muscular contraction produced by stretch. Like the lengthening reaction, it may also be due to operation of stretch reflex and inverse stretch reflex sequence. For example: ***Ankle clonus*** is initiated by sudden, *maintained dorsiflexion* of the foot and the response is series of rhythmic plantar flexion at the ankle **(Fig. 90.9)**.

(ii) It can occur on the basis of synchronized motor neuron discharge without Golgi tendon organ discharge. The spindles of the tested muscle are hyperactive, and the burst of impulses from them discharges all the motor neurons supplying the muscle at once. The subsequent muscle contraction stops spindle discharge. However, the stretch has been maintained, and as soon as the muscle relaxes, it is again stretched and the spindles stimulated.

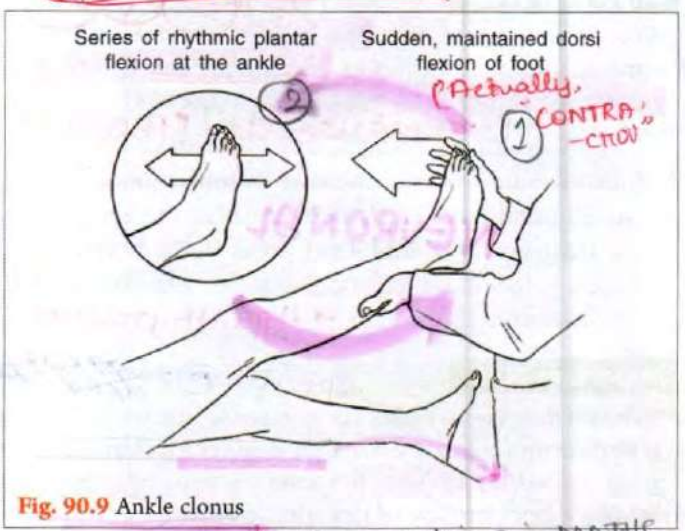


Fig. 90.9 Ankle clonus

POLYSYNAPTIC REFLEXES: THE WITHDRAWAL REFLEX

1. The reflexes in which there are many synaptic connections between afferent and efferent neurons is called *polysynaptic reflex*. Its reflex pathway branches in a complex fashion and the number of synapses in each of their branches is variable from two to many hundreds.
2. As the synaptic delay (page 858) occurs at each synapse, therefore, activity in branches with few synapses reaches the motor neurons first, followed by activity in the larger pathways **(Fig. 90.10)**.
3. Some of the branch pathways may turn back on themselves, allowing activity to strike back; such ***reverberating circuits*** are common in the brain and spinal cord. This causes prolonged bombardment of the motor neurons from a single stimulus and results in prolonged responses.
4. *Examples:* withdrawal reflex; abdominal and cremasteric reflexes.

WITHDRAWAL REFLEX

(A) Definition

It is a polysynaptic reflex that occurs in response to a noxious or painful stimulus (page 863). Therefore, when

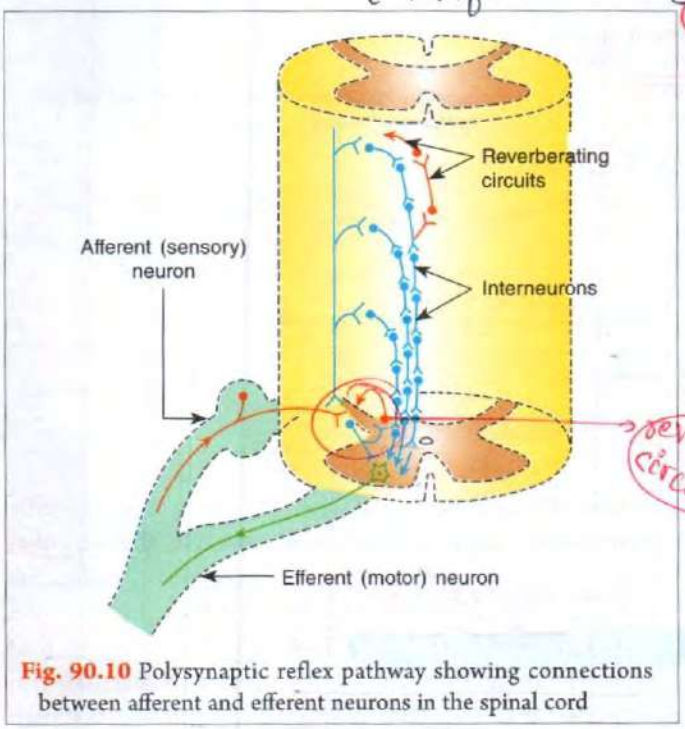


Fig. 90.10 Polysynaptic reflex pathway showing connections between afferent and efferent neurons in the spinal cord

a noxious stimulus is applied to a limb it leads to:

(i) Contraction of flexor group of muscles and inhibition of extensor muscles, therefore limb stimulated is flexed and withdrawn from the stimulus. This is called *flexor response* or *flexor reflex;* **(Fig. 90.11)**.

(ii) With a stronger stimulus, in addition to flexor reflex there occurs extension of the opposite limb also. This is called *crossed extensor reflex/response.*

(B) *Mechanism:* A strong stimulus causes spread of excitatory impulses up and down the spinal cord to more and more motor neurons. This is called *irradiation of the stimulus;* and the increase in the number of active motor units is called *recruitment of motor units.*

(C) Significance

The withdrawal reflex is a *protective reflex,* as the 'flexor responses' can be produced by non-damaging (innocuous) stimulation of skin or by stretch of the muscle, but strong flexor responses with withdrawal are produced only by 'nociceptive stimuli'. Therefore, while the stimulated limb is withdrawn to get away from the source of the stimulus, the extension of the other limb supports the body.

Important Note

Withdrawal reflexes are prepotent (more stronger than other), therefore, they block the spinal pathways from any other reflex activity taking place at that moment.

Characteristic features

1. *Recruitment and after discharge*

(i) As noted above, a weak stimulus produces only one quick 'flexor response'; with a stronger stimulus, 'crossed extensor reflex' is also produced and consequently a prolonged response. This prolonged response is due to prolonged repeated firing of the motor neurons. This repeated firing even after the sensory nerve has stopped firing is called *'After discharge'* and is due to continued bombardment of motor neurons by the *reverberating circuits.*

(ii) The salient features of this *reflex activity* are summarized in **Fig. 90.12**.

Important Note

Recruitment gives inertia (sluggishness), and *after-discharge* provides momentum (driving force) to reflex movements, making these movements smoother in onset and termination.

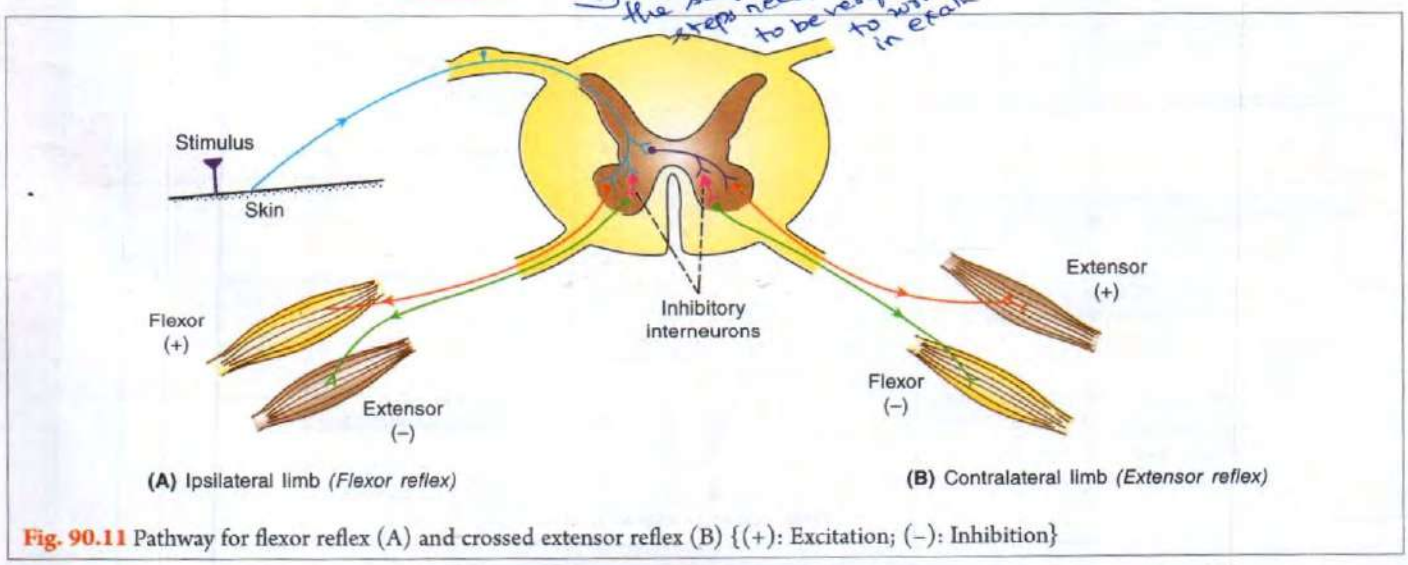


Fig. 90.11 Pathway for flexor reflex (A) and crossed extensor reflex (B) {(+): Excitation; (−): Inhibition}

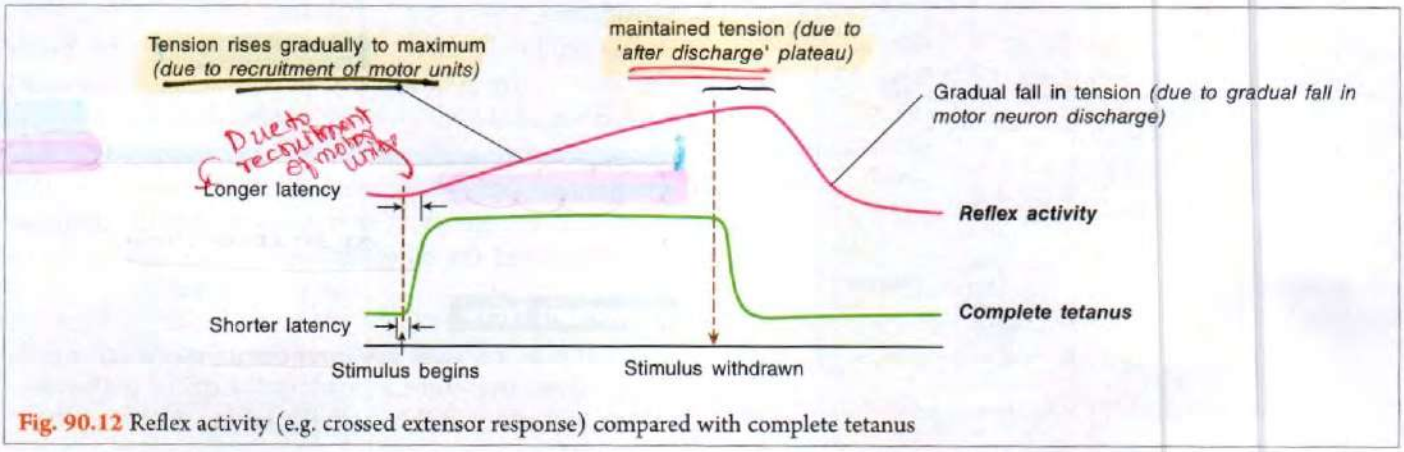


Fig. 90.12 Reflex activity (e.g. crossed extensor response) compared with complete tetanus

2. *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.
3. *Summation* (page 853), *occlusion* and *subliminal fringe* (page 859) are of great importance in reflex coordination. They enable one level in the nervous system to reinforce the action of another.

GENERAL PROPERTIES OF REFLEXES

1. **Adequate stimulus.** The reflex activity is stereotyped (fixed) and specific in terms of both the stimulus and the response. Therefore, a particular stimulus produces a particular response. As the receptors respond maximally only when an appropriate specific stimulus is applied (page 869), likewise, the stimulus that produces a reflex is very precise and is called the *adequate stimulus* for the particular reflex.
2. **Final common pathway.** The 'α-motor neurons' that supply the extrafusal muscle fibers in the skeletal muscles are the *final common pathway* over which the neural control system coordinates the activity of skeletal muscle fibers (Fig. 90.13). All neural influences (excitatory and inhibitory) affecting muscular contraction ultimately funnel through them to the muscles.
   If an α-motor neuron is stimulated, skeletal muscle fibers contract; if the α-motor neuron is not stimulated, the skeletal muscle fibers relax. Therefore, the α-motor neuron is the *final common pathway*, serving both as the *integrating center* and *efferent pathway*.
3. **Central excitatory and inhibitory states.** The spinal cord shows prolonged changes in excitability because

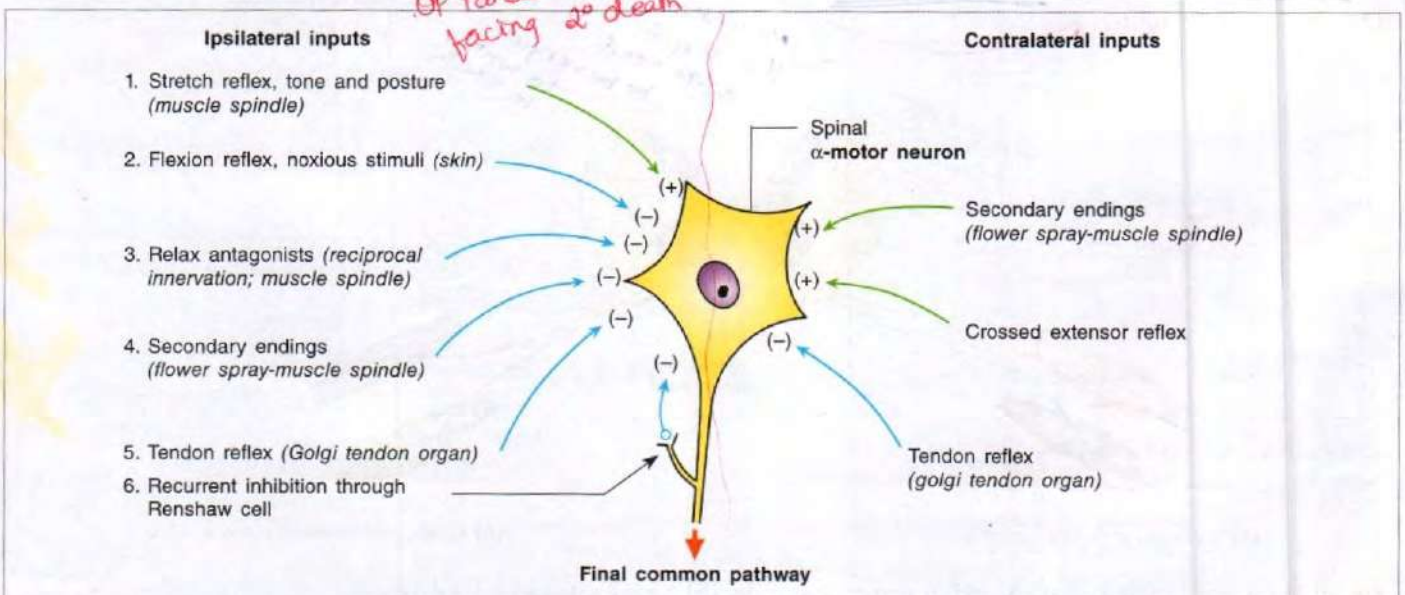


Fig. 90.13 ***Summary*** of the major inputs to the cell body of a single spinal α-motor neuron (the final common pathway)

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;* 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 limbs may cause withdrawal reflex and autonomic changes like urination, defecation, sweating and fluctuations in B.P. This is referred as *Mass Reflex.* It occurs when 'central excitatory state' is marked.

4. Habituation and Sensitization of reflex responses. Though the reflex responses are stereotyped, still they can be modified by experience. Therefore,

(i) If the stimulus is benign and repeated at frequent intervals, the response declines and disappears, a phenomenon called *'habituation'* (mechanism, page 858).

(ii) Opposite response *i.e.* prolonged facilitation of synaptic conduction in a reflex can be produced by noxious stimulus, this phenomenon is called *'sensitization'* which can last from hours to days (page 860).

SUMMARY

Table 90.1: Compare and contrast between monosynaptic and polysynaptic reflexes

	Monosynaptic reflexes	Polysynaptic reflexes
Differences		
1. Pathway	Monosynaptic *i.e.* only one synapse is present between afferent and efferent neurons.	Polysynaptic *i.e.* many synaptic connections are present between afferent and efferent neurons.
2. Examples	Stretch reflexes such as knee jerk, biceps or triceps jerk (*i.e.* deep tendon reflexes).	Withdrawal reflex; superficial reflexes (cremasteric and abdominal reflex)
3. Important feature	They do not show phenomenon of 'after discharge' (page 881) because of monosynaptic pathway.	They show 'after discharge' and irradiation of impulses.
4. Latency of response	Shorter because of rapidly conducting afferent fibers.	Longer due to slow conducting fibers in the polysynaptic pathway.
Similarities		
(1) both reflexes are basically 'protective reflexes';		
(2) both are characterized by reciprocal innervation;		
(3) both show 'integration' at the level of α-motor neurons which serve as the 'final common pathway' (page 882).		

Study Questions

1. **Define and give physiological significance of:**
   (i) Reaction time
   (ii) Recruitment of motor units and after discharge
   (iii) Local sign
   (iv) Final common pathway
   (v) Irradiation of stimulus and reverberating circuits
   (vi) Flexor response
   (vii) Prepotent withdrawal reflex (viii) α-γ coactivation and α-γ linkage
2. **Draw a diagram of reflex arc. How can an activity in it be modified?**
3. **Classify reflexes. Give two examples of each type.**
4. **What are antigravity muscles? Give examples.**
5. **Differentiate between:**
   (i) Intra and extra-fusal muscle fibers.
   (ii) Two types of sensory innervation to muscle spindles.
   (iii) α and γ-efferent fiber.
   (iv) Spasticity and rigidity.
   (v) Mono and polysynaptic reflexes.
   (vi) α-r coactivation and α-r linkage

6. Give the innervation and functions of muscle spindle.
7. What is stretch reflex. Give its characteristic features. Name the higher centres which control it.
8. How does Jendrassik's manoeuvre help to elicit deep tendon reflexes?
9. What do you understand by terms 'length servo' and 'follow-up servo' mechanisms?
10. Define muscle tone. Name the conditions in which it gets altered.
11. How is inhibition of stretch reflex brought about?
12. Define autogenic inhibition and give its physiological significance.
13. Give the physiological basis of clasp knife effect and clonus.
14. Give characteristic features of polysynaptic reflexes.
15. Draw diagrams depicting.
    (i) Pathway for stretch reflex and inverse stretch types
    (ii) Innervation of muscle spindles
    (iii) Operation of length-serve mechanism
    (iv) Pathway for flexor and cross extensor reflex
16. Describe briefly the general properties of reflexes.
17. Can flexor responses be produced by non-noxious stimulation of skin? What is mass reflex?
18. Write short notes on:
    (i) Bell Magendie law
    (ii) Characteristic feature of stretch reflexes
    (iii) Functions of muscle spindles
    (iv) Higher control of stretch reflex
    (v) Factors affecting muscle tone
    (vi) Lengthening reaction
    (vii) Clonus
    (viii) Withdrawal reflex
    (ix) Final common pathway

MCQs

1. Lowest level of integration of stretch reflex is:
   (a) Cerebrum
   (b) Cerebellum
   (c) Pons
   (d) Spinal cord
2. Muscle spindle is:
   (a) Receptor for a variety of multisynaptic reflex
   (b) Receptor for stretch reflex
   (c) Occurs only in antigravity muscles
   (d) Excited by both stretch and contraction of the muscles in which it is located
3. Which muscles have high density of muscle spindles:
   (a) Flexor muscles
   (b) Extensor muscles
   (c) Antigravity muscles
   (d) Agonist muscles
4. Main function of primary or annulospiral endings in muscle spindle is to:
   (a) Respond to static change in length and to rate of change of elongation of receptors
   (b) Transmit the sensation of pain in the muscle to CNS
   (c) Respond to total tension imposed on the muscle but not on the rate of change of length of receptors
   (d) Respond to marked muscular tension which then results in inhibition of contraction
5. Length servo mechanism:
   (a) A system of negative feedback device
   (b) It operates to maintain muscle tension
   (c) Acts to regulate posture at rest
   (d) Causes sustained contraction of the muscle
6. Increased gamma efferent discharge is seen in all *except*:
   (a) Jendrassik's manbuvre
   (b) Anxiety
   (c) Rapid shallow breathing
   (d) Stimulation of skin
7. *Not* a cause of hypotonia:
   (a) During sleep
   (b) Tranquilizers overdose
   (c) Anxiety
   (d) Tabes dorsalis
8. Lengthening reaction:
   (a) Muscle is contracted further as the tendon is elongated
   (b) Increased activity of golgi tendon organ stimulate internuncial cells in spinal cord and further stimulate α-motor neurons
   (c) Contracting muscle fibers are suddenly relaxed through inhibition of α-motor neurons
   (d) There is lengthening of muscle and tendon in response to a suprasegmental inhibition of γ-motor neurons

9. **Abrupt cessation of skeletal muscle contraction in normal weight lifting is caused by:**
   (a) Activation of stretch receptors in muscle spindle
   (b) Activation of golgi tendon organs
   (c) Loss of ATP
   (d) Ischemia

10. **Withdrawal reflex:**
   (a) Is more rapid than stretch reflex
   (b) Is antigravitational
   (c) Is polysynaptic
   (d) Does not appear if spinal cord is separated from suprasegmental level

11. **Which of the following is an autonomic reflex?**
   (a) Mass reflex
   (b) Withdrawal flexor reflex
   (c) Cross extensor reflex
   (d) Stretch reflex

12. **Polysynaptic reflexes differ from monosynaptic reflexes in that:**
   (a) Basically protective reflexes
   (b) Characterized by reciprocal innervation
   (c) Show integration at the level of α-motor neurons
   (d) Show after discharge and irradiation of impulses

13. **In monosynaptic reflexes, central delay is:**
   (a) 0.6-0.9 msec
   (b) 1.5-2.0 msec
   (c) 10-14 msec
   (d) 19-24 msec

14. **The rate of change of muscle spindle (dynamic response) is sensed by:**
   (a) Primary endings
   (b) Annulospiral endings
   (c) Group Ia fibers
   (d) All of the above

15. **Which of the following situations would cause stimulation of annulospiral endings contained within muscle spindles?**
   (a) Contraction of extrafusal fibers
   (b) Contraction of synergistic muscles
   (c) Contraction of intrafusal fibers
   (d) Contraction of antagonistic muscles

16. **The brain area that facilitates the stretch reflex:**
   (a) Motor cortex
   (b) Basal ganglia
   (c) Cerebellum
   (d) Vestibular nucleus

17. **Stretch reflex becomes hypoactive by all the following *except*:**
   (a) Deafferentation
   (b) Unexpected movements
   (c) Hypothyroidism
   (d) Hypoxia

18. ***Not true* about muscle tone:**
   (a) It is the tension present in the resting muscle
   (b) It is due to low frequency α-motor neuron discharge
   (c) It is a state of partial tetanus
   (d) It depends on the stretch reflex

19. **What ensures the movement of the agonist muscle is *not* obstructed by contraction of the antagonist muscle:**
   (a) Inverse stretch reflex
   (b) Reciprocal innervation
   (c) Autogenic inhibition
   (d) Clasp knife effect

20. **The average number of muscle fibers attached to one golgi tendon organ are:**
   (a) 1-3
   (b) 3-25
   (c) 25-50
   (d) 50-75

21. **The neuronal circuit with the greatest potential for producing a long-lasting output is the:**
   (a) Diverging circuit with multiple inputs
   (b) Converging circuit with multiple outputs
   (c) Reverberating circuit
   (d) Integrative circuit

22. **After discharge is of greatest extent in case of:**
   (a) Stretch reflex
   (b) Withdrawal flexor reflex
   (c) Crossed extensor reflex
   (d) Phillipson's reflex

Answers

1. (d)	2. (b)	3. (c)	4. (a)	5. (a)	6. (c)	7. (c)	8. (c)	9. (b)	10. (c)
11. (a)	12. (d)	13. (a)	14. (d)	15. (c)	16. (d)	17. (b)	18. (b)	19. (b)	20. (b)
21. (c)	22. (c)								

Chapter

91

The Sensory System

Specific ascending pathways: These are the ascending pathways carrying impulses from a particular type of stimulus on body, to Brain cortex

I. Introduction
II. Ascending (sensory) tracts in the spinal cord
III. Somatosensory cortex
IV. Somatic sensation
A. Touch-pressure B. Proprioception and kinesthesia
C. Temperature D. Pain
E. Others: Itch, vibratory sense, two-point discrimination and stereognosis

More receptive field ⇒ Less point discriminative sensitivity

INTRODUCTION

1. *Sensory system* is a part of nervous system that consists of:
   (i) *sensory receptors* that receive stimuli from the external or internal environment;
   (ii) the *neural pathways* that conduct information from the receptors to the brain (*i.e.* the ascending or sensory tracts in the spinal cord); and
   (iii) parts of the brain that deal primarily with processing the information (*i.e. somatosensory cortex*).
2. If the sensory information reaches consciousness, it is called a *sensation*. The understanding of the sensation's meaning is called *perception*. For example, pain is a sensation but its awareness is a perception.
3. A single afferent neuron with all its receptor endings makes up a *sensory unit*. In general, the peripheral end of an afferent neuron divides into many fine branches, each terminating at a *receptor*. The area of the skin or body surface that, when stimulated, leads to activity in the neuron is called the *receptive field* for that neuron **(Fig. 91.1)**. Generally, the areas supplied by one unit overlap and interdigitate with the areas supplied by others.

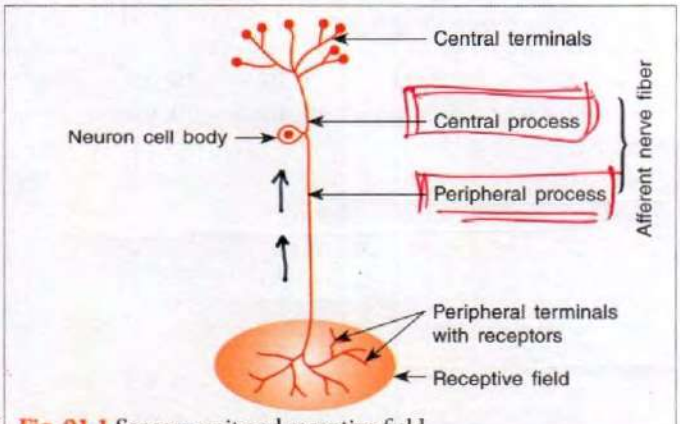


Fig. 91.1 Sensory unit and receptive field

Important Notes

(i) All the receptors of a sensory unit are sensitive to the same type of stimulus. For example, they are all sensitive to cold or all to pressure.
(ii) The ability to distinguish between two adjacent mechanical stimuli to the skin (*two-point discrimination*) is greater on the thumb, fingers and lips, where the sensory units are small and overlap considerably, than on the back, where the sensory units are large and widely spaced.
(iii) Locating sensation from the internal organs is less precise than from the skin because there are fewer afferent neurons in the internal organs and each has a larger receptive field.

Thus two point discrimination threshold is a measure of tactile acuity (Also see to page 901).

4. Afferent neurons are sometimes called *primary afferents* or *1st-order neurons* because they are the first cells entering the CNS in the synaptically linked chains of neurons that handle incoming information. The interneurons upon which the afferent neurons synapse are termed *2nd-order neurons* which synapse with *3rd-order neurons* and so on.

Important Note

The afferent terminals are influenced by presynaptic inhibition (page 857), whereas the 2nd order cells receive both pre and postsynaptic inputs.

5. The ascending pathways in the spinal cord and brain that carry information about single types of stimuli are known as the *specific ascending pathways* **(Fig. 91.2)**.

Greater the receptive field, ⇒ Fewer receptors ⇒ Lesser the sensitivity of Two-pt

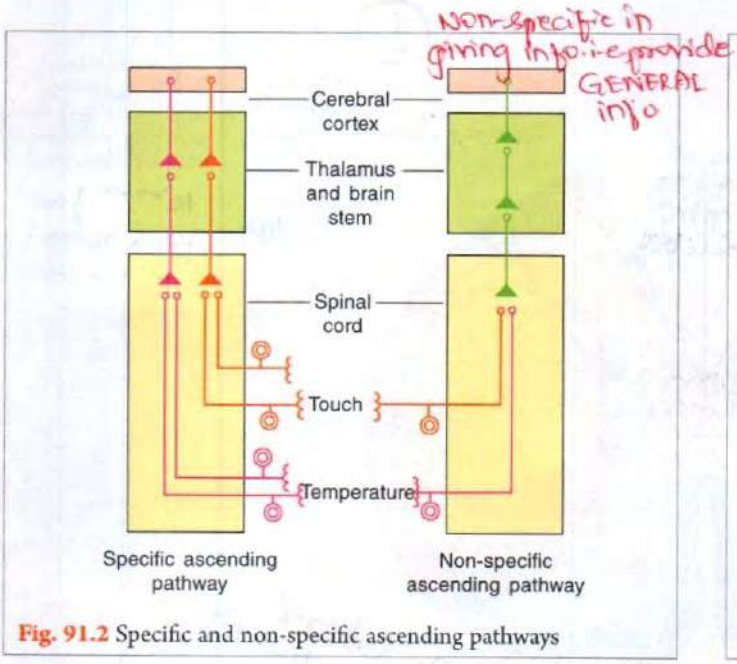


Fig. 91.2 Specific and non-specific ascending pathways

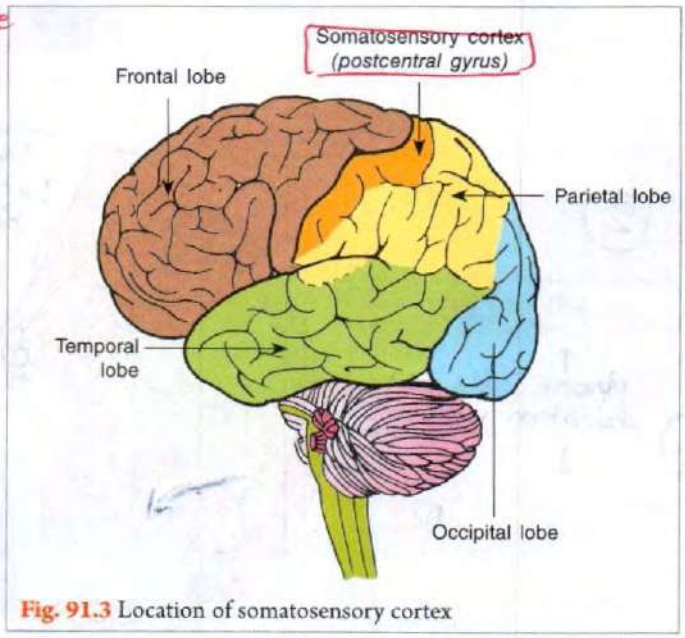


Fig. 91.3 Location of somatosensory cortex

They transmit information from *somatic receptors i.e.*, the receptors in the skeletal muscle, tendon and joints.

Important Note

The neurons in the *non-specific ascending pathways* are activated by sensory units of several different types and therefore signal only general information. For example, they indicate something is happening, usually without specifying just what or where. The non-specific pathways feed into the brain reticular formation and regions of the thalamus and cortex that are not highly discriminative.

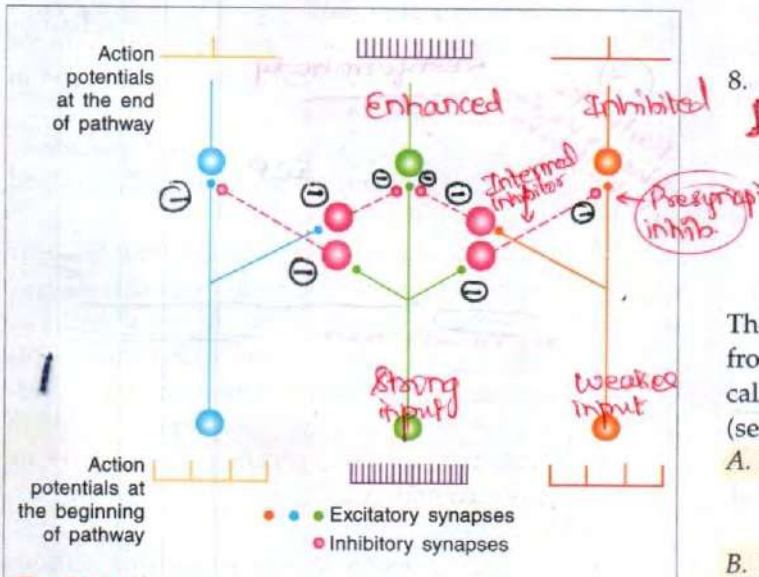


Fig. 91.4 Afferent pathways showing lateral inhibition.
Note: The central fiber (firing at highest frequency) inhibiting the lateral neurons more strongly via inhibitory interneurons.

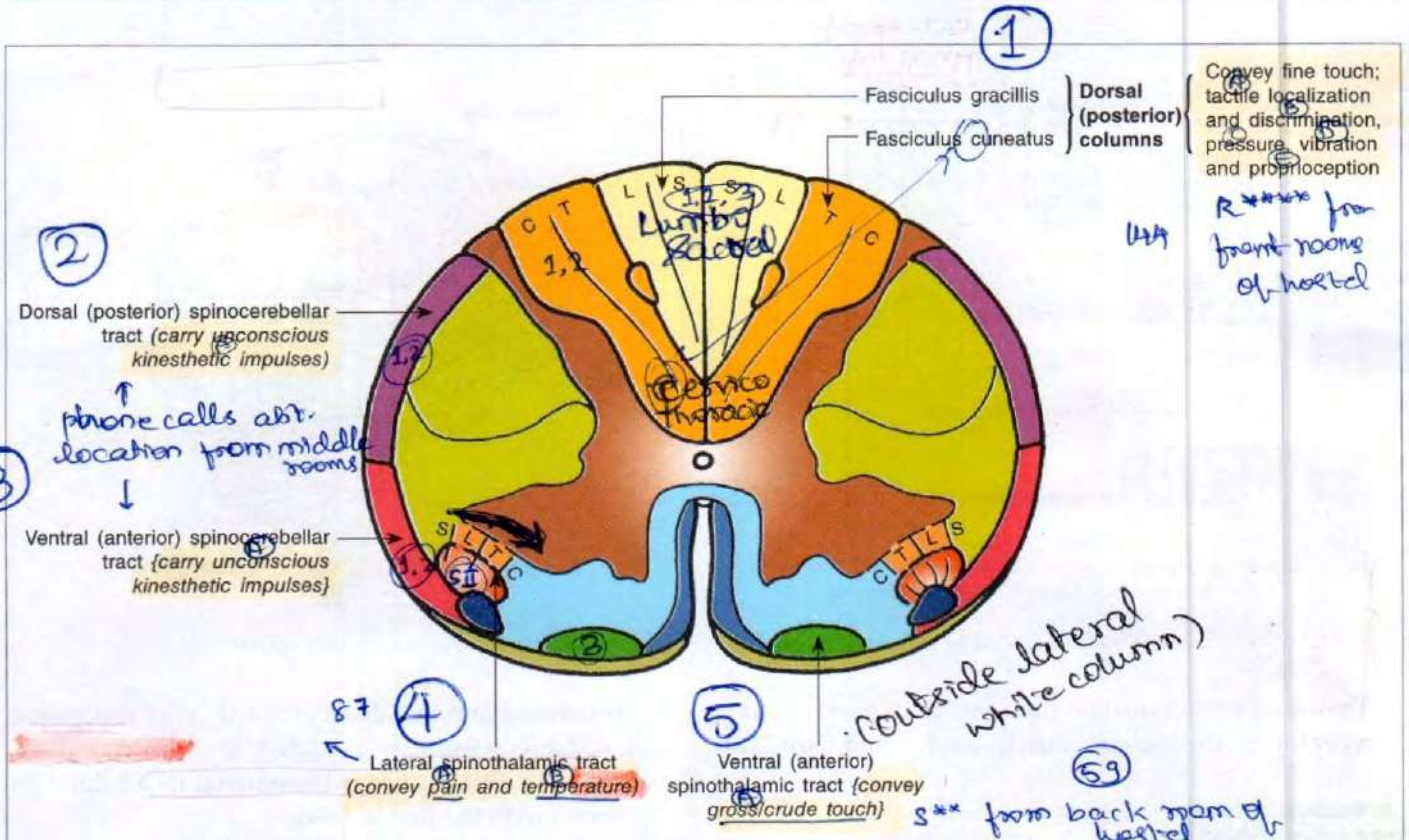
6. The part of brain that deals primarily with processing of somatic sensations is called the somatosensory cortex (Fig. 91.3). It lies in the parietal lobe behind its junction with the frontal lobe.
7. In most sensory systems, the control is organized in such a way that stronger inputs are enhanced and the weaker inputs of adjacent sensory units are simultaneously inhibited. This is called *lateral inhibition* and is utilized to the greatest degree in the pathways providing the most accurate localization (Fig. 91.4). For example, movements of skin hair can be located quite well which activates pathways that have significant lateral inhibition; compared to temperature which is located only poorly as it activates pathways that lack lateral inhibition.
8. A group of nerve fibers travelling in the CNS is called a ***tract*** or ***pathway***. Functionally these tracts are grouped in each column into ascending and descending tracts.

ASCENDING (SENSORY) TRACTS IN THE SPINAL CORD

The ascending tracts carry a group of sensory fibers from the receptor to the CNS; therefore they are also called ***sensory*** or ***afferent tracts***. The important ascending (sensory) tracts in the spinal cord are: (Fig. 91.5)

A. Tracts in dorsal (posterior) white column
1. Fasciculus Gracilis (Goll)
2. Fasciculus Cuneatus (Burdach)

B. Tracts in lateral white column
1. Lateral spinothalamic tract
2. Dorsal (posterior) spinocerebellar tract
3. Ventral (anterior) spinocerebellar tract



{Lamination of tracts: S – sacral; L – lumbar; T – thoracic and C – cervical. Because of this lamination, tumors arising outside the spinal cord first compress the spinothalamic fibers from sacral and lumbar areas, causing early symptoms of loss of pain and temperature sensation in the sacral region. Intraspinal tumors cause anaesthesia first in the higher segments.}

Fig. 91.5 A cross-section of the spinal cord showing location of major ascending tracts and sensations they convey.

C. Tract in ventral (anterior) white column

Ventral (anterior) spinothalamic tract

1. Fasciculus gracilis and fasciculus cuneatus

Origin: from the axons of 1st-order neuron in posterior root ganglia. Fasciculus gracilis receives afferents from lower half (lumbar and sacral segments) of the body while fasciculus cuneatus receives afferents from upper half (cervical and thoracic segments).

Situation, extent and termination (**Figs. 91.7** and **91.10**).

(i) After entering the spinal cord, fasciculus gracilis fibers run in ***Dorsal (posterior) column*** of same segment occupying the whole of its width upto mid thoracic region; above this level, its fibers are pushed medially by fasciculus cuneatus. Therefore, in this ascending system the fibers are represented as sacral to cervical segments from medial to lateral in the spinal cord **(Fig. 91.5)**.

(ii) Majority of fibers end in medulla in *nucleus gracilis* and *nucleus cuneatus* respectively (***1st relay station***); second-order neuron arises from here whose axons are divided into 2 groups **(Fig. 91.10)**:

(a) *External arcuate fibers*, subdivide into dorsal and ventral group;
- *dorsal group* of fibers pass via inferior cerebellar peduncle of same side to end in the cerebellum
- *ventral group* of fibers cross to the opposite side via inferior cerebellar peduncle and end in the cerebellum.

(b) *Internal arcuate fibers*, cross to the opposite side and pass through mid brain in the *medial lemniscus* to end in specific relay nuclei of thalamus (ventroposterior nucleus). This forms the ***2nd relay station***. Axons of 3rd-order neurons pass via posterior limb of internal capsule to end in the sensory cortex (postcentral gyrus).

Functions

It conveys the following informations from various parts of the body to the higher centre:

(i) fine touch (touch with low threshold);

(ii) tactile localization and discrimination;
(iii) proprioceptive and kinesthetic sensation *i.e.* sensation of body position in space and joint movements;
(iv) vibration sense;
(v) sense of deep pressure;
(vi) some unconscious kinesthetic impulses to the cerebellum via external arcuate fibers which are essential for control of body posture;
(vii) constitutes sensory pathway for some superficial reflexes.

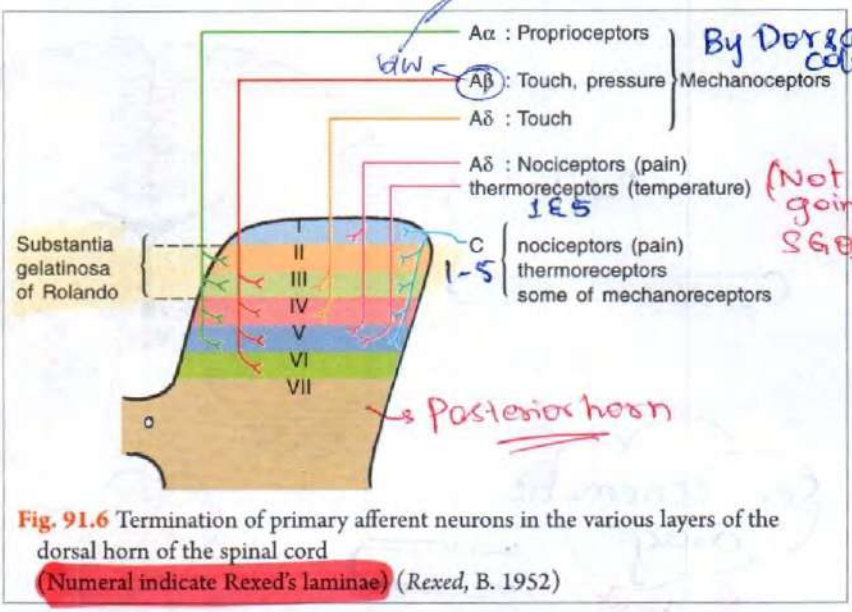


Fig. 91.6 Termination of primary afferent neurons in the various layers of the dorsal horn of the spinal cord
(Numeral indicate Rexed's laminae) (*Rexed*, B. 1952)

Note
Lamina VII receive input from both sides of the body, whereas other laminas receive only unilateral input.

2. **Lateral spinothalamic tract**
Origin: from the axons of 1st-order neurons in posterior root ganglia.
Situation, extent and termination
(i) After entering the spinal cord, fibers of all segments end around nociceptive neurons *i.e.* cells in dorsal horn cells of grey matter of spinal cord. *Histologically* dorsal horn is divided into laminas I-VII with I being the most superficial and VII the deepest (details **Fig. 91.6**).
(a) Aδ terminating in neurons in Laminas I and V. (**Fig. 91.6** and **91.10**)
(b) 'C'-group of fibers terminating in neurons in substantia gelatinosa and laminas IV and V.
(ii) Most of the axons of 2nd-order neurons *'cross'* in anterior white commissure obliquely to opposite side of the same segment, and ascend in the lateral spinothalamic tract to end in the thalamus (ventroposterior nucleus) **(Fig. 91.8)**.
(iii) Some axons of the 2nd-order neurons, before crossing, run up and down for few segments and then cross in anterior white commissure to reach the lateral column of opposite side of the spinal cord.
(iv) Axons from the sacral and lumbar segments of the body are pushed laterally by axons crossing the midline at successive higher levels. Therefore, the fibers are represented as cervical to sacral segments from medial to lateral in the spinal cord.
(v) At higher brain stem level, this tract sends several collaterals into the reticular formation and tegmentum before ending in the thalamus.
(vi) In thalamus, 3rd-order neuron starts and axons of this neuron via *posterior limb of internal capsule* end in sensory cortex (postcentral gyrus).

Functions
It carries fibers of all types of 'pain' and 'temperature' impulses (both hot and cold).

Important Notes
1. Unilateral section of this tract produces complete loss of pain and temperature on the opposite side of the body. The contralateral sensory loss extends to a level one segment below that of the lesion.
2. Patients suffering from severe intractable pain (*e.g.* from carcinomatous metastasis) can be treated by *anterolateral cordotomy* – an operation in which the lateral spinothalamic tract in anterior white commissure is cut using a special knife.

3. **Dorsal (posterior) spinocerebellar tract**
Origin from the axons of 1st-order neurons in the posterior root ganglia.
Situation, extent and termination **(Fig. 91.10)**
(i) In the spinal cord the fiber ends round the *Clarke's column of cells* on the same side (1st-relay station).
(ii) 2nd-order neuron fibers bend laterally, enter the lateral white column, occupy the most peripheral part lateral to spinothalamic tract. *The tract makes its appearance in segment C_7 to T_1.*
(iii) In medulla, fibers enter the inferior cerebellar peduncle of the same side and end in 'vermis of the cerebellum', from where 3rd-order neurons arise.

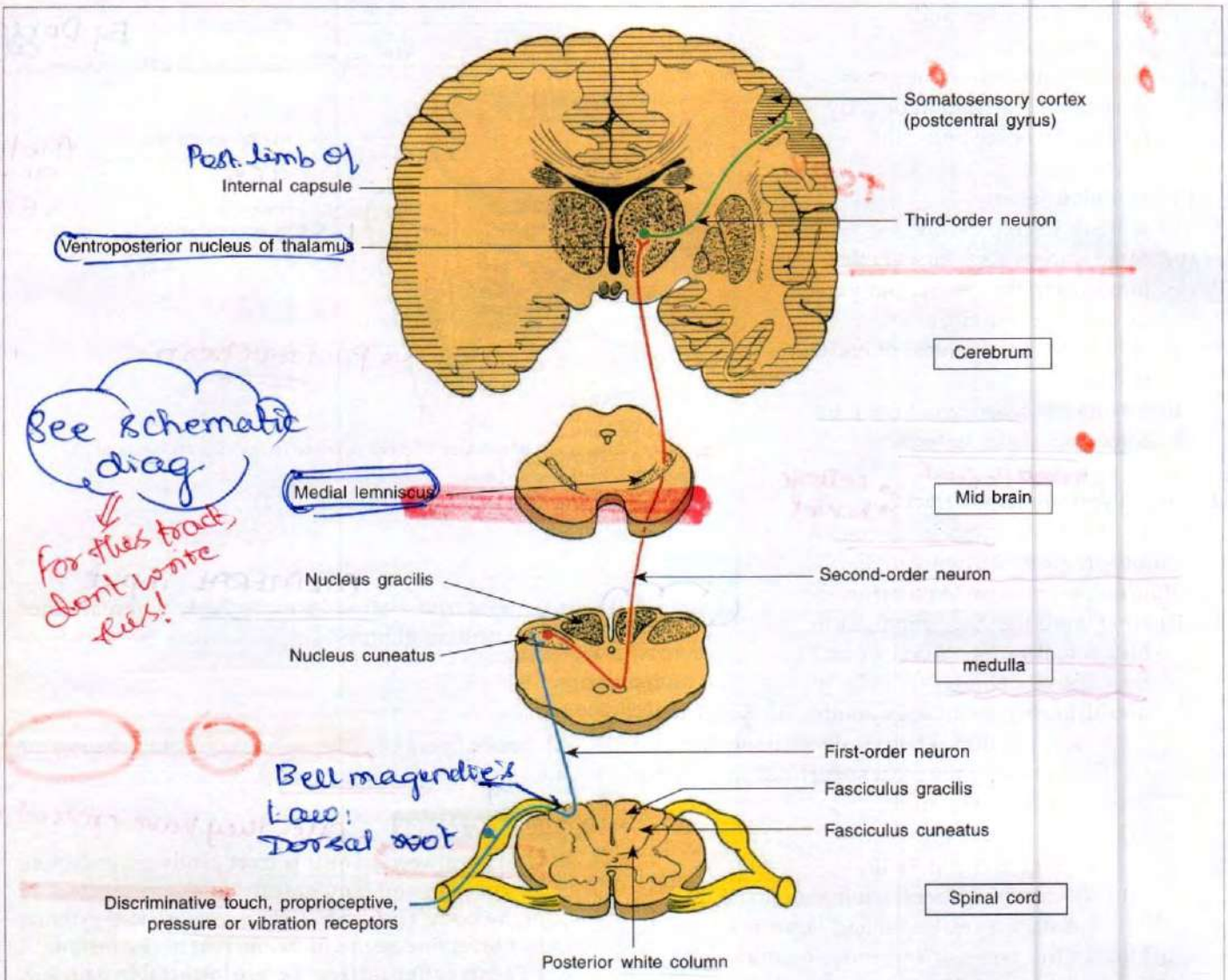


Fig. 91.7 Sensory pathway for fine touch, tactile localization and discrimination, pressure, proprioception and vibration – the dorsal (posterior) column pathway

Its axons passes to the anterior and posterior lobes of the cerebellar cortex.

Function – It carries 'unconscious' kinesthetic impulses to the cerebellum which are essential for the regulation of body posture.

4. **Ventral (anterior) spinocerebellar tract**

Origin: from the axons of 1st-order neurons in the posterior root ganglia.

Situation, extent and termination (Fig. 91.10)

(i) In the spinal cord the fiber ends round the *Clarke's column of cells* on the same side (1st-relay station).

(ii) Axons of the 2nd-order neurons are made up of fibers arising from the Clarke's column of both sides (mostly crossed and partly uncrossed fibers). The presence of crossed fibers is an apparent violation of ipsilateral cerebellar control.

(iii) The tract make its appearance in the lumbosacral region (mainly L_3 to L_5) of spinal cord and fibers remain in lateral white column, just ventral to dorsal spinocerebellar tract.

(iv) It extends upto the level of red nucleus without termination. At red nucleus, fibers turn sharply backwards and downwards and then enter the superior cerebellar peduncle of same side to end in the 'vermis of cerebellum'. From here 3rd-order neuron arises and goes to the anterior lobe of the cerebellar cortex.

Function – Same as that of dorsal (posterior) spinocerebellar tract.

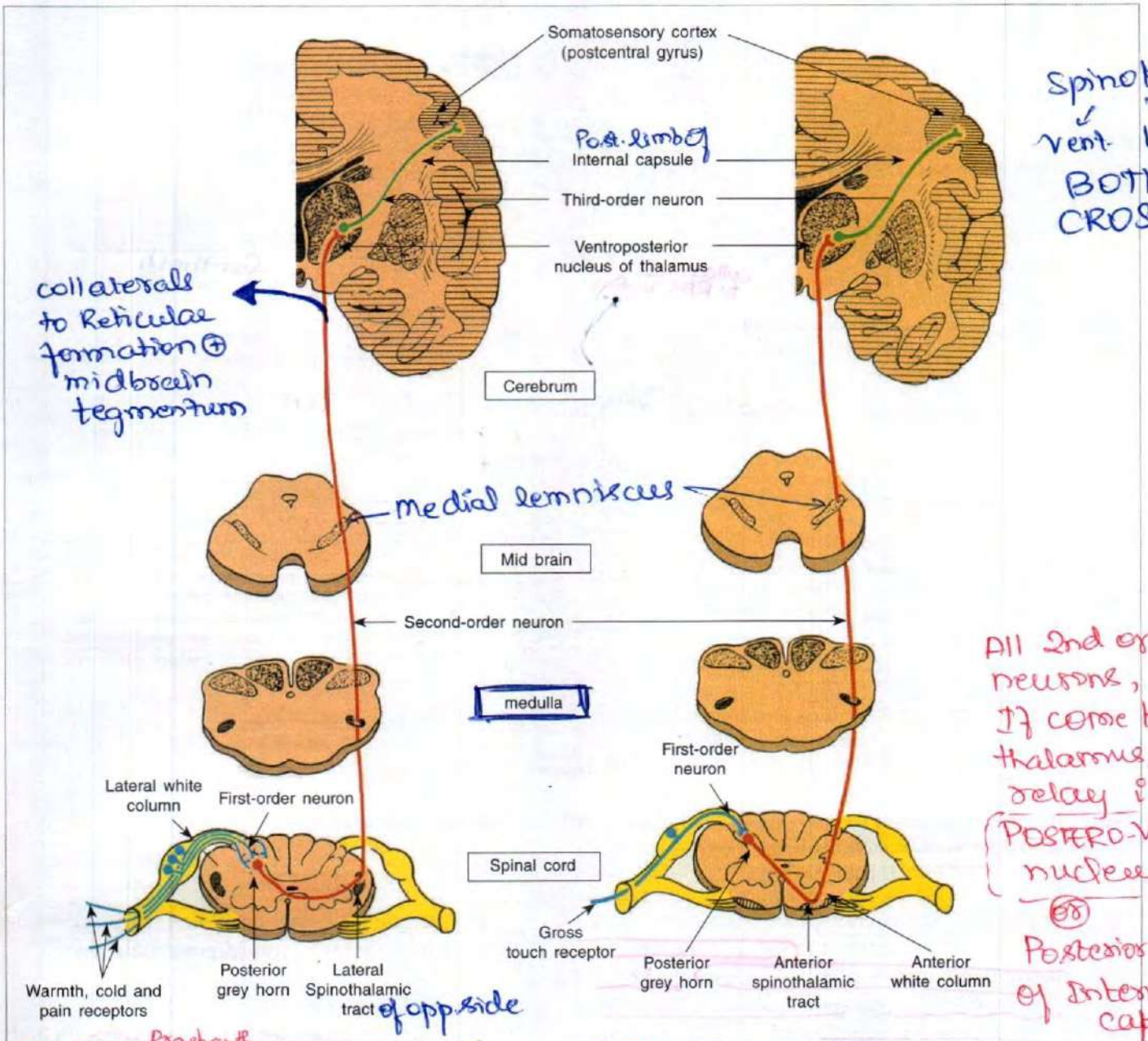


Fig. 91.8 Sensory pathway for pain and temperature - the lateral spinothalamic pathway

Fig. 91.9 Sensory pathway for gross (crude) touch - the ventral (anterior) spinothalamic pathway

5. **Ventral (anterior) spinothalamic tract**

Origin: from the axons of 1st-order neurons in the posterior root ganglia.

Situation, extent and termination (Figs. 91.9 and 91.10)

(i) 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.

(ii) Most of the axons of 2nd-order neurons cross in anterior white commissure obliquely to opposite side of the same segment, and ascend in anterior column of spinal cord to end in the thalamus (ventroposterior nucleus).

Important Note

Thalamus is known as 'subcortical centre' for the spinothalamic tract. It also forms the 'subcortical sensory relay station'.

(iii) Small number axons of 2nd-order neurons are *uncrossed* and may ascend homolaterally as anterior spinothalamic tract; while ascending upwards ventral (anterior) spinothalamic tract runs in

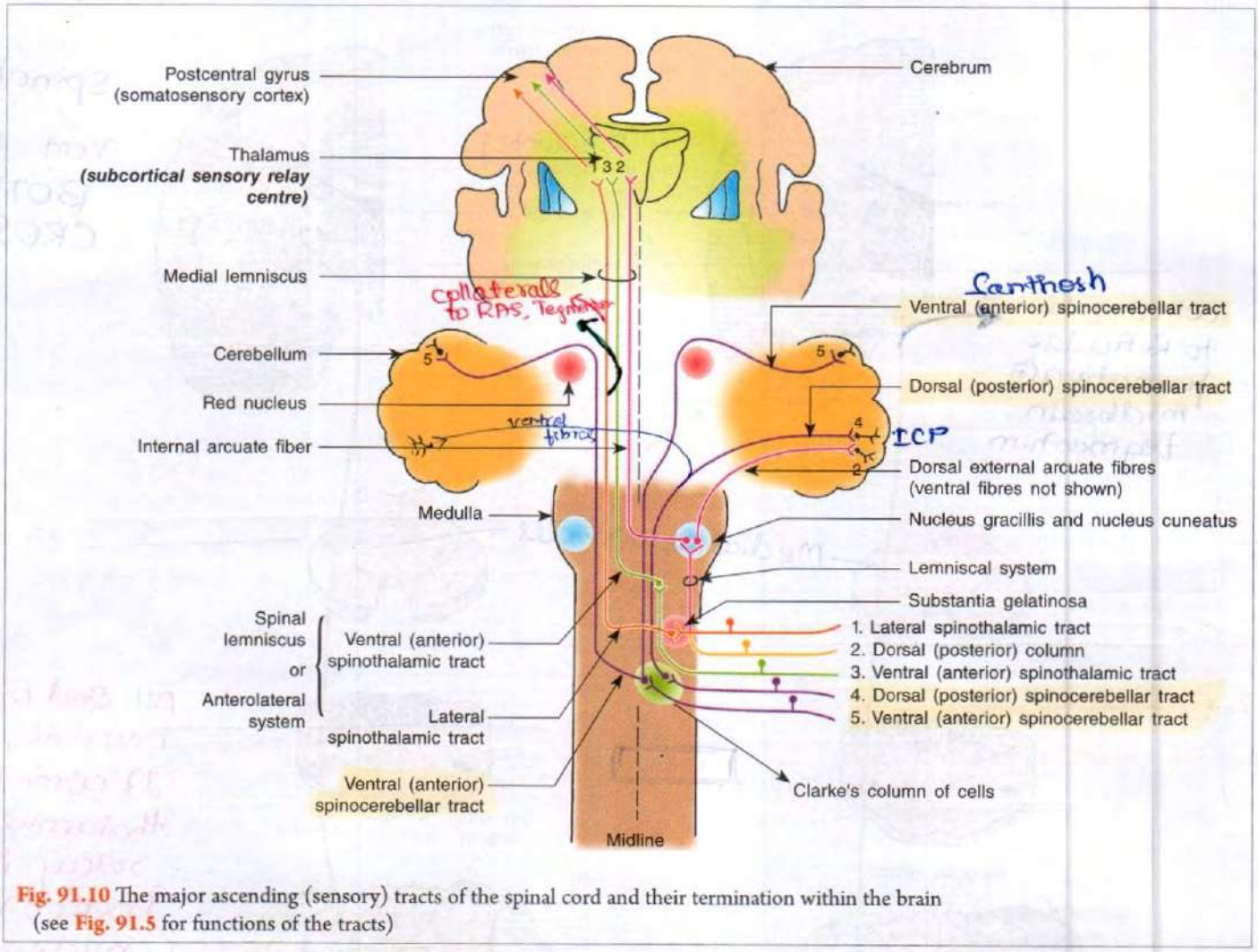


Fig. 91.10 The major ascending (sensory) tracts of the spinal cord and their termination within the brain (see **Fig. 91.5** for functions of the tracts)

parallel with the lateral spinothalamic tract and together they constitute the *spinal lemniscus* or *anterolateral system of ascending fibers*. In upper medulla or lower pons, spinal lemniscus joins with the fibers from the gracilis and cuneatus nucleus to form *medial lemniscus*.

Important Note

Some of the fibers of the anterolateral system also project to the midline and intralaminar *non-specific thalamic nuclei* and to the mesencephalic reticular formation where they play an important role for maintaining the cortex in the alert state. This makes perception possible (page 958).

(iv) At higher brain stem level, this tract sends several collaterals into the reticular formation and tegmentum before ending in the thalamus.

(v) In thalamus, 3rd-order neuron starts and axons of this neuron via posterior limb of internal capsule ends in the sensory cortex (postcentral gyrus).

Functions – It conveys:

(i) Gross (crude) touch sensation *i.e.* touch with high threshold.

(ii) Tactile localization.

Important Note

The sensory pathways from somatic receptors on the left side of the body go to the somatosensory cortex on the right cerebral hemisphere, and vice versa.

SOMATOSENSORY CORTEX

From the specific sensory nuclei of the thalamus, neurons project in a highly specific way to the 'two' somatic sensory areas of the cortex: *primary and secondary sensory areas.*

A. PRIMARY SENSORY AREA: FIRST SOMATIC SENSORY AREA (S I)

Characteristic features

1. It is located in the *postcentral gyrus* containing the Brodmann's area 3, 1, 2 **(Fig. 91.11)** (*Brodmann, K.* a histologist - 1914 divided the cerebral cortex into numbered areas based on their histological characteristics) (page 1013).
2. *Area 3* neurons respond to 'light touch' and receive a dense input from the thalamus; while *areas 1 and 2* neurons respond to deep stimuli such as 'pressure and joint' movements and receive few thalamic fibers.

Important Note

None of the S I neurons are influenced by nociceptive (painful) stimuli.

3. It is supplied by afferents from the opposite side of the body but from both sides of the face.
4. There is a detailed (somatotropic) localization of fibers from the various parts of the body in the postcentral gyrus.
5. The arrangement of thalamic projection is such that the body is represented upside down (*i.e. inverted representation* of the body parts) with the legs on the top and head at the foot of the gyrus. The extent of its representation depends on the parts of the body that are most densely innervated (*i.e.* the number of specialized sensory receptors); therefore, fingers, thumb and lips are represented by the largest areas of the somatosensory cortex **(Fig 91.12)**.
6. **Removal of S I produces:**
   (i) deficits in fine touch, position sense (proprioception) and discrimination power;
   (ii) deficits in sensory processing in S II.

B. SECONDARY SENSORY AREA: SECOND SOMATIC SENSORY AREA (S II)

Characteristic features

1. It is located in the parietal cortex and is mostly buried in the superior wall of the sylvian fissure (lateral cerebral sulcus).
2. Unlike S I, it is supplied by afferents from both sides of the body.
3. Like S I, it manifests a dermatomal (point-to-point) sequence of representation (although there is more overlap). The posterior region receives afferents from the legs whereas the anterior parts receive afferents from the face; the face area of S II is immediately adjacent to that of S I. Thus the body is represented 'twice' in the somatic sensory cortex, in areas S I and S II.
4. Neurons in the anterior part respond to touch whereas neurons in the posterior part can be excited by touch, auditory, visual and nociceptive stimuli.

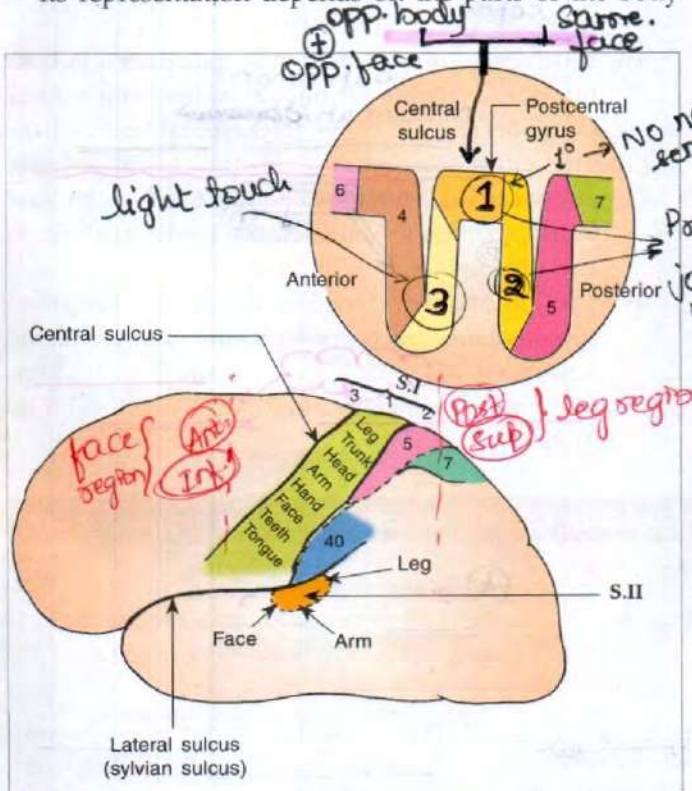


Fig. 91.11 Brain areas concerned with somatic sensation [**Inset**: Sagittal section (i.e. in anteroposterior direction) of fronto-occipital region]

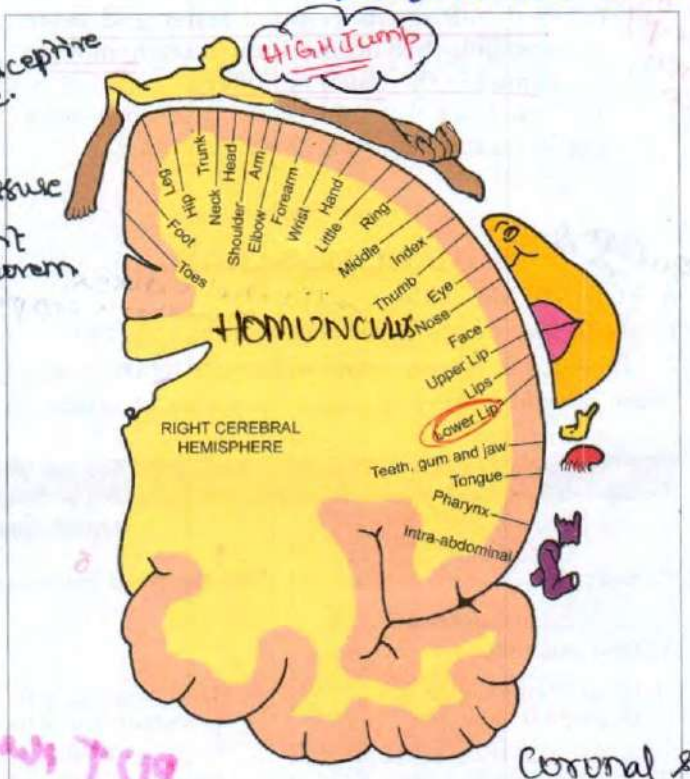


Fig. 91.12 Location of pathway termination of different parts of the body in the somatosensory cortex

5. **Removal of S II produces** deficits in learning based on tactile discrimination power whereas sensory processing in S I is not affected.

Important Notes

(i) S I and S II process sensory information in series.

(ii) Cortical lesions do not abolish somatic sensation. However, proprioception and fine touch are most affected; temperature sensibility is less affected; and pain sensibility is only slightly affected. Thus perception is possible in the absence of the cortex.

(iii) The highly specific neuronal connections to two somatosensory areas (S I and S II) are not present at birth and have extensive convergence and divergence (page 858). These can be changed over time by experience, a phenomenon called *cortical plasticity* (also see to pages 859 and 1073). Plasticity of this type become weak with disuse and strong with use. It occur with inputs from cutaneous receptors and also with input in other sensory systems. Therefore, if a part of the body is removed, the cortical representation of the neighbouring parts spread into the cortical areas that was formerly occupied by the representation of the removed body part. Plastic changes also occur from one sensory modality to another. For example:

(a) tactile and auditory stimuli increase metabolic activity in the visual cortex in blind individuals;

(b) deaf individuals respond faster and more acurately then normal individuals to moving stimuli in the visual periphery.

Thus the brain shows the capability of being easily moulded (i.e. changed) and its ability to adapt.

SOMATIC SENSATION

A. TOUCH-PRESSURE

1. *Tactile receptors* – Types and location, page 864.
2. The skin mechanoreceptors sensitive to touch-pressure are classified into two major categories according to their response to sustained pressure: *rapidly adapting and slow adapting* (**Table 91.1** and **Fig. 91.13**).

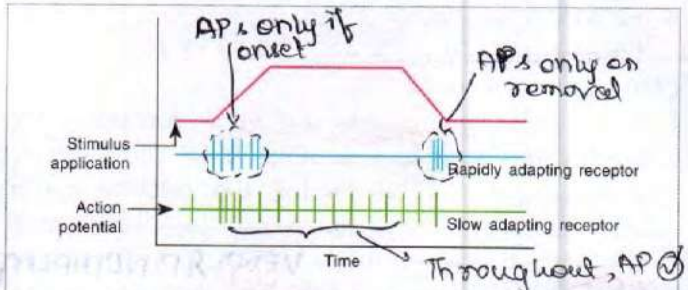


Fig. 91.13 Rapidly and slowly adapting touch-pressure receptors

3. In both categories, some receptors have small, well defined receptive fields and are able to provide precise information about the contours of objects intending the skin. These receptors are concentrated at the fingertips. Conversely, other receptors have large receptive fields, with ill defined boundaries sometimes covering a whole finger or a larger part of the palm. These receptors are not involved in detailed spatial discrimination but signal information about vibration, skin stretch and joint movement.
4. *Neural pathways*
   (i) The touch-pressure sensations are conveyed to the CNS by A (β and δ group) sensory fibers; some touch impulses are also conducted via unmyelinated 'C' fibers (page 147).
   (ii) Touch-pressure information is transmitted in both the 'dorsal column' (lemniscal system) and ventral (anterior) spinothalamic tract (spinal lemniscus).
   (iii) The information carried in the dorsal column is concerned with *fine touch* (touch with low threshold of excitation), detailed tactile localization and discrimination (**Fig. 91.7**).
   (iv) The information carried in the ventral (anterior) spinothalamic tract is concerned with gross tactile sensations of *crude touch i.e.* touch with high threshold of excitation and is poorly localized (**Fig. 91.9**).

Table 90.1: Differences between rapidly adapting and slow adapting touch-pressure receptors

	Rapidly adapting	Slow adapting
1. Examples	Meissner's and pacinian corpuscles	Merkel's discs and Ruffini's end organ
2. Percentage of distribution of total touch-pressure receptors.	50%	50%
3. Effect of stimulation (**Fig. 91.13**)	(i) They respond with a burst of action potentials only at the onset and removal of the stimulus *i.e.* with change in strength of stimulus. (ii) They give rise to the sensations of touch-pressure, movement, vibration and tickle.	(i) They respond with a sustained discharge throughout the duration of the stimulus. (ii) They give rise to the sensation of pressure mainly.

Important Notes

1. When the *dorsal columns are destroyed*, vibratory sensation and proprioception are lost, the touch threshold is elevated, and the number of touch-sensitive areas in the skin are decreased. Therefore, localization of touch sensation is impaired.
2. When the *ventral (anterior) spinothalamic tracts are destroyed*, touch deficit is slight and touch localization remains normal.

B. PROPRIOCEPTION AND KINESTHESIA

Proprioception means the sense of the body's position in space and ***kinesthesia*** refers to the sensation associated with joint movement.

Note

Knowledge of position, depends on knowing the degree of angulation of all joints in all planes and their rates of change.

1. *Receptors* – The major receptors responsible for these senses are *proprioceptors*, which include:
   (i) The muscle spindle (page 874),
   (ii) Joint receptors (page 865),
   (iii) Golgi tendon organs (page 879),
   (iv) Vestibular receptors (page 939),
2. *Neural pathways* –
   (i) 'Conscious' sense of position, vibration and deep pressure is carried by axons from joint receptors and pacinian corpuscles. These, entering via the posterior root, branch and enter the *dorsal column* of the same side (page 888).
   (ii) 'Unconscious proprioception' is carried by the dorsal (posterior) and ventral (anterior) spinocerebellar tracts (page 889).

Important Notes

1. Inability to identify the location or position of an extremity is called *position agnosia*.
2. Loss of control over the voluntary movements (muscular incoordination) is called ATAXIA. A disturbance of muscular coordination from defective sensory information (usually found in injury or diseases of the dorsal column) is called *sensory ataxia*; while muscular incoordination due to lesions of the cerebellum is called *cerebellar ataxia*.

C. TEMPERATURE

1. *Temperature receptors.* The thermoreceptors in the skin are classified according to their responses to cold and heat, called 'cold' and 'warm' receptors respectively (details on page 865).
2. *Neural pathways.* The temperature sensations are carried to the CNS by Aδ and 'C' group of sensory fibers (page 147) in lateral spinothalamic tract **(Fig. 91.8)** to the somatosensory areas (page 892).

D. PAIN

Definition

Sherrington defined pain as "the *psychical* (= pertaining to mind) *adjunct* (joined to) *of an imperative* (urgent) *protective reflex*", *i.e.* pain is a sensation which draws attention of the individual as a whole.

A stimulus that causes (or is on the verge of causing) tissue damage usually produces a sensation of pain. *Pain differs from other sensations* in that it is associated with:

(i) emotions such as fear and anxiety and feeling of unpleasantness;
(ii) it also produces a reflex *withdrawal response* (page 880); and
(iii) autonomic changes mediated by the sympathetic nervous system such as increase in heart rate, blood pressure and respiration, and sweating.

Types of pain

Pain varies greatly in type (quality or nature) according to the nature of stimulus and the site of the stimulation; accordingly different terms such as pricking, burning, tearing, cutting, stabbing, crushing and aching are commonly used. The main difference between *superficial and deep pain* is the different quality (nature) of pain produced by noxious stimuli **(Table 91.2)**.

Table 91.2: Main differences between superficial and deep pain

Superficial (cutaneous) pain	Deep pain
1. It involves the skin and subcutaneous tissue.	1. It involves muscles and hollow viscera.
2. It is sharp in character and well localized; localization is based on the richness of skin innervation with receptors.	2. It is dull and poorly localized because receptors are relatively few and due to relative deficiency of Aδ nerve fibres.
3. It leads to reflex withdrawal movements, increase in heart rate, BP and respiration.	3. It produces faintness, nausea, vomiting, sweating, bradycardia and fall in BP.
4. It usually does not radiate.	4. It is both local and radiates to the distant site.

Pain Receptors

1. The receptors which mediate pain are called *Nociceptors*. They are located at the ends of small unmyelinated 'C' fibers or myelinated Aδ afferent

neurons. The difference between two types of nociceptors is given in Table 91.3.

Table 91.3: Two types of nociceptors compared

Aδ fiber nociceptors	C-fiber nociceptors
1. These are small myelinated fibers, 2-5 um diameter with conduction velocity 12–30 mts per sec. They subserve *fast pain.*	1. These are non-myelinated fibers, 0.4–1.2 µm diameter with conduction velocity 0.5–2 mts per sec. They subserve *slow pain.*
2. Synaptic neurotransmitter released at primary afferent endings is glutamic acid.	2. Substance P is the neurotransmitter.
3. They are less in number as compared to 'C' group of fibers.	3. They are relatively more in number than Aδ group of fibers.
4. They conduct impulses only in response to a noxious stimulus.	4. They conduct impulses also in response to thermal and mechanical stimulation (thus more important in producing pathological pain).
5. These fibers are most sensitive to pressure, therefore called mechanosensitive (page 147).	5. These fibers are most sensitive to local anaesthetics and chemical agents like histamine, kinins and prostaglandins.
6. Sensitivity to electrical stimulation: More.	6. Sensitivity to electrical stimulation: Less.

2. These receptors get *stimulated by:*
   (i) Thermal stimulation. Raising skin temperature above 45°C or exposure to cold (0°C) is painful.
   (ii) Mechanical stimulation due to:
      (a) excessive pressure or tension on nerves. *Examples:* a blow on the head, pulling of hair, pain of child birth, stiff neck, etc.;
      (b) compression of nerves by tumour, a prolapsed intervertebral disc.
   (iii) Chemical stimulation by irritant chemicals such as histamine, kinins (page 323) and prostaglandins released from damaged tissue.

Neural pathways for pain

1. The primary afferents Aδ and 'C' group of fibers coming from nociceptors synapse on interneurons after entering the spinal cord (Fig. 91.8). *Glutamic acid* and *Substance P* are the transmitter released at these synapses.
2. Information about pain is then transmitted to higher centres via both *specific* (lateral spinothalamic tract) and *non-specific* ascending pathways:
   (i) the *specific pathways* convey information about where, when and how strong the stimulus was applied and about the sharp, localized aspect of pain;
   (ii) the *non-specific pathways* convey information about the aspect of pain that is dull, longer lasting and less well localized.
3. Neurons in the reticular formation and thalamus are activated by the pain pathways and connected with the hypothalamus and other brain areas, such as limbic system that integrate autonomic and endocrine stress responses. It also generates the behavioural patterns of aggression and defense.

Important Note

The somatosensory areas (page 892) are primarily concerned with discrimination, exact and meaningful interpretation of pain but perception of pain alone does not require the cerebral cortex and it can occur at subcortical level (page 893). Damage to the thalamus experimentally or following vascular blockage may be associated with a peculiar overreaction to painful stimuli, known as *Thalamic Syndrome.* In this condition, even the minor stimulus leads to prolonged, severe and very unpleasant pain. Such sudden attacks of pain may occur spontaneously.

Fast and Slow Pain

A brief noxious stimulation of skin such as by pinprick or sudden exposure to temperature above 55°C produces a ***Double Pain*** sensation.

1. The first *Fast component* (fast pain) is due to activation of Aδ nerve fibers. This causes a bright, sharp, localized sensation of pain.
2. The second *Slow component* (slow pain) is due to activation of 'C' group of nerve fibers. This causes a dull, intense, diffuse and unpleasant feeling of pain.

The two components may be separated by 1.0-1.5 sec. according to the site of stimulation.

Ischaemic Muscular Pain

Muscular activity releases a pain producing chemical factor, called *Lewis P-factor,* which passes out into the tissue spaces and is normally removed by the blood stream. During exercise, this substance accumulates and when it reaches a certain concentration, pain develops. However, recovery occurs within few seconds after restoration of circulation and pain disappears. *Lewis P-factor* may consist of more than one substance, for example: K^+, *adenine nucleotides and lactic acid.*

Clinical examples

1. *Intermittent claudication.* The recurrent pain produced in legs during exertion in patients with atherosclerosed

limb blood vessels. In this disease, the blood supply to the muscle is adequate for their needs during periods of rest, but during activity there is a relative ischaemia. The P-factor accumulates giving rise to pain which increases in intensity until the patient is compelled to stop. During the period of rest the P-factor is washed away and the pain disappears.

2. *Pain of Angina pectoris* (also see page 304). Here pain is produced by ischaemia of the affected area of heart muscle. In addition there is also release of 5-HT and prostaglandins from platelets and of K^+, kinins and adenine nucleotides from muscle. The pain persists as long as the sensory nerve endings in the ischaemic patch of the heart remain alive.

Visceral Pain

1. Pain from visceral structures is poorly localized (because pain receptors are relatively few), unpleasant and associated with nausea and autonomic changes. It is particularly unpleasant because of the emotional effects and activation of many visceral afferents activated that initiate nausea, vomiting and other autonomic effects.
2. It often radiates or is referred to other sites. *Mechanism:* (see below).
3. Some **common causes** of visceral pain are:
   (i) Excessive distension of hollow viscera, such as the intestine or urinary bladder,
   (ii) Intestinal obstruction, by the contractions of the distended intestine above the obstruction,
   (iii) Inflamed viscous, here a relatively minor stimulus causes severe pain (a form of primary hyperalgesia, page 901),
   (iv) Traction on the mesentry.
   (v) Spasm of a portion of a gut or any hollow viscus such as gall bladder, urinary bladder, ureter etc.
4. *Neural pathway*
   (i) The *receptors* in the walls of the hollow viscera are specially sensitive to distension of these organs. Such distension causes activation of unmyelinated 'C' fibers. Afferents from visceral structures reach the CNS via autonomic nerves (sympathetic and parasympathetic). Their cell bodies are located in the dorsal roots and the homologous cranial nerve ganglia.
   (ii) In the CNS, visceral pain sensation travels along the same *pathways* as somatic pain sensation in the *lateral spinothalamic tracts*. The cortical receiving area for visceral sensation is same as for somatic in postcentral gyrus.
5. Visceral pain initiates reflex spasm (contraction) of skeletal muscle in the abdominal wall and makes it rigid. It is most marked when inflammation of the viscera involves the peritoneum. Clinically this reflex spasm is called *guarding*. It is a protective reflex and helps to protect the underlying inflammed structures from unintentional injury.

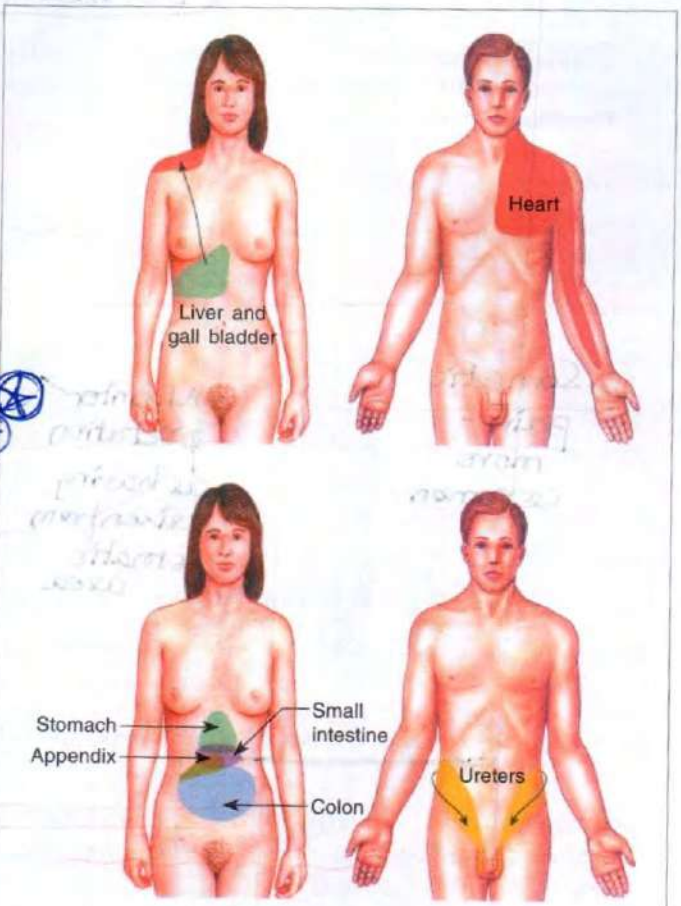


Fig. 91.14 Referred pain
(**Note:** Pain in internal organs is often sensed on the surface of the body.)

Referred and Radiating Pain

1. When the sensation of pain is experienced at the site other than the injured or diseased part, it is called *Referrell pain*. If it seems to spread from the local area to the distant site, it is called *Radiating pain* (**Fig. 91.14**). For example:
   (i) Phantom limb pain (page 870).
   (ii) Pain of stone in the gall bladder referred to the tip of the right shoulder.
   (iii) Pain in testicles due to stone in the ureter.
   (iv) During a heart attack, pain is often experienced at the tip of left shoulder and tends to spread in the inner aspect of left arm. (Also refer to page 304)
2. Pain is usually referred to a structure that developed from the same segment during the embryonic development. This principle is called the *Dermatomal Rule*. For example, the heart and the arm have the same

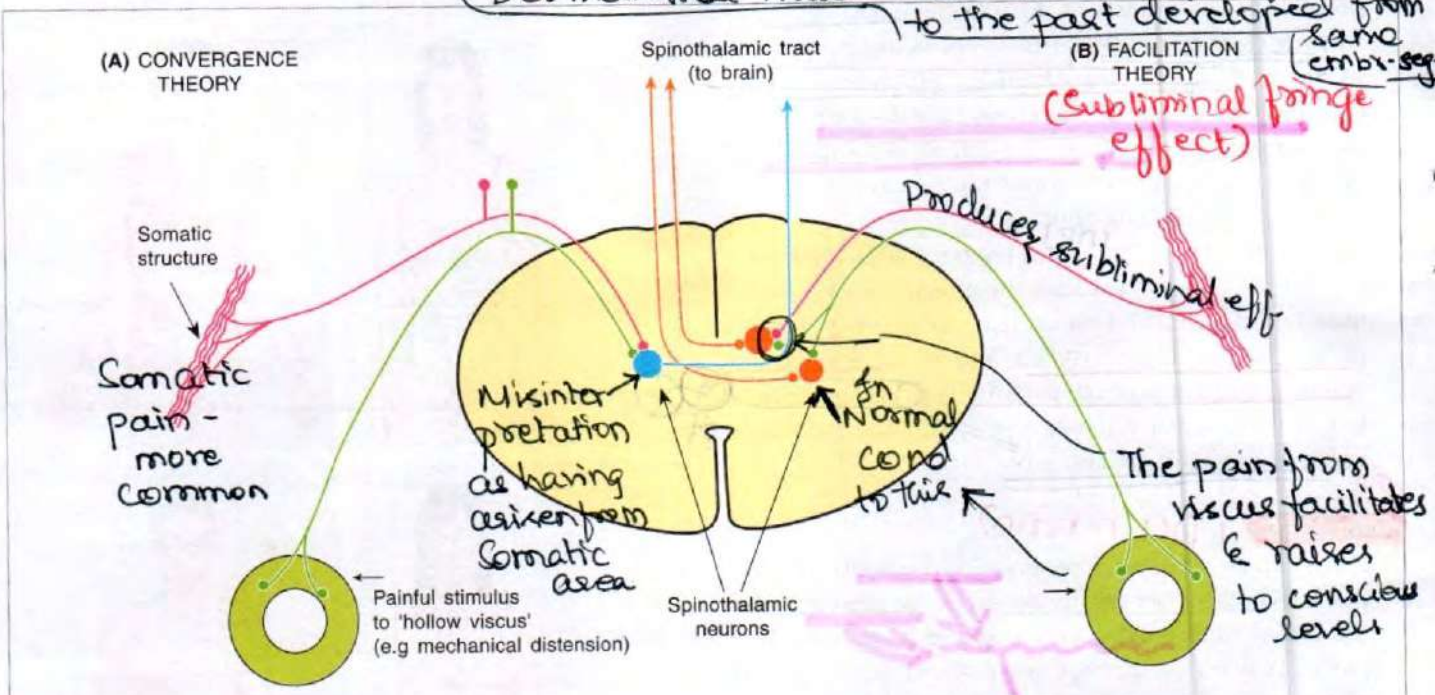


Fig. 91.15 The two theories of referred pain: convergence (A) and facilitation theory (B)

segmental origin; similarly, the testicles and kidney developed from the same primitive urogenital ridge.

3. *Theories of referred pain* (Fig. 91.15)

(i) *Convergence theory*

(a) The nerves from the visceral structures and the somatic structure to which pain is referred enter the CNS at the same level and converge on the same spinothalamic neurons.

(b) Since somatic pain is far more common than visceral pain, therefore, when the same afferent pathway is stimulated by signals that originate in visceral afferent nerves, the signal that reaches the somatosensory cortex is identical and is misinterpreted as having arisen within the somatic area (law of projection, page 870).

(ii) *Facilitation theory.* The afferent impulses from visceral structures produce *subliminal fringe* effects (page 859) that lower the excitability threshold of spinothalamic neurons which receive afferent fibers from somatic areas. Therefore, any slight activity in the pathways transmitting pain impulses from somatic regions, and which normally would die out within the spinal cord, is facilitated and thus reaches conscious levels

Inhibition of Pain: ANALGESIA

Inhibition of pain (*Analgesia*) can be achieved by two mechanisms: (1) *Stimulation produced analgesia;* and (2) By *release of Endogenous opioid peptide.*

1. Stimulation produced analgesia

Electrical stimulation of specific areas of the CNS can produce a profound reduction of pain by inhibiting pain pathways, a phenomenon called *stimulation-produced analgesia.* Thus, within CNS are pathways which inhibit the activity of the central neurons by peripheral noxious stimulation. Two main pathways involved are: *segmental* and *supraspinal inhibition.*

(i) Segmental inhibition

Stimulation of nerves in the same segment in which pain is felt can relieve such pain. It can be achieved by:

(a) activation of group A afferent nerve fibers; or

(b) stimulation of the dorsal column of the spinal cord which in turn activates segmental collaterals. This can be explained on the basis of: ***Gate control theory of pain*** *(Melzack and Wall)*

According to this theory, pain is determined by interaction among the 3 systems in the dorsal horn of spinal cord (Fig. 91.16); the systems are:

(i) *Central transmission cells (T-cells)* in the dorsal horn. This system activates lateral spinothalamic tracts (LSTT) which comprises the *action system* responsible for perception of pain and its motor responses.

(ii) The *afferent pattern* in the dorsal column. This system acts as a central control trigger that influence the regulating properties of the gate control system. How?

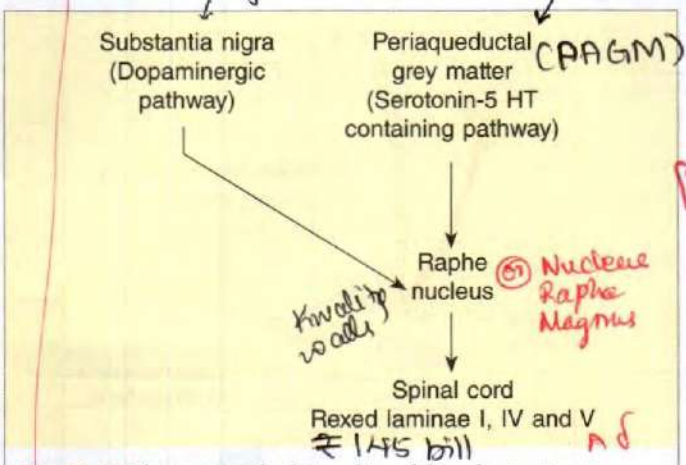


Fig. 91.16 The proposed relationship of three brain sites at which electrical stimulation or morphine administration produces analgesia

- Activation of large peripheral fibers (such as touch fibers) stimulates both T-cells and SG cells; and
- Activation of small peripheral fibers (such as pain fibers) causes stimulation of T-cells with inhibition of SG cells.

(iii) *The cells of substantia gelatinosa (SG cells)* in the dorsal horn. This system regulates the *afferent pattern* before they influence the T-cells. How? *Activity in* SG cells *is increased by large fibers and decreased by small fibers. SG cells* inhibit activity in the afferent fiber terminals of both large and small fibers. Therefore,

- stimulation of T-cells by large fibers is rapidly cut off by *negative feedback* via SG cells, and
- conversely, stimulation of T-cells by small fibers will be increased by *positive feedback* through inhibition of SG cells activity.

Thus, the dorsal horn is the 'GATE' through which pain impulses reach the lateral spinothalamic system. Stimulation of large fibers closes the gate, whereas stimulation of small fibers opens the gate.

Clinical Application

(a) Soldiers wounded in the heat of battle may feel no pain until the battle is over (*Stress analgesia*).

(b) Touching or shaking an injured area, decreases the pain of injury.

(c) *Acupuncture* has been used to relieve pain. During acupuncture analgesia, needles are introduced into specific parts of the body to stimulate afferent fibers, which cause analgesia.

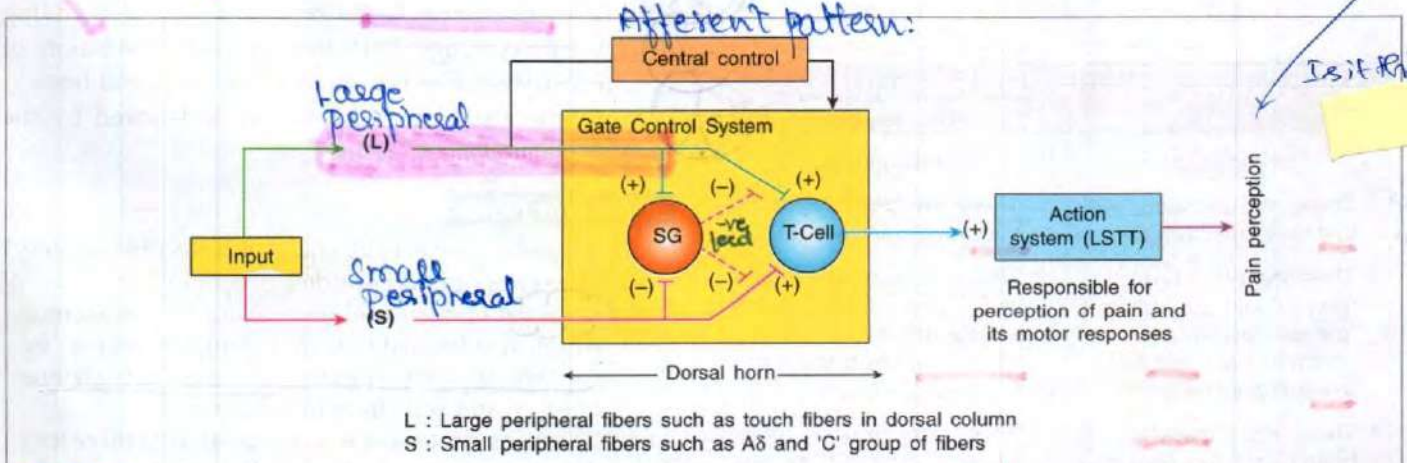
(d) *Counterirritants i.e.* stimulation of skin over an area of visceral inflammation produces some relief of the pain due to visceral disease.

(e) *Transcutaneous electrical nerve stimulation* (TENS) is often used in lessening pain. Here the pain site itself or the nerves leading from it are stimulated by electrodes placed on the surface of the skin. It works because the stimulation of non-pain, low-threshold afferent fibers such as the fibers from the touch receptors leads to inhibition of neurons in the pain pathways.

(ii) Supraspinal inhibition.

A descending inhibitory pathway from the brain stem to the Rexed laminae I, IV and V (**Fig. 91.6**) can also produce analgesia. One such important pathway is ***mesencephalic pain inhibitory system*** (**Fig. 91.17**). This system arises from mid brain and descends to the dorsal horn cells, in the spinal cord. It contains *Opiate Receptors* (see below). The system is stimulated in the following regions:

(a) structures immediately surrounding the IIIrd ventricle



L : Large peripheral fibers such as touch fibers in dorsal column
S : Small peripheral fibers such as Aδ and 'C' group of fibers

Fig. 91.17 Gate control theory of pain: Factors involved in the transmission of impulses from peripheral nerve to control transmission cells (T-cells) in the dorsal column.
SG: substantia gelatinosa cells. LSTT: Lateral spino thalamic tracts

(b) periaqueductal grey matter in mid brain
(c) substantia nigra of basal ganglia
(d) nucleus raphe magnus (dorsal raphe nucleus) in medulla (page 986).

Stimulation of this system selectively inhibits the responses in 2nd order nociceptive neurons in the dorsal horn of the spinal cord.

2. By release of Endogenous opioid peptides: ENKEPHALINS AND ENDORPHINS

(i) *Substance P* is a peptide containing 11 aminoacids, a mediator of pain (different from Lewis P-factor, page 897). Its release from the primary afferent nerve endings is brought by neuronal stimulation of afferent Aδ and 'C' group fibers in peripheral nerves.

(ii) The terminals of substance P containing afferents possess *Opiate Receptors* on the membrane surface. Morphine and *opioid peptides* produce analgesia (*i.e.* relieves pain) by binding to these receptors.

(iii) Three types of 'opiate' receptors have been described: μ, κ and δ (*All are coupled to Gq* protein and all inhibit adenylyl cyclase). All on stimulation produce analgesia but by a different mechanism, described as under:

Opiate Receptor Type	Natural ligand	Mechanism of action
μ	β-endorphin	Increases K^+ permeability hyperpolarizing neurons in CNS and primary afferents.
κ	dynorphins	Closes Ca^{2+} channels
δ	enkephalins	Closes Ca^{2+} channels

(iv) The two major types of opioid peptides are known, *Enkephalins and Endorphins* (Table 91.4).

Table 91.4: Differences between two main types of opioid peptides

Enkephalins	Endorphins
1. These are peptides with low molecular weight.	1. These are peptides with high molecular weight.
2. They occur in 2 forms: 'prepro' and 'pro' form; 'pro-enkephalin' precursors are met and leu-enkephalins.	2. They also occur in 'prepro' and 'pro' form; 'pro-endorphins' precursors are α- and β-endorphins.
3. They are 'unstable' in brain tissue; half life 1 min; however, they are more abundantly distributed in the CNS than endorphins.	3. They are much more 'stable', confined to the hypothalamus and secreted into the blood stream by the pituitary gland.

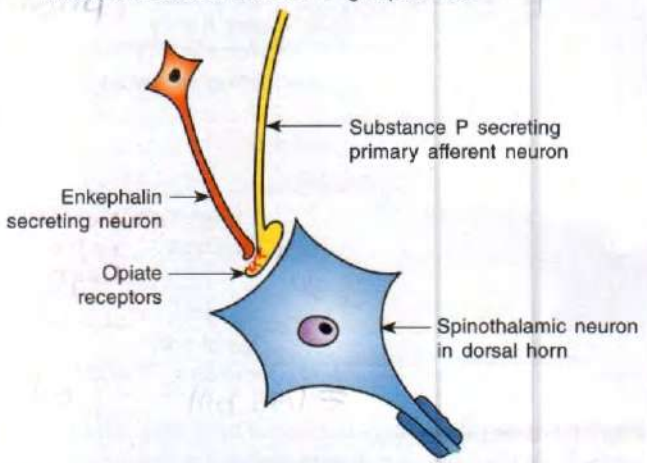


Fig. 91.18 Location of opiate receptors and their relationship with Enkephalin secreting neuron (mechanism of presynaptic inhibition)

(v) These peptides (Enkephalins and Endorphins) function as 'synaptic transmitters' and bind to opiate receptors therby produce analgesia (Fig. 91.18). Enkephalin containing neurons probably act presynaptically at the site of the receptors on *substance P* secreting primary afferent neurons and in turn decrease the release of substance P in the dorsal horn. Thus inhibiting the transmission in pain pathway in the spinal cord.

(vi) *Opioid peptides* are found in nerve endings in the GIT and many different parts of the brain, specially in high concentration in substantia gelatinosa. *Naloxone* is a specific antagonist of these peptides.

Physiological significance

Morphine relieves pain by two mechanisms:

(i) At spinal level by binding to opiate receptors and thereby decrease the release of substance P; and
(ii) At supraspinal level by activating descending pathways (page 891) that produce inhibition of primary afferent transmission in the dorsal horn.

Morphine analgesia is known to be blocked by the naloxone (*morphine antagonist*).

Important Notes

(i) *Acupuncture* exerts its analgesic effect by causing release of opioid peptides.
(ii) *Placebos* (a pharmacologically inactive substance which is administered as a drug) appear to be capable of producing the release of endogenous opioids, and thus help to relieve pain.
(iii) Chronic irritation of nerves apparently increases the number of substance P receptors in the spinal cord on the side of the injury and cause increase responses to painful stimuli.

HYPERALGESIA

This is a condition in which pain threshold is decreased, therefore, even non-noxious stimulus produces pain; and a noxious stimulus causes more pain than they normally do.

Causes – *Tissue damage* (main cause) and *nerve lesion*.

1. **Hyperalgesia due to tissue damage.** It is of 2 types: primary and secondary.
   (i) *Primary hyperalgesia.* It occurs within an area of tissue damage particularly caused due to a burn or bacterial infection. The condition is characterized by *decrease in pain threshold*, inflammation and flare (page 376). This is due to release of chemical substances like histamine, 5HT, plasma kinin and prostaglandins from damaged tissues which sensitize the unmyelinated 'C' afferent endings.
   (ii) *Secondary hyperalgesia.* It occurs in undamaged tissue adjacent to the site of injury. There is *no lowering of pain threshold* but with a given noxious stimulus, the pain produced is unpleasant, prolonged and more severe. It is probably due to spread of excitation impulse within the CNS from the injured area and occurs when *central excitatory state* is marked (page 882).
2. **Hyperalgesia due to nerve lesion.** Selective damage to large sensory fibers allows light *tactile stimuli* to produce severe pain even in the absence of peripheral tissue damage (page 898).

E. OTHER SENSATIONS

Separate receptors exist for the somatic sensations (touch, pressure, pain and temperature). Combination of these sensations can produce entirely different experience of new sensations called *synthetic senses*. These are:

1. *Itch (Pruritus)*
   (i) Itch is an irritative skin disease produced by a relatively mild stimulation of the skin.
   (ii) Like pain it originates from stimulation of *free nerve endings* in the skin and the nerve pathway ('C' group of fibers) mediating itch accompanies fibers carrying pain in the lateral spinothalamic tract in the spinal cord.
   (iii) Itching can also be produced by chemical agents:
      (a) Histamine and kinins (page 323) cause severe itching. In urticaria (*i.e.* formation of red/pink elevations on the skin) itching is due to the histamine released by the antigen-antibody reaction.
      (b) *Itch powder.* It is made up of very fine sharp, pointed spicules from the seed pods of the tropical plant *cowhage*. Itch producing agents in itch powder are *histamine liberator* and *mucunain*, a proteolytic enzyme.

Note

Scratching relives itching because it activates large, fast conducting afferents that gate transmission in the dorsal horn (Fig. 91.15).

2. *Vibration Sense*
   (i) If the foot of a vibrating tuning fork is placed on the surface of the body, a sensation described as a 'buzzing' or 'electrical' is felt. The sensation is most marked over bones; the *receptors* involved are touch-pressure receptors, specially pacinian corpuscles and Meissner's corpuscle. Former can detect signal vibrations from 30 to 1000 Hz (cps) whereas latter trasmit low frequency vibrations upto 100 Hz. A pattern of rhythmic pressure stimuli is interpreted as vibration and the impulses are carried in the dorsal columns.
   (ii) The ability to appreciate mechanical vibrations (***pallesthesia***) may be *lost in* various diseases such as tabes dorsalis, peripheral neuropathies (due to diabetes mellitus, vitamin deficiencies) and in posterior column disorders.
   (iii) There is often some loss of vibration sense in the feet and legs in old age.
3. *Two point discrimination*
   This is the ability to distinguish two points (page 886). It depends upon the intactness of touch sensibility and parietal lobe. It is used to test the integrity of the dorsal column (page 888). Normally 2-3 mm of separation of the points can be recognised as two separate stimuli on the fingertips, whereas two points on the back must be separated by 65 mm or more before they can be distinguished as separate points.
4. *Stereognosis*
   (i) The ability to recognise familiar objects such as coins, a pencil, pen, scissors, etc. by handling them without looking at them is called *stereognosis*. It depends upon intact touch-pressure sensation, but cerebral cortex plays a major role (Fig. 91.19).
   (ii) Loss of stereognosis *(astereognosis or Tactile agnosia)* is an early sign of damage to the parietal lobe when touch-pressure sensation is normal.

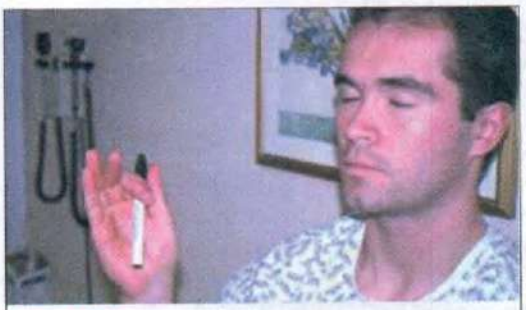


Fig. 91.19 Testing for Stereognosis

Study Questions

1. **Define sensory unit. Give its physiological significance.**
2. **Differentiate between:**
   (i) Sensation and perception.
   (ii) Specific and non-specific ascending pathways.
   (iii) Fine and crude touch.
   (iv) Fasciculus gracilis and cuneatus.
   (v) Lateral and anterior spinothalamic tracts.
   (vi) Proprioception and kinesthetic sensations.
   (vii) Anterior and posterior spinocerebellar tracts.
   (viii) Somato-sensory area I and II.
   (ix) Fast and slow pain.
   (x) Primary and secondary hyperalgesia.
   (xi) Referred and radiating pain.
   (xii) Substance P and Lewis P-factor.
   (xiii) Superficial and deep pain.
3. **Draw a well labelled diagram:**
   (i) Cross-section of the spinal cord showing location and functions of major ascending tracts.
   (ii) Pathway for lateral inhibition.
   (iii) Specific and non-specific ascending pathway.
   (iv) Termination of neurons in dorsal horn.
   (v) Sensory pathway for fine touch
   (vi) Pathway for pain and temperature
   (vii) Brain areas concerned with somatic sensations
   (viii) Referred pain theories
   (ix) Location of opiate receptors and their relationship
4. **Define and give physiological significance:**
   (i) Vibration sense and pressure sense
   (ii) Fine touch and crude touch
   (ii) Proprioception and kinesthetic sensation
   (iv) Intermittent claudication
   (v) Double pain sensation
   (vi) Stereognosis
   (vii) Hyperalgesia
   (viii) Lateral inhibition
5. **Why is S I called the primary sensory area? Justify.**
6. **What will happen and why to the perception of sensations if:**
   (i) Somatosensory cortex is removed?
   (ii) Dorsal columns are destroyed?
   (iii) Anterolateral system gets destroyed?
   (iv) Vascular blockage to the thalamus occurs?
7. **How does pain sensation differ from other sensations? How does the nociceptors get stimulated?**
8. **Define referred and radiating pain. Give suitable examples. How is inhibition of pain brought about?**
9. **Give physiological basis of the following:**
   (i) Acupuncture
   (ii) TENS therapy
   (iii) Touching an injured area relieves pain
   (iv) Counter irritants
   (v) Morphine analgesia
   (vi) Placebos as pain relievers
   (vii) Endogenous peptide produces analgesia
   (viii) Hyperalgesia due to selective damage to touch fibers
   (ix) Discrimination power is greater on the thumbs than on the back
   (x) When a non-noxious stimuli can produce severe pain
   (xi) Visceral pain poorly localized

10. **Explain gate control theory of pain. Draw diagram also.**
11. **Give an early sign of damage to the parietal lobe.**
12. **Write short notes on:**
    (i) Cortical plasticity (ii) Ischaemic muscular pain (iii) Thalamic syndrome
    (iv) Double pain sensation (v) Opioid peptides (vi) Stereognosis
    (vii) Hyperalgesia (viii) Supraspinal inhibition of pain

MCQs

1. **The area of skin or body surface that, when stimulated, leads to activity in the neuron is called:**
   (a) Sensory unit (b) Sensory receptors
   (c) Receptive field (d) All of the above
2. **The ascending pathways that have significant lateral inhibition are utilized for providing:**
   (a) Accurate localization of sensation (b) Intensity discrimination
   (c) Specificity of response (d) All of the above
3. **Unconscious kinesthetic sensations are carried by:**
   (a) Anterior spinocerebellar tract (Is it exists?) (b) Anterior spinothalamic tract
   (c) Lateral spinothalamic tract (d) Posterior columns

   → Dorsal spinal tract
   Watchman + (59)
4. **Which of the following is *not* transmitted in anterolateral system?**
   (a) Crude touch (b) Pain
   (c) Temperature (d) Vibration
5. **Which of the following body part is represented by the smallest area in somatosensory area I (S I)?**
   (a) Fingers (b) Lips
   (c) Thumb (d) Arm
6. **Damage to somatosensory area I of the cerebral cortex results in:**
   (a) Loss of perception of pain (b) Loss of tactile and two point discrimination
   (c) Loss of perception of touch (d) Loss of only tactile discrimination
7. **Lesion in ..... leads to sensory ataxia:**
   (a) Posterior column (b) Spinocerebellar tract
   (c) Cerebellum (d) Vestibular apparatus
8. ***Not* an example of referred pain:**
   (a) Phantom limb pain
   (b) Pain in testicles due to stone in ureter
   (c) Substernal pain of angina spreading on to the left shoulder and inner aspect of left arm (Radiating)
   (d) Pain at tip of right shoulder due to stone in gall bladder
9. **GATE through which pain impulses reach the lateral spinothalamic system is closed by:**
   (a) Stimulation of large fibers (b) Stimulation of small fibers
   (c) Central transmission cells activation (d) Inhibition of dorsal columns
10. **Which of the following is *not* transmitted in dorsal column?**
    (a) Vibration sense (b) Position sense
    (c) Itch sensation (Involves many) (d) Fine touch
11. **Transcutaneous electrical nerve stimulation (TENS) is often used in lessening pain, acts by:**
    (a) Blocking release of substance P
    (b) Stimulation of non-pain, low threshold afferent fibers
    (c) Activating descending inhibitory pathway
    (d) By release of endogenous opioid peptides
12. **Loss of feel of size and shape of an object is seen in lesions of:**
    (a) Tractus solitarius (b) Parietal cortex
    (c) Lateral spinothalamic tract (d) Spinoreticular tract
13. **Specific ascending pathways:**
    (a) Its neurons can be activated by several different types of stimuli
    (b) Signal only general information
    (c) Carry information about single types of stimuli
    (d) Feed informations into cortex that are not highly discriminative

14. **Sensory tract *not* contained within the lateral white column of spinal cord:**
(a) Lateral spinothalamic tract
(b) Posterior spinocerebellar tract
(c) Anterior spinocerebellar tract
(d) Anterior spinothalamic tract

15. **Somato sensory vibratory information reaches the brain through:**
(a) Dorsal columns of spinal cord (main)
(b) Lateral spinothalamic tract
(c) Anterior spinothalamic tract (minor)
(d) Dorsal spinocerebellar tract

16. **Nucleus gracilis and nucleus cuneatus are the first synapse for:**
(a) Dorsal columns
(b) Dorsal lateral tract
(c) Ventral spinothalamic tract
(d) Lateral spinothalamic tract

17. **The somasthetic sensations relay in which part of the thalamus?**
(a) Ventro lateral nucleus
(b) Ventro posterior nucleus
(c) Anterior nucleus
(d) Pulvinar

18. **Sexual sensation ascend to the brain through the:**
(a) Spinothalamic tract
(b) Anterior spinocerebellar tract
(c) Posterior spinocerebellar tract
(d) All of the above

19. **Spinothalamic tract transmits all the following sensations *except*:**
(a) Proprioception
(b) Pain
(c) Temperature
(d) Touch

20. **Gross (crude) touch sensations are carried by:**
(a) Lateral spinothalamic tract
(b) Ventral spinothalamic tract
(c) Posterior columns
(d) Pyramidal tract

21. **First synapse of fibers conducting pain takes place at the level of:**
(a) Medulla in nucleus cuneatus
(b) Grey matter of dorsal horn of spinal cord
(c) Medulla in nucleus gracilis
(d) Thalamus in posterior ventricular nucleus

22. **First synapse for peripheral sensation is:**
(a) Cerebellum
(b) Anterior horn cells
(c) Posterior horn cells
(d) Midbrain

23. **Somatosensory area I of the cerebral cortex respond maximum to:**
(a) Pain fibers
(b) Touch fibers
(c) Fibers for fine movement
(d) Tactile discrimination and two point discrimination

24. **Very light stimulation of the primary sensory cortex is most likely to cause:**
(a) Movement of an area of the body to which the sensory cortex is connected
(b) Pain in the area of representation
(c) A feeling that someone has touched the area of representation
(d) A mild electric, tingling feeling in the area of representation

25. **All sensations relay in sensory cortex *except*:**
(a) Pain
(b) Touch
(c) Temperature
(d) Olfaction

26. **What is the most important deficit that occurs when the second somatic sensory area (S II) is removed?**
(a) Loss of tactile sensation
(b) Loss of thermal sensation
(c) Loss of pain sensation
(d) Loss of discrimination power

27. **Kinesthetic sensations are detected mainly by what type of receptors?**
(a) Muscle spindles
(b) Golgi tendon apparatus
(c) Skin receptors
(d) Joint receptors

28. **Headache can be produced by all *except*:**
(a) Dilatation of intracranial blood vessels
(b) Presence of blood in CSF
(c) Loss of CSF following lumbar puncture
(d) Mechanical damage to parietal lobe

29. **Superficial pain:**
(a) Involves the skin and subcutaneous tissues
(b) Is dull and poorly localized
(c) Associated with faintness, vomiting and fall in BP
(d) Is both local and radiates to distant site

30. **Non-specific pain pathways:**
(a) Convey about sharp, localized aspect of pain
(b) Convey information about where, when and how strong the stimulus was applied
(c) Convey pain that is dull, long lasting and less well localized
(d) Are lateral spinothalamic tract

31. **Following a noxious stimulus of skin, the two components of pain (slow and fast) are separated by:**
(a) 0.1 sec (b) 1-1.5 sec (c) 4-5 sec (d) 5-7 sec

32. **Pain producing substance (Lewis P-factor) consists of:**
(a) Potassium ions (b) Adenine [PAL]
(c) Lactic acid (d) All of the above

33. **True visceral pain arises from:**
(a) Compression (b) Irritation
(c) Distension (d) Chemical stimulation

34. **Analgesia system of brain consists of all *except*:**
(a) Periaqueductal grey matter in mid-brain (b) Raphe magnus nucleus in medulla
(c) Thalamus (d) Substantia nigra of basal ganglia

35. **Hyperalgesia is a condition in which:**
(a) Pain threshold is decreased
(b) Even non-noxious stimulus produces pain
(c) A noxious stimulus causes more pain than it normally does
(d) All of the above

36. **Primary hyperalgesia:**
(a) Occurs in undamaged tissue adjacent to site of injury
(b) Ther is no lowering of pain threshold
(c) Particularly caused due to a burn or bacterial infection
(d) All of the above

Answers

1. (c)	2. (a)	3. (a)	4. (d)	5. (d)	6. (b)	7. (a)	8. (c)	9. (a)	10. (c)	11. (b)	12. (b)	13. (c)	14. (d)	15. (a)
16. (a)	17. (b)	18. (a)	19. (a)	20. (b)	21. (b)	22. (c)	23. (d)	24. (c)	25. (d)	26. (d)	27. (d)	28. (d)	29. (a)	30. (c)
31. (b)	32. (d)	33. (c)	34. (c)	35. (d)	36. (c)									

The Motor Areas and Descending Tracts

Chapter 92

I. Motor areas
II. Descending tracts: Motor pathways
  A. Pyramidal tracts
  B. Extrapyramidal tracts
  C. Pyramidal versus extrapyramidal tracts
III. Applied aspects
  A. Lower versus upper motor neuron lesion
  B. Lesion of the pyramidal tracts: Hemiplegia

MOTOR AREAS

The part of the cerebral cortex of the *frontal lobes* which on stimulation gives rise to the skeletal muscle responses constitute the *motor areas*. As this region lies anterior to the central sulcus, therefore, also called *Precentral Motor Cortex*. *Histologically* it is divisible into several separate zones (areas 4, 6 and 8) with fairly different functions (Fig. 92.1).

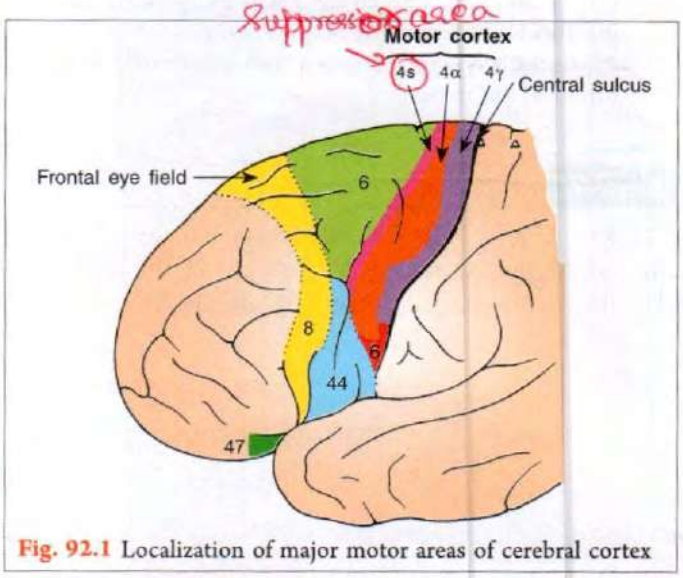


Fig. 92.1 Localization of major motor areas of cerebral cortex

AREA 4: MOTOR CORTEX or MOTOR AREA

1. The major portion of *motor cortex* occupies almost the whole length of the precentral gyrus. A small portion, *supplementary motor area* extends medially beyond the margin of the central sulcus over on to the medial surface of the hemisphere which lies above the cingulate sulcus. This area projects to the motor cortex (Fig. 92.2:B).
2. It is the main region of origin of the ***pyramidal tracts*** (page 908),
3. The body is represented upside down in the cortex; very similar to the corresponding 'sensory cortex' in the postcentral gyrus (page 893).
   (i) The size of the representation of the individual body part is proportional to the skill with which the part is used in fine, voluntary movements. Thus, there is large areas for the hands, fingers, face, lips, tongue, pharynx and vocal cords (Fig. 92.2:A).
   (ii) Separate foci exists for each of the fingers. The focus for the thumb is most inferior and that for the little finger most superior.
   (iii) The face, the pharynx, the vocal cords and the muscles for closing the jaws are *bilaterally represented.*
   (iv) The *axial musculature i.e.* muscles of the trunk and the proximal limb muscles are represented along the anterior edge of the precentral gyrus and the distal limb muscles along the posterior edge (Also see to page 947).
   (v) Electrical stimulation of this area produces:
      (a) Discrete isolated movements of the *opposite side of the body.*
      (b) Stimulating the most inferior parts of the precentral gyrus causes rhythmic co-oridnated movements of the lips, tongue, mandible, larynx and pharynx.

Important Note

Jacksonian epilepsy i.e. epileptic attacks beginning in this area begin with the same type of movements, such as chewing, licking, swallowing and harsh sound.

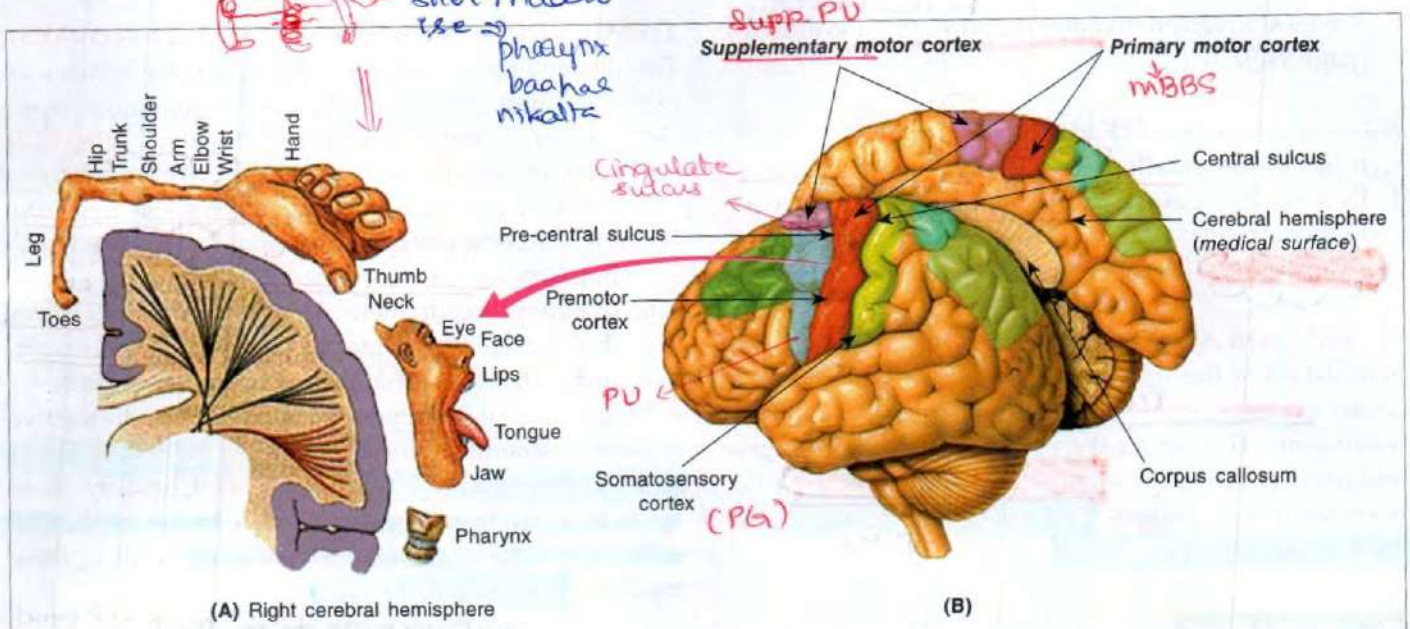


Fig. 92.2 (A) Representation of the body in the primary motor cortex and (B) Primary and supplementary motor area.

Note

The large area represented to the thumb and fingers and to the face.

(vi) **Histologically** it is divided into two zones:
- (a) [redacted] – which lies most posteriorly, called *Giganopyramidalis* due to the presence of the giant cells of Betz in the V layer of this region.
- (b) [redacted] – which constitutes the bulk of area 4 and lies most anteriorly.

(vii) Neurons in the motor area also receive input from the somatic sensory area I and II (page 893). This information contributes to movements involving the use of individual muscle groups, thus increase the accuracy of motor control.

(viii) *Supplementary motor area* (page 906) is organized somatotropically but is less precise than in the motor cortex. It is primarily involved in voluntary movements which are complex and involve planning *i.e. in programming motor sequences*. Lesion of this area produces difficulty in performing complex activities specially those requiring bimanual cordination.

Important Notes

(i) Cerebral dominance (page 1031) also affect the motor cortex.

(ii) The motor cortex shows the same kind of *plasticity* as the sensory cortex (page 894).

AREA 6: PREMOTOR CORTEX or PREMOTOR AREA

1. It lies anterior to the precentral gyrus and contributes:
   (i) descending fibers to the pyramidal tract;
   (ii) horizontal fibers which pass posteriorly to excite area 4 neurons; and
   (iii) descending motor fibers which do not run in pyramidal tract, therefore, called *Extrapyramidal fibers*.
2. It is also organized somatotropically and receive afferents from the somatosory cortex (page 893).
3. It is *involved in complicated motor functions* such as:
   (i) a change in the force or velocity of a movement, a change from one task to another;
   (ii) a movement made in response to visual input or a spoken command;
   (iii) two-handed coordination; and
   (iv) postural support for a wide variety of detailed movements, i.e. setting posture at the start of a planned movement.
4. It is also an important 'gateway' for relaying processed information to the primary motor cortex or directly to the descending pathways from other regions of the brain. For example, the relayed information from the somatic sensory areas I and II indicates the body's position in space and the direction in which the body must be moved to achieve the desired goal.
5. Stimulation of this area produces predominantly *excitatory effects* i.e. gross rotation of the eyes, head and trunk to the 'opposite' side of the body. These movements are in part due to stimulation of extrapyramidal pathways and also in part due to intracortical spread of the stimuli to the pyramidal system.

6. It is most involved in control of proximal limb muscles (page 947).

AREA 8: FRONTAL EYE FIELD

1. It lies in the middle frontal gyrus anterior to area 6.
2. Its stimulation causes conjugate deviation of the eyes to the opposite side, therefore, this area is also called *frontal eye field* (details page 1093).

SUPPRESSOR AREAS

Stimulation of the anterior edge of the precentral gyrus causes inhibition of stretch reflex and cortically produced movements. This region also projects to the basal ganglia and has been named area 4s or the *Suppressor Strip*. Four other suppressor regions, *Brodmann's areas 2s, 8s, 19s and 24s* have also been described.

Important Note

The term *sensorimotor cortex* includes all those parts of the cerebral cortex that act together in the control of movement, including motor cortex, the premotor cortex and somatosensory cortex and the parts of the *parietal lobe* association cortex adjacent to somatosensory cortex.

DESCENDING TRACTS (MOTOR PATHWAYS)

The descending (motor) pathways alter the balance of excitatory and inhibitory input that converge upon the α-motor neurons by three mechanisms: (Fig. 92.3)

(i) by synapsing directly upon the α-motor neurons; this pathway has the advantage of *speed* and *specificity*;
(ii) by synapsing directly on the γ-motor neurons which precisely *control the stretch reflex*; and
(iii) by synapsing on interneurons which act as *switches* that enable a movement to be turned 'on' or 'off' under the demand of the higher motor centres.

Many areas of the cerebral cortex give rise to the two types of descending (motor) pathways: *Pyramidal Tracts* and *Extrapyramidal Tracts* (Fig. 92.4). Clinically, these tracts are considered together because lesions within the cortex almost always involve both of them; however, these tracts are functionally different.

A. PYRAMIDAL TRACTS

CORTICOSPINAL AND CORTICOBULBAR TRACT

1. This is the *longest* tract starting from the *motor cortex* and reaching upto the last segment of the spinal cord (Fig. 92.5). It is present only in the higher animals and man where cerebrum has developed. 85%-90% of the

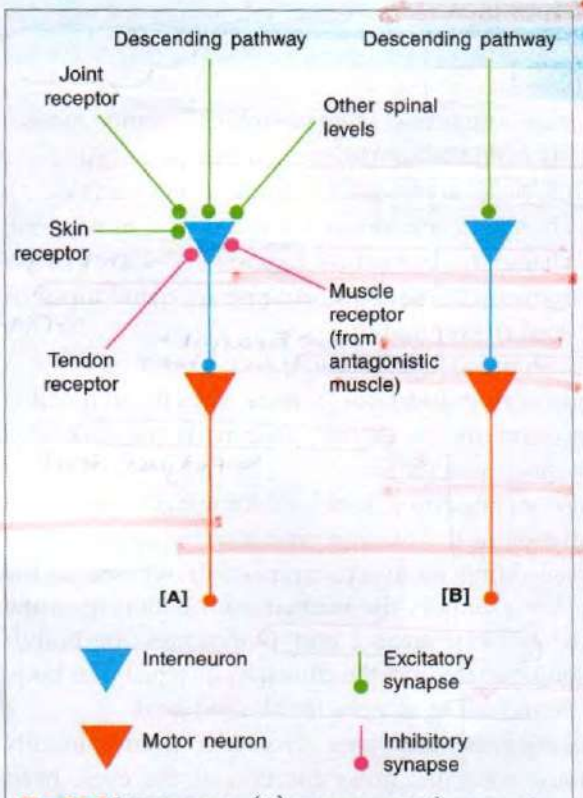


Fig. 92.3 Interneurons: (A) convergence of axons onto a local interneuron; (B) an inhibitory interneuron reverses the action of an excitatory descending pathway.

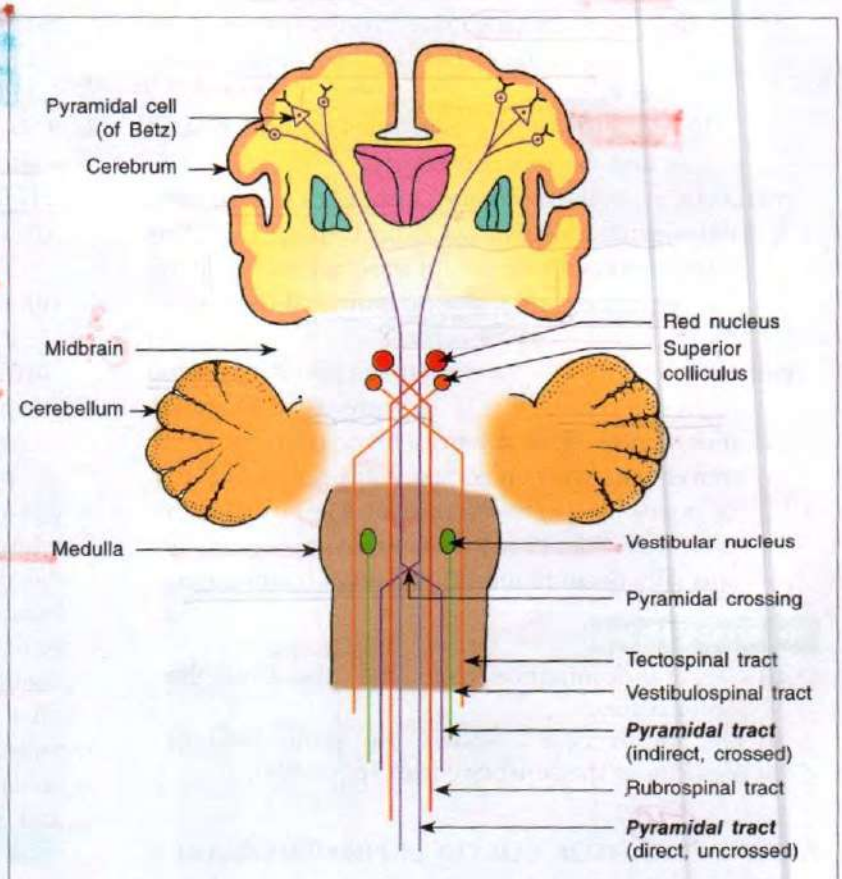


Fig. 92.4 The major descending (motor) tracts and their origin within the brain

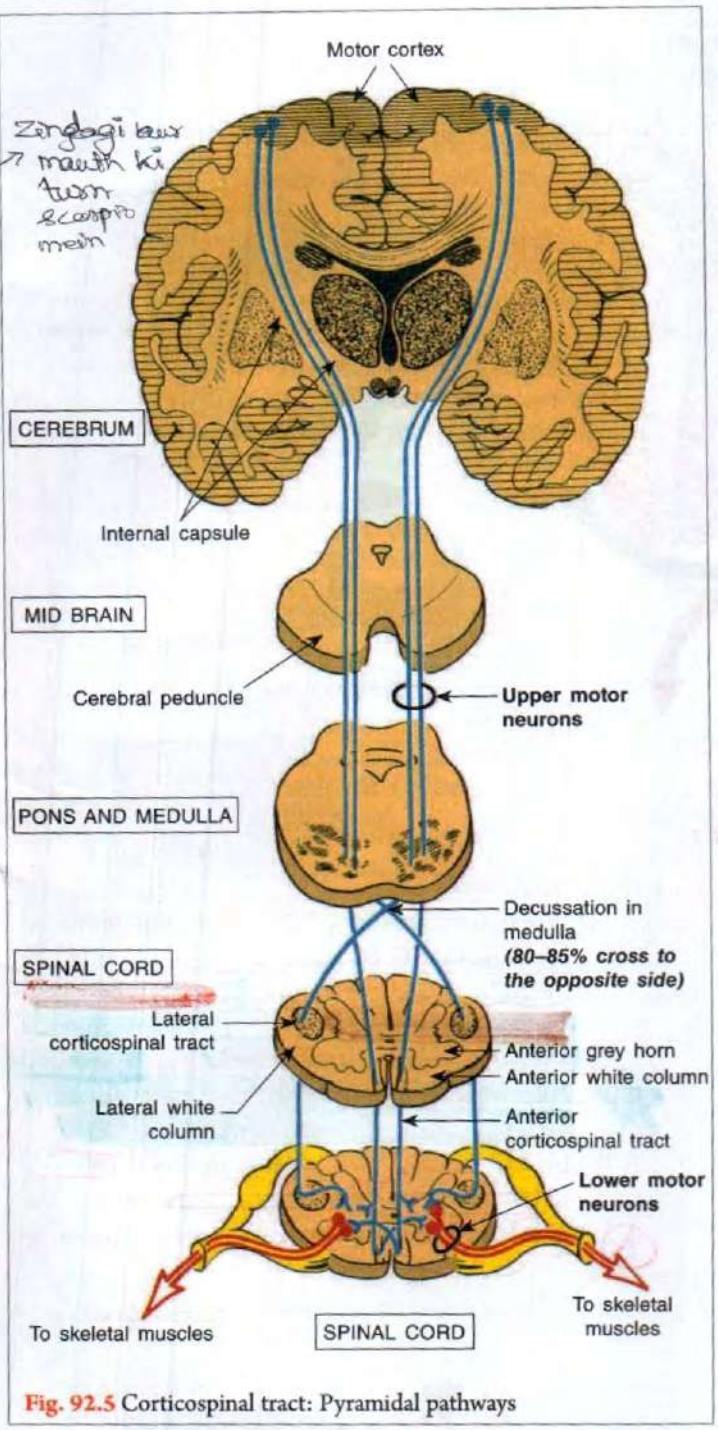


Fig. 92.5 Corticospinal tract: Pyramidal pathways

fibers in the pyramidal system are of small diameter (≤ 1 µm diameter). Therefore, it is a *slowly conducting* pathway and 50% of the fibers are unmyelinated.

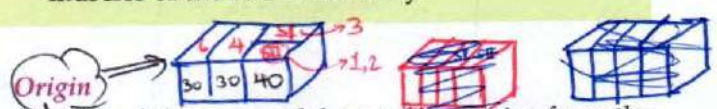
2. The pyramidal fibers pass from the motor area to the spinal ventral horn cells and to all the motor cranial nuclei *except* those supplying the external eye muscles.
   (i) The pyramidal tract fibers to the spinal ventral horn cells constitute the *Corticospinal Tracts*; and
   (ii) The pyramidal tract fibers to the motor cranial nuclei (*particularly V, VII and XII*) constitute the *Corticobulbar Tracts* or *Corticonuclear Tracts*. This is a pathway that begins in the cerebral cortex and ends in the brain stem (*bulbar* means pertaining to the brainstem where all 'motor' cranial nuclei are located).

Important Notes

(i) Whereas the neurons in the brain and spinal cord that can influence the activity of the LMNs constitute the *upper motor neurons;* The spinal and cranial motor neurons which directly innervate the muscles, constitute the *lower motor neurons* (LMNs). (Also refer to page 914)

(ii) The *corticobulbar fibers* end near the motor neurons that innervate muscles of the eye, face, tongue and throat. These fibers are the main source of control for the voluntary movement of the muscles of the head and neck, whereas the corticospinal fibers serve this function for the muscles of the rest of the body.

3. *Origin*



   (i) 30% of the pyramidal tract fibers arise from the motor cortex, area 4 (page 906) in precentral gyrus,
   (ii) 30% from the premotor cortex, area 6 (page 907), and the remaining
   (iii) 40% from the somatosensory areas I and II (page 893), and adjacent parietal lobe association cortex.

4. *Course of the pyramidal tract.* The pyramidal tract fibers which arise from the cerebral cortex converge towards the brain stem as a radiating mass of fibers known as *Corona Radiata* to reach the internal capsule.
   (i) *In the internal capsule.* Internal capsule is a mass of white fibers lying between the basal ganglia, limited laterally by the 'lenticular nucleus' (putamen and globus pallidus) and medially by the caudate nucleus and thalamus. In horizontal section the internal capsule is V-shaped, the point of the 'V' looking medially **(Fig. 92.6)**.
      (a) the pyramidal tracts lie in the bend *(the genu)*, and the anterior 2/3rd of the posterior limb;
      (b) *point to point discrimination* in internal capsule substance: the fibers concerned with control of head, shoulder, elbow, wrist, fingers, trunk, hip, knee and toe movements are arranged from anterior to posterior in this sequential order named.
   (ii) *In the mid brain.* In the crus of the mid brain the pyramidal fibers lie ventral to the substantia nigra, occupying the *middle 3/5th* of this region. (The medial fifth carries the corticonuclear and

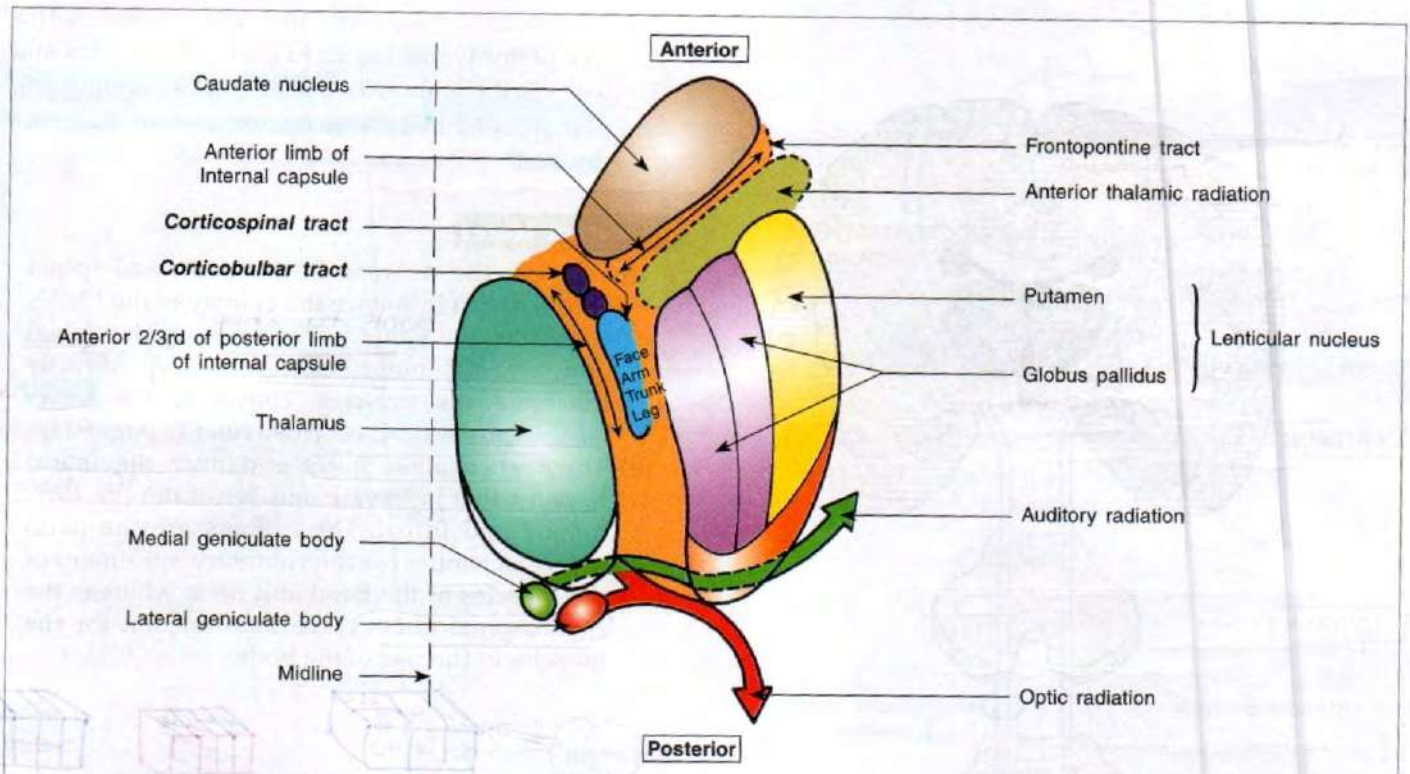


Fig. 92.6 Arrangement of pyramidal tract fibers in the internal capsule

frontopontine; and lateral fifth the temporopontine fibers) **(Fig. 92.7:A)**.

(iii) *In the pons.* The pyramidal fibers occupy the *most ventral aspect* in front of trapezium while passing through the pons **(Fig. 92.7:B)**. Here, the tract is broken up into a series of *scattered bundles* by the nuclei pontis and the crossing fibers of middle cerebellar peduncle.

In the mid brain and pons there is well marked localization of the pyramidal fibers for different parts of the body.

(iv) *In the medulla*

(a) While coming out of the pons, the scattered corticospinal fibers are reunited and enter the medulla as a thick bundle. It *occupies the most ventral (anterior) part* of the medulla producing a separate bulge – the ***Pyramid***. The pyramidal tract were so called because of their shape as they pass along the surface of the medulla.

(b) In the lower part of the medulla, 80-85% fibers *cross to the opposite side*, enter the lateral white column and descend down as

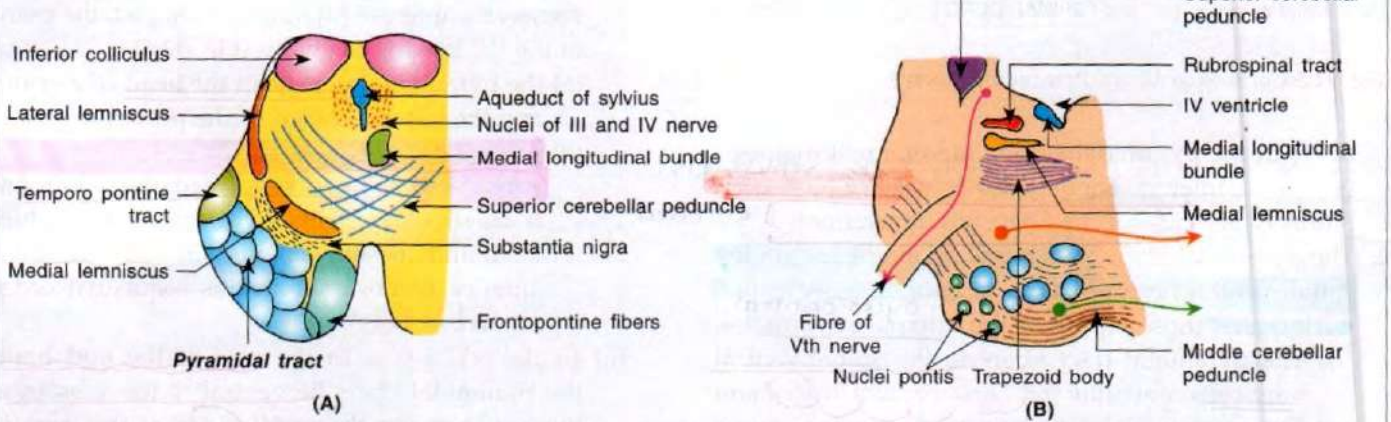


Fig. 92.7 Arrangement of pyramidal tract fibers in the mid brain (A) and pons (B)

lateral corticospinal tract or *crossed/indirect pyramidal tract* (Fig. 92.4 and 92.5). It extends throughout the whole cord and at each segment some fibers leave the tract, turn inward and end round the anterior horn cells (motor neurons), either directly or through interneurons.

(c) About 15-20% fibers do not cross (stay on their own side), enter the anterior white column near the median fissure and descend down as *anterior corticospinal tract* or *uncrossed/direct pyramidal tract*. The fibers, ultimately also end round the anterior horn cells of the same side. However, some fibers cross the midline to end round the anterior horn cells of the opposite side (Fig. 92.5). *As a rule, the direct pyramidal tract does not extend beyond the lower cervical or mid-thoracic region.*

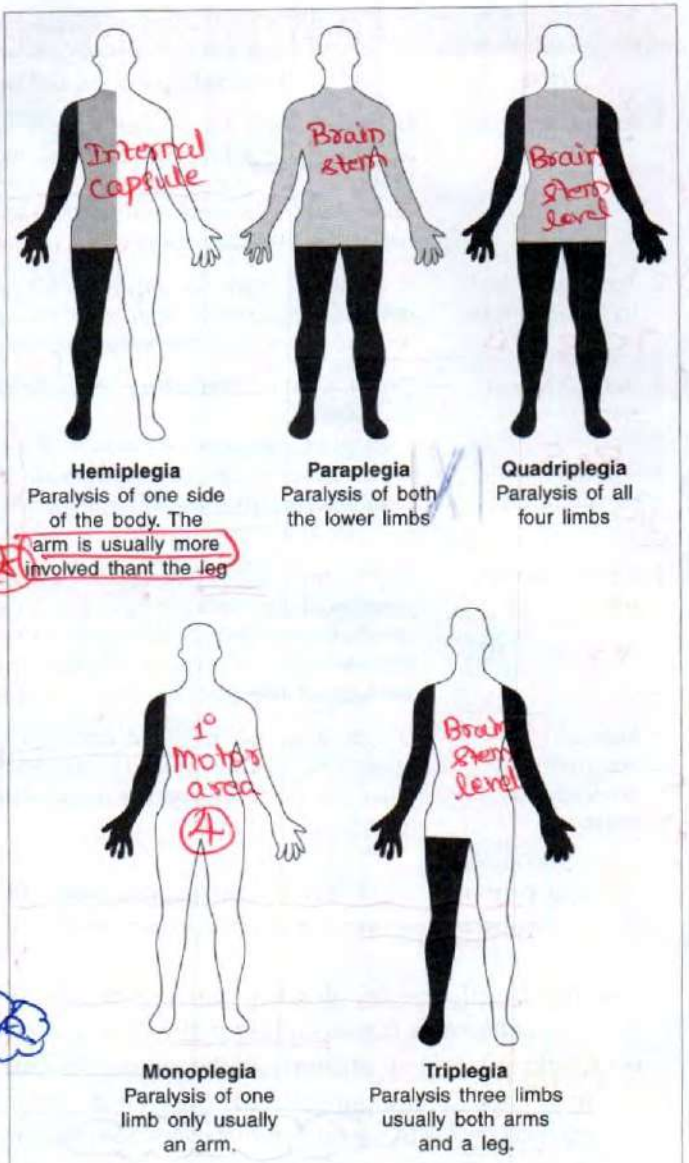


Fig. 92.8 Types of Apoplexy (or stroke)

Important Notes

(i) *Phylogenetically*, the anterior pathways are old, whereas the lateral pathways are new.

(ii) Throughout the 'brain stem' (medulla, pons and mid brain), the corticobulbar fibers are crossing to reach the motor cranial nuclei of the opposite side.

(iii) Of all the pyramidal fibers 55% end in the cervical, 20% in the thoracic and 25% in the lumbosacral region.

(iv) *Most common site of lesion* to the pyramidal tract is in the internal capsule due to thrombosis or haemorrhage of lenticulostriate artery, branch of middle cerebral artery. In this region pyramidal tract fibers are compact (join firmly).

(v) *Apoplexy* or *Stroke* means a sudden attack of paralysis (Fig. 92.8):

(a) damage or injury to area 4 produces ***monoplegia*** *i.e.* paralysis of one limb only because the motor neurons are scattered here;

(b) injury at the internal capsule level causes ***hemiplegia*** i.e. paralysis on one side of the body;

(c) injury at the brain stem level produces either ***paraplegia*** (paralysis of both the lower limbs) or ***quadriplegia*** (paralysis of all 4 limbs) with involvement of cranial nerves.

5. *Functions of the pyramidal tracts*

Functions of corticospinal tracts

(i) ***Lateral corticospinial tracts*** convey motor impulses to the spinal cord for controlling the voluntary movements, specially of the distal limb muscles and are concerned with the fine, precise movements of the fingers and hands to carry out skilled work. *Anterior corticospinal tracts* are concerned with the control of muscles of the trunk and proximal portions of the limbs to carry out postural adjustments and gross movements.

(ii) They form a part of the *pathways for superficial reflexes* such as cremasteric, abdominal and plantar reflexes.

(iii) Some corticospinal fibers end at excitatory synapses on α and γ-motor neurons, wheras other end on interneurons that may excite or inhibit the α-motor neurons. Thus the effect of the corticospinal pathway on the α-motor neurons may be excitatory or inhibitory.

(iv) Some of these fibers transmit information from the brain to 'afferent' neurons and so *can affect afferent system;* they do this by ending either:

Table 92.1: Descending pathways that contribute to the extrapyramidal system

Tracts	Description (origin and course)	Main function
1. Rubrospinal tract	It originates from the ***Red nucleus*** (nucleus Magnocellularis *i.e.* large nucleus) located in the mid brain; crosses immediately to the opposite side, some fibers end in the cerebellum. The tract does not extend below the thoracic region.	Facilitatory influence over flexor muscle tone and inhibits extensor motor neurons. Thus it play a role in the control of posture of decorticate rigidity (page 954)
2. Tectospinal and tectobulbar tract	It originates from the ***superior colliculus*** (which is an optic centre); crosses at once to the opposite side. The tract descends upto the lower cervical region.	Mediate reflex postural movements in response to visual and auditory stimuli.
3. Reticulospinal tract	*Origin:* from neurons of the ***reticular formation*** in pons and medulla. (i) medial division *i.e.* fibers from the pontine reticular formation are mainly crossed (ii) lateral division *i.e.* medullary reticular fibers descend uncrossed.	(i) Facilitate (by pontine fibers) or inhibit (by medullary fibers) voluntary movement, mainly influence γ-motor neurons (Also see to page 958). (ii) Alteration in muscle tone, respiration and blood pressure.
4. Vestibulospinal tract	*Origin:* from ***lateral vestibular nucleus*** located at the junction of pons and medulla. It receives fibers from the vestibular division of VIII nerve. Both lateral and medial division descend uncrossed throughout the entire length of the spinal cord.	Facilitatory influence upon reflex activity in the spinal cord and upon the mechanism which control muscle tone (mainly extensor group *i.e.* antigravity group of muscles).
5. Medial longitudinal fasciculus (or bundle)	*Origin:* from the ***medial vestibular nucleus***, reticular formation, superior colliculus and interstitial nucleus of Cajal; the tract descend uncrossed upto upper cervical region.	Coordination of reflex ocular movements and integration of eye and neck movements.

(a) presynaptically on the axon terminals of afferent neurons as these fibers enter the CNS; or

(b) directly on the dendrites or cell bodies of neurons in the ascending pathways;

(v) Corticospinal fibers arising from the somatic sensory area (I and II) and parietal lobe association cortex are *concerned with sensory-motor coordination*. For example, aiming the hands towards an object and manipulating it, hand-eye coordination etc. Lesion of these areas causes defects in motor performance that are characterized by *inability to execute learned sequences of movements* such as eating with a knife and fork.

Functions of corticobulbar (corticonuclear) tracts

These are responsible for voluntary control of muscles of larynx, pharynx, palate, upper and lower face, jaw, eye etc. ***Pseudobulbar Palsy*** is a condition resulting in paralysis or weakness of the muscles which control swallowing, talking, tongue and lip movements due to bilateral lesion of these tracts.

B. EXTRAPYRAMIDAL TRACTS

Extrapyramidal system is made up of those areas in the CNS (other than the pyramidal and cerebellar system) that are concerned with muscular movement and posture. Its fibers have *many synapses* in their descending path with cells of the nuclear masses on the way which include: *nuclei of the cerebral cortex, basal ganglia, hypothalamus and nuclei of the reticular formation in the brain stem*. In the spinal cord the fibers form separate groups according to their site of origin (Table 92.1).

Functions of extrapyramidal tracts

1. Corticobulbar (corticonuclear) fibers *control the movement of the eye balls.*
2. They are responsible for *control of tone, posture and equilibrium* (rubrospinal for tone and posture; tectospinal for visuospinal reflex; vestibulospinal for the equilibrium). (Also see to page 943)
3. They *control complex movements* of the body and limb such as coordinated movements of arms and legs during walking.
4. They exert tonic inhibitory control over the lower centres. Their damage increases *rigidity* of the muscles, called *release phenomenon*.
5. If the pyramidal tracts are damaged, they can carry out voluntary movement to some extent.

C. PYRAMIDAL VERSUS EXTRAPYRAMIDAL TRACTS

The main differences between pyramidal and extrapyramidal tracts are given in Table 92.2.

Table 92.2: Major differences between pyramidal and extrapyramidal tracts

Pyramidal tracts	Extrapyramidal tracts
1. Origin (page 909)	1. Origin (page 912)
2. Its axons pass without relay to the spinal segmental levels where they form synapses with either interneurons in the dorsal horn or directly with the motor neurons themselves.	2. They have many synapses in their descending path with cells of nuclei of the striatum (caudate and putamen), the globus pallidus, the hypothalamus and the nuclei of the reticular formation.
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 more 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. Lesion of this tract produces 'spasticity' (page 996) in the muscles involved.	4. Its lesion produces 'rigidity' of the involved muscles.

Important Notes

1. Both pyramidal as well as extrapyramidal tracts cause effects on the motor neurons of the opposite side of the spinal cord.
2. Some pyramidal tract fibers end on interneurons that play important roles in posture, whereas the extrapyramidal tract fibers sometimes end directly on the α motor neurons to control discrete muscle movements. Because of this extra control mechanisms, loss of function resulting from damage to one system may be compensated for by the remaining system, although the compensation is generally not complete.
3. A total separation of *structure and function* between pyramidal and extrapyramidal tract is not clear cut, therefore, all movements, whether automatic or voluntary require the continuous coordinated interaction of both the systems. (Fig. 92.9)

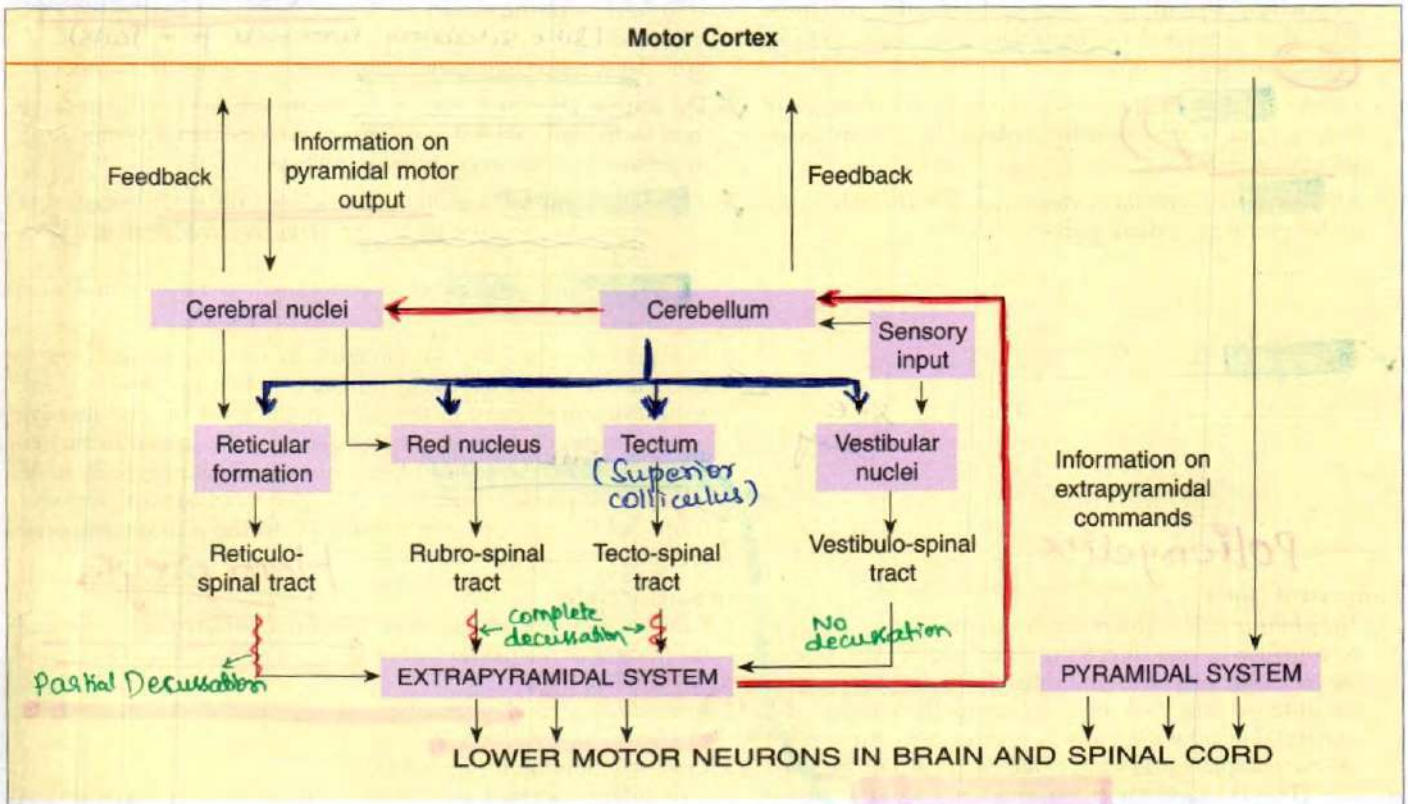


Fig. 92.9 Summary: Important interconnections and tracts of the pyramidal and extrapyramidal systems.
Note the central role played by the cerebellum.

APPLIED ASPECT

A. LOWER VERSUS UPPER MOTOR NEURON LESION (Table 92.3)

B. LESION OF THE PYRAMIDAL TRACTS: *HEMIPLEGIA*

This condition gives rise to marked weakness or paralysis on the opposite side of the body due to injury to the pyramidal tracts in the brain. In general, there is both weakness and loss of voluntary movements associated with *spasticity*. *Commonest site* of lesion to the pyramidal tract is in the internal capsule (page 909).

Characteristic features

Acute stage

1. *Initially* a *stage of shock* in which all the muscles of the opposite side are toneless (hypotonic) and in which no reflex movements can be aroused (*flaccid paralysis*). The condition resembles *spinal shock* (page 931). This is a temporary stage, since two or three weeks later good recovery occurs.
2. The paralysis on the affected side affects voluntary movements of the face, leg and arm. The hand is most severely affected and discrete movements of the fingers are lost (*permanent loss*).
3. Movements which usually involve both sides of the body such as those of respiration, movements of the head, trunk, and abdominal wall, are generally retained. This is because one pyramidal tract can control the lower motor nuclei supplying the muscles concerned on both sides.
4. If the corticonuclear fibers escape injury, eyeball movements persist.

Table 92.3: Differences between lower and upper motor neuron lesion

Lower motor neuron lesion (LMNL)	Upper motor neuron lesion (UMNL)
1. It is due to lesion of the *lower motor neurons* (LMNs) *i.e.* the spinal and cranial motor neurons that directly innervate the muscles (Fig. 92.10)	1. It is due to lesion of the *upper motor neurons* (UMNs) *i.e.* the neurons in the brain and spinal cord that can influence the activity of LMNs; major cause being lesion of pyramidal tracts.
2. Here usually single or individual muscle is affected.	2. It involves a group of muscles.
3. Muscle becomes hypotonic and completely paralysed (***flaccid paralysis***). This is due to complete loss of muscle tone which depends on integrity of the reflex arc. There may also associated ***fasciculations***, i.e. visible muscle twitches under the skin.	3. Affected muscles due to pyramidal tract lesion become hypertonic (***spastic paralysis***). This is due to: (i) release phenomenon *i.e.* loss of higher inhibitory control; and (ii) denervation hypersensitivity of centres below the transection.
4. ***Disuse atrophy*** of the muscle occurs *i.e.* shrinkage of muscle fiber which is finally replaced by fibrous tissue (***fibrous muscle***).	4. The muscle atrophy is not severe (if present, very mild) because muscles though not used in voluntary movements are continuously in action to maintain posture by 'reflexes'.
5. All ***reflexes*** (superficial or deep) are ***absent (lost)*** as the motor pathway is damaged.	5. (i) ***Deep reflexes*** are ***hyperactive*** (accentuated) because of increased γ-motor discharge (***Hyperactive stretch reflex***); and (ii) superficial reflexes; only abdominal, cremastric and anal reflexes are lost.
6. *Babinski sign not elicited.*	6. **Babinski sign:** ***elicited*** **(abnormal).** In UMNL, stroking outer edge 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 (Anatomists misleadingly call it an 'extensor response'), *physiologically a 'flexor' (withdrawal) response.* (*Note:* All the muscles which contract during a flexor response are called *physiological flexors.*)
Important Notes 1. ***The plantar reflex:*** The reflex is obtained by stroking (to pass gently in one direction) outer edge of the sole of the foot with firm tactile stimulus (from the heel towards the little toe and then medially across the metatarsals). In normal healthy individuals, it produces a downward movement (plantar flexion) of the great toe and the small toes (This is called the ***flexor plantar response***). This is due to contraction of flexor hallucis longus (Fig. 92.11). 2. This flexor plantar response appears with the development of the pyramidal tracts. Therefore, its presence indicates the development of these tracts.	**Important Notes** 1. Babinski sign if once becomes abnormal, will remain abnormal for the rest of the life thereafter. In some normal individuals it is always abnormal. 2. Individuals with abnormal Babinski sign neither can run fast nor can travel long distances. 3. ***Causes of abnormal Babinski sign:*** (i) Infants (below 1 year of age) as the pyramidal tracts are not developed till child starts walking. (ii) During deep sleep. (iii) Inhibition of pyramidal tracts. (iv) Cheyne-stokes respiration due to hypoxia (page 451)

5. Emotional movements remain intact and are very strong. For example, the muscles of facial expression though paralysed for voluntary movements, yet these muscles are employed perfectly when the patient's face expresses pleasure, surprise or irritation.
6. All reflexes (superficial or deep) are lost.

Stage of recovery

Some two or three weeks later reflex activity returns to the affected side of the body, showing that such reflexes can be mediated by the *isolated* lower levels.

1. *Muscle tone and posture.* The affected muscles become *spastic*, therefore, the limbs are placed in an abnormal position and tend to be fixed there.
   (i) The upper limb is adducted at the shoulder, the elbow is semiflexed, the forearm is pronated, and the wrist and fingers are flexed. The limb remains in this position indefinitely without fatigue. It can only be moved passively with difficulty.
   (ii) The leg is adducted, extended at the knee and ankle (plantar flexion).
2. *Associated reactions.* These are *semi-voluntary movements* which can be 'reflexly' aroused on the affected side by any forceful sustained voluntary muscular contraction on the normal side. These are further modified by *neck reflexes* (i.e. by the position of the head relative to the trunk). For example, in a hemiplegic subject, when the normal fist is clenched, the spastic arm moves slowly into increased flexion at elbow, wrist and digits. If the procedure is repeated with the head rotated towards the hemiplegic side, the spastic arm moves into extension and abduction.
3. *Deep or tendon reflexes.* In hemiplegia there is commonly increased extensor tone. The tendon jerks (like knees, ankle, biceps, triceps) are hyperactive (exaggerated), and are more sustained i.e. relaxation is still further prolonged. 'Knee and ankle clonus' (page 880) is often present.
4. *Superficial reflexes.* The superficial reflexes commonly tested are:
   (i) *abdominal reflex:* stroking the skin of the abdomen produces contraction of the underlying muscle.
   (ii) *Cremasteric reflex:* stroking the inner side of the thigh results in the testis being retracted towards the inguinal canal.
   (iii) *Plantar reflex* see above.

   All the superficial reflexes are lost on the affected side because they are mediated by the pyramidal tract. In some hemiplegic, noxious stimulation of the sole of the foot produces a more extensive reaction; there may be dorsiflexion of the ankle, flexion of the knee, and even flexion of the hip.
5. *Disturbances in voluntary movements.* Considerable improvement occurs in the leg and patient may walk about with a slight limp; a good degree of power returns to the arm and face.
6. *Gait* (way of walking). The patient walks on a narrow base, has difficulty in bending his knees and drags his feet along as if they were glued to the floor. This is referred as *spastic (hemiplegic) gait* (Fig. 9

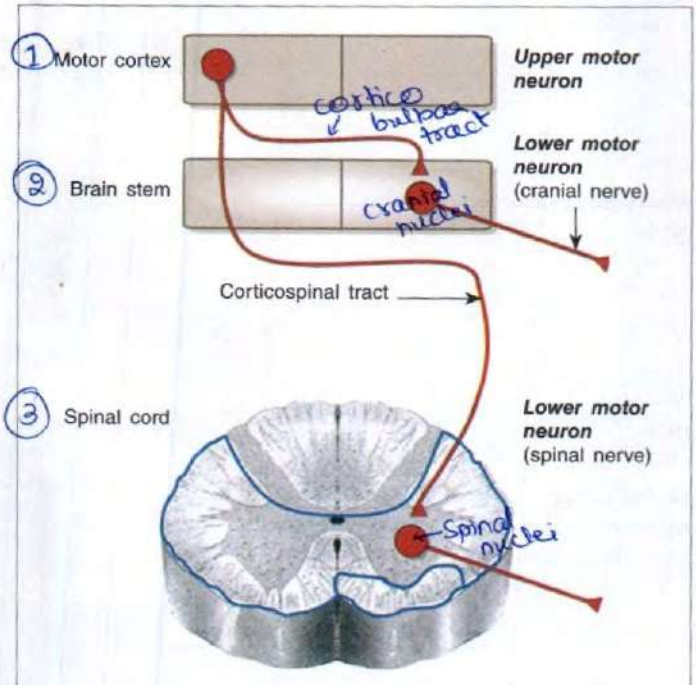


Fig. 92.10 Lower and upper motor neuron

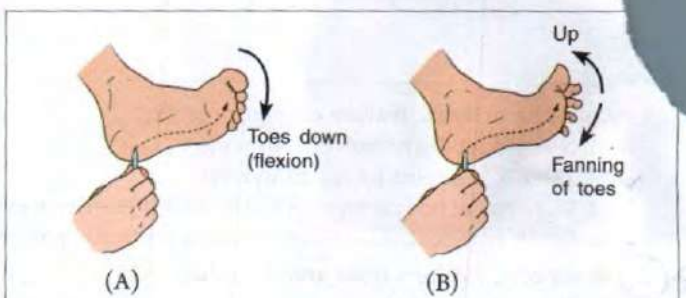


Fig. 92.11 Testing plantar response (A) Normal plantar response; (B) Extensor plantar response (Babinski sign)

Fig. 92.12 Spastic (hemiplegic gait)

The recovery is partly due to:

(i) restoration of function to temporarily damaged pyramidal fibers, and

(ii) to the more effective use of extrapyramidal pathways arising in the cortex.

Other types of Gaits:
- Waddling gait
- High Step gait
- Drunken gait
- festinent gait
- Tandem walking
- Ramp walking

Study Questions

1. **Differentiate between:**
   (i) Main and supplementary motor area.
   (ii) Pyramidal and extrapyramidal tracts functions.
   (iii) Lower and upper motor neuron paralysis.
   (iv) Lateral and anterior corticospinal tracts.
   (v) Corticobulbar and corticospinal tracts.
2. **Give origin and functions of pyramidal and extrapyramidal tracts.**
3. **Diagrammatically show the arrangement of pyramidal tract fibers in the internal capsule. Mention characteristic features of a lesion of the internal capsule.**
4. **Describe how skilled movements are planned and carried out.**
5. **Enumerate the major salient features of pyramidal tracts.**
6. **Explain sensory-motor coordination.**
7. **How can pyramidal tracts affect the sensory system? Explain.**
8. **To what extent does the loss of functions resulting from damage to one major motor system get compensated for by the other system?**
9. **Give physiological basis of positive Babinski sign. Is it a flexor or extensor response?**
10. **List the causes of abnormal Babinski plantar response. Give its clinical significance.**
11. **Define hemiplegia. Give its characteristic features during acute stage.**
12. **Draw a well labelled diagram pathway of pyramidal tract.**

Write short notes on

(i) Motor areas
(ii) Lower and upper motor neuron
(iii) Apoplexy/stroke
(iv) Corticospinal tracts
(v) Testing plantar response

MCQs

1. ***Not* a characterisic feature of motor cortex:**
   (a) Inverted representation of body parts
   (b) There is large area for hands and feet
   (c) Right half of body is represented in the left precentral gyrus
   (d) Face is represented in the most inferior portion of precentral gyrus
2. **Motor area 6 differs from area 4 in that:**
   (a) Give origin to pyramidal tracts
   (b) Give origin to extrapyramidal fibers
   (c) Receive inputs from the somatic sensory area I and II
   (d) Control discrete isolated movements of the opposite side of the body
3. **The percentage of pyramidal fibers which are <1 µm in diameter:**
   (a) 25-30 (b) 45-50 (c) 65-70 (d) 85-90
4. **Anterior 2/3rd of posterior limb of internal capsule has all the following *except*:**
   (a) Sensory fibers from thalamus to brain
   (b) Motor fibers from lower limb
   (c) Motor fibers from upper limb
   (d) Motor fibers from trunk
5. ***Not a true* statement about pyramidal tract:**
   (a) Anterior corticospinal tract contains fibers from ipsilateral motor cortex
   (b) Lateral corticospinal tract contains 80-85% of pyramidal fibers
   (c) It is so called as its fibers originate from pyramidal cells
   (d) Its stimulation causes presynaptic inhibition of cutaneous afferents

third and the fourth lumbar vertebrae. Histological and biochemical study of CSF gives an indication about various disease processes affecting the CNS.

CSF changes in common disorders are as follows:

- **Pressure:** It is increased in subarachnoid hemorrhage, acute bacterial meningitis, and tuberculous meningitis.
- **Color:** It is blood stained in subarachnoid hemorrhage and cloudy in acute bacterial meningitis and tuberculous meningitis.
- **RBC:** RBC count is increased in subarachnoid hemorrhage.
- **Glucose:** It is decreased in acute bacterial meningitis and tuberculous meningitis.
- **Proteins:** They are increased in subarachnoid hemorrhage, acute bacterial meningitis, viral meningitis, multiple sclerosis, and tuberculous meningitis.
- **Microorganisms:** They are demonstrated in infective meningitis.

BLOOD–BRAIN BARRIER

Blood–brain barrier is a hypothetical barrier present between the brain and the blood. It selectively permits the passage of substances from the blood to the brain and vice versa. Thus, it is a protective mechanism maintaining stable environment for the brain.

The blood–brain barrier does not cover the vomiting center and hypothalamus. It is incomplete in newborns and premature infants; hence, toxic substances can enter CNS and cause damage.

Localized breakdown of the blood–brain barrier is reported following injury to brain.

Oxygen, carbon dioxide, glucose, water, amino acids, electrolytes, fats, fatty acids, fat-soluble molecules, and drugs such as sulfonamides and tetracycline cross this barrier.

Hence alcohol, nicotine, and anesthetics present in blood can affect the brain.

Blood-borne metabolic wastes, proteins, toxins, and most of the drugs cannot cross the blood–brain barrier.

Potassium and nonessential amino acids are prevented from entering the brain. In addition, they are actively pumped out from the brain.

Structure of Blood–Brain Barrier

- The capillaries of the brain consist of endothelial lining which has tight junctions. These junctions close the pores in blood vessels.
- Astrocytes completely cover the capillaries and make them less porous.
- Blood vessels in the brain have a thick basement membrane. They prevent the passage of substances across them.

Functions of Blood–Brain Barrier

- Maintains constancy of environment for the neurons in CNS
- Protects brain from the effect of endogenous toxins
- Prevents the escape of neurotransmitters from the CNS

Inflammation, irradiation, and tumors destroy the blood–brain barrier. This permits free entry to the substances, toxins, and drugs that do no[t] barrier under normal conditions.

Lipid-soluble drugs cross the blood–brain b[a]rrier freely when compared to water-soluble drugs.

Circumventricular Organ

The areas of brain located outside the blood–brain barrier are called circumventricular organs, which are as follows:

- Posterior pituitary
- Median eminence of hypothalamus
- Subfornical organ
- Area postrema
- Organum vasculosum of lamina terminalis

	Subarachnoid Haemorrhage	Bacterial Acute ⊕ Tuberculo Meningitis
· Pressure	↑	↑
· Colour	Stained	cloudy
· RBC	↑	-
· Glucose	-	↓
· Proteins	↑	↑
· Microorg.	-	↑

Anomic Aphasia It is the difficulty to understand the written language and pictures due to lesion in the angular gyrus of the categorical hemisphere. The visual information is not analyzed and transmitted to Wernicke's area.

Global Aphasia It is a condition in which Wernicke's area and Broca's area are damaged. The individual lacks the ability to speak, write, or understand the language.

Dyslexia

Dyslexia is an inherited abnormality characterized by the impaired ability to read. The subject has a reduced ability to recall speech sounds or has trouble in translating mentally into sound units.

Slurring or Scanning Speech

Slurring is seen in conditions of cerebellar dysfunction. There is a defect in skilled movements involved in production of speech. ■

CEREBROSPINAL FLUID

Cerebrospinal fluid (CSF) is a specialized extracellular fluid. It is present in the ventricles of the brain, central canal of the spinal cord, and subarachnoid space.

...on and Circulation of CSF

...id plexus of the lateral and the third ventricle of ...s CSF by the processes of filtration and secretion. ...s through the fourth ventricle and the central canal ... the spinal cord. CSF in the ventricles flows through the foramens of Magendie and Luschka to the subarachnoid space. Constant motion of CSF is facilitated by the movement of cilia of ependymal cells lining the ventricles. It gets absorbed through the arachnoid villi present in sagittal sinus.

Composition and Properties of CSF

CSF is a colorless, transparent fluid with a specific gravity of 1005.

It is alkaline in reaction.

The volume of CSF is about 150 mL. (About 500 mL of CSF is produced per day.) The normal CSF pressure is 5–15 mm Hg.

CSF contains 99% water and 1% solids.

The organic constituents are amino acids, sugar, proteins, cholesterol, urea, uric acid, and creatinine.

The inorganic constituents are sodium, calcium, potassium, magnesium, chlorides, bicarbonates, and phosphates.

Functions of CSF

- Acts as a cushion between the brain and the rigid cranium
- Supports the weight of brain. The net weight of brain in CSF is about 50 g as compared to its weight of 1400 g in air.
- Prevents the brain from crushing under its own weight by significantly reducing its weight
- Distributes force of blows on the head
- Maintains intracranial pressure by balancing the volume of blood and CSF
- Drains metabolites from the brain
- Supplies nutrients and oxygen to the brain
- Carries chemical signals such as hormones and sleep-inducing substances from one part to the other part in brain

■ *Clinical Notes*

(A) *Hydrocephalus*

Hydrocephalus is a condition of increased intracranial pressure due to defective absorption or circulation of CSF. The baby shows enlargement of the cranial cavity and associated damage to the brain because of pressure effect.

It is of two types:

1. External or communicating hydrocephalus
2. Internal or noncommunicating hydrocephalus

(A) In communicating hydrocephalus, a large quantity of CSF accumulates due to defective reabsorption by arachnoid villi.

Blockage of foramens of Magendie and Luschka results in accumulation of CSF proximal to the block, thus distending the ventricles. This results in (B) noncommunicating hydrocephalus.

In adults, tumors can obstruct the circulation and drainage of CSF. Hydrocephalus can result in brain damage. Accumulating fluid compresses the soft nervous tissue and blood vessels as the skull is rigid and hard.

Hydrocephalus is treated by draining the excess fluid through a shunt from ventricles to veins in the neck.

(B) *Lumbar Puncture*

Lumbar puncture is a procedure by which CSF is taken out from the subarachnoid space. Normally, CSF is drawn by introducing a needle between the

6. **Lateral corticospinal tracts differs from anterior ones by:**
   (a) Being uncrossed
   (b) Control fine, precise voluntary movements of fingers and hands to carry out skilled work
   (c) Control trunk and proximal limb muscles to carry out posture and gross movements
   (d) Form pathways for superficial reflexes

7. ***Not a true* statement for extrapyramidal tracts:**
   (a) Originate from the cerebellum
   (b) A polysynaptic descending path
   (c) Play an important role in maintenance of upright body posture
   (d) Its lesion produces rigidity of affected muscles

8. ***Not* a function of extrapyramidal tracts:**
   (a) Responsible for control of muscle tone, posture and equilibrium
   (b) Control the movements of eye balls
   (c) Control coordinated movements of arms and legs during walking
   (d) Exert tonic excitatory control over the lower centres

9. **Pure pyramidal tract lesion results in impairment of movements of:**
   (a) Head (b) Shoulder girdle (c) Fingers (d) Trunk

10. **Lower motor neuron lesion is characterized by all *except*:**
    (a) Usually a single muscle is involved (b) Flaccid paralysis
    (c) Muscle atrophy is not severe (d) Deep reflexes are absent

11. ***Not* a cause of abnormal Babinski sign:**
    (a) In infants (b) During deep sleep
    (c) Inhibition of pyramidal tracts (d) A normal healthy individual

12. **An individual with abnormal Babinski sign:**
    (a) Neither can run fast nor can travel long distance (b) Associated with extrapyramidal tract lesion
    (c) Indicative of fully developed corticospinal tract (d) Is normal

13. **Following hemiplegia, reflex activity returns after:**
    (a) 1-2 days (b) 7-10 days (c) 2-3 weeks (d) 2-3 months

14. **Lower motor neuron lesion is characterized by:**
    (a) Loss of voluntary movements but preservation of reflex movements
    (b) If long standing, associated with involuntary contraction of small fasciculi in the affected muscles (Rigidity)
    (c) Is a later stage in development of upper motor neuron lesion
    (d) If long standing, is typically associated with wasting of affected muscles (Atrophy)

15. **Giant Betz cells in brain are found in:** (Origano pyramidalis)
    (a) Motor cortex (b) Thalamus (c) Hypothalamus (d) Sensory cortex

16. **Supplementary motor area:**
    (a) Located on the medial surface of cerebral hemisphere above the cingulate sulcus
    (b) Exhibit point to point representation of body parts
    (c) Primarily involved in voluntary complex movements which involve planning
    (d) All of the above

17. **Major suppressor area that inhibits the stretch reflex is:**
    (a) 2 s (b) 4 s (c) 8 s (d) 19 s

18. ***Not a true* statement about pyramidal tracts:**
    (a) Spinal ventral horn cells constitute the corticospinal tract
    (b) Motor cranial nuclei constitute corticobular tracts
    (c) Maximum percentage of its fibers originate from the ~~somatosensory~~ motor cortex
    (d) Its cells constitute the lower motor neurons

19. **Pyramidal tracts originate in:**
    (a) Somatosensory cortex (b) Premotor cortex (c) Motor cortex (d) All of the above

20. **Percentage of sensory fibers in a pure motor nerve is:**
    (a) 5 (b) 10 (c) 20 (d) 40

21. **During the descent of pyramidal tracts, point to point discrimination of body parts occurs in the substance of:**
    (a) Internal capsule (b) Midbrain (c) Pons (d) Medulla

22. **The percentage of pyramidal fibers making direct synaptic connections with motor neurons:**
    (a) 5-10 (b) 15-20 (c) 25-30 (d) 35-45

23. **Of all the pyramidal fibers:**
(a) 55% end in cervical region
(b) 40% end in thoracic region
(c) 5% end in lumbosacral region
(d) All of the above are true

24. **Most common site of lesion to the pyramidal tracts:**
(a) Internal capsule (d) Midbrain (c) Pons (d) Medulla

25. **Pre-central gyrus and corticospinal tracts are required for:**
(a) Voluntary movement
(b) Position sense appreciation
(c) Orientation in time and place
(d) Stereognosis and spatial skills

26. **Apoplexy means:**
(a) Injury to motor area 4
(b) Paralysis on one side of the body
(c) Paralysis of both the lower limbs
(d) Sudden attack of paralysis

27. **Pseudobulbar palsy:**
(a) Leads to paralysis or weakness of muscles that control swallowing and tongue movements
(b) Results following injury to extra-pyramidal tracts
(c) Seen as a consequence of cortico-spinal tract injury
(d) All of the above

28. **Body posture and complex coarse movements are controlled mostly by:**
(a) Cerebrum (b) Cerebellum (c) Spinal cord (d) Extrapyramidal system

29. **Extrapyramidal tract includes all *except*:**
(a) Rubrospinal tract (b) Tectospinal tract (c) Corticospinal tract (d) Medial longitudinal fasciculus

★ 30. **Which part of brain helps supporting the body against gravity?**
(a) Superior colliculus (b) Medial longitudinal bundle (c) Vestibular nuclei (d) Red nucleus
Medial

31. **Lower motor neurons (LMNs) are:**
(a) Neuron located at the level of medullary pyramid
(b) Neurons in the cerebellum that are concerned with muscular movements
(c) Neurons that give rise to pyramidal system
(d) Spinal and cranial motor neurons that directly innervate the muscles

32. **Transection at the level of medullary pyramids leads to:** (UMNL)
(a) Flacidity (b) Positive grasping reflex (c) Abnormal Babinski's sign (d) Hypotonia

33. **Following hemiplegia, reflex activity returns after:**
(a) 1-2 days (b) 7-10 days (c) 2-3 weeks (d) 2-3 months

Answers

1. (b) 2. (b) 3. (d) 4. (a) 5. (c) 6. (b) 7. (a) 8. (d) 9. (c) 10. (c) 11. (d) 12. (a) 13. (c) 14. (d) 15. (a)
16. (d) 17. (b) 18. (d) 19. (d) 20. (d) 21. (a) 22. (b) 23. (a) 24. (a) 25. (a) 26. (d) 27. (a) 28. (d) 29. (c) 30. (c)
31. (d) 32. (c) 33. (c)

Chapter 93

The Autonomic Nervous System

I. Difference between Somatic and Autonomic Nervous System (ANS)

II. Organization of the ANS
A. Sympathetic division
B. Parasympathetic division

III. Chemical transmission at autonomic junctions

IV. Responses of effector organs to autonomic nerve impulse

The innervation of all tissues other than skeletal muscle is by way of the autonomic nervous system (ANS). It regulates the activity of smooth muscles, heart, glands of GIT, sweat glands, adrenal gland and of certain endocrine organs. Its *main aim* is to maintain the optimal internal environment of the body (page 3). Thus it governs the body functions which are normally carried out without conscious control or awakeness. This is why ANS is also called ***Vegetative*** or ***Efferent visceral*** or ***Involuntary nervous system***. (*Vegetative* because it is concerned with growth *i.e.* vegetative aspects of the day-to-day living.)

DIFFERENCE BETWEEN SOMATIC AND ANS

The major differences between the somatic and ANS are given in Table 93.1 and shown in Fig. 93.1.

ORGANIZATION OF THE ANS

Based on anatomical and physiological differences, the ANS is divided into two divisions: *sympathetic and parasympathetic*.

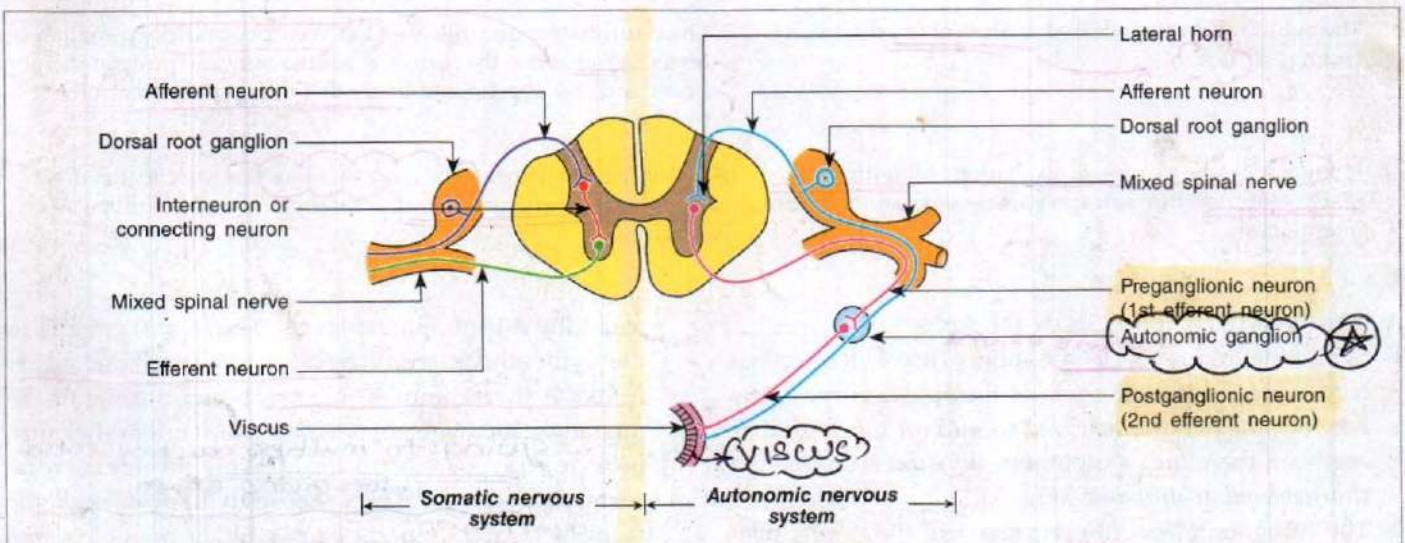


Fig. 93.1 General arrangement of somatic nervous system (left) and autonomic nervous system (right)

Important Note

Multiple System Atrophy (MSA) is a neurodegenerative disorder associated with autonomic failure due to loss of pre-ganglionic autonomic neurons in the spinal cord and brain stem. This results in difficult to regulate body temperature, fluid and electrolyte balance and blood pressure. In addition there may be associated cerebellar and basal ganglia dysfunction.

Table 93.1: Somatic and Autonomic nervous system (ANS) compared

Somatic nervous system	Autonomic nervous system
1. In somatic polysynaptic pathway at least 'three' neurons are involved. (i) *Afferent (sensory) neuron* with its cell body in the dorsal root ganglion. (ii) *An interneuron (connector neuron)* in the dorsal horn of the grey matter which by means of its axon transmits the impulses to the efferent neuron. (iii) *Efferent (motor) neuron* i.e. ventral horn cell with its axon which transmits the motor impulses to the skeletal muscle (effector organ).	1. In autonomic nerve supply to viscera, 'three' neurons can also be recognized. (i) Afferent (sensory) neuron proceeding from an internal organ. Its cell body lies in the dorsal root ganglion (or its cranial equivalent) and a central process is sent into the grey matter. (ii) Interneuron called ***preganglionic neuron*** whose cell body is situated in the 'intermediolateral' column of spinal cord (also called 'lateral horn'). Its axon synapses on the cell body of postganglionic neuron. (iii) ***Postganglionic neuron***, whose cell body is always located outside the CNS and its axon ends on the visceral effector. (Each preganglionic axon diverges to an average of 8-9 postganglionic neuron, therefore, ***autonomic output is diffuse***.)
2. It consists of 'single' efferent neuron between CNS and effector organ.	2. It has 'two' efferent neuron chains between CNS and the effector organ; the 1st efferent neuron has its cell body in the CNS.
3. The nerve fiber of efferent neuron leaves the CNS and passes without any synapse to the skeletal muscle.	3. The synapse between the two efferent neurons lies outside the CNS in a cell cluster called *autonomic ganglion*. The nerve fibers passing between the CNS and the ganglia are called *preganglionic* autonomic fibers (myelinated, B group of fibers); those passing between the ganglia and the effector cells are the *postganglionic* fibers (non-myelinated, C group of fibers).
4. It innervates skeletal muscle.	4. It innervates smooth and cardiac muscles, glands and GIT neurons.
5. The neurotransmitter released at efferent (motor) neuron endings is A-ch.	5. The neurotransmitter released between pre and postganglionic fibers is A-ch while the neurotransmitter between postganglionic fibers and the effector cell depends on the component of ANS (see below).
6. It always leads to muscle excitation; inhibition takes place 'centrally' through the participation of inhibitory interneurons.	6. It can lead to either excitation or inhibition of effector organ; inhibition occurs peripherally through a direct influence on effector

A. SYMPATHETIC DIVISION OF ANS

1. Sympathetic preganglionic fibers leave the spinal cord with the ventral roots of the spinal nerves only between the first thoracic and second (or third) lumbar segment, therefore, sympathetic division is also called ***thoracolumbar division***. (Fig. 93.2)
2. The preganglionic fibers pass via the *white rami communicantes* to the paravertebral sympathetic ganglia which lies close to the spinal cord. These ganglia form the two chains of ganglia, one on each side of the cord called *sympathetic trunk*. Most of the preganglionic fibers end on the cell bodies of the postganglionic neurons in the sympathetic chain.
3. The sympathetic trunk extends the entire length of the spinal cord from the cervical levels high in the neck down to the sacral levels. The 'extra' ganglia in the sympathetic trunk receives preganglionic fibers from the thoracolumbar regions because some of the preganglionic fibers, once in the paravertebral chains, turn to travel upward or downward for several segments before forming synapses with postganglionic neurons (Fig. 93.3; parts 1 to 4). Other possible paths taken by the sympathetic preganglionic fibers are shown in (Fig. 93.3, parts 2, 3 and 5).
4. The postganglionic fibers:
   (i) pass to the viscera in the various sympathetic nerves;
   (ii) others re-enter the spinal nerves via the *grey rami communicantes* from the chain ganglia and are distributed to the autonomic effectors in the areas

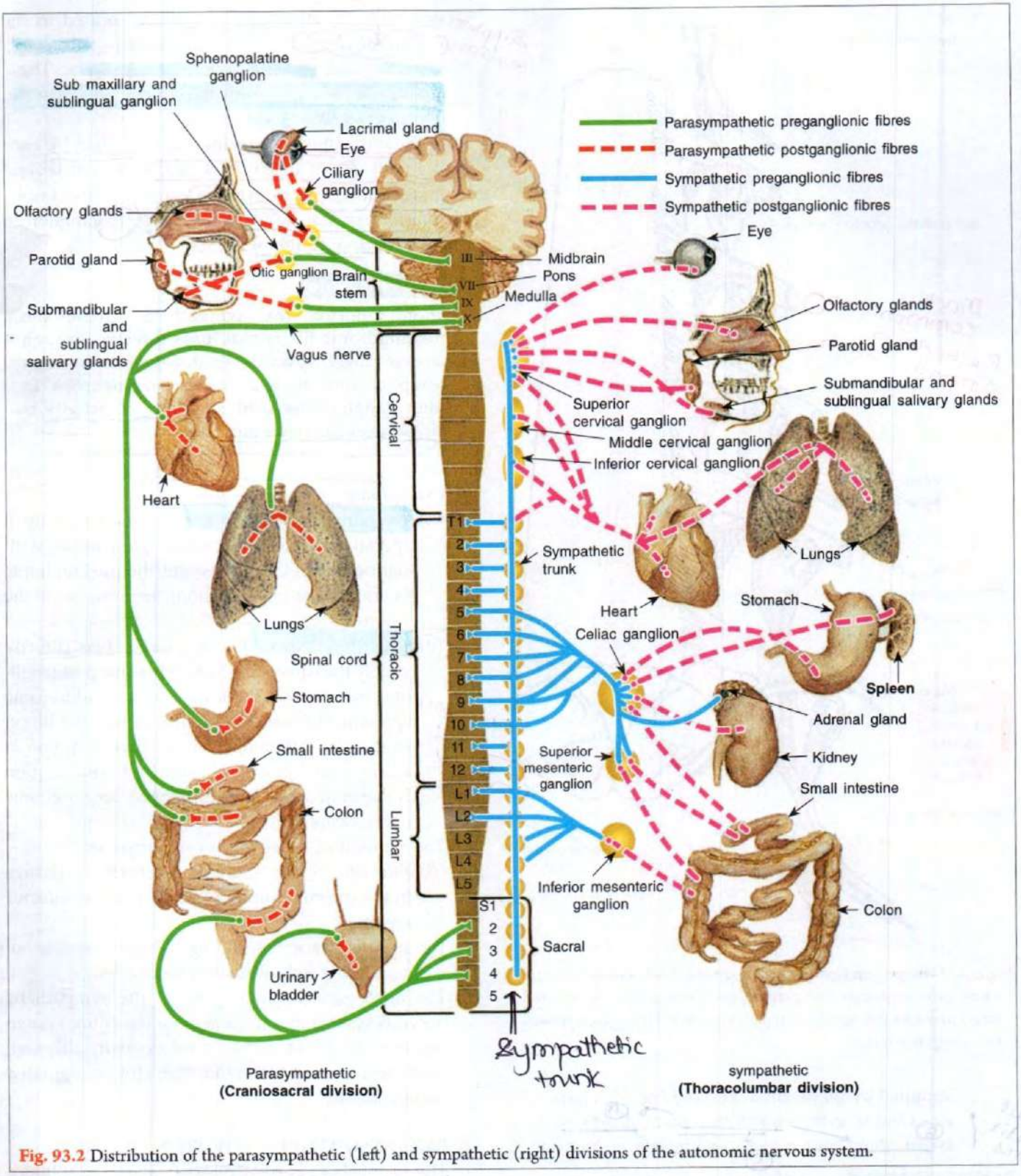


Fig. 93.2 Distribution of the parasympathetic (left) and sympathetic (right) divisions of the autonomic nervous system.

Notes

1. Inferior cervical ganglion fused with T_1 ganglion to form 'Stellate' ganglion
2. Preganglionic sympathetic fibres directly supply the adrenal medulla gland.

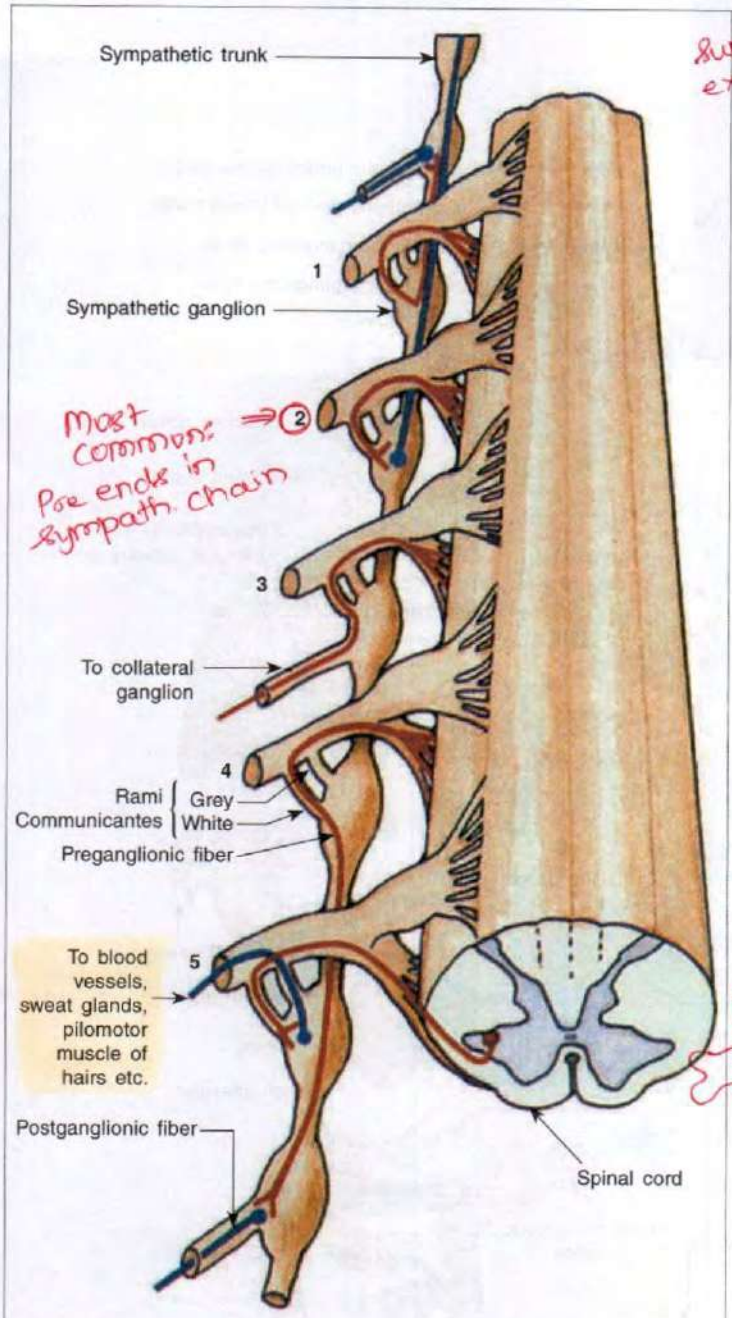


Fig. 93.3 Relationship between a sympathetic trunk and spinal cord. (1-5) various courses that preganglionic sympathetic fibers (red lines) may take through the sympathetic trunk. Blue lines represent postganglionic fibers.

supplied by these spinal nerves (Fig. 93.3, part 5); for example, to the smooth muscles of blood vessels, sweat gland and piloerector muscle of hair, etc.

Important Note

Approx. 80% of the fibers in the average skeletal nerve are sympathetic fibers.

5. Some preganglionic fibers pass through the paravertebral ganglion chain (sympathetic trunk) and end on the postganglionic neurons located in the *collateral ganglia* (*prevertebral ganglia*) – the coeliac, superior and inferior mesenteric ganglia. These ganglia lie far away from the spinal cord, closer to the innervated organs.
6. In the sympathetic chain, there is a ganglion for each segment except in the neck region, where several ganglia merge to form large ganglia. For example, inferior cervical ganglion fuse with T_1 ganglion to form ***stellate ganglion***.

Important Note

Upon entering the sympathetic chain, the preganglionic fibers may pass directly through or else travel upwards or downwards to form synaptic contacts with ganglionic neurons in other ganglia, therefore, sympathetic activity is spread over many segments.

7. *Exceptions*
   (i) *Myometrium of the uterus* is innervated by a special system of ***short adrenergic neurons***, with cell bodies in the uterus and the preganglionic fibers to these postganglionic neurons go all the way to uterus.
   (ii) *In adrenal medulla,* preganglionic fibers directly supply the adrenal medulla, where the postganglionic neurons have lost their axons and become specialized for secretion directly into the blood stream. It is, therefore, not really a ganglion at all, it is an 'endocrine gland' whose secretion is controlled by the sympathetic preganglionic nerve fibers.
8. The sympathetic ganglia can act either as:
   (i) *automatic relay stations* with practically no change in the information they transmit to the effector organ; or
   (ii) as important *integrating centers* capable of generating individualized responses.

The anatomical arrangements in the sympathetic nervous system to some extent tie the entire system together so it can act as a single ***unit***, although small segments of the system can still be regulated independently.

B. PARASYMPATHETIC DIVISION OF ANS

1. The nerve fibers of this division leave the CNS from the brain and the sacral portion of the spinal cord, therefore, it is also called the ***Craniosacral division***. Here the synapse between the pre and postganglionic neurons occur in the parasympathetic ganglia which are located within or near the effector organs (*exceptions:* sphenopalatine and otic ganglia).

2. *Cranial outflow.* It supplies the visceral structures in the head via the oculomotor (III) nerve; facial (VII) nerve and glossopharyngeal (IX) nerve; and those in the thorax and upper abdomen via vagus (X) nerve.

Note

Approx. 75% of all parasympathetic nerve fibers are in the vagus (X) nerve.

3. *Sacral outflow.* It supplies the pelvic viscera via the pelvic branches of the 2nd to 4th sacral spinal nerves.

Important Notes

1. In sympathetic division of the ANS, preganglionic fibers are short and postganglionic fibers are long; while in parasympathetic division, preganglionic fibers are long and postganglionic fibers are short.
2. In both the divisions, the preganglionic autonomic fibers are myelinated, B group of fibers whereas the postganglionic autonomic fibers are non-myelinated, C group of fibers.

CHEMICAL TRANSMISSION AT AUTONOMIC JUNCTIONS

1. In both sympathetic and parasympathetic divisions, the major neurotransmitter released between pre and postganglionic fibers is A-ch (Fig. 93.4).
2. In the parasympathetic division, the main neurotransmitter between the postganglionic fibers and the effector cells is also A-ch.
3. In the sympathetic division, the main transmitter between the postganglionic fibers and the effector cells is usually nor-epinephrine (NE).

Important Note

A-ch is released by some sympathetic postganglionic endings (page 332). Moreover, one or more substances known as *cotransmitters* are usually stored and released with the autonomic neurotransmitters; for example – VIP is released with A-ch; ATP and neuropetide Y with NE (page 1050).

4. On the basis of the chemical transmitter released, the neurons in the entire nervous system are either *cholinergic or adrenergic.*
   (i) *Cholinergic neurons i.e.* neurons which secrete A-ch at their nerve endings. Examples include:
      (a) all preganglionic autonomic (parasympathetic as well as sympathetic) endings
      (b) postganglionic parasympathetic endings
      (c) postganglionic sympathetic endings which innervate sweat glands, skeletal muscle blood vessels *i.e. sympathetic vasodilator* nerves
      (d) neuromuscular junction
      (e) many parts of the brain (specially cerebral cortex [page 1040], thalamus [PGO spike page 986] and forebrain nuclei [page 1027])
      (f) endings of some amacrine cells in the retina (page 1110).
   (ii) *Adrenergic neurons i.e.* neurons which secrete NE or epinephrine at their nerve endings. *Examples:*

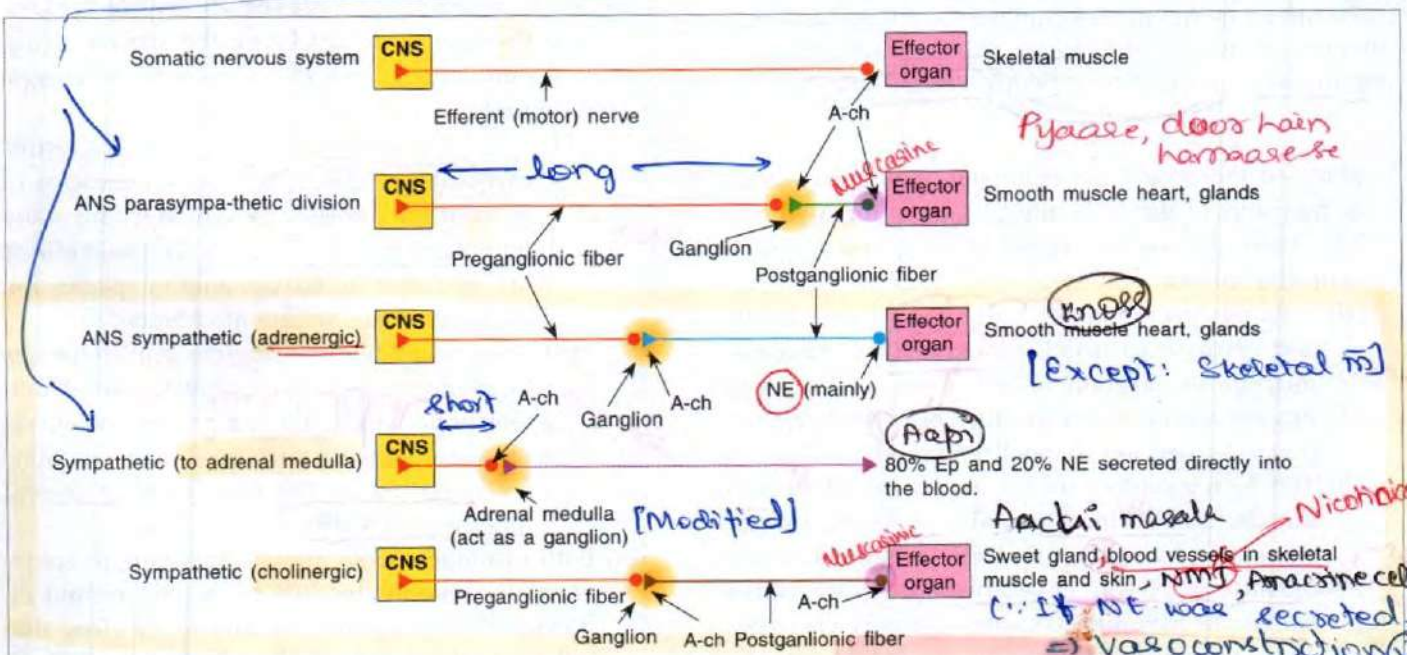


Fig. 93.4 Transmitter used in various components of the peripheral nervous system (Ep: Epinephrine, NE: Nor-epinephrine)

Summary: Adrenergic and Cholinergic receptors in the ANS

Receptor	Location	Response	Mechanism
Adrenergic Receptors			
α_1	Widespread, found in most tissues; not in the heart.	Excitation, stimulation of metabolism.	Activation of enzymes (especially phospholipase C), release of intracellular Ca^{2+}.
α_2	Sympathetic and parasympathetic neuroeffector junctions.	Inhibition of neurotransmitter release.	Reduction in cAMP concentrations.
β_1	Heart, kidneys, liver, adipose tissues.	Stimulation, increased energy consumption.	Enzyme activation.
β_2	Smooth muscles in vessels of heart and skeletal muscle, intestinal muscles, lungs and bronchi.	Inhibition, relaxation.	Enzyme activation.
Cholinergic Receptors			
Nicotinic	All autonomic (sympathetic and parasympathetic) synapses between pre and postganglionic neurons; neuro muscular junctions.	Stimulation, excitation.	Opening of chemically regulated Na^+ channels
Muscarinic	All parasympathetic neuro-effector junctions, cholinergic sympathetic neuroeffector junctions.	Variable.	Enzyme activation via G-protein causing changes in membrane permeability to K^+.

(a) postganglionic sympathetic endings other than (c) above
(b) cerebral cortex
(c) hypothalamus
(d) cerebellum
(e) brain stem
(f) spinal cord, and
(g) adrenal medulla.

Note

Initially it was believed that epinephrine (British name *adrenaline*) is the major sympathetic postganglionic neurotransmitter and nerve fibers that release epinephrine came to be called *adrenergic fibers*.

5. Many of the drugs that stimulate or inhibit various components of the ANS affect *receptors* for A-ch and NE. There are several types of receptors for each neurotransmitter.
   (i) ***A-ch receptors*** on all autonomic (sympathetic and parasympathetic) postganglionic neuronal membranes respond to low doses of the drug nicotine and are therefore called ***nicotinic receptors***. (Ligand-gated ion channel receptors).
   (ii) The A-ch receptors on the membrane of smooth muscle, cardiac muscle, and gland cells are not stimulated by nicotine but are stimulated by the mushroom poison 'muscarine'; they are called ***muscarinic receptors***. (G-protein-coupled receptors). These receptors are blocked by atropine.

(For *differences between two types of A-ch receptor actions*, refer page 1031.)

Note

Cholinergic receptors on the neuromuscular junction of the skeletal muscle fibers, innervated by the 'somatic' motor neurons, are also nicotinic (page 156).

   (iii) There are two major classes of ***adrenergic receptors***, also distinguished largely by the specific drugs that stimulate or block them, ***α- and β-adrenergic receptors:***
      (a) **activation of α-adrenergic receptors** results in excitatory effects on smooth muscles of most of the tissues; and inhibitory on many neural and metabolic functions. These effects are mediated by the opening of specific ion channels in the plasma membrane;
      (b) **activation of β-adrenergic receptors** results in excitatory effects on heart, neural and metabolic functions; and inhibitory effects on some smooth muscles. These functions are mediated by the generation of second messenger (cAMP).
   (iv) Both nicotinic and α- and β-adrenergic receptors are further subdivided into N_1, N_2; α_1, α_2 and β_1, β_2 respectively; again according to the drug that influences them (for details, refer to page 735).

Note

The responses produced in postganglionic neurons by stimulation of their preganglionic neuron include not only a *fast EPSP* that generate action potential but also a slow EPSP and IPSP (page 855). These slow response modulate and regulate transmission in autonomic ganglia.

RESPONSES OF EFFECTOR ORGANS TO AUTONOMIC NERVE IMPULSE

General Principles

(Also refer to page 735)

1. Some of the *organs are innervated by one division of ANS only*, such as:
   (i) uterus, adrenal medulla, pilomotor muscle in the skin, sweat gland and most arterioles from the sympathetic division only; while
   (ii) the lacrimal glands, ciliary muscle of eyes, glands of stomach and pancreas from the parasympathetic division only.
2. *Two divisions of ANS act in a complementary (opposite) manner*. Some of the organs like the heart and many glands and smooth muscles in walls of the hollow viscera are innervated by both sympathetic and parasympathetic fibers, that is, they receive ***dual innervation***. Whatever effect one division has on the effector cells, the other division frequently has just the *opposite* effect. Dual innervation by nerve fibers that cause opposite responses *provides a very fine degree of control* over the effector organ.
3. *Two divisions of ANS act in a synergistic (cooperative) manner:* In the case of ***sphincter muscles***, both adrenergic and cholinergic innervation are *excitatory*, but one supplies the constrictor component of the sphincter and other the dilator. *Example:* Iris muscles in the eyes, sexual function (Table 93.2).
4. (i) There is usually **no** A-ch in the circulating blood, and the effects of localized cholinergic discharge are generally discrete and of short duration because of the high concentration of acetyl cholinesterase at cholinergic nerve endings.
   (ii) NE spreads farther and has a more prolonged action than A-ch. It diffuses into the blood stream from adrenergic nerve endings; while epinephrine and dopamine come from the adrenal medulla.
5. *NE acts mainly* on α-receptors; it also acts on β_1 receptors but has no action on β_2 receptors. While *epinephrine* acts equally on both or α and β receptors, it has a special property of stimulating β_2 receptors.
6. NE and epinephrine are equally potent with respect to their action on α_1, α_2 and β_1 receptors but β_2 receptors are relatively selectively activated by epinephrine, *i.e.* they are more sensitive to epinephrine than NE. Therefore, both NE and epinephrine are equally strong as vasoconstrictors in many tissues (skin, viscera) but they differ with reference to effects on huge vascular bed of skeletal muscles; where epinephrine is vasodilator while NE is vasoconstrictor.
   Similarly, NE increases SBP and DBP thereby increasing MBP; while epinephrine increases SBP and decreases DBP, thus maintaining the MBP to normal levels.

Important Note

In humans, β-adrenergic mechanism predominates.

Stimulation of the ANS

Preganglionic fibers of the ANS are activated by inputs from the afferent fibers of the visceral, somatic and special sense organs.

1. *Afferents from the visceral organs*
   (i) most of these fibers transmit pain impulses, other serve as afferent links eliciting reflexes *e.g.* emptying of urinary bladder, colon, rectum, etc.
   (ii) Baroreceptors and chemoreceptors: afferents from large vessels, lungs, heart etc. play a significant role in respiratory and circulatory reflexes.
2. *Somatic afferent fibers.* These fibers come mainly from the skin, mucous membrane, muscles and tendons.
3. Afferents from the taste, olfactory tract and vestibular organ can also modify the activity of ANS.
   A reference list of the ANS effects are given in **Tables 93.2 and 93.3.**

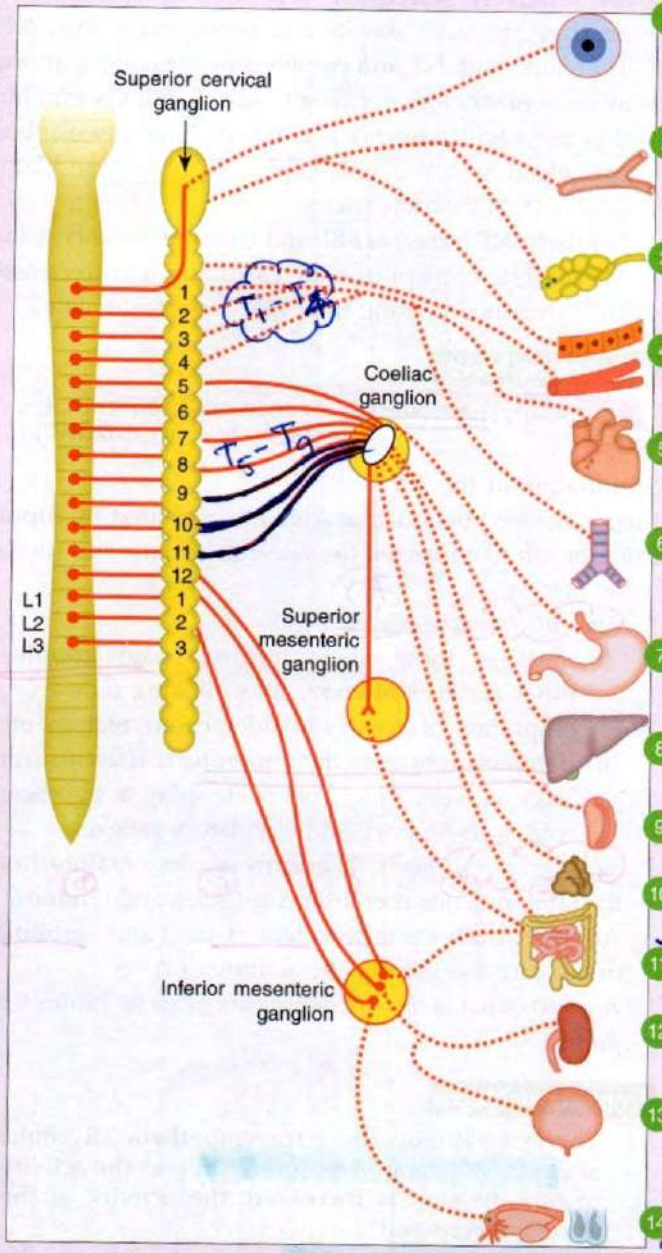
Important Notes

1. The sympathetic and parasympathetic divisions are usually activated *reciprocally; i.e.* as the activity of one division is increased, the activity of the other is decreased.
2. Integration of the ANS occurs mainly in the hypothalamus (page 1004), in addition, certain cortical areas also help.
3. The *enteric nervous system* (page 199) is considered as the third division of ANS. It is also referred as ***mini (little) brain*** as it contains all elements of nervous system viz sensory neurous, motor neurons and interneurous.

NOR	EPI
• Bad; MBP ↑	• Good; MBP =
• Stimulates $\alpha_1, \alpha_2, \beta_1$	Stimulates $\alpha_1, \alpha_2, \beta_1, \beta_2$
• Vasoconstrict	• Vasodilator only

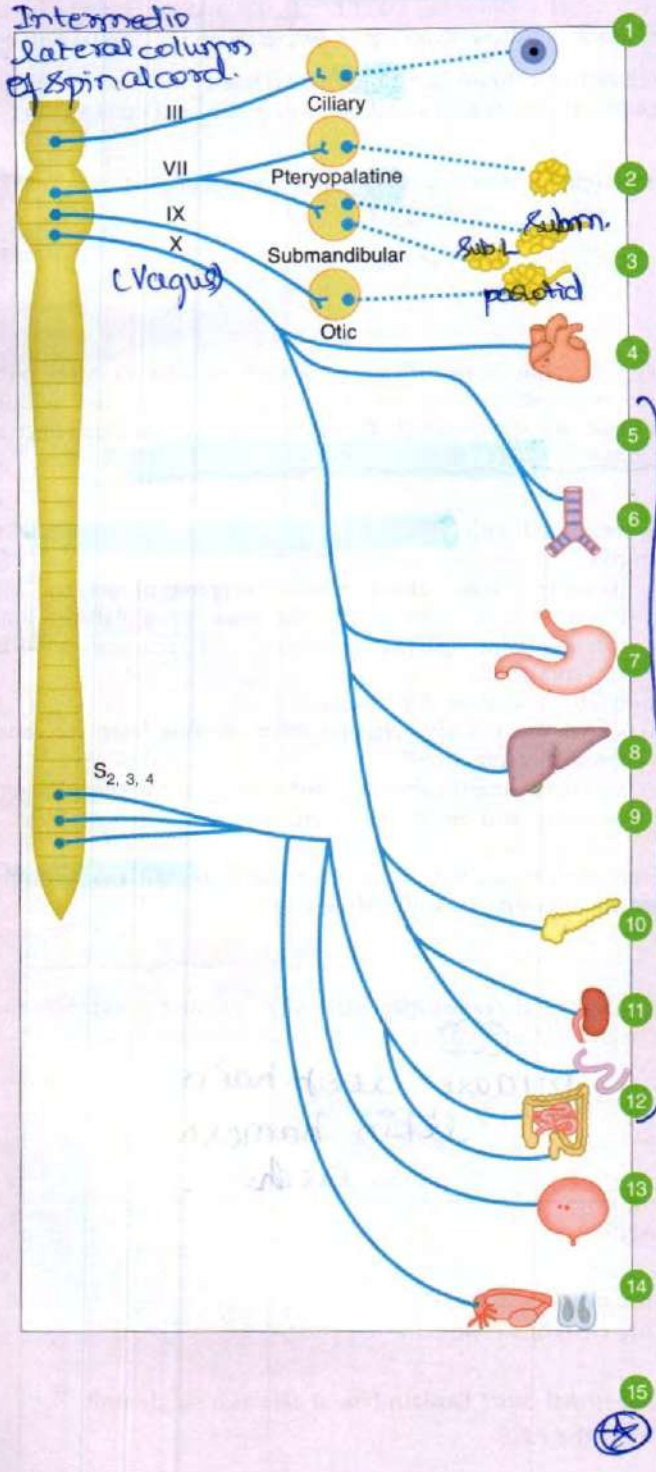
Table 93.2 A: Sympathetic effect

Spinal cord	Lateral chain of gangila	Structures	Effects of stimulation
		1 **Eye** a. Iris muscle b. Ciliary muscle	Contracts radial muscle (dilates pupil) via α_1 Relaxes (flattens lens for far vision) via β_2
		2 **Arteriola** Coronary/skin/GUT/ Renal	Constricts (via α_1, α_2) or dilates (via β_2)
		3 **Salivary glands**	Stimulates secretion (thick) via α_1
		4 **Skeletal blood vessels**	Constricts (via α_1) or dilates (via β_2)
		5 **Heart**	↑s Rate and force of contraction via β_1 and β_2
		6 **Lungs** a. Bronchial muscles b. Bronchial glands	(Relaxes via β_2) inhibits secretion (via α_1) or stimulates (via β_2)
		7 **Stomach**	Peristalsis reduced and sphincters closed via (via α_1, α_2)
		8 **Liver**	Glycogenolysis (via α_1, β_2) Gluconeogenesis
		9 **Spleen**	Contraction (via α_1)
		10 **Adrenal medulla**	Ep and NE secretion into blood
		11 **Large and small intestine**	Same as in stomach (S. No. 7)
		12 **Kidney**	Urine excretion decreased
		Urinary bladder 13 a. Detrusor muscle b. Sphincter	Relaxes (via β_2) Constricts (via α_1)
		Sex organs and genitalia 14 a. Uterus (pregnant and non-pregnant) b. Males	Relaxes via β_2 Ejaculation via α_1
		15 **Skin** a. Pilomoter muscles b. Sweat glands	Contracts→erection of hair (via α_1) Localised (adrenergic) sweating (via α_1)



i.e, Lateral horn

Table 93.2 B: Parasympathetic effect



Spinal cord / Cranial nerve numbers	Structures	Effects of stimulation
1	**Eye** a. Iris muscle b. Ciliary muscle	Contracts sphincter muscle (constricts pupil) (α_1) (Miosis) Contracts (makes lens to become more convex for near vision) (β_1 stimulo-ory)
2	**Lacrimal gland**	↑s tear secretion
3	**Salivary glands**	Stimulates secretions (watery secretions)
4	**Heart**	↓s HR, contractility and conductivity (α_1 & α_2)
5	**Coronary arteries**	Dilates
6	**Lungs** a. Bronchial muscles b. Bronchial glands	Constricts Stimulate secretion
7	**Stomach**	Increases motility, relaxes sphincters, stimulate secretions (specially enzymes)
8	**Liver**	↑s Glycogen synthesis
9	**Gall bladder**	Contracts [for digestion]
10	**Pancrease**	↑ secretion (exocrine gland) ↑ insulin and glucagon secretion (endocrine gland)
11	**Kidney**	Urine excretion increased
12	**Small and large intestine**	Same as in stomach (S. No. 7)
13	**Urinary bladder** a. Detrusor muscle b. Sphincter	Contracts Relaxes] Emptying of bladder
14	**Sex organs and genitalia** a. Uterus b. Males	Variable Erection } synergistic effects
15	**Skin** Sweat gland	Generalised (cholinergic) sweating

Note

Sympathetic and parasympathetic nerves produce antagonistic effects on the organs which they both supply; however, normally the two systems act synergistically to meet the specific demands of any given situation.

Eg: In sex organs, Ciliary m.

Table 93.3: Main differences between two major divisions of the ANS compared

Sympathetic component	Parasympathetic component
1. It is also called ***thoracolumbar division*** of the ANS (T_1 to $L_{2 \text{ or } 3}$).	1. It is also called ***craniosacral division*** of the ANS (i) cranial outflow is via III, VII, IX and X cranial nerves (ii) sacral outflow is via pelvic branches of $S_{2,3,4}$ spinal nerves.
2. Preganglionic fibers are short, myelinated and end either in paravertebral sympathetic ganglionic chain or prevertebral ganglion.	2. Preganglionic fibers are long, myelinated and end on short postganglionic neurons located on or near the visceral structure.
3. Postganglionic nerves are long and nonmyelinated: (i) to the head originate in superior, middle and inferior cervical ganglia and travel to the effector organs with blood vessels; (ii) to viscera originate in coeliac and lower abdominal and pelvic ganglia.	3. Postganglionic nerves are short and nonmyelinated.
4. Upon entering the sympathetic chain, preganglionic fibers travel upwards or downwards to form sympathetic contacts with ganglionic neurons in other ganglia, therefore, sympathetic activity is spread over many segments.	4. Very few connections link the preganglionic neuron. Moreover, parasympathetic post-ganglionic neurons are located within the organ to be controlled. Therefore, parasympathetic effect is localized i.e. target is usually a single organ or system.
5. It prepares the individual to cope with the emergency *i.e.* prepare for either *flight* or *fight reactions* (as described by Walter *Cannon*). For example, its stimulation: (i) relaxes accommodation and dilates the pupil (letting more light into the eyes); (ii) increases heart rate and blood pressure (providing better perfusion of the vital organs and muscles); (iii) constricts skin blood vessels (limits bleeding from wounds); (iv) decreases threshold in the reticular formation (reinforcing the alert and arousal states); (v) increases blood glucose and FFA levels (supplying more energy). Because of these actions, therefore, this division of ANS is sometimes known as ***Catabolic Nervous System (i.e. Principally involved with expenditure of body resources).***	5. It is concerned with vegetative aspect of day-to-day living. For example, (i) its action favours digestion and absorption of food by: (a) increasing activity of intestinal musculature; and (b) increasing gastric secretion and relaxing pyloric sphincter. (ii) dilates sexual erectile tissues; (iii) shows down body activities by decreasing heart rate and force of contraction; (iv) favours storage of absorbed nutrients by increasing glyogen synthesis and insulin secretion. Therefore, sometimes, this division is referred as ***Anabolic Nervous System (i.e. Conservation of body energy).***
6. The major transmitter released between pre and postganglionic fibers is A-ch whereas at postganglionic endings is usually nor-epinephrine.	6. The major neurotransmitter released at pre and postganglionic nerve endings is A-ch.

Study Questions

1. **Explain and justify why different terms are assigned to the ANS.**
2. **List main differences between:**
   (i) Somatic and autonomic nervous system.
   (ii) Two divisions of the ANS.
   (iii) Cholinergic and adrenergic neurons.
   (iv) Two types of acetylcholine receptors.
   (iv) Adrenergic and cholenergic receptors in ANS.
3. **How is sympathetic activity spread over many segments of the spinal cord? Explain how it acts as a single unit.**
4. **Enumerate the exceptions in the organization of two divisions of the ANS.**
5. **Justify the following statements:**
   (i) Autonomic output is diffuse.
   (ii) Two divisions of the ANS act synergistically in any given situation.
   (iii) Sympathetic nervous system is sometimes referred as catabolic nervous system whereas parasympathetic as anabolic.
6. **Which component of the ANS prepares the individual to cope with the emergency situation? List the body responses which are associated with it.**

7. **Draw diagram:**
   (i) General arrangement of ANS
   (ii) Neurotransmitter released in peripheral nervous system
8. **Write short notes on:**
   (i) Major effects of ANS activity
   (ii) Anabolic and catabolic nervous system
   (iii) Chemical transmission at autonomic junction

MCQs

1. **Autonomic ganglia are:**
   (a) Cholinergic (b) Adrenergic (c) Noradrenergic (d) Dopaminergic
2. **Sympathetic nerves in spinal cord originate between:**
   (a) $C_1 - C_6$ (b) $C_7 - T_1$ (c) $T_1 - L_2$ (d) $T_{12} - L_5$
3. **The maximum parasympathetic fibers are contained in the:**
   (a) III nerve (b) VII nerve (c) IX nerve (d) X nerve
4. **Atropine blocks A-ch receptors in all areas *except*:**
   (a) Iris (b) Auerbach plexus (c) A-V node (d) Neuromuscular junction
5. **α_1-adrenergic receptors *do not* exist in:**
   (a) Iris muscle (b) Heart (c) Lungs (d) Liver
6. **β-blockade leads to all *except*:**
   (a) Hypotension (b) Bradycardia (c) Bronchodilatation (d) Loss of libido
7. **Head ganglion of autonomic nervous system is:**
   (a) Thalamus (b) Hypothalamus → Relay centre of ANS
   (c) Superior cervical ganglion (d) Stellate ganglion
8. **Vagal stimulation cause the following *except*:**
   (a) Increase in intestinal secretion (b) Constriction of intestinal musculature
   (c) Relaxation of bronchial musculature (d) Fall in blood pressure
9. **Fight or flight response include all *except*:**
   (a) Pupillary dilatation (b) Generalised vasodilatation
   (c) Decreased threshold in reticular formation (d) Increased blood glucose
10. **ANS regulates the activity of all of the following *except*:**
    (a) Glands of GIT (b) Sweat (c) Heart (d) Skeletal muscle
11. **Internucial neurons are:**
    (a) Essential part of stretch reflex (b) Essential part of all polysynaptic reflexes
    (c) Always excitatory (d) Always inhibitory
12. **ANS is also called:**
    (a) Vegetative nervous system (b) Efferent visceral nervous system
    (c) Involuntary nervous system (d) All of the above
13. **What percentage of fibers in an average skeletal nerve are sympathetic:**
    (a) 20 (b) 40 (c) 60 (d) 80
14. **Stimulation of postganglionic sympathetic neurons *does not* cause:**
    (a) Dilatation of pupil (b) Secretion of saliva
    (c) Release of epinephrine from adrenal medulla (d) Sweating
15. **Post-ganglionic sympathetic neurons stimulation causes all *except*:**
    (a) Secretion of saliva (b) Dilatation of pupils
    (c) Hepatic glycogenolysis (d) Release of epinephrine from adrenal medulla
16. **The ratio of afferent to efferent nerve fibers in vagus is:**
    (a) 1:1 (b) 2:1 (c) 3:1 (d) 4:1
17. **Sympathetic cholinergic innervation is seen in:**
    (a) Apocrine sweat glands (b) Eccrine sweat glands (c) Iris (d) Pancreas

18. **Acetylcholine through nicotinic receptors provides:**
    (a) Contraction of skeletal muscle
    (b) Decrease of heart rate
    (c) Secretion of saliva
    (d) Contraction of pupils
19. **The most important response to the stimulation of β-adrenergic receptors is:**
    (a) Cerebral vasodilation
    (b) Splanchnic vasoconstriction
    (c) Decreased blood sugar
    (d) Increased cardiac activity
20. **Which of the following arterioles is least sensitive to epinephrine?**
    (a) Skeletal muscle
    (b) Cerebral
    (c) Cutaneous
    (d) Renal afferent
21. **Parasympathetic stimulation would decrease the following *except*:**
    (a) SA node rhythmicity
    (b) Heart rate
    (c) A-V conduction time
    (d) Atrial contractility
22. **Widespread discharge of the sympathetic nervous system will *not* cause:**
    (a) Dilatation of the pupils of the eyes
    (b) Increased heart rate
    (c) Decreased blood glucose concentration
    (d) Increased myocardial contractility
23. **Vagal stimulation following intake of food *does not* affect secretion of:**
    (a) Stomach
    (b) Pancreas
    (c) Parotid
    (d) Gall bladder

Answers

1. (a)	2. (c)	3. (d)	4. (d)	5. (b)	6. (c)	7. (b)	8. (c)	9. (b)	10. (d)
11. (b)	12. (d)	13. (d)	14. (c)	15. (d)	16. (d)	17. (b)	18. (a)	19. (d)	20. (b)
21. (c)	22. (c)	23. (c)							

Chapter

94

Spinal Cord Lesions

I. Functions of the spinal cord

II. Transection of the spinal cord
   A. Complete
   B. Incomplete
   C. Hemisection: Brown sequard syndrome

III. Sensory disturbances

FUNCTIONS OF THE SPINAL CORD

Functions of the spinal cord can be divided into: *sensory, motor and autonomic functions.*

A. SENSORY FUNCTIONS

All the sensations after entering the spinal cord in dorsal nerve root are conveyed to the brain (postcentral gyrus) by ascending either in the:

(i) in the *Dorsal column* of the same side which conveys fine touch, tactile localization and discrimination, pressure, proprioception and kinesthetic sensation *i.e.* sensation of body position in space and joint movement and vibration sense, or

(ii) in the *Spinothalamic tracts* of the opposite side: anterior (ventral) tract conveys gross (crude) touch and tactile localization whereas lateral tract conveys pain and temperature sensations.

B. MOTOR FUNCTIONS

The spinal cord controls:

(1) the tone and power of the muscles
(2) the movements of muscles and joints
(3) the deep (tendon) reflexes and
(4) the superficial reflexes

The motor functions are conveyed to the spinal cord by pyramidal (page 911) and extrapyramidal tracts (page 912).

C. AUTONOMIC FUNCTIONS

The spinal cord regulates:

(i) the body temperature, and
(ii) the visceral functions *i.e.*, regulates the activity of smooth muscle, heart, glands of the GIT, sweat gland, adrenals etc. The *main aim* of the autonomic function is to maintain the optimal internal environment of the body.

TRANSECTION OF THE SPINAL CORD

Spinal cord transection *i.e.* cut across the cord can be divided into 3 types: *complete, incomplete and hemisection of the spinal cord.*

A. COMPLETE TRANSECTION OF THE SPINAL CORD

Causes

1. Gun shot injury
2. Dislocation of the spine
3. Occlusion of the blood vessel

Commonest site of involvement is at the mid thoracic level.

Clinical states

It is seen in 2 stages: Immediately after transection of the spinal cord there is marked reduction of all the functions and activity below the level of the section, called *stage of Spinal Shock or Stage of Flaccidity.* However, gradually the patient gains few functions called the *Stage of Reflex Activity.*

Stage of Spinal Shock or Stage of Flaccidity

Characteristic features

Patient feels as if he is cut into two portions, the upper portion (higher centre and the mind) is unaffected but the whole of the body below the level of section is deprived of all activities.

(1) Isolated segments of the spinal cord have lost their power of mediating reflex functions, therefore, the muscles are completely paralysed (*flaccid paralysis*)

and lie in any position imposed on them by gravity.

(i) If both the lower limbs get paralysed the condition is called *paraplegia* and paralysis of all 4 limbs is referred as *quadriplegia*.

(ii) Paralysis of muscles decreases the venous return producing cold and blue extremities, skin becomes dry and scaly, and bed sores develop.

Important Note

Muscular contraction is a major source of heat production and after paralysis of the muscles the body temperature becomes subnormal, therefore, if hot bottles are given to raise the temperature, bed sores develop.

(2) Muscle tone is completely lost.

(3) All the reflexes (superficial and deep) are markedly decreased or lost. (The RMP of the spinal motor neurons is 2-6 mV greater than the normal).

(4) All the sensations below the transection are lost.

(5) The urinary bladder and rectum are generally paralysed; however, the sphincter vesicae recovers very rapidly resulting in retention of urine.

(6) The penis is flaccid and erection is impossible.

(7) All the sympathetic vasoconstrictor fibers leave the spinal cord between T_1 to L_2 (page 325), therefore,

(i) *a transection below L_2* produces no effect or very little fall of blood pressure;

(ii) *a transection at T_1* level cuts off all the thoracolumbar sympathetic neurons from the medullary cardiovascular centre producing marked fall in MBP from a normal resting value of 100 mmHg to 40 mmHg; and

(iii) fall of BP is less marked as the section shifts more distally towards L_2.

(8) *If lesion is at T_6* level, all impulses coming in from the abdominal viscera are cut off from the brain; gripping sensations or distension of viscera are thus not appreciated.

Duration of spinal shock is a direct function of *degree of encephalization* of motor functions *i.e.*, level of development of cerebral functions. Therefore, it lasts for few minutes in frogs; few hours in dogs and cats; few days in monkeys and for about *3 weeks in men*. In the higher animals the entire nervous system is integrated as a *functional unit;* damage to any part of the nervous system disturbs its smoothness of working and the functional failure is more severe. To this functional depression of the nervous system is called *Diaschisis.*

Cause of spinal shock

It is uncertain. Fall in BP is **not** responsible for shock because the fall is equally marked in the headward part which shows no flaccidity after transection. It may be due to stoppage of tonic bombardment of spinal motor neurons by excitatory impulses in the descending pathways.

Stage of Reflex activity

Intermediate grey column of spinal cord are rich in NE and 5HT, therefore after one week of cord transection, when the autonomic reflexes are hyperactive, NE and 5HT content of the cord below the transection are markedly reduced.

1. *Autonomic reflexes.* Within days or weeks of cord transection, spinal sympathetic cell bodies appear to recover some tonic discharge and moreover, are capable of responding by increased activity to noxious stimulation.

Result

(i) As the stage of shock passes off, functional activity *first appears* in smooth muscle. The sphincter vesicae (if affected at all) recovers very soon but detrusor of the urinary bladder regains its power more slowly (why? not known) resulting in retention of urine (for further urinary bladder dysfunction, refer page 577). Reflex evacuation of urinary blader is gradually established in a perfectly normal manner. Similarly, reflex defecation also occurs.

(ii) Next, tone returns to the paralysed blood vessels because the connector cells in spinal cord begin to act independently of the VMC; thus:

(a) the skin which has become dry and scaly, now shows sweating again and it becomes more healthy;

(b) ulcers heal up rapidly;

(c) because of accompanying return of reflex activity to the skeletal muscles, the circulation through the limbs is greatly improved and they become warm and of good colour.

(iii) BP is generally normal at rest because isolated segment of spinal cord can mediate as centre for vasomotor reflexes; but the precise feedback regulation normally supplied by baroreceptor reflexes is absent and wide fluctuations in BP are common.

(Also see to page 325)

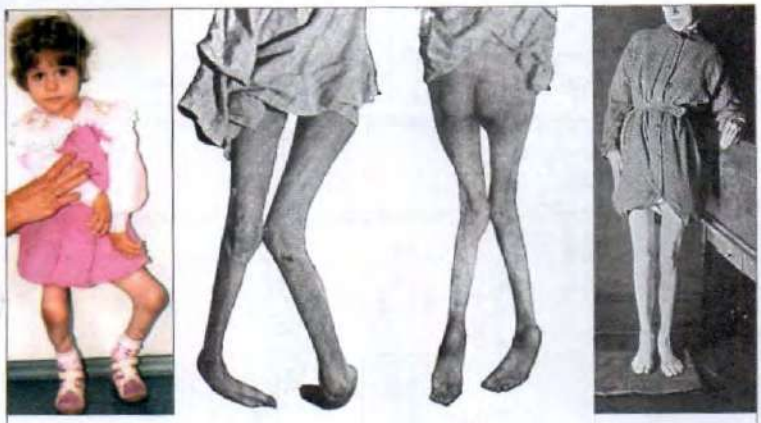
2. *Muscle tone.* Tone in the skeletal muscle *returns slowly after 2 or 3 weeks,* this returning tone is reflex in character and is *produced by* impulses entering the spinal cord from the muscles.

(i) Spinal cord isolated from the influence of higher centres *favours* the flexor neurons and muscles, therefore, extensor muscles remain flabby for a longer period and do not attain the same degree of tone as the flexors.

(ii) All the muscles are *hypotonic* (even the flexors) because stretch reflexes which are responsible for muscle tone are feebly mediated by the spinal cord alone and need reinforcement from the brain stem centres.

(iii) Limbs adopt a position of slight flexion and paraplegia is, therefore, known as *Paraplegia in Flexion;* the limb cannot support the body weight **(Fig. 94.1 A)**.

(iv) *No wasting of muscles* is seen because though the muscles are paralysed for voluntary movements they are in constant reflex activity.



(A) (B)

Fig. 94.1 Paraplegia in flexion (A) and extension (B)

Note

Spinal Man **cannot stand unsupported.**

3. *Reflex movements.* If no complications occur the interval between the spinal cord transection and the beginning of *return* of reflex activity is *approx. 2 weeks.* Recovery of reflex excitability is due to: the development of *denervation hypersensitivity* to the mediators released by the remaining spinal excitatory endings; and the *growing of collaterals* from existing neurons with the formation of additional excitatory endings on interneurons and motor neurons.

(i) *Flexor reflex.* The first reflex response to appear is spontaneous involuntary flexor movements of the limb. This can be observed from abnormal Babinski response (page 915). Contraction of these flexor groups of muscles is accompanied by reciprocal inhibition of the extensor muscles of the limbs. As a result, reflex movements that return first are the *flexor reflex* or *withdrawal reflex* (page 880).

(ii) *Mass reflex.* It is usually seen several months after the original lesion due to irradiation of afferent stimuli from one reflex centre to another (page 883). In some cases, scratching any point on the lower limb or the anterior abdominal wall below the level of lesion produces a very widespread reaction which *causes:*

(a) flexor spasm of both lower extremities and contraction of anterior abdominal wall;

(b) evacuation of the urinary bladder due to hyperactive autonomic reflex activity and abdominal compression which increases intra vesical pressure to threshold level; similarly, reflex evacuation of rectum also occurs;

(c) profuse sweating below the level of the lesion; the sweat fibers to head and neck arise from $T_{1,2}$ and those to the arms from $T_{5\text{-}9}$, therefore, a lesion at T_1 level causes sweating of the whole body when mass reflex is obtained, as all sympathetic fibers leave the cord below the level of the lesion.

(iii) *Deep (or tendon) reflexes.* The knee or ankle jerk returns about 1 to 5 weeks later than the flexor responses.

(a) Initially, knee jerk is sluggish but later becomes normal. It is a *fractionated stretch reflex* and stretch reflexes are generally feeble in spinal persons. Therefore, though the quadriceps may contract fairly briskly, it relaxes immediately.

(b) The *ankle jerk* may return still later.

(c) Generally about six months after the occurrence of transection, marked activity appears in the extensor arcs. This results in exaggerated extensor reflexes with the appearance of extensor spasms.

Important Note

The mass reflex can be used to give paraplegic patients a degree of bladder and bowel control. They can be trained to initiate urination and defecation by stroking or pinching their thighs, thus producing an intentional mass reflex.

(iv) *Coitus (sexual) reflex.* The coordinated sexual activity depends upon a series of reflexes integrated at many neural levels and is absent after spinal cord transection. However, genital manipulation in male spinal man produces erection and even ejaculation. In female spinal dogs, vaginal stimulation causes tail deviation and movement of pelvis into the copulatory position.

Stage of Failure of Reflex Activity

In general, malnutrition, infection or toxaemia causes failure of reflex function. The *features include:*

(i) The reflexes become increasingly difficult to obtain.

(ii) The receptive fields (page 886) narrowed down to the optimum areas from which reflexes can be obtained.

(iii) The mass reflex disappears.

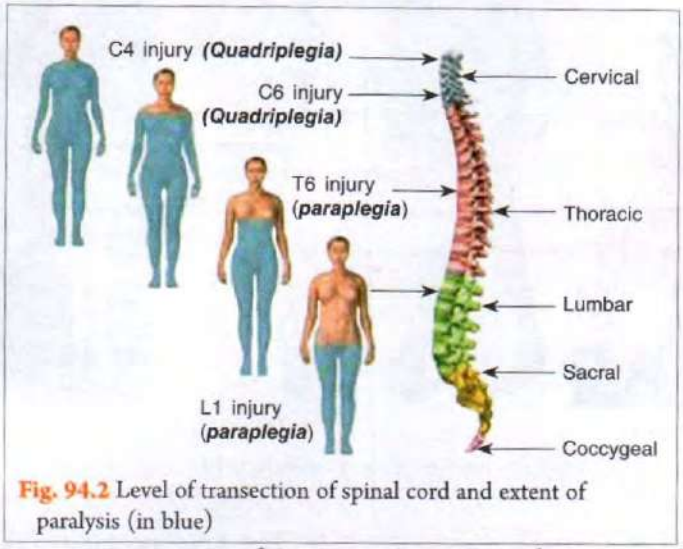


Fig. 94.2 Level of transection of spinal cord and extent of paralysis (in blue)

#: Upper limb → Brachial plexus ($C_5 - T_1$)

(iv) The threshold of all reflexes is increased and few groups of muscles are involved in the motor responses.

(v) The muscles waste and become flaccid and bed sores develop, which further decrease the general state of the patient.

REGIONAL PRECULITIES: Refer to **Fig. 94.2**.

B. INCOMPLETE TRANSECTION OF THE SPINAL CORD

In this type of lesion of the spinal cord, although the cord is severely injured but few tracts escape injury and are not cut.

Stage of Spinal Shock. It is identical with as described on page 931.

Stage of Reflex Activity. Because transection of the spinal cord is irregular, therefore, some of the descending tracts in the ventrolateral columns of spinal cord (specially vestibulospinal and reticulospinal tracts page 912) may escape injury and so some connections persist between the brain and spinal cord. These tracts mainly reinforce the activity of the extensor motor neurons producing *extensor hypertonia i.e. Paraplegia in Extension.* As a result the legs lie extended at hip and knee with the toe pointing slightly downwards **(Fig. 94.1 B)**.

Characteristic features

1. All features of upper motor neuron lesion are seen (page 914).
2. *Involuntary movements* are relatively infrequent, but when they occur, involve an increase of extensor tone, producing downward movements of feet and toes.
3. *Reflex movements*

(i) *Extensor thrust reflex.* To obtain this reflex the lower limb is passively flexed and allowed to rest on the bed, the patient's foot is then pressed up with the palm of the hand. Active contraction of quadriceps and posterior calf muscle occurs, and the limb straightens out. Physiologically, it is an extensor response because all the muscles which contract during an extenso response are called *physiological extensors.* This reflex is absent in complete transection of the spinal cord.

(ii) *Crossed extensor reflex.* A noxious stimulus to the sole of foot produces withdrawal (flexor) reflex (page 881) extending upto the knee only. It is usually accompanied by active and forcible extension of the opposite limb.

(iii) *Phillipson's reflex.* Gentle flexion of one limb produces extension of the opposite limb. The flexed limb then becomes extended and the opposite one flexed; the response alternates in each limb producing a steppage movements *i.e.* movements in which the legs are lifted abnormally high, occurring due to foot drop.

The range of reflex response is greater now that more of the nervous system is available. Therefore, the movements of locomotion can be carried out to some extent (reflexly) by the lower levels of CNS; but *walking as such is impossible.*

Stage of failure of reflex activity. It is identical as described on page 933.

C. HEMISECTION OF THE SPINAL CORD: BROWN SEQUARD SYNDROME

It is a lesion involving one lateral half of the spinal cord **(Fig. 94.3)**. Here, autonomic functions are usually normal. The other functional changes which take place can be divided into 3 categories: changes below the level, at the level and above the level of the hemisection.

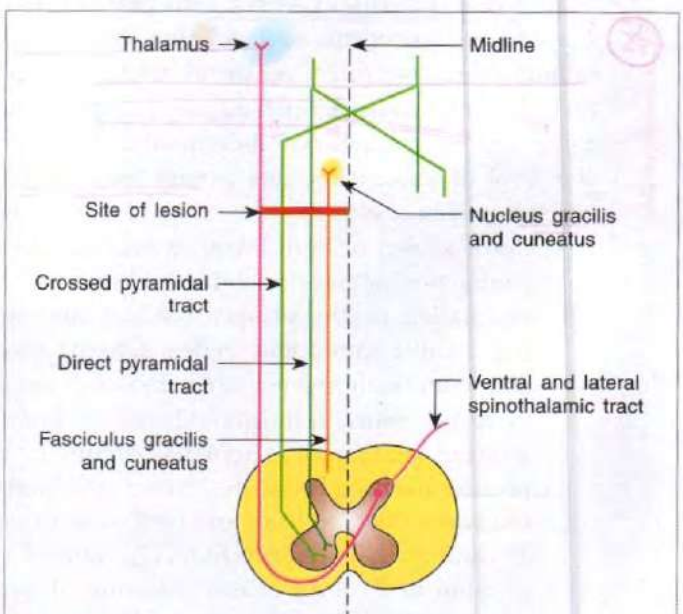


Fig. 94.3 Hemisection of the spinal cord

Changes below the level of the hemisection

On the same side

1. **Sensory changes**
   (i) Fine touch, tactile localization and tactile discrimination, vibration sense and kinesthetic senses *i.e.*, sense of movement and position is lost due to damage of the dorsal columns (page 888).
   (ii) Pain, temperature and crude touch remain unaffected as the spinothalamic tracts (anterior and lateral) carrying these sensations cross to the opposite side and escape injury.
2. **Motor changes**
   (i) Extensive paralysis of upper motor neuron type (page 914) due to damage of crossed pyramidal tracts. Since some fibers of direct pyramidal tract of opposite side (which end in the same side) escape injury, therefore, some muscles on the same side of the lesion may not be paralysed.
   (ii) Temporary loss of vasomotor tone due to damage to the descending fibers from the VMC in the medulla to the lateral horn cells. This leads to the dilatation of blood vessels and fall in BP. Later, intact lateral horn cells start acting as supplementary VMC and tone returns.

On the opposite side

1. **Sensory changes**
   (i) Complete loss of pain, temperature and crude touch due to damage to the spinothalamic fibers which come from the opposite side.
   (ii) Kinesthetic sensations, fine touch etc. will persist because the posterior columns of the opposite side are not damaged.
2. **Motor changes**
   (i) Either no paralysis or paralysis of few muscles occurs (UMNL type, page 914). This is due to possible involvement of some fibers of direct pyramidal tracts 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*** (Fig. 94.4).

Changes at the level of the hemisection

On the same side

1. *Sensory changes.* Complete anaesthesia occurs due to damage to the posterior nerve root, posterior horn cells and spinothalamic fibers (which cross to the opposite side).
2. *Motor changes*
   (i) Complete lower motor neuron type paralysis (page 914) is seen due to damage to the anterior horn cells.

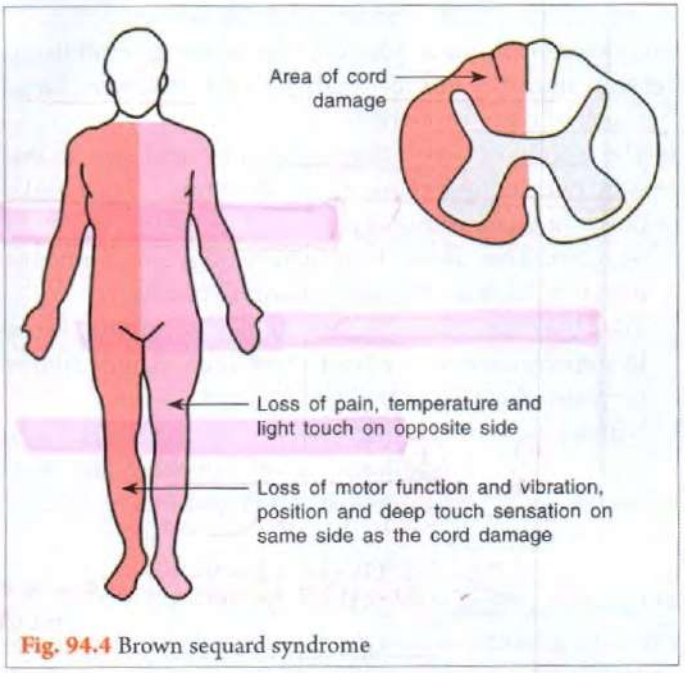


Fig. 94.4 Brown sequard syndrome

   (ii) Complete and permanent vasomotor paralysis occurs due to damage of the lateral horn cells.

On the opposite side

1. *Sensory changes.* Some loss of pain sensations due to injury of pain fibers of spinothalamic tract which cross horizontally in the same segment and may be caught up in the lesion.
2. *Motor changes.* Nil or very slight due to damage of some pyramidal tract of the same side.

Changes above the level of the hemisection

On the same side

A band of *hyperaesthesia* present due to irritation of upper cut end of the damaged fibers.

On the opposite side

Hyperaesthesia may be referred.

Regional Peculiarities

1. Hemisection in the *cervical region* causes:
   (i) Constriction of pupil on the same side because pupillary dilator fibers coming from medulla and passing via $T_{1,2,3}$ anterior roots are damaged.
   (ii) Loss of biceps, triceps and supinator and pronator jerks if $C_{4,5,6}$ segments are involved
   (iii) Paralysis of the diaphragm on the same side due to phrenic nerve ($C_{3,4,5}$) involvement.
2. Hemisection in the *lumbar region*
   If it involves the $L_{3,4}$ loss of knee jerk and disturbances in the micturition occurs.
3. Hemisection in the *lumbosacral region*
   This leads to loss of control over the sphincters of the urinary bladder and anus.

Complications of the Spinal Cord Transection

Paraplegic and quadriplegic patients get immobilized, develop negative nitrogen balance and catabolize large amounts of body protein.

1. The weight of body compresses the circulation to the skin over bony prominences; therefore, skin breaks down at these points and *Decubitus (postural) ulcers* develop. The ulcers heal poorly and are prone to infection because of body protein depletion.
2. The breakdown of protein from the bone matrix leads to hypercalaemia, hypercalciuria and calcium stones may also develop in the urinary tract.
3. Urinary stasis with paralysis of the urinary bladder causes stones, precipitates urinary infection. This may lead to septicemia, uraemia, coma and finally death.

SENSORY DISTURBANCES

SYRINGOMYELIA

This is a condition involving the grey matter round the central canal of spinal cord in which excessive growth of neuroglial tissue occurs with cavity formation. Signs and symptoms are usually referred in the hands and arms at and below the level of the lesion due to prevalence of the disease for the cervical segment of the spinal cord (Fig. 94.5).

Characteristic features

1. Loss of pain and temperature sense due to damage to fibers carrying these sensations, which cross in anterior white commissure.
2. Touch is retained as it has double pathway; fibers which cross in grey columns get damaged while the fibers which descend in the dorsal columns escape. (1) and (2) thus produce *Dissociated Anaesthesia i.e.* loss of pain and temperature sense while sense of touch is retained.
3. At the level of the lesion, initially gliosis and cavitation spread and involve the anterior horn cells producing *flaccid* paralysis of muscles (usually of the hands).

In later stages, involvement of pyramidal and extra-pyramidal tracts leads to *progressive spastic paraplegia i.e. spastic* paralysis of the legs.

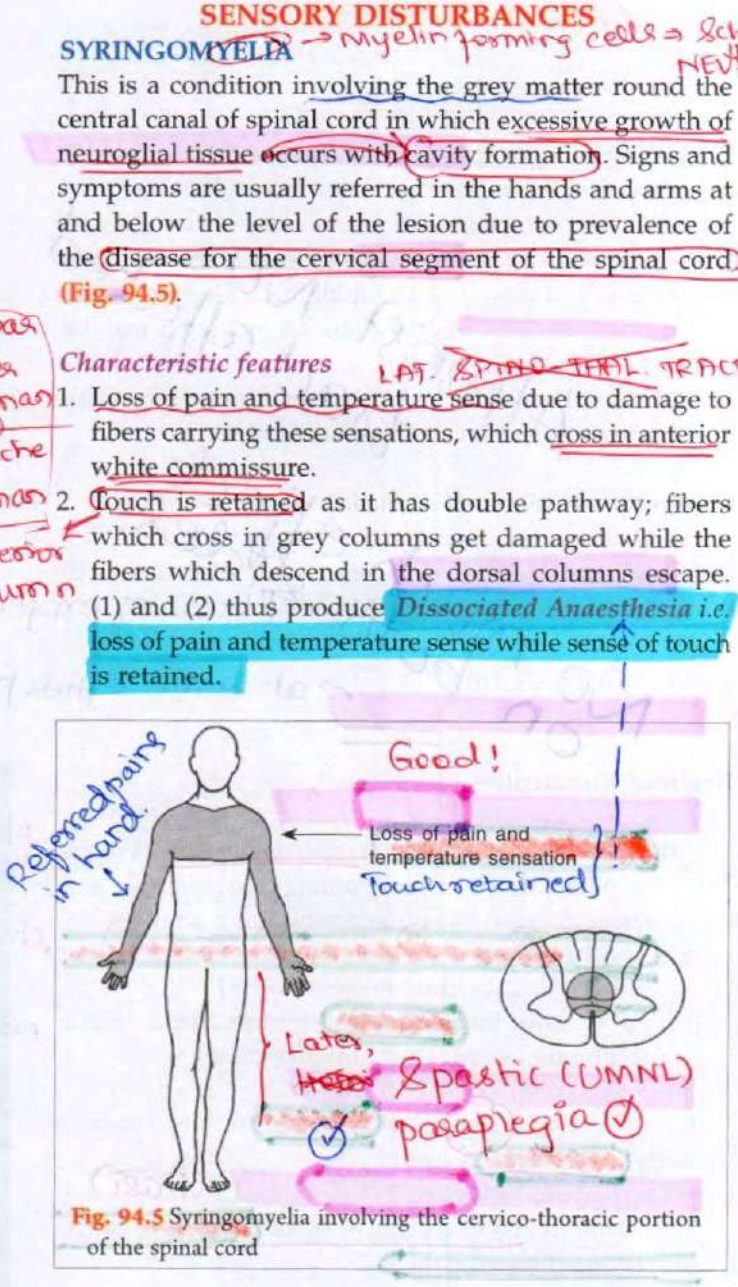


Fig. 94.5 Syringomyelia involving the cervico-thoracic portion of the spinal cord

TABES DORSALIS

In this condition degeneration of dorsal (sensory) nerve roots occurs; affecting specially fibers in dorsal columns and fibers which convey pain. The disease is usually caused by syphilis.

Characteristic features (Fig. 94.6)

1. *Lightning pains* of varying intensity which come in attacks with pain free intervals in between. It is due to stimulation of pain fibers in dorsal nerve roots.

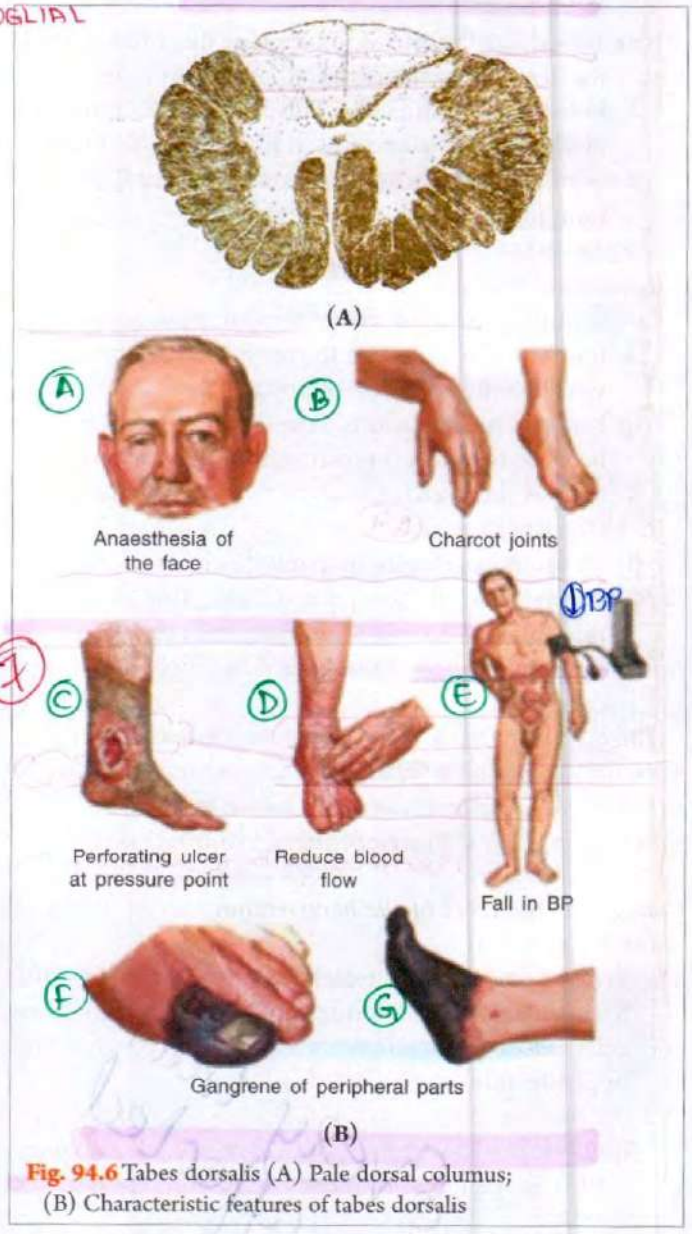


Fig. 94.6 Tabes dorsalis (A) Pale dorsal columus; (B) Characteristic features of tabes dorsalis

2. Loss or decrease in pain sensibility produces:
   (i) *trophic disturbances* such as perforating ulcers at pressure points;
   (ii) anaesthesia around the anus, over legs, upper chest and inner border of hands due to involvement of dorsal nerve roots in lumbosacral and cervicothoracic regions of the spinal cord;
   (iii) anaesthesia of central part of the face due to involvement of Vth cranial nerve;
   (iv) *Charcot joints* occur due to repeated trauma to joints, finally leading to damage to the articular surface.
3. *Loss of deep sensibility* *i.e.* loss of position sense, passive movement and vibration sense.
4. *Reflexes.* Deep tendon reflexes like knee, ankle, bicep, tricep jerks which depend on the intactness of the reflex arc are *lost.*
5. Marked disturbance of voluntary movements.

DEAFFERENTATION: SECTION OF DORSAL NERVE ROOT

The effect of injury to afferent nerves are:

1. Loss of all forms of sensations such as pain, temperature, touch, muscles and visceral sensibility. This leads to development of *trophic* changes.
2. Loss of all reflexes (superficial and deep) with loss of muscle tone.
3. Marked weakness in the movements of the part which makes its use almost impossible because higher centres concerned with reflex control of posture are deprived of afferent impulses from joints and muscles.

DISSEMINATED (MULTIPLE) SCLEROSIS

Disseminated means widespread throughout an organ; ***Sclerosis*** means increase of connective tissue in the nervous system. It usually occurs between the ages of 20 to 50 years and affecting women about twice as often as men.

Causes

1. Genetic predisposition; and
2. Environmental factors include early exposure to viruses such as Epstein-Barr virus, measles, herps, chicken pox or influenza.

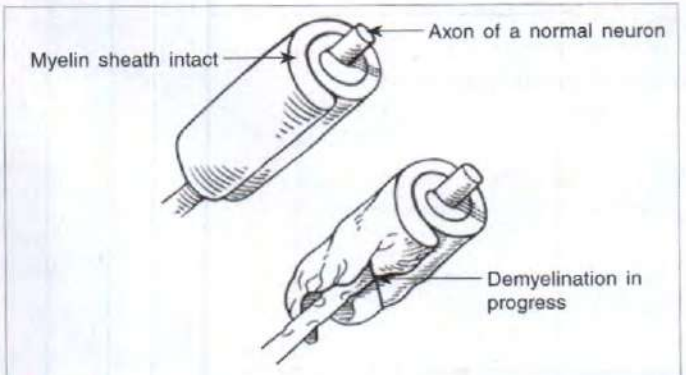


Fig. 94.7 Disseminated (multiple) sclerosis

Characteristic features

1. It is a widespread demyelinating disease of the CNS, which produces both sensory and motor disturbances, How? **(Fig. 94.7)**
   Here nerve cells get replaced by neuroglial cells due to their proliferation. This leads to multiple inflammatory foci, disseminated irregularly throughout the length of the cerebrospinal axis. Grey and white matter both get involved and show demyelination. Thus there is patchy destruction of myelin in the CNS.
2. It is a crippling disease associated with delayed or blocked conduction in the demyelinated axons. (Why? refer to page 139)
3. Signs and symptoms manifest according to the ascending and descending pathways involved **(Fig. 94.8)**.
4. *Diagnosis* is very different (Magnetic resonance imaging–MRI and nerve conduction tests may be of some help.
5. There is no cure for multiple sclerosis; immuno supressive drugs, e.g. interferon may slow the progression of the disease.

SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

This condition is associated with demyelination of white fibers of the spinal cord affecting the dorsal columns and later lateral columns. It is commonly seen in pernicious anaemia patients (page 71) and characteristic features manifest according to the tracts involved.

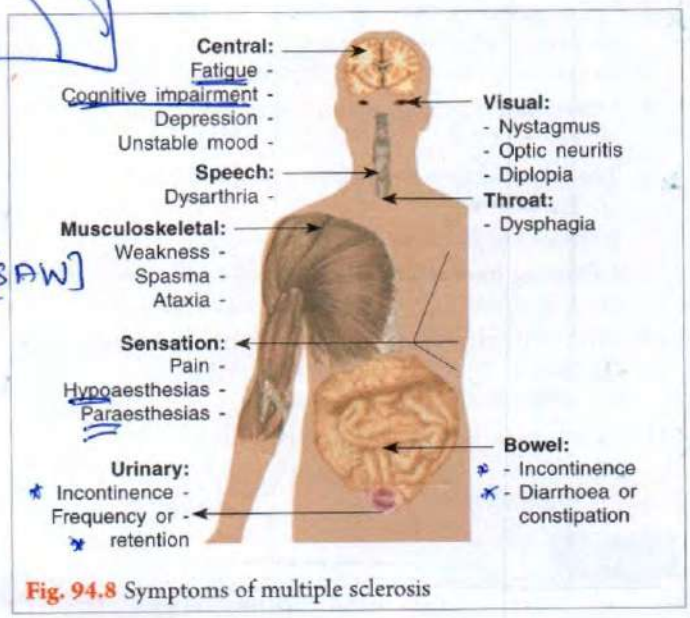


Fig. 94.8 Symptoms of multiple sclerosis

Study Questions

1. Give an account of major functions of the spinal cord.
2. Describe briefly:
   (i) Spinal shock (ii) Diaschisis (iii) Paraplegia in flexion (iv) Paraplegia in extension
   (v) Fractionated stretch reflex (vi) Extensor thrust reflex (vii) Crossed extensor reflex
   (viii) Phillipson's reflex (ix) Decubitus ulcer (x) Dissociated anaesthesia (xi) Syringomyelia
   (xii) Tabes dorsalis (xiii) Charcot joints (xiv) Disseminated sclerosis (xv) Brown sequard syndrome
   (xv) Subacute combined degeneration of spinal cord.
3. Why is the duration of spinal shock more in humans?
4. Why do paraplegic individuals manifest subnormal body temperature?
5. Spinal man cannot stand unsupported. Explain.
6. What is mass reflex? Give its characteristic features and physio-clinical significance.
7. Give characteristic features of hemisection of spinal cord at C_5 level.
8. Mention features due to injury to the dorsal nerve.
9. Describe the changes in spinal reflexes that follow the transaction of the spinal cord.
10. Classify transection of the spinal cord and describe any one of them in detail.
11. List sensory disturbances and describe any one of them in detail.

MCQs

1. Immediately following the transection of spinal cord in man there is:
   (a) A period of spinal shock that rarely lasts more than 24 hours
   (b) General increase in skeletal muscle tone
   (c) Retention of urine and faeces
   (d) Retention of urine and faeces with increase in skeletal muscle tone
2. Subnormal body temperature following complete transection of spinal cord is due to:
   (a) Shock (b) Inactive sympathetic neurons in the spinal cord
   (c) Muscular paralysis (d) Inefficient thermoregulatory mechanisms
3. As the stage of spinal shock passes off, functional activity first appears in:
   (a) Tone of blood vessels (b) Sphincter vesicae
   (c) Detrusor muscle of urinary bladder (d) Muscle tone
4. After the spinal cord transection, reflex movement that appears quite early is:
   (a) Flexor reflex (b) Mass reflex (c) Deep reflexes (d) Coitus reflex
5. All of the following may occur as complication of spinal cord transection, *except*:
   (a) Postural ulcers (b) Renal stones (c) Paraplegia (d) Dissociated anaesthesia
6. *Not* an effect of injury to afferent nerve:
   (a) Loss of all forms of sensations (b) Loss of all reflexes
   (c) Marked weakness in the movements (d) Hypotension
7. Duration of spinal shock in humans:
   (a) Few minutes (b) Few hours (c) Few days (d) Three weeks
8. The cause of spinal shock is:
   (a) Hypotension (b) Functional depression of the nervous system
   (c) Muscular paralysis (d) All of the above
9. Following transection of the spinal cord, muscle tone in the skeletal muscle returns after:
   (a) 1 or 2 days (b) 2 or 3 weeks (c) 3 or 4 months (d) 1 year
10. Brown sequard syndrome is characterized by all *except*:
    (a) Pain and temperature loss on opposite side (b) Loss of kinesthetic sensations on opposite side
    (c) Motor paralysis on same side (d) Fine touch preserved on same side
11. Tabes dorsalis is usually caused by:
    (a) Syphilis (b) Intramedullary tumour of spinal cord
    (c) Deafferentation (d) Spinal cord transection

Answers

1. (c) 2. (c) 3. (b) 4. (a) 5. (d) 6. (d) 7. (d) 8. (b) 9. (b) 10. (b) 11. (a)

Chapter

95

The Vestibular Apparatus (Labyrinth)

I. Physiological anatomy
II. The vestibular pathways
III. Functioning of the vestibular apparatus
  A. Mode of action of otolith organ (saccule and utricle)
  B. Mode of action of semicircular canals
  C. Role in regulation of posture
IV. Vestibular dysfunctions: Motion and sea sickness; Meniere's diseases; Labyrinthectomy; Barany's caloric test.

PHYSIOLOGICAL ANATOMY

The ***vestibular apparatus (labyrinth)*** is a complex sense organ of the inner ear (page 1067). It consists of:
(1) *three semicircular canals;* and
(2) *the otolith organ* – two saclike swellings, *the saccule and utricle.*

These are series of fluid-filled membranous tubes that connect with each other and with the cochlear duct. All these structures lie in tunnels in the temporal bone on each side of the head **(Fig. 95.1)**.

THE SEMICIRCULAR CANALS

1. The 3 membranous canals are: *horizontal (lateral); superior (anterior) and inferior (posterior);* each being at right angles to the others. They contain the ***endolymph*** and are separated from the bony canal by the ***perilymph***.
2. Each canal begins as a dilation (or *ampulla*), containing a projecting ridge, the *crista.*

OTOLITH ORGAN: THE UTRICLE AND SACCULE

1. The utricle communicates with the saccule by means of the ***ductus endolymphaticus***. Both the utricle and saccule contain a projecting ridge, the *macula.*
2. ***Structure of the receptor: the crista and macula*** **(Fig. 95.2)**
   (i) The crista and macula are the *specific receptors* of the vestibular apparatus and have a similar structure.
   (ii) Covering the projecting ridge is a tall columnar epithelium giving attachment to 30-150 long stiff hairs (called, *hair cells*) which project into a firm gelatinous material, the *cupula terminalis.*
   (iii) A large non-motile hair (*cilium*) called *kinocilium*, is located at one end of the hair cell. In the remaining hair cells, small cilia with progressive increase in height are present, called *stereocilia* **(Fig. 95.2 C)**.
   (iv) Between the hair cells lie the fibers of origin of the vestibular division of the VIII nerve.
   (v) In the canals the *cupula* rises to the roof of the ampulla, acting as a movable partition which divides the ampulla into two compartments.
3. In the saccule and utricle, the *cupula* contains many chalky (calcium carbonate) particles, the ***otoliths (or otoconia)***, hence the name the *otolith organ.* The otoliths

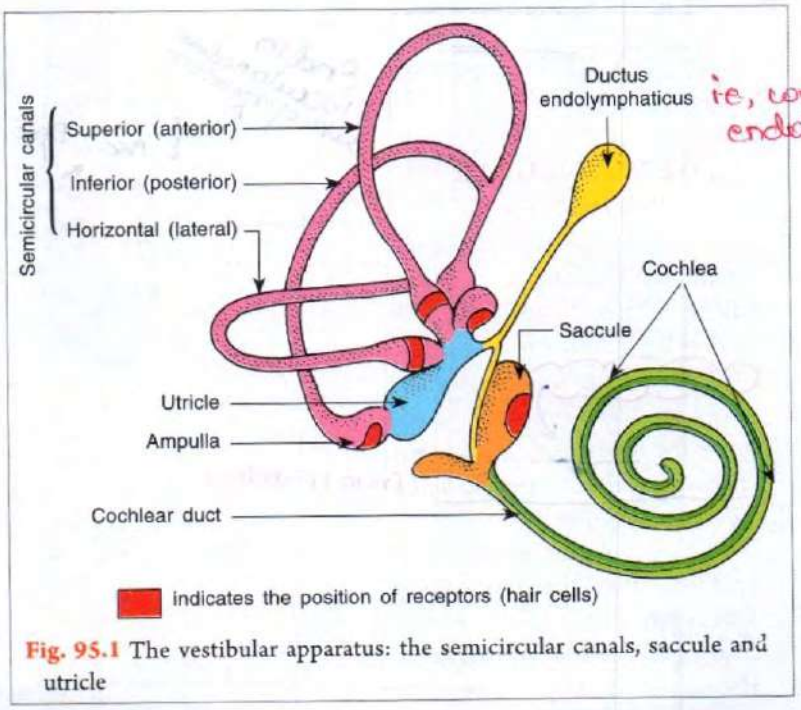


Fig. 95.1 The vestibular apparatus: the semicircular canals, saccule and utricle

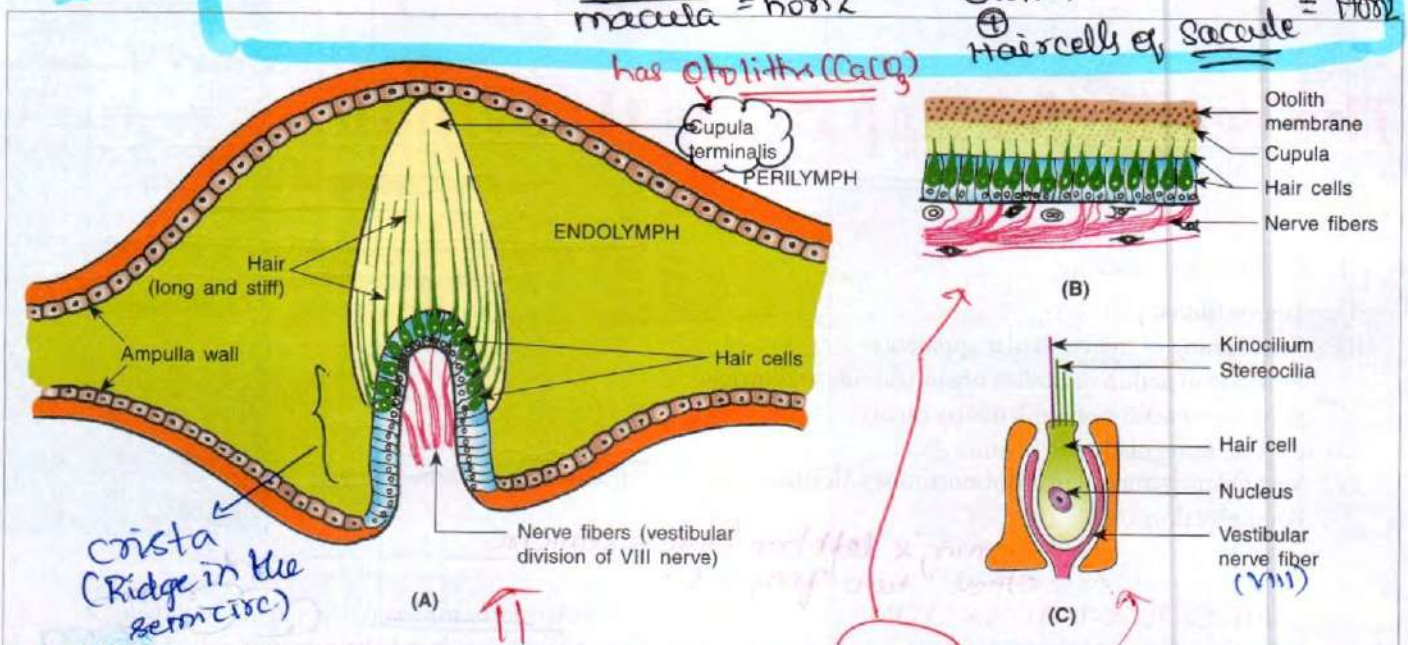


Fig. 95.2 Structure of (A) crista (of semicircular canals) and macula (of saccule and utricle); (B) the otolith membrane and (C) the hair cell

make the gelatinous substance (cupula) heavier than the surrounding fluid.

4. When the head is in the normal erect position:
   (i) the *macula of each utricle* is approximately in the horizontal plane, with the cupula, hair and otoliths rising vertically from the macular epithelium; and
   (ii) the *macula in each saccule* lies in the vertical plane, with the hair and otoliths projecting horizontally sideways into the cupula.

Note

For all practical purposes four-part *vestibular nuclei* is treated as a *single* functional entity. It is concerned with maintaining the position of the head in space.

THE VESTIBULAR PATHWAYS

1. The nerve endings in the crista and macula continue as nerve fibers which have their cell bodies in the bipolar cells of the *vestibular ganglion*. The central axons of the vestibular nerve enter the medulla ventral to the inferior cerebellar peduncle.
2. The axons divide into *ascending* and *descending* branches which end in the ***flocculonodular lobe of the cerebellum*** and in four-part ***vestibular nuclei*** on the same side (Fig. 95.3).

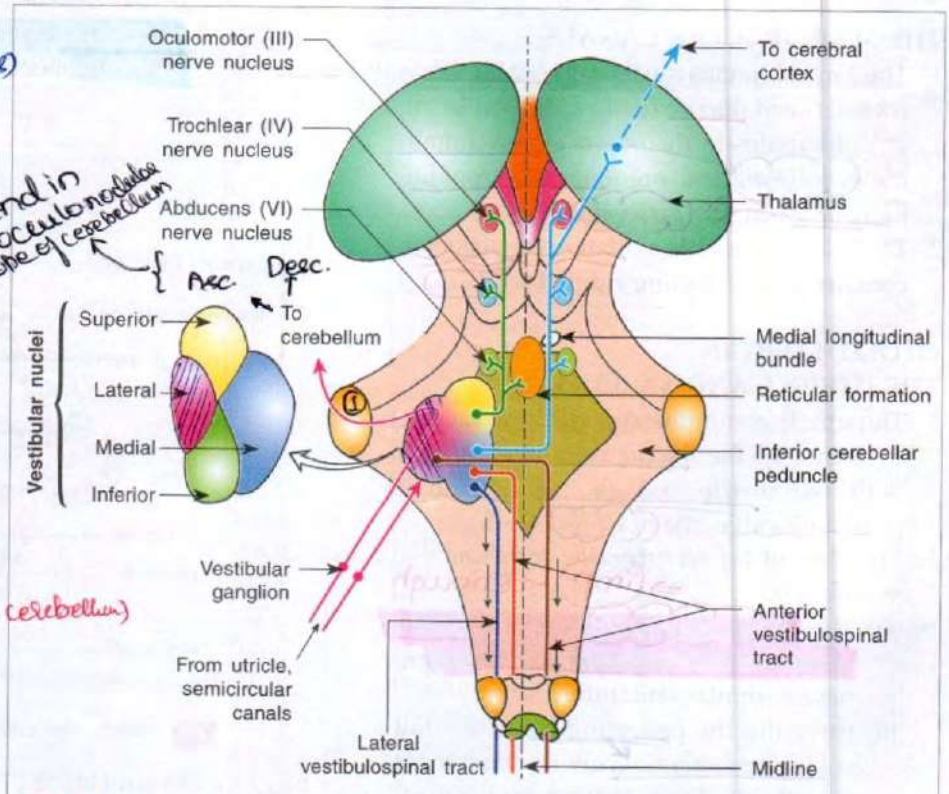


Fig. 95.3 The neural pathways from the vestibular apparatus

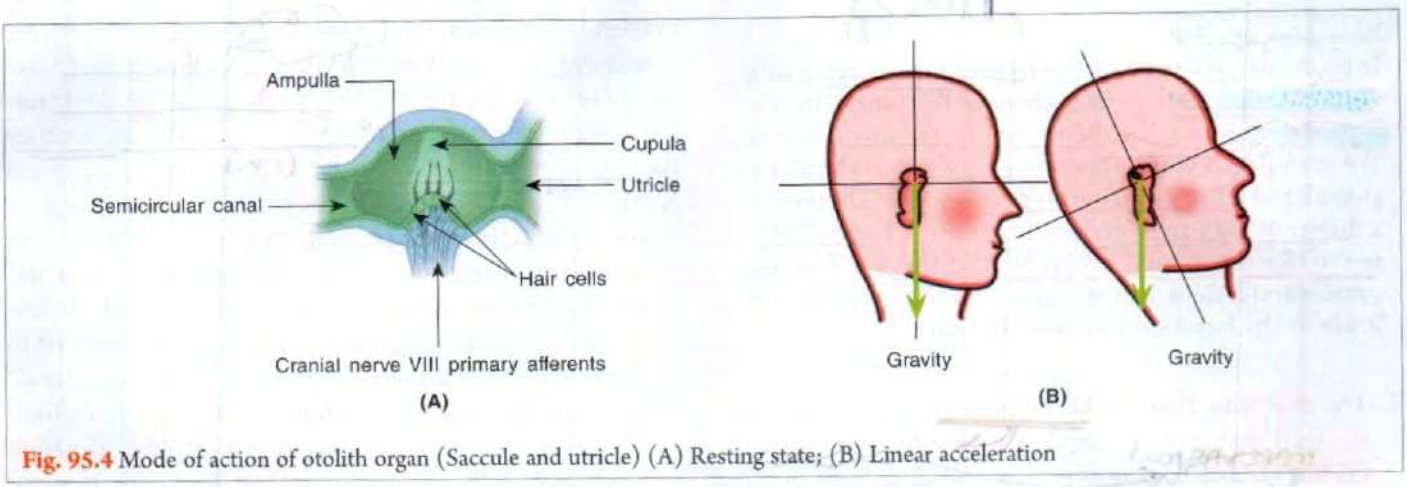


Fig. 95.4 Mode of action of otolith organ (Saccule and utricle) (A) Resting state; (B) Linear acceleration

3. ***Fibers from semicircular canals*** end primarily in *superior and medial* (principal) divisions of the vestibular nucleus, which projects mainly to III, IV and VI cranial nerve nuclei of both sides *controlling eye movements.*
4. ***Fibers from the utricle and saccule*** end mainly in the *lateral (Deiter's) nucleus*, which projects down the anterior and lateral vestibulospinal tracts to the ventral columns of the spinal cord to end directly round the ventral horn cells **(Fig. 95.3)**
5. **Fibers from the vestibular nuclei** also pass:
   (i) to the cerebellum of both sides via the inferior cerebellar peduncles;
   (ii) directly and via the cerebellum to the red nucleus and the nuclei of the reticular formation in the brain stem;
   (iii) via the medial lemniscus to the opposite thalamus and thence to the opposite temporal lobe.

FUNCTIONING OF THE VESTIBULAR APPARATUS

A. MODE OF ACTION OF OTOLITH ORGAN: SACCULE AND UTRICLE

The saccule and utricle provide information about ***linear acceleration*** and change in head position relative to the *force of gravity* **(Fig. 95.4)**. In general, the saccule responds to *vertical acceleration* and the utricle to *horizontal acceleration*. How?

1. ***The maculae*** of the saccule and utricle are ***stretch receptors***, the effective stimulus being the pull of the gravity on the *cupula*. The hair cells are thus deformed with resulting stimulation of the nerve fibers which lie between them **(Fig. 95.5)**.
2. ***The saccules*** *are affected by a lateral tilt of the head,* therefore, if the head is tilted laterally to the right, *i.e.* to rest on the shoulder:
   (i) the cupula of the right saccule hangs downwards and pulls on its macula which is *maximally* stimulated; and
   (ii) the cupula of the left saccule points upwards and *rests* on the macula, this being the position of *minimal* stimulation of the nerve endings.
3. ***The utricular maculae*** *are affected by nodding* the head up and down as in signifying 'yes':
   (i) with the head erect (upright position) the cupulae in the utricles point upwards providing a *minimal* stimulus; and
   (ii) when the head is bent well forward or backwards, the cupulae are hanging, pulling on the maculae and so stimulating them *maximally.*
4. *A tilt of as little as 2.5°* stimulates the appropriate maculae. As the tilt increases, the frequency of the discharge progressively rises.

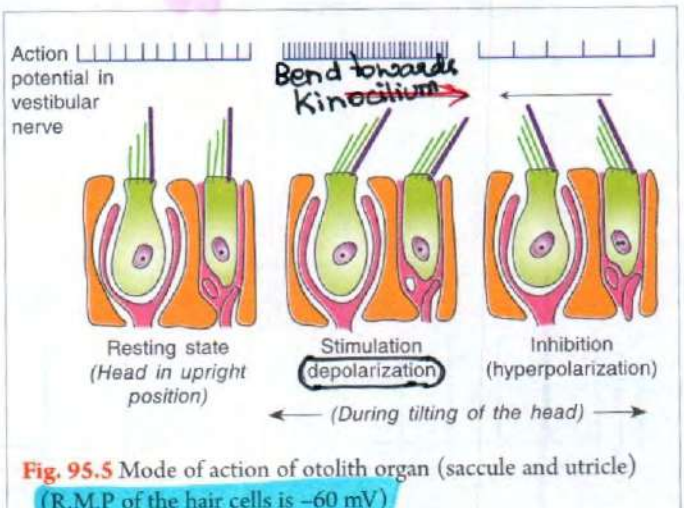


Fig. 95.5 Mode of action of otolith organ (saccule and utricle) (R.M.P of the hair cells is –60 mV)

Note

Movement of stereocilia towards the kinocilium increases the action potential frequency in the afferent nerve; while stereocilia movement away from kinocilium decreases the rate relative to the resting state.

Important Note

In each macula, each of the hair cell is oriented in a different direction so that some of the hair cells are stimulated when the head bends forwards; some are stimulated when it bends backwards; others are stimulated when head bends to other side. Therefore, a different pattern of excitation occurs in the macular nerve fibers for each orientation of the head in the gravitational field. It is this patterns that apprise, the brain of the head's orientation in space.

5. The maculae also discharge *tonically* in the absence of head movement, because of the pull of gravity on the otoliths. Therefore, if the head is kept in any particular position, the impulse discharge pattern slightly decreases but persists as long as the position is maintained.
   Thus the receptors show little adaptation.

B. MODE OF ACTION OF THE SEMICIRCULAR CANALS

The semicircular canals detect *angular (rotational) acceleration* during rotation of the head along three perpendicular axes. The three axes of the semicircular canals are those activated while *nodding the head up and down* (as in signifying *yes*); *shaking the head from side to side* (as in signifying *no*), and *tilting the head* so the ear touches the shoulder on the same side.

1. The *effective stimulus* to each ampulla is rotation of the head in the plane of its canal (Fig. 95.6). Whenever the head is moved, the semicircular canal and the attached bodies of the hair cells all turn with it. The endolymph filling the canal, however, is not attached to the skull, and because of inertia the endolymph tends to retain its original position, *i.e.* to be ***left behind***. This is equivalent to a flow in the reverse direction from that of the head movement. Thus, the moving ampulla is pushed against the stationary endolymph, and a *pressure gradient* is created across the cupula. This causes bending of the hair and stimulation of hair cells, that activates the nerve terminals synapsing with the hair cells.
2. *For example*, in case of rotation of the head towards right side in the horizontal plane (Fig. 95.6) the initial endolymph movement is thus towards the right ampulla and away from the left ampulla; both

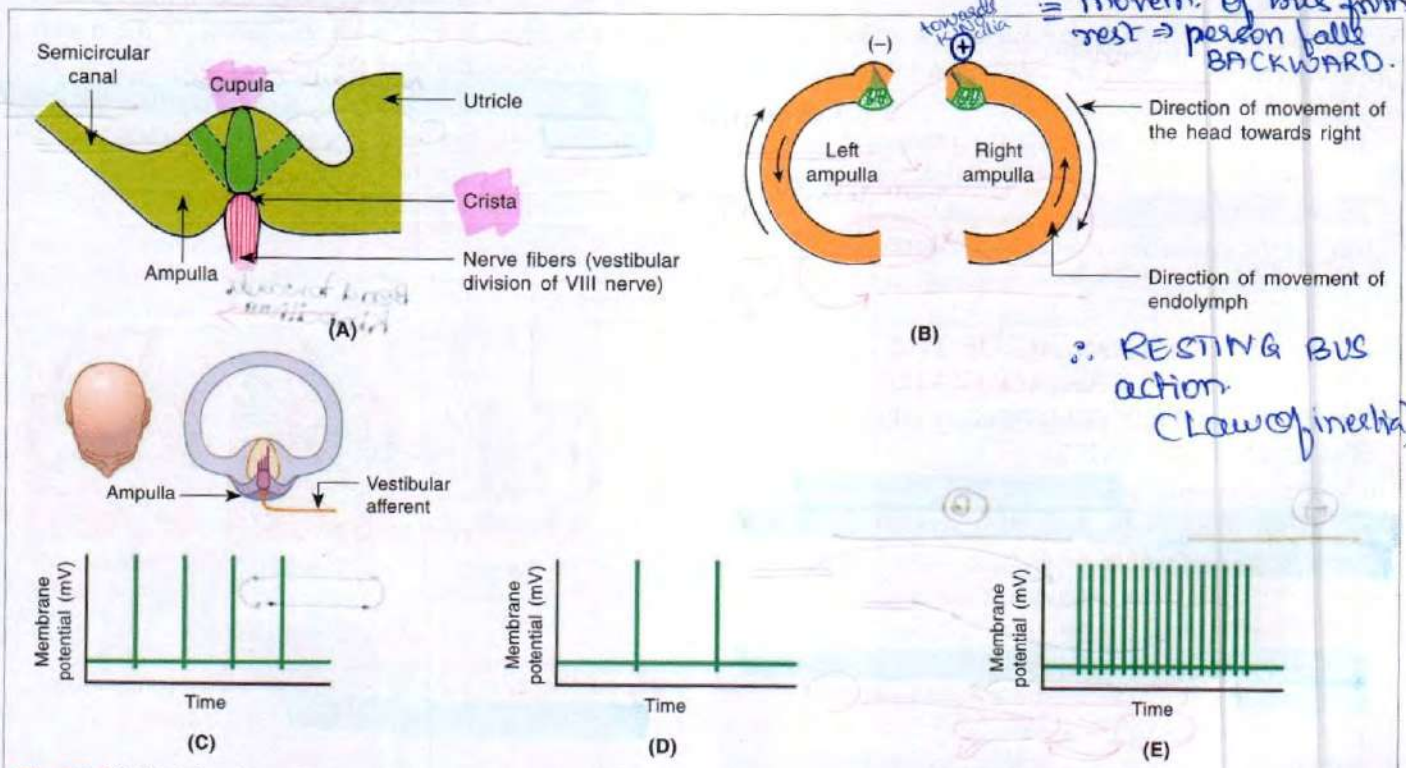


Fig. 95.6 (A) Mode of stimulation of semicircular canals; (B) mode of action of horizontal (lateral) semicircular canal when the head is moved towards the right; (C) Rest or constant rate of motion: frequency of action potential in left ampulla (D) and right ampulla (E) respectively

Note

The right ampulla is stimulated (+) whereas the left ampulla is inhibited (–). Also see Fig. 95.5

cupulae swing to the left. Vestibular action potentials show that the frequency of the impulses from the right ampulla is increased while that from the left ampulla is decreased.

3. The *stimulus to the cristae* is due to the swinging of the cupula set up by the endolymph. The combination of increased impulse discharge from one ampulla and decreased impulse discharge from the other, form the basis of the direction of the movement.
4. The *frequency of action potential* in the afferent nerve fibers that synapse with the hair cells is related to the rate of acceleration of rotational movement *i.e.* the amount of force bending the hairs on the receptor cells and to the direction in which this force is applied.
5. As the rotation is continued, the endolymph takes up the same rate of movement as its canal, the cupula by reason of its own elasticity, then returns (in about 30 seconds) to its original resting position and the resting nervous discharge is resumed. Therefore, the discharge in the *active* ampulla decreases and that in the *depressed* ampulla increases.
6. *On cessation or deceleration of the movement*, changes occur which are the reverse of the initial ones. Thus, the semicircular canals signal changes in acceleration but are insensitive to movements at a constant angular velocity.
7. The vertical inferior (posterior) canal acts similarly except that the ampulla which is *leading* is stimulated.
8. The left superior (anterior) and the right inferior (posterior) canals act as *a functional pair*, as do the right superior (anterior) and the left inferior (posterior) canal.

With the head at rest there is a steady *spontaneous* discharge of impulses from all the six ampullae.

Important Notes

1. *The semicircular canals* give information about movements, the *otolith organ* about the *position* of the head.
2. Reading newspaper or magazine in a moving bus puts maximum strain to the ***vestibulo-visual fixation*** mechanism (see below). That is why, reading prints from a moving bus is so difficult.

C. ROLE OF VESTIBULAR APPARATUS IN REGULATION OF POSTURE

1. The tracts that descend from the vestibular nuclei into the spinal cord (vestibulospinal tract and medial longitudinal bundle, page 912) *maintain tone in antigravity muscles* and coordinate the adjustments made by the limbs and eyes in response to changes 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 reflexes (*tonic labyrinthine and labyrinthine righting reflexes*, page 953) accompanying locomotion. This is why the vestibular apparatus is sometimes called the sense organ of *balance (equilibrium)*.
2. The vestibular information after relay via the thalamus to the cortex helps in conscious awareness of the position and acceleration of the body.
3. *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 the right in order to prevent an image from moving off the fovea (Fig. 95.7).

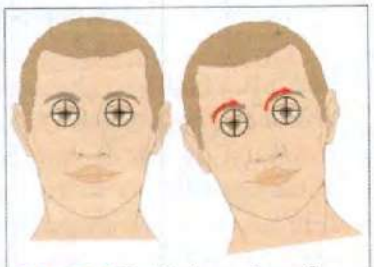


Fig. 95.7 Vestibulo-ocular reflex

Note

If the rotation of the head continues, the eyes once again move in the direction opposite to head rotation. These movements of the eyes are called *nystagmus*, page 1117)

4. *Orientation in space*. Orientation *i.e.* relative position of various body parts in space depends upon four inputs:
   (i) from the vestibular receptors,
   (ii) from visual informations,
   (iii) by impulses from proprioceptors in joint capsule, and
   (iv) by impulses from cutaneous exteroceptors, specially touch and pressure receptors.

   These four inputs are synthesized at a cortical level into a continuous picture of the individual's orientation in space.

Important Note

The vestibular apparatus initiates *otolith reflexes* that prevent leg injuries when a person walks downstairs or jumps from a platform. Because of these reflexes, the muscles in the leg begin to contract before the feet reach the ground in order to cushion the force of impact. This explains why the individuals with poor (or lacking) *otolith reflexes* are prone to leg injuries, while stepping off a bus.

VESTIBULAR DYSFUNCTIONS

MOTION SICKNESS

1. It is a *syndrome* (*i.e.* collection of symptoms) consisting of a tendency to yawning, increased salivation, gastrointestinal discomfort, nausea, retching and vomiting, pallor, headache, ***vertigo*** (*i.e.* sensation of rotation in the absence of actual rotation) and mental depression.
2. All forms of travel where there is irregular motion, specially in a vertical plane may induce it.
3. It can be induced in most people from an unexpected combination of inputs from the vestibular apparatus and other sensory system, presumably linear and rotational acceleration occur in an unpredicted way.

SEA SICKNESS

This is a type of motion sickness that may affect persons travelling by sea. It may be *due to excessive stimulation of the labyrinth*, to which the victim is not accustomed, resulting from the irregular and repetitive motion of the ship. Apprehension and other psychological factors play a part.

MENIERE'S (DISEASE) SYNDROME

1. A disorder involving the vestibular apparatus; it is associated with episodes of abrupt and often severe dizziness (*vertigo*), ringing in the ear (*tinnitus*) and bouts of hearing loss.
2. It is *caused by over-distension of the membranous labyrinth* probably through hypersecretion.
3. The dizziness occurs because the inputs from the two ears are not balanced, either because only one ear is affected or because the process begins in one ear sooner than the other.

LABYRINTHECTOMY

It means removal of the labyrinth.

A. Unilateral labyrinthectomy. It gives rise to complex derangements of postural activity and the effects are divided into immediate and permanent effects.

The immediate effects are:

1. Oblique deviation of the eye *i.e.* one eye rolls upwards and outwards and the other downwards and outwards.
2. ***Nystagmus*** *i.e.* there is a slow swaying movements towards the side of the lesion and a quick return towards the midline.
3. Rotation and lateral flexion of the head, so that the occiput is turned to the side of the lesion.
   These changes are due to the unopposed action of the intact labyrinth.
4. The limbs on the side of the lesion flex, and the limbs on the opposite side extend.

The permanent effects are:

1. Nystagmus.
2. The reciprocal changes in tone and the head rotation persist.
3. The rotation of the trunk decreases.

B. Bilateral labyrinthectomy.

1. The individual behaves fairly normally if allowed to use the vision. He cannot *right* himself when blindfolded.
2. Muscle tone is decreased but it is not the permanent loss.

Barany's Caloric Test

The semicircular canals can be stimulated by introducing water at 30°C or 44°C (7°C above and below the normal body temperature) into the external auditory meatus. The temperature difference sets up convection currents in the endolymph, as a result cupula is set into motion.

This technique of *caloric stimulation* is used clinically for diagnostic purposes. It causes some nystagmus, vertigo and nausea.

Important Note

When irrigating the ear canals in the treatment of ear infections, it is important to be sure that the fluid used is at body temperature so that above symptoms can be avoided.

Study Questions

1. Give the structure of receptors in the vestibular apparatus (labyrinth). How do these receptors get stimulated?
2. Mention the role of vestibular apparatus in control of postural activity.
3. Give the mode of action of otolith organ and semicircular canals.
4. Define vestibulo-ocular reflex. Give its physiological significance.
5. Explain why is reading newspaper/magazine in a moving bus so diffricult.
6. What determines the individual's orientation in space?

7. In some individuals, irrigating the ear canals causes vertigo. Explain.
8. How does motion sickness differ from sea sickness?
9. What will happen and why, if:
   (i) membranous labyrinth is over distended?
   (ii) otolith reflexes are lacking?
10. Mention the differences in the functional aspect of saccule, utricle and semicircular canals.
11. Name the tracts which descend from the vestibular nuclei to the spinal cord. Give their physiological significance.
12. What are the effects of unilateral and bilateral labyrinthectomy?
13. Draw labelled diagram:
    (i) Structure of vestibular apparatus receptors
    (ii) Otolith membrane
    (iii) The hair cells in otolith organ
    (iv) Vestibular pathway
14. Justify receptors of vestibular apparatus show little adaption.
15. List differences between linear and angular acceleration. Give examples.

MCQs

1. The otoliths or otoconia are:
   (a) Ca carbonate
   (b) Ca gluconate
   (c) Ca oxalate
   (d) Ca lactate
2. The otolith organ (saccule and utricle) of vestibular apparatus is stimulated by:
   (a) Gravity
   (b) Rotational movement
   (c) Angular acceleration
   (d) All of the above
3. The saccule maculae are affected by:
   (a) Lateral tilt of the head
   (b) Nodding the head up and down as in signifying 'yes'
   (c) Shaking the head from side to side as in signifying 'no'
   (d) Rotational movement
4. The minimum tilt which is required to stimulate the maculae of saccule and ultricle is:
   (a) 1°
   (b) 1.5°
   (c) 2°
   (d) 2.5°
5. Head rotation is primarily detected by:
   (a) Utricle
   (b) Saccule
   (c) Crista ampullaris
   (d) All of the above
6. The semicircular canals contain hair cells which are stimulated by:
   (a) Movement of perilymph
   (b) Linear acceleration
   (c) Cessation of rotation
   (d) Rotation of constant velocity
7. Reading newspaper in a moving bus is so difficult because of:
   (a) Motion sickness
   (b) Imperfect visual inputs
   (c) Disorientation in space
   (d) Strains to vestibulo-visual fixation
8. Motion sickness is characterized by:
   (a) Increased salivation
   (b) Intestinal hurry
   (c) Bradycardia
   (d) All of the above
9. Irrigation of ear canal in the treatment of ear infections, fluid used should be at:
   (a) 30°C
   (b) 44°C
   (c) ±7°C normal body temperature
   (d) Any of the above
10. Maculae are specific receptors of:
    (a) Semicircular canals
    (b) Utricle
    (c) Saccule
    (d) Only (b) and (c)
11. *False* about the macula of the utricle:
    (a) Is a type of receptor organ
    (b) Is stimulated by movement of the otoliths
    (c) Helps to maintain equilibrium
    (d) Is non-functional in persons with hearing deficits
12. The kinocilium in macula is:
    (a) Small cilia with progressive increase in height
    (b) Chalky particles in the cupula
    (c) A large non-motile hair
    (d) All of the above

13. **When the head is in the normal erect position:**
    (a) The macula of each utricle is in the horizontal plane
    (b) The macula in each saccule lies in the vertical plane
    (c) The cupula, hair and otoliths rising along the perpendicular axis from the macular epithelium
    (d) All of the above are true
14. **The portion of the vestibular system that is most important for preventing a person from suddenly falling if he makes a sudden turn while moving forward is the:**
    (a) Saccule
    (b) Utricle
    (c) Cochlea duct
    (d) Semicircular canals
15. **Vestibular fibers relay in:**
    (a) Vermis
    (b) Lateral geniculate body
    (c) Floculonodular lobe of cerebellum
    (d) Auditory cortex
16. **What happens to frequency of action potential in afferent nerves with the movement of stereocilia towards the kinocilium:**
    (a) Increases
    (b) Decreases
    (c) No change
    (d) Variable
17. **A sudden forward acceleration of head produces a sensation that whole body is:**
    (a) Falling forward
    (b) Falling backward
    (c) Moving sideways
    (d) Rotating
18. **With the head at rest there is:**
    (a) Steady spontaneous discharge of impulse from all the six ampullae
    (b) No discharge of impulses from any of the six ampullae
    (c) Only one functional pair of ampullae discharge spontaneously
    (d) None of the above is true
19. **Otolith reflexes:**
    (a) Prevent leg injuries when a person walks downstairs or jumps from a platform
    (b) Cause muscles in the leg to contract before the feet reach the ground during jumping
    (c) Initiated by the vestibular apparatus
    (d) All of the above are true
20. **Meniere's disease, *not a true* statement:**
    (a) Caused by overdistension of membranous labyrinth
    (b) Associated with abrupt episodes of vertigo
    (c) Bouts of hearing loss may be the presenting complaint
    (d) Both the ears are involved

Answers

1. (a)	2. (a)	3. (a)	4. (d)	5. (c)	6. (c)	7. (d)	8. (a)	9. (d)	10. (d)
11. (d)	12. (c)	13. (d)	14. (d)	15. (c)	16. (a)	17. (b)	18. (a)	19. (d)	20. (d)

Chapter

96

Control of Body Movement and Posture

I. Introduction

II. Control of body movement: Levels of motor control system

III. Control of body posture: Postural reflexes
Posture in spinal, decerebrate, mid brain and decorticate preparations
Mechanism of normal standing posture
Walking

INTRODUCTION

1. Carrying out a coordinated movement is a complicated process involving nerves, muscles and bones. The skeletal muscle contraction in the body is controlled through the *'motor units'* (page 170). All the motor neurons for a given muscle make up the *motor neuron pool* for the muscle. When all motor neurons in a pool get activated at one time, this leads to a *coarse* movement; while partial activation gives much *finer* degree of control.
   Therefore, the skeletal muscle activity depends ultimately upon the pattern and rate of discharge of the motor neurons.
2. There are many *inputs to each spinal motor neuron* viz.,
   (i) from the same spinal segment,
   (ii) suprasegmental inputs,
   (iii) from other spinal segments,
   (iv) the brain stem, and
   (v) the cerebral cortex.
   Some of these inputs end directly on α-motor neurons, but many exert their effects via interneurons or via γ-motor neurons to the muscle spindles.

   Functions
   (i) bring about voluntary movement,
   (ii) adjust body posture and provide stable background for movement; and
   (iii) provide coordination of the various muscles to make movements smooth and precise (page 969).
3. These neurons form the *final common path* to the skeletal muscle (page 882). It is integrated activity of these multiple inputs that regulates the posture of the body and makes coordinated movement possible.

Important Note

No one input source to a 'motor unit' is completely essential for movement, but a balanced input from all sources is necessary to provide the precise, speedy and normal coordinated activities.

4. The pattern of voluntary movement is planned within the brain, and the *commands* are sent to the muscles via the descending pathways (page 908). Posture is continuously adjusted before and also during movement by posture regulating systems (see below).
5. In the brain stem and spinal cord, ***medial or ventral (anterior) descending pathways*** (anterior corticospinal tracts, tectospinal, reticulospinal and vestibulospinal tracts) are concerned with the control of muscles of the trunk and proximal parts of the limbs; whereas ***lateral pathways*** (lateral corticospinal tracts and rubrospinal tracts) are concerned with the control of the distal group of muscles of the limbs. They also control skilled voluntary movements.
6. The *axial muscles* (*muscles of the trunk and proximal limb muscles* - page 906) are concerned with postural adjustments and gross movements, while the *distal limb muscles* are concerned with fine, skilled movements. (Also refer to **Fig. 87.3** and important note on page 847).

CONTROL OF BODY MOVEMENTS (LEVELS OF MOTOR CONTROL SYSTEM)

Throughout the CNS, the neurons that are involved in controlling movements are organized at 3 levels, called

the *Motor Control Systems*, each level having a limited *task* in motor control (Fig. 96.1).

A. THE HIGHEST LEVEL
THE CEREBRAL CORTEX

1. It comprises many regions of cerebral cortex including those involved with memory and emotion, supplementary motor cortex and association cortex. These, in turn, receive and correlate inputs from many other brain areas.
2. ***It forms complex plans/programmes*** according to individual's desire and is responsible for:
   (i) generating the idea for voluntary movements; and
   (ii) issuing the motor *commands* for their execution.
   Information is relayed from the *command* neurons of the highest level to the parts of the brain that make up the *middle* level of the motor control system.

B. THE MIDDLE LEVEL
SUBCORTICAL CENTRES

1. These structures specify the postures and movements necessary to carry out the desired action.
2. Its structures are located in parts of the cerebral cortex, specially sensory-motor cortex, cerebellum, basal ganglia and some brain stem nuclei.
3. It receives inputs from the *command* neurons and simultaneously receives (afferent) information from the receptors in the muscles, tendons, joints, skin, vestibular apparatus and eyes. All these informations are integrated by neurons of the middle level.
4. It is ***responsible for*** adjusting and coordinating the motor *commands* so that *tasks* are properly carried out. Thus it converts *complex* plans to a number of *smaller* motor programmes, which determines the pattern of neural activation required to perform the movement. These programmes are transmitted via the descending pathways (page 908) to the *lowest* control level.

C. THE LOWEST LEVEL:
BRAIN STEM AND SPINAL CORD

1. The *brain stem* is the ***major relay station*** for all motor commands except those requiring the greatest precision, which are transferred directly to the spinal cord. It is also responsible for maintaining normal body posture during motor activities.
2. The *spinal cord*. It contains the *final common pathways* (page 882) through which a movement is executed. By selecting the proper motor neurons for a particular *task* and by reflexely adjusting the amount of motor neuron activity, the spinal cord contributes to the proper performance of a motor *task*.

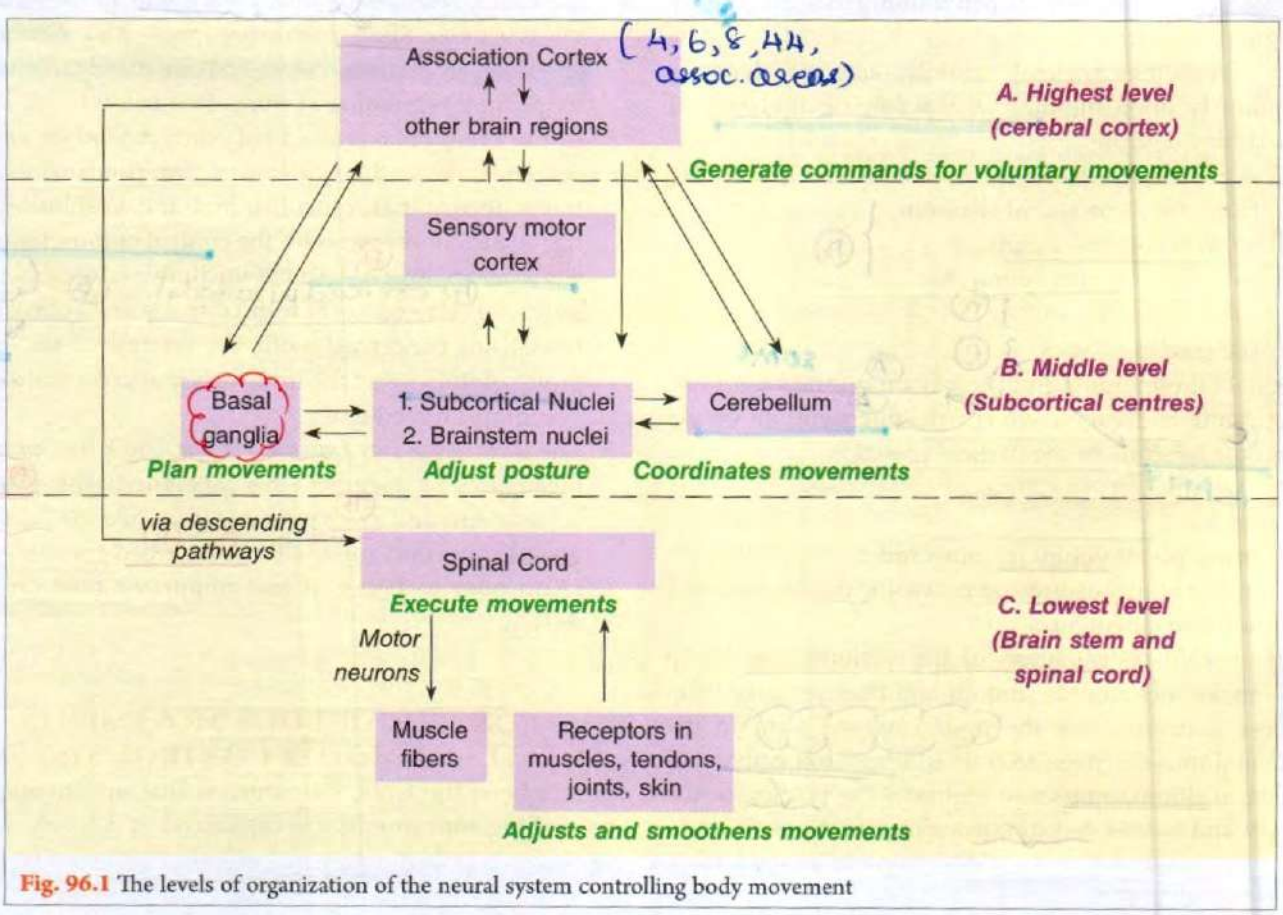


Fig. 96.1 The levels of organization of the neural system controlling body movement

Important Notes

1. After the initial motor programme is implemented and the action has begun, those brain regions concerned with motor control continue to receive a constant *feedback* of updated information from the receptors in the periphery about the movements taking place.
2. Any discrepancies (differences) between the intended and actual movements are detected, programme corrections are determined, and the corrections are relayed via the lowest level of the motor control system to its *final* output stage, the *motor neurons*. The motor programme is thus continuously adjusted during the course of most movements.
3. When learning has taken place and movement becomes *skilled*, the initial information from the middle level is more accurate and fewer corrections need to be made.
4. The motor system *"learns by doing"* (page 970) and performance improves with repetition. This involves synaptic plasticity.

CONTROL OF BODY POSTURE (POSTURAL REFLEXES)

1. *Definition:* The muscles that maintain comfortable upright posture, *i.e.* support the body's weight against gravity (Fig. 96.2). It is controlled by the brain and by reflex mechanisms that are passed into the neural networks of the brainstem and spinal cord. They are concerned with maintaining upright static posture and that of maintaining balance.
2. The maintenance of posture and balance is accomplished by means of *complex* interacting *postural reflexes*. It has *3 major components* (Fig. 96.3):
   (i) The *afferent* pathways of the reflex arc come from the eyes, the vestibular apparatus and the proprioceptors;
   (ii) The *efferent* pathways are the α-motor neurons to the skeletal muscles; and
   (iii) The *integrating centers* are neuronal networks in the brain stem and spinal cord.
3. *The postural reflexes* not only maintain the body in an upright balanced position but also provide the constant adjustments necessary to maintain a stable possible background for voluntary activity. These adjustments include:
   (i) *Static reflexes* which involve sustained contraction of the musculature; and
   (ii) *Phasic reflexes* which involve transient movements.
4. A major factor in control of posture is variation in the threshold of the spinal *stretch reflexes* (page 876). This in turn is caused by:
   (i) changes in the excitability of motor neurons; and
   (ii) changes in the rate of discharge in the γ-motor neurons to muscle spindles.

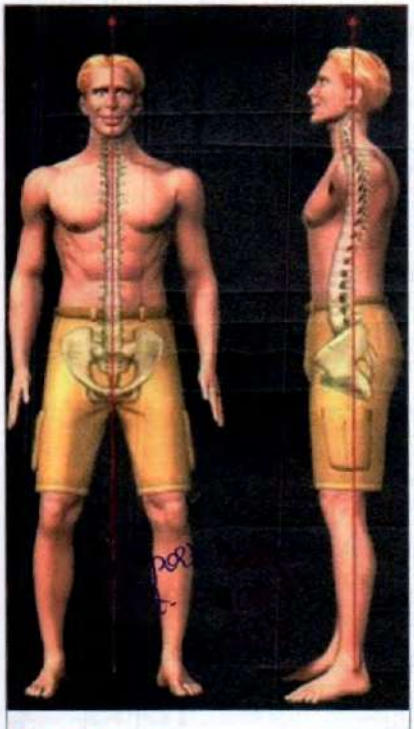


Fig. 96.2 Normal body posture

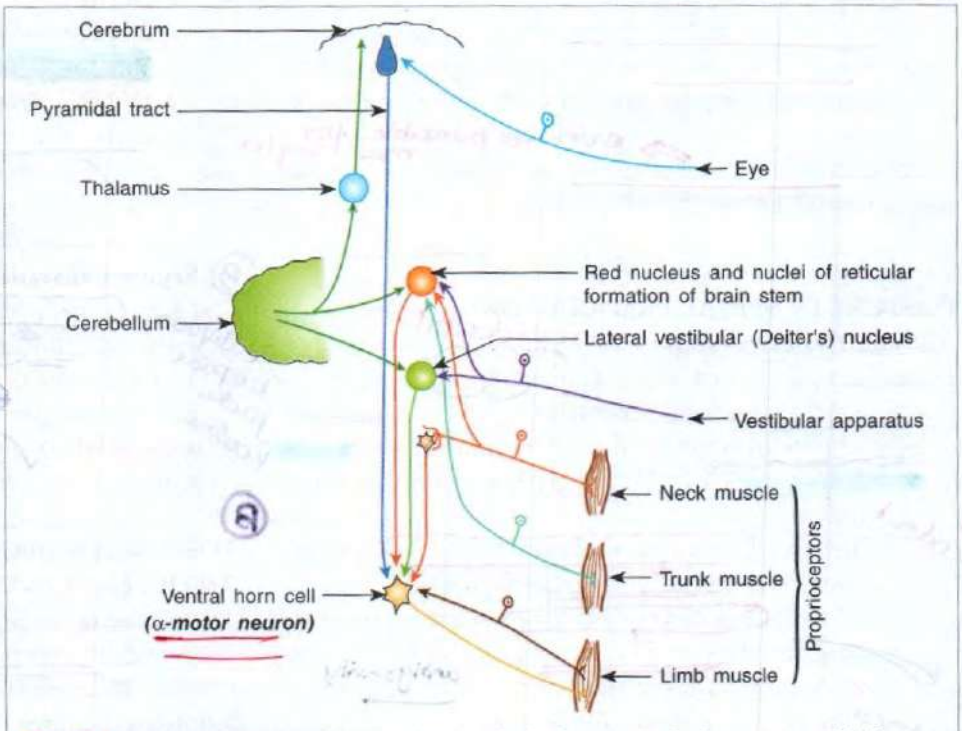


Fig. 96.3 Major components of 'postural reflexes' which maintain body posture and balance

5. The postural reflexes are integrated at various levels in the CNS from the spinal cord to the cerebral cortex. The main *levels of integration* are given in **Table 96.1**.

Table 96.1: The Major levels of motor integration (principal postural reflexes)

Level of integration	Principal function/Reflexes/Reflexes
1. Spinal cord	Control of *spinal reflexes*. (Stretch reflex - page 873; Positive and negative supporting reactions - see above)
2. Medulla	Regulation of heart, respiration and *antigravity reflexes*. (Tonic labyrinthine and tonic neck reflexes - page 951)
3. Midbrain	Regulation of *Righting reflexes*. (page 951)
4. Midbrain, thalamus	Regulation of *locomotor reflexes*.
5. Hypothalamus, limbic system	Emotional functions.
6. Cerebral cortex	Initiation of voluntary movements, emotions and memory; involved in *Conditioned reflexes*. (page 1035)

6. The part played by different regions of the nervous system in the regulation of posture can be obtained by a study of animals in which parts of the *neural axis* (CNS) has been removed. When the neural axis is transected, the activities integrated below the section are cut off or *released* from the *control of higher brain centres* and often appear to be hyperactive. This is due to:
   (i) removal of an inhibitory control by *higher centres*,
   (ii) loss of differentiation of the reaction, so that it no longer fits into the gross pattern of motor activity, and
   (iii) denervation hypersensitivity (page 171) of the centres below the transection.

(A) POSTURE IN SPINAL PREPARATION: *SPINAL INTEGRATION*

1. At the spinal cord level, afferent impulses produce *simple reflex* responses. Transection of the spinal cord (*spinal preparation*) in man or in animals e.g. in the cervical region, show the integration of reflexes at the spinal cord level:
   (i) There is an initial stage of marked *flaccidity* (*spinal shock*) and *absence of reflexes* (page 931).
   (ii) Later, the isolated cord recovers some of its reflex function (*stage of reflex activity*, page 932); but the reflex contraction in the affected limb muscles is quite poor to support the weight of the animal.

Important Note

Spinal man cannot stand unsupported (without support).

2. Posture basically depends on a harmonically operating group of *stretch reflexes*. These are highly *localized* reflexes which produce contraction of the antigravity muscles (page 984) and reciprocal inhibition of the antagonistic muscles. The posture is thus *actively* maintained against the force of gravity.

3. Once the *spinal reflexes* begin to reappear after spinal shock, their *threshold* steadily decreases. Therefore, the stretch reflexes (page 873) are hyperactive, and so are the *reactions* based on this reflex. The resulting posture is thus reinforced and modified by the *local and segmental static postural reactions*.

(A) Local static postural reactions

(i) ***Positive supporting reaction (magnetic reaction).*** This is a remarkable *irradiating* reflex which produces simultaneous contraction of extensors and flexors of a limb (*i.e.* both the protagonists and the antagonists) converting it into a *solid rigid pillar*. The modified posture is well adapted to resist gravity and supporting the body weight. The reaction is most easily observed by pressing against the limb; the afferent impulses arise from the stimulated skin (touch-pressure) and from the muscles (proprioceptors).

(ii) ***Negative supporting reaction.*** Disappearance of positive supporting reaction is also an *active* phenomenon initiated by stretch of the extensor muscles. This helps a limb to be used for activities other than supporting the body weight. Thus, walking movements can be initiated when suitably stimulated.

(B) Segmental static postural reactions

As the threshold of the withdrawal reflex (page 880) is specially low, therefore even minor noxious stimuli may cause not only prolonged withdrawal of that limb but reflexly produce extension of the opposite limb (*crossed extensor response*) or marked flexion-extension pattern in the other three limbs (*shifting reaction*).

(B) POSTURE IN DECEREBRATE PREPARATION: *MEDULLARY INTERATION*

Transection of the brainstem at superior border of the pons in animals between the 2 colliculi (superior and inferior) is called ***Decerebrate preparation*** **(Fig. 96.4)**. It shows the following features. It permits the brain stem pathways

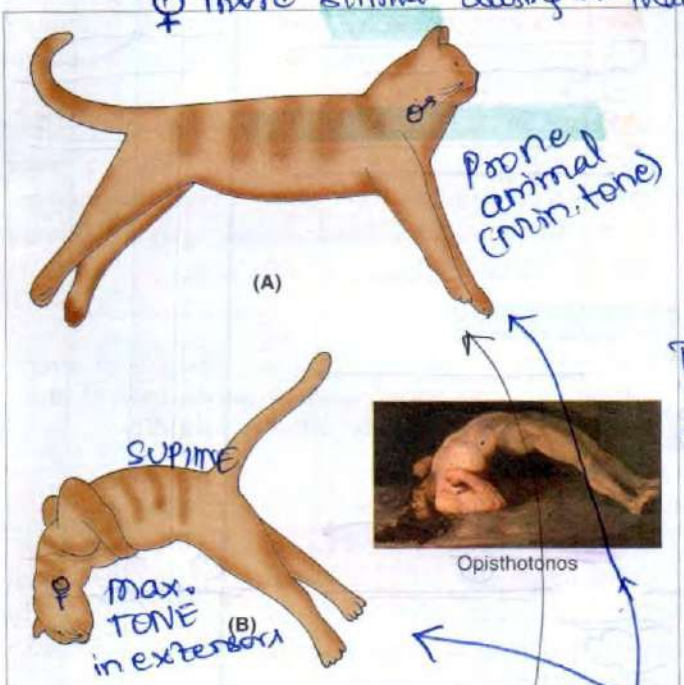


Fig. 96.4 (A) Decerebrate cat with intact labyrinths, suspended to show extensor rigidity. (B) Decerebrate cat following labyrinthectomy, the head drops forward which causes flexion of the forelimbs with concomitant extension of the hind limbs.

to function independent of their inputs from the higher brain centres. Therefore,

1. All impulse from the motor cortex (Corticospinal and corticobulbar tract) and red nucleus (rubro spinal tract page 912) are lost.
2. The excitatory and inhibitory reticulospinal tracts (page 903) to postural extensor muscles remain intact.
3. The drive from ascending sensory pathways to the exitatory reticulospinal tracts leads to the hyperactivity in the extensor muscles in all 4 limbs, called *Decerebrate Rigidity*.
4. The limbs are hyperextended, the tail and the head are dorsiflexed (extended) and the back is concave due to extreme hyperextension of the spine (*opisthotonos*).
5. The animal can be carefully balanced to show a strange posture of standing on its four legs, but the slightest displacement causes the animal to fall down.
6. *It has no righting reflexes*, the animal thus stays in the position in which it is placed.

Important Note

Righting reflex consists of a chain of reactions following one another in an orderly sequence to maintain normal standing position and keep the head upright. These responses are integrated mainly in the nuclei of the mid brain (page 953)

7. *Postural reflexes*

(i) The postural activities exceed those found in the spinal preparation. The posture is now a coordinated one of the whole body instead of being limited to all 4 limbs.

(ii) The degree of tone is adequate to maintain the upright position but it is not sufficient to 'take up' the upright position.

(iii) The posture of the trunk and limbs can be adjusted accordingly:

(a) with alternations in the position of the head in space; the afferent impulses arise solely from the otolith organ (page 939) of the vestibule (*tonic labyrinthine reflexes*); and

(b) by changing the position of the head relative to the trunk. Here *additional* afferent impulses come from the neck muscles (*tonic neck reflexes*).

Tonic Labyrinthine Reflexes

The labyrinthine reflexes are due to alteration in the position of the head relative to the horizontal plane. Therefore,

1. in the supine position, maximum tone is present in the *antigravity muscles* and decreases when the body is turned to either side **(Fig. 96.4)**,
2. in the prone position, tone in the extensor muscles is reduced to a minimum,
3. in the in-between positions, intermediate grades of tone are present.

Pathways of the reflex arc

(i) The *receptors* are in the otolith organ (*stretch receptors*, the effective stimulus being the pull of the gravity on the cupula - page 941); alterations in the position of the otoliths thus reflexly modify tone in the muscles of the limbs;

(ii) The *centres* for the labyrinthine reactions are the vestibular and reticular nuclei (*i.e.* in the medulla);

(iii) The *efferent* paths are the vestibulospinal and reticulospinal tracts; and

(iv) *Response:* Contraction of limb extensor muscles.

Tonic Neck Reflexes

The reflexes which are set up from neck muscles by alterations of the position of the head relative to the body are called *tonic neck reflexes* **(Fig. 96.5)**. The typical neck reflexes can be obtained by:

1. *The head turned down* (flexion of the head): The forelimbs flex and the hind limbs become more extended. The position of the body is being adapted e.g. *for looking under a shelf*.

2. *The head is turned up* (extension of the head): The forelimbs extend and the hind limbs flex. The body position *of looking on to a shelf.*
3. *Head is turned to side* (the head in various directions). In general, the ***jaw limbs*** (the limb, on the side to which the jaw is turned) extend (to support the weight of the head); and the ***skull or vertex limbs*** (the limbs to which the vertex is turned) flex. Therefore, when the head is rotated to the right, the right arm extends at the elbow and becomes abducted; the left arm becomes fully flexed with the hand touching the neck; the right leg is extended and the left leg is flexed.

Pathways of the reflex arc:

(i) The *receptors* are pacinian corpuscles in the ligaments of the cervical vertebral joints and also from neck muscle spindles.

(ii) The *centre* for reflexes is in the upper cervical region of the spinal cord/medulla.

(iii) The *efferent* paths are the long corticospinal tracts.

Mechanism of decerebrate rigidity

Decerebrate rigidity is a *release phenomenon* (page 950). It is a state of release in which hyperactive proprioceptive reflexes are responsible for a state of increased muscle tone. The hyperactivity of muscle reflexes, in turn, is due to:

1. *Release* of spinal γ-motor neurons from an inhibitory extrapyramidal discharge, which increases muscle spindle sensitivity to stretch; and
2. A residual *facilitatory* discharge from descending facilitatory reticular projection (page 959) to γ-motor neurons contributes to the state of *functional* increase of the stretch reflexes (via Ia muscle spindles afferent activity - page 876).

Important Note

This rigidity is reflex in origin as it disappears after cutting the appropriate dorsal nerve root of the limbs. It is thus popularly called as γ-rigidity.

Significance of Decerebrate Rigidity in Man

The extensor muscles of the lower limb (ankle, knee, hip), the muscles of the back and flexor muscles of the upper limb (wrist, elbow, shoulder) are the *antigravity muscles.* Contraction of these muscles helps to maintain a comfortable balanced position in the upright position; *the body cannot remain upright if these muscles get paralysed.*

In man, true decerebrate rigidity (though rare) causes extension of all the 4 limbs (Fig. 96.5). Although the defect that is produced is incompatible with life but it helps supporting the body against gravity.

Intercollicular Versus Ischaemic Decerebration

Refer Table 96.2

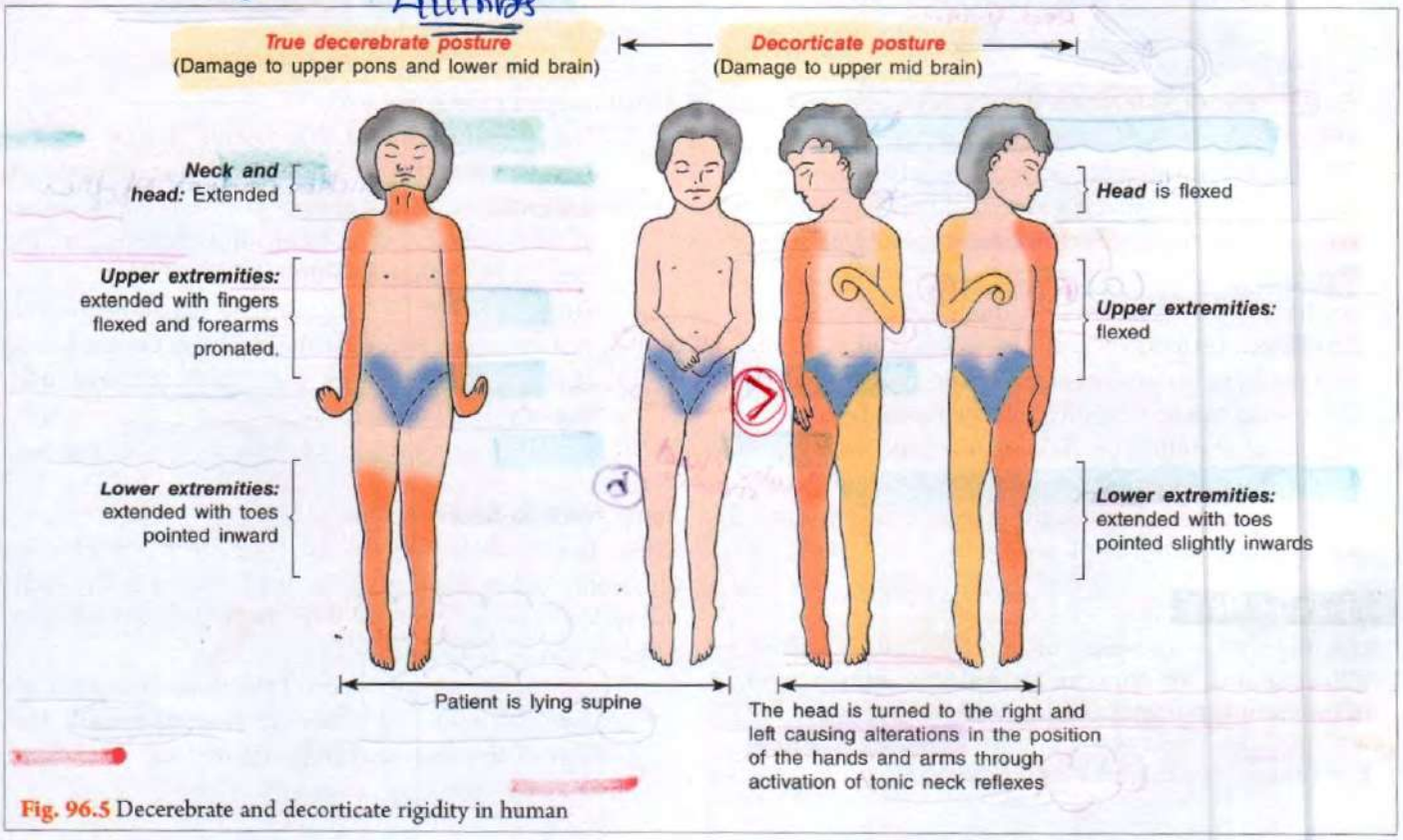


Fig. 96.5 Decerebrate and decorticate rigidity in human

Table 96.2: Differentiating features between intercollicular and ischaemic decerebration

Intercollicular Decerebration	Ischaemic Decerebration
1. It involves transection of brain stem between two colliculi (superior and inferior), called *Sherrington (or classical) decerebration.*	1. It is produced by tying both carotid arteries and the basilar artery at the junction of the pons and medulla.
2. It is usually a *fatal* traumatic procedure.	2. It is relatively a safe procedure.
3. It leads to decerebrate rigidity of *Sherringtonian type* which is particularly evident in the extensor antigravity limb muscles (see above).	3. It produces marked increase in muscle tone that resembles decerebrate rigidity.
4. *Mechanism of development of rigidity.* It is due to a *release phenomenon* (see above) which increases γ-motor neurons' activity, called *γ-rigidity.*	4. It is due to an excessive discharge of α-motor neurons from vestibulospinal tracts (page 912), therefore, also called *α-rigidity.*
5. *Effect of deafferentation* i.e. dorsal root section. Hypertonia (rigidity) of extensor muscle is abolished, indicating hypertonia is 'reflex' in origin.	5. Hypertonia in no way is reduced, indicating hypertonia is induced 'directly'.
6. It gets abolished by administration of drug chlorpromazine or local anaesthetic procaine which abolishes γ-motor neuron activity.	6. It remains unaffected by administration of such drugs.
7. Removal of anterior lobe of cerebellum (which normally inhibits γ-motor neuron discharge) increases the rigidity (page 967). (Also see to page 879)	7. It is not affected by removal of the anterior lobe of the cerebellum.

POSTURE IN MID BRAIN PREPARATION: *MIDBRAIN INTEGRATION*

In *transection of the neural axis at the superior border of the midbrain* (***midbrain preparation***) extensor rigidity as seen in decerebrate preparation is present only when the animal lies quietly on its back. When the animals are engaged in *phasic* activities, the *static* phenomenon of decerebrate rigidity is **not** seen. Therefore, midbrain animals can rise to the standing position, walk and right themselves.

Righting Reflexes

Definition (page 951).

By means of the righting reflexes the midbrain animal can bring its head right way up and get the body into the erect position under all circumstances. If the animal is laid on its side or on its back, the head at once rights itself, the body follows the same, and finally the animal resumes the upright posture. The familiar examples of righting reflexes are:

1. ***Labyrinthine Righting Reflex.*** With the animal's head in the lateral position impulses arise in the saccules (page 941) which lead reflexly to *righting* of the head.
2. ***Body Righting Reflex.*** With the animal on its side, the side of the trunk in contact with the floor is undergoing constant stimulation, while the other side in contact with air is not. This asymmetric stimulation of the deep structures in the body wall reflexly *rights* the head. The head can thus be *righted* even after bilateral labyrinthectomy (page 944).

These reflexes (1 and 2) act primarily on the neck muscles and right the head. The trunk, however, remains as before in the lateral position, so that the neck is twisted. This produces a further reaction – *the neck righting reflex.*

3. ***Neck Righting Reflex.*** It brings the thorax and lumbar region successively into the upright position. If righting of the head is prevented, impulses from the body surface may cause righting of the body directly *(Body on body righting reflex).*
4. ***Limbs Righting Reflex.*** The appropriate posture of the limbs is largely attained by impulses arising in the limb muscles themselves. *The "chief centre" for above righting reflexes is in the region of the red nucleus in the midbrain.*

The *red nucleus* extends from the hypothalamus to the caudal border of the superior colliculi. It consists of two groups of cells:

(i) *nucleus magnocellularis* – comprising of large nerve cells (few in number) which give rise to the rubrospinal tract; and

(ii) *nucleus parvocellularis* – consists of small nerve cells (more in number) and give rise to a rubroreticular tract which ends in reticular formation in the brain stem from which reticulospinal fibers send the impulses to the spinal cord.

The red nucleus plays an important part in helping to maintain normal body posture and normal muscle tone.

5. *Optical Righting Reflexes.* In animals (cat, dog or monkey) with the visual cortex intact, righting of the head is also brought about reflexly by means of optical impulses even after removal of labyrinthine or body stimulation. The centre for the reflex is in the visual (calcarine) cortex, from where impulses pass ultimately to the neck muscles to right the head.

Important Note

In man, the optical righting reflexes are far more important than those of the labyrinth. Righting reflexes still occur after removal of the cerebellum but they are imperfectly executed as the cerebellum is essential for all precise movements.

Other Midbrain Responses

1. *Pupillary light reflex* (page 1099).
2. Nystagmus, the reflex response to rotational acceleration (page 943).
3. *Vestibular placing reaction* *i.e.* response to linear acceleration that prepares the animal to land on the floor. Therefore, if a blind-folded animal is lowered rapidly, its fore limbs extend and its toes spread. (Also see to *vestibulo-ocular* reflex - page 943)

POSTURE IN DECORTICATE PREPARATION: *CEREBRAL CORTEX INTEGRATION*

Here the whole cerebral cortex is removed but the basal ganglia and the brain stem are left intact.

1. *The postural findings* are:
   (i) moderate rigidity is present due to loss of the cortical area that inhibits spinal γ-motor neuron discharge via the reticular formation - page 912 (*Decorticate rigidity*);
   (ii) the legs are fully extended (*extensor hyperactivity in the lower extremities*, similar to as seen in decerebration - page 950), the arms lie across the chest, semiflexed at the elbow, the forearms slightly pronated and the wrists and fingers flexed (flexion of the upper extremities due to activation of rubrospinal tracts - page 912) **(Fig. 96.5)**.

   Decorticate rigidity is seen *only* when the animal is at rest. It commonly occurs on the hemiplegic side after haemorrhage or thrombosis in the internal capsule.
2. *Postural reflexes*
   (i) The typical 'neck reflexes' (page 951) and 'righting reflexes' (see above) can be obtained.
   (ii) ***Hopping and placing reactions***. The former are the hopping movements that keep the limbs in position to support the body when a standing animal is pushed laterally. The latter are the reactions that place the foot firmly on a supporting surface.

These reactions are seriously disrupted by decortication.

Important Note

Decorticate animals are *easier* to maintain than midbrain animals because temperature regulation and other visceral homeostatic mechanisms integrated in the hypothalamus are present. However, ability to react in terms of past experience is severely affected.

MECHANISM OF NORMAL STANDING POSTURE IN MAN

1. When a man is comfortably balanced in the upright position, the arrangement of the skeleton, the ligaments and the soft parts is such that a *momentary insecure* balance can be maintained *passively*. *In the absence of all muscular activity*, the person would immediately fall if muscular activity did not develop. Because a person whose muscles are paralysed cannot stand, therefore, once he begins to fall, *reflex* compensatory muscular reactions set in which restore the state of balance.
2. A standing man can fall in any direction (forwards, backwards or sideways); the muscles which oppose the fall are referred as *antigravity muscles* (page 952). Therefore,
   (i) when the body leans *forwards*, the extensors of the trunk and flexors of the legs contract sufficiently to restore the balance;
   (ii) when the body leans *backwards*, the recti abdominis and the leg extensors contract; and
   (iii) when the body leans *sideways*, the contra-lateral external oblique muscle responds.
3. These responses are *reflexly* produced as a result of:
   (i) impulses from stretch receptors in the trunk and legs; and
   (ii) from the receptors in the head, mainly the eyes.

Important Note

With the eyes closed, the upright posture is less steady and more *swaying* (bending) of the trunk occurs. This shows that *visual* afferents are concerned in the reflex maintenance of the upright posture in man.

WALKING

1. The cyclic, alternating movements of walking are controlled within the CNS:
   (i) by the spinal cord at the level of the motor neurons; and
   (ii) by the brain stem.
2. Walking is ***initiated by*** allowing the body to fall forward to an unstable position and then moving one

leg forward to regain equilibrium. The legs may be activated out of phase with each other. The spinal motor neurons utilize *reciprocal inhibition* (page 879) so that when the extensor muscles are activated on one side of the body, to bear the body's weight, the contralateral extensors are inhibited to allow that limb to flex and swing forward.

3. Although the *higher centres* can control the rhythmic movement of a limb in the absence of feedback information from the proprioceptors, afferent inputs from the vestibular apparatus and eyes contribute to locomotion by acting *directly* on the higher centres and indirectly on the motor neurons themselves. The output of the *higher centres* is optimally adopted to the requirements.
4. The spinal motor neurons are also affected by input from the descending pathways, both during the initiation of activity and during ongoing activity. Such input helps adjust the movement according to the situation. For example, depending upon commands from the descending pathways, the two limbs may be operated together, as in jumping, instead of reciprocally.

Study Questions

1. **Differentiate between:**
   (i) Medial and lateral descending pathways (ii) Static and phasic reflexes
   (iii) Local and segmental static postural reactions (iv) α and γ rigidity
   (v) Tonic labrynthine and tonic neck reflexes (vi) Decerebration and decortication
   (vii) Intercollicular and ischaemic decerebration (viii) Labyrinthine and neck righting reflexes.
2. **Give the characteristic features at various levels of motor control system.**
3. **Define and give physiological significance:**
   (i) Righting reflexes (ii) Decerebrate rigidity (iii) Antigravity muscles
   (iv) Opisthotonos (v) Postural reflexes.
4. **Give the levels of integration of principal postural reflexes.**
5. **Describe the posture in an animal in:**
   (i) Spinal preparation (ii) Decerebrate preparation (iii) Midbrain preparation (iv) Decorticate preparation.
6. **Give the physiological significance of decerebrate rigidity in man.**
7. **Explain how a normal man is comfortably balanced in the upright position.**
8. **Write short notes on:**
   (i) Motor neuron pool and its functions (ii) Righting reflexes.
9. **Define normal body posture in humans. How is this maintained?**
10. **Draw labelled diagram:**
    (i) Major components of postural reflexes (ii) Decerebrate and decorticate rigidity in humans.

MCQs

1. **Skeletal muscle activity depends upon:**
   (a) Inputs to each spinal motor neuron from the brain stem (b) Pattern and rate of discharge of motor neurons
   (c) Motor units (d) Cerebral cortex activity
2. **The subcortical centres that control body movements include all *except*:**
   (a) Cerebellum (b) Basal ganglia (c) Spinal cord (d) Brain stem nuclei
3. **The basic spinal reflex of posture is:**
   (a) Stretch reflex (b) Extensor reflex (c) Cross extensor reflex (d) Flexor reflex
4. **Learning of motor skill is mainly carried out at which level of motor control system?**
   (a) Cerebral cortex (b) Subcortical centre (c) Brain stem (d) Spinal cord
5. **Most remarkable feature in a spinal man is:**
   (a) Cannot stand without support (b) Loss of sweating
   (c) Marked hypotension (d) Deep reflexes become hyperactive
6. **Decerebrate animal shows all *except*:**
   (a) Marked increase in muscle tone in extensor group of muscles
   (b) Opisthotonus
   (c) Absence of righting reflexes
   (d) Cannot stand unsupported

7. **Where is the centre located for causing body flexing movements of the head and body and turning movements of the body:**
   (a) Cerebral cortex (b) Limbic system (c) Thalamus (d) Midbrain
8. ***Not* an example of antigravity muscles:**
   (a) Extensor muscles of the lower limb (b) Muscles of the back
   (c) Flexor muscles of the upper limb (d) Muscles of the trunk and neck
9. **Extensor muscle hyperreflexia in inter-collicular decerebration is due to:**
   (a) Generalized loss of facilitation (b) Decreased stretch of muscle spindles
   (c) Increased gamma efferent neurons activity (d) Decreased alpha efferent neuron activity
10. **Chief centre for righting reflexes is in the region of:**
    (a) Cerebral cortex (b) Midbrain (c) Medulla (d) Spinal cord
11. **Which of the following statements is *not true*?**
    (a) Decorticate rigidity is greater than decerebrate rigidity (b) Righting reflexes are absent in the decerebrate animal
    (c) Visual righting reflex is present in a thalamic animal (d) Decorticate rigidity is seen only when the animal is at rest
12. **Which sensory system might be more important for maintaining a person's balance when he is running against the wind than when he is running with the wind?**
    (a) Vestibular apparatus (b) Proprioceptors of the neck (c) Exteroceptors (d) Eyes
13. **Anterior descending pathways are concerned with control of:**
    (a) Distal group of muscles of limbs (b) Muscles of trunk and proximal limbs
    (c) Both distal and proximal groups of muscles of limbs (d) Muscles of the trunk only
14. **Where is motor activity probably initiated in the brain?**
    (a) Motor cortex (b) Premotor cortex (c) Basal ganglia (d) Cerebellum
15. **Lowest level of integration of stretch reflex is at:**
    (a) Cerebral cortex (b) Upper medulla (c) Lower medulla (d) Spinal cord
16. **The basic posture reflex is:**
    (a) Crossed extensor reflex (b) Golgi tendon reflex (c) Stretch reflex (d) Positive supporting reflex
17. ***Not true* about the postural reflexes is:**
    (a) Maintain the body in an upright balanced position (b) Provide constant adjustments during body activities
    (c) Maintain a stable background for voluntary activity (d) Integrating centres are located in the cerebral cortex
18. **Which of the following reflexes is likely to disappear in the absence of connection between spinal cord and the brain?**
    (a) Sweating reflex (b) Swallowing reflex (c) Withdrawal reflex (d) Erection of penis
19. **The term decerebration denotes:**
    (a) Section of the whole cerebrum (b) Removal of one lobe of cerebral cortex
    (c) Removing cerebellum from the rest of brain (d) A mid collicular section
20. ***False* statement about tonic labyrinthine reflexes:**
    (a) Are due to alteration in position of head relative to the horizontal plane
    (b) In supine position, maximum tone is present in the antigravity muscles
    (c) In prone position, tone in the extensor muscle is minimum
    (d) With extension of head, the fore-limbs extend and hind limbs flex (Tonic-Neck Reflex)
21. **Decerebrate rigidity is *not* characterized by:**
    (a) Marked increase in muscle tone in extensor group of muscles
    (b) A state of release phenomenon
    (c) It is popularly called as α-rigidity (d) It is reflex in origin
22. **A feature *not* seen in the midbrain animal:**
    (a) Produced by transection of neural axis at the superior border of midbrain
    (b) Extensor rigidity is only seen at rest
    (c) Presence of righting reflexes
    (d) Absence of pupillary light reflex
23. **Selective damage to cerebral cortex without involvement of basal ganglia, patient still able to:**
    (a) Perform arithmatical calculations (b) Maintain equilibrium (Cerebellum ✓)
    (c) Perform fine movements with his hand (d) Think

Answers

1. (b) 2. (c) 3. (a) 4. (b) 5. (a) 6. (d) 7. (d) 8. (d) 9. (c) 10. (b) 11. (a) 12. (c) 13. (b) 14. (a) 15. (d)
16. (c) 17. (d) 18. (b) 19. (d) 20. (d) 21. (c) 22. (d) 23. (b)

Chapter

97

The Reticular Formation

I. Ascending reticular system: Reticular activating system (RAS)

II. Descending reticular system
   A. Inhibitory reticular projection
   B. Facilitatory reticular projection

III. Functions of the reticular formation

The term ***reticular formation*** is used for those parts of the *brain stem* (the medulla, pons and midbrain) which are characterized by an interlacing network of fiber bundles. It is composed of more than 50 *nuclear masses*, which together constitute the ***reticular nucleus*** and scattered throughout the central part of the brain stem.

It is the one part of the brain which is *absolutely essential for life* because:

(1) some reticular formation neurons are clustered together, forming *centres* of the brain stem nuclei and integrating centres. These include the cardiovascular, respiratory, swallowing and vomiting centres and centre for control of equilibrium and balance.

(2) it receives and integrates information from all regions in the CNS; and

(3) its neurons send axons to most regions of the brain and spinal cord, which indicates the very large influence the reticular formation has over the other parts of the CNS.

The pathways that convey information from the reticular formation are divided into two systems: *ascending and descending reticular systems.*

ASCENDING RETICULAR SYSTEM (RETICULAR ACTIVATING SYSTEM)

The ascending reticular pathway is also called ***reticular activating system*** **(RAS) (Fig. 97.1).**

Characteristic Features

1. It is a complex ***polysynaptic*** pathway which extends from the lower pons to the level of the thalamus. It contains the cell bodies and fibers mainly of the cholinergic systems.

2. RAS throughout its course receives afferent collaterals from:
   (i) the long somatic sensory pathways;
   (ii) the trigeminal, olfactory, auditory and visual pathways; and
   (iii) visceral pathways.

3. The degree of convergence in it abolish sensory modality specificity, therefore, a single peripheral stimulus gives rise to impulses which ascend to the cerebral cortex via two pathways:
   (i) in the classical sensory pathways with great speed to the primary receiving areas (*specific ascending pathways*); and

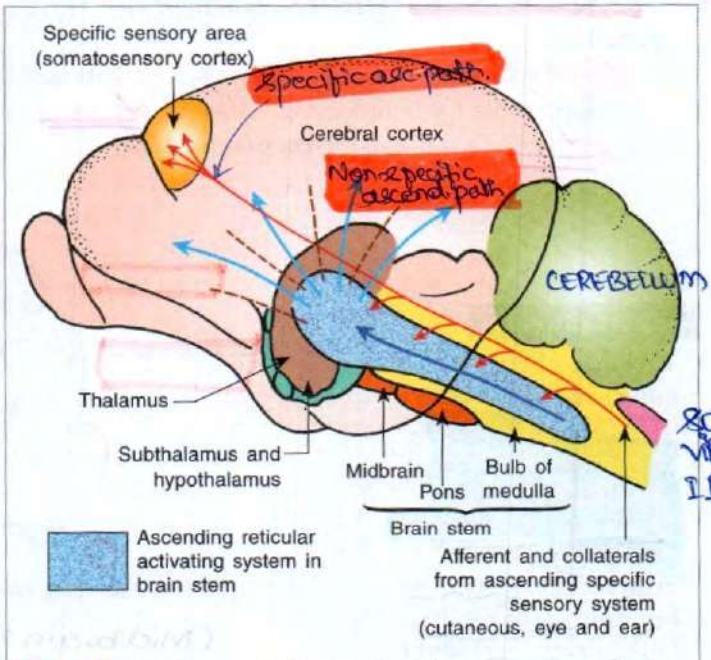


Fig. 97.1 Distribution of afferent collaterals to ascending reticular activating system in brain stem

(ii) in the ascending reticular system by *multisynaptic* relays to widespread areas of the cortex (*non-specific ascending pathways*).

This shows that the specific sensory pathways serve *discriminative* sensory perception, whereas the reticular system functions by arousing consciousness or alertness without which sensory discrimination and effective response would be impossible.

4. ***Pathway for arousal and alert states***

Some fibers from the superior temporal gyrus and orbital surface of the frontal lobe descend and join to form *corticofugal fibers*. Together with the RAS, the system:

(i) provides a pathway by which intra-cortical events can initiate arousal; and

(ii) is responsible for the alerting response to emotions and related psychic phenomenon that occur in the absence of any apparent external stimulus.

Proof: Stimulation of these cortical areas (wakes) a sleeping animal but causes no movements and has few visible effects in the conscious animals.

5. Some of the thalamic connections of the RAS relay in the midline and in the intralaminar nuclei of the thalamus (page 978) before passing on to the thalamic *reticular nucleus* where there is a further relay. From this nucleus fibers are widely distributed to all parts of the cortex. This pathway contains the cell bodies and fibers of *many adrenergic, nor-adrenergic* and *serotonergic systems*. The RAS by increasing excitability of the cortical neurons is thus intimately concerned with the electrical activity of the cortex (***Electroencephalogram*** – EEG).

Functions

1. Activity in the RAS produces the conscious state and is responsible for maintaining a state of *wakefulness or alertness*. This makes perception possible.

Proof

(i) Deactivation of RAS produces sleep (page 983).

(ii) Stimulation of RAS causes a strong desynchronization of the EEG (page 983).

(iii) Tumours or destruction of RAS produce coma or unconsciousness.

2. It is responsible for the electrical activity of the cerebral cortex.

DESCENDING RETICULAR SYSTEM

The reticular fibers that descend to the spinal cord form the *reticulospinal tracts* (page 912) – they influence activity in both the efferent and afferent neurons. This system comprises the *descending inhibitory* and *facilitatory reticular projections* (Fig. 97.2).

A. THE DESCENDING INHIBITORY RETICULAR PROJECTION

1. *Location:* The ventromedial part of the medulla is the site of the *bulbar* inhibitory reticular region. It causes the reduction of movements either reflexly by pyramidal stimulation or by stimulation of the motor cortex.
2. The *bulbar* reticular region itself is under the influence of the inhibitory areas of the cerebral cortex and the caudate nucleus of basal ganglia (page 994). The corticospinal inhibitory extrapyramidal pathway projects over this route to the medullary reticulum, which in turn relays the projection by reticulospinal tracts.
3. *Nor-adrenergic neurons* from many areas of the reticular formation project to the cerebellum. The anterior lobe and paramedian lobules of the cerebellum, in turn, project via the fastigial nucleus to the medullary region

Important Note

The anaesthetics (like ether) and sedatives in high dose (such as barbiturate) produce unconsciousness by depressing conduction in the RAS. This is achieved by decreasing building up of EPSPs to the firing level of the postsynaptic neurons in multisynaptic paths of RAS.

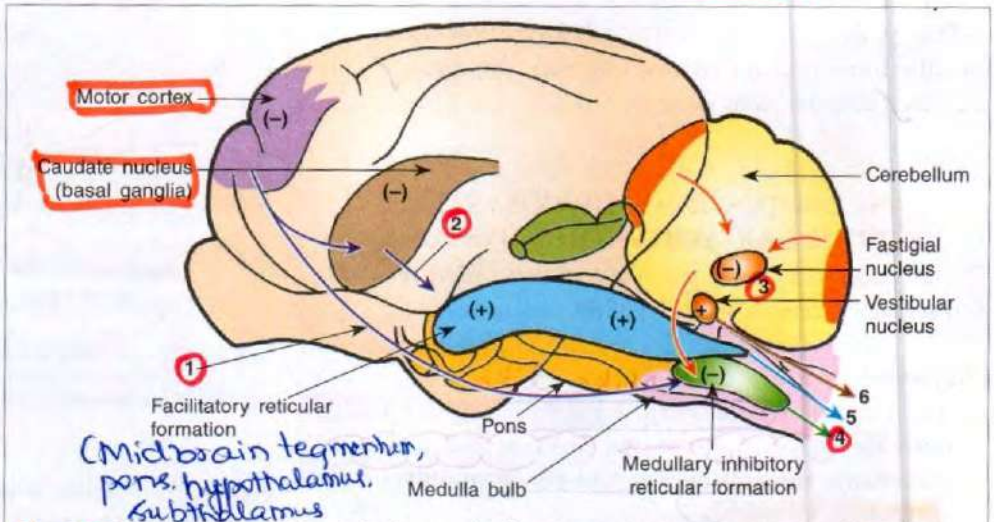


Fig. 97.2 Inhibitory (1 to 4) and facilitatory (5,6) systems concerned in spasticity (Also see to **Fig. 90.7**) (page 877)

(page 967) and further reinforce the inhibitory influence of this medullary reticulum upon the spinal neurons.

B. THE DESCENDING FACILITATORY RETICULAR PROJECTION

The reticular formation also sends and relays facilitatory extrapyramidal fibers to the spinal neurons.

1. A large area of the brain stem causes facilitation of cortically or reflexly induced movements.
   Proof: Electrical stimulation of the tegmentum of the midbrain and pons, or hypothalamus and subthalamus produces facilitatory movements.
   The effects are mediated by the reticulospinal pathways which run in the lateral columns of the spinal cord.
2. The *vestibular nuclei* also produce facilitatory influence of the spinal motor neurons via vestibulospinal tract (page 912) which influences the tone of extensor (antigravity) group of muscles.

Important Notes

1. Vestibular nuclei themselves are more active following the interruption of the extrapyramidal corticobulbar tracts.
2. Stimulation of the facilitatory reticular neurons increases the rate of discharge of the γ-motor neurons, conversely stimulation of the inhibitory reticular neurons reduces or abolishes γ-efferent activity.
3. The balanced activity of the inhibitory and facilitatory reticular projections helps in
   (i) control of smooth and purposeful movements; and
   (ii) control of posture and muscle tone.

Proof

(i) Decerebrate rigidity (page 951) is abolished by cutting the vestibulospinal tracts in the ventral columns of the spinal cord.

(ii) A unilateral lesion of the lateral vestibular nucleus abolishes decerebrate rigidity in the ipsilateral limbs.

FUNCTIONS OF THE RETICULAR FORMATION

1. The RAS and related reticular components are concerned with conscious alert states that make perception possible (page 958).
2. There is a major input from the anterolateral systems into the midbrain reticular formation which activates the RAS, which in turn maintains the cortex in the alert state.
3. The descending fibers in it:
   (i) inhibit transmission in sensory pathways in the spinal cord; and
   (ii) are concerned with spasticity and adjustment of stretch reflexes that control body movement and posture.
4. It contains many of the areas concerned with regulation of heart rate, BP and respiration.
5. It contains the cell bodies and fibers of many of the serotonergic, cholinergic, nor-adrenergic and adrenergic systems (pages 1045-1046).

Important Note

There is considerable interaction between the ascending, descending and cerebellar reticular pathways. For example, all three components function in controlling muscle activity.

Study Questions

1. Which component of the nervous system is absolutely essential for life, and why?
2. Give the role of reticular formation in:
   (i) discriminative sensory perception
   (ii) genesis of EEG
   (iii) maintaining state of alertness
   (iv) control of posture and equilibrium.
3. Define and give the functions of:
   (i) non-specific ascending pathway
   (ii) corticofugal fibers
   (iii) reticular nucleus
   (iv) reticulospinal tracts.
4. Mention the characteristic features of ascending and descending reticular systems.
5. Explain how sedatives in high dosage produce unconsciousness.
6. Draw labelled diagram:
   (i) Distribution of afferent collaterals to ascending reticular activating system.
   (ii) Inhibitory and facilitatory systems concerned with spasticity.

MCQs

1. **The one part of the brain which is absolutely essential for life is:**
   (a) Cerebral cortex
   (b) Basal ganglia
   (c) Cerebellum
   (d) Reticular formation

2. **The ascending reticular system, spot the *wrong* statement:**
   (a) A complex polysynaptic pathway
   (b) Extends from lower pons to thalamus
   (c) Mainly comprises of adrenergic system
   (d) Throughout its course receive afferents from sensory pathways

3. **For arousal response, important ascending pathway is:**
   (a) Reticulocortical
   (b) Corticogeniculate
   (c) Spinoreticular
   (d) Limbal

4. **Anaesthetics produce unconsciousness by:**
   (a) Decreasing excitability of cortical neurons
   (b) Depressing conduction in ascending reticular system
   (c) Desynchronization of EEG
   (d) All of the above

5. **The reticular formation is a diffuse collection of:**
   (a) Only sensory neurons
   (b) Only motor neurons
   (c) Only autonomic centres
   (d) All of the above

6. **Function of reticular activating system is:**
   (a) Produces the conscious state
   (b) Responsible for electrical activity of cerebral cortex
   (c) Maintains a state of alertness
   (d) All of the above

7. **Descending reticular system:**
   (a) Influence activity in both the afferent and efferent neurons
   (b) Comprises of inhibitory and facilitatory reticular projections
   (c) Fibers that descend to the spinal cord form reticulospinal tracts
   (d) All of the above are true

Answers

1. (d) 2. (c) 3. (a) 4. (b) 5. (d) 6. (d) 7. (d)

Chapter

98

The Cerebellum

I. Physiological anatomy: Divisions-lobes
II. The Cerebellar cortex
  A. Structure
  B. Inputs: Afferent fibers
  C. Neural circuits
III. Connections of the cerebellum
IV. Functions of the cerebellum
V. Cerebellar lesions/dysfunctions

PHYSIOLOGICAL ANATOMY

1. The cerebellum lies dorsal to the brain stem in the posterior (occipital) fossa. On each side it is connected to the brain stem by three peduncles:
   (i) by *inferior cerebellar peduncle* (restiform body) to the medulla,
   (ii) by *middle cerebellar peduncle* (brachium pontis) to the pons, and
   (iii) by *superior cerebellar peduncle* (brachium conjunctivum) to the midbrain.
2. The cerebellum weighs only 10% as much as the cerebral cortex, but its surface area is approx. 75% of that of the cerebral cortex.

DIVISIONS-LOBES

A. Anatomical Divisions (Fig. 98.1)

Anatomically the cerebellum is divided into:

1. two large laterally placed *cerebellar hemispheres;* and
2. a small medial portion, the *vermis,* which is so called because it resembles a worm bent on itself to form almost a complete circle.

It is further divided into two parts by *posterolateral fissure* into:

1. ***Flocculonodular lobe*** consisting of *floccule* and *nodule;* and
2. ***Corpus cerebellum.*** It is divided by *primary fissure* into anterior lobe and a posterior lobe.
   (i) *Anterior lobe* consisting of ***lingula, lobulus centralis*** and ***culmen;*** and
   (ii) *Posterior lobe* which subdivides to form:
   (a) *Lateral* part containing ***ansiform*** and ***paramedian lobules;*** and
   (b) *Median* and *paramedian* part containing: ***lobulus simplex, declive, tuber, pyramis, uvula*** and ***paraflocculle.***

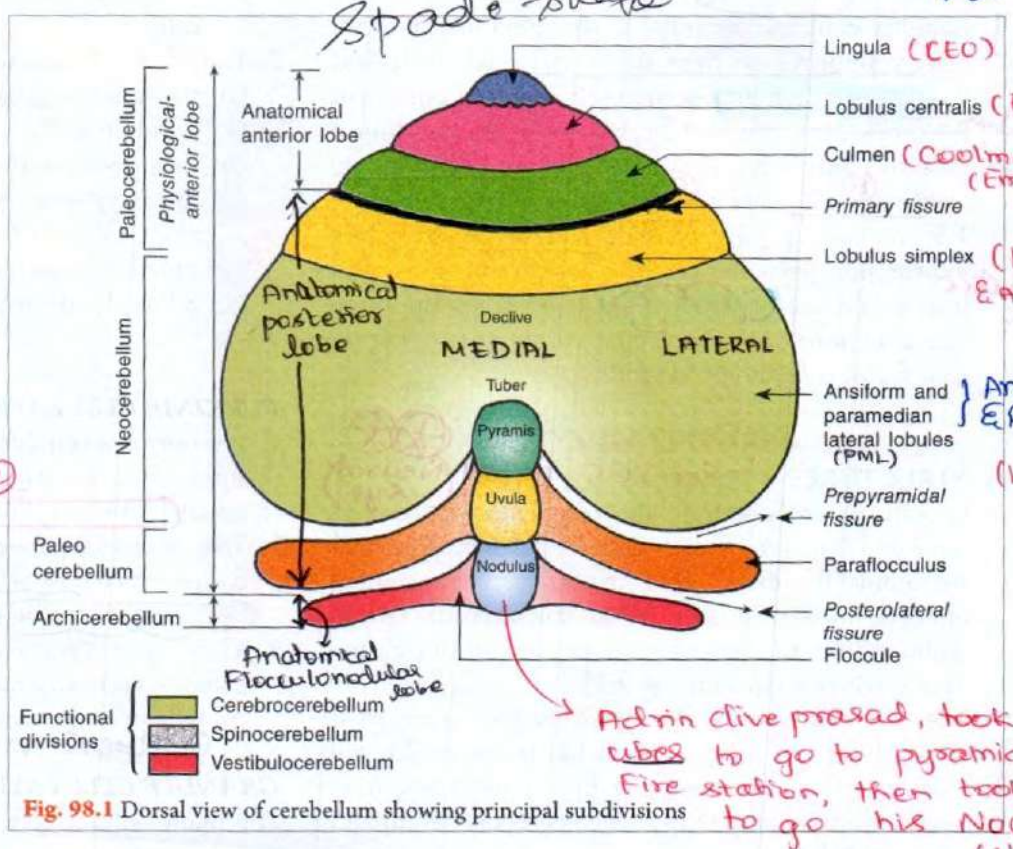


Fig. 98.1 Dorsal view of cerebellum showing principal subdivisions

B. Phylogenetical Divisions

This is based on development of divisions/lobes of the cerebellum at different times during evolution (Fig. 98.1).

1. *Archicerebellum*, the first part to develop during evolution and is represented by *flocculonodular lobe*.
2. *Paleocerebellum*, evolved next and is represented by the entire *anterior lobe* and parts of the *posterior lobe* (pyramis, uvula, paraflocculle).
3. *Neocerebellum*, a newer part was last to evolve with *greatest development in humans*. It comprises of remaining parts of the posterior lobe viz., the declive, tuber and the lateral ansiform and paramedian lobules.

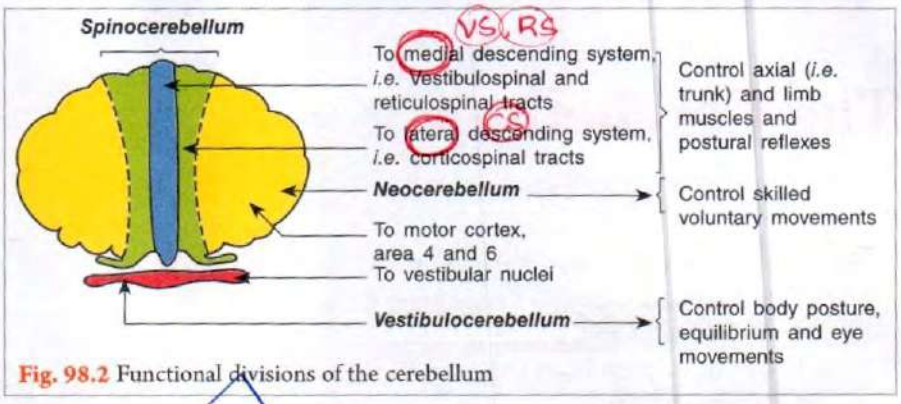


Fig. 98.2 Functional divisions of the cerebellum

C. Functional Divisions

Functionally the divisions/lobes are named according to the connections they make with other components of the motor control system (Fig. 98.2).

1. The *flocculonodular lobe* – It is functionally related to the vestibular apparatus and, therefore, also called the *vestibulocerebellum*. It is *concerned with control of body posture, equilibrium and maintaining visual fixation i.e. vestibulo-ocular reflex* (page 943).
2. The entire *anterior lobe* and parts of the posterior lobe (lobulus simplex, pyramis, uvula, paraflocculle) that receive information from the spinal cord, are called the *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* (page 947).
3. The remaining part of the *posterior lobe* receives information from the cerebral cortex and pons, and thus called the *neocerebellum*. It occupies the more lateral regions of the cerebellar cortex. It is *concerned with skilled voluntary movements*.

THE CEREBELLAR CORTEX

A. STRUCTURE

1. Grossly in cross-section, the cerebellum is seen to have an outer grey matter called *cerebellar cortex* that surrounds the inner white matter (an arrangement opposite to what is seen in the spinal cord). Within white matter are embedded four pairs of nuclei, the ***deep cerebellar nuclei*** (page 967).
2. The cerebellar cortex is extensively folded on itself constituting the *folia*, *i.e.* leaf like parts which are marked off from one another by fissure. These folia overlie the white matter which consists of afferent and efferent fibers.
3. Upon microscopic examination, the cerebellar cortex is seen to be composed of *three* layers: (Fig. 98.3)
   (i) an outer *molecular layer*,
   (ii) a middle, *Purkinje cell layer*, and
   (iii) an inner, *granule cell layer*.

MOLECULAR LAYER

It contains endings of unmyelinated *nerve fibers* and *nerve cells*.

1. The *nerve endings* are:
   (i) the dendrites of the Purkinje cells;
   (ii) the axons of the Granule cells; and
   (iii) the afferent fibers from inferior olivary nucleus which ascend into this layer as the ***climbing fibers*** and form synapses with dendrites of the Purkinje cells.
2. The *nerve cells* are of two types:
   (i) the star-shaped ***Stellate Cells***, more superficial in location; and
   (ii) deep located, ***Basket Cells***. These cells possess a relatively sparse dendritic tree which receives input from the ***parallel fibers*** (see below). They are so called because their axons form a *basket* around the cell body of each Purkinje cell they innervate.

PURKINJE CELL LAYER

1. It is only one cell thick consisting of large flask-shaped *Purkinje Cell, the biggest neuron in the body*. There are about 15 million Purkinje cells in man.
2. Their axons form the ***only output*** of the whole cerebellar cortex which passes to form synaptic connection in the deep cerebellar nuclei.
3. They have very extensive dendritic network that extends vertically into the outer molecular layer and provides a huge surface area for *axodendritic* synapses.

GRANULE CELL LAYER

The main cellular components of this layer are *granule* and *golgi* cells.

1. *Granule Cells*
   (i) They are small, very numerous (about 10 billion) and have their cell bodies located in this layer.
   (ii) Each cell axon ascends to the outer molecular layer and then bifurcates to form a 'T'. The two branches of the 'T' run along the long axis of the folium and are called *parallel fibers*.
   (iii) The parallel fibers make *excitatory* synaptic contact with dendrites of many Purkinje cells, golgi cell, basket cell and stellate cell.
2. *Golgi Cells*
   (i) These are large cells and less numerous than granule cells.
   (ii) Their dendrites project outwards into the molecular layer and receive input from the parallel fibers.
   (iii) Their cell bodies receive input via collaterals from the incoming *climbing fibers* and Purkinje cells.
   (iv) Their axons branch extensively and form ***inhibitory*** synaptic connections with the dendrites of the granule cells.

B. INPUTS: AFFERENT FIBERS

The main source of *input* in the form of afferent fibers enters the cerebellar cortex; the *climbing fibers* and the *mossy fibers*. ***Both are excitatory.***

1. *Climbing Fibers*
   (i) These fibers arise mainly from cells in the inferior olivary nucleus (page 965). *Their activity is increased when a new movement is being learned.*

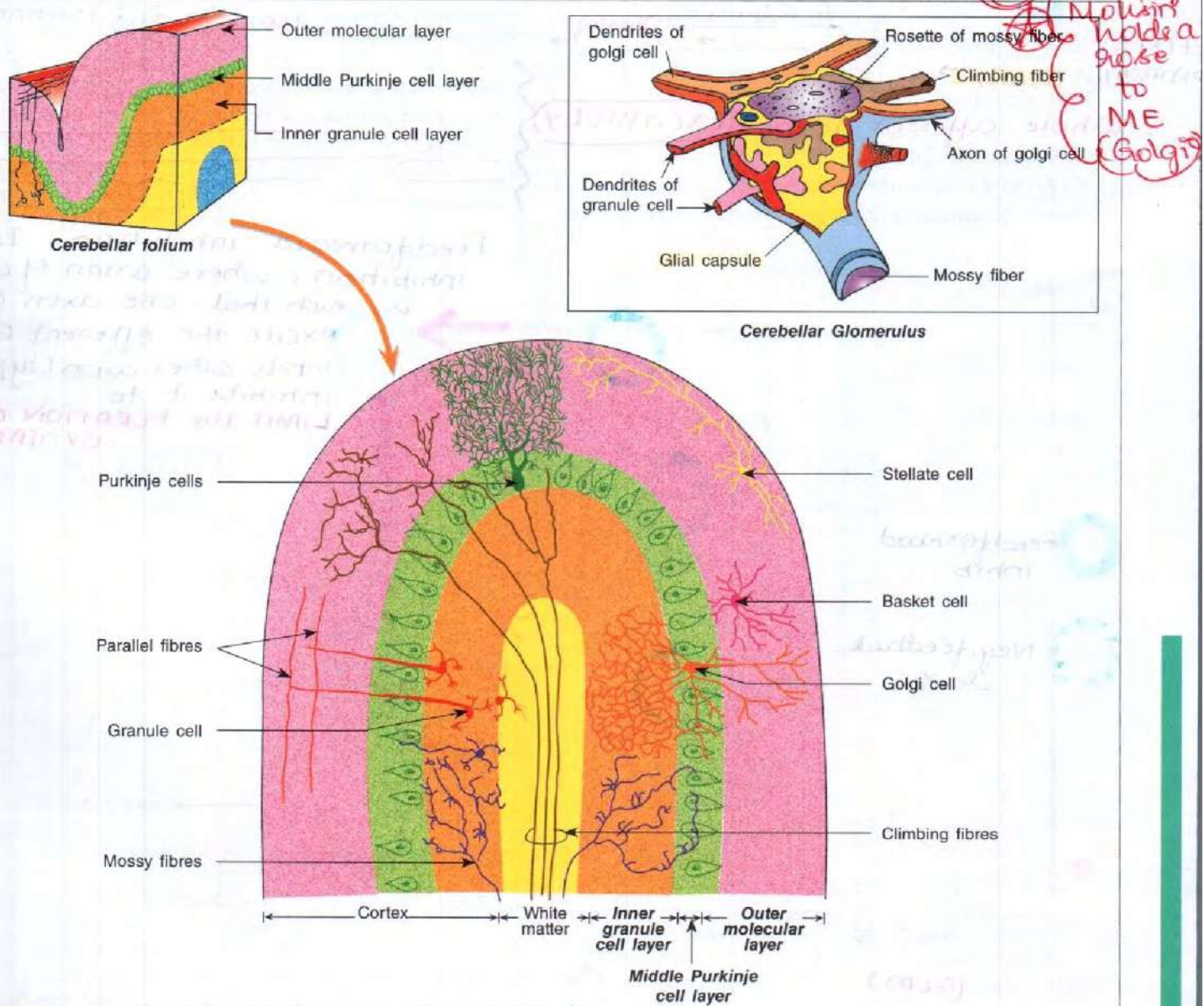


Fig. 98.3 Histology of cerebellar cortex (cross section of cerebellar folium) (**Inset:** Structure of cerebellar glomerulus)

(ii) They establish *'one-to-one' connection* with the Purkinje cell dendrites and *excite* it to discharge.

(iii) The collaterals of these fibers also excite the golgi cells.

2. ***Mossy Fibers***

(i) They are axons of spinocerebellar, vestibulocerebellar, reticulocerebellar, cuneocerebellar and cortico-ponto-cerebellar tracts.

(ii) Each mossy fiber makes synaptic connections with *many* granule cells. They end on the dendrites of granule cell in a series of moss-like ***Glomeruli*** (*axo-dendritic synaptic connections*). The glomeruli also contain the inhibitory endings of the golgi cell **(Fig. 98.3: inset)**.

(iii) They are *excitatory* to dendrites of all the fibers. They exert a *weak* excitatory effect on *many* Purkinje cell dendrites via the parallel fibers of the granule cell.

Therefore, the sequence, mossy fiber → granule cell → parallel fiber → Purkinje cell provides *excitation* of the Purkinje cell.

C. NEURAL CIRCUITS

1. The output of granule cell (whose axons form parallel fibers) is always ***excitatory***. They specially make synaptic connections with dendrites of Purkinje cells, basket cells and stellate cells **(Fig. 98.4)**.
2. The output of the Purkinje cells, golgi cells and basket cells is always ***inhibitory***.

Important Note

Granule cell axons (parallel fibers) excite golgi cell dendrites, whose axons inhibit the granule cells. Thus excitation of the granule cell is rapidly extinguished by a *negative feedback loop*.

3. The basket cells and the stellate cells are excited by the granule cells via the parallel fibers, and their output *inhibits* Purkinje cells discharge.

Important Note

The stimulation of basket cells produces IPSPs in the Purkinje cells. However, the basket cells and the Purkinje cells are excited by the same excitatory input. This arrangement is called *feed-forward inhibition* and helps to limit the duration of the excitation produced by any given afferent impulse.

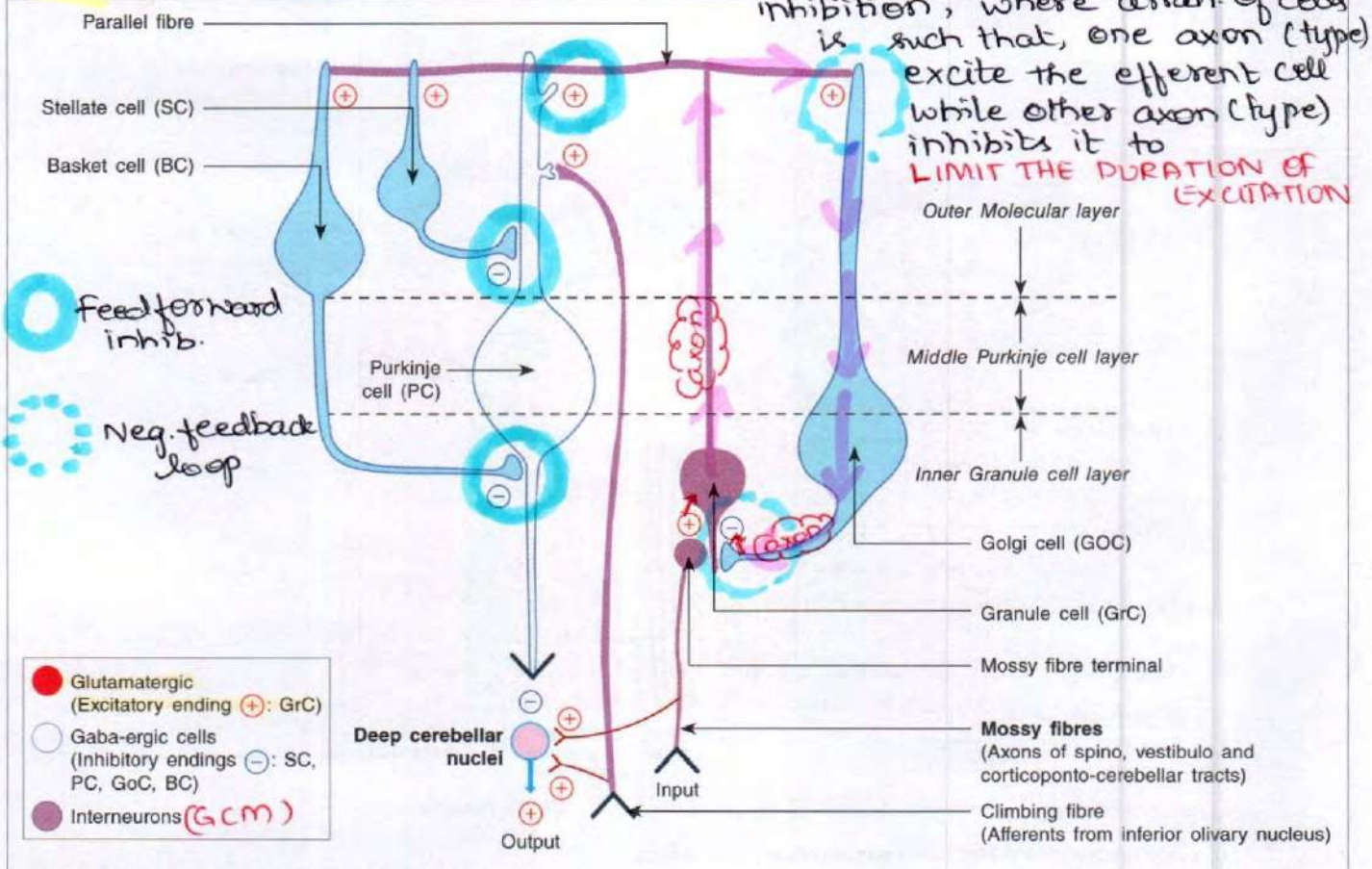


Fig. 98.4 Neural connections within the cerebellar cortex.

4. The Golgi cells are excited by the collaterals from the climbing fibers, Purkinje cells and parallel fibers; and they *inhibit* transmission from mossy fibers to the granule cells.
5. The Purkinje fiber output is *inhibitory* to deep cerebellar nuclei. These nuclei also receive excitatory inputs via collaterals from the mossy fibers, climbing fibers, and also other excitatory inputs. However, the *ultimate impulse coming out of the deep cerebellar nuclei* is *excitatory*.
6. The cerebellar cortex shows ***basic electrical rhythm*** of 150-300/sec *(10 times greater than that of cerebral cortex α-rhythm-page 981)* with amplitude of 200μV and, superimposed on this is a 1000-2000/sec component of smaller amplitude.
7. ***The basis of the learning*** in the cerebellum is the input from the inferior olivary nuclei in the climbing fibers. Each Purkinje cell receives input from 25,000 to 1 million mossy fibers, but each has only a single climbing fiber. Climbing fiber activation produces a large, complex spike in the Purkinje cells which produces long term modification of the pattern of mossy-fiber input to that Purkinje cell. *Climbing fiber input is increased when a new movement is being learned.* The entire cerebellar neural circuit is thus concerned with modulating or timing the ***excitatory output*** of the deep cerebellar nuclei to the brain stem and thalamus. This helps the cerebellum in coordinating the muscle movements (page 969).

Important Note

The transmitter secreted by the stellate, basket, golgi and Purkinje cells is GABA (gamma amino butyric acid), whereas the granule cells secrete glutamic acid.

CONNECTIONS OF THE CEREBELLUM

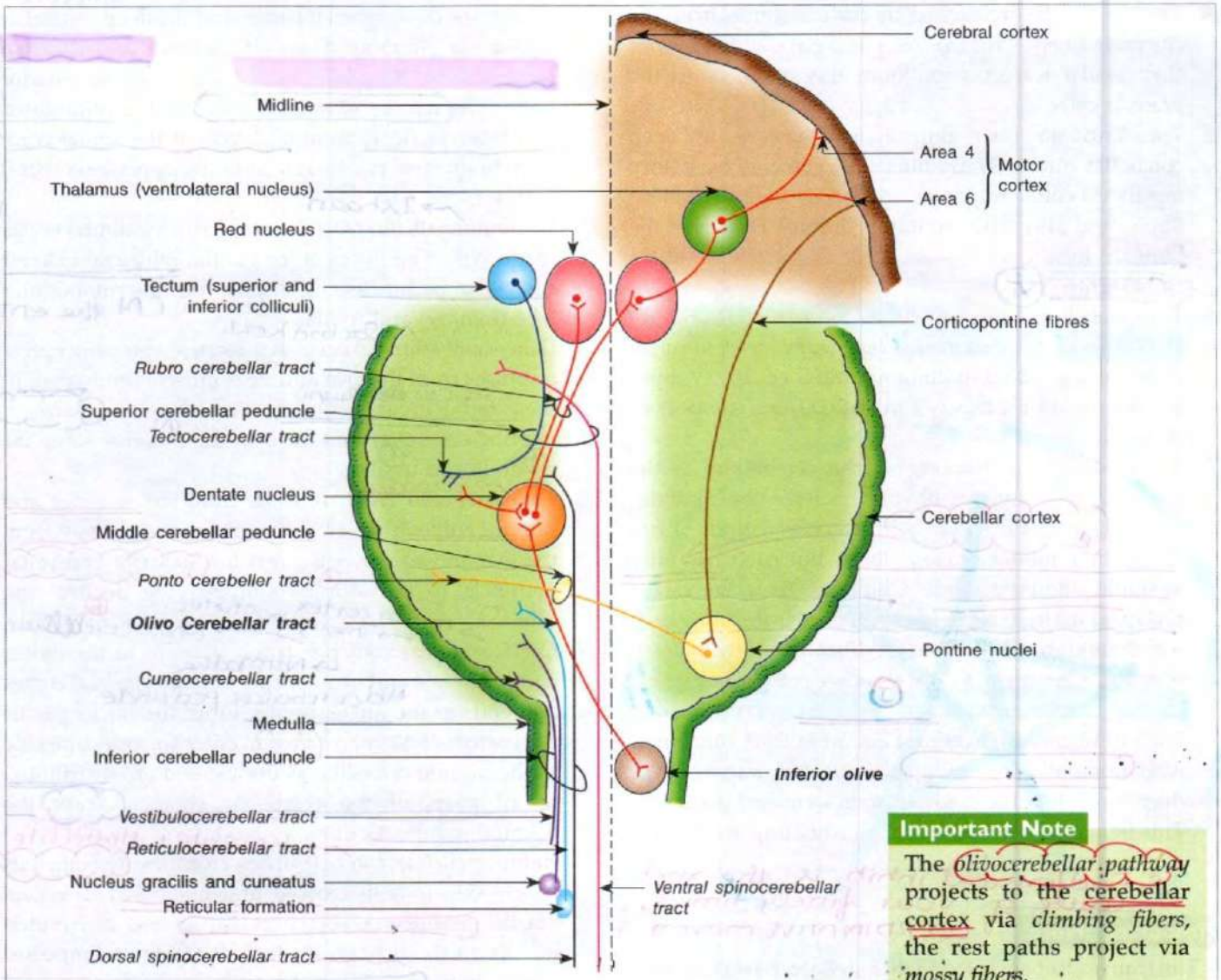
A. AFFERENT CONNECTIONS (Fig. 98.5)

1. ***Dorsal spinocerebellar tract*** (page 889). It carries mainly *unconscious* kinesthetic (joint movements) and cutaneous afferents from the trunk and leg. It enters the *ipsilateral* inferior cerebellar peduncle and is distributed to the anterior lobe, pyramis, uvula and the median part of the paramedian lobe.
2. ***Ventral spinocerebellar tract*** (page 890). It carries a large proportion of exteroceptive (cutaneous) and proprioceptive fibers from all parts of the body. It enters the cerebellum via the *ipsilateral* superior cerebellar peduncle and is distributed mainly to the vermis and the anterior lobe.
3. ***Olivocerebellar tract***. It is mainly a *crossed* pathway. It enters via the superior cerebellar peduncle to supply all parts of the cerebellar cortex and the deep cerebellar nuclei via ***climbing fibers***. It carries proprioceptive inputs from the whole body via relay in inferior olive. The *inferior olivary nucleus* itself is stimulated and receives fibers from all levels of the spinal cord, from brain stem nuclei and from the opposite cerebral cortex.
4. ***Vestibulocerebellar tract***. It arises in the vestibular nuclei (page 949). The fibers enter via the *ipsilateral* inferior cerebellar peduncle and supply the flocculonodular lobe (mainly) and uvula.
5. ***Cuneocerebellar tract***. It carries proprioceptive impulses from the arm and neck muscles and arises in the external arcuate nucleus. It enters via the *ipsilateral* inferior cerebellar peduncle to the anterior lobe, the pyramis and uvula.
6. ***Tectocerebellar tract***. It arises from the superior and inferior colliculi which relays fibers respectively from the eye and ear. It enters via the superior cerebellar peduncle to the lobulus simplex, the declive and tuber.
7. ***Cortico-ponto-cerebellar tract***. It arises in the motor cortex (areas 4 and 6) and other parts of cerebral cortex and ends in the nuclei pontis. From the nuclei pontis the *pontocerebellar fibers cross* to enter the opposite side in the middle cerebellar peduncle and are distributed to all parts of the cerebellar cortex (except the flocculonodular lobe).
8. ***Rubrocerebellar tract***. It arises from the red nucleus (page 953), is both crossed and uncrossed. It enters via the superior cerebellar peduncle and distributed mainly to the dentate nucleus. It transmits impulses which have originated from the motor cortex and relays in the red nucleus.
9. ***Reticulocerebellar tract***. It arises in the lateral reticular nucleus (page 957) and is *uncrossed*. It is distributed via the ipsilateral inferior cerebellar peduncle to the whole of the cerebellar cortex.

Localization of Sensory Impulses to the Cerebellum

Like the sensory and motor cortex, there is 'point-for-point' representation of sensory impulses (tactile, proprioceptive, auditory and visual) from the whole body in the cerebellum. Two such separate ***sensory areas*** have been recognized; one in the anterior lobe and the other in the posterior lobe **(Fig. 98.6)**.

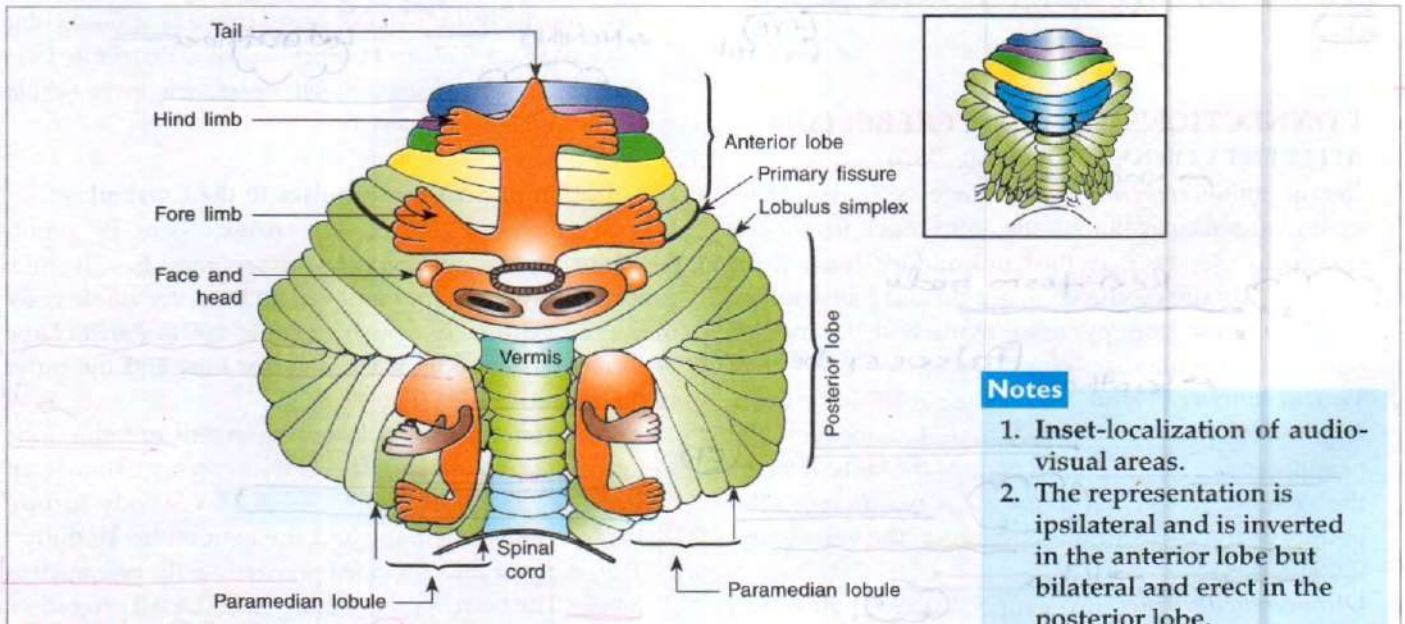
1. The ***anterior area*** encloses the entire anterior lobe and lobulus simplex. The body representation is an *ipsilateral* projection and is *inverted*; axial body surface is represented medially and the extremities laterally.
2. The ***posterior area*** is located primarily in the paramedian lobule. The body representation is a bilateral projection, less defined and is *erect*.



Important Note

The *olivocerebellar pathway* projects to the cerebellar cortex via *climbing fibers*, the rest paths project via *mossy fibers*.

Fig. 98.5 Principal afferent cerebellar connections



Notes

1. Inset-localization of audio-visual areas.
2. The representation is ipsilateral and is inverted in the anterior lobe but bilateral and erect in the posterior lobe.

Fig. 98.6 Localization of sensory areas of the cerebellum

3. The *auditory and visual areas* lie primarily in the lobulus simplex, folium and the tuber vermis.

Important Notes

1. There is the same topographical representation of motor areas in the cerebellum as is found for the sensory areas.
2. The cerebellum is *not* concerned *with* consciousness of sensations.

B. 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*.

Note

Purkinje cells have high GABA content.

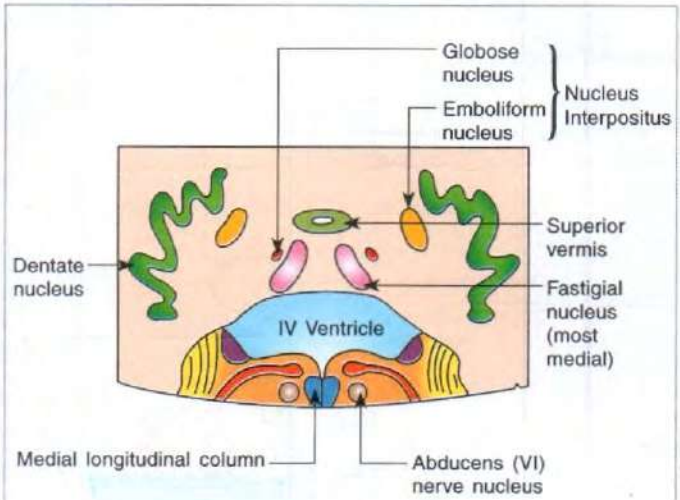


Fig. 98.7 Frontal section through the cerebellum showing relationship among the deep cerebellar nuclei.

Within the white matter are embedded four pairs of nuclei. These are the ***Dentate, Emboliform, Fastigial and Globose***. As the emboliform and globose nuclei have similar connections, these are together known as the *Nucleus Interpositus* (Fig. 98.7). The pathways to and from the individual cerebellar nuclei are summarized in Table 98.1 and Fig. 98.8.

Important Note

As the dentatothalamocortical path is crossed and as the corticopontocerebellar pathway is also crossed, each cerebellar hemisphere provides and receives information which assists its *comparator of a servo-mechanism* function (page 969) in modifying movements on its own side of the body.

Table 98.1: Deep cerebellar nuclei and their connections

Nucleus	Afferent fibers from	Efferent fibers to	Remarks
Dentate (located most lateral)	Neocerebellar portion of posterior lobe (page 962)	Via superior cerebellar peduncle to red nucleus and ventrolateral nucleus of thalamus.	The fibers finally get projected to the areas 4 and 6 of motor cortex.
Fastigial (located medially lies and most superficial)	1. Mainly from flocculonodular lobe (vestibulocerebellum) (page 962) 2. Some from spinocerebellum (page 962)	1. Via inferior cerebellar peduncle to vestibular nucleus and medullary reticular formation. 2. Medial longitudinal bundle. 3. Ascending reticular formation.	1. Vestibulospinal and reticulospinal activity is modified accordingly. 2. Integrates the activity of the nuclei III, IV and VI nerves supplying the extrinsic eye muscles.
Emboliform	Spinocerebellum	Via superior cerebellar peduncle to red nucleus.	Emboliform and globose nuclei have similar connections, these are together known as the *nucleus interpositus*.
Globose	Spinocerebellum	Via superior cerebellar peduncle to red nucleus and also to reticular formation of midbrain.	

To summarize:

1. The deep cerebellar nuclei provide the only output for the spinocerebellum and neocerebellum.
2. The axons of the 'deep cerebellar nuclei' project to the vestibular and reticular nuclei, to the nuclei of III, IV and VI nerves controlling the extrinsic eye muscles and to the contralateral red nucleus.
3. Some axons of the dentate nucleus also project to the contralateral ventolateral thalamic nucleus.
4. The *lateral cerebellar zone* (dentate nucleus) primarily influences the lateral descending system i.e. corticospinal tract; the *medial cerebellar zone* (fastigial nucleus) influences the medial descending system i.e. vestibulospinal and reticulospinal tracts; and the *intermediate cerebellum* (emboliform and globose nuclei) influences the rubrospinal tracts.

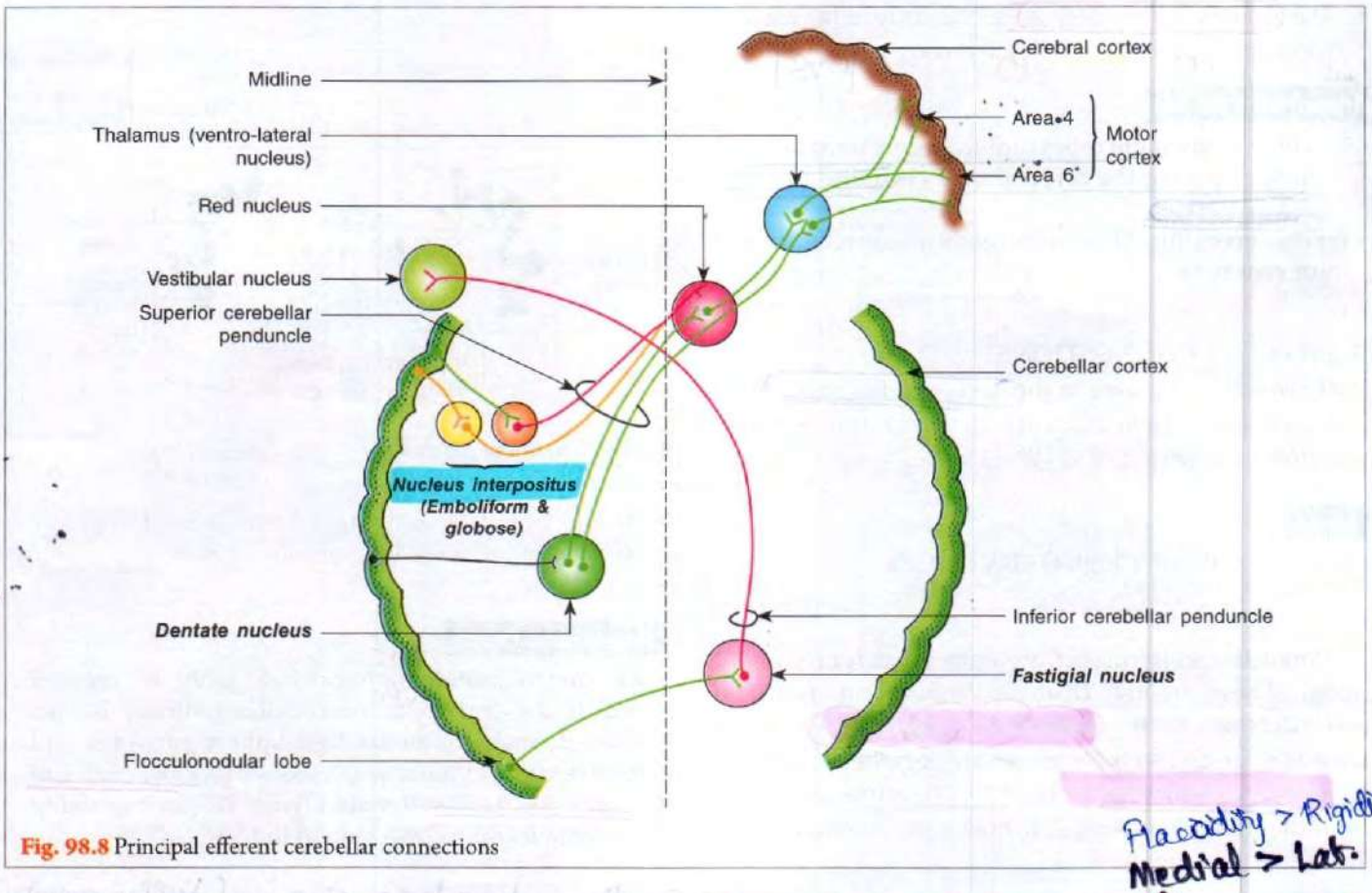


Fig. 98.8 Principal efferent cerebellar connections

FUNCTIONS OF THE CEREBELLUM

1. Control of Body Posture and Equilibrium

The flocculonodular lobe (*vestibulo-cerebellum*) is concerned with control of body posture and equilibrium. *Afferents* from the vestibular apparatus (from saccule, utricle and semicircular canals) pass directly or after relay in the vestibular nuclei to the flocculonodular lobe. The *efferents* therefrom return back to the vestibular nuclei. From these nuclei, the vestibulospinal tract connects with the spinal motor neurons.

Important Notes

(i) Children are commonly affected by a tumour, *medulloblastoma* which develops from cell rests in the nodulus. This produces disturbance of equilibrium as seen by an inability to maintain erect posture.

(ii) Removal of flocculonodular lobe abolishes motion sickness (page 944).

2. Control of Muscle Tone and Stretch Reflexes

The ***medial part*** of anterior lobe of cerebellum ***inhibits*** the muscle tone (stretch reflex); whereas the ***lateral parts*** of the anterior lobe *facilitates* the muscle tone.

In normal man, the influence of the cerebellum on the muscle tone and stretch reflexes is *inhibition*. However, ***hypotonia*** is characteristic of cerebellar lesion, why, not known.

Pathway

The anterior lobe inhibits the muscle tone (mainly in the extensor muscles) of the same side of the body. The effects are mediated via the *fastigial nucleus* to the ipsilateral vestibular nuclei and to the bulbar reticular formation. These nuclei in turn relay the effects to the spinal motor neurons.

Mechanism

The anterior lobe effects are brought out by *inhibiting γ-efferent discharge to the muscle spindles* which decreases the excitability of the stretch reflex.

Proof

(i) Stimulation of the medial parts of the anterior lobe inhibits the Ia afferent discharge from ipsilateral muscle spindles.

(ii) Temporary suppression of anterior lobe activity by surface cooling, abolishes γ-discharge to the intrafusal fibers of the muscle spindle; this discharge reappears by warming.

Important Note

The cerebellum forms an important site of linkage of α-γ *systems* responsible for muscle tone. *Proof. Intercollicular decerebrate rigidity* (page 953) increases after removal of the cerebellum, because cerebellectomy abolishes all signs of γ-activity on the muscle spindle. The increased (hyperactive) muscle tone is due to excessive discharge of the α-motor neurons which is no longer reflexly modified by γ-effects. This excessive α-firing is due to vestibulospinal projections which have escaped from the inhibitory influence of the cerebellum.

3. Control of Movements

The cerebellum does not initiate movements, rather it *coordinates movements* that are initiated in the motor system. *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 of the regions of the CNS to which it is connected (page 966). The function of the cerebellum in control of body movements, may be discussed under two headings: control of *involuntary* and *voluntary* movements.

(A) *Control of involuntary movements*

The terms ***unconscious, automatic*** and ***reflex*** are often taken to be synonyms for *involuntary.*

The cerebellum *coordinates* the subconscious *gross* movements. How?

Pathway

(i) The *afferent* pathways to the cerebellum (page 968) transmit proprioceptive, kinesthetic and sensory information from all parts of the body. The proprioceptive and kinesthetic inputs relayed via the inferior olive, and the olivocerebellar fibers form the excitatory *climbing* fiber input (page 964).

(ii) In addition, collateral extrapyramidal impulses from the motor cortex, basal ganglia and reticular formation are transmitted to the cerebellum via the cortico-ponto-cerebellar pathways. [CPC]

(iii) The cerebellum ***integrates*** these impulses and provides *feedback* impulses starting from the *deep cerebellar nuclei* back to the motor cortex, basal ganglia and reticular formation that correct the *error* in the involuntary movements.

(B) *Control of voluntary movements*

The cerebellum guides and controls all the voluntary movements *i.e.* movements accompanied by a conscious awareness of an individual. *The movements produced are accurate in time, rate, range (extent), force and direction.*

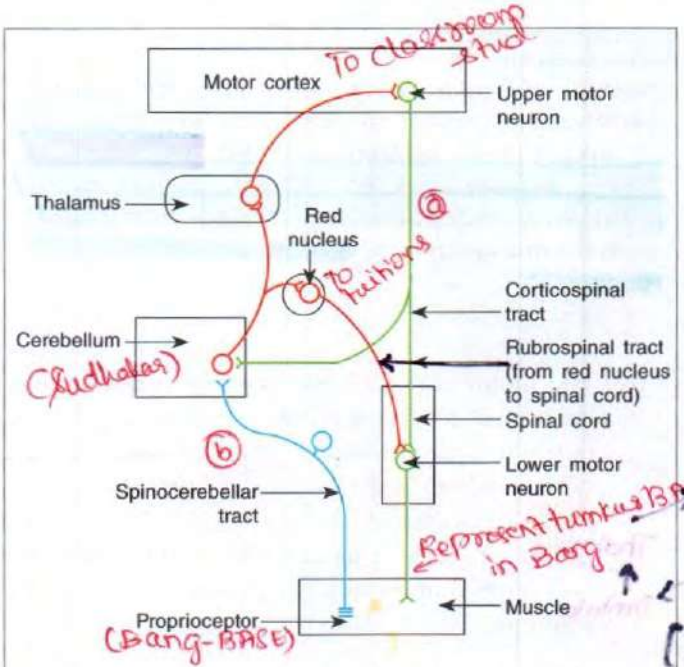


Fig. 98.9 Pathway – "Comparator of a servo-mechanism" function of the cerebellum

Pathway and mechanism

Although three lobes of the *cerebellum*, *vestibulo*, *spino* and *neocerebellum* are *functionally* different, yet they work in close *cooperation*, *i.e.* it acts as a ***comparator of a servo-mechanism*** **(Fig. 98.9)**. How?

(i) The cerebellum receives:

(a) a representation of the corticospinal activity which is transmitted to the muscles, and

(b) a representation of the *result* in terms of the muscle movement from the proprioceptors of the muscles.

(ii) In addition, it receives further information from tactile receptors, from the eye and ear, which allows a comparison of the *true* corticospinal input and the proprioceptive indication of the position of the limb.

(iii) The cerebellum ***integrates/coordinates*** all above information and then by cerebellocortical relays, the motor activity caused by the corticospinal discharge can be modified appropriately. Therefore, if there is a discrepancy between the two, the cerebellum adjusts the activity in the descending pathways to correct the ongoing movement, and it sends an error signal to the motor cortex and subcortical centres to modify the *central motor programmes* so that future movements of the same kind will be performed more accurately.

Important Note

Normal muscular coordination is made possible because the cerebellum forms an important site of linkage of *α-γ system* (page 969). Movements in which the *γ-system* plays no part are movements which occur without adequate cerebellar information from the muscle spindle; such movements are poorly controlled.

(iv) The motor cortex of one cerebral hemisphere is connected to the cerebellar hemisphere of the opposite side through a closed *feedback* circuit, called ***cerebral-cerebellar-cerebral circuit*** *i.e. cortico-ponto-dentato-thalamo-cortical circuit* (Fig. 98.9). By means of these interconnections, the cerebrum and cerebellum mutually influence one another's activities.

Important Note

Each cerebellar hemisphere influences the opposite cerebral cortex; in its turn the motor cortex via the corticospinal tracts, controls the movements of the opposite side of the body. Because of the *double decussation* (*i.e.* of the superior cerebellar peduncle and of the pyramidal tracts) *each cerebellar hemisphere controls voluntary movements on its own side of the body.*

To summarize: The cerebellum's role in *control of movements* is to perform the critical task of comparing informations *what the muscles should be doing with information about what they are actually doing.* The cerebellum thus plays an important role in the ***learning of motor skills.*** (Also see to page 969)

4. **Other Functions:** *Functions of pyramis, uvula and paraflocculus*
   (i) ***Pyramis***
      (a) It is concerned with movement of eyeball because its stimulation causes upward eye movements to the ipsilateral side.
      (b) After removal of the pyramis, monkeys crash along the wall repeatedly in spite of good vision and coordination showing it is also concerned with judgement of distance.
   (ii) ***Uvula.*** It has vestibular function, its removal in animals produces disturbance of equilibrium.
   (iii) ***Paraflocculus.*** It is rudimentary in man but highly developed in aquatic diving animals, showing that it plays important role in extensive reflex adjustment necessary for diving.

CEREBELLAR LESIONS/DYSFUNCTIONS

General

1. 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.
2. *Lesions of cerebellar cortex* cause movement abnormalities which gradually disappear as compensation occurs; while lesion of the deep cerebellar nuclei produce generalized defects and abnormalities persist.
3. *Damage to the neocerebellum* causes **most** of the dysfunction or of clinical cerebellar disease in man since it forms a bulk of the total mass of the organ.

Characteristic Features (Refer to Fig. 98.10)

A. Disturbance of Posture

1. *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 (or loose) and the limb moves to and fro freely.
2. *Attitude*
   (i) The face is rotated towards the opposite side (pulled by the healthy muscles).
   (ii) The homolateral shoulder is lower than the opposite normal shoulder.
   (iii) The leg is abducted and rotated outwards.
   (iv) The body weight is thrown on the healthy leg so the trunk is bent with the concavity towards the affected side.
3. *Spontaneous deviation.* If the eyes are closed and the arms are held straight out in front of the body, the homolateral arms bend laterally.
4. *Nystagmus.* It is a tremor of the eyeballs which occurs when the patient attempts to *fix* his eyes on an object (page 943). 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.
5. *Deep (or tendon reflexes).* The deep reflexes become weak and pendular, *e.g.* ***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 the quadriceps muscle.

B. Disturbances of Voluntary Movement

1. *Asthenia i.e.* feebleness of movements. The muscles tire readily, therefore, voluntary movements are carried out slowly.
2. *Ataxia i.e. incoordination of movement* is marked. Therefore there is:

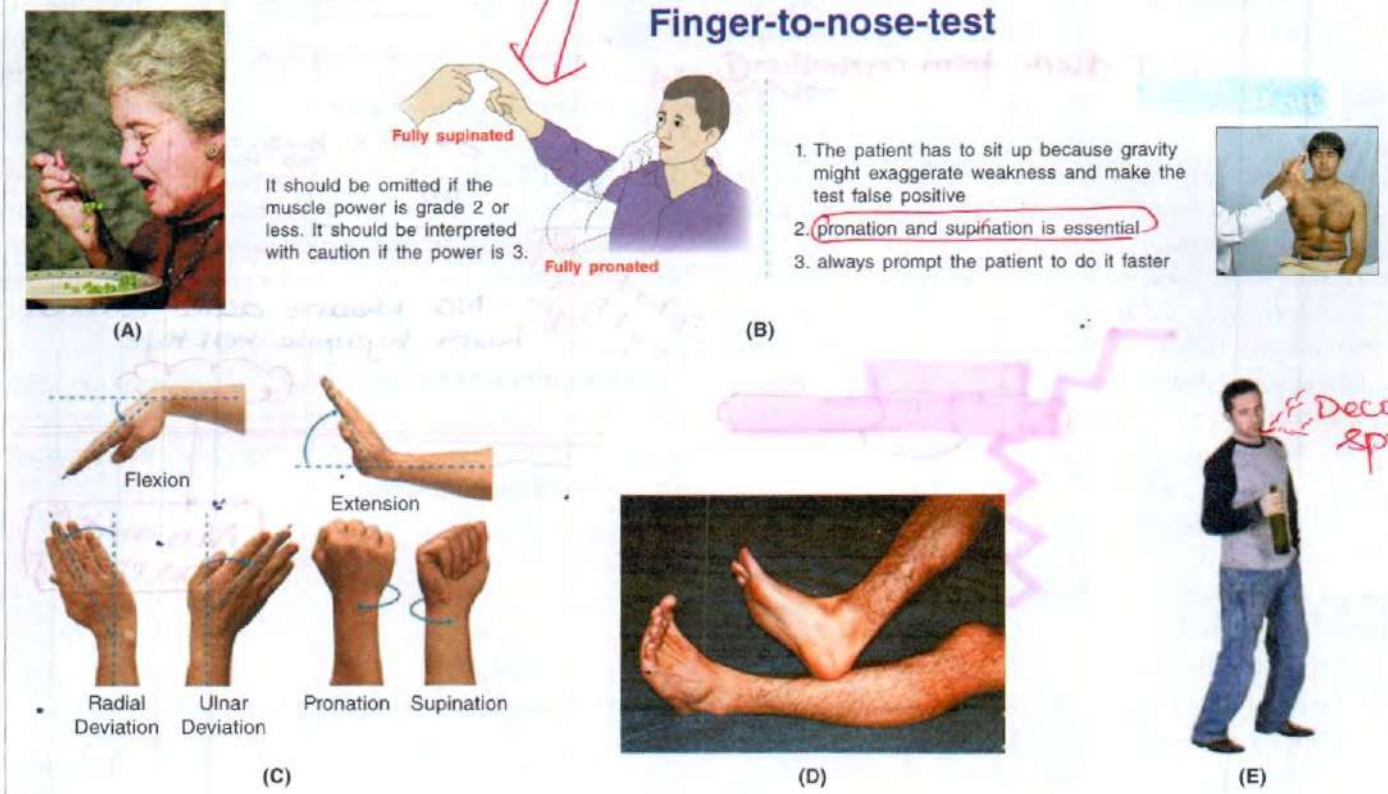


Fig. 98.10 Characteristic features and tests in cerebellar dysfunction. (A) Intentional tremors; (B) Finger nose test; (C) Adiadokokinesia; (D) Heel-knee test; (E) Drunken gait

(i) *Decomposition of the movement* – The movement seems to occur in stages. The patients 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* – 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. past pointing* (or ***hypermetria***) or fall short of it (*i.e.* ***hypometria***) It results from the loss of the neural circuit (page 964) required to control the duration and strength of a movement.

Important muscle movement – Definitions:

Protagonists – are prime movers, the chief or main muscle during movement.

Antagonists – muscles which neutralize the effect of another muscle.

Synergists – Muscles which though not essential for the prime movement, but all the same facilitate its execution.

Agonists – One which by contraction and against its opposing muscle, causes movement.

Accessory muscle – *Helper* muscle in an act of movement.

Antigravity muscle (page 952).

3. ***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*** which occur at a *frequency of 4-6/sec.* and can clearly be seen when the part is used in a voluntary movement. They occur because an entire movement cannot be directed by a single motor command; several other motor commands are required before the movement is completed.

Clinically these disturbances can be demonstrated by:

(i) *Finger-nose test* – The patient is asked to place the index finger of his extended arm over his nose with eyes closed. This test detects above mentioned (1), (2) and (3) disturbances.

(ii) *Rebound phenomenon* – If the patient is asked to flex his forearm against resistance, then the resistance is suddenly released, the patient cannot *brake* the movement and the released forearm flies backward and strikes his face.

(iii) *Adiadochokinesis* – The patient is unable to carry out rapidly alternate and opposite movements, *e.g.* rapid supination and pronation of the forearm. This

is because they cannot start or stop movements quickly or easily and their motions are slow and irregular.

(iv) *Heel-knee test* – The patient lies in the lying down position. He is asked to touch his knee by the opposite heel then moving the heel along the tibia downwards. This test detects *decomposition* of movements.

4. *Gait* – The patients walks awkwardly (in clumsy manner), with the feet well apart (wide base). They have such difficulty maintaining balance that their gait appears drunken, called *drunken gait*. The patient walks in a *zigzag* line and deviates to the affected side due to hypotonia.

5. *Speech* – It is slow and *lalling* (like a baby) due to imperfect use of the movements of the laryngeal muscles and tongue. Each syllable in a word is pronounced separately and slowly (*decomposition*).

CHARCOT'S TRIAD. It is a syndrome characterized by nystagmus, intention tremors and lalling speech. It is seen in stages of disseminated sclerosis (page 937) which causes disturbance of the cerebellar connections with the brain stem.

FRIEDREICH'S DISEASE. It is a *hereditary ataxia* in which the spinocerebellar tracts or other cerebellar connections tend to degenerate early, producing characteristic signs of cerebellar dysfunction.

Study Questions

1. **Which was the first part of the cerebellum to appear in the course of evolution?**
2. **Draw labelled diagram to show functional divisions of the cerebellum. Add a note on its physiological significance.**
3. **Define and give physiological significance:**
   (i) Feed forward inhibition and feed back inhibition
   (ii) Coordination of movement
   (iii) Rebound phenomenon and adiadochokinesia
   (iv) Asthenia, Decomposition of movements, asynergia and dysmetria
   (v) Protagonist, antagonist, synergists muscles, agonist and antigravity muscles
   (vi) Ataxia.
4. **Write short notes on:**
   (i) Purkinje cells and golgi cells
   (ii) Climbing and mossy fibers
   (iii) Charcot's triad
   (iv) Parallel fibers
   (v) Mechanism of learning of motor skills
   (vi) Medulloblastoma
   (viii) Functions of cerebellum
5. **Illustrate with the help of labelled diagram:**
   (i) Structure of cerebellar glomerulus
   (ii) Neural circuit within cerebellar cortex
   (iii) Cerebro- cerebellar-cerebral circuit
   (iv) Localization of sensory areas of the cerebellum.
6. **Differentiate between:**
   (i) Cerebellar and sensory ataxia
   (ii) Intention and resting tremors.
7. **Give the sequence of activation of Purkinje cells.**
8. **How does the activation of granule cells get rapidly extinguished?**
9. **What is the main source of 'input' to the cerebellar cortex? Give its physio-clinical significance.**
10. **Give the physiological significance of neural circuit within the cerebellar cortex. Draw diagram also.**
11. **Name the excitatory and inhibitory transmitters in the cerebellum. Give their role in muscle movement.**
12. **Mention a few important tracts entering through three peduncles into the cerebellum.**
13. **What will happen and why if the anterior lobe of the cerebellum is cooled or warmed in case of classical decerebrate animal?**
14. **Give the role of cerebellum in:**
   (i) Control of body posture and equilibrium
   (ii) Control of muscle tone and stretch reflex
   (iii) Control of movements.

15. Explain how each cerebellar hemisphere modifies movements on its own side of the body.
16. Give the role of cerebellum in learning of motor skills.
17. Explain how cerebellum acts as a comparator of servo mechanism. Draw labelled diagram also.
18. Which will produce greater abnormalities and why? The lesion of cerebellar cortex or of deep cerebellar nuclei?
19. Which part of the cerebellum is responsible for clinical cerebellar dysfunction in humans? Add a note on its salient features.
20. What will happen and why to deep reflexes in cerebellar lesion?
21. How will you clinically assess the disturbances in a man due to cerebellar dysfunction?
22. Give the physiological basis of the following:
    (i) Pendular knee jerk (ii) Intention tremors (iii) Drunken gait
    (iv) Lalling speech (v) Dysmetria (vi) Rebound phenomenon.
23. List the pathways to and from the cerebellum. Describe their functions. Add a note on their physio-clinical significance.

MCQs

1. **The oldest lobe of cerebellum is:**
   (a) Flocculonodular lobe (b) Anterior lobe (c) Posterior lobe (d) Paramedian lobules
2. **Control of axial and limb muscles and postural reflexes is a function of:**
   (a) Vestibulocerebellum (b) Spinocerebellum (c) Neocerebellum (d) Archicerebellum
3. **Neocerebellum is concerned with control of:**
   (a) Skilled voluntary movements (b) Trunk limb muscles
   (c) Postural reflexes (d) Equilibrium
4. **The mossy fibers in cerebellum make direct synaptic connection with:**
   (a) Granule cells (b) Purkinje cells (c) Stellate cells (d) Basket cells
5. ***False* statement in connection with the neural circuit within the cerebellum:**
   (a) Output of granule cell is always excitatory
   (b) Output of purkinje cells, golgi cells and basket cells is always inhibitory
   (c) Granule cells make synaptic connections with dendrites of purkinje, basket and stellate cells
   (d) Output of basket and stellate cells excite the purkinje cell discharge
6. **Flocculonodular lobe of cerebellum is concerned with:**
   (a) Equilibrium (b) Hearing (c) Impulse control (d) Fine movements
7. **Feed forward inhibition:**
   (a) Helps to limit the duration of excitation of purkinje cells produced by any given afferent impulses
   (b) Refers to exitation of granule cells is rapidly stopped by negative feedback loop
   (c) Determines inhibitory Purkinje fiber discharge
   (d) Regulates excitatory Purkinje fiber discharge
8. **The role of cerebellum as a comparator of a servo-mechanism is:**
   (a) To compare informations what the muscles should be doing with information about what they are actually doing
   (b) Learning of motor skills
   (c) To modify the central motor programmes so that future movements of the same kind will be accurately performed
   (d) All of the above
9. ***Not true* of the cerebellar dysfunction:**
   (a) Cerebellar lesion of one hemisphere produces dysfunction of the same side of the body
   (b) Lesions of the vermis affect both the sides of the body
   (c) Lesions of cerebellar cortex produces permanent movement abnormalities
   (d) Lesions of deep cerebellar nuclei produce generalized defects and abnormalities persist
10. **Involuntary oscillatory movements of eye (Nystagmus)**
    (a) Are not seen in people whose nervous system is normal
    (b) May result from disease of cochlea
    (c) Do not affect the acuity of vision
    (d) Feature of cerebellar disease

11. **Tremors associated with cerebellar disease are:**
(a) Present at rest
(b) Present with action
(c) Restricted to hands and trunk
(d) Associated with fine movements only

12. **Spot the *wrong* combination defined:**
(a) Asthenia: feebleness of movements
(b) Asynergia: Incoordination of movements
(c) Dysmetria: Movements poorly carried out in direction, range and force
(d) Past pointing/hypermetria: Movements overshoot their intended mark

13. **Clinically cerebellar disturbances can be demonstrated by all of the following *except*:**
(a) Finger-nose test (b) Adiadochokinesia (c) Rebound phenomenon (d) Shuffling gait

14. ***Not* a phylogenetical division of cerebellum:**
(a) Archicerebellum (b) Paleocerebellum (c) Neocerebellum (d) Vestibulocerebellum

15. **To what part of the brain do most of the signals from the proprioceptors go?**
(a) The sensory cortex (b) The thalamus (c) The motor cortex (d) The cerebellum

16. **Purkinje cell is a:**
(a) Output cell (b) Input cell (c) Interneuron (d) Connector neuron

17. **The mossy fibers in cerebellum make direct synaptic connection with:**
(a) Granule cells (b) Purkinje cells (c) Stellate cells (d) Basket cells

18. **The cerebellum:**
(a) Has a totally inhibitory output from its cortex
(b) Has only inhibitory signal output from its deep nuclear layers
(c) Has a conscious interpretation of motor activity
(d) Has inhibitory influence on muscle tone in humans

19. **Which of the following is *not* an inhibitory cell in the cerebellum?**
(a) Stellate cell (b) Basket cell (c) Golgi cell (d) Granule cell

20. **Movements which occur without adequate cerebellar information:**
(a) Are poorly controlled (b) γ-system plays no role (c) Lacks accuracy (d) All of the above

21. **Cerebellum controls activity of:**
(a) α-motor neurons only
(b) γ-motor neurons mainly
(c) Both α and γ motor neurons
(d) Corticospinal tracts

22. **Characteristic features of cerebellar disease include all *except*:**
(a) Reduced muscle tone
(b) Loss of muscle-joint sensation
(c) Intention tremor
(d) Involuntary eye movements (Nystagmus) when fixing the gaze on an object

23. **Cerebellar nystagmus occurs with damage to:**
(a) Vermis (b) Flocculonodular lobe (c) Anterior lobe (d) Posterior lobe

24. **In cerebellar disease, all the statements are correct *except*:**
(a) The Romberg's sign is positive
(b) There is adiodokokinesia
(c) Pendular knee jerk
(d) Involuntary tremor

25. **Charcot's triad include all *except*:**
(a) Nystagmus (b) Intention tremors (c) Hypertonia (d) Lalling speech

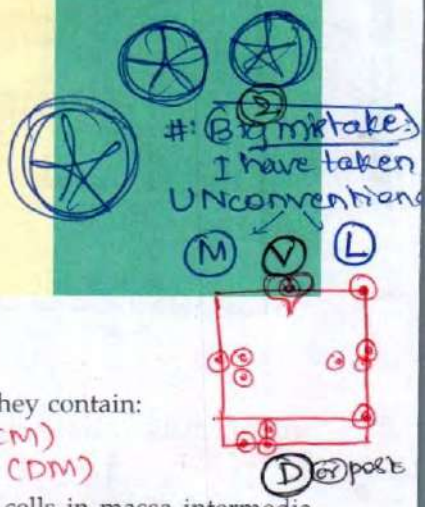
Answers

1. (a)	2. (b)	3. (a)	4. (a)	5. (d)	6. (a)	7. (a)	8. (d)	9. (c)	10. (d)
11. (b)	12. (b)	13. (d)	14. (d)	15. (d)	16. (a)	17. (a)	18. (a)	19. (d)	20. (d)
21. (c)	22. (b)	23. (b)	24. (d)	25. (c)					

Chapter 99

The Thalamus

I. Introduction
II. Classification of thalamic nuclei
III. Connections of the thalamus
IV. Functions of the thalamus
V. Applied: Thalamic syndrome



INTRODUCTION

The ***diencephalon***, the component of fore-brain, contains two major parts: the *thalamus* and the *hypothalamus*.

1. Each thalamus is a large, egg-shaped cluster of nuclei (mass of grey matter) which lies in the upper part of the lateral wall of the third ventricle of the brain.
2. The two thalami lie close together in their cephalic 2/3rd and are joined across the midline by mass of grey matter, the *massa intermedia*. Their caudal thirds are more widely separated.
3. The thalamus is *a major sensory relay station*. All general and special sensations (*except* the smell) and afferent impulses from the RAS (page 957) synapse here. It is an important integrating centre for most inputs before relaying them to the cerebral cortex.

CLASSIFICATION OF THALAMIC NUCLEI

EUROANATOMIC CLASSIFICATION

he thalamus is divided into three nuclear groups by the *ternal medullary lamina* consisting of white matter (Fig. .1).

. ***Lateral group of nuclei.*** They are subdivided into ventral and dorsal group of nuclei.

1. The *ventral group* of nuclei contains:
   - (i) Ventral anterior nucleus
   - (ii) Ventral lateral (lateroventral) nucleus
   - (iii) Ventral posterior (posteroventral) nucleus
   - (iv) Medial geniculate body, and
   - (v) Lateral geniculate body.
2. The *dorsal group* of nuclei contains:
   - (i) Pulvinar *i.e.* cluster of nerve cells lying most posteriorly
   - (ii) Lateral posterior nucleus, and (LP)
   - (iii) Lateral dorsal nucleus. (LD)

B. *Medial Group of Nuclei.* They contain:

1. Centromedian nucleus (CM)
2. Dorsomedial nucleus, and (DM)
3. Midline nucleus *i.e.* nerve cells in massa intermedia.

C. *Anterior Group of Nuclei.* They are enclosed by the bifurcation of the internal medullary lamina.

DEVELOPMENTAL CLASSIFICATION

Developmentally, the thalamus can be divided into: *Dorsal thalamus, ventral thalamus and epithalamus.*

A. *Dorsal thalamus.* It is subdivided into two groups: extrinsic and intrinsic nuclei.

1. *Extrinsic nuclei* or *cortical relay nuclei.* They receive afferents from extra thalamic sources which synapse here and then are distributed to the primary cortical areas. The extrinsic nuclei comprise:
   - (i) posteroventral nucleus,
   - (ii) lateroventral nucleus,
   - (iii) anterior nucleus,
   - (iv) medial geniculate bodies, and
   - (v) lateral geniculate bodies.

   Medial and lateral geniculate bodies are classed together as ***metathalamus.***
2. *Intrinsic nuclei.* They are the nuclei which interconnect with each other and mainly receive afferents from other structures in the thalamus. They comprise:
   - (i) midline nucleus, (Massa Intermedia)
   - (ii) intralaminar nuclei. These are cluster of nerve cells in the internal medullary lamina which include:
     - (a) centrum medianum (centromedian) nucleus,
     - (b) parafascicular nucleus,

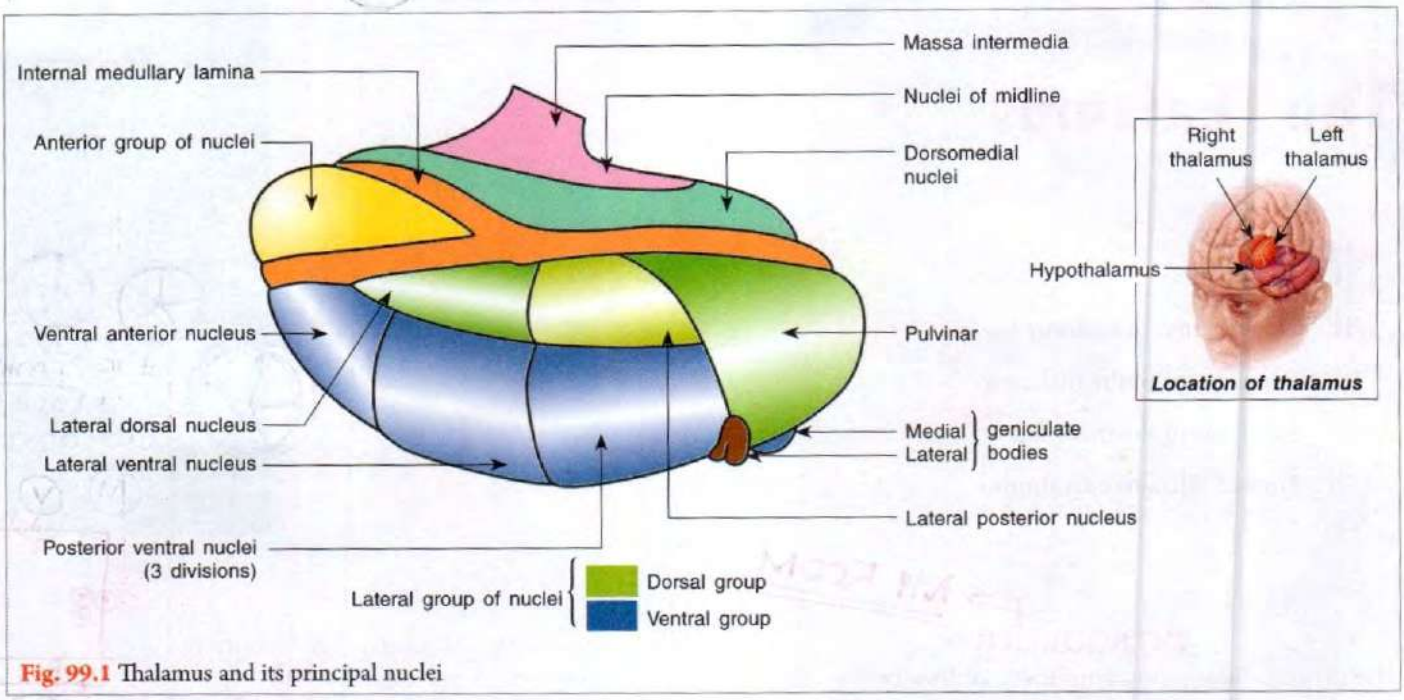


Fig. 99.1 Thalamus and its principal nuclei

(c) limitans nucleus,
(d) central nucleus,
(e) paracentral nucleus, and
(f) central lateral nucleus.

B. ***Ventral thalamus***

C. ***Epithalamus.*** It has connections with the olfactory system. For example:
1. Pineal body and
2. Habenular complex

FUNCTIONAL CLASSIFICATION

Functionally thalamic nuclei may be discussed under two headings: the *non-specific* and *specific* projection nuclei.

A. ***Non-specific projection nuclei.*** They receive impulses from the RAS and project diffusely to the whole of the neocortex. Examples: *midline* and *intralaminar* nuclei. Impulses in them are responsible for the diffuse secondary responses and the alerting effect of RAS (page 957).

B. ***Specific projection nuclei.*** They project to the specific portions of neocortex and limbic system. They can be divided into three groups:

1. The ***specific sensory relay nuclei***. For example:
   (i) *Medial and lateral geniculate bodies* which relay auditory and visual informations to the auditory and visual areas of the cerebral cortex respectively.
   (ii) *Posteroventral* group of nuclei which relay somesthetic information to the postcentral gyrus *i.e.* sensory cortex.
2. The nuclei concerned with ***motor control*** mechanism. For example:
   (i) *Ventrolateral* group of nuclei are concerned with motor functions. They receive inputs from the basal ganglia and cerebellum and project to the motor cortex.
   (ii) *Anterior group* of nuclei which receive afferents from mammillary bodies and project to the limbic cortex. They are concerned with recent memory and emotion.
3. The nuclei concerned with ***complex integrative functions*** are the dorsolateral nuclei which project to the cortical association areas of the cerebral cortex. They are concerned with functions such as language (speech).

Note

Most of the thalamic nuclei are excitatory neurons that release glutamic acid. The thalamic interneurons that release GABA (inhibitory neurotransmitter) modulate the responses of other thalamic neurons and their axons do not project to the cortex.

CONNECTIONS OF THE THALAMUS

The major connections of the principal thalamic nuclei are summarized in **Table 99.1**, **Fig. 99.2** and **99.3**.

FUNCTIONS OF THE THALAMUS

1. The thalamus is a ***great sensory relay station*** and integrating center for most inputs before relaying them to the cerebral cortex. For example:

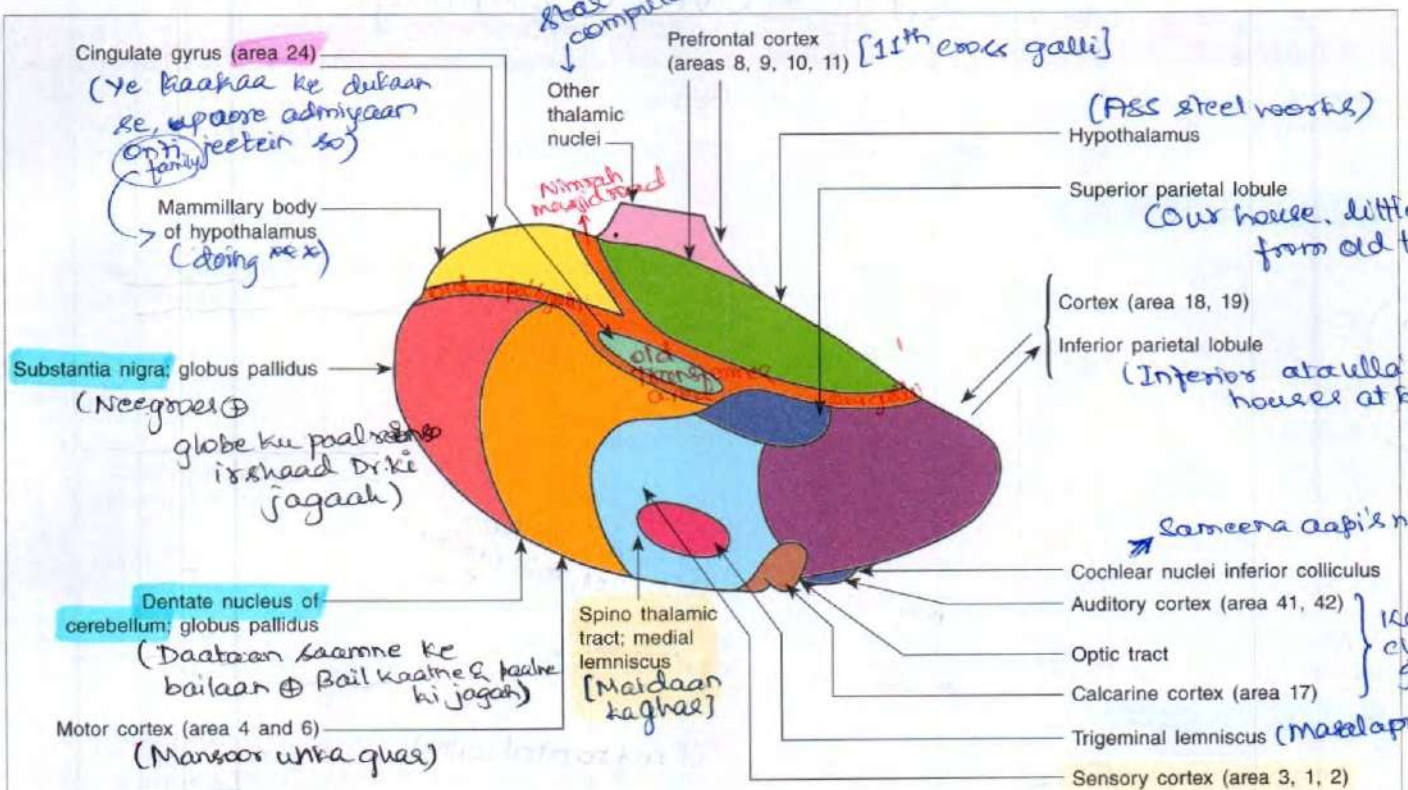


Fig. 99.2 Major thalamic projections to the cerebral cortex (also see Fig. 99.1)

Note

The majority of cortical areas reciprocally project fibers back to the thalamic nuclei

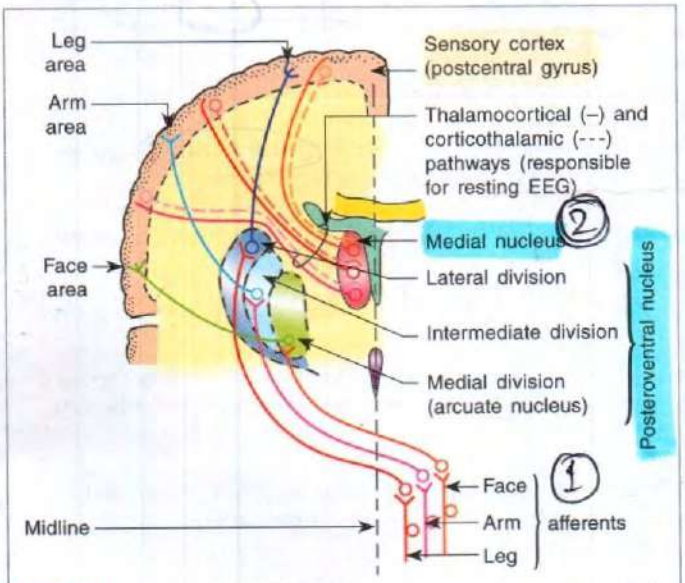


Fig. 99.3 Connections of the posteroventral nucleus and medial nucleus of the thalamus.

Note

The afferent fibers from the face, arm, leg end respectively in medial, intermediate and lateral divisions of the posteroventral nucleus. Thus showing topographical, (*i.e.* point-to-point) representation.

(i) Relay station in the pathway of somesthetic sensations coming from the opposite half of the body.

(ii) Relay station for the impulses coming from the opposite cerebellum on their way to the motor cortex.

(iii) Relay station for the impulses coming from the reticular formation.

(iv) Relay station in the inhibitory closed circuit beween the basal ganglia and cortical motor areas.

(v) Relay station in the auditory and visual pathways.

(vi) Relay station for autonomic and emotional reactions due to its connections with the hypothalamus and limbic lobe.

2. It is responsible for maintaining *conscious and altering* responses of RAS (page 957).

3. It is responsible for *subcortical perception of sensations.* Perception of sensations to some extent is possible without the sensory cortex; this is specially true for *pain.*

4. It is concerned with *control of muscular movements* via its various connections with the basal ganglia, cerebellum and motor cortex.

5. It is an *integrating center for sleep*. *Proof*: electrical stimulation of thalamus lateral to vasa media induces sleep.

Table 99.1: The major connections of the thalamus

Principal thalamic nucleus (functional classification)	Principal Connections		Principal function(s)
	Afferent fibers	Efferent fibers	
Non-Specific Projection Nuclei			
1. Midline nuclei	From spinothalamic; trigemino-thalamic tracts; medial lemniscus; reticular formation; other thalamic nuclei; hypothalamus.	To hypothalamus and neocortex; basal ganglia (caudate nucleus, putamen); other thalamic nuclei.	Center for integrating 'crude' visceral and somatic sensations.
2. Intralaminar nuclei (scattered nerve cells in internal medullary lamina)	From RAS, basal ganglia and other thalamic nuclei.	To prefrontal cortex.	1. Integrates somatic and visceral sensory impulses before projecting this information to cortex. 2. Responsible for alerting effects of RAS (page 957).
3. Dorsomedial nucleus	From hypothalamic nuclei; pre-frontal cortex.	To prefrontal cortex (areas 8, 9, 10 and 11).	Association center for synthesis of crude somatic sensations.
Specific Projection Nuclei			
1. Anterior group of nuclei	From mamillary body of hypothalamus via mammillothalamic tract (bundle of Vicq d'Azyr).	To cingulate gyrus (area 24) of cerebral cortex.	1. Form part of *Papez circuit* (page 1018). 2. Involved in limbic system: concerned with recent memory and emotions.
2. Lateral ventral nucleus	1. From dentate nucleus of cerebellum via dentato thalamic tract. 2. From globus pallidus via thalamic fasciculus.	To cerebral cortex (pre motor areas 4 and 6) via posterior limb of internal capsule.	Relay proprioceptive information and voluntary motor functions.
3. Posteroventral nucleus (Fig. 99.3)	1. Termination of spinothalamic tracts; medial lemniscus. 2. Termination of trigeminal and medial lemniscus (face and taste fibers).	To sensory cortex, areas 3, 1, 2 (post central gyrus) via posterior limb of internal capsule.	1. Relay somatosensory impulses (touch-pressure, pain, proprioceptive, temperature and kinesthetic) from trunk and limbs. 2. Relay sensory impulses from face.
4. Dorsal lateral nucleus	From other thalamic nuclei; parietal lobe of cerebral cortex.	To cerebral cortex (parietal lobe).	Concerned with language (speech) and complex integrated functions.
5. Pulvinar	From other thalamic nuclei; cerebral cortex (parietal, temporal, occipital lobes).	To cerebral cortex (parietal, temporal, occipital lobes).	Integrates auditory, visual and somatic informations.
6. Medial geniculate bodies	Receive a 'topically' organized projection of auditory fibers from the cochlear nuclei and inferior colliculi.	To auditory cortex via internal capsule (bilateral projection).	Hearing.
7. Lateral geniculate bodies	From optic tract (cranial nerve II).	To ipsilateral calcarine cortex via geniculo-calcarine tract.	Vision.

6. It is concerned with recent memory and emotion as it forms a part of the *Papez circuit* (page 1018).
7. It is concerned with language (speech) function. Integration between different cortical parts by *subcortical connections* in the thalamus helps to *achieve speech* (details page 1031).
8. It plays an important role in *genesis of synchronization* of electroencephalogram – *EEG* (page 983).

APPLIED: THALAMIC SYNDROME

Blockage of thalamogeniculate branch of posterior cerebral artery usually *damages the posteroventral and posterolateral nuclei* of the thalamus. The symptoms and signs occur on the opposite side of the body and may be accompanied by emotional disturbances.

1. The ***posteroventral nucleus*** relays skin, muscle and taste afferents to the postcentral cortex. Its involvement leads to loss of discriminative aspects of sensation such as occurs in lesion of the sensory cortex itself. It includes:
   (i) Loss of tactile localization, tactile discrimination and stereognosis.
   (ii) Loss of kinesthetic sensations, therefore, when the eyes are closed, the patient finds it difficult to locate his body parts and he catches in air to locate them, called ***thalamic phantom limb*** (compare page 870).
   (iii) Overreaction to painful stimuli (page 901).
2. The *posterolateral nucleus* relays cerebellar impulses to the motor cortex, areas 4 and 6. Its involvement produces:
   (i) Profound muscular weakness, decrease in muscle tone and ataxia due to damage of the cerebellar afferents (page 970).
   (ii) Intention tremors (page 971).
   (iii) Abnormal posture of the hand called ***thalamic hand*** *i.e.* flexion of the wrist with hyperextended fingers.
   (iv) Involvement of fibers coming from globus pallidus leads to choreoathetosis *i.e.* quick jerky movements.

Study Questions

1. Justify the statement, "Thalamus is a major sensory relay station."
2. Give the functional classification of thalamic nuclei.
3. Draw labelled diagram to show:
   (i) Major thalamic nuclei
   (ii) Major thalamic projections to the cerebral cortex.
4. Give the principal connections and functions of posterolateral nucleus of thalamus.
5. Give the functions of following thalamic nuclei:
   (i) Anterior group of nuclei
   (ii) Intralaminar nuclei
   (iii) Ventrolateral nucleus
   (iv) Posteroventral nucleus
   (v) Pulvinar
   (vi) Medial geniculate body
   (vii) Lateral geniculate body.
6. Describe briefly:
   (i) functions of thalamus
   (ii) thalamic syndrome
   (iii) thalamic hand and thalamic phantom limb
7. What will happen if the following portion of the thalamus gets damaged?
   (i) Posteroventral nucleus.
   (ii) Posterolateral nucleus.

MCQs

1. Thalamus is a relay centre for all of the following sensations *except*:
   (a) Smell (b) Proprioception (c) Pain (d) Temperature

2. **Almost all of the cerebral cortex has direct two-way communication with which one of the following subcortical structures?**
   (a) Cerebellum
   (b) Thalamus
   (c) Hypothalamus
   (d) Bulboreticular facilitatory area

3. **All are the functions of thalamus *except*:**
   (a) A major sensory relay station
   (b) Plays an important role in genesis of EEG
   (c) Maintains conscious and alert state
   (d) Control of circadian rhythm

4. ***Wrong* statement about thalamic syndrome:**
   (a) Caused by posteroventral and posterolateral thalamic nuclei
   (b) Symptoms and signs occur on the opposite side of the body
   (c) Pain sensation is least affected
   (d) Astereognosis

5. **Lesion of posterolateral nucleus of thalamus results in:**
   (a) Hyperalgesia
   (b) Thalamic phantom limb
   (c) Thalamic hand
   (d) Astereognosis

6. **Specific thalamic sensory relay nuclei include all *except*:**
   (a) Medial geniculate body
   (b) Lateral geniculate body
   (c) Posteroventral group of nuclei
   (d) Ventrolateral group of nuclei

7. **Thalamic nucleus which relays somesthetic information to the sensory cortex:**
   (a) Posteroventral
   (b) Ventrolateral
   (c) Ventroanterior
   (d) Anterior

8. **Part of the brain serving as a great sensory relay station:**
   (a) Thalamus
   (b) Hypothalamus
   (c) Medulla
   (d) Midbrain

9. **Destruction of dorsolateral nucleus of thalamus causes:**
   (a) Hyperphagia → Curious to taste & Eat & see everything!
   (b) Aphasia
   (c) Somnolence
   (d) Resetlessness

10. ***Wrong* statement about thalamic syndrome:**
    (a) Caused by posteroventral and posterolateral thalamic nuclei
    (b) Symptoms and signs occur on the opposite side of the body
    (c) Pain sensation is least affected → ↑ pains
    (d) Astereognosis

11. **Damage to posteroventral nucleus in thalamic syndrome results in:**
    (a) Hyperalgesia → ↑ pain
    (b) Loss of tactile localization
    (c) Ataxia → phantom limb (Thalamic)
    (d) All of the above

Answers

1. (a) 2. (b) 3. (d) 4. (c) 5. (c) 6. (d) 7. (a) 8. (a) 9. (b) 10. (c) 11. (d)

Chapter 100

The Electroencephalogram and Sleep

I. Electroencephalogram (EEG)
   A. Normal EEG B. Physiological basis of the EEG C. Uses of EEG
II. Sleep
   A. General: factors affecting; physiological changes
   B. Types of sleep: NREM versus REM sleep; sleep cycle
   C. Genesis of sleep
   D. Control of 'sleep-waking' cycle
   E. Sleep disorders

δ-waves in awaken stat
⇒ Organic Brain disease

ELECTROENCEPHALOGRAM (EEG)

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). This method of EEG recording was first introduced by German psychiatrist, *Hans Berger*. A similar record resembling EEG may be obtained by placing the electrodes directly on the exposed surface of the cerebral hemispheres – this is termed, the *Electrocorticogram (ECoG)*.

A. 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, temporal area or parietal area.
2. ***Unipolar method.*** It is a record of potential difference between an active cortical electrode and an indifferent electrode applied on some part of the body distant from the cortex such as ear lobe.

If an EEG record is taken in a normal subject who abstains from mental activity and keeps his eye closed, the usual pattern of electrical activity consists of sequence of *rhythmic* waves. The waves are classified according to their *frequency* and *voltage* (amplitude). **(Table 100.1)**.

Important Notes

1. Each EEG tracing is a complex rhythmic wave which *never repeats* itself precisely.
2. In general, *lower* EEG frequencies indicate less responsive behaviour, such as sleep, whereas *higher* frequencies indicate arousal.

α-Rhythm: Characteristic features

1. 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. 100.1)**.

Table 100.1: 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 overbreathing or evidence of organic brain diseases when seen in awake state.

Amp. wise: δ α θ β (DAT B)
Freq. wise: β α θ δ (BAT B)

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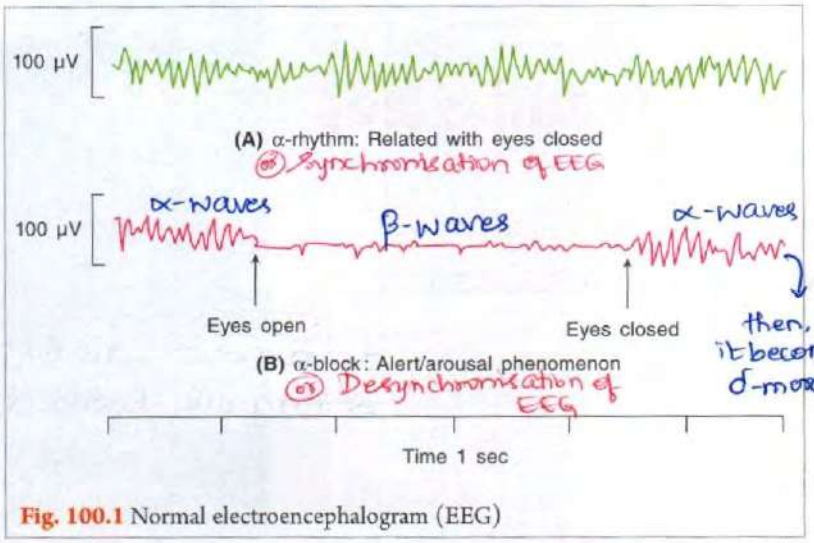


Fig. 100.1 Normal electroencephalogram (EEG)

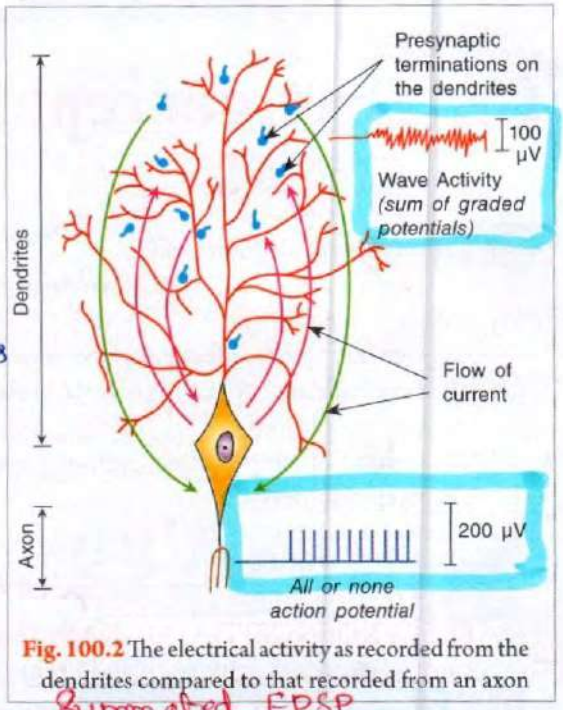


Fig. 100.2 The electrical activity as recorded from the dendrites compared to that recorded from an axon

2. Its frequency is:
   (i) ***Decreased by***
   (a) low blood glucose level,
   (b) low body temperature,
   (c) a high arterial pCO_2,
   (d) low levels of adrenal glucocorticoid hormones,
   (e) anaesthesia or analgesia, and
   (f) sleep.
   (ii) ***Increased by***
   (a) high blood glucose level,
   (b) rise in body temperature,
   (c) a low arterial pCO_2,
   (d) high levels of adrenal glucocorticoid hormones,
   (e) alerting states, and
   (f) forced overbreathing which decreases arterial pCO_2.
3. It is *associated with decreased levels of attention*, and when α-rhythms are being generated, subjects commonly report that they feel relaxed and happy.
4. The replacement of regular α-rhythm with fast, high frequency, irregular low amplitude (voltage) activity is called *Alpha-block*, or *Desynchronization of EEG*. It represents a breaking up of the *synchronized* activity of the cortical neurons responsible for α-wave pattern. A break up of the α-pattern is also produced by any form of sensory stimulation such as opening of the eyes or mental concentration. Because desynchronization is produced by sensory stimulation and is correlated with the aroused, alert state, it is also called the ***arousal*** or ***alerting response***.

B. PHYSIOLOGICAL BASIS OF THE EEG

SOURCE OF THE EEG

The activity recorded in the EEG is that of rhythmically discharging cell bodies in the most superficial layers of the cortical grey matter. The EEG is due to graded potentials which are *summated* postsynaptic potentials in the brain neurons **(Fig. 100.2)**.

1. The potential changes in the EEG are due to current flow in the fluctuating *dipoles* formed on the dendrites of the cortical cells and the cell bodies.
2. The dendrites are the site of *non-propogated* hypo and hyperpolarizing local potential changes. The cell-dendrite relationship is, therefore, that of a constantly shifting dipole. Current flow in this dipole produces wave-like potential fluctuations in a volume conductor (page 291). When the sum of the dendritic activity is *positive* relative to the cell, the cell is hyperpolarized and less excitable; when it is *negative*, the cell is depolarized and hyperexcitable.
3. ***Evoked cortical potentials***
   The record of electrical events that occur in the cortex after stimulation of a sense organ are called *evoked potentials* **(Fig. 100.3)**. The response consists of:
   (i) ***Primary evoked potential***. It is highly specific in location. This is recorded when the exploring electrode is applied over the primary receiving area for the particular sense. It consists of a *positive-negative wave sequence* which appears with a latency of 5-12 msec. It indicates depolarization in the dendrites and somas of the cells in the cortex, followed by hyperpolarization.
   (ii) ***Diffuse secondary response***. This follows the primary evoked potential after a latency of 20-80 msec. It consists of a large prolonged positive deflection. It is not highly localized and can be recorded over most of the cortex. It is due to non-specific thalamic projections.

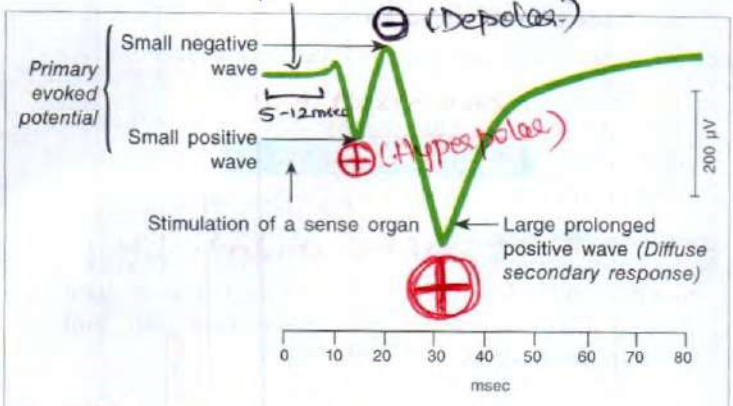


Fig. 100.3 Evoked cortical potential record from the sensory cortex (**Note:** Upward deflection is surface negative)

SYNCHRONIZING MECHANISMS

The activity of many of the dendritic units is synchronized by two factors:

1. The synchronizing effect on each unit of activity in its neighbours. This may be due to:
   (i) the neurons connected to one another by inhibitory pathways and are also hyperexcitable after the inhibition. Therefore, the synaptic activity they generate tends to become synchronized; and
   (ii) the effect of parallel neural processes on each other in a volume conductor.
2. The rhythmic discharge of impulses from the thalamus.

Proof

(i) Large lesion of the thalamus produces disturbances in the synchronized activity of the EEG on the side of the lesion.

(ii) Stimulation of the thalamic nuclei at low frequency (8-12 Hz) produces a similar characteristic response throughout most of the ipsilateral cortex (*synchronization* of the EEG), while high frequency stimulation produces arousal and *desynchronization*. Because the amplitude of this response increases and decreases, it is called the ***recruiting response*** **(Fig. 100.4)**.

The ascending reticular impulses thus *break* a resting mark-time cortical rhythm, which is a function of the non-specific thalamocortical pathway.

DESYNCHRONIZING MECHANISMS

Desynchronization means the replacement of a rhythmic EEG pattern with irregular low-voltage activity. The RAS is responsible for desynchronization of EEG following sensory stimulation (page 958).

Fig. 100.4 'Recruiting response' in the cortex, produced by slow stimulation of the intralaminar thalamic areas

Evidences

1. Desynchronization is *produced by* stimulation of the specific sensory system upto the level of the midbrain; but stimulation of these systems above the midbrain does not produce desynchronization.
2. *High-frequency stimulation* of the reticular formation in the midbrain tegmentum and of the non-specific projection nuclei of the thalamus produces desynchronization and arouses a sleeping animal.
3. Large *lesions of the midbrain* that interrupt the medial lemnisci and other ascending specific sensory systems ~~fail to prevent~~ the desynchronization produced by sensory stimulation.
4. *Lesions in the midbrain* tegmentum that disrupt the RAS without damaging the specific systems are associated with a synchronized pattern that is unaffected by sensory stimulation.

Important Note

Although arousal and EEG desynchronization generally co-exist, yet they do not always do so. For example:

1. Presence of desynchronized EEG in paradoxical sleep (page 986).
2. Strong nociceptive peripheral stimulation can produce arousal without desynchronization in animals with lesions of the midbrain tegmentum; and
3. Desynchronization can be produced without arousal in animals with lesions in the posterior hypothalamus.

C. USES OF EEG

1. ***Localization of pathological conditions*** such as:
   (i) Subdural hematoma or fluid collection over cortex is associated with decreased EEG activity over this area.
   (ii) Lesion in the cortex causes local formation of irregular or slow waves in the EEG.
2. ***Diagnosis of Epilepsy.*** Epilepsy (or *Seizures*)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

(i) ***Grand mal epilepsy.*** It is characterized by loss of consciousness without ***aura*** (*i.e.* warning sign). This is followed by generalized convulsions with tonic muscle contraction and clonic jerks. The EEG shows **(Fig. 100.5 A)**:
   (a) high voltage (upto 1000 μV) activity during the tonic phase,

(b) slow waves, each preceded by a *spike* at the time of each clonic jerk, and
(c) slow waves are present for some time after the attack is over.

(ii) ***Petit mal epilepsy (or Absence Seizures).*** It is a form of epilepsy in children (usually) characterized by abrupt loss of consciousness without falling or incontinence, and lasting for a few seconds. Here, convulsive movements are absent or confined to slight twitching. EEG shows 3 per sec doublets, each consisting of a typical spike and rounded waves (Fig. 100.5 B).

(iii) ***Psychomotor epilepsy.*** It is a form of epileptic fit characterized by clouding of consciousness and coordinated but inappropriate movements, which are often accompanied by a hallucinatory experience. There are no typical associated EEG changes.

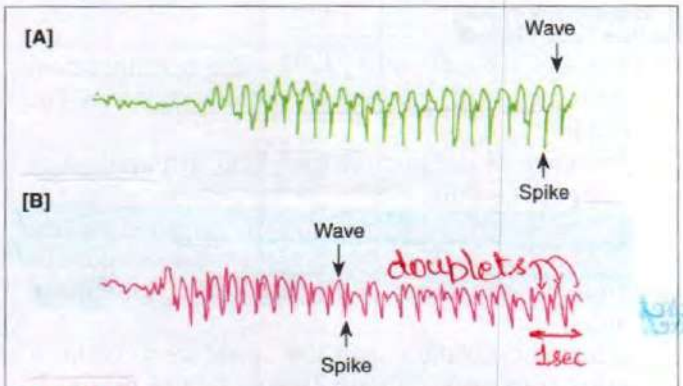


Fig. 100.5 Spike and wave pattern in the EEG of a patient during a grand mal epileptic fit (A) and petit mal epileptic fit (B)

SLEEP

A. GENERAL

1. Sleep is a *physiological process* by which bodily functions are periodically rested. During sleep, *consciousness* and *power of will* are partially or completely suspended and bodily activity generally is greatly reduced.

Important Note

The sleeping brain consumes as much energy as the awake brain and, sometimes, even more. Thus sleep is considered to be an active state.

2. Sleep *differs from alert wakefulness* by loss of critical reactivity to events in the external environment, therefore, subject can be aroused by sensory stimulation.
3. ***Factors affecting sleep.*** Sleep results from a reduction in the sensory inputs. Therefore, the procedures which minimize sensory stimulation favour the onset of natural sleep. For example:
   (i) darkened room
   (ii) relaxed body musculature
   (iii) comfortable warm surroundings, and
   (iv) silence

However, *anxiety* and *emotion* stimuli by release of epinephrine cause activation of RAS and make sleep more difficult.

Important Note

Sleep is more likely when the subject is *tired* even though the surroundings themselves do not predispose to sleep.

4. ***Physiological changes during sleep***
   (i) *CVS* – Heart rate, cardiac output, vasomotor tone and BP decrease.
   (ii) *Respiratory system* – Tidal volume, respiratory rate, pulmonary ventilation decrease. Sometimes the respiration remains unchanged or even becomes faster due to shallow breathing.
   (iii) *BMR* – decreases by 10-15%.
   (iv) *Urine* – volume decreases while phosphate content and specific gravity increases. Therefore, more concentrated urine is formed.
   (v) *Secretions*
      (a) salivary and lacrimal secretion decreases
      (b) sweat secretion increases
      (c) gastric secretion either remains unaltered or increases.
   (vi) *Muscles* are completely relaxed and the tone is minimum.
   (vii) *Eyes*
      (a) eye balls 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.
   (viii) *Blood volume* increases resulting in dilution of the plasma.
   (ix) *Nervous system*
      (a) EEG shows appearance of δ waves
      (b) deep reflexes are reduced
      (c) superficial reflexes remain unchanged
      (d) vasomotor reflexes become more brisk, and
      (e) light reflex is retained.

B. TYPES OF SLEEP

The neurophysiologists recognise two types of sleep:

1. *Non-rapid eye movement (NREM) sleep or slow wave sleep;* and
2. *Rapid eye movement (REM) sleep or paradoxical sleep.*

The behavioural observation and EEG changes in two types of sleep are summarized in Table 100.2 and Fig. 100.6.

NREM (SLOW WAVE) SLEEP

Physiological events

1. Each successive stage having an EEG pattern characterized by a *slower frequency and higher voltage* than the preceding one.
2. Initially there is considerable tone in the postural muscles, but *muscle tone* progressively *decreases*.
3. The eyes begin slow, rolling movements until they finally stop in stage 4 (deep sleep) with the eyes turned upwards.
4. When awakened, person does not report dreaming.
5. *Physiological significance:* During slow wave sleep, there is *pulsatile* release of growth hormone and gonadotrophins from the pituitary. BP, heart rate and respiration decrease. This indicates that slow wave sleep may serve as a *period of the body's rest and metabolic restoration*.

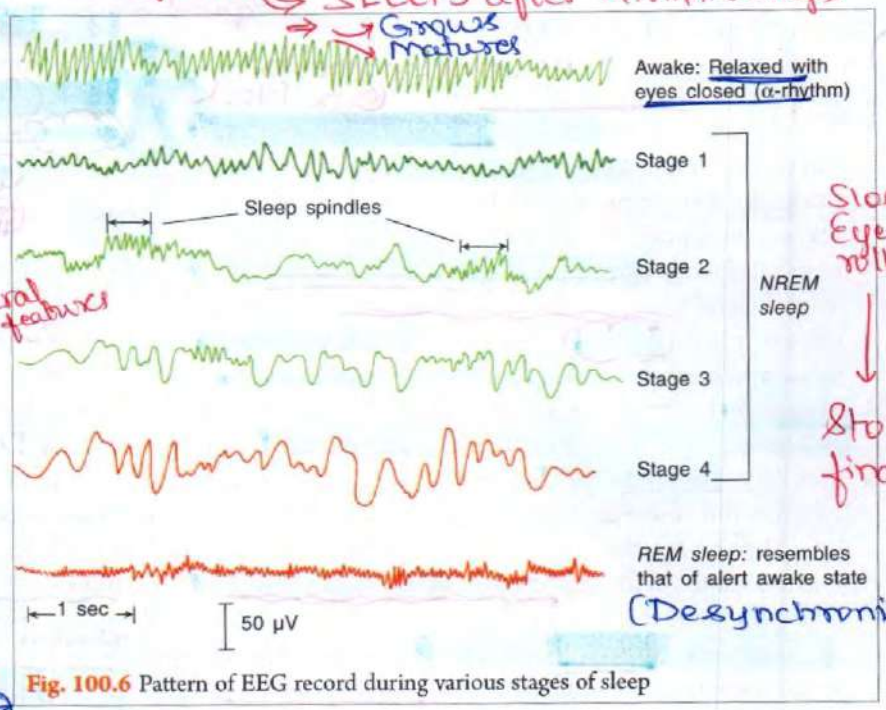


Fig. 100.6 Pattern of EEG record during various stages of sleep

Table 100.2: Behavioural and EEG changes in two types of sleep

Stage	Behavioural observation	EEG changes
Relaxed wakefulness	Awake, relaxed with eyes closed	Mainly α-rhythm; changes to α-block in response to internal or external stimuli.
Relaxed drowsiness	Fatigued, tired, eyelids may narrow and close; head may start to droop; momentary lapse of attention and alertness; sleepy but not asleep.	Decrease in α-wave amplitude and frequency.
NREM (slow wave) sleep		
Stage 1	***Light sleep:*** (1) Easily aroused by moderate stimuli or even by neck muscle jerks triggered by muscle stretch receptors as head nods. (2) Continuous lack of awareness.	α-waves reduced in frequency and amplitude.
Stage 2	***True sleep:*** further lack of sensitivity to activation and arousal.	Characterized by appearance of ***sleep spindles***. These are bursts of regular waves (frequency 14-15 Hz, 50 μV) of a few seconds duration. They are due to *reverberating* activity between the thalamus and the cerebral cortex.
Stage 3	Sleep deepens.	***Sleep spindles*** (occasional) now superimposed on a background of waves of δ type (frequency 1-2 Hz and of 100 μV amplitude).
Stage 4	***Deep sleep:*** (1) Activation and arousal occurs only with vigorous stimulation (high threshold of awakening). (2) When awakened, person does not report dreaming.	Slow high voltage δ waves.
REM (Paradoxical) sleep		
	Deepest sleep: (1) Greatest relaxation and difficulty of arousal, therefore, cannot easily be aroused by sensory stimuli (high threshold of awakening). (2) Skeletal muscle tone is markedly reduced except in the eye where REM occurs. (3) When awakened, subjects report 80-90% of the time that they have been dreaming.	EEG resembles that of alert awake state; rapid low voltage, irregular waves (***Desynchronized EEG***).

Important Note

REM sleep is also called PARADOXICAL SLEEP because the sleeping person is difficult to arouse despite having a desynchronized EEG that is characteristic of the alert, awake state.

Important Note

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.

REM (PARADOXICAL) SLEEP

Physiological events

1. EEG shows *desynchronized pattern*.
2. It is characterized by bursts of *Saccadic eye movements*. These are small jerky, fast movements that rapidly bring the eye from one fixation point to another to allow a sweeping search of the visual fields. It may be associated with *watching* the visual images of dreams.
3. 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.
4. *Dreaming* is closely associated with this sleep. When awakened the persons report 80-90% of the time that they have been dreaming. This is *true* even in people who do not remember dreaming when they awaken later spontaneously.
5. It is associated with an increase and irregularity in BP, heart rate, and respiratory rate.
6. Teeth grinding *(bruxism)* in children, erection of penis, engorgement of the clitoris, and twitches of the facial or limb muscles may occur.
7. It 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.
8. *Physiological significance*
   - (i) If subjects are aroused repeatedly in REM phase they become irritable, but on subsequent nights they manifest many more periods of REM sleep.
   - (ii) The correlation between dreaming and REM sleep indicates that the brain is highly active at this time. This may allow for the expression, through dreams, of concern in the *subconscious* and for long-term chemical and structural changes that the brain must undergo to make learning and memory possible.
   - (iii) Experimental animals completely deprived of REM sleep for long periods lose weight in spite of increased caloric intake and finally die. This indicates that REM sleep *plays important role in homeostatic mechanism*.

Thus, REM sleep is necessary for mental well being.

Important Note

Barbiturates (sedative) and monoamine oxidase inhibitor (MAOI) which reduce REM sleep, do cause untoward psychological effects.

SLEEP CYCLE

A ***sleep cycle*** consists of two phases: NREM (slow wave) sleep followed by REM (paradoxical) sleep.

1. Continuous recordings of adults show that the average total sleep period comprises of 4 or 5 such cycles, each lasting 90 to 100 minutes.
2. NREM sleep constitutes about 80% of the total sleeping time and REM sleep about 20%.

Note

In neonates and infants, REM sleep constitutes up to 50% of the total sleeping time.

3. The time spent in REM sleep increases towards the morning, at the end of an undisturbed night.

C. GENESIS OF SLEEP

Genesis of NREM (or Slow Wave) Sleep

NREM sleep is produced by *two factors*:

1. Inhibition of RAS inputs by the descending pathways which arise from the preoptic area and diagonal band of Broca. This prevents desynchronizing activity and called, *Basal forebrain sleep zone*; and
2. Stimulation of ***sleep promoting mechanism***, *i.e.* the rhythmic discharge of impulses from the thalamus (synchronizing mechanisms, page 983). These mechanisms get influenced by:
   - (i) *Diencephalic sleep zone* in the posterior hypothalamus and intralaminar and anterior thalamic nuclei.
   - (ii) *Medullary synchronizing zone* in the reticular formation of the medulla oblongata.

Important Note

It is a common knowledge that regularly repeated monotonous stimuli put children to sleep. This is due to stimulation of afferents from mechanoreceptors in the skin, which in turn generate synchronizing activity of the diencephalon.

Mechanism of generation of synchronization

1. It is probably due to stoppage of discharge of serotonin secreting neurons (*serotonergic neurons*) of the midline ***raphe nuclei*** of the pons and medulla. (*Raphe* means line of junction of the two halves of a structure which is formed in the embryo from bilateral rudiments.)
2. It may be also due to prostaglandin D_2 (PGD_2) which exists in the hypothalamus.

Proof:

1. Selective stimulation of these nuclei produces a marked increase in the total duration of wakefulness. Serotonergic neurons discharge rapidly in the awake state, slowly during drowsiness, more slowly with bursts during sleep, and not at all during REM sleep.
2. Serotonin agonists suppress sleep and the serotonin antagonist *ritanserin* increases NREM sleep.

3. Release of prostaglandin D_2 (PGD_2) in the medial preoptic area of the hypothalamus causes increased NREM and REM sleep, whereas release of PGE_2 causes wakefulness.

Genesis of REM (or paradoxical) Sleep

REM sleep shows increased activity in the pons, amygdala and anterior cingulate gyrus but decreased activity in the prefrontal and parietal cortex. Activity in visual association areas is increased but there is a decrease in the primary visual cortex.

Genesis of REM sleep is due to *two factors*:

1. Discharge of nor-epinephrine (NE) from the neurons located in the pontine reticular formation and in the locus ceruleus.
   (*Locus ceruleus* is a pigmented elongated elevation in the anterior part of the floor of the 4th ventricle.)

   Proof:
   (i) Selective destruction of these nuclei prevents REM sleep (both behavioural observations and EEG) without affecting the NREM sleep.
   (ii) Drugs which inhibit MAO, decrease the brain NE levels and cause total suppression of REM sleep.
2. PGO spikes (page 986) are due to discharge of *cholinergic* neurons. The cholinergic system is necessary for shifting NREM sleep to REM sleep.

Important Note

Barbiturate (a sedative) decreases the amount of REM sleep.

D. CONTROL OF SLEEP-WAKING CYCLE

(Jouvet. M. 1972)

Two mechanisms are suggested for the control of sleep-waking cycle: *neural and humoral mechanisms.*

Neural Mechanism

1. Periods of *sleep* and being *awake* alternate about once a day. They manifest a *circadian rhythm* consisting typically of 8 hours sleep and 16 hours awake. This basic rhythm is controlled by the *biological-clock* functions of the hypothalamic suprachiasmatic nucleus (page 1003). Within the sleep portion of this circadian cycle, NREM and REM sleep alternate **(Fig. 100.7)**.
2. The ***sleep-waking cycle*** involves two interacting systems in the brain stem: an *arousal system* and a *sleep producing system* **(Fig. 100.8)**.
   (i) The mechanisms that activate ***arousal system*** include:
      (a) stimulation of sensory receptors,
      (b) stimulation of midline reticular formation of the brain stem, hypothalamus and locus ceruleus, and

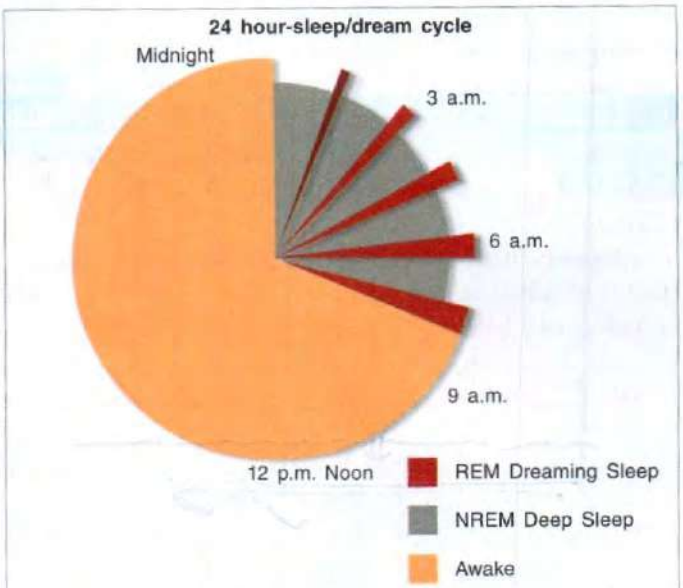


Fig. 100.7 Sleep-waking cycle: ***Circadian rhythm*** (Based on normal 8 hour night of sleep and a 90 minute sleep cycle rhythm)

   (c) stimulation of *raphe nuclei* (page 986).
   (ii) The mechanisms that activate *sleep producing system* are:
      (a) removal of afferent stimuli which in turn decreases the activity in RAS; and
      (b) stimulation of hypothalamic areas (anterior and dorsal).

Important Notes

1. Neurons in the *arousal system* region are most active during waking and are inhibited during sleep, while neurons in sleep *producing system* region show the opposite activity pattern.
2. A separate group of neurons is responsible for the cyclical imposition of REM sleep upon NREM sleep (see above).

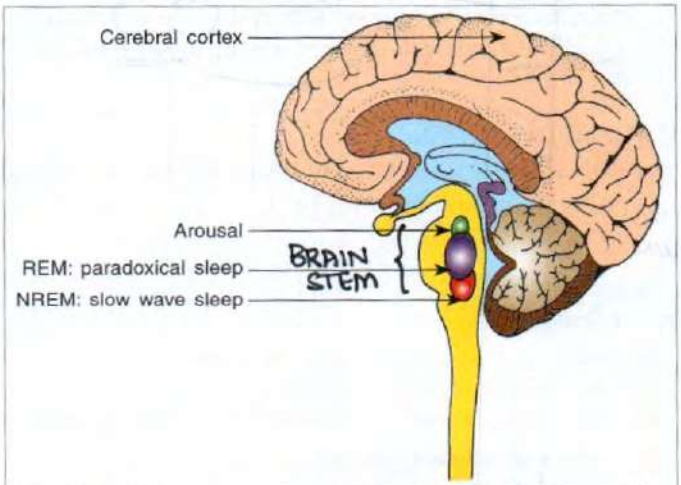


Fig. 100.8 Brainstem structures involved in arousal, NREM and REM sleep

Humoral or Chemical Mechanism

In addition to neurotransmitters *NE, serotonin* and *A-ch* mentioned above, there are a number of other *sleep-inducing* chemical substances, such as ***hypotoxin, delta-sleep inducing peptide (DSIP)*** and ***sleep promoting factor (factor S)***. These substances are found in blood, urine, CSF and brain.

Adenosine has been considered as *sleep promoting* factor (***factor S***), since caffeine, an adenosine antagonist is well known for its alerting effects.

Proof

When CSF from dogs *sleep-deprived* for several days is injected into cisterna magna of normal dogs it produces sleep in recipient dogs for many hours.

The sequential changes which occur in control of ***sleep-waking cycle*** are summarized in **Fig. 100.9**.

Fig. 100.9 Summary: Control of Sleep waking cycle (RAS: reticular activating system)

1. Discharge of serotoninergic neurons in raphe nuclei → serotonin → wakefulness.
2. Monoamine oxidase inhibitor (MAOI) decreases the brain NE levels → more than normal NREM sleep, called ***hypersomnia*** with total suppression of REM sleep.
3. Discharge of adrenergic neurons in pons and locus ceruleus → NE → REM sleep.
4. Discharge of cholinergic neurons → release of A-ch → PGO spike → Shift NREM sleep to REM sleep.

Important Notes

1. NREM (slow wave) sleep to waking is a reversible process for which 5 HT is responsible as neurotransmitter. In addition, from NREM to REM (paradoxical) sleep is also reversible with NE acting as a neurotransmitter.
2. Waking to REM (paradoxical) sleep is never possible.
3. During infancy, approx. 16 hours of every day are spent asleep. Thereafter, it drops to 10 hours during childhood and to 6-7 hours during adulthood.

E. SLEEP DISORDERS

1. *Insomnia.* It is a condition of being unable in initiating and/or maintaining sleep. This is a subjective feeling of an individual in spite of an adequate opportunity for sleep. Persistent insomnia can be due to many different mental and medical conditions.
2. *Fatal Familial insomnia*, a progressive encephalopathy that occur in inherited form. It is characterized by persistent insomnia, impaired autonomic and motor functions, dementia, severe neurological deficiencies and eventually leads to death.
3. *Somnambulism or Sleepwalkings.* 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.
4. *Nocturnal enuresis i.e.* involuntary voiding of urine occurring during sleep at night.
   Conditions 3 and 4 usually occur during NREM (slow wave) sleep.
5. *Narcolepsy.* It is a chronic brain disease which start with sudden onset of REM sleep and there is an uncontrollable urge to sleep during day time activities with loss of muscle tone (*Cataplexy*).
6. *Sleep Apnoea.* Refer to page 450.
7. *REM behaviour disorder.* In this condition, REM sleep is not associated with hypotonia; as a result, such persons may jump out of bed during sleep and *act out their dream.*

Study Questions

1. **Define and give physiological significance of:**
   (i) EEG and ECoG
   (ii) Arousal/alerting response.
2. **Give the main features of normal EEG rhythm. Draw well labelled diagram also.**
3. **Draw well labelled diagram of:**
   (i) normal EEG
   (ii) evoked cortical potential record
   (iii) pattern of EEG during various stages of sleep
   (iv) Control of sleep waking cycle
   (v) Brainstem structure involved in arousal and sleep

4. Give an account of physiological basis of:
   (i) Source of EEG (ii) Evoked cortical potential
   (iii) Synchronization mechanisms (iv) Desynchronization mechanisms.
5. Write short notes on:
   (i) Uses of EEG (ii) Sleep spindles (iii) Paradoxical sleep (iv) PGO spikes
   (v) Sleep cycle (vi) Sleep disorders. (vii) α-block (viii) Uses and types of sleep
   (ix) Physiological changes during sleep (x) Genesis of sleep
6. Define sleep. Enumerate the factors affecting it.
7. Differentiate between NREM and REM sleep under the following heads:
   (i) Behavioural observations (ii) EEG changes
   (iii) Physiological significance (iv) Genesis.
8. Give the role of various neurotransmitters in the genesis of sleep-wakefulness.
9. Describe briefly the mechanisms involved in control of sleep-waking cycle.
10. Which is more difficult to wake up and why—a young person or an elderly person?
11. What is paradoxical sleep. Why is it so called?
12. How does sleep differ from unconsciousness or general anaesthesia?
13. Give the conditions that generate delta waves.
14. How can you prove that desynchronization mechanism occurs via activation of RAS and not due to stimulation of specific sensory system?
15. Justify: "Sleep is passive reticular deactivation."

I like RAS & 5HT. ∵ they keep me awake

I hate Ritak sheeeen didi

MCQs

1. The electroencephalographic (EEG) waves are sometimes also called as:
   (a) ABCDE waves (b) Berger's rhythm (c) Neurogenic rhythm (d) REM rhythm
2. The fastest frequency EEG wave is:
   (a) α-wave (b) β-wave (c) θ-wave (d) δ-wave
3. The term desynchronization indicates:
   (a) Sleep response (b) Replacement of rhythmic wave with α-waves
   (c) Replacement of rhythmic EEG pattern with low voltage, irregular waves
   (d) All of the above
4. Source of EEG is:
   (a) End plate potential of nerve cells (b) Polarity of nerve ganglions
   (c) Parietal cortex (d) EPSPs and IPSPs of cortical cells which behave like dipoles
5. The EEG has an edge over modern available equipments in diagnosis of:
   (a) Subdural hematoma (b) Brain tumours (c) Epilepsy (d) Lesion in the cortex
6. EEG with a typical spike and rounded waves pattern is characteristic of:
   (a) Jacksonian epilepsy (b) Grand mal epilepsy (c) Petit mal epilepsy (d) Temporal lobe epilepsy
7. Which of the following is *not* associated with rolling eye movements?
   (a) NREM stage 1 (b) NREM stages 2 and 3 (c) NREM stage 4 (d) Paradoxical sleep
8. Sleep spindles:
   (a) Appear during stage 1 of NREM sleep (b) Persists till stage 4 of NREM sleep
   (c) Are bursts of regular waves of few seconds duration (d) Slow high voltage waves
9. The condition known as REM is:
   (a) That point at which the individual becomes awake and alert [No, he is in that condition, still he cannot be awaken also in such state]
   (b) Also referred to as paradoxical sleep
   (c) Characterized by total lack of all muscular activity [In NREM]
   (d) Characterized by slow high voltage regular EEG activity [In NREM]
10. Paradoxical sleep consists of: PGO → Ponto-Lateral Geniculo-occipital spike
    (a) REM, sharp wave and fast rhythm (b) REM, spike and slow wave
    (c) NREM, delta wave (d) NREM, high spike, theta wave
11. *False* statement about sleep cycle:
    (a) Each cycle lasts for about 90-100 minutes (b) Total sleep period comprises of 4 or 5 sleep cycle
    (c) NREM sleep constitute about 20% of total sleeping time (d) NREM sleep followed by REM sleep
12. *Correct* statement regarding control of sleep-waking cycle:
    (a) NREM sleep to waking is a reversible process with 5 HT acting as neurotransmitter
    (b) NREM to REM sleep is reversible with nor-epinephrine acting as a neurotransmitter
    (c) Waking to REM sleep is never possible
    (d) All of the above

13. **Somnambulism is:**
(a) Common in children
(b) Uncontrollable urge to sleep during day time activities
(c) REM sleep is not associated with hypotonia
(d) Involuntary voiding of urine during sleep

14. **An EEG:**
(a) es indication of intelligence
(b) Tends to show waves of small amplitude during deep sleep
(c) waves with a lower frequency during alert state
(d) Is bilateraly symmetrical

15. **The EEG rhythm having lowest frequency is:**
(a) Alpha (b) Beta (c) Delta (d) Theta

16. **In hippocampus EEG wave is:**
(a) Alpha wave (b) Beta wave (c) Theta wave (d) Delta wave

17. **Delta waves in EEG are seen in:**
(a) Deep sleep (b) REM sleep (c) Awake with eyes open (d) Awake with eyes closed

18. **Alpha waves in EEG are seen in:**
(a) Children over fronto-parietal region
(b) Children over parieto-temporal region
(c) Adults over parieto-occipital region
(d) Adult over fronto-parietal region

19. ***Not true* about EEG rhythms, in general:**
(a) Each EEG tracing is a complex rhythmic wave which never repeats itself precisely
(b) Lower EEG frequencies indicate less responsive behaviour
(c) Higher EEG frequencies indicate arousal
(d) α-wave forms most prominent component of EEG in an awake alert person

20. **α-rhythm frequency is decreased by all *except*:**
(a) Alerting states (b) Hypothermia (c) Hypercapnia (d) Low blood glucose level

21. ***Not true* regarding evoked cortical potentials:**
(a) A record of electrical events that occur in the cortex after stimulation of a sense organ
(b) Primary response is highly specific in location
(c) Secondary response is due to non-specific thalamic projections
(d) Also called as electrocorticogram

22. **If the connections are cut between the cortex and the thalamus, which one of the following types of brain waves can still be recorded in the cortex:**
(a) Alpha waves (b) Beta waves (c) Theta waves (d) Delta waves

23. **EEG findings in all forms of epilepsy is:**
(a) High voltage waves (upto 1000 μV)
(b) Spike and rounded waves
(c) Slow waves preceded by a spike
(d) No typical associated EEG changes

24. **Which of the following statements is *not true* about brain waves?**
(a) The brain wave of petit mal epilepsy is a spike and dome pattern
(b) Grandmal epilepsy is characterized by high frequency high voltage waves
(c) Psychomotor epilepsy is characterized by lower than normal frequency waves
(d) Deep sleep is characterized by alpha waves

25. **Sleep spindles are characterized by:**

	Voltage	Frequency
(a)	High	High
(b)	High	Low
(c)	Low	High
(d)	Low	Low

Answers

1. (b) 2. (b) 3. (c) 4. (d) 5. (c) 6. (c) 7. (c) 8. (c) 9. (b) 10. (a) 11. (c) 12. (d) 13. (a) 14. (d) 15. (c)
16. (c) 17. (a) 18. (c) 19. (d) 20. (a) 21. (d) 22. (d) 23. (a) 24. (d) 25. (a)

Chapter 101

The Basal Ganglia

I. Physiological anatomy
II. Connections of the basal ganglia
III. Functions of the basal ganglia
IV. Diseases of the basal ganglia: Parkinson's disease; chorea; athetosis

PHYSIOLOGICAL ANATOMY

The term basal ganglia is applied to group of nuclei in the forebrain and upper part of the brain stem that have motor function of great importance. It is the *primary motor area* in lower animals (reptiles and birds) and called the *basal ganglia* of neural control.

The basal ganglia includes (Fig. 101.1):

1. Caudate nucleus,
2. Putamen (a Latin word for a shell),
3. Globus pallidus or pallidium or paleostriatum
4. Subthalamic nucleus (body of Luys); and
5. Substantia nigra,

Caudate nucleus

1. It possesses a head and a tail (terminating at the amygdaloid nucleus).
2. The caudate nucleus and putamen are together called the *Corpus Striatum* or *Neostriatum*. It is phylogenetically more recent part.
3. The anterior limb of the internal capsule lies between the head of the caudate nucleus and the putamen.
4. Numerous grey strands extended between the caudate nucleus and putamen passing across the internal capsule; hence the name corpus striatum.

Putamen and Globus pallidus

1. These two nuclei are *phylogenetically older* parts and are together called *Lenticular Nucleus* (bean shaped).
2. Globus pallidus is also called *paleostriatum*. It is so called because it looks *pale* in fresh sections of the brain.
3. Globus pallidus is subdivided into *External* and *Internal* segments by a medial medullary lamina.

Substantia nigra

It is subdivided into two parts: the dorsomedial *pars compacta* and the ventrolateral *pars reticulata*. It is particularly *rich in copper* content.

Important Notes

1. The oxygen consumption of the basal ganglia is high.
2. Red nucleus, claustrum and amygdala are functionally related to the basal ganglia.

HISTOLOGY

Upon microscopic examination, the basal ganglia contains two types of cells:

1. *Small cells*. They are concerned with receptive function

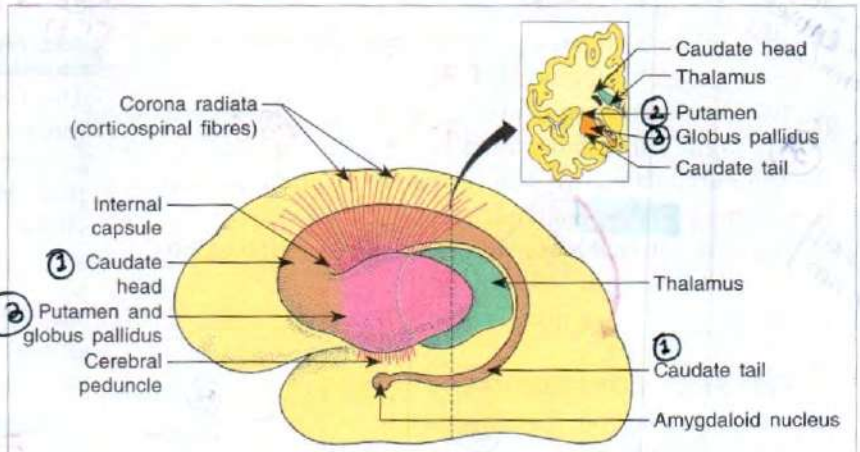


Fig. 101.1 Relationship between basal ganglia, thalamus and cerebral cortex in sagittal section and coronal section (inset)

i.e. receive fibers from other structures. *Example:* The neostriatum.

2. *Large cells.* They are concerned with motor (efferent) functions *i.e.* give rise to fibers which go to other structures. *Example:* globus pallidus.

CONNECTIONS OF THE BASAL GANGLIA

The basal ganglia forms extensive interconnection with the cerebral cortex and the thalamus. These connections can be discussed under three headings: *Afferent, Internuclear* and *Efferent* connections.

See the flowchart → 994

A. AFFERENT CONNECTIONS (Fig. 101.2 A)

The main afferent connections to the basal ganglia terminate topographically in the neostriatum and are ***excitatory (cholinergic neurons)***. They include:

1. *Corticostriate projection.* They form afferents from all four lobes of the cerebral cortex but mainly from the frontal (motor areas, page 906) and parietal lobes to the neostriatum.
2. *Thalamostriate fibers.* A projection from the intralaminar, medial, ventralanterior and centromedian nuclei of the thalamus to the neostriatum.

B. INTERNUCLEAR CONNECTIONS (Fig. 101.2B)

1. *Dopaminergic nigrostriatal tract.* Pars compacta of substantia nigra contains cell body having dopamine (***inhibitory transmitter***) and its axons terminate in a topographic manner in the neostriatum.
2. *GABA-ergic inhibitory projections*
   (i) The neostriatum (caudate nucleus plus putamen) projects:
   (a) to the pars reticulata of the substantia nigra; and
   (b) to both internal and external segments of the globus pallidus.
   (ii) The external segment of the globus pallidus projects to the subthalamic nucleus.
3. The subthalamic nucleus projects via *glutamic acid secreting excitory neurons* to:
   (i) both internal and external segments of the globus pallidus; and
   (ii) the substantia nigra.

C. EFFERENT CONNECTIONS (Fig. 101.2C)

The main output from the basal ganglia is from the globus pallidus and substantia nigra.

1. From the *internal* segment of the globus pallidus:
   (i) Via the *thalamic fasciculus* to the ventral lateral; ventral anterior and centromedian nuclei of the thalamus. From the thalamic nuclei, fibers project to the prefrontal and premotor cortex.
   (ii) Via *Ansa (loop) lenticularis tract* sends fibers to the subthalamic nucleus, substantia nigra, red nucleus of the midbrain and reticular formation of the brain stem.

Note

Ansa lenticularis is comprised of fibers which have curved round the cerebral peduncle.

2. The ventrolateral pars reticulata of the substantia nigra projects to the ventrolateral and ventroanterior nuclei of the thalamus. There are few additional projections from this part to the *habenula* and the *superior colliculus*.

Important Note

The projections from the globus pallidus and substantia nigra to the thalamus are *inhibitory* (*GABA-ergic*), whereas the thalamic nuclei projections on to the motor cortex are *excitatory* (mainly *cholinergic*).

Feedback Circuit

There is a *feedback circuit between the cerebral cortex and basal ganglia*. How?

The *neostriatum* receives extensive inputs from the *cerebral cortex* and thalamus; via the *internuclear connections* the neostriatum sends most of its output to the *globus pallidus* and to the *reticular nucleus of the substantia nigra*. This, in turn, projects to the *thalamus*. The information received by the thalamus is conveyed back to the cortex, thus completing the *feedback circuit* (Fig. 101.2 B and C).

Important Note

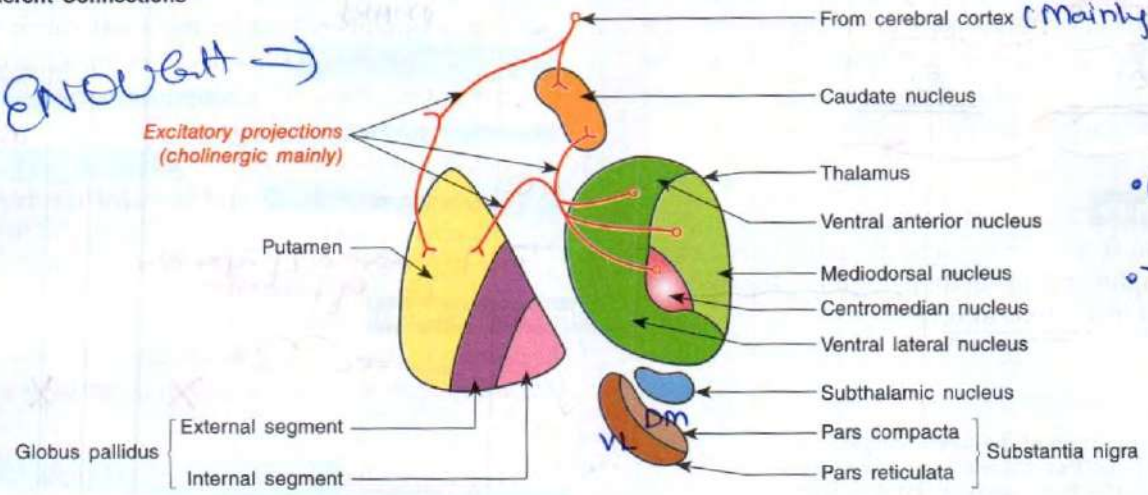
This feedback circuit is *integrated* in the ventrolateral nucleus of the thalamus with another circuit *i.e. cortico-ponto-dentato-thalamo-cortical circuit* (Fig. 98.9, page 969) and inhibits excessive activity of the motor cortex, areas 4 and 6).

Similarities and dissimilarities between the basal ganglia and the cerebellar connections:

Similarities: Both basal ganglia and cerebellum:
(i) receive information from all parts of the cerebral cortex and project back to the motor cortex via the ventrolateral and ventroanterior thalamus;
(ii) exert an influence on motor performance.

• Neostriatum = Sensory Basal ganglia;
• Lenticular nucleus = Motor Basal ganglia (Gen.);

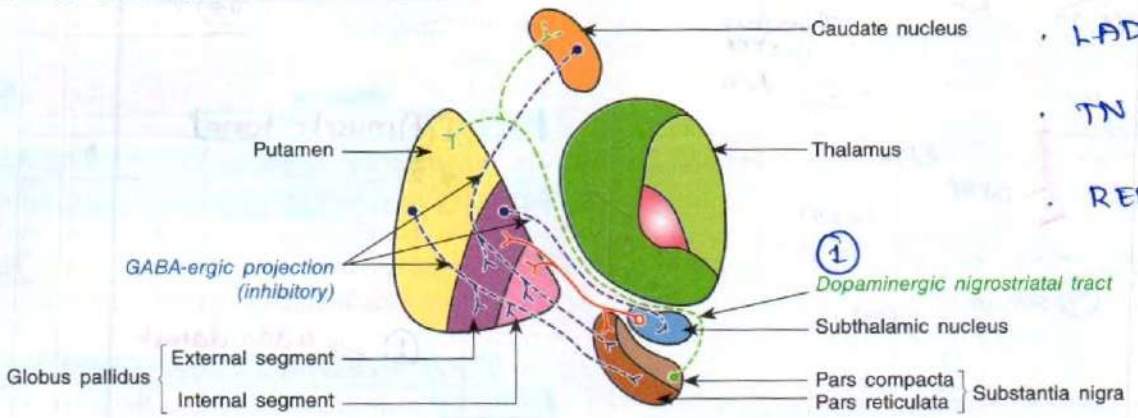
A. Afferent Connections



ENOUGH ⇒

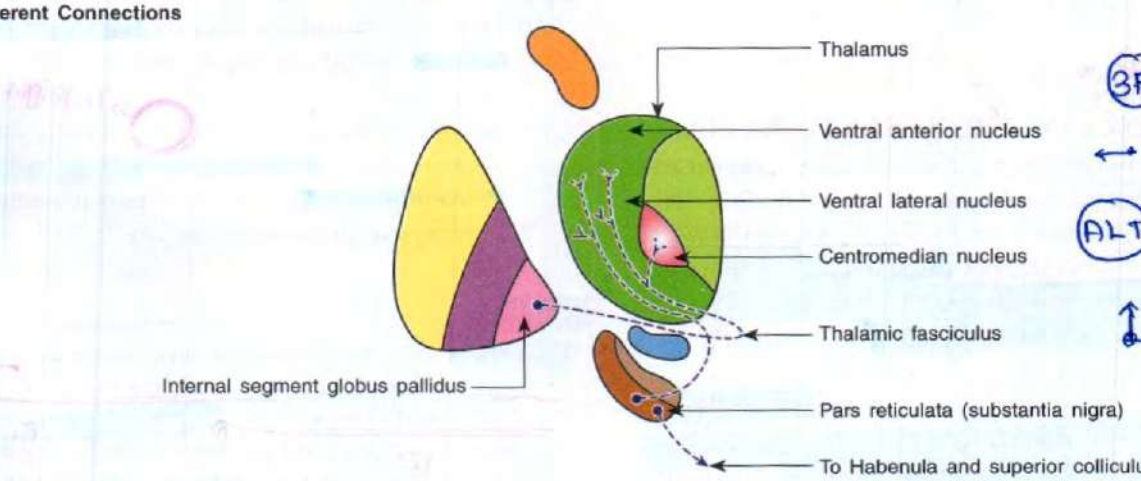
• Cortico striatal
• Thalamo striatal

B. Internuclear Connections



• LADEN inhibited
• TN fears — camel & snakes
• REAL RAM

C. Efferent Connections



3A 5 ↔ ↕

ALT Red reticular

↕ Habib's superior coli

O (—): *Excitatory neurons* (cholinergic mainly or glutaminergic)
● (---): *Inhibitory neurons* (GABA-ergic or dopaminergic)

Fig. 101.2 Connections of the basal ganglia

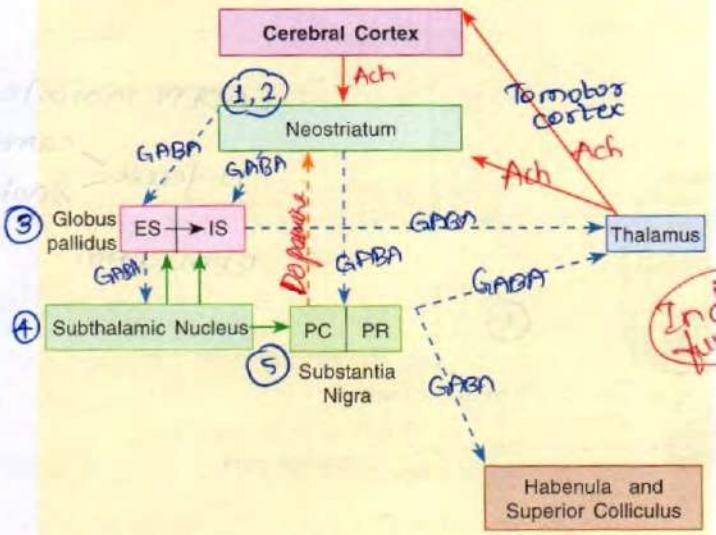
Dissimilarities

1. The cerebellum receives large synaptic inputs from the spinal cord and the basal ganglia does not.
2. The cerebellum has direct influence on the major extrapyramidal pathways (such as the vestibulospinal and rubrospinal tracts), whereas the basal ganglia has only indirect influence.

Important Note

Because of these similarities and dissimilarities both the basal ganglia and cerebellum influence the motor functions but in a different way.

Summary: Connection of the basal ganglia
(ES, IS: External and internal segment;
PC, PR: Pars compacta and reticulata)



Excitatory neurons: A-ch (–); glutamic acid (–); Inhibitory neurons: GABA (– – –); dopamine (– – –)

FUNCTIONS OF THE BASAL GANGLIA

Physiological studies (electrical stimulation, removal and recording of electrical potentials) and clinical findings have made it clear that neurons in the basal ganglia *discharge before movements begin*. They discharge via the thalamus to areas related to the motor cortex, and the descending tracts provide the *final common pathway* to the spinal motor neurons.

1. The basal ganglia is involved in the ***Planning and Programming*** of movements by preventing *oscillation* and *after discharge* in the motor system, *i.e.*, in the processes by which an idea of voluntary movement is converted into the precise action.
   Mechanism: The subthalamic nuclei provide *excitatory* input to the globus pallidus (the origin of the main efferent pathways from the basal ganglia); the globus pallidus sends fibers back to the subthalamic nuclei. Activity in this circuit is an important regulator of basal ganglia output that in turn maintains movements in a smooth and appropriate state.
2. The activity of the basal ganglia increases during slow, steady damp movement and is silent during rapid, *saccadic* movement (page 1115).

Important Note

The neurons in the basal ganglia are stimulated mainly by A-ch and are inhibited by the dopamine and GABA.

3. The basal ganglia ***inhibits the stretch reflex*** (muscle tone) throughout the body by stimulation of the caudate nucleus. How?
   (i) By stimulation of *inhibitory motor cortex* through thalamocortical feedback pathway; and
   (ii) By stimulation of *inhibitory reticular formation* (page 958).
   This is why damage to the basal ganglia produces rigidity.
4. The ***neostriatum*** regulates the subconscious gross movements occurring in groups of the muscles.
   Proof: Decortication (page 954) results in loss of fine movements, specially in the distal body parts. However, the person can maintain equilibrium and can walk *crudely*.
5. The ***caudate nucleus*** plays an important role in *cognitive processes* (page 1025) because of the interconnections of this nucleus with the orbitofrontal and dorsolateral prefrontal lobe.
   Proof:
   (i) Lesions of the caudate nucleus disrupt performance on tests involving object reversal and delayed alternation.
   (ii) Lesions of the head of the left caudate nucleus is associated with ***dysarthric aphasia*** *i.e.*, difficulty in articulating words. Therefore, patient cannot utter in words what he wishes to say.

Note

Cognition is a psychological term for that activity of the brain by which one is aware of processes of thinking and perceiving. *Cognitive abnormalities* include: difficulties with complex tests, long-term planning, memorizing or retrieving new information, working memory, attention, word fluency and mental flexibility.

6. The *globus pallidus* provides appropriate muscle tone for performance of skilled movements.
7. The *substantia nigra* is *centre* for coordination of those impulses which are essential for skilled movements.
8. The 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, area 6.

DISEASES OF THE BASAL GANGLIA

A. PARKINSON'S DISEASE (PARALYSIS AGITANS)

(Originally described by *James Parkinson*)

Agitans means shaking, therefore, this condition is also called ***shaking palsy*** which is characterized by *rigidity*, tremors (*hyperkinesia*) and weakness of movements (*hypokinesia*).

Note

The hyperkinetic conditions are those in which movement is excessive and abnormal. The hypokinetic abnormalities include akinesia and bradykinesia.

Causes

This condition usually occurs in late middle age due to *degeneration of dopaminergic nigrostriatal tract* (page 992). Therefore, concentration of *dopamine* in this region *i.e.* ***nigrostriatal system*** is reduced (Neurodgenerative disorder), the fibers to the putamen are most severely affected. This is commonly seen in:

(i) Primary or idiopathic *i.e.* condition occurring without apparent cause;
(ii) Cerebral arteriosclerosis;
(iii) Complication of encephalitis; and
(iv) Complications of tranquilizer drugs such as phenothiazine which blocks the D_2 dopamine receptors (page 1048)

Note

Dopaminergic neurons and dopamine receptors are steadily lost with aging in the basal ganglia in normal individuals. Symptoms appears when 60-80% of these neurons are lost. Genetic factors also play an important role.

Characteristic features (Fig. 101.3)

1. *Rigidity*
   (i) It affects mainly *large proximal group of muscles* of the limbs, involving both protagonists and antagonists (page 971).
   (ii) The commonly affected muscles are the biceps, knee flexors and sternomastoids.
   (iii) *Posture* is that of *flexion attitude*. The back is flexed, the arms adducted and flexed and the knees are bent.

In *early stage*, the disease is characterized by *cog wheel rigidity*. In *advanced cases*, as a result of marked rigidity, (plastic quality) *statue* like state is produced and both voluntary or involuntary movements become progressively more difficult.

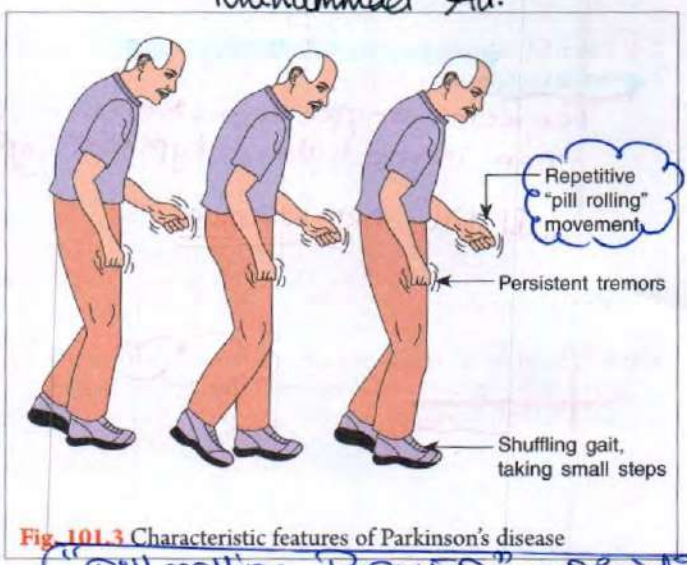


Fig. 101.3 Characteristic features of Parkinson's disease

Note

For differences between spasticity and rigidity, refer to Table 101.1.

Causes of rigidity

It is due to increased discharge of γ-efferents supplying the muscle spindle. *Proof:* Local injection of 1% procaine solution into the appropriate muscles will decrease the rigidity by abolishing γ-discharge (page 953).

Mechanism

The activity of the neostriatum is influenced by:

(i) the *excitatory* effect of the cholinergic fibers (page 992), and
(ii) the *inhibitory* influence of the dopaminergic fibers (page 992).

Normally there exists a balanced effect of these two opposite innervation on the neostriatum activity. The lack of dopaminergic activity due to degeneration of neurons in the substantia nigra shifts the balance towards the excitatory cholinergic fibers. This results in ***hyperkinetic features*** of Parkinson's disease. (Also refer to page 996)

Table 101.1: Differences between spasticity and rigidity

Spasticity	Rigidity
1. It is seen following the lesion of the pyramidal tract (corticospinal tract). The commonest site of lesion being the *internal capsule*.	1. It is seen following the lesion of the basal ganglia, therefore, called the ***extrapyramidal rigidity***.
2. It involves only one group of the muscle either agonist or antagonist. Usually antigravity muscles (page 952) are involved.	2. It involves both the agonist as well as antagonist muscles, therefore, hypertonia is more uniform and often is so distributed as to produce a *general attitude of flexion* of the limbs and trunk.
3. It describes a state of increased tone which is of *clasp-knife* type (page 880).	3. Hypertonia described here is of two types: (i) ***Lead-Pipe Rigidity*** – passive movement of an extremity (about a joint throughout the full range of motion) meets with *a plastic dead feeling resistance* as if bending a lead pipe. (ii) ***Cog-Wheel Rigidity*** – The resistance to passive movement about a joint of an extremity shows brief, regular interruptions. This is described as like a lever rubbing on the teeth of a cog-wheel *i.e.* a series of catches during passive movement of the extremity.
4. It is a 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 such phenomenon is seen here.

Proof:

1. Reserpine (by depleting dopamine stores in the appropriate nerve endings) and phenothiazines (which block D_2 dopamine receptors in the neostriatum) increase the signs and symptoms of the disease.
2. Physostigmine which increases the action of A-ch increases tremor and rigidity.

Important Notes

1. Administration of levo-dopa (L-dopa), a precursor of dopamine, decreases the rigidity and tremors. Dopamine cannot cross the blood brain barrier but L-dopa can.
2. Atropine, an anticholinergic agent can control the tremors of the disease.
3. Parkinson's disease usually occurs in late middle age and is more commonly seen in males; as there is steady loss of dopamine receptors in the basal ganglia with age, the loss being greater in men than in women.

2. *Tremor*

(i) It is present in 85% of patients. It consists of regular, rhythmic, alternate contraction of antagonist and agonist muscles @ 6-8 times/sec. Its frequent presence can be seen as *pill-rolling movements i.e.* rhythmic contraction of thumb over first two fingers.

(ii) *Common sites:* fingers, hands, lips or tongue, and often it causes movements of pronation and supination.

(iii) It is present at rest but disappears during activity, therefore, popularly called as *resting (static) tremor.*

Note

Cerebellar disease is characterized by intention tremor, page 971.

Mechanism. During voluntary movements, impulses from the motor cortex pass down the descending pathways and stimulate both α and γ motor neurons. The γ-efferents stimulate the *stretch reflex* to stop the involuntary movements. This is called the ***damping effect***.

(iv) It increases in emotional states, excitement or anxiety due to secretion of epinephrine from the adrenal medulla, which in turn excites the RAS. However, the tremor disappears during sleep due to decreased activity of the RAS.

Cause of tremor. It may be due to the associated degenerative lesions in the reticular formation and its ascending connections.

3. ***Akinesia and Hypokinesia (or bradykinesia)***

Note

Akinesia is difficulty in initiating movement and decreased spontaneous movement. **Bradykinesia** is slowness of movement.

In early stage, the weakness and poverty of movements leads to:

(i) *Difficulty in initiating voluntary movement* (Akinesia). This produces defect in fine movements of the fingers.

(ii) Defects in the fine variations in speech. *It causes slow and monotonous speech.*

(iii) Defects in movement of expression and decrease in eye blinking. The *face* becomes *mask-like* and emotional movements of the facial muscles rarely occur.

(iv) Loss of normal subconscious ***associated movements***. Therefore, no swinging of arms occurs during walking.

(v) *Gait: Festinant type (shuffling gait)*. The patient is bent forward, and walks quickly with short steps as if trying to "catch up" with the body's centre of gravity or preventing himself from falling down. If he is suddenly pulled backwards, he begins to walk backwards and is unable to stop himself *(retropulsion)*.

(vi) *Tendon jerks* become progressively more difficult to elicit as the rigidity increases.

Note

The exact mechanism responsible for poverty of movement is uncertain. Neuro-pharmacologic evidence suggests that akinesia itself results from dopamine deficiency. In addition, presence of rigidity is a certain contributory factor.

4. *Non-motor features:* Loss of smell (anosmia), depression, sleep disorders (daytime frequent napping) and autonomic dysfunctions due to involvement of brain stem, olfactory and cortical structures.

Important Note

The presence of at least two of the three cardinal signs (rigidity, resting tumors and bradykinesia) confirms the diagnosis of Parkinson disease.

***Pathogenesis of the movement disorders in Parkinson disease* (Fig. 101.4)**

A. *In normal individuals*, basal ganglia output is inhibitory via GABA-ergic fibers. How?

1. The dopaminergic neurons that project from the substantia nigre to the neostriatum (putamen

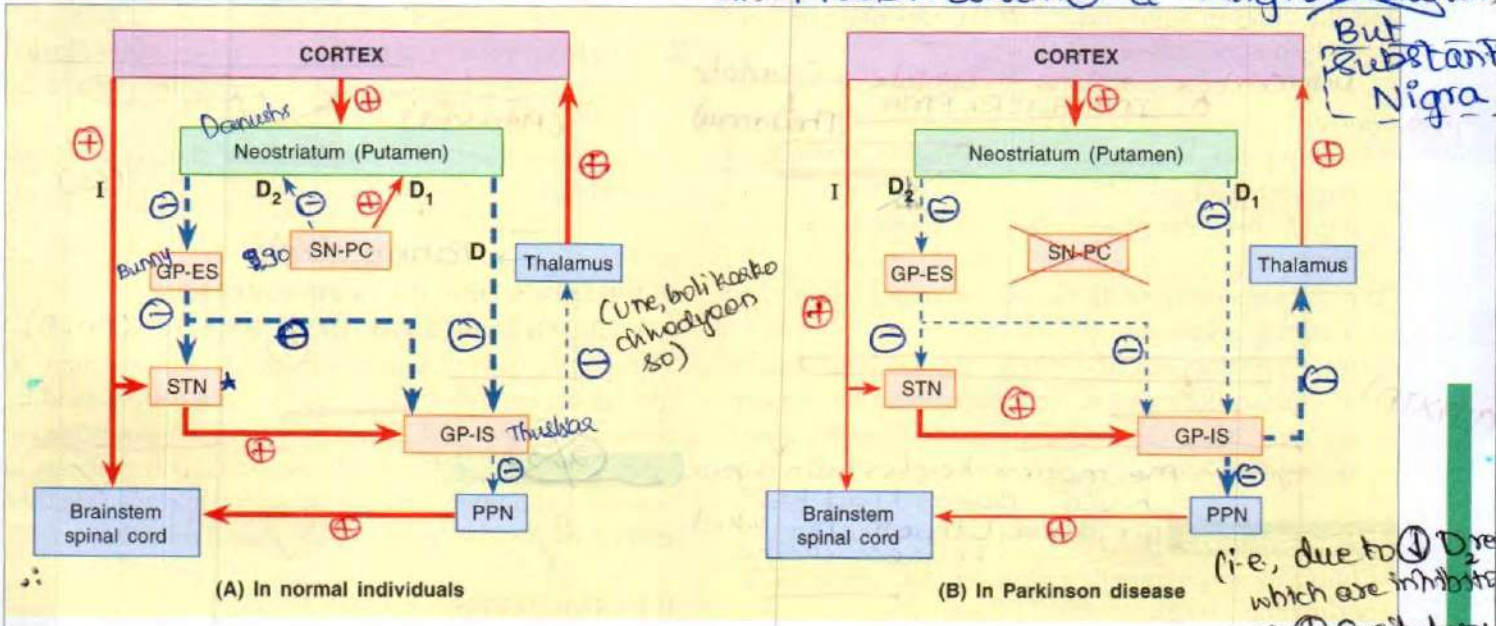


Fig. 101.4 Schematic diagram of the basal ganglia-thalamocortical circuit civenit under normal conditions (A) and in Parkinson's disease (B).

(i) **Red solid arrows:** excitatory output; (ii) **Blue dashed arrows:** inhibitory GABA-ergic output (the strength of each output is indicated by the width of the arrows); (iii) **GP-ES:** Globus pallidus-external segment; (iv) **GP-IS:** Globus pallidus-internal segment; (v) **SN-PC:** Substantia nigra-pars compacta; (vi) **STN:** Subthalamic nucleus; (vii) **Thal:** Thalamus; (viii) **I:** Indirect pathways; (ix) **D:** Direct pathways; (x) **PPN:** Pendunculopontine nucleus; (xi) **D_1 and D_2:** Dopamine receptors; (x) Site of lesion in Parkinson's disease.

mainly) normally have two effects:

(a) they *stimulate* the D_1 *dopamine receptors*, which inhibit globus pallidus internal segment (GpIS) via *direct* GABA-ergic receptors; and

(b) they *inhibit* the D_2 *dopamine receptors*, which also inhibit Gp-IS. via *indirect* GABA-ergic receptors.

2. In addition, the inhibition of subthalamic nucleus via globus pallidus-external segment (GP-ES), reduces the excitatory discharge from subthalamic nucleus to the GP-IS.

Thus the balance between inhibition and excitation maintains the normal motor function.

B. **In Parkinson Disease**, the dopaminergic input to neostriatum (putamen mainly) is lost. This results in:

1. *Decreased inhibition* and increased excitation from the subthalamic nucleus to the Gp-IS.
2. The overall increase in inhibitory output to the thalamus and brainstem produces movement disorders.

B. CHOREA AND ATHETOSIS

These two disorders are characterized by spontaneous involuntary movements due to interruption of the inhibitory pathway from area 4s via the caudate nucleus to the thalamus. This blocks the thalamocortical circuit and thus prevents the cortical motor area of an afferent control from the subcortical ganglia.

Chorea

It is mainly due to involvement of *caudate nucleus and is characterized by:*

(1) Rapid, irregular involuntary movements of short duration.

(2) It is associated with decreased muscle tone and muscular weakness.

(3) It is superimposed on voluntary movements leading to their incoordination. Therefore, these movements are not carried out smoothly and tend to be abrupt and sudden.

Important Note

Chorea is seen frequently in children as a complication of rheumatic fever.

Athetosis

It is primarily due to *lesion of the lenticular nucleus* and is characterized by continuous, slow twisting movement (one phase of movement getting merged with the next).

Important Note

The pattern of the involuntary movements of chorea and athetosis suggests that they are caused by impulse discharge which arises in the cerebral cortex. The movements only occur when the descending paths from the motor cortex are intact.

C. HUNTINGTON'S DISEASE

1. It is an *autosomal dominant* inherited disorder. The abnormal gene responsible for the disease is located on the short arm of chromosome 4. It usually occurs between 30-50 years of age.
2. It is *due to* damage to GABA-ergic and cholinergic neurons that project to the putamen **(Fig. 101.2)**. Damage to this inhibitory pathway releases inhibition resulting in *hyperkinetic features*, which include:
   (i) hyperkinetic choreiform movements, (see above);
   (ii) slurred speech, and
   (iii) progressive loss of memory (dementia).
3. It is a gradually progressive disease with no effective treatment which eventually leads to death (within 10-15 years after the onset of symptoms).

D. HEMIBALLISM

1. It is due to damage of the *subthalamic nucleus;* common cause, haemorrhage within the nucleus.
2. It is *characterized by* spontaneous attacks of incoordinated movements affecting whole of the opposite side of the body.
3. The movements are mediated by the corticospinal tracts.

E. WILSON'S DISEASE or PROGRESSIVE HEPATOLENTICULAR DEGENERATION (PHLD)

The copper content of the substantia nigra is high. In this condition, the *ceruloplasmin* (plasma copper binding protein) is low and there is severe degeneration of lentiform nucleus (also see to page 53) with cirrhosis of liver. The condition is characterized by muscular rigidity, tremor, cirrhosis of liver and emotional disturbances.

F. KERNICTERUS

This is a hemolytic disease of newborn which results from the noxious action of Rh-antibodies. Thus *indirect* bilirubin increases, which crosses the blood brain barrier, damages the globus pallidus and finally leads to death. If child survives, it may show rigidity, chorea, athetosis and mental deficiency (also see to page 109).

Study Questions

1. Give the functional anatomy of the basal ganglia.
2. Describe the feedback circuit between cerebral cortex and basal ganglia. Give its physiological significance.
3. How does the influence of basal ganglia on motor functions differ from that of the cerebellum?
4. Write short notes on:
   (i) functions of basal ganglia
   (ii) spasticity versus rigidity
   (iii) festinant gait, chorea, athetosis and hemiballisms
   (v) Wilson's disease
   (vi) damping effect
   (vii) Huntington's disease.
   (viii) Kernicterus
   (ix) Parkinson's disease
5. Explain and give physiological basis: "Diseases of the basal ganglia are characterized by both hyperkinetic as well as hypokinetic features."
6. Give the physiological basis of basal ganglia dysfunctions producing:
   (i) rigidity
   (ii) cognititive abnormalities
   (iii) resting tremors
   (iv) non-motor features in basal ganglia dysfunctions
7. Give an account of the role of the subthalamic nucleus in control of movements.
8. Name the transmitters related with Parkinson's disease. How do they act?
9. Draw labelled diagram to depict: Afferent, efferent and internuclear connections of basal ganglia.
10. Describe briefly pathogenesis of movement disorders in Parkinson's disease.

MCQs

1. The major afferent input to basal ganglia is from:
   (a) Motor cortex (b) Association cortex
   (c) Cerebellum (d) Thalamus
2. The internuclear connections of the basal ganglia include all *except*:
   (a) Dopaminergic nigrostriatal tract (b) GABA-ergic inhibitory projections
   (c) Glutaminergic excitatory projections (d) Thalamostriate projections
3. *Not* a GABA-ergic internuclear inhibitory projection of the basal ganglia:
   (a) The neostriatum projects to substantia nigra (b) The neostriatum projects to globus pallidus
   (c) The globus pallidus projects to subthalamic nucleus (d) The subthalamic nucleus projects to globus pallidus
4. Most important neurotransmitter at substantia nigra is:
   (a) Gamma amino butyric acid (b) Histamine
   (c) Serotinin (d) Bradykinin
5. *Not a correct* statement with reference to basal ganglia and cerebellum:
   (a) Both are reciprocally connected to the motor cortex
   (b) Both exert an influence on motor performance
   (c) Cerebellum receive large synaptic inputs from the spinal cord and the basal ganglia does not
   (d) Basal ganglia has direct influence on extrapyramidal pathways whereas the cerebellum has only indirect influence
6. *False* about neurons in the basal ganglia:
   (a) Discharge before movements begin (b) Are stimulated by acetylcholine
   (c) Are inhibited by GABA and dopamine (d) Are tonically active
7. *Not a true* match of basal ganglia component to its function:
   (a) Globus pallidus: provides appropriate muscle tone
   (b) Substantia nigra: centre for coordination of impulses essential for skilled movements
   (c) Caudate nucleus: controls automatic movements
   (d) Neostriatum: regulates subconscious gross movements

8. **Parkinson's disease is characterized by:**
   (a) Paralysis of one side of body
   (b) Tremors which is worse when a skilled movement is being carried out than at rest
   (c) Increase in muscle tone which is maintained throughout the range of passive flexion and extension of a joint
   (d) Increase in spontaneous facial movements during conversation

9. **Spasticity differs from rigidity in all *except*:**
   (a) It is seen following the lesion of pyramidal tracts
   (b) Usually involves antigravity muscle
   (c) Resting muscle tone is high
   (d) Stretch sensitive

10. **Tremors of Parkinson's disease disappears during activity because of:**
   (a) Damping effect
   (b) Increased muscle blood flow
   (c) Can be inhibited voluntarily
   (d) Diverted attention

11. **A child demonstrates irregular, spasmodic, involuntary movements of limbs and facial muscles. He is most likely to have a lesion in:**
   (a) Caudate nucleus
   (b) Precentral gyrus of cortex
   (c) Postcentral gyrus of cortex
   (d) Rubrospinal tract

12. **Huntington's disease is due to loss of:**
   (a) Acetylcholine
   (b) Dopamine
   (c) 5-HT
   (d) All of the above

13. ***Not a true* statement for caudate nucleus and putamen:**
   (a) Together called lenticular nucleus
   (b) Phylogenetally more recent part
   (c) Receive main afferents from all 4 lobes of cerebral cortex
   (d) Give out inhibitory projections to the substantia nigra

14. **Which one of the following is present in high concentration in the putamen and caudate nucleus?**
   (a) Acetylcholine
   (c) Dopamine
   (c) Histamine
   (d) Gamma amino butyric acid

15. **Negrostriatal pathway is:**
   (a) Cholinergic
   (b) Dopaminergic
   (c) Nor-adrenergic
   (d) Serotonergic

16. ***Not* a feature of feedback circuit between the cerebral cortex and basal ganglia:**
   (a) It is integrated in the thalamus
   (b) It integrates with cortico-ponto-dentato-thalamo-cortical circuit
   (c) Inhibits excessive activity of motor cortex
   (d) Involved in initiation of movements

17. **The basal ganglia inhibits the stretch reflex by all *except*:**
   (a) Stimulation of caudate nucleus
   (b) Stimulation of inhibitory motor cortex
   (c) Stimulation of inhibitory reticular formation
   (d) Inhibition of facilitatory reticular formation

18. **Which group of nucleus of the basal ganglia plays greatest role in regulating gross movements of the body?**
   (a) Substantia nigra
   (b) Globus pallidus
   (c) Subthalamic nucleus
   (d) Corpus striatum

19. **The caudate nucleus is essential for:**
   (a) Fine muscular movements
   (b) Maintain equilibrium
   (c) Cognitive processes
   (d) Muscle tone

20. **Dysarthric aphasia (i.e. difficulty in articulating words) is due to lesion of:**
   (a) Neostriatum
   (b) Caudate nucleus
   (c) Globus pallidus
   (d) Putamen

21. **Destruction of which of the following structures is the usual cause of Parkinson's disease?**
   (a) Subthalamus nucleus
   (b) Putamen
   (c) Substantia nigra
   (d) Caudate nucleus

22. **Rigidity in Parkinson's disease is characterized by all *except*:**
   (a) Affects mainly large proximal group of limb muscles
   (b) Involves both protagonists and antagonists
   (c) Biceps, knee flexers and sterno-mastoids are the muscles most commonly affected
   (d) Posture is that of extension attitude

23. **Hyperkinetic features in Parkinson's disease can be controlled by all of the following *except*:**
    (a) Administration of levo-dopa
    (b) Atropine
    (c) Reserpine
    (d) Anticholinergic agents

24. ***Not* a characteristic features of tremors in Parkinson's disease is:**
    (a) It consists of regular, rhythmic, alternate contraction of antagonist and agonist muscles
    (b) Common site being the face muscles
    (c) Present at rest but disappears during activity
    (d) Occurs @ 6-8 times/sec.

25. **In early stage of Parkinson's disease, hypokinesia leads to all *except*:**
    (a) Defect in fine movements of the finger
    (b) Slow and monotonous speech
    (c) Mask-like face
    (d) Posture is that of flexion attitude

26. **Basal ganglia lesion causes all *except*:**
    (a) Spasticity (b) Resting tremors (c) Akinesia (d) Dysmetria

27. **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

28. **Chorea is characterized by all *except*:**
    (a) Rapid, irregular involuntary movements of short duration
    (b) Muscular weakness
    (c) Hypertonia
    (d) Incoordination of voluntary movements

Answers

1. (a)	2. (d)	3. (d)	4. (a)	5. (d)	6. (d)	7. (c)	8. (c)	9. (c)	10. (a)	11. (a)	12. (a)	13. (a)	14. (b)	15. (b)
16. (d)	17. (d)	18. (d)	19. (c)	20. (b)	21. (c)	22. (d)	23. (c)	24. (b)	25. (d)	26. (d)	27. (d)	28. (c)		

Chapter 102

The Hypothalamus

I. Physiological anatomy

II. Connections of the hypothalamus

III. Functions of the hypothalamus: Control of food and water intake

PHYSIOLOGICAL ANATOMY

1. The hypothalamus is a diencephalic structure (page 846) which lies below the thalamus. It is separated from the thalamus by the hypothalamic sulcus. It forms the antero-inferior wall and floor of the third ventricle. It receives a more liberal blood supply than does any other structure in the brain.
2. ***Boundaries***
   - *Anteriorly* – the optic chiasma,
   - *Posteriorly* – the mammillary bodies, a pair of white masses, and
   - *Laterally* – the internal capsule.
3. ***Hypothalamic nuclei***

   The hypothalamus contains many nuclear masses which may be grouped into the following areas: (Fig. 102.1)

   (i) ***Preoptic area*** – preoptic nucleus.

   (ii) ***Anterior (supraoptic) area*** includes:
   - (a) supraoptic nucleus,
   - (b) suprachiasmatic nucleus,
   - (c) paraventricular nucleus and
   - (d) anterior nucleus.

   (iii) ***Middle (tuberal) area*** includes:
   - (a) Ventromedial nucleus,
   - (b) Dorsomedial nucleus and
   - (c) Arcuate nucleus.

   (iv) ***Posterior (mammillary) area*** includes:
   - (a) Mammillary body; and
   - (b) Posterior nucleus

   (v) ***Lateral area*** – lateral nucleus

CONNECTIONS OF THE HYPOTHALAMUS

A. AFFERENT CONNECTIONS

The main afferent connections of the hypothalamus are with the *limbic system* and the *midbrain tegmentum* (*i.e.* part between the cerebral peduncle anteriorly and the two colliculi posteriorly). The major afferent connections are summarized in **Table 102.1**.

B. EFFERENT CONNECTIONS

The main efferents from the hypothalamus are projected to the limbic system, *midbrain*, *thalamus*, *posterior pituitary* and *the spinal cord*. These are summarized in **Table 102.2**.

FUNCTIONS OF THE HYPOTHALAMUS

1. Regulation of body temperature
2. Regulation of activity of the anterior pituitary gland
3. Formation of the posterior pituitary hormones and the regulation of their secretion
4. Control of circadian rhythm
5. Control of *sleep-waking* cycle
6. Control of integration of the ANS
7. Control of hunger and feeding
8. Control of water intake and the sensation of thirst
9. Control of emotional behaviour
10. Integrated control of the CVS

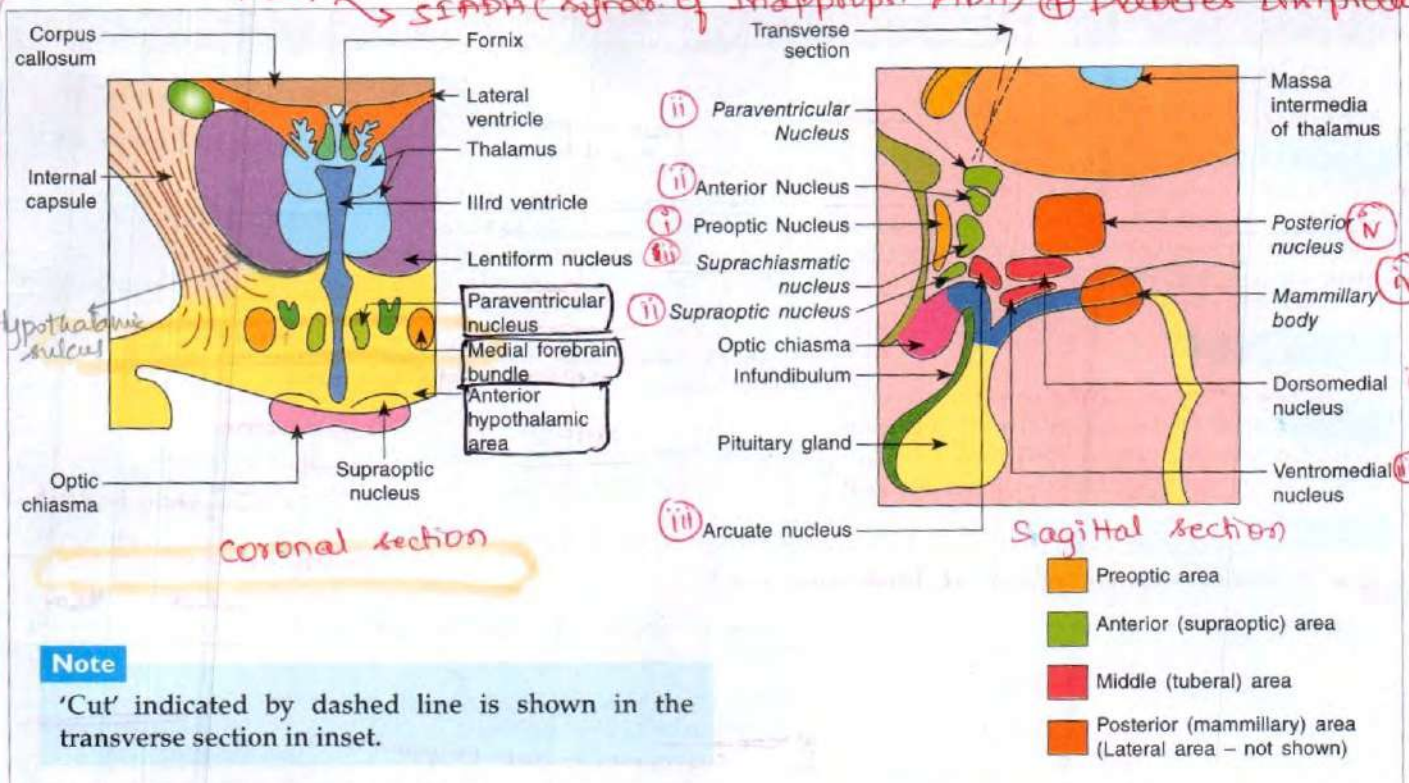
(1) Regulation of body temperature

The hypothalamus plays an important role in the integrated control of heat production and heat loss from the body (details page 585).

(2) Regulation of the anterior pituitary gland activity

The hypothalamus regulates the activity of the anterior pituitary through the release of *releasing factors* and *release-inhibiting factors* into the hypothalamus-hypophysial portal system (page 656).

The role of hypothalamus in the regulation of secretion of anterior pituitary hormones is discussed in detail in the endocrine system viz., control of secretion of *GH*



Note

'Cut' indicated by dashed line is shown in the transverse section in inset.

Fig. 102.1 Relationship among the hypothalamic nuclei

(page 662), prolactin (page 671), *TSH* (page 685), *ACTH* (page 717), *Gonadotrophins-FSH* and *LH* (page 779).

(3) Regulation of the posterior pituitary hormone secretion

The role of hypothalamus in the formation and release of posterior pituitary hormones has been discussed earlier; *ADH* (page 666) and *oxytocin* (page 669).

(4) Control of circadian rhythm

There is a *circadian rhythm* or *diurnal variation* for many body functions, which is about 24 hours. For example, the rhythm in the secretion of *ACTH* (page 718), *GH* (page 663), *melatonin* (page 676), *sleep-waking cycle* (page 987), the *body temperature rhythm* (page 582) and *gonadotrophin secretion* (page 779). Other cycles have much longer periods, the *menstrual cycle* (about 28 days) being the most well known.

An important point concerning most bodily rhythm is that they are *internally* driven. Environmental factors, such as light-dark cycle, temperature, meal-timing only provide a *hint* for the timing important for occurrence *i.e.* setting of the actual hours, of the rhythm. For example, altering the duration of the light-dark cycle, the *sleep-wake cycles* could be altered to between 23 and 27 hours, but shorter or longer durations could not be obtained. This shows that *free-running rhythm* can exist in the absence of environmental factors but these factors are required to get a circadian rhythm cycle at 24 hours.

Neural basis of circadian rhythm

The suprachiasmatic nuclei (SCN) are the main site for many circadian rhythms in the body. These nuclei receive important inputs from:

(i) the eyes via the retinohypothalamic fibers (page 1091); and

(ii) the lateral geniculate nuclei.

Efferents from the SCN initiate neural and hormonal signals that form circadian rhythms. Their normal function is to *synchronize* the various body rhythms to the 24 hour light-dark cycle.

Physiological significance

1. The circadian rhythms enable *homeostatic mechanisms* to be utilized immediately and automatically. For example, there is a rhythm in the urinary excretion of ACTH.
2. It has effects on the body's resistance to various drugs. For example, differences in the sensitivity of dose of a potentially lethal drug depends markedly on the time the drug is given.

(5) Control of sleep-waking cycle

The hypothalamus plays an important role in the

Table 102.1: Major 'afferent' connections of the hypothalamus

Tracts	Description
Afferents from the Limbic System	
1. *Medial forebrain bundle* (MFB)	It connects (i) *piriform cortex* (*i.e.* uncus of the hippocampus gyrus in the temporal lobe), and (ii) *amygdala* with the lateral hypothalamus (page 1025). [This includes 'direct' amygdalo hypothalamic fibers which are referred as a separate '*ventral pathways*'.]
2. *Stria terminalis*	Connects amygdaloid nucleus with the ventromedial nucleus of the hypothalamus.
3. *Fornix* (largest fiber system of the hypothalamus) (i) the post commissural fibers (ii) the precommissural fibers	Connects the hippocampus with the mammillary bodies. Connects the hippocampus with the lateral hypothalamus.
4. *Medial corticohypothalamic tract* (MCHT)	Connects the hippocampus with the 'arcuate nucleus' of the hypothalamus.
Afferents from the Midbrain Tegmentum	
1. *Adrenergic fibers*	Axons of epinephrine-secreting neurons from medulla to 'ventral' hypothalamus.
2. *Serotonergic fibers*	Axons of serotonin-secreting neurons projecting from dorsal and other 'raphe nuclei' to hypothalamus.
3. *Nor-adrenergic fibers* (i) Ventral (anterior) bundle	Axons of nor-epinephrine (NE)-secreting neurons projecting from nucleus of tractus solitarius and ventrolateral medulla to 'paraventricular' nuclei. (NTS + VLM) → (PVN)
(ii) Dorsal (posterior) bundle	Axons of NE-secreting neurons projecting from locus ceruleus to dorsal hypothalamus.
Afferents from Retina; thalamus, basal ganglia	
1. Retinohypothalamic tract (RH)	Connects optic nerve fibers from optic chiasma with 'suprachiasmatic' nucleus.
2. Thalamohypothalamic tract (TH)	Connects medial and midline thalamic nuclei to hypothalamus.
3. Pallidohypothalamic tract (PH)	Connects lenticular nucleus (putamen and globus pallidus) to hypothalamus.

Note

The areas of neocortex project to the hypothalamus indirectly, through their connections with the hippocampus.

control of sleep-waking cycle (page 987). The basic rhythm is controlled by the ***biological clock*** function of the hypothalamic suprachiasmatic nucleus (SCN).

Efferents from the SCN initiate neural and hormonal signals that form circadian rhythms.

Genes proteins in the SCN neurons are activated diurnally and discharge rhythmically at two different peaks of circardian activity. Exposure to bright light can either advance, delay or have no effect on the sleep-waking cycle depending on the time of day when it is experienced. During the usual *daytime* it has no effect, but just *after dark* it delays, and just *before dawn* it accelerates the onset of the sleep period.

Evidence: Individuals isolated from the external environment *i.e.* all environmental time *hints* were eliminated, and the individuals were allowed to control the light themselves. Immediately, their sleep-wake patterns began to change. On the average, bedtime got about 30 min later *each day* and so did wake-up time. Thus a sleep-wake cycle persisted in the complete absence of environmental hints, but the cycle was about 25 hours rather than 24.

(6) Control of the ANS

The hypothalamus is called the ***head ganglion of the ANS*** by *Sherrington*. Stimulation of the hypothalamus produces autonomic responses. For example:

(i) Stimulation of the *anterior hypothalamus* causes

Table 102.2: Major 'efferent' connections of the hypothalamus

Tracts	Description
1. Ventral pathways (page 991)	Connects lateral hypothalamus with amygdaloid nucleus.
2. Stria terminalis	Connects ventromedial nucleus with amygdaloid nucleus. (Both the above fibers, after relaying in the amygdaloid nuclei are projected to the piriform cortex.)
3. Medial forebrain bundle	Connects lateral hypothalamus with septal nuclei where they relay and then projects to the hippocampus.
4. Mammillo-thalamic tract (of Vicq d'Azyr)	Arises from the medial mammillary nucleus, passes to the anterior thalamic nucleus and finally ends in the cingulate gyrus.
5. Mammillotegmental tract (i) Contributes to descending extrapyramidal facilitatory pathway, and (ii) These fibers constitute a route over which the hypothalamus can exert its effect upon the ANS.	Connects hypothalamus with 'reticular formation' of midbrain. The tract arises mainly from the lateral hypothalamic nuclei lying in the course of medial forebrain bundle, passes to the reticular formation of the tegmentum and finally projects to the spinal motor neurons.
6. Hypothalamo-hypophysial tract (page 660)	Arises from the supraoptic and paraventricular nuclei and runs to the posterior pituitary.
7. Neurons containing hypophysiotropic hormones	Run from various hypothalamic nuclei to the median eminence.

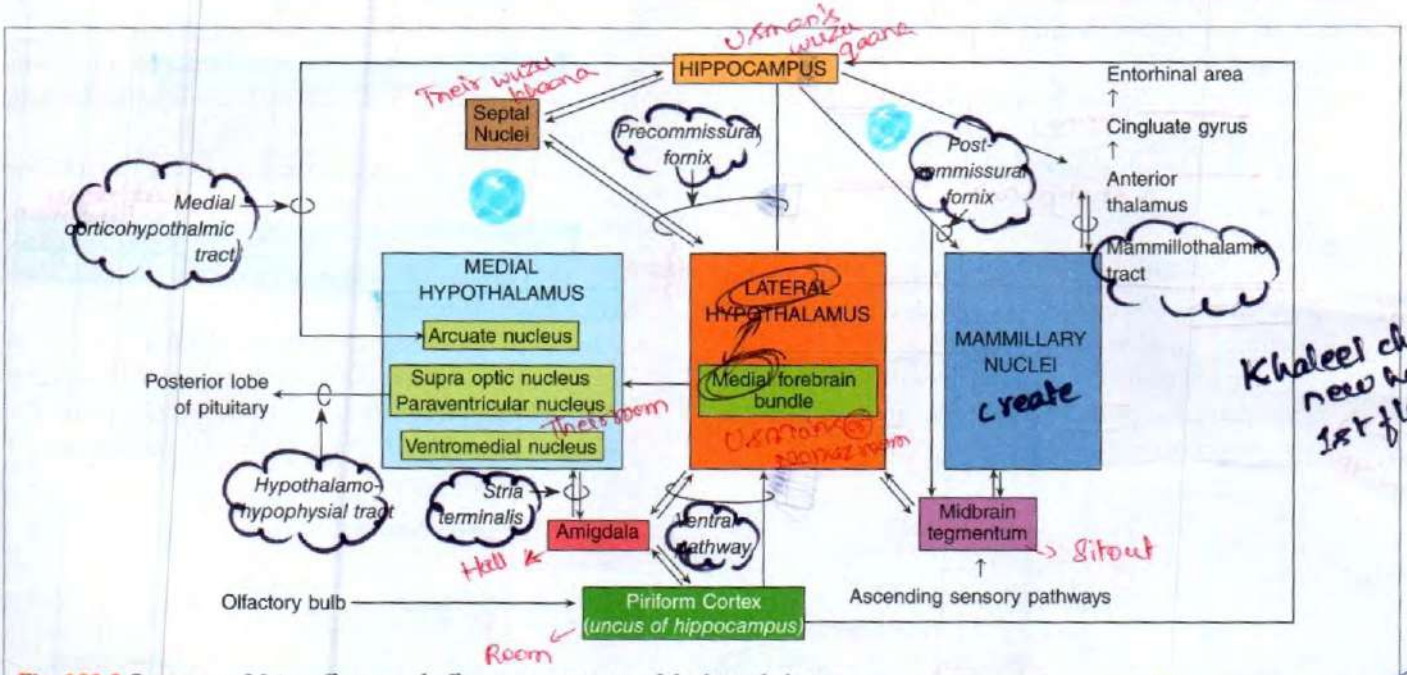


Fig. 102.2 Summary: Major afferent and efferent connections of the hypothalamus

parasympathetic response like contraction of the urinary bladder.

(ii) Stimulation of *lateral areas of the hypothalamus* produces sympathetic responses such as rise in BP, pupillary dilation, piloerection etc. and increased adrenal medullary secretion in response to stress (*flight* or *fight reactions* - page 928)

(iii) Stimulation of *mid-dorsal area* of the hypothalamus causes cholinergic sympathetic vasodilatation.

(iv) Stimulation of the *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

The body weight of an individual is usually maintained relatively constant over a long period of time. It is determined by the balance between *caloric intake* and *energy expenditure*. The control of food intake is the main important mechanism for keeping the body weight constant. There appears to be many *inputs* that are involved in the control of food intake and are

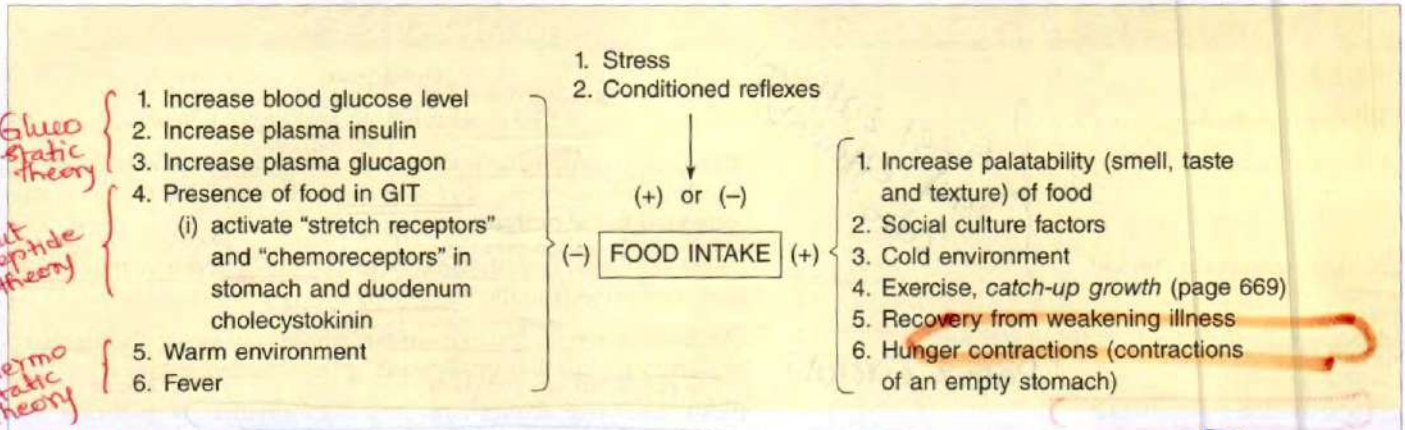


Fig. 102.3 Inputs controlling food intake {(–): hunger inhibition; (+): hunger stimulation}

summarized in **Fig. 102.3**. *The hypothalamus integrates all these afferent* inputs and causes the individual either to feel hungry or not. Thus food intake is regulated that *generally maintains weight at a given set point*.

Role of the hypothalamus

There are *two* hypothalamic centers concerned with hunger and feeding:

1. The *ventromedial nuclei* acts as a *Satiety Center*; and
2. The *lateral hypothalamic* area as a *Feeding Center*.

Proof

(i) Bilateral lesions in the ventromedial nuclei cause *hyperphagia* (excessive eating) and the animal becomes grossly obese *(hypothalamic obesity)*. Subsequent destruction of the lateral hypothalamic area produces *anorexia* and the animal dies of starvation even though food is plentiful.

(ii) Stimulation of the lateral hypothalamic area, caudolateral to the mammillary bodies, caused animals to eat voraciously (greedy for eating) during the period of stimulation.

Mechanism (Fig. 102.4)

1. The *satiety center* is the ***primary center*** that controls the food intake. It functions by inhibiting the feeding center.
   (*Proof:* Destruction of both satiety as well as feeding centres in rats produces anorexia.)
2. The *feeding center* is ***chronically active*** and its activity is inhibited by the activity in the satiety center after the ingestion of food.
3. The cells of the ventromedial nuclei act as a satiety center due to their functioning as ***glucoreceptors***, also called ***glucostats*** *i.e.* receptors which sense the glucose in the blood. The activity of the satiety center

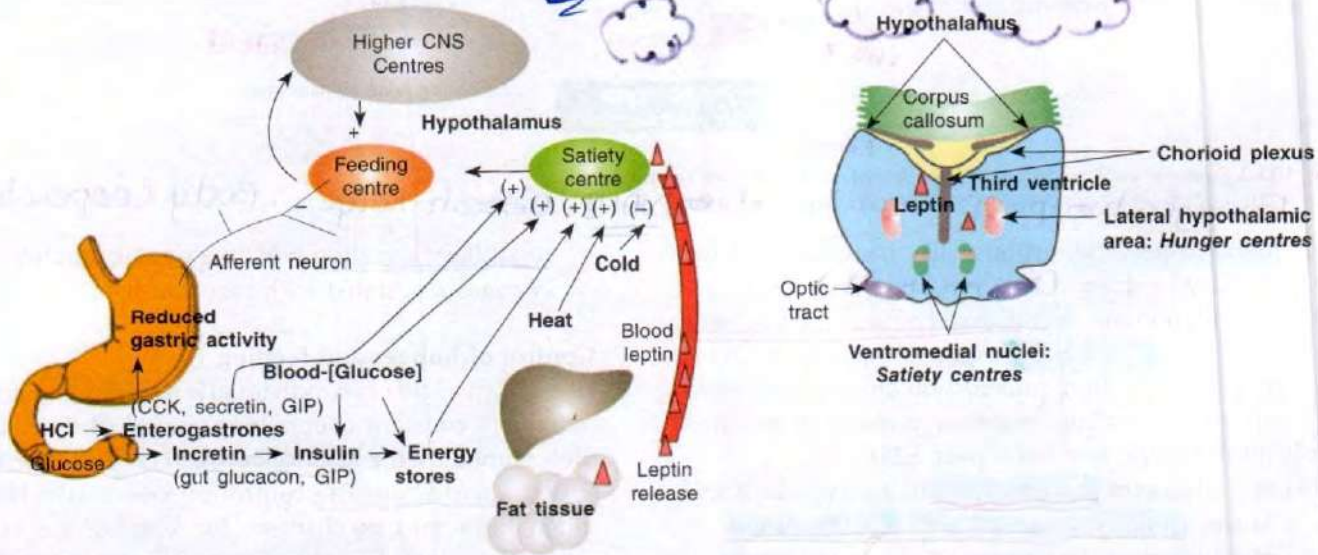


Fig. 102.4 Control of hunger and feeding (Negative feedback and feedforward factors)

GLUCOSTATIC theory

is thus governed by the level of glucose utilization of cells within the center (*Glucostatic Theory*). Therefore,

(i) If the *glucoreceptors are inadequately supplied with glucose*, their activity is decreased. As a result the activity of the feeding center is unchecked *i.e.* they get activated and the individual is hungry.

(ii) If the *glucoreceptors* are *supplied with sufficient glucose*, their activity is increased; the satiety center then actively inhibits the feeding centre and the individual feels satisfied.

Important Note

This explains the polyphagia (excessive eating) in diabetes mellitus, in which the blood sugar level is high but the glucose utilization of the *glucoreceptors* is low because of insulin deficiency. The glucoreceptors in the ventromedial nucleus are different from the rest of the brain cells in that they require insulin for glucose utilization (page 747).

Neurotransmitters and feeding

1. Food intake is *increased by*:
   (i) stimulation of α_2-adrenergic receptors in the medial hypothalamus; and
   (ii) centrally acting opiate agonists.
2. Food intake is *decreased by*:
   (i) Stimulation of β-adrenergic and dopaminergic receptors in the lateral hypothalamus; and
   (ii) Stimulation of serotoninergic pathways.

Important Note

Amphetamine and related drugs decrease food intake by acting on the lateral hypothalamus.

Role of Hypothalamic peptides

Principal hypothalamic peptides concentration increases during feeding and decreases during satiety. Thus they seem to play an important role in the regulation of food intake.

1. Food intake is *increased* by:
   (i) ***Neuropeptide Y***, synthesized by neurons in the *arcuate nucleus* of the hypothalamus. It exerts its effect through three receptors, Y1, Y2 and Y5 (mainly); all are coupled to G-proteins.
   (ii) ***Orexin-A and Orexin-B***, synthesized by lateral hypothalamic neurons.
   (iii) ***Ghrelin***, secreted by the stomach (pages 273 and 662)
2. Food intake is *decreased* by:
   (i) ***α-MSH*** (page 676)
   (ii) ***CART*** (cocaine and amphetamine regulated transcript),
   (iii) ***CRH*** (page 717)
   (iv) ***Malonyl-CoA*** produced from acetyl-CoA during fatty acids synthesis (page 612)

LIPOSTATIC THEORY

Lipostatic Theory: There are evidences that neurons in the hypothalamic *feeding centre* also respond to changes in the level of fatty acids and amino acids. The size of body fat depots initiates either neural or hormonal signals that are relayed to the hypothalamus., thus controlling the food intake.

Leptin (means *thin*). It is a circulating protein hormone *produced mainly in the adipose cells*. It acts on the hypothalamus to decrease the release of neuropeptide Y and produces *decreased food intake* and increased energy expenditure.

Leptin Receptors are found in various body tissues as well as in brain microvessels (for rapid transport of leptin into the brain). There is a *linear relationship* between the concentration of leptin mRNA produced by the adipose tissue and percentage of body fat. Leptin thus operates to control the size of the body's fat depots (Fig. 102.5).

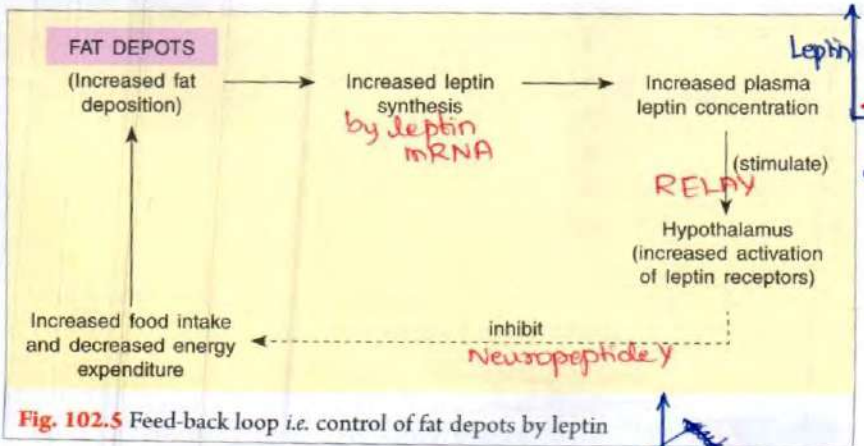


Fig. 102.5 Feed-back loop *i.e.* control of fat depots by leptin

Important Note

Decrease in plasma leptin produced *by fasting* is associated with inhibition of the onset of puberty, decreased thyroid function, and increased glucocorticoid secretion. These are adaptive responses to the shortage of calories signaled by the decrease in leptin.

Therefore, any defect in the *leptin receptor genes* result in ***obesity*** (page 745)

Gut peptide theory

Food in the GIT causes the release of polypeptides/hormones (CCK, glucagon, GRP, peptide YY_{3-26} and somatostatin) which act on the hypothalamus to inhibit food intake. Circulating CCK seems to play a major role due to its anorectic effect. It acts via peripheral/visceral (GIT) *i.e.* ***CCK-A receptors*** as well as central/hypothalamic *i.e.* ***CCK-B receptors***.

Note

The *gut peptides* provide short-term, meal-to-meal control of food intake whereas the effects of *leptin* is relatively prolonged that generally maintains weight at a given set point.

Thermostatic theory

A fall in core temperature stimulates the food intake whereas a rise inhibits it.

(8) Control of water intake: *Thirst*

One of the most important mechanisms for securing an adequate level of fluid intake is the sensation of *thirst*. Thirst is a sensation aroused by dryness of the mouth and like hunger it has a complex *internal* sensation with a considerable emotional component. The feeling of thirst which drives one to obtain and ingest water is influenced by many inputs, summarized in Fig. 102.6.

Pathways controlling thirst

1. *True thirst* (increase water intake) is always associated either with a *decrease in ECFV* or an *increase in plasma osmolality*. Note that these are precisely the same two changes that stimulate ADH secretion by directly stimulating ***osmoreceptors*** (located in the anterior hypothalamus) and ***baroreceptors*** (venous and arterial) (pages 329, 558 and 673).
   These receptors form the afferent side of the reflex arc that increases ADH secretion (page 673).
2. The effect of decrease in ECFV on thirst is also mediated via the ***renin-angiotensin system*** (page 558). The angiotensin II stimulates thirst by a direct effect on the specialized receptors in the OVLT area of the circumventricular organs in the brain (page 373).
   Thus the renin-angiotensin system helps regulate not only sodium balance but water balance as well.
3. *Other pathways controlling thirst:*
   (i) Dryness of the mouth and throat causes profound thirst, which is relieved by merely moistening them.
   (ii) Dehydrated animals (dog, cat, camel) drink just enough water to make up their water deficit. They stop drinking before the water is absorbed (while their plasma is still hypertonic), so some kind of ***metering*** of the water intake by the GIT has occurred; but its nature remains uncertain.

Role of the hypothalamus

The hypothalamus is involved in the maintenance of

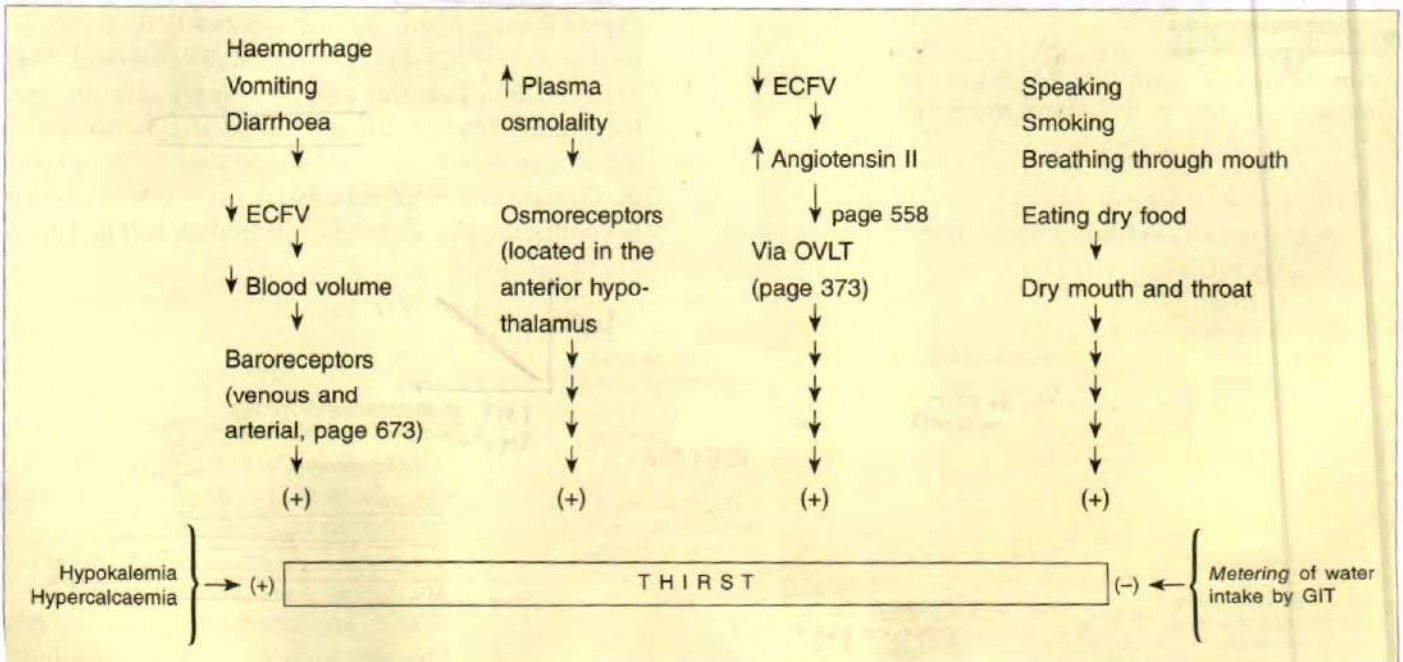


Fig. 102.6 Inputs reflexly controlling thirst {(+): Stimulation; (−): Inhibition}

fluid balance by participating in the control of water intake as well as in the control of water loss by the body.

1. *Role in control of water intake – thirst*

(i) The *osmoreceptors* which initiate drinking in response to increased plasma osmolality are located in the *lateral preoptic area*. These are separate from the osmoreceptors involved in ADH release.

Proof:

(a) Injection of hypertonic saline into this area in animals (rabbit, rat), induces drinking but neither isotonic saline and distilled water, nor hypertonic urea caused any drinking.

(b) The drinking that normally follows I.V hypertonic saline was abolished by destruction of the lateral preoptic area.

(ii) The neurons that induce thirst in response to decrease ECFV are more diffusely spread in the lateral hypothalamus.

However, the loss of response to thirst of either origin when lesions are placed in the lateral hypothalamus suggests that both neural systems converge in this region.

Important Note

Though the hypothalamus is primarily involved in the control of drinking, other areas such as septal nuclei, amygdala and hippocampus can influence water intake.

2. *Role in control of water loss*

The excretion of water is regulated by the kidneys via the ADH mechanism. The role of the hypothalamus in control of ADH secretion is discussed on page 673.

Neurotransmitters and thirst

1. A system of *cholinergic neurons* subserve drinking which converge on the lateral hypothalamus.

Proof: The injection of A-ch into lateral hypothalamus of rats causes drinking. Atropine blocks this response.

2. The *renin-angiotensin* system is concerned with drinking caused by β-adrenergic stimulation.

Proof: Subcutaneous injection of β-adrenergic agonist (isoprenaline) induces copious drinking in rats. This response is prevented by the β-adrenergic blockers (propanolol). This action of isoprenaline is abolished by nephrectomy.

(9) **Control of emotional behaviour**

Emotions accompany many of our conscious experiences. Emotional behaviour includes such complex behaviours as attack and such simple actions as laughing, sweating, crying or blushing. It is achieved by integrated activity of the ANS and somatic efferent system. They provide an outward sign that an inward emotion has occurred. The hypothalamus integrates the endocrine, autonomic and some of the motor activities that form appropriate emotional behaviour (page 1022).

(10) **Integrated control of the CVS**

The hypothalamus is the major relay station of the *corticohypothalamic descending pathways* which discharge by emotions. The hypothalamus integrates the information conveyed by these fibers thus controlling emotional effects on the CVS (pages 332).

Study Questions

1. Briefly describe the functions of the major afferent and efferent connections of the hypothalamus.
2. Enumerate the functions of hypothalamus.
3. Describe briefly the role of hypothalamus in:
   (i) hunger and feeding (ii) thirst and water intake (iii) sleep-waking cycle (iv) cyclic phenomenon
4. Define circadian rhythm giving suitable examples. Describe the neural basis and physiological significance.
5. Illustrate with the help of line diagram the different inputs controlling:
   (i) food intake (ii) water intake
6. Describe briefly pathways controlling thirst.
7. Give physiological basis of polyphagia in diabetes mellitus.
8. How changes in plasma osmolality and ECFV affect thirst?
9. What will be the effect of hypothalamic lesions on feeding?
10. Write short notes on:
    (i) hypothalamic obesity (ii) OVLT (iii) osmoreceptors (iv) glucostats (v) Leptin
11. Give the role of various neurotransmitters in control of thirst.
12. Give an account of various theories that control the food intake.
13. How does the hypothalamus act as a thermodetector and thermostat?

14. Give experimental evidence to show that the hypothalamus manufactures posterior pituitary hormones.
15. Mention the areas of the hypothalamus concerned with autonomic responses.
16. Name the hypophysiotropic hormones. Outline the effects that each has on pituitary functions.
17. Depict diagrammatically:
    (i) Control of hunger and feeding
    (ii) Control of fat depots by leptin

MCQs

1. Largest fiber system of hypothalamus that connects it with limbic system is:
   (a) Medial forebrain bundle (b) Stria terminalis
   (c) Fornix (d) Mammillo-thalamic tract
2. The hypothalamus regulates the activity of anterior pituitary by all of the following *except*:
   (a) By formation of anterior pituitary hormones (b) Through release of releasing factors
   (c) Through release of inhibitory factors (d) By control of circadian rhythm
3. *Not* a feature of circadian rhythm:
   (a) It has a fixed duration of 24 hours
   (b) It is internally driven
   (c) Environment factors provide only a hint for its occurrence
   (d) Enable homeostatic mechanisms to be utilized immediately and automatically
4. The satiety centre is located in which portion of hypothalamus?
   (a) Dorsomedial nucleus (b) Ventromedial nucleus (c) Preoptic area (d) Lateral nucleus
5. Bilateral lesions in lateral hypothalamic area produce:
   (a) Anorexia (b) Hyperphasia (c) Omniphagia (d) Diabetes insipidius
6. Drinking can be induced by injection of hypertonic saline into the hypothalamus in:
   (a) Posterior region (b) Supraoptic nucleus (c) Paraventricular nucleus (d) Preoptic nucleus
7. Alcohol produces diuresis by:
   (a) Inhibiting release of ADH from the hypothalamus (b) Increasing GFR
   (c) Decreasing water reabsorption from the loop of Henle (d) Decreasing medullary interstitium osmolarity
8. Angiotensin II stimulate thirst by a direct effect on receptors located in:
   (a) Posterior pituitary (b) Area postrema (c) Supraoptic crest (d) Subfornical organ
9. The major efferent connections of hypothalamus project to all of following *except*:
   (a) Limbic system (b) Mid-brain (c) Anterior pituitary (d) Thalamus
10. Hypothalamus regulates all *except*:
    (a) Food intake (b) Temperature
    (c) Anticipatory rise in heart rise (d) Hypophysis
11. Circadian rhythm is controlled by:
    (a) Suprachiasmatic nuclei (SCN) (b) Raphe nuclei
    (c) Thalamus (d) Reticular nucleus
12. Which is an important reflex centre for autonomic nervous activity?
    (a) Cerebellum (b) Basal ganglia (c) Sympathetic chain (d) Hypothalamus
13. Sympathetic nervous system in hypothalamus is located in:
    (a) Anterior areas (b) Lateral areas (c) Supraoptic areas (d) Posterior areas
14. Amphetamine decreases food intake by:
    (a) Inhibiting lateral hypothalamus (Feeding centre (b) Increasing glucose utilization in satietary centre
    (c) Increasing plasma insulin (d) Activating stretch receptors in the GIT
15. Injection of hypertonic saline into which area causes diuresis?
    (a) Supraoptic nucleus (b) Paraventricular nucleus (c) Preoptic nucleus (d) Posterior pituitary

Answers

1. (c) 2. (a) 3. (a) 4. (b) 5. (a) 6. (d) 7. (a) 8. (d) 9. (c) 10. (c) 11. (a) 12. (d) 13. (b) 14. (a) 15. (a)

Chapter

103

The Cerebral Hemisphere (Cerebrum)

I. Physiological anatomy: Structure, methods of study
II. Parietal lobe
III. Frontal lobe
IV. Prefrontal lobe: Frontal lobe syndrome
V. Occipital lobe
VI. Temporal lobe: Kluver-Bucy syndrome

PHYSIOLOGICAL ANATOMY

A. GROSS APPEARANCE

1. The two cerebral hemispheres, although separated by a space in which the *falx cerebri* invaginates, are connected with each other by bundle of nerve fibers called the *corpus callosum*.
2. The most superficial part of each cerebral hemisphere called the ***cerebral cortex (cerebral grey matter)***, is 2-4 m.m. thick. Its total surface area is 2200 cm^2, of which major part lies within the sulci.
3. Underneath the cerebral cortex lies the *subcortical white matter* in which embedded are *masses* of the grey matter, called *subcortical* nuclear masses, such as the basal ganglia. These nuclear masses consist of nerve cells (soma), packed up very densely together with their axons and dendrites.
4. Each cerebral hemisphere has *three poles* and *three surfaces*. The *three poles* are:
   (i) Frontal Pole
   (ii) Temporal Pole, and
   (iii) Occipital Pole

   The *three surfaces* are:
   (i) Supero-lateral surface
   (ii) Medial surface; separated by falx cerebri, and
   (iii) Inferior surface. It consists of two parts:
      (a) anteriorly-*orbital part*, which rests on the roof of orbital and nasal cavities; and
      (b) posteriorly-*tentorial part*, which rests on the tentorium cerebelli between temporal and frontal pole.
5. The entire cerebral hemisphere is marked by ridges called *gyri* and fissures or canals called *sulci* which give characteristic appearance to it.

#: Fissures are very deep & Large sulci.

6. The *important sulci* include: (Fig. 103.1)
   (i) *Central sulcus* or sulcus of Rolandic. It runs from the midpoint of occipital and frontal pole.
   (ii) *Lateral sulcus* or Sylvian sulcus. It lies between the frontal and temporal pole. It has three divisions (rami), anterior, ascending and posterior rami.
   (iii) *Parieto-occipital sulcus*
   (iv) *Calcarine sulcus*

   These sulci form a Y-shaped arrangement on the medial aspect of the posterior part of cerebral hemisphere. Their ends extend on to the superolateral surface of parietal and occipital lobes respectively. The end of the calcarine sulcus is surrounded by the *Lunate Sulcus*.
7. Because of these major sulci, whole of cerebral hemisphere is divided into *four* lobes:

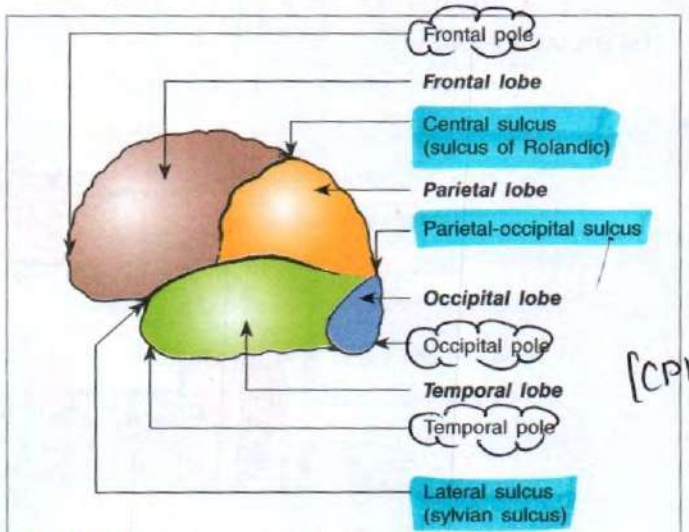


Fig. 103.1 Principal lobes of cerebral hemisphere

(i) ***Frontal Lobe.*** It lies in front of the central sulcus and is concerned with *motor* functions.

(ii) ***Parietal Lobe.*** It lies between the central sulcus and parieto-occipital sulcus. It is concerned with *sensory* functions.

(iii) ***Occipital Lobe.*** It lies behind the parieto-occipital sulcus, and is concerned with *vision*.

(iv) ***Temporal Lobe.*** It lies below the lateral sulcus and is concerned with *hearing*.

8. In addition, there is a ***Limbic Lobe.*** It is the region of the cerebral cortex that lies on the medial side adjacent to the corpus callosum and the attachment of the brain stem with the cerebral hemisphere (**Fig. 104.1**, page 1022).

9. *Other sulci* include: **(Fig. 103.2)**

(v) Precentral sulcus, in front of central sulcus.

(vi) Postcentral sulcus, behind the central sulcus.

(vii) Superior and inferior frontal sulci in the frontal lobe.

Algo: Remember main sulcus, then remaining sulcus ⊕ Every lobe has 2-3 sulci

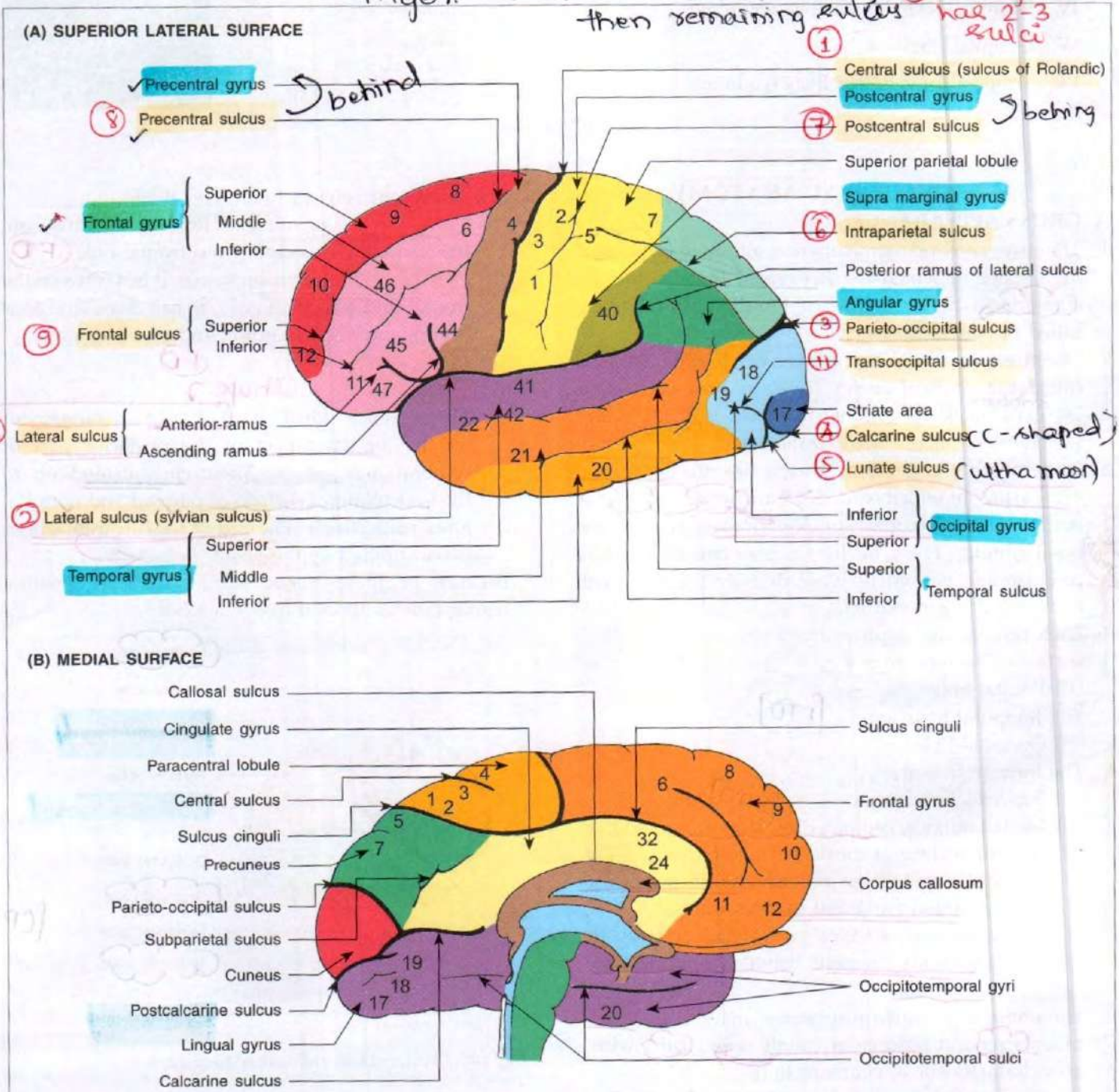


Fig. 103.2 Principal gyri and sulci and cortical Brodmann's areas of left cerebral hemisphere

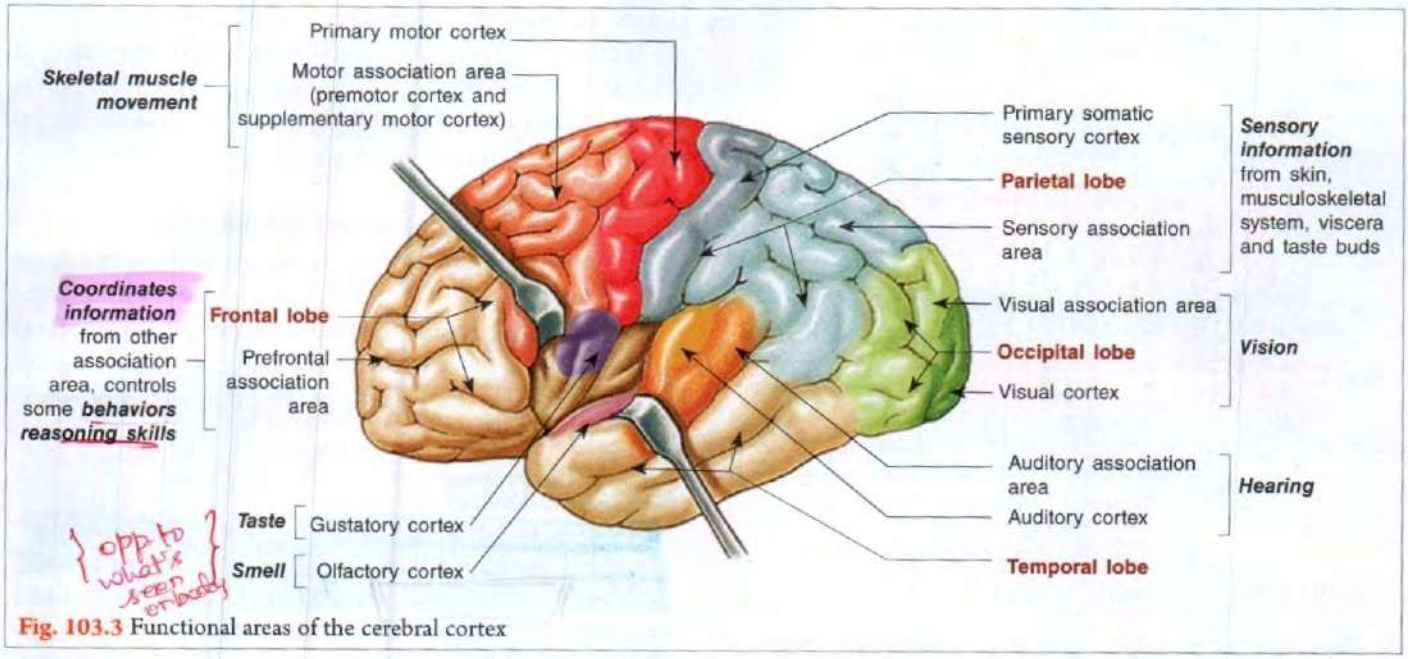


Fig. 103.3 Functional areas of the cerebral cortex

(viii) Superior and inferior temporal sulci in the temporal lobe.

(ix) Intra-parietal sulcus in the parietal lobe.

10. *Brodmann* divided each of the cerebral hemisphere into several areas, called ***Brodmann Areas***. Each cerebral hemisphere contains a total of '47' such areas. These areas were originally numbered separately thinking that each area has an absolutely selective function **(Fig. 103.3)**. For example:

(i) The area between central sulcus and precentral sulcus is called *pre-central gyrus;* the *motor area* of the brain (Brodmann area 4).

(ii) The area between central sulcus and postcentral sulcus is called *postcentral gyrus;* the *sensory area* of the brain (area 3, 1, 2).

(iii) Superior and inferior frontal sulci in the frontal lobe form, *superior, middle and inferior frontal gyri*. (Pre-motor area and area of frontal eye field: area 6, 8 to 13, 24, 32, 44 to 47). It forms the frontal association area and is concerned with higher intellectual and psychic functions.

(iv) Superior and inferior temporal sulci in the temporal lobe form, *superior, middle and inferior temporal gyri*. It comprises primary auditory area (area 41) and auditory association areas (area 20, 21, 22).

(v) Intra-parietal sulcus in the parietal lobe forms:

- *Superior parietal lobule* (area for sensory stimuli discrimination (area 5, 7).
- *Inferior parietal lobule.* It is divided into 3 parts by posterior ramus of the lateral sulcus and superior and inferior temporal sulci:
  - (a) two anterior parts form *supra marginal gyrus* (*stereognosis area*, area 40); and
  - (b) third posterior part forms *Angular Gyrus*

(a) and (b) help in *Spatial Recognition*, *i.e.* tactile localization, tactile discrimination, joint displacement and stereognosis (page 901). (Also refer to page 1017).

(vi) Calcarine sulcus, lunate sulcus and transoccipital sulcus in occipital lobe form:

(a) Superior occipital gyrus

(b) Inferior occipital gyrus

They form visual association areas (area 18, 19).

(c) Striate area, forms primary visual area (area 17).

B. CYTOARCHITECTURE (DETAILED HISTOLOGY) OF CEREBRAL CORTEX

According to *Von Economo C. 1929*, the typical cortex (*Isocortex* or *Neocortex*, page 1014) contains six layers, numbered I to VI from outside to inside **(Fig. 103.4)**.

Layer I: Molecular or Plexiform Layer

1. It contains:
   (i) Horizontal cells of Cajal and
   (ii) Axon terminals of Martinotti cells, *i.e.* pyramidal shaped cells with short axons.
2. The apical dendrites from the pyramidal cells in deeper layers ascend and ramify horizontally in this layer.

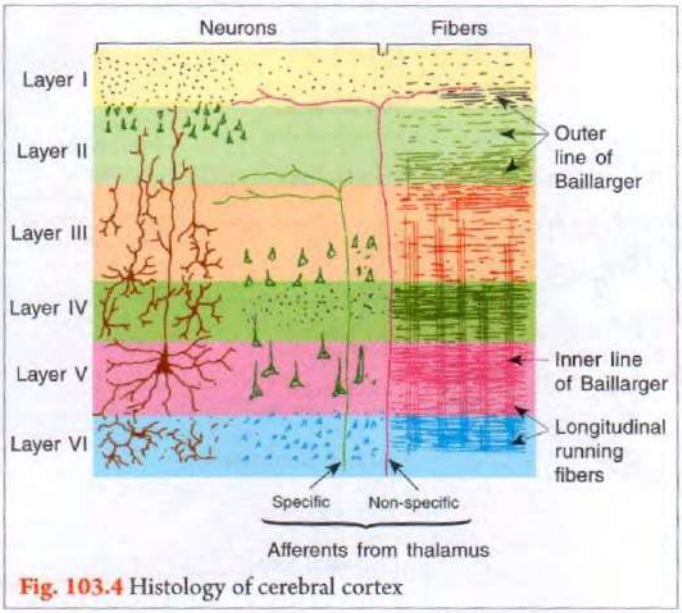


Fig. 103.4 Histology of cerebral cortex

3. This layer is perhaps a site of a horizontal spread of neuronal activity either excitatory or inhibitory by releasing glutamate or GABA respectively, thus it perform most of the inter-cortical functions.

Layer II: External Granular Layer

1. It contains closely packed small fusiform cells where:
   (i) the dendrites either ascend to layer I or spread laterally within this layer, and
   (ii) Axons pass to layer V and VI and synapse with their cells.
2. Its cells receive afferents from:
   (i) Martinotti cells and
   (ii) granular cells of layer IV.

Layer III: External (Outer) Pyramidal Layer

1. It contains larger cells whose:
   (i) apical dendrites ascend to layer I; and
   (ii) basilar dendrites pass horizontally in the same layer.
2. Their efferent axons pass to layer V and VI.
3. Its cells receive afferents from:
   (i) the axons of granular cells of layer IV and
   (ii) Martinotti cells of layer V and VI.

Layer IV: Internal Granular Layer

1. It contains densely packed small star-shaped cells called *Stellate Cells*. They are excitatory interneurons that release glutamic acid.
2. Their dendrites are distributed within this layer and receive a dense supply of specific thalamocortical afferents. Such a pattern is characteristic of sensory cortical areas.
3. Axons of these cells terminate in layer V and VI.
4. The stellate cells are an example of a *multipolar neuron*.

Layer V: Internal (Inner) Pyramidal Layer

1. It contains larger pyramidal cells (larger than layer III cells). Therefore, also called *Giant Cells of Betz*. (Size: 60-120 μm × 30-80 μm). These cells are characteristically seen in motor cortex, area 4.
2. The cells have:
   (i) apical dendrites pass to the outer layer,
   (ii) basilar dendrites are confined within this layer, and
   (iii) axons project to the white matter (with collaterals to the same and more external cortical layers) and terminate on the cells of the brain stem and spinal cord.

Important Note

Pyramidal neurons are the only projection neurons of the cortex and they are excitatory neurons that release glutamic acid at their terminals. The other cortical cells types are interneurons (local circuit neurons). They are mainly inhibitory interneurons and release GABA as their neurotransmitter.

Layer VI: Fusiform Layer

1. It contains many spindle shaped cells whose:
   (i) dendrites form network in the outer layer, and
   (ii) the axons project to sub-cortical nuclear groups.

There are *four principal bands* of *transversely* running nerve-fibers; that in layers I, III and IV are called outer *line of Baillarger* and in the layer V, as inner line of Baillarger. The *longitudinally* running fibers penetrate outwards as far as layer II.

The classical six layered structure is not found everywhere in the cerebral cortex. The areas of the cortex where number of layers are less than six are called *Allocortex* (Allo means old). The allocortex includes: the uncus, hippocampus and gyrus dentatus. The areas of the cortex where number of layers are six are called *Neocortex* (*Neo* means new).

Important Note

The actual extent of the allocortical areas has changed little as mammals have evolved, but this region has been overshadowed by the immense growth of the *neocortex*, which reaches its greatest development in human (Fig. 103.5). Thus the ***most prominent gross feature of the human brain*** is the immense growth of the major lobes: frontal, parietal, temporal and occipital. The parietal and temporal lobes have increased markedly in particular.

Types of Neocortex (or Isocortex)

The classical 6 layered structure is not found everywhere in the cortex. Local variations occur which classify the

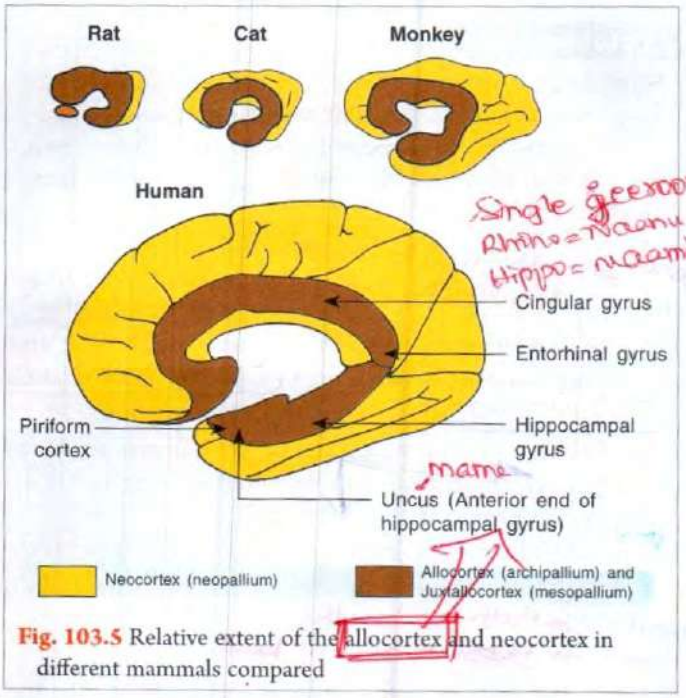


Fig. 103.5 Relative extent of the allocortex and neocortex in different mammals compared

neocortex into five *column* types: **(Fig. 103.6)**. Neurons with in a column have similar response properties, i.e. they comprise a local processing network.

Type 1. Agranular Cortex

(i) The granule cells are completely absent.

(ii) The cells in layer II and IV are replaced by pyramidal cells.

(iii) *Sites:*

(a) Excitomotor region of the cortex (area 4) *i.e.* posterior 1/3rd of frontal lobe anterior to central sulcus;

(b) Broca's area (area 44; motor speech center, page 1033);

(c) anterior part of the island of Reil.

Types 2, 3 and 4 are essentially alike but differ from one another in detail.

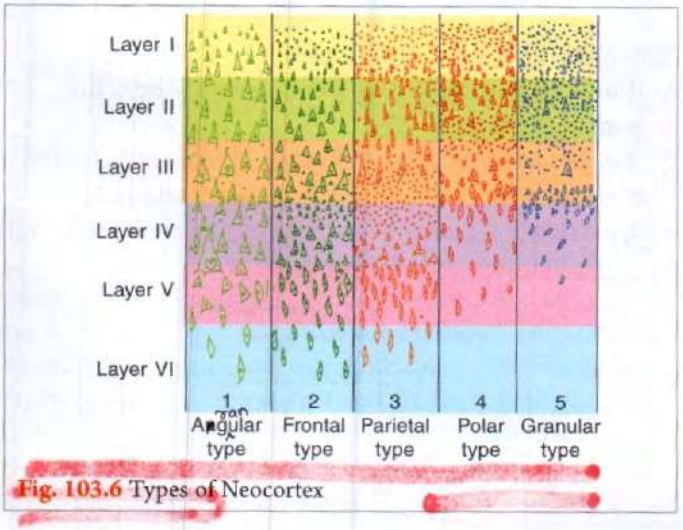


Fig. 103.6 Types of Neocortex

Type 2. Frontal type

Granule cells are triangular; site: anterior 2/3rd of the frontal lobe.

Type 3. Parietal type

(i) There is an increase in depth and density of two granule layers II and IV.

(ii) These cells are round in shape.

(iii) The pyramidal cells are smaller, slender and more numerous.

(iv) *Sites:*

(a) parietal lobe

(b) junctional region of parietal, occipital and temporal lobes.

Type 4. Polar type

(i) The cortex is narrow and all layers are reduced in depth though the cells are more densely packed.

(ii) *Site:* frontal and occipital poles.

Type 5: Granular Cortex

(i) The granules have largely replaced the pyramidal cells in layers III and V.

(ii) *Sites:*

(a) Sensory cortex (post central gyrus)

(b) Calcarine region (vision)

(c) Heschl's gyrus in superior temporal gyrus (hearing area 41).

C. CLASSIFICATION OF CORTICAL FIBERS

The fibers to the cortex can be classified into *two* types: *afferent* and *efferent*.

Cortical Afferent Fibers include:

1. *Specific thalamocortical fibers:* These fibers terminate in layers IV (mainly) and III. They may give collaterals to cells of layer V.
2. *Non-specific thalamocortical fibers:* These fibers terminate in layer I but also give collaterals to cells of remaining layers II to VI.
3. *Association fibers:* They connect different areas of the cerebral cortex within a hemisphere.
4. *Commissural fibers:* These fibers cross the midline and connect different parts of the two hemispheres with one another. The association and commissural fibers terminate in layers I to IV.
5. *Projection fibers:* They connect the cerebral cortex with other regions of the CNS.

Cortical Efferent Fibers include:

1. The pyramidal cell axons of layers V and VI which give rise to the projection, commissural and association fibers.

2. The pyramidal and granule cell axons of layers II and IV which are mainly distributed within these same cortical layers.
3. The axons of Martinotti (pyramidal) cells, horizontal cells of layer I and granule cells which are distributed within the cortex itself.

D. METHODS OF THE STUDY OF THE HIGHER FUNCTIONS

Limitations: Some of the higher functions of the nervous system, such as learning and memory, can easily be studied in animals. However, other functions like judgement, language etc. are hard to study, because:

(1) it is difficult to communicate with animals; and
(2) moral and legal considerations limit experimental studies in humans.

In general, available information on the higher functions of nervous system has been obtained by *six methods.*

Method 1. The latest method consists of "correlating clinical observations in humans with the site and extent of brain abnormalities either by radiological examinations like X-ray, ***CT*** (*computed tomography*) and ***MRI*** (*magnetic resonance imaging*) or at autopsy."

Method 2. Supplementing the information obtained by the above method by "studying the effects of stimulation of the exposed cerebral cortex during neuro-surgical procedure under local anaesthesia."

Method 3. Study of the effects of stimulating subcortical structures with chronically implanted electrodes in patients with parkinsonism, schizophrenia, epilepsy and incurable malignancies.

Method 4. Study of changes in brain electrical activity and chemistry coincident with learning in animals.

Method 5. Study on the measurement of regional variations in cortical blood flow during mental activities.

Method 6. Study of conditional reflexes (page 1035).

PARIETAL LOBE

The parietal lobe lies between the central sulcus and the parieto-occipital sulus **(Fig. 103.1)**. It is primarily concerned with ***sensory*** functions. The ***major areas*** in the parietal lobe are mainly the somatic sensory areas which include:

(i) *Primary sensory area* or First somatic sensory area (S.I),
(ii) *Secondary sensory area* or Second somatic sensory area (S.II),
(For details on (i) and (ii), refer to page 918).
(iii) *Area 5*
(iv) *Area 7*, and
(v) *Area 40.*

Important Note

Stimulation of sensory area produces some motor responses whereas stimulation of motor area causes some sensory perception, therefore, these two areas taken together constitute the *Somato Sensory Cortex.*

Area 5

1. It lies posterior to area 'S.I' in the parietal lobe and contains neurons which react to *passive or active rotation of a joint or joints.* Few respond to tactile stimuli.
2. It receives mainly afferents from neurons of areas 1 and 2 which themselves are excited by joint and deep tissue receptors via thalamic relays.
3. Like the other areas in 'S.I' and S.II', area 5 displays a columnar organization (point-to-point representation).

Area 7

1. It is located in superior parietal lobule deep into the intraparietal sulcus extending close upto the occipital lobe.
2. It is associated with the more elaborate process of *discrimination between the stimuli* (page 1017).

Area 40

1. It is located in supramarginal gyrus.
2. It is concerned with recognition of common objects placed in the hand without looking at them. Therefore, also called as *stereognosis area* (page 1013).

Note

Though area 4 is a *classical motor* area (page 906), it contains neurons which are activated by joint movements and muscle palpation. Some of these neurons may receive an input from muscle spindles.

CONNECTIONS OF THE PARIETAL LOBE

A. Role of Association and Commissure Fibers in Somatic Sensation (Fig. 103.7)

1. The ***Association Fibers*** interlink the areas 'S.I', 'S.II', area 5 and area 4 involved in somatic sensation.
   (i) Areas 'S.I' and 'S.II' are reciprocally connected with each other and with area 4.
   (ii) Area 'S.I' projects to area 5 which in turn projects to area 7 and to area 6.
   (iii) A small projection passes from the areas 'S.I' and 'S.II' to the supplementary motor area (page 893).
   (iv) Area 3 neurons are predominately excited by thalamic fibers, whereas areas 1, 2, 5 and 'S.II'

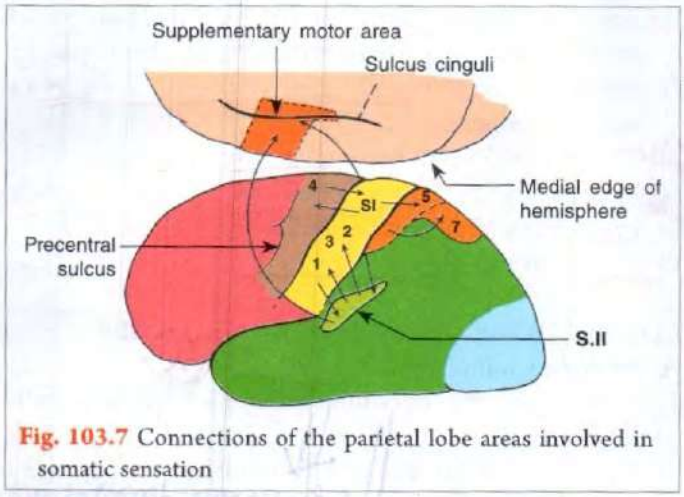


Fig. 103.7 Connections of the parietal lobe areas involved in somatic sensation

receive more association fibers than from thalamic nuclei.

2. The *Commissural Fibers* are mostly axons of pyramidal cells situated in layer III and connect the corresponding somatosensory areas with those of the opposite hemisphere.
   Area 'S.I' projects to the contralateral areas S.I and S.II, but S.II only supplies its opposite counterpart.

B. Somatosensory Areas Efferents

1. All somatosensory areas (particularly S.I) send fibers to the caudate nucleus and putamen.
2. Area 'S.I' sends fibers:
   (i) back to its own thalamic projection nuclei;
   (ii) to the tectum, pons and cerebellum;
   (iii) to spinal segments terminating in the dorsal part of the dorsal horn; and
   (iv) to the gracile and cuneate nuclei.

Important Note

Each area of the somatosensory cortex is affecting important relays on the descending somatic pathways thereby contributing to the cortical control of fine skilled movements.

FUNCTIONS OF THE PARIETAL LOBE

1. *Post Central Gyrus* (Areas 3, 1 and 2).
   (i) It is concerned with appreciation of the elementary sensations of touch, pain, pressure, temperature (heat and cold) and joint movements.
   (ii) Face area here is closely associated with the taste area.
2. *Superior parietal lobule* (areas 5 and 7) is associated with more elaborate process of *discrimination between the stimuli*. Thus helps differentiating in the relative intensity of different stimuli. Therefore, warm objects are distinguished from warmer, cold from colder and rough from rougher, etc.
3. *Inferior parietal lobule*
   (i) *Supramarginal gyrus* (area 40). It helps recognition of common familiar objects placed in the hand without looking at them (*Stereognosis*, page 901).
   (ii) *Angular gyrus*. It helps recognition of *Spatial relationship*, *i.e.*
      (a) *Tactile localization* – the precise point stimulated is accurately localized;
      (b) *Tactile (two point) discrimination* – two points of a compass placed close together are recognised as two and not as one; and
      (c) The extent and direction of small joint displacements can be estimated accurately.
   (a), (b) and (c) help the relations of a stimulus in one, two or three-dimensional space to be clearly defined.

APPLIED ASPECT

1. **Unilateral Removal of Parietal Lobe**
   Removal of the parietal lobe on one side causes:
   (i) Severe mental imbalance of perception of sensations: proprioception and fine touch are most affected; temperature sensibility is less affected and pain sensibility is only slightly affected (because thalamus can cause *crude* sense perception but not the finer ones). Thus, there is a defective response to all stimuli that arise in the opposite side of the visual or somatic fields.
   (ii) Loss of finer forms of sense perception on the opposite side, such as tactile discrimination and localization; and temperature sense.
   (iii) Loss of control over the voluntary movements *(Ataxia)* and uselessness of muscles on the opposite side.

Note

The proprioceptive function, which had been lost after unilateral parietal lobectomy, gets corrected after symmetrical bilateral parietal lobe destruction.

2. **Bilateral Removal of Post Central Gyrus** (Areas 3, 1, 2, 5)
   (i) Initially visual placing is retained but tactile placing is completely lost. However, recovery is slow and imperfect, therefore, with eyes closed, the animal's hand and foot are inactive to tactile stimulation.
   (ii) If upper lip of the sylvian fissure is also removed, avoiding responses to touch *i.e.* withdrawal reflexes, are exaggerated and explosive. As a result, violent withdrawal occurs in response to a pinprick.

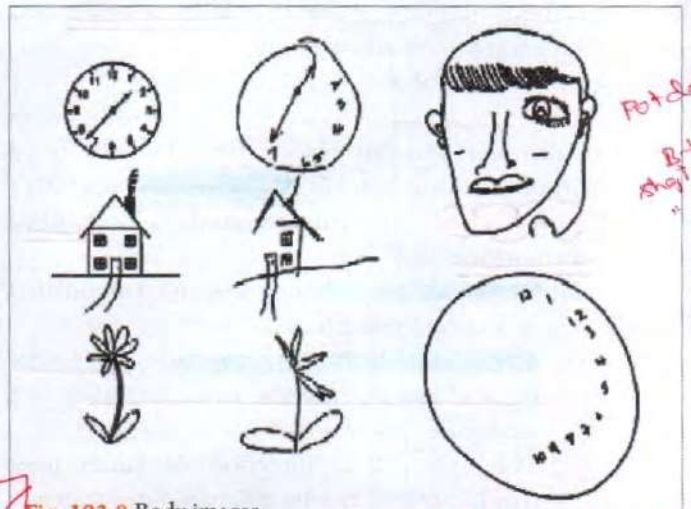


Fig. 103.8 Body images

3. **Removal of Inferior Parietal Lobule**, specially area 7
   (i) *Unilateral lesion* causes marked neglect of the opposite perceptive field, both visual and somatic in spite of normal visual and somatic senses. This leads to failure to care for half of the body; since the *body images* can no longer be appreciated. (Normally we are aware of the positions of various parts of the body relative to one another and to other objects around us. We are also aware of changes in all these relationships. This sort of awareness is called *body image*.) (Fig. 103.8)
   In extreme case such individuals shave half their faces; dress, half their bodies or read half of each page.
   (ii) *Bilateral lesion*
      (a) abolishes visual placing but coarse tactile placing is retained;
      (b) optic righting reactions are lost.

   There is an inability to make use of visual information, such as:
   - inability to copy designs or objects, called ***constructional apraxia*** (*apraxia* means inability to perform organised movements in the absence of paralysis), and
   - patient cannot find his way about even in familiar surroundings, called ***spatial disorientation***.

FRONTAL LOBE

The frontal lobe lies in front of the central sulcus and is concerned with *motor* functions. The major *motor areas* are located in this lobe (for details, refer to pages 906–908).

PREFRONTAL LOBE

Prefrontal lobe is also called *Orbito-frontal region*. It lies anterior to the motor areas 4, 6 and 8. The ***major areas*** of the prefrontal lobe are: *Brodmann's areas 9 to 13, 24, 32 and 44 to 47.*

(1) *Areas 9 to 12* lie in superior frontal gyrus and also extend on to the adjacent medial surface of the hemisphere;
(2) *Area 13* lies in the orbital part of the inferior surface of frontal lobe;
(3) *Areas 44 to 47* lie in the inferior frontal gyrus;
(4) *Area 24* lies in the precallosal part of the cingulate gyrus on medial surface; and
(5) *Area 32* lies in the cingulate gyrus.

CONNECTIONS OF THE PREFRONTAL LOBE

A. Afferent Connections (Fig. 103.10 A)

1. Fibers **from the dorsomedial nucleus** of thalamus project on to:
   (i) areas 8, 9, 10, 11, 12 on the lateral and adjacent medial surface; and
   (ii) areas 44 to 47 in the inferior frontal gyrus.

   As the dorsomedial nucleus of the thalamus receives afferents from the posterior hypothalamus, therefore, the impulses which reach the prefrontal lobes via the medial nucleus *represent a resultant of hypothalamic and thalamic activity.*
2. Fibers **from the anterior nucleus of the thalamus** project on to the precallosal part of the cingulate gyrus (area 24).

   As the anterior nucleus of the thalamus receives afferents from the mammillary bodies of the hypothalamus which, in turn, receives the afferents from the hippocampus via the fornix. The hippocampus is thus ultimately projected to inhibitory area 24.

Important Note

The prefrontal lobe thus forms a closed circuit connection with the thalamus called *Papez Circuit*, described by *Papez J.W.* (1959) (Fig. 103.9). This circuit is responsible for resting EEG (page 981) and plays an important role in control and genesis of emotions (page 1022).

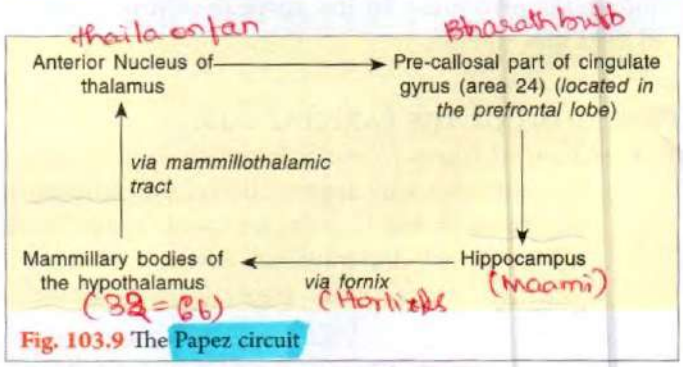


Fig. 103.9 The Papez circuit

3. Area 32 receives afferent fibers from the:
   (i) frontal inhibitory areas 8s and 24s; and
   (ii) other inhibitory areas 4s, 2s and 19s.

B. Efferent Connections (Fig. 103.10 B)

1. The inhibitory areas 8s and 24s discharge **to the caudate nucleus**.
2. *Fronto-pontine tract i.e.* fibers from area 10 pass between the head of the caudate nucleus and the putamen in the anterior limb of the internal capsule **to the pontine nuclei** and thence to the cerebellum.
3. *Corticotegmental fibers i.e.* fibers from area 8 are projected **to the tegmentum** of the mid brain.
4. Fibers from areas 9 and 10 pass:
   (i) to the **ventral and medial thalamic nuclei**, and
   (ii) to the **tegmental reticular formation**.
5. Fibers from the area 13 the hippocampus, uncus and amygdala project via the fornix **to the mammillary bodies** of the hypothalamus.

C. Intercortical Connections (Fig. 103.10 C)

1. *Fronto-occipital projection* – A long tract which runs back from the frontal eye field in area 8 to area 18 in the occipital lobe (***visual association area***).

Physiological significance: The *proprioceptive* data from the eye muscles are integrated in area 8 and through the fronto-occipital projection these data can be correlated with retinal impressions. Therefore, damage to this projection produces *Object Vision Hemianopsia (Visual Agnosia)*, i.e.nature of the object is not recognized in spite of good vision.

2. Fibers from the prefrontal areas 44 to 47 and occipital area 18 pass into the temporal lobe, which in turn receives numerous association fibers from most part of the cerebral cortex.

FUNCTIONS OF THE PRE-FRONTAL LOBE

As the pre-frontal lobes establish to and fro connections with the thalamus, hypothalamus and many other regions of the cerebral cortex, the entire system may be considered as functioninig as an *integrated unit*. The activities of this *Nervous Complex* are concerned with:

1. Control of the ANS via the hypothalamus and the brain stem;

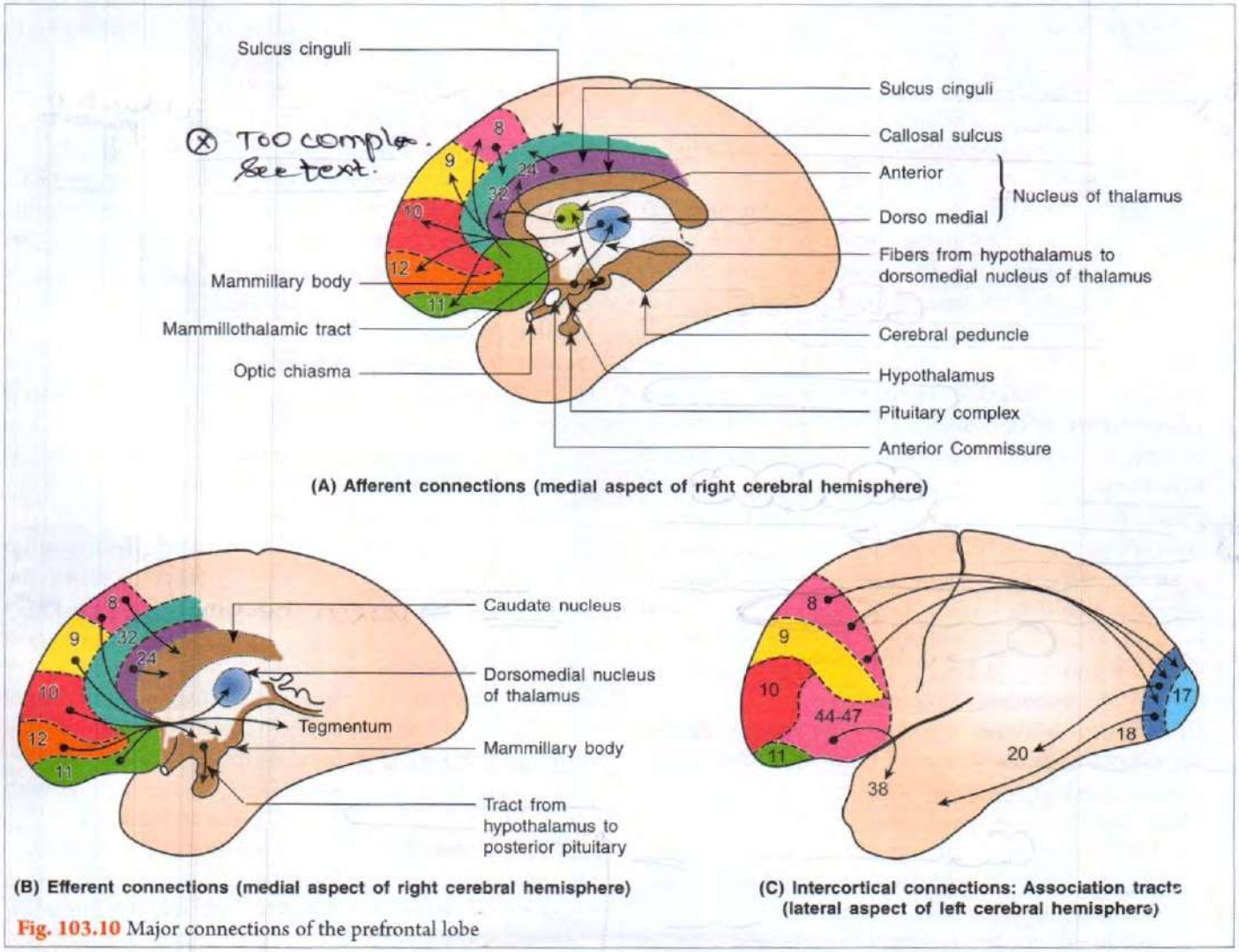


Fig. 103.10 Major connections of the prefrontal lobe

2. Control of some of the higher intellectual activities;
3. Control of personality;
4. Control of emotional affects;
5. Control of behaviour and social consciousness; and
6. Responsible for the resting EEG (page 1015).

The activities of this *nervous complex* can be summarized by the following experimental studies based on removal or stimulation of pre-frontal areas in monkeys.

1. ***Alteration of Activity***

Removal of the prefrontal region, specially involving area 13, causes interruption of projection from area 13 to the hypothalamus and the caudate nucleus.

(i) Initially it produces *apathy, i.e.* indifference to surroundings and to anything that would excite interest in normal circumstances. Therefore:
   (a) the animal sits with blank expression on the face,
   (b) his head is hung down,
   (c) it stares (looks with fixed eyes) into space ignoring the approach of human beings, and
   (d) his movements are sluggish.

(ii) After some days or weeks, there appears a *hyperactive state* which persists unchanged for months, therefore,
   (a) animal is constantly on the move, such as walking continuously or pacing about like a caged lion;
   (b) the movements are without aim and the animal seems unable to control or check them;
   (c) sometimes the movements become almost maniacal in their violence; they disappear during the hours of darkness.

2. ***Alteration in Emotional Mental State***

Monkeys were trained to discriminate between weights when they chose the heavier weights correctly, they were suitably rewarded. *Pavlov Pavlov, I.P.* (1927) described this *discrimination power* as *experimental neurosis*. By removal of post central gyrus, the discrimination power was grossly impaired, therefore, the animal finding itself in difficulties about discriminating between weights often flew into fits of violent anger (tantrum of rage). These *fits* were abolished by destroying area 24 in the prefrontal lobe.

3. ***Alterations in Social Behaviour***

Unilateral or bilateral removal of the anterior part of the cingulate gyrus produces immediate changes in social behaviour *i.e.* *moral sense of right and wrong*. Therefore, such was the change:

(i) The monkey lost its preoperative shyness and fear of man. It would approach the experimenter and examine his fingers with curiosity. (Normally, it sits quietly in the far corner of the cage.)

(ii) In a large cage with other monkeys, it showed no affection towards its companions. In fact, it behaved as though they were dead; therefore,
   (a) it would walk over them, would even sit on them;
   (b) it would openly take food from them and appeared surprised when they revenged;
   (c) it remained non-aggressive.

4. ***Impairment of Memory***

The monkey was shown two inverted cups and food was placed under one of them; the monkey was trained to raise the cup covering the food; if it chose correctly it was given the food to eat.

To test the memory a screen was placed between the monkey and the cups immediately after one cup had been filled with food. The normal monkey could still make a correct choice after the cups had been out of sight for 90 secs; after removal of the pre-frontal lobe it might choose wrongly after an interval of only 5 secs.

5. ***Impairment of Learning Capacity and Intellectual Functions***

This loss of learning power is proportional to the extent to which the neocortex or its projections are involved.

6. ***Changes in Autonomic Activities***

Stimulation of area 13 produces:
(i) changes in HR, BP and respiration;
(ii) affects the motility and secretory activity of GIT.

Mechanism: Pre-frontal area by its indirect connections with the hypothalamus and direct connections with the brain stem, can influence autonomic activities.

Applied Aspects

Prefrontal Lobectomy in Man

1. *Unilateral removal* (if excitomotor areas are intact) causes:
   (i) no impairment of voluntary movements or alteration of muscle tone or reflexes;
   (ii) little change in the personality.
2. *Bilateral removal* produces marked deterioration in social behaviour, specially inability to check the emotions.

Prefrontal Leucotomy in Man

It involves cutting the connections between the thalamus and the prefrontal lobe. Thus most of the prefrontal cortex is put out of action, as the cortical association fibers are relatively few. This is associated with *Frontal Lobe Syndrome*, which is characterized by:
(1) *Flight of ideas.* It results in difficulty in planning.
(2) *Euphoria i.e.* a sense of well being and failure to realise or indifference to seriousness of other feelings or emotions.

(3) *Memory (recent memory)* impaired with loss of moral and social sense.
(4) *Attention and power of concentration lost* and restlessness develops; it is due to loss of area 13.
(5) *Lack of initiative* following marked depression of intellectual activity leads to reduction in mental drive.
(6) *Emotional instability.* Therefore, patient becomes less self-critical holding a high opinion of his abilities though his higher intellectual faculties are impaired.

In addition, it may be associated with urinary and faecal incontinence and hyperphagia.

Clinical Significance

In some mental patients, tension resulting from real or imagined failure of performance or by delusions (false belief), compulsions and phobias, are so great, that it makes them unfit. Prefrontal lobectomy or leucotomy operations were done previously to reduce tension. After the operation delusions and other symptoms are still there but they no longer bother the patient. Nevertheless, the complications are frequent and because the desirable effects of lobectomy can generally be achieved with tranquilizers and other drugs, therefore, lobectomies are rarely performed, if ever, for the treatment of mental disease.

OCCIPITAL LOBE

The occipital lobe lies behind the parieto-occipital sulcus and is concerned with vision. The major areas in this lobe are areas 17, 18 and 19 (for details, refer to page 1092).

TEMPORAL LOBE

The temporal lobe lies below the lateral sulcus and is concerned with hearing. The major areas in this lobe are 41, 20, 21 and 22 (for details, refer to page 1071).

Functions of the temporal lobe

1. Destruction of temporal lobe causes no deafness because of its bilateral representation but causes tinitus (ringing in ears) or auditory hallucination (false impression).
2. Sense of equilibrium in conscious man is represented in posterior part of the superior temporal gyrus. Electrical stimulation of this part produces nausea, vomiting, dizziness and sense of rotation and falling.
3. It is concerned with language (speech) function (page 1031) and memory function.

Applied Aspect

A. *Unilateral removal* of the temporal lobe causes no deafness because of its bilateral representation.
B. *Bilateral temporal lobe removal* in monkeys produces *Kluver-Bucy Syndrome.* This was first described by *Kluver and Bucy* and such animals are called *Kluver-Bucy animals.* The characteristic features are mainly due to destruction of limbic system, specially amygdaloid nucleus, and include:
1. Animals are obedient, hyperphagic and males are hypersexual.
2. The animal becomes omniphagic, *i.e.* starts eating diets such as meat which it was not taking previously. For example, the monkey lost its preoperative fear of snakes, it would approach the snakes without fear, pick them up and even eat them.
3. *Visual agnosia i.e.* inability to recognise the objects inspite of good vision.
4. Marked increase in oral activity: Monkeys repeatedly pick up all *movable* objects in their environment. They manipulated each object in a compulsive way; mouth, lick and bite it; and then, unless it is edible, discard it. However, discarded objects are picked up again in a few minutes as if the animal had never seen them before and subjected to the same manipulation and oral exploration. This peculiar behaviour disorder may be due to:
   (i) inability to identify object; or
   (ii) manifestation of memory loss due to removal of the hippocampus.
5. The attention of animals can easily be diverted. They respond to every stimulus, whether it is experienced before or not and usually approach, explore, manipulate and, if possible, bite its source. This failure to ignore *peripheral stimuli* is called hypermetamorphosis.

Clinical Significance

In humans with temporal lobe diseases or lesions, various above-mentioned symptoms are seen. However, impairment in recent memory may also be due to bilateral damage to the hippocampus and hypersexuality may also be due to damage to amygdaloid nuclei and piriform cortex.

Study Questions

1. Give the functional divisions of lobes of cerebral cortex.
2. Differentiate between:
   (i) neocortex and allocortex (ii) prefrontal lobectomy and leucotomy.
3. What is the most prominent gross feature of the human brain as compared to other animals? Give its physiological significance.
4. Define neocortex and give its types and function.
5. Name the major areas located in the parietal lobe. Give their functions.
6. Define and give physiological significance of:
   (i) Stereognosis (ii) Spatial relationship (iii) Ataxia (iv) Body images
   (v) Apraxia (vi) Visual agnosia (vii) Apathy (viii) Experimental neurosis
   (ix) Hypermetamorphosis. (x) Brodmann areas
7. What will happen and why:
   (i) If parietal lobe on one side gets injured? (ii) If inferior parietal lobule is removed?
   (iii) If all connections between prefrontal lobe and thalamus are cut?
8. What is Papez circuit? Give its physiological significance.
9. Mention the major connections of the prefrontal lobe. Draw diagram also.
10. Enumerate the functions of the prefrontal lobe.
11. Give experimental evidence to correlate the functions of prefrontal lobe.
12. What is frontal lobe syndrome? Give its clinical features.
13. What is area 13 and what happens if there is lesion in this area?
14. What is Kluver-Bucy syndrome? Give its characteristic features.
15. Mention methods of study of the higher functions in humans.

MCQs

1. Spot the *wrong* match:
   (a) Parietal lobe: concerned with motor functions (b) Occipital lobe: concerned with vision
   (c) Temporal lobe: concerned with hearing (d) Limbic lobe: control of autonomic functions
2. Incoming sensory signals excite which neuronal layer of cerebral cortex?
   (a) Layer II (b) Layer III (c) Layer IV (d) Layer V
3. *True* about allocortex:
   (a) The area of cortex where number of layers are less than six
   (b) The area of cortex where number of layers are six
   (c) Also called isocortex
   (d) It has grown immensely with the human evolution
4. *Not* a feature of areas of the parietal lobe:
   (a) Area 5 displays point to point representation
   (b) Area 7 is associated with process of discrimination between the stimuli
   (c) Area 40 is stereognosis area
   (d) Stimulation of sensory area in the parietal lobe causes sensory perception only
5. Awareness of positions of various parts of the body relative to one another is called:
   (a) Apraxia (b) Spatial orientation (c) Body images (d) Stereognosis
6. Papez circuit, *not true* is:
   (a) A close circuit connection of prefrontal lobe with the thalamus
   (b) Comprises of thalamus → cingulate gyrus → hippocampus → mammillary bodies → thalamus
   (c) Plays an important role in control and genesis of emotions
   (d) Responsible for sleep
7. Higher intellectual functions are linked to:
   (a) Limbic system (b) Parietal cortex (c) Prefrontal cortex (d) Motor cortex
8. Commonest feature of prefrontal lobe lesion:
   (a) Psychic blindness (b) Aphasia (c) Distractibility (d) Amnesia

9. **Kluver-Bucy syndrome is *not* characterized by:**
   (a) Loss of fear (b) Hearing loss (c) Hypersexuality (d) Timidity
10. ***Not* a feature of prefrontal leucotomy:**
   (a) Involves cutting the connections between the thalamus and prefrontal lobe
   (b) Refers to removal of prefrontal lobe
   (c) Done in psychiatric patients to reduce tension
   (d) Associated with frontal lobe syndrome
11. ***Not* a feature of cerebral cortex:**
   (a) 2-4 mm thick (b) Total surface area is 2200 cm^2
   (c) Major portion lies within the gyri (d) Mainly comprises of nerve cells
12. **The term spatial recognition refers to:**
   (a) Tactile localization and discrimination (b) Joint displacement
   (c) Stereognosis (d) All of the above
13. **Primary sensory cortex is predominantly comprises of:**
   (a) Betz cells (b) Pyramidal cells (c) Granular cells (d) Spindle cells
14. **Most of the output signals leave the cerebral cortex from cell layer:**
   (a) Layer II (b) Layer III (c) Layer IV (d) Layer V
15. ***False* statement regarding the neocortex:**
   (a) It essentially contains all the six layers
   (b) Phylogenetically a new cortex
   (c) Greatest developed in human as compared in other mammals
   (d) Actual extent of its area has changed little as mammals have evolved
16. **The fibers that join different parts of the two cerebral hemisphere are known as:**
   (a) Specific thalamocortical fibers (b) Association fibers
   (c) Projection fibers (d) Commisural fibers
17. **Which of the following Brodmann's areas *do not* function as somatosensory cortex?**
   (a) Areas 3, 1, 2 (b) Areas 5 and 7 (c) Areas 4 and 6 (d) Area 40
18. **Apraxia refers to:**
   (a) Inability to recognise faces
   (b) Inability to read
   (c) Inability to perform movements in the absence of paralysis
   (d) Inability to find the way out even in familiar surroundings
19. **The prefrontal lobe receives the major projections from the:**
   (a) Thalamus (b) Hypothalamus (c) Pituitary (d) Mid-brain
20. **Following structure is referred to as organ of mind:**
   (a) Thalamus (b) Hypothalamus (c) Prefrontal lobe (d) Medulla
21. **Capacity of an animal to concentrate on a task depends to very great extent on an intact:**
   (a) Parietal lobe (b) Temporal lobe (c) Occipital lobe (d) Prefrontal lobe
22. **Damage to which area of the cerebral cortex is likely to cause the greatest degree of loss of intellectual capabilities in a right-handed person?**
   (a) The prefrontal lobes (b) The left somesthetic sensory cortex
   (c) The right somesthetic sensory cortex (d) The right posterior temporal gyrus
23. **In frontal lobe lesion following are *true except*:**
   (a) Right-left dissociation (b) Urinary incontinence (c) Personality change (d) Monoparesis
24. ***Not* a feature of prefrontal leucotomy:**
   (a) Involves cutting the connections between the thalamus and prefrontal lobe
   (b) Refers to removal of prefrontal lobe
   (c) Done in psychiatric patients to reduce tension
   (d) Associated with frontal lobe syndrome

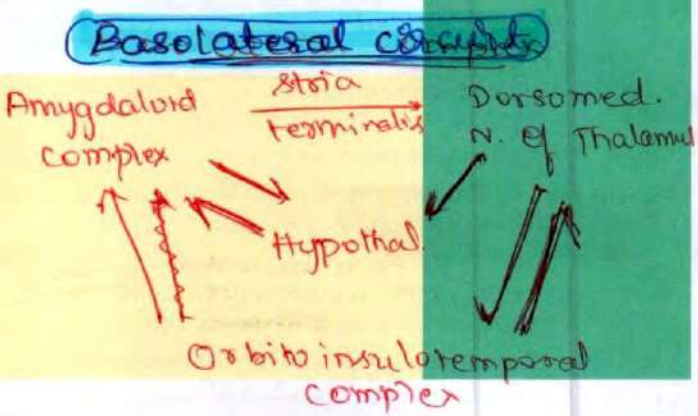
Answers

1. (a) 2. (c) 3. (a) 4. (d) 5. (c) 6. (d) 7. (c) 8. (c) 9. (b) 10. (b) 11. (c) 12. (d) 13. (c) 14. (d) 15. (d)
16. (d) 17. (c) 18. (c) 19. (a) 20. (c) 21. (d) 22. (a) 23. (d) 24. (b)

The Limbic System (Emotion and Motivation)

Chapter 104

I. The Limbic System
A. Structure B. Connections
C. Functions D. Unique features
II. Emotion: Fear and rage
III. Motivation: Reward and punishment system
IV. Sexual behaviour



THE LIMBIC SYSTEM

A. STRUCTURE

Limbus means a ring, the term ***limbic system*** is applied to the parts of the cortical and subcortical structures that form a *ring* around the brain stem.

1. The limbic system consists of the ***limbic lobe*** and the related subcortical nuclei. The limbic lobe includes: *cingulate gyrus, isthmus, hippocampal gyrus* and *uncus* (anterior end of the hippocampal gyrus in the temporal lobe) (Fig. 104.1). The related subcortical nuclei include:
   (i) Amygdala (group of nuclei on the tip of temporal lobe)
   (ii) Septal nuclei
   (iii) Hypothalamus, and
   (iv) Anterior thalamic nuclei.
2. This area was formerly called the ***rhinencephalon*** because of its relation to olfaction, but only a small part of it is actually concerned with smell.
3. The limbic cortex is phylogenetically the *oldest* part of the cerebral cortex. Histologically, it is made up of a primitive type of cortical tissue called ***Allocortex*** (page 1014).

B. CONNECTIONS

The major afferent and efferent connections of the limbic system are given in Fig. 104.2.

1. The ***fornix*** is the main projection of the hippocampus, uncus and amygdala to the hypothalamus (mammillary bodies).
2. ***Papez circuit*** (page 1018) by means of mammillothalamic tract (of Vicq d'Azyr), the anterior nuclei of the thalamus, and in turn the cingulate gyrus, can be excited by this cortico-hypothalamo-thalamo-cortical circuit.

C. FUNCTIONS

1. The limbic system represents the primary area of *control of autonomic functions* in the forebrain. Intense changes in heart rate, blood pressure, GIT movements and pupillary reaction etc. can be induced by its stimulation.
2. It plays an important role in:
   (i) the *emotions of rage* (violent anger) and *fear*; and
   (ii) the motivation.
3. It is concerned with *behavioural aspect of hunger* (page 1005) and sex.
4. It is also concerned with *olfaction* (page 1055) and *memory* (page 1037).

D. UNIQUE FEATURES

1. There are few connections between the limbic system and the neocortex. Thus the neocortex sits with the legs on each side of the limbic system like a rider on a horse without controls. From a functional point of view, neocortical activity does modify *emotional behaviour* but it cannot be turned on and off at will.
2. It shows prolonged *after discharge* (page 881) following stimulation. Thus the emotional responses are generally *prolonged* and outlast the stimuli that produce them.

EMOTION

Emotions accompany many of our *conscious* experiences. It is an aroused state involving intense feeling, autonomic activation and related behaviour. It has two major components, a *mental* and *physical*.

A. Mental component. It consists of *cognitive, affective* and *conative* changes (Fig. 104.3).

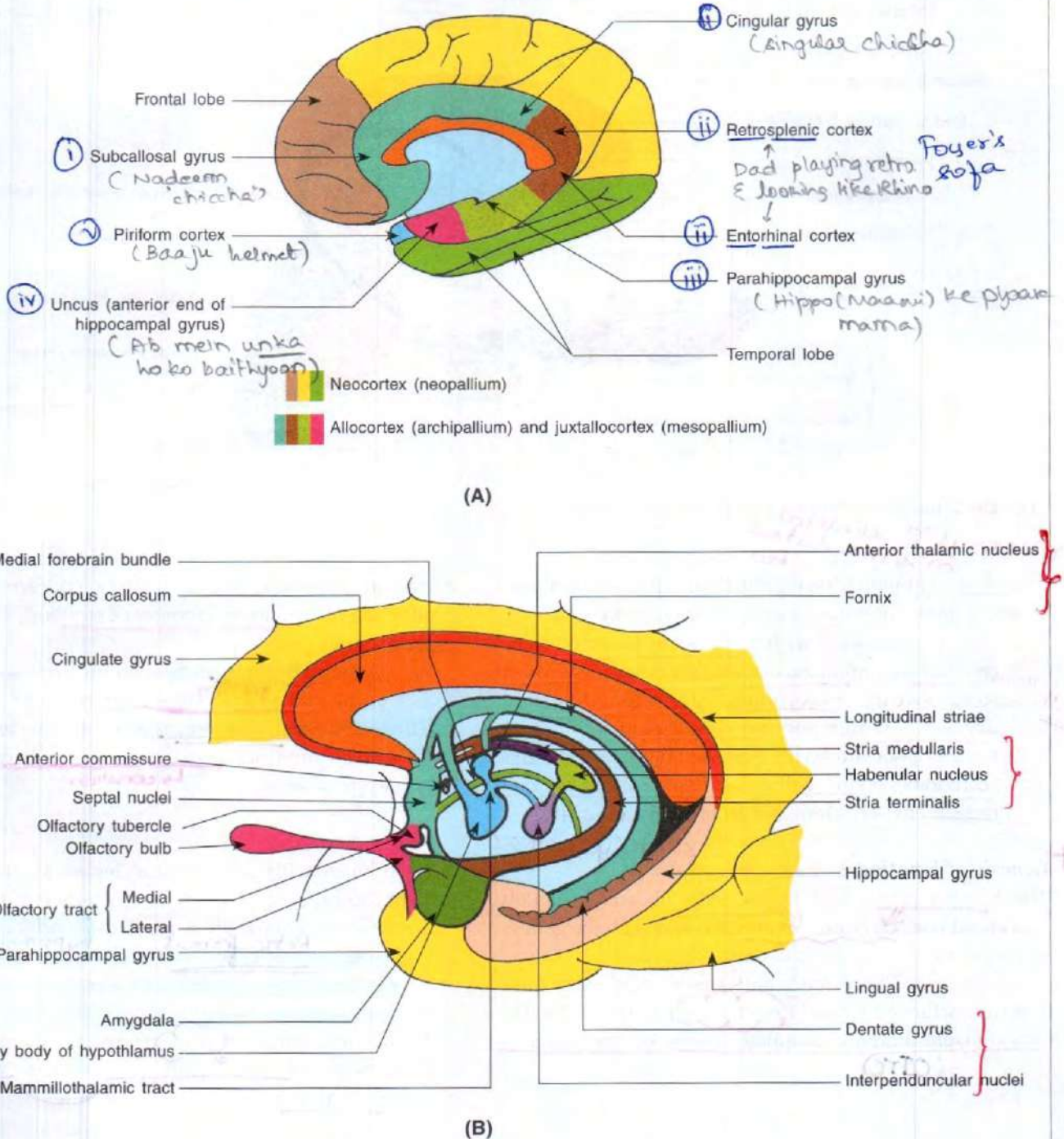


Fig. 104.1 The medial surface of right cerebral hemisphere showing: (A) the limbic lobe, and (B) limbic system (rhinencephalon) i.e. the limbic lobe and related structures

1. *Cognition*, i.e. the means by which one is aware of the processes of thinking and perceiving. It involves an awareness of sensation and usually its cause.
2. *Affect*, i.e. the reflection of a mental state. It involves the feeling itself.
3. *Conation*, i.e. the force which directs to take action and involves the urge to take action.

The following example illustrates the meaning of these terms: thus, I hear a noise, which I recognize as that of an exploding bomb (*cognition*); I feel frightened (*affect*), and I want to take shelter (*conation*).

B. **The physical change**. It consists of changes in viscera and skeletal muscles. These changes are often generalised and involve the coordinated activity of

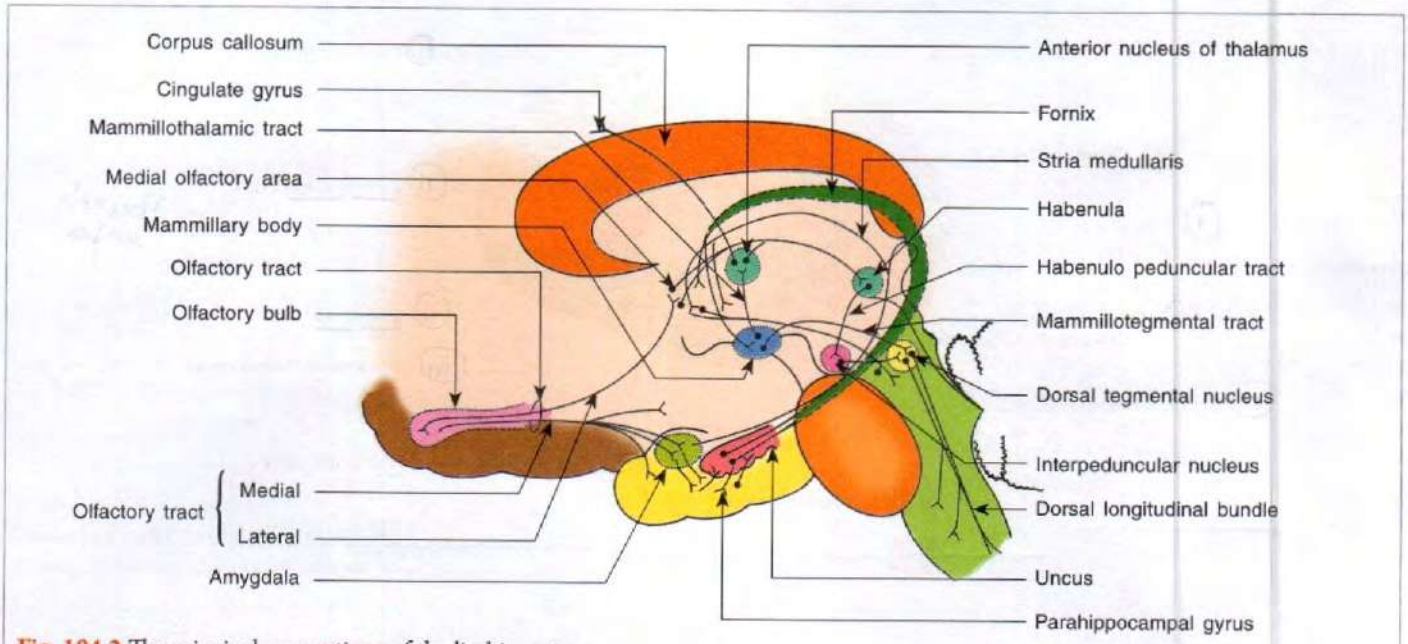


Fig. 104.2 The principal connections of the limbic system

both the autonomic (sympathetic and parasympathetic) and somatic nervous systems. For example:

1. *Fear* is associated with increase in heart rate and respiration, cutaneous vasoconstriction, sweating (cold sweat), piloerection, pupillary dilatation, dryness of mouth and muscular tremors.
2. *Grief* is associated with increased nasal and lacrimal secretions, skin pallor, reduced muscle tone, movements are slow and feeble.

Genesis of Emotion

The hypothalamus and limbic systems are intimately concerned with emotional expression and with the genesis of emotions.

Mechanism. The complex patterns of emotional mental state are achieved by the ***Papez circuit*** (page 1018). The orbito-insulo-temporo-cingulate areas of the cerebral cortex in particular are intimately concerned in the production of autonomic changes of emotion. These areas project mainly:

(i) to the hypothalamus which, in turn, sends fibers to the bulbar autonomic centers; and

(ii) to the reticular formation of the brain stem which modifies somatic motor neuronal activity appropriately.

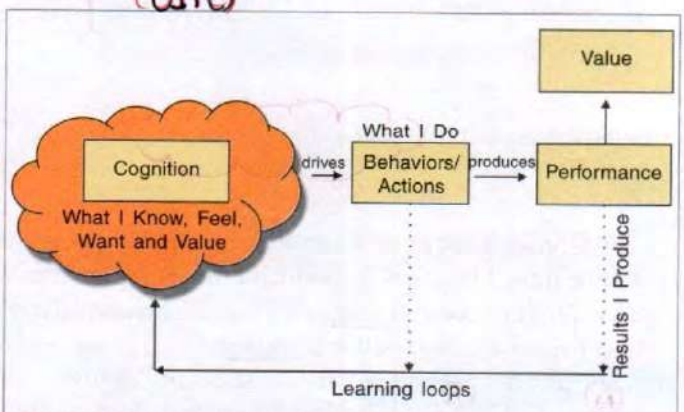


Fig. 104.3 Mental components of emotions

Proof

1. Animals with diencephalic lesion i.e. transection of the brain stem immediately above the thalamus cause the remarkable reaction of ***Sham Rage*** i.e. only intense somatic (motor) and autonomic changes (similar to those that occur in ***rage*** in a normal animal in response to mild stimuli) *without the emotion*.
2. Similar outbursts of *rage* can be produced in conscious animal by electrical stimulation of the posterolateral hypothalamus.

FEAR AND RAGE

Fear and rage are closely related emotions. They are related *natural* protective responses to threat in the environment.

Fear. In animals, the *fear reaction* is associated with autonomic responses such as sweating and pupillary dilatation, bending, and turning the head from side to side to look for escape. This response is also called ***fleeing*** or ***avoidance reaction***. It can be produced in conscious animals by stimulation of the hypothalamic and amygdaloid nuclei. Conversely, the fear reactions

are absent when the amygdaloid nuclei are destroyed (page 1020).

Rage. The *rage reaction* in animals is associated with hissing, spitting, growling, piloerection, pupillary dilatation, biting and clawing. This reaction is also called ***fighting*** or ***attacking reaction.***

Normally, minor irritations are usually ignored but major stimuli make an individual lose their temper. However, rage responses to minor stimuli are observed often after:

1. removal of the neocortex
2. destruction of the ventromedial hypothalamic nuclei
3. destruction of the septal nuclei
4. stimulation of amygdaloid nuclei
5. the *placidity* (calmness) produced by bilateral amygdaloid destruction is converted into *rage* by subsequent destruction of the ventromedial nuclei of the hypothalamus
6. stimulation of the area around the posterolateral hypothalamus
7. gonadal hormone, androgens.

The normal emotional state is determined by afferent impulses that adjust the balance between the hypothalamus and limbic system, one promoting placidity and the other rage.

Role of Hypothalamus

1. The non-hypothalamic parts of the limbic system receive information from cortical association areas, particularly those in the frontal lobe, and send output directly to the hypothalamus.

Important Note

Violent criminals generally have lower activity in the prefrontal cortex than normal; also refer to page 1020.

Thus, the limbic system serves as the route by which information about the emotional meaning of an external stimulus (threatening or friendly), including information gathered from memory and understanding, is passed to the hypothalamus.

2. The hypothalamus then *integrates* the endocrine, autonomic and some of the motor activities that form appropriate emotional behaviour.

Role of Cerebral Cortex

The cerebral cortex plays an important role:

1. in detailed *processing the conscious experience* of emotional feeling;
2. it provides the neural mechanisms that direct the *motor responses* to the external event during emotional behaviour; for example, to approach or avoid a situation;
3. it accounts for the modulation, direction, understanding, or even inhibition of *emotional behaviour*.

Thus the limbic system participates in:

1. the elaboration and integration of the activity whereby emotion is expressed; and
2. it is also involved in the ascending pathways leading to some unknown areas of the brain where emotion is experienced.

MOTIVATION

Motivation literally means "that which moves the will". It is a factor in most of the behaviours. Thus, those processes, which are responsible for *goal directed* quality of behaviour are the *motivations* for that behaviour.

Concept of Reward (approach system) and Punishment (avoidance system)

Rewards are things that an individual works for. They make the behaviour that leads to them occur more often.

Punishments are the opposite to rewards and are associated with *avoidance* that leads to behaviours in which an individual tries to escape from a painful or life threatening situation.

NEURAL MECHANISM INVOLVED

The neural mechanisms of motivation has been obtained by studying the effects of brain ***self-stimulation.*** In this technique, an unanaesthetised experimental animal (usually a rat) regulates the rate at which electrical stimuli are delivered through electrodes implanted in a defined area of the limbic system.

1. The animal is placed in a box containing a bar (lever) it can press **(Fig. 104.4)**. If no stimulus is delivered to the brain when the bar is pressed, the animal usually presses it occasionally (accidentally) at *random.*

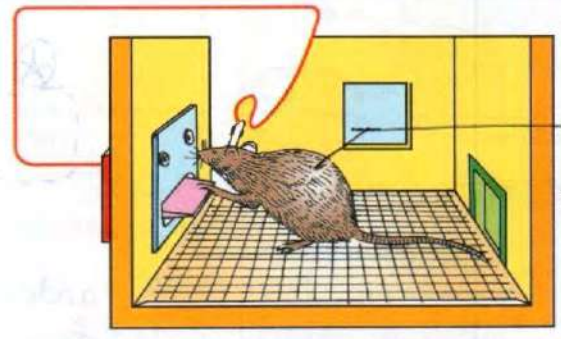


Fig. 104.4 Experimental set up for brain self-stimulation

2. If a stimulus is delivered to the brain as a result of the bar press, a different behaviour occurs, depending on the location of the electrodes:
   (i) If the animal increases the bar-pressing rate above the level of *random* presses, the electric stimulus is by definition ***rewarding***.
   (ii) If the animal decreases the press rate below the *random* level, the stimulus is ***punishing***.
3. Thus the rate of bar pressing with the electrode in different brain areas is taken to be a measure of the effectiveness of the reward or punishment. Different pressing rates were found in different areas of the limbic system.
4. The brain areas where stimulation leads to *repeated bar pressing* are located in **(Fig. 104.5 and 104.6)**:

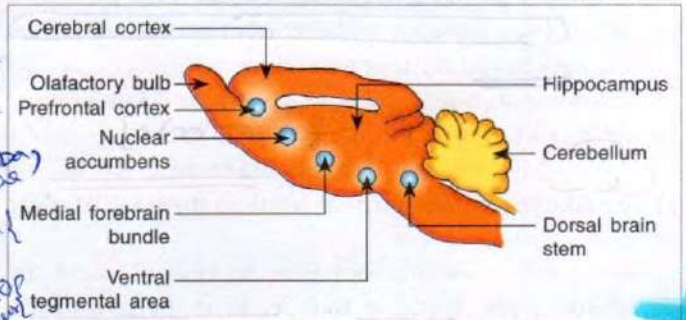


Fig. 104.5 The rat brain regions where stimulation leads to repeated bar pressing.

   (i) The *medial forebrain bundle* (page 1004) with highest rates of *self stimulation*. Fibers in this tract affect virtually every level of the brain, but they have a particularly strong influence on the hypothalamus. The axons of *locus ceruleus* neurons (a brain stem nucleus - page 987) constitute a significant portion of the fibers in this bundle;
   (ii) Midbrain tegmentum;

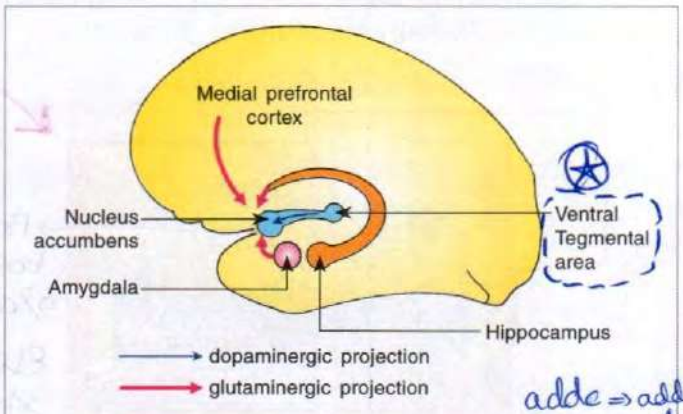


Fig. 104.6 Major excitatory projections to nucleus accumbens which is the key brain area involved in addiction.

   (iii) Prefrontal cortex;
   (iv) Nucleus accumbens (located at the base of striatum);
   (v) Dorsal brain stem; and
   (vi) Ventral tegmental area.

   The animal will stimulate itself repeatedly, as often as 5000 times an hour. If permitted, the animal will continue to stimulate itself even to the point of exhaustion.

   Stimulation of these sites produces *pleasurable* sensations like relief of tension, a quiet relaxed feeling, etc.
5. **The brain areas where *stimulation is avoided*** are:
   (i) lateral portion of posterior hypothalamus
   (ii) dorsal midbrain; and
   (iii) entrorhinal cortex

   Stimulation of these sites produces sensations ranging from vague fear to terror.
6. ***Self stimulation***
   (i) *increases* when the animal is deprived of food, and
   (ii) it is *decreased by* castration and restored by the administration of sex hormones.

Important Note

Stimulation of the reward system provides a potent motivation for learning.

Role of Neurotransmitters

The *catecholamines* [dopamine (mainly) and norepinephrine], *morphine* and *enkephalin* are neurotransmitters involved in the pathways that mediate the brain reward system.

A. The *drugs that increase synaptic activity* in catecholamine pathways and hence increase the *self stimulation* (reward system) are:
   1. Amphetamine – It causes increased release of dopamine.
   2. Nicotine and alcohol increase the amount of dopamine.
   3. Cocaine –
      (i) it binds to and inhibits the dopamine transporter; therefore dopamine uptake is reduced and the extracellular dopamine level is increased;
      (ii) it also inhibits reuptake of serotonin and norepinephrine.

Important Notes

1. A variety of ***habit-forming substances*** (morphine, heroin, cocaine, nicotine etc.) that produce addictive behaviour act by increasing dopaminergic activity via D_3 receptors in the reward system of the brain

particularly the nucleus accumbens (Fig. 104.5). Also see to page 1047.
2. Catecholamines and enkephalins are also involved in pathways responsible for learning (page 1037). This implies, rewards and punishment are believed to constitute the incentives for learning.

B. Drugs that block postsynaptic D_3 *dopaminergic receptors* such as chlorpromazine hydrochloride (largectil), an antipsychotic agent, lower activity in the catecholamine pathways and *decrease self stimulation*. The main site of action is in the *nucleus accumbens*.

SEXUAL BEHAVIOUR

Coitus or the sexual intercourse is a complex phenomenon which involves series of reflexes integrated in many parts of the nervous system (page 810). Neocortex, limbic system and hypothalamus play an important role in determining sexual behaviour in an individual. This is based on certain experimental findings in animals, mainly the cats and monkeys. The extent to which these findings are applicable to humans is, of course, difficult to determine.

A. ROLE OF LIMBIC CORTEX

1. Partial removal of neocortex and limbic system inhibits the sexual behaviour. This is more evident after the removal of the frontal lobes.
2. Bilateral destruction of *amygdaloid nuclei* results in hypersexuality in male animals. This is true in men also.

B. ROLE OF HYPOTHALAMUS

1. Stimulation along *medial forebrain bundle* in neighbourhood of hypothalamus causes penile erection with marked sexual excitement reactions in males.
2. Destruction of *anterior hypothalamus* abolishes interest in sex. (Supraoptic area)

C. EFFECT OF HORMONES

Implantation of small amounts of sex hormones (testosterone in males and oestrogen in females) in anterior hypothalamus in rats with gonads removed restores the complete pattern of sexual behaviour. This shows that some part of the hypothalamus is stimulated by circulating sex hormones to initiate sex drive.

Note

In women, sexual activity occurs throughout the menstrual cycle, but there is more spontaneous *female initiated* sexual activity at about the time of ovulation. Also refer to page 1058.

Nucleus accumbens
• Controls reward & Punishment center
Post. hypoth. (Lateral part)
Lat. hypoth.
Septum
Tegmentum
Dorsal area of pons

Study Questions

1. List the components of limbic system and give its major connections.
2. Enumerate the functions of limbic system. Why cannot the emotional behaviour be turned 'on' and 'off' at will?
3. Define emotional state. Describe briefly the mental and physical changes associated with it.
4. What is Papez circuit? Give its physiological significance.
5. Give the body's natural protective response to threat in the environment.
6. Define and give physiological significance of:
   (i) Fear, rage, placidity and sham rage
   (ii) Emotion and motivation.
   (iii) Habit forming substances
   (iv) Sexual behaviour
7. How is normal emotional state adjusted in an individual?
8. Explain the concept of reward and punishment with suitable examples.
9. Name the areas in the brain whose stimulation produces a sensation of pleasure.
10. Which will produce a potent motivation for learning, stimulation of reward or punishment system?
11. Give the role of different neurotransmitters that mediate reward system in the brain.
12. Explain how habit forming substances can produce addictive behaviour in an individual.
13. Differentiate between:
    (i) punishment and reward
    (ii) rage and sham rage
    (iii) fear and rage.

← Flaccidity (HYPO tonia)

MCQs

1. *Not* a function of limbic system:
   (a) Control of autonomic functions
   (b) Concerned with olfaction and memory
   (c) Plays important role in emotions of rage and fear
   (d) Control intellectual activities

2. *Not* a correctly defined term accompanying mental changes of emotions:
   (a) Cognition: awareness of sensation and its cause
   (b) Affect: feeling
   (c) Conation: urge to take action
   (d) Tremors: involuntary muscle movements (rhythmic regular)

3. Sham rage is produced when:
   (a) Section is made at L_2 vertebrae
   (b) Pons is removed
   (c) Medulla is removed
   (d) All the cortex is removed from the brain

4. Rage responses to minor stimuli are observed often after all of the following *except*:
   (a) Androgen administration
   (b) Removal of neocortex
   (c) Destruction of septal nuclei
   (d) Bilateral amygdaloid destruction (Placidity) (Calmness)

5. *Not* a feature of brain reward (approach) system:
   (a) A potent motivation for learning than the punishment
   (b) Catecholamines are major neurotransmitter involved in the pathway
   (c) Nicotine and alcohol stimulate this system
   (d) Antipsychotic agents inhibit its pathway

6. Sexual behaviour of a person is dependent upon:
   (a) Thalamus
   (b) Hypothalamus
   (c) Frontal lobe
   (d) Temporal lobe

7. *Not* a feature of limbic cortex:
   (a) Phylogenetically the oldest part of cerebral cortex
   (b) Made up of allocortex
   (c) Its actual extent has increased enormously as humans have evolved
   (d) Arranged in a form of a ring around the brain stem.

8. *Not* a mental component of emotion:
   (a) Cognition
   (b) Affect
   (c) Conation
   (d) Muscular tremors

9. The brain area *not* directly concerned with emotional expression:
   (a) Limbic system
   (b) Hypothalamus
   (c) Thalamus (Papez circle)
   (d) Brainstem

10. The rage reaction, *not true* is:
    (a) Also called fighting reaction
    (b) Also called attacking reaction
    (c) In animals is associated with pilo-erection, hissing, biting, etc.
    (d) Minor irritations are usually ignored

11. Which of the following role is not played by the cerebral cortex in genesis of emotions?
    (a) Detailed processing the conscious experience of emotional feeling
    (b) Direct the motor responses to external event
    (c) Modulation of emotional behaviour
    (d) Integrates endocrine, autonomic and motor activities

12. Sex behaviour in an individual is determined by:
    (a) Neocortex
    (b) Limbic system
    (c) Hypothalamus
    (d) Coordinated activity of all of the above

Answers

1. (d) 2. (d) 3. (d) 4. (d) 5. (b) 6. (b) 7. (c) 8. (d) 9. (d) 10. (d) 11. (d) 12. (d)

Grading of Reflexes
0 → Absent
1 → Present (as Normal ankle jerk)
2 → As knee jerk reflex (Brisk)
3 → Very brisk
4 → Clonus

Grading of m power (str.)
0 → No active movem.
1 → Flicker movem.
2 → without grav. (Horiz. movem)
3 → against grav. But NOT examiner resistance
4 → ✓✓ But, NOT fully
5 → Normal

Chapter 105

Higher Functions of the Nervous System

- I. Language (Speech)
  - Dominant versus representational hemisphere
  - Speech centers, speech pathways
  - Speech disorders: Aphasia
- II. Learning: Conditioned reflexes
- III. Memory: Alzheimer's disease and senile dementia

The most important feature of the human brain is the immense growth of the *Neocortex* with the evolution, resulting in greater development of its four major lobes as compared to other animals (page 1014). Consequently, the *human is regarded as the highest intellectual animal*. The higher functions of the nervous system thus include the major functions sof its four lobes as summarised under (For details see chapters 103 and 104):

1. *Control of higher intellectual activities* such as: emotional affects, motivation, behaviour and social consciousness, personality, thinking, reasoning, moral sense etc.
2. *Control of sensory* (general and special) and *motor functions*.
3. *Control of autonomic functions*; and
4. *Control of language (speech), learning* and *memory*.

This chapter is the review of the higher functions of the nervous system that include: *language (speech)* and other intellectual functions like *learning*, *memory* and *judgement*.

LANGUAGE (SPEECH)

INTRODUCTION

To understand the spoken and printed words and to express ideas in speech and writing is called *Language*. It is an example of *skilled voluntary movements*.

1. In general, higher functions of the nervous system in humans depend more on one cerebral hemisphere than on the other. This hemisphere is concerned with categorization and symbolization and has often been called the *Dominant* or *Categorical Hemisphere*. However, other hemisphere is specialized in the area of *spatio-temporal* relations (page 1017) called the *Representational Hemisphere*. The main characteristic features of these two cerebral hemispheres are summarized in **Table 105.1**.
2. Hemispheric specialization is related to *handedness*, which appears to be genetically determined. In right handed individuals, who constitute about 90% of the human population, the left hemisphere is the *dominant* or *categorical hemisphere*. In about 30% of left-handed

Table 105.1: Main differences between categorical and representational hemisphere

Categorical Hemisphere (Dominant)	Representational Hemisphere
1. It is specialized with *categorization* and symbolization, i.e. for higher functions of the nervous system and sequential-analysis processes.	1. It is specialized in the area of *spatio-temporal relations* such as with the recognition of faces, identification of objects by their form and recognition of musical themes etc.
2. Its *disorder or lesion* produces: (i) Language disorders. (ii) Patients are disturbed about their disability and often depressed. (iii) If the lesion is in the temporal lobe it results in loss of recent verbal memory.	2. Its *disorder or lesion* produces: (i) *Astereognosis* (page 901). (ii) *Agnosia*, *i.e.* inability to recognise objects by a particular sensory modality even though the sensory modality itself is intact. (This is generally seen with parietal lobe lesion.) (iii) Patients are unconcerned of their disability, cheerful and have trouble recognizing emotions in other individuals. (iv) If the lesion is in the temporal lobe, it results in loss of recent memory for visual and spatial materials.

individuals, the right hemisphere is the *categorical* hemisphere; however, in the remaining 70% left hemisphere is the *categorical* hemisphere.

3. Children vary greatly in the rate and manner of acquiring speech. For example:

0-3 months	: Cries usually express hunger or discomfort.
By 3 months	: Child acquires several *vowels* and has learned to smile.
By 6 months	: He can vocalise *consonants* and he is learning how to laugh.
By 9-10 months	: He speaks first word usually Dada or Mama.
By 1 year	: He has acquired another word, e.g. Ta.
By $1^1/_2$ year	: The vocabulary is about 12 words.
In 2nd year	: He often uses one-word sentences e.g. 'up' meaning 'lift me up'.
At the end of 2nd year	: Two word phrases are uttered.

From 2 years onwards the vocabulary increases rapidly.

THE ORGANS OF SPEECH

1. Normally speech is *produced on expiration* by movement of *vocal cords* (vocal folds) but an abnormal type of speech can be produced on inspiration.
2. The vocal cords stretch from the thyroid cartilage (anteriorly) to the mobile arytenoid cartilage (posteriorly) at the back of the larynx. The triangular space between them is called the *Glottis* or *Rima Glottidis* (Fig. 105.1).
3. The muscles controlling the arytenoids determine opening and closing of the glottis; while the tension of the vocal cords is regulated (i) by the *vocalis* muscle (lying in each fold); and (ii) by the *cricothyroid* muscle, which tilts the thyroid cartilage and so elongates the vocal cords.
4. In quiet breathing (resting position), the vocal cords are midway between full adduction and full abduction. During vigorous breathing the folds open farther in inspiration.
5. *During phonation* i.e. when the subject is asked to say *ah* or *ee* the cords approximate. The frequency of a *note* can be regulated by the tension in the vocal cords. If the tension increases, the frequency rises and there may be considerable increase, upto 50%, in the length of the vocal cords.
6. In *whispering* the anterior 2/3rd of the vocal cords are approximated and free escape of air occurs posteriorly in the space between the two arytenoid cartilages.
7. The sound produced in the larynx is greatly modified by:
   (i) The ***tongue***, by alterations in its shape and position. It has the main control over the resonant characteristics of the oral cavity.
   (ii) The positions of the ***lips*** and ***jaws***.
   (iii) The *vowel sounds* are produced by vibrations of the vocal cords (i.e. vowel are *voiced*) and the air stream passing freely through the mouth.
   (iv) In the production of a *consonant* the air stream is partially or completely obstructed so that it cannot pass freely from the mouth. The larynx does not appear to be involved in the production of many consonants, i.e. the majority are *unvoiced*.

Important Notes

1. For natural and normal speech, the larynx produces the sound and determines the fundamental *pitch* of the voice.
2. The variable resonances of the mouth determine the *quality* of the sound that conveys the information from speaker to listener. This is shown by the fact that the intelligibility of words is only slightly affected by singing them at different pitches.

8. *Applied Aspect*
   (i) *Unilateral section of recurrent laryngeal* nerve (it supplies all intrinsic muscles of larynx except cricothyroid muscle which is supplied by external laryngeal nerve) produces:
      (a) Vocal cords on the denervated side lie in or close to the midline. The cricothyroid muscle (which is not paralysed) stretches the paralysed vocal cords by tilting the thyroid cartilage.

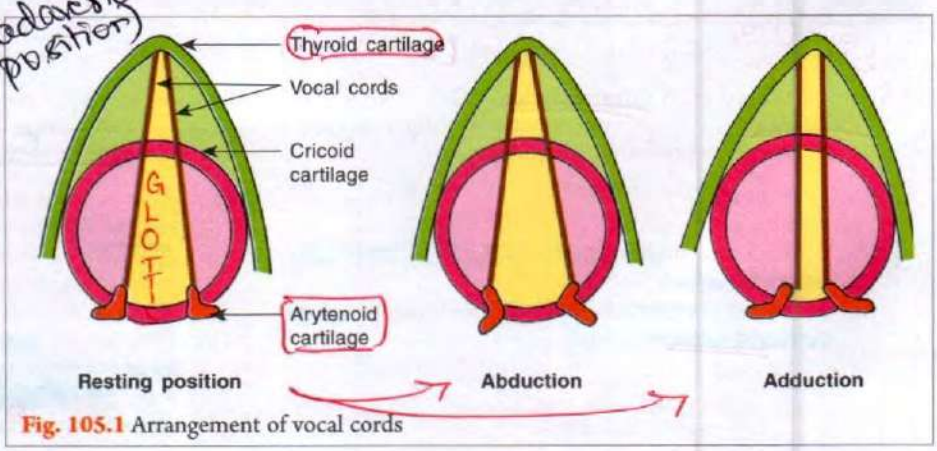


Fig. 105.1 Arrangement of vocal cords

(b) Full adduction or overadduction of the opposite vocal folds brings the folds together and in many cases speech is normal.

(ii) *In bilateral recurrent nerve paralysis* the folds lie motionless near the midline, producing ***hoarseness of voice.***

(iii) *Bilateral division of superior laryngeal nerves* (which is sensory to the upper larynx) produces anaesthesia in the upper part of the larynx and voice becomes *hoarse* because the vocal cords cannot be made tense.

TYPES OF SPEECH AND SENSORY SPEECH CENTERS

Two major types of speech are recognized:

1. Spoken speech, and 2. Written speech

Spoken speech

This means understanding the spoken words and expressing *ideas* in speech.

Mechanism

1. First, we must be able to hear sounds. This process requires an intact auditory pathway from the *ears* to the *primary auditory centers*, area 41 (page 1071).
2. Second, we must be able to understand them. This process is related to the activity of the adjacent *auditory-psychic areas* (area 20, 21).
3. Third, we must be able to express the ideas in speech. This process involves the activity of *auditory speech center*, called ***Wernicke's area*** (area 22) **(Fig. 105.2)**.

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.

Written speech

This means understanding written words and expressing the *ideas* in writing.

Mechanism

1. First, we must be able to see the words. This process requires an intact visual pathway from the *eyes* to the *primary visual cortex* (area 17) (page 1131).
2. Second, written symbols must be correctly interpreted. This process is related to the activity of *visuo-psychic areas* (area 18, 19).
3. Third, we must be able to express the *ideas* in writing. This 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)*.

Note

Wernicke's and Dejerine areas are together called the *Sensory Speech Centers*.

MECHANISM OF EXPRESSION OF SPEECH: SPEECH PATHWAYS

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 pre-frontal lobe in the dominant (categorical) hemisphere in the neighbourhood of higher centres for voluntary movements **(Fig. 105.2)**.

Motor Speech Centers include *Broca's and Exner's areas*:

1. ***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 Wernicke's area into a detailed and coordinated pattern for vocalization. This pattern is then projected to the *motor cortex* which initiates the appropriate movements of the lips, tongue and larynx to produce speech.

2. ***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

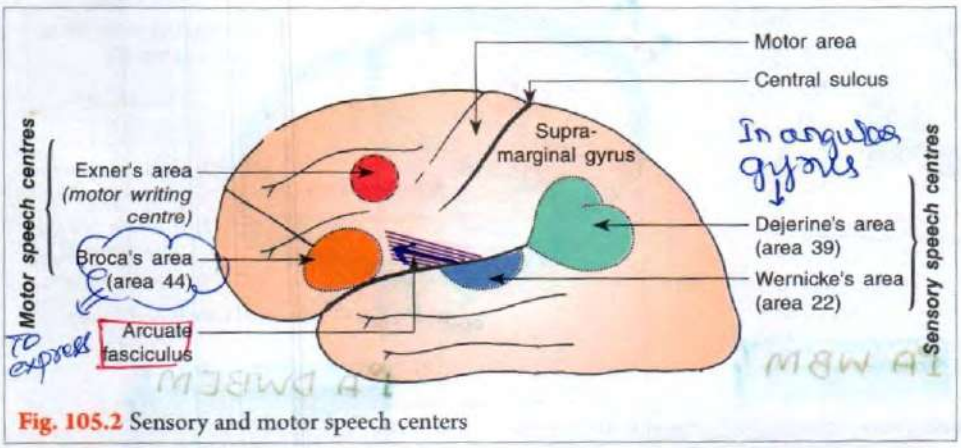


Fig. 105.2 Sensory and motor speech centers

appropriate movements of the hands and fingers to produce written speech.

***Expression of spoken speech* (Fig. 105.3 A)**

Suppose, person 'A' says *cat*, and person 'B' says *where*, then sequence of events in person 'B' will be as follows:

1. Person 'B' hears the word cat, highest area for hearing is in gyrus of Heschl *(area 41)*, i.e. in superior temporal gyrus.
2. From area 41, information goes to the *Wernicke's area* (area 22), which interprets and understands the word *cat* fully.
3. The Wernicke's area sends information via ***arcuate fasciculus*** to the *Broca's area* (area 44), where detailed and coordinated pattern for vocalization occurs.
4. The Broca's area ultimately sends information to *motor area* (area 4), which causes movements of appropriate muscles of the lip, tongue and larynx to produce the word *where* and person utters *where*.

***Expression of both spoken and written speech* (Fig. 105.3-B)**

Suppose somebody is reading a book aloud and then wishes to write what he has read, the sequence will be as follows:

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 understood words are converted into *internal speech* by the *Dejerine area* (in angular gyrus).
4. The *Wernicke's area* (area 22) then interprets and understands the internal speech. This, in turn, sends the information to the Broca's area for pattern coordination.
5. The *Broca's area* (area 44) sends detailed pattern coordination information to:
   (i) *Motor area* (area 4) for the spoken speech; and
   (ii) to the *Exner's area* for the written speech *(motor writing centre)*, the Exner's area along with motor area (area 4) initiates appropriate muscle movements of hand and fingers to produce written speech.

APPLIED ASPECT

General

As speech is dependent on visual, auditory and proprioceptive impulses, the speech area must be in the closed functional and anatomical connections with those regions of the cortex which primarily receive these impulses. The principal cortical receptive sites of the speech areas are:

(i) The temporal lobe
(ii) The parts of the parietal lobe including the *supramarginal* and angular gyri
(iii) The island of Reil
(iv) The part of the prefrontal lobe.

Whole of this large area is correlated with the highest intellectual activities, therefore, injury to this region not only depresses the speech but also other intellectual activities.

SPEECH DISORDERS

Aphasias. This means abnormalities of language (speech) functions that are not due to defects of vision or hearing or motor paralysis. It can be grouped under 3 heads: *sensory, motor* and *global aphasia.*

A. ***Sensory Aphasia*** or ***Fluent Aphasia.*** The condition is produced due to *lesion in the Wernicke's area* (sensory speech center).

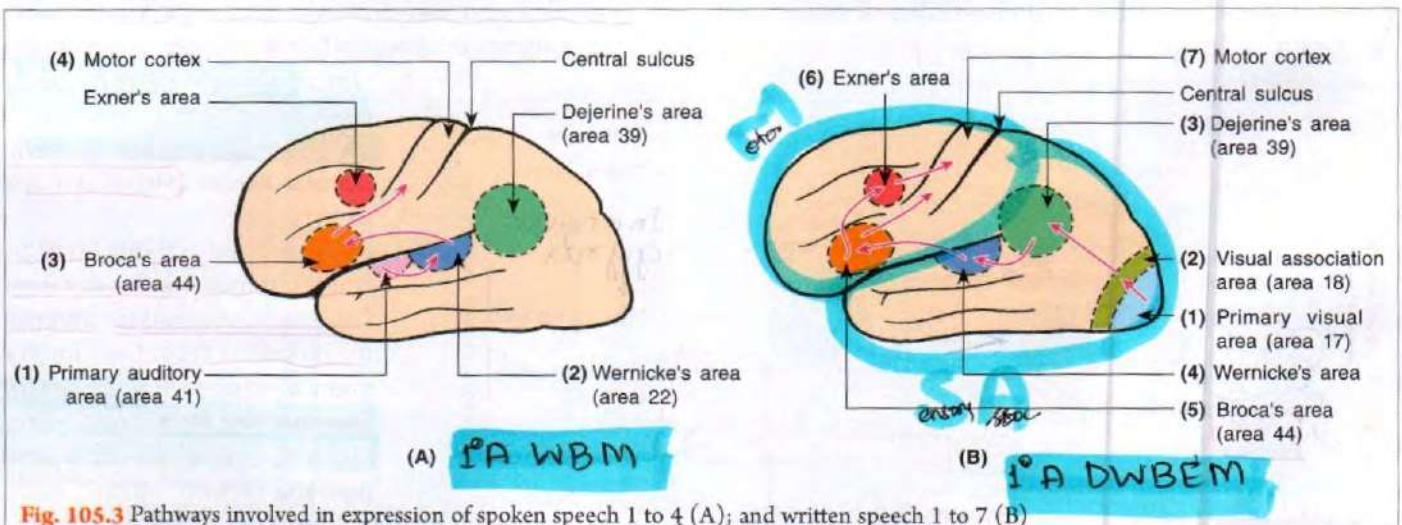


Fig. 105.3 Pathways involved in expression of spoken speech 1 to 4 (A); and written speech 1 to 7 (B)

Characteristic features

1. In general, speech is not disturbed but sometimes the patient *talks excessively* which makes little sense.
2. Patient *fails to understand the meaning of spoken or written words*, therefore, other aspects of the use of language are also compromised.

Important Notes

1. Lesion in the *Dejerine area* produces ***Pure word blindness (alexia/dyslexia)*** or ***anomic aphasia.*** There is inability to understand the written words which appear as *Hieroglyphics* (written in sacred symbol). The patient is unable to read aloud or copy print into writing.
2. Lesion in and around the auditory cortex, areas 40.41 and 42 produces ***conduction aphasia,*** a form of *fluent aphasia* in which person can speak relatively well but cannot put parts of words together.

B. ***Motor Aphasia*** or ***Non-Fluent Aphasia.*** It is seen due to ***lesion in the Broca's area*** (motor speech center).

Characteristic features

1. Loss of articulate speech or *inability to write* (*Agraphia*) or both without mental confusion or deterioration.
2. The patient is dumb, though the motor cortex and its efferent paths are intact.
3. The speech is slow and words are hard to come by and are *limited to 2 or 3 words* with which patient expresses the range of meaning and emotion.
4. The patient frequently uses ***automatic words,*** such as days of week.

C. ***Global Aphasia.*** This condition is produced as a result of loss of both Wernicke's and Broca's area. As a result all the functions of speech are involved.

Dysarthria (less common). In this condition there is difficulty in spoken speech *(imperfect vocalization).* Since muscles for expressing the speech cannot be used effectively, the main defect lies in the motor areas (area 4, 6 and 8) and their connections.

LEARNING: CONDITIONED REFLEXES

The ability to alter behaviour on the basis of experience is called *learning.*

Conditioned reflexes are an important type of learning. Two separate classes of reflexes are described by *Pavlov. I.P.* (1927) (of Russia): *inborn and acquired.*

The Inborn or Unconditioned Reflex. This reflex is present in all normal individuals, such as superficial, deep (or tendon) and organic reflexes.

Examples:

(i) *Superficial reflexes:* plantar and abdominal reflex (page 912),

(ii) *Deep (or tendon) reflexes:* knee and biceps jerk (page 904), and

(iii) *Organic reflexes:* deglutition (swallowing), defecation, sucking, grasping and micturition reflex.

The Acquired or Conditioned Reflex

Features

1. It is a *reflex response* to a stimulus that did not previously produce the response; however, it can be developed (acquired) by repeatedly pairing the stimulus with another stimulus that normally does produce the response.
2. It is, therefore, *peculiar* to the individual and refers to the fact that certain conditions must be present if this class of response is to develop.
3. It depends for its appearance on the formation of new functional connections in the CNS.

Example: **Pavlov's classical dog experiment (Fig. 105.4).**

(i) The introduction of food (***unconditioned stimulus***) into the mouth sets up *reflex* salivation in a dog. This is called ***unconditioned reflex.***

(ii) Application of a *neutral* stimulus like ringing of a bell alone produces *no* salivation.

(iii) Application of ringing of a bell just before the unconditioned stimulus (the taking of food) produces salivation. If this procedure is repeated several times, the ringing of a bell alone produces salivation. Therefore, the *initial* neutral stimulus finally develops (acquires) fresh properties i.e. new connections in the CNS and can now by itself produce salivation.

In this example, the flow of saliva in response to ringing of the bell (***conditioned stimulus***) is referred to as ***conditioned reflex.***

Mechanism of Development of Conditioned Reflex

The conditioned reflexes are always built up primarily on the basis of *inborn reflexes.* Habituation and sensitization (page 860) are simple form of learning in which the organism learns about a single stimulus. A classic example of such type of learning is a conditioned reflex. In more complex form of learning, the organism learns about the relation of one stimulus to another by means of 'synaptic plasticity' in the brain (page 860).

Factors which influence conditioned reflex to develop are:

1. The animal must be alert and in good health.
2. For conditioning to occur, the *conditioned stimulus (CS)* must begin to operate before the *unconditioned*

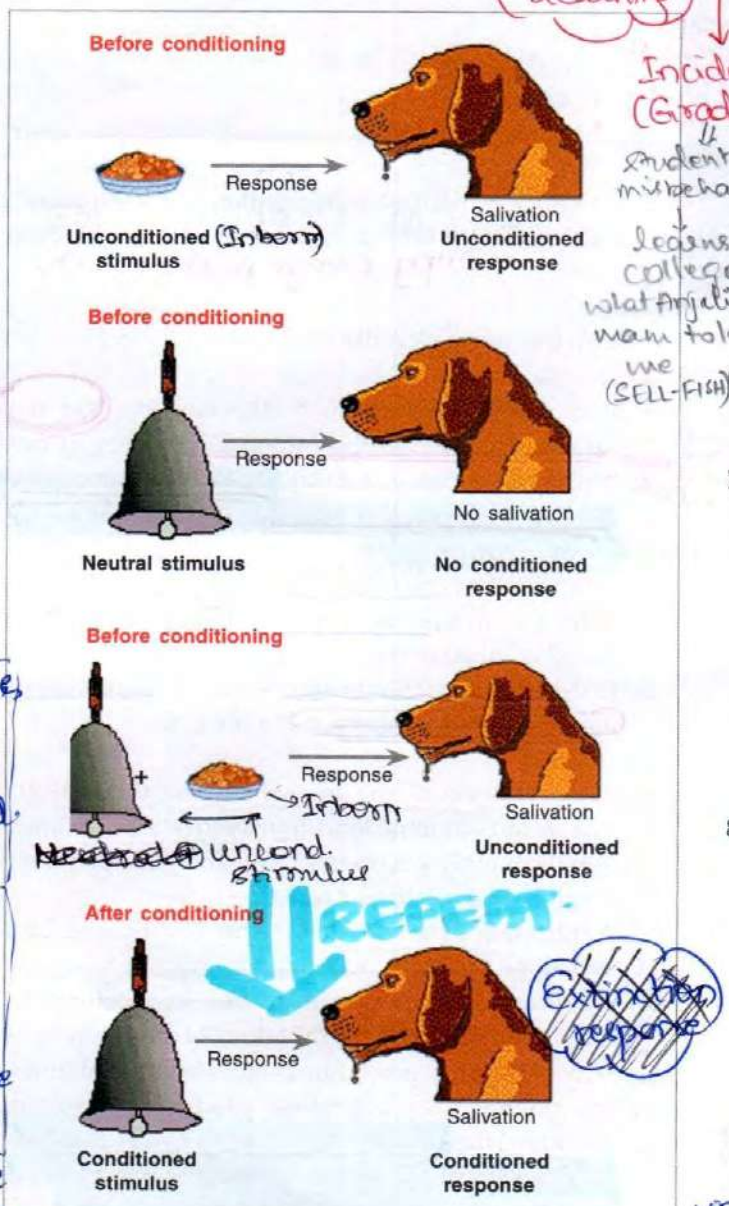


Fig. 105.4 Pavlov's classical dog experiment

stimulus (US) is applied. If the *CS* follows the *US*, no conditioned response develops.

3. The *CS* must be allowed to continue to act so as to overlap the *US*. Almost any stimulus, if suitably employed, may become a *CS*.
4. The conditioned response follows *CS* by the time the interval that separated the CS and US during traininig. The delay between stimulus and response may be as long as 90 secs. When the time interval is more than 90 secs, the response is called as ***Delayed Conditioned Reflex***.
5. *Necessity for Reinforcement*

For a *CS* to retain its new properties, it is essential that it should always be followed by the *US*. Therefore,

(i) If the *CS* is carried out several times alone and is not followed by *US*, it soon ceases to elicit the response. This phenomenon is known as ***Extinction*** or ***Internal Inhibition***.

(ii) If the animal is disturbed by an external stimulus immediately after the *CS* is applied, the conditioned response may not occur. This is called ***External Inhibition***.

Thus the process of following up a *CS* with the basic *US* is termed ***reinforcement***.

6. Conditioned reflexes are difficult to form if the *US* proves *a pure motor response*; since the motor responses are also under voluntary control.
7. Conditioned reflexes are relatively easily formed if the US is associated with a pleasant or unpleasant effect. Here a repeated stimulus produces a greater response, a form of sensitization (page 860). For example,
   (i) Stimulation of the brain reward system is a powerful *US;* this is called ***Pleasant*** or ***positive reinforcement;*** and
   (ii) Stimulation of the avoiding system or a painful shock to the skin is called ***unpleasant*** or ***negative reinforcement***.
8. *Operant Conditioning. Operant* means to operate on the environment. This is a form of conditioning in which a naturally occuring response is strengthened by positive reinforcement (*reward*) or weakened by negative reinforcement (*punishment*). This is a classical example of simple form of learning based on phenomenon of *sensitization* and *habituation* (page 860). Experimentally, the animal is taught to perform some task in order to obtain a reward or avoid punishment. The *US* is the pleasant or unpleasant event, and the *CS* is a light or any signal that alerts the animal to perform the task.

Conditioned motor responses that permit an animal to avoid an unpleasant event are called ***Conditioned Avoidance Reflexes.*** For example, an animal is taught that by pressing a bar it can prevent an electric shock to the feet. Reflexes of this type are used mainly in testing tranquilizers and other drugs that affect behaviour.

Important Note

An alcoholic can be made to develop a strong aversion to alcohol if it is coupled to a drug that produces severe nausea or illness (***Food Aversion Conditioning***).

9. ***Discriminate Conditioning.*** When a conditioned reflex is first established, it can be produced not only by the *CS* but also by similar stimuli. However, if only one particular CS is reinforced and the similar stimuli are

not, the animal can be taught to discriminate between different signals with great accuracy. This phenomenon is called *Discriminate Conditioning*.

Biochemical Basis of Conditioned Reflex

The biochemical events involved in synaptic plasticity (habituation, sensitization, post-tetanic potentiation and long-term potentiation) are described on page 860.

In conditioned reflex, the unconditioned stimulus (US) acts presynaptically on the endings of neurons activated by the conditioned stimulus (CS). This leaves free Ca^{2+} in the cell resulting in long-term change in the adenylate cyclase molecule, therefore, when this enzyme is activated by the CS, more cAMP is produced. This in turn closes K^+ channels and prolongs action potentials.

Physiological Basis of Conditioned Reflexes

One of the essential features of a conditioned reflex is the formation of a new functional connection in the nervous system. This may be caused by specific *nerve growth factors* released from the stimulated cells. For example, in *Pavlov classical experiments*, salivation in response to a bell ringing indicates that a functional connection has developed between the auditory pathways and the autonomic centers controlling salivation (a process called *Neurogenesis*).

Site of formation of functional connections

The site of formation of new connection in the nervous system occurs at two levels:

1. intracortical level (mainly), and
2. subcortical level.

Evidences

(i) Conditioned reflexes can be built up with difficulty in decorticate animals.

(ii) When the *CS* is a complex sensory stimulus, the cortical sensory area for the sensory modality involved must be present.

(iii) Non-discriminative conditioned reflexes to simple sensory stimuli can be formed in the absence of the whole neocortex. This indicates that new functional connections can be formed at sub-cortical levels.

Important Note

The phenomenon resembling learning occurs at subcortical and spinal levels (synaptic plasticity - page 859); whereas more advanced type of learning, such as discriminating conditioning, are largely cortical phenomenon.

Clinical significance

1. By means of discriminative conditioning, dogs can be taught to distinguish between different pitches of sounds, different colours, smells and other sensory modalities.
2. A large number of somatic, visceral and other neural changes can be made to occur as conditioned reflex responses. The conditioning of visceral responses is called ***Biofeedback***. The changes that can be produced include alteration in bowel movements, heart rate and blood pressure. Conditioned decrease in BP has been used for the treatment of hypertension.
3. The words like *Hare Rama* are associated with mental calmness, bliss and purity and so the emotions disappear. *Hare*, i.e. Haran means removal of grief; *Rama* i.e. attraction. (He also removes grief, is supreme attractor, the god.) Therefore, the words *Hare Rama* are the *CS* for control of rage (page 1036) (which is normally not easy to control).

Intercortical Transfer of Learning

1. If animals (cats/monkeys) are conditioned to respond to a visual stimulus with one eye covered and then tested with the blind fold transferred to the other eye, it performs the conditioned response. This is true even if the optic chiasma has been cut, making the visual input from each eye to go only to the ipsilateral cortex. However, if in addition, anterior and posterior commissures and corpus callosum are sectioned *(Split Brain Animal)*, no transfer of learning occurs. This demonstrates that the neural coding necessary for learning and memory has been transferred somehow to the opposite cortex via the commissures.
2. Similar results are seen in humans in whom either corpus callosum is congenitally absent or it has been sectioned surgically to control epileptic seizures (fits).

(Also refer to page 894 for *cortical plasticity*)

MEMORY

Memory is the ability to recall past events at the conscious or unconscious level. It is the relatively permanent retention and storage form of the learned information.

Forms of Memory

Memory is divided into: **Declarative** (or **Explicit memory**) and **non-declarative** (or **implicit/reflexive memory**). The major differences between the two are given in **Table 105.2.**

Types of Declarative Memory

Depending on how long a conscious memory lasts, it is divided broadly into two major types: *recent and remote memory.*

Table 105.2: Differences between two major forms of memory

Declarative (explicit) memory	Non-declarative (implicit) memory
1. It is for the real knowledge about people, place and things.	1. It is important for training reflexive motor or perceptual skills.
2. **Types:** (i) **Semantic memory** for facts (e.g. words, rules and languages) (ii) **Episodic memory** for events	2. **Types:** (i) **Procedural memory** for skills and habits (ii) **Priming memory:** for recognition of words or objects
3. It is associated with consciousness of awareness	3. It does not involve consciousness/awareness and is largely unconscious (reflexive)
4. It is dependent on the hippocampus and parts of the medial temporal lobes of the brain for its retention.	4. It does not involve processing in the hippocampus.

Note

Declarative (explicit) memories that are initially required for learning activities can become non-declarative (implicit) memories once the task is thoroughly learnt.

1. ***Recent or short-term memory:*** It involves mechanisms mediating *immediate* recall of events that occurred seconds to hours before. It is lost in individuals with certain neurological disorders.

Note

When it occurs for very short periods it is named ***Working memory.*** For example, to look up a telephone number before dialing.

2. ***Remote or long-term memory:*** It involves mechanism mediating memory of the *remote* (distant) past. It is remarkably resistant and persists in the presence of severe brain damage.

Note

Factors influencing conditioned reflexes based learning is a classical example of non-declarative memory (page 1035).

Physiology of Memory

It is based on certain *clinical and experimental* observations.

Example 1. Stimulation of certain portions of the ***temporal lobe*** produces detailed memories of events that occurred in remote past, often beyond the power of voluntary recall. A particular memory is generally produced by stimulation of a definite area. It unfolds as long as the stimulus is applied and stops when the stimulus is discontinued.

However, these areas in the temporal lobe have not been proven, since stimulation of temporal lobe or patients with temporal lobe disorders generally manifest with epilepsy.

Thus it seems unlikely that the memories themselves are localized in the temporal lobes. Instead, the *temporal lobe points* are probably ***keys*** that unlock memory traces stored elsewhere in the brain and the brain stem. Normally, a key is turned by some sort of comparing, associating circuit when there is a similarity between the memory and the current sensory input or a stream of thought. It is a common experience, the memory of an *intense* scene can be produced not only by a similar scene but also by a sound or smell associated with the scene. (***deja Vu phenomenon***), the French words means *already seen.*

Example 2. There is frequently a loss of memory for the events immediately before brain concussion or electroshock therapy. This phenomenon is termed as ***Retrograde Amnesia,*** which persists from few hours to even years, but remote memory is not affected. (*Concussion* means transient loss of consciousness resulting from a head injury.)

Example 3. In animals, acquisition (gaining and restoration) of learned responses is prevented if within 5 minutes after each training session, the animals:

(i) are anaesthetized,
(ii) given electroshock treatment,
(iii) subjected to hypothermia, or
(iv) treated with antibiotics that inhibit protein synthesis.

Such a treatment 4 hours after the training session has no effect on the memory acquisition.

This shows that there is a period of ***encoding*** or ***consolidation*** of memory during which the *memory trace*

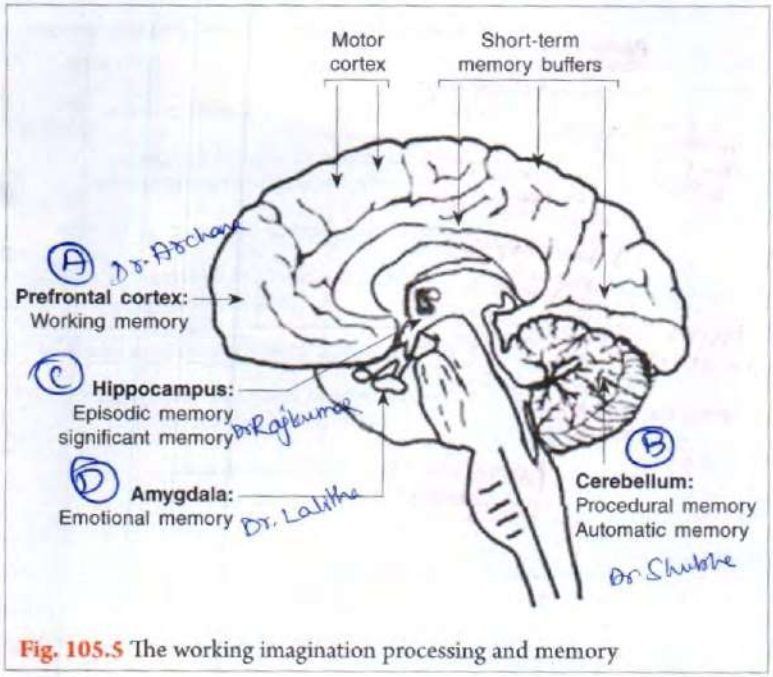


Fig. 105.5 The working imagination processing and memory

is liable to injury. Following this period, a stable and remarkably resistant memory develops.

Note

Biochemical events involved in memory are the same as already have been decribed for learning, page 1036.

The working imagination processing and memory refer to **Fig. 105.5**.

Mechanism of declarative memory encoding

There is considerable evidence that the encoding process involves the *hippocampus* (and its connections) and the neighbouring cortex viz. entorhinal, perirhinal and parahippocampal areas. These connections contain cell bodies and fibers of the *cholinergic system*. However, glutamic acid also play an important role (page 1048).

Proof

1. *Bilateral destruction of the ventral hippocampus* in humans or animals that destroys cholinergic neurons produces striking *defects in recent memory* with intact remote memory. In addition, they cannot form new long-term memories.
2. Stimulation of hippocampus with chronically implanted electrodes in humans which produce seizures is often associated with loss of recent memory.
3. Chronic alcoholics with brain damage develop considerable impairment of recent memory, which correlates well with the presence of pathologic changes in the mammillary bodies, a major site of projection for hippocampal fiber (page 1018).

Important Note

Several drugs that impair memory or alter recent memory produce abnormal discharges in the hippocampus.

Protein Synthesis and Memory

Nature of *stable memory* is unknown, but its resistance to electroshock and concussion suggests that memory might be stored as a biochemical change in the neurons. There is evidence that protein synthesis and activation of genes is involved in some way in the processes responsible for memory.

Evidences

1. In rats, *increased RNA synthesis* occurs in nerve cells subjected to intense stimulation.
2. In experimental animals, administration of drugs which inhibit protein synthesis, such as puromycin, acetoxycycloheximide etc. disrupts recent memory.
3. The ability of *regenerated planarians* to retain learned habits. Planarian are flat worms with rudimentary nervous system and a remarkable ability to regenerate when cut into pieces. They can be taught to avoid certain visual stimuli. If a trained worm is divided into two, not only does the worm regenerated from the head piece retains the response but from the tail also. The response does not persist in the regenerated worm if the worm is exposed to ribonuclease, an enzyme that destroys RNA.

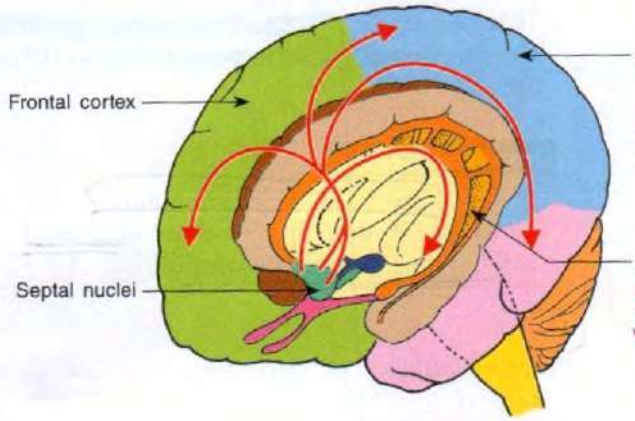
Mechanism

Discharge of neuron during learning session could lead to changes which increase mRNA synthesis and hence increase synthesis of particular proteins. These proteins could *modify synaptic transmission* by affecting:

(i) transmitter synthesis
(ii) membrane permeability, or
(iii) some other neural processes.

Drugs That Facilitate Memory

Various CNS stimulants can improve learning in animals when administered immediately before or after the learning sessions. These agents act probably by facilitating consolidation of ***memory trace***. The molecular or cellular



The sequence of events in the affected neurons

Mutation of amyloid precursor protein gene
↓
Aggregation of β-amyloid peptides
↓
Formation of extracellular plaques
(***Senile plaques: toxic polypeptide***)
↓
Inflammatory reaction with oxidative damage
↓
Altered nerve fibers and reactive glial cells (Gliosis)
↓
Formation of intracellular ***neurofibrillary tangles***
↓
Degeneration of *cholinergic neurons* in the cerebral cortex and hippocampus
↓
Alzheimer's disease

(B)

Fig. 105.6 The major cholinergic pathways involved (A) and pathogenesis (B) in Alzheimer's disease

change that takes place somewhere along the neural pathways is called the memory trace. The agents that facilitate memory include:

(i) Caffeine.
(ii) Physostigmine. It inhibits acetyl-cholinesterase and hence breakdown of A-ch.
(iii) Amphetamine.
(iv) Nicotine. It stimulates nicotinic cholinergic receptors.
(v) Pemoline (cylert). It also stimulates the RNA synthesis.
(vi) Convulsants e.g. picrotoxin, strychnine and pentylene tetrazol (Metrazol).

ALZHEIMER'S DISEASE AND SENILE DEMENTIA

Alzheimer's disease is characterized by *progressive loss of memory* and *cognitive* function (page 1025) in middle aged individuals. Thus the condition is frequently associated with:

(i) memory failure for recent events
(ii) lack of spontaneous activity and initiative with loss of intellectual functions
(iii) extrapyramidal and akinetic hypertonic symptoms (page 996)
(iv) loss of spatial orientation (page 1017).

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***.

Note

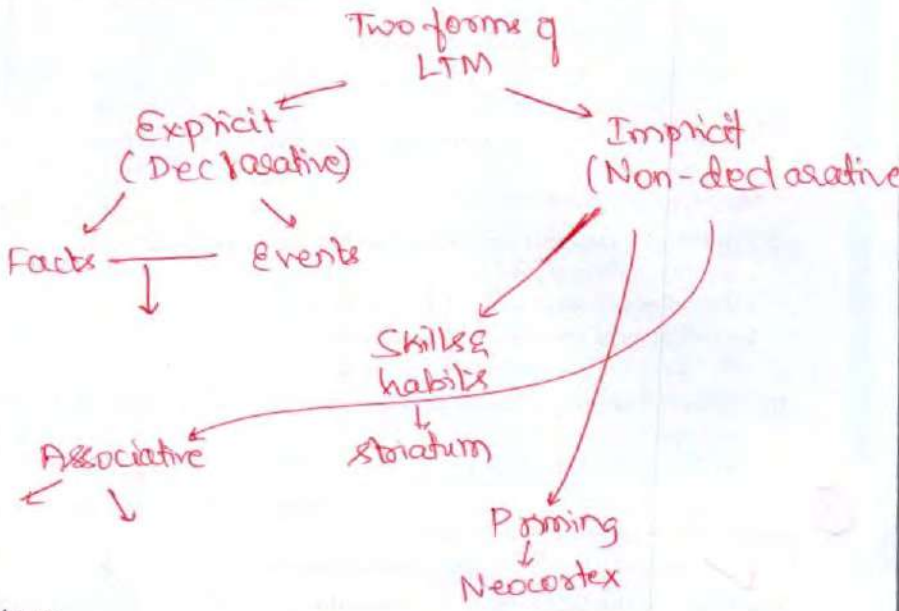
10-15% of the population over 65 years of age and 50% of population over 85 years have some degree of dementia.

Pathogenesis: Both the conditions are caused by degeneration of cholinergic nerve terminals in the cerebral cortex and hippocampus (Fig. 105.6). There is a severe *loss of cholinergic neurons* in the nuclei of septal region of the forebrain that forms a major source of cholinergic innervation of the cerebral cortex.

Study Questions

1. **Enumerate higher functions of the nervous system. Justify hemisphere specialization is related to handedness.**
2. **Justify, why are the humans regarded as the highest intelectual animals?**
3. **Define and explain giving physiological significance:**
   (i) Language (ii) Spatio-temporal relations (iii) Wernicke's area and Dejerine area
   (iv) Internal speech (v) Aphasia and Alexia (vi) Hieroglyphics and Agraphia
   (vii) Dysarthria (viii) Reinforcement (ix) Biofeedback
   (x) Retrograde amnesia (xi) Memory trace.

4. **Differentiate between:**
   (i) Dominant and representational hemisphere
   (ii) Sensory and motor aphasia
   (iii) Spoken and written speech
   (iv) Conditioned and unconditioned reflex
   (v) Internal and external inhibition
   (vi) Recent and remote memory.
5. **Write short notes on:**
   (i) Expression of spoken speech
   (ii) Expression of written speech
   (iii) Conditioned avoidance reflex
   (iv) Operant conditioning
   (v) Drug that facilitates memory
   (vi) Alzheimer's disease
   (vii) Senile dementia
   (viii) Types of speech and speech centres
   (ix) Aphasias
   (x) Conditioned reflexes



6. **Define conditioned reflex. Give its important features.**
7. **Mention the conditions essential for development of conditioned reflexes.**
8. **Give the conclusion of Pavlov's classical experiments. Give its physio-clinical significance.**
9. **Illustrate with examples the site of development of functional connections in the nervous system during the development of conditioned reflexes.**
10. **Define and give physiological significance of discriminative conditioning.**
11. **How can visceral reflexes be conditioned? Explain.**
12. **How can one control the rage reactions?**
13. **Give experimental evidences to show intercortical transfer of learning.**
14. **Explain various types of memory.**
15. **How will you justify vulnerability period during acquisition of memory?**
16. **Mention the role of protein synthesis in memory.**
17. **Depict diagramatically the pathways involved in the expression of spoken and written speech.**

MCQs

1. ***Not* a feature of categorical (or dominant) hemisphere?**
   (a) Specialized for higher functions of the nervous system
   (b) Genetically determined and related to handedness
   (c) In most individuals, left hemisphere is dominant
   (d) In its disorders, persons are unconcerned of their disability
2. **Representational hemisphere is specialized for:**
   (a) Categorization and symbolization
   (b) In the area of spatio-temporal relation
   (c) Higher functions of the nervous system
   (d) Sequential-analysis process
3. **The posterior end of superior temporal gyrus in dominant hemisphere is location of:**
   (a) Wernicke's area (b) Dajerine area (c) Broca's area (d) Exner's area
4. **The Brain area that processes the information from Broca's area into detailed and coordinated pattern to produce written speech is:**
   (a) Wernicke's area (b) Dejerine area (c) Exner's area (d) All of the above
5. **Pathway involved in expression of spoken speech:**
   (a) Primary auditory area → Wernicke's area → Broca's area → Exner's area
   (b) Primary auditory ara → Wernicke's area → Broca's area → motor area
   (c) Wernicke's area → Broca's area → Exner's area → motor area
   (d) Primary visual area → Dejerine's area → Wernicke's area → Exner's area → motor cortex
6. **Fluent aphasia is characterized by all *except*:**
   (a) Lesion in the Wernicke's area
   (b) Damage to sensory speech centre
   (c) Speech is not disturbed
   (d) Agraphia (: can perform drawings)

7. **Pure word blindness occurs in the lesion of:**
   (a) Superior temporal gyrus (b) Inferior temporal gyrus
   (c) Middle temporal gyrus (d) Angular gyrus

8. **Motor (or non-fluent) aphasia is characterized by all *except*:**
   (a) Agraphia (b) Patient uses automatic words
   (c) Patient is dumb (d) Alexia

9. **In Pavlov's classical dog experiment: *not a correct* statement:**
   (a) Introduction of food into dog's mouth: unconditioned stimulation
   (b) Reflex salivation: unconditioned reflex
   (c) Ringing of bell alone: conditioned stimulus
   (d) Flow of saliva in response to ringing of bell: conditioned reflex

10. **When an animal is taught to differentiate between different signals with great accuracy, this is called:**
    (a) Operant conditioning (b) Positive reinforcement
    (c) Negative reinforcement (d) Discriminate conditioning

11. **In a person with a history of alcohol abuse which of the following aspects of memory is most likely to be impaired?**
    (a) Accurate perception of stimuli (b) Immediate recall of new information
    (c) Recall of events occurring a few weeks earlier (d) Recall of events in the remote past

12. **Which of the following neurotransmitter deficiency is implicated in Alzheimer's dementia?**
    (a) Dopamine (b) Serotonin (c) GABA (d) Acetylcholine

13. **When a person wishes to speak a certain thought, where does the thought originate?**
    (a) In Broca's area (b) In the posterior end of superior temporal cortex
    (c) In the supramarginal gyrus (d) In the facial region of the motor cortex

14. **Broca's area of speech lies at:**
    (a) Superior frontal gyrus (b) Inferior frontal gyrus (c) Posterior frontal gyrus (d) Superior temporal gyrus

15. **Broca's area: which is *not true*?**
    (a) Present bilaterally in brain (b) Also called Brodmann's area 44
    (c) Projects the vocalization pattern to the motor cortex (d) Present in the inferior frontal gyrus

16. **Written speech means:**
    (a) Understanding written words and expressing the ideas in writing
    (b) Understanding spoken words and expressing the ideas in writing
    (c) Expressing the ideas in writing
    (d) Understanding the spoken and written words and expressing the ideas in speech and writing

17. **Aphasia refers to:**
    (a) Speech disorders
    (b) A person talking excessively which makes little sense
    (c) Abnormalities of speech functions that are not due to defects of vision or hearing or motor paralysis
    (d) None of the above

18. **Damage to Wernicke's area in the dominant hemisphere is likely to make a person unable to:**
    (a) Hear high-frequency sounds (b) Perform complex mathematical functions
    (c) Read words (d) Interpret the meaning of a sentence

19. **A person, who after a 'stroke' is able to write to his thought but is unable to express the ideas as spoken words is affected by:**
    (a) Motor aphasia (b) Sensory aphasia (c) Apraxia (d) Visual agnosia

20. **Motor aphasia results from damage to:**
    (a) Broca's area (b) The angular gyrus area
    (c) The superior temporal cortex (d) The prefrontal area

21. **Inborn reflexes, *not true* is:**
    (a) Also called unconditioned reflexes (b) Present in all normal individuals
    (c) Examples include: all superficial and deep reflexes (d) Organic reflexes do not come under this category

22. **Characteristic features of conditioned reflexes include all *except*:**
    (a) A reflex response to a stimulus that earlier did not produce the response
    (b) Peculiar to the individual
    (c) Certain conditions must be present for its appearance
    (d) Once acquired, it persists thereafter

23. **Factors which influence conditioned reflex to develop are all *except*:**
    (a) An unhealthy individual
    (b) Conditioned stimulus (CS) must begin to operate before the unconditioned stimulus (US)
    (c) Necessity for reinforcement
    (d) Time interval between application of CS and US should not be more than 90 seconds

24. **Which part of the brain principally stores memory?**
    (a) Amygdala
    (b) Hippocampus
    (c) Neocortex
    (d) Uncus

25. **Which theory probably explains long-term memory the best?**
    (a) It causes actual physical or chemical changes at the synapses
    (b) There is increase in RNA synthesis inside the neuron
    (c) The glial cells arouse the neuron change
    (d) The ionic composition of the neuron changes

26. **Damaging what area of the brain is likely to cause anterograde amnesia?**
    (a) Prefrontal cortex
    (b) Occipital cortex
    (c) Amygadala
    (d) Hippocampus

∴ My hippocampus got hurt slightly in accident !!

Answers

1. (d)	2. (b)	3. (a)	4. (c)	5. (b)	6. (d)	7. (d)	8. (d)	9. (c)	10. (d)	11. (c)	12. (d)	13. (b)	14. (b)	15. (a)
16. (a)	17. (c)	18. (c)	19. (a)	20. (a)	21. (d)	22. (d)	23. (a)	24. (b)	25. (b)	26. (d)				

Speech genesis area = Wernicke's

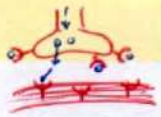
Memory storing area = HIPPOCAMPUS

BDEW

Chemical Transmission in the Nervous System

Chapter 106

I. Introduction: Classification of neurotransmitters
II. Small molecule neurotransmitters:
   A. Biogenic monoamines: Acetylcholine (A-ch); Serotonin (5HT); Histamine
   B. Catecholamines (epinephrine, nor-epinephrine, dopamine)
   C. Amino acid neurotransmitters: Excitatory and inhibitory
III. Large molecule neurotransmitters:
   A. Polypeptide neurotransmitters: Enkephalins, endorphins and substance P, Neuropeptide Y, CGRP;
   B. Purinergic neurotransmitters: Adenosine, ATP
   C. Other neurotransmitters: Nitric oxide (NO), prostaglandins



INTRODUCTION

The term chemical transmission is applied to substances formed by neurons and released from axonal terminals. They travel very small distance between the presynaptic endings and postsynaptic membranes of neuronal, muscular or glandular cells.

Neuroeffector communication

Nerve endings have been called *Biological tranducers* that *convert electrical energy into chemical energy*. The neurotransmitter thus released by the efferent neuron's terminals provides the link by which electrical activity of the nervous system is able to regulate effector-cell activity. How?

1. The neurotransmitter is released from the efferent neuron upon the arrival of an action potential at the axon terminals.
2. The transmitter then diffuses to the surface of the effector cell, where it binds to receptors on the cell's membrane.
3. The receptor of the effector cell may be associated with:
   (i) *ion channels* that alter the membrane potential of the cell, or
   (ii) an *enzyme* that results in the formation of a *second messenger* in the effector cell.

Classification of Neurotransmitters

There are many different substances known to be neurotransmitters, the major ones are classified in Table 106.1.

In general, the neurotransmitters:

(1) influence ion channels by changing the membrane potential;
(2) action occurs within milliseconds, therefore, changes induced are fast and direct;
(3) can activate both postsynaptic and presynaptic receptors.

SMALL MOLECULE NEUROTRANSMITTERS

Important Note

The small molecule neurotransmitters cause most acute response of the nervous system such as transmission of sensations and motor signals. In contrast, *neuropeptides* cause more prolonged actions such as long-term changes in the number of receptors or synapses, long-term opening or closing of ion⁻ channels.

Table 106.1: Major neurotransmitters of the nervous system

Small molecule neurotransmitters
A. *Biogenic monoamines*
1. Acetylcholine: A-ch
2. Serotonin (5-hydroxytryptamine; 5-HT)
3. Histamine
B. *catecholamines:* Epinephrine (Ep), Nor-epinephrine (NE), Dopamine
C. *Amino acids*
1. Excitatory amino acids: Glutamic acid, Aspartic acid
2. Inhibitory amino acids: Gamma-aminobutyric acid (GABA), glycine
Large molecule neurotransmitters
A. *Polypeptide neurotransmitters*
1. Enkephalins and endorphins
2. Substance P
3. Neuropeptide Y
B. *Purinergic neurotransmitters:* Adenosine, ATP.
C. *Other neurotransmitters:* Nitric oxide (NO), prostaglandins

A. BIOGENIC MONOAMINES

Acetylcholine: A-ch

Characteristic features

Acetylecholine (A-ch) exists in high concentration in the terminal buttons and synaptic vesicles of cholinergic neurons.

1. *Synthesis, storage and release of A-ch;* refer to page 155.
2. *Removal of A-ch.* A-ch is rapidly removed from its site of action (**Fig. 5.2**, page 157). This is brought about by two mechanisms:
   (i) *Diffusion.* After A-ch release and the activation of receptors on the post-synaptic membrane, its concentration is reduced; thereby stopping receptor activation by diffusion away from the receptors.
   (ii) *Acetylcholinesterase.* It is located on the pre and postsynaptic membranes and rapidly destroys A-ch, releasing choline. The choline is then actively transported back into the axon terminals where it is reused in the synthesis of A-ch.
   (Refer to page 158 for *pseudo* or ***non-specific cholinesterase***)
3. ***A-ch receptors.*** Muscarinic and nicotinic receptors (page 924).
4. ***A-ch actions on the postsynaptic membrane.*** A-ch has two main types of action on postsynaptic membranes: a *muscarinic action* and a *nicotinic action*. The differences between the two types of A-ch actions are given in **Table 106.2**.
5. *Sites* in the nervous system where A-ch is a **major neurotransmitter**. (Refer to page 923)
6. The cell bodies of the brain's ***cholinergic neurons*** are concentrated in relatively few areas, but their axons are widely distributed (**Fig. 105.6**, page 1040).
   (i) Cholinergic neurons in the brain cease to function normally in Alzheimer's disease (page 1040); and
   (ii) Cholinergic projections are also involved in motivation, perception and cognition (page 1024).
7. Cholinergic neurons in the pons and lateral tegmental nuclei project through the pons-midbrain reticular formation to the thalamus and are involved in the attention and arousal functions of the RAS (page 958).
8. A-ch is an excitatory transmitter in the basal ganglia (page 997).
9. The PGO spike system responsible for REM sleep is cholinergic (page 986).
10. A-ch role as a local hormone (page 761).

SEROTONIN: 5-hydroxytryptamine (5 HT)

1. It is produced from tryptophan (an essential amino acid) and is metabolized by monoamine oxidase. (For details, refer to page 762)
   Serotonin receptors are made up of multiple subunits coded by different genes, for example: $5HT_1$ to $5HT_7$ receptors. With each group there are subgroups A to F (i.e. $5HT_{1A}$, $5HT_{1B}$ and so on). Most of these receptors are *coupled to G-proteins* and affect adenylyl cyclase or phospholipase C.

Table 106.2: The major differences between two types of A-ch actions

Muscarinic action	Nicotinic action
1. Action in which A-ch acts like muscarine, an alkaloid from the poisonous mushroom (Amanita muscaria).	1. Actions in which A-ch acts like nicotine.
2. Muscarinic cholinergic receptors are made up of five subunits (M_1 to M_5) coupled via G-proteins to adenylyl cyclase, K^+ channels and/or phospholipase C.	2. Each nicotine cholinergic receptor is made up of five subunits (α, β, γ, δ and ε); when activated, increases permeability of Na^+ and other cations. Their high permeability to Ca^{2+} suggest their involvement in synaptic facilitation and learning (page 860).
3. These actions are typically those exerted by Ach released from postganglionic parasympathetic nerve terminals in the brain (M_1), heart (M_2), smooth muscle (M_3 and M_4) and exocrine glands (M_4).	3. These are those actions of A-ch that are produced on autonomic ganglia and skeletal muscle and sympathetic ganglia. ***Small amounts*** of A-ch stimulate postganglionic neurons and ***large amounts*** blocks transmission of impulse from pre to postganglionic neurons.
4. These actions are slow in onset, and prolonged.	4. These actions are quick in onset and are of brief duration.
5. They are antagonized (blocked) by atropine which combines with A-ch receptors at the sites of muscarinic actions.	5. They are antagonized by hexamethonium (at autonomic ganglia) or by tubocurarine (at skeletal muscle).

Note

Both muscarinic and nicotinic A-ch receptors are found in the CNS, however, most of these are muscarinic.

(i) *5-HT$_{2A}$* receptors mediate platelet aggregation and smooth muscle contraction.
(ii) *5-HT$_{2C}$* receptors regulate food intake
(iii) *5-HT$_{3\ and\ 4}$* receptors facilitate secretion and motility in the GIT. H_1 receptors also play a role in regulating cells of the immune system.
(iv) *5-HT$_{6\ and\ 7}$* receptors are distributed throughout the limbic system.

2. Its effects generally have a slow onset, indicating that it works as a ***neuromodulator***. *Neuromodulators* often modify the postsynaptic cell's response to specific neurotransmitters.
3. It is contained mainly in the brainstem neurons that innervate practically all other areas of the CNS.
4. In general, 5 HT has:
   (i) an *excitatory effect on motor pathways*; and
   (ii) an *inhibitory effect on the sensory pathways*.
5. The activity of ***serotonergic neurons*** is lowest or absent in sleep and highest during states of alert wakefulness when increased 5 HT activity increases motor responsiveness and suppresses sensory systems to screen out distracting stimuli (page 988).
6. It plays important role in the neural pathways controlling mood.

Notes

(i) Several substances chemically related to 5-HT, such as *psilocybin*, a hallucinogenic agent found in some mushrooms, have potent psychic effects.
(ii) LSD (lysergic acid diethylamide), the most potent hallucinogenic drug known, activates serotonergic neurons.

7. *Serotonergic pathways* function in regulation of carbohydrate intake and hypothalamic releasing hormones, and they have been implicated in alcoholism and other obsessive-compulsive disorders.
8. 5 HT is also present in many non-neural cells, *e.g.* blood platelets (*highest concentration*), mast cells and myenteric plexus.
9. The presence of descending serotonergic neurons in the brainstem and spinal cord is essential for the analgesic action of morphine (page 899).
10. In the pineal gland, 5 HT is converted into melatonin (page 759).
11. The discharge in serotonergic neurons in the dorsal raphe nucleus causes migraine. (*Proof:* Antimigraine drugs inhibit the firing from these neurons.)

Important Note

NE and serotonin both are involved in the control of food intake (page 1007) and the regulation of body temperature (page 587).

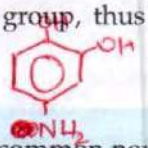
HISTAMINE

1. ***Histaminergic neurons*** have their cell bodies in the tubero-mammillary nucleus of the posterior hypothalamus, and their axons project to all parts of the brain including the cerebral cortex and the spinal cord.
2. Histamine is also found in the gastric mucosa (page 219) and heparin containing mast cells. (page 761)
3. It is formed by decarboxylation of the amino acid histidine.
4. ***Histamine receptors*** are of 3 types: H_1, H_2 and H_3; and all three are found in peripheral tissues and the brain.
   (i) *H_1 receptors* activate phospholipase C;
   (ii) *H_2 receptors* increase intracellular cAMP concentration, and
   (iii) *H_3 receptors* are presynaptic, and they mediate inhibition of the release of histamine via G protein.
5. Histamine plays important role in arousal and sexual behaviour, regulation of secretion of some anterior pituitary hormones, BP, drinking and pain thresholds, also involved in the sensation of itch (page 901).

B. CATECHOLAMINES

Dopamine, NE and Ep.

1. Dopamine, NE and Ep all contain a *catechol* ring (a six-sided carbon ring with two adjacent hydroxyl group) and an amine group, thus they are called catecholamines.



Note

Epinephrine (Ep) is not a common neurotransmitter in the brain or peripheral nervous system but is the major hormone secreted by the adrenal medulla.

2. ***Biosynthesis,*** *metabolism and excretion of catecholamines.* Refer to page 733.

Important points to note

(i) Depending on the enzymes present in the axon terminals, the neurotransmitter finally formed may be any one of the three catecholamines.
(ii) Catecholamine released from the presynaptic terminals is strongly modulated by presynaptic receptors.

(iii) After activation of the receptors on the postsynaptic cell, the catecholamine concentration in the synaptic cleft declines because:
   (a) the catecholamine is actively transported back into the axon terminal, and
   (b) it is also broken down by the enzymes monoamine oxidase (MAO) and catechol-o-methyl-transferase (COMT).

3. *Sites* in the nervous system where catecholamine, particularly NE is the major neurotransmitter (page 923).
4. *Actions of catecholamines* - refer to page 925.
5. The time course of action of *catecholamines* is often much slower than that of other substances. Their receptor action is linked to the second messenger cAMP, cGMP, etc. Thus, they may alter the actions of the postsynaptic neurons as these neurons respond to other transmitters that act more rapidly.
6. **Distribution of *adrenergic*** (particularly NE) and ***dopaminergic neurons*** in the CNS are shown in **Fig. 106.1**.

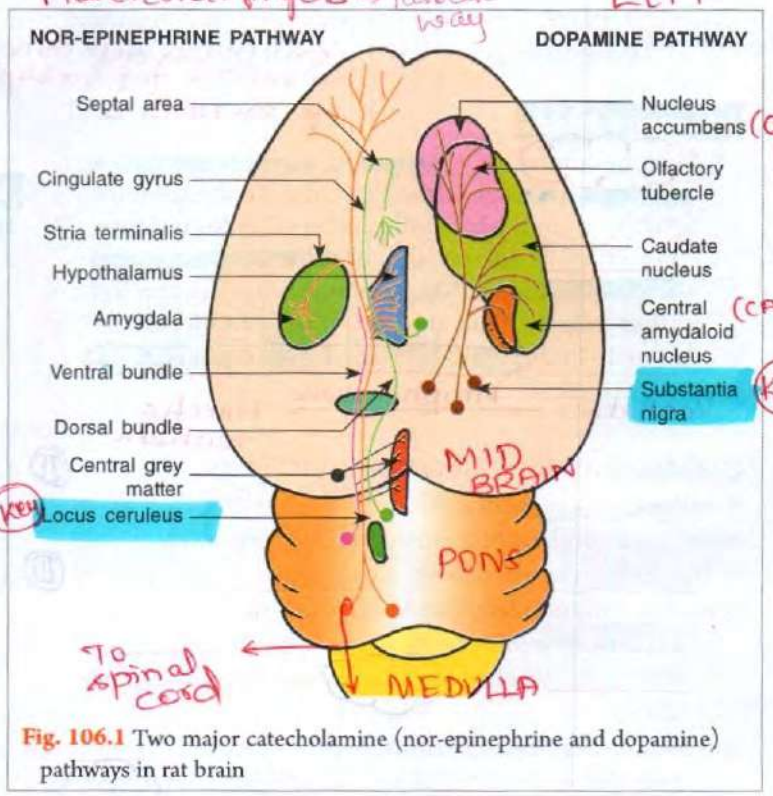


Fig. 106.1 Two major catecholamine (nor-epinephrine and dopamine) pathways in rat brain

   (i) ***Nor-epinephrine – NE***
   The cell bodies of the NE – containing neurons in the brain, are located in the *locus ceruleus* (page 987) and other nuclei in the brain stem. From the locus ceruleus, the axons of the nor-adrenergic neurons descend into the spinal cord; and ascend to innervate the hypothalamic nuclei, the thalamus and the entire neocortex.

   (ii) ***Dopamine***
   Dopaminergic neurons have their cell bodies in the midbrain. They project from the substantia nigra to the:
   (a) striatum (nigrostriatal tract, page 997),
   (b) olfactory tubercle,
   (c) nucleus accumbens (page 1028), and
   (d) limbic system areas.

Dopamine acts on 5 types of *dopamine receptors* (D_1 to D_5), most of the responses to these receptors are mediated by G-proteins. The D_1 receptors, activate dopamine sensitive cAMP via G_s; the D_2 receptors inhibit cAMP via G_i. The brain contains more of D_2 dopamine receptors. D_3 receptors are highly localized to nucleus accumbens. D_4 receptors have a greater affinity than the other dopamine receptors for anti-psychiatric drugs.

7. ***Functional aspects*** of catecholamines in the CNS.

Role of NE

   (i) NE is an *inhibitory* transmitter in the thalamus, cerebral cortex and cerebellar cortex.

   (ii) Nor-adrenergic neurons suppress ACTH secretion by inhibiting the activity of the neurons which synthesize and secrete corticotrophin-releasing factor (page 717).

   (iii) The NE-containing neurons in the hypothalamus are involved in:
   (a) regulation of the secretion of ADH (page 672) and oxytocin (page 674); and control of body temperature (page 587).
   (b) they adjust the secretion of the hypophyseotrophic hormones that regulate the secretion of anterior pituitary hormones.

   (iv) Drugs that increase extracellular NE in the brain elevate mood and drugs that decrease it cause depression. (Also see to page 1028)

Role of dopamine

   (i) Dopamine exerts inhibitory action on the abundant cholinergic neurons in the caudate nucleus and putamen (corpus striatum). Degeneration of the nigrostriatal tract, and loss of dopamine produces *Parkinsonism* (page 997).

   (ii) The retina also contains some inhibitory dopaminergic neurons.

   (iii) the dopaminergic neurons in the hypothalamus stimulate the release of GnRH (page 779).

   (iv) Dopamine is the prolactin inhibiting factor in the median eminence (page 671).

(v) It plays an important role in habit forming substances (page 1061).

Important Notes

1. Amphetamine, which stimulates the secretion of NE and dopamine, produces a psychosis that resembles schizophrenia, when administered in high doses.
2. Tranquilizers (drugs that decrease anxiety and various psychiatric symptoms) are effective in relief of the schizophrenia, and their antipsychotic activity is due to their ability to block dopamine receptors.

C. AMINO ACID NEUROTRANSMITTERS

A number of neurotransmitters are synthesized from amino acids and are the most abundant transmitter class in the CNS. There are two main types of amino acid neurotransmitters: *excitatory and inhibitory.*

(i) ***Excitatory amino acids.*** These include *glutamic* and *aspartic acids.* They depolarize most neurons in the CNS.

(ii) ***Inhibitory amino acids.*** These include *gamma-aminobutyric acid (GABA)* and *glycine.* They hyperpolarize neuronal cell membrane.

Characteristic features

1. Except GABA all the above mentioned amino acid neurotransmitters occur in higher concentrations in grey matter (containing synapses) than in the white matter.
2. They are mainly inactivated by reuptake processes, but metabolic degradation also occurs.

(I) Glutamic Acid

1. It is the most abundant amino acid in the brain and is concentrated in dorsal sensory nerve terminals.
2. It depolarizes spinal motor neurons and cortical neurons by increasing Na^+ permeability of the membrane.
3. It is an important excitatory neurotransmitter in dorsal root afferents and at other sites in the CNS.
4. Its receptors are of two types:
   (i) *metabotropic receptors* are *G-protein coupled receptors.* They are mainly involved in production of synaptic plasticity (page 859). Their destruction causes severe motor incoordination and defects in learning.
   (ii) *ionotropic receptors* are *ligand gated ion channels* and are of three subtypes, of which *NMDA receptors* (*N-mehthyl-D-aspartate*) are of importance. The channel is blocked by Mg^{2+} at the RMP. This block is removed if partial depolarization is produced by Ca^{2+} and Na^+ influx or when glycine and glutamic acid binds to the receptor. These receptors are found in high density in the hippocampus and blockage of these receptors prevents *long term potentiation* (page 860). Thus, these receptors play important role in memory and learning.

Important Note

Ischaemia to brain tissue (such as during a stroke) causes marked release of glutamic acid, much of the brain damage is then due to the action of this neurotransmitter as an excitotoxin, rather than to lack of oxygen per se.

(II) Aspartic Acid. It is an *excitatory* neurotransmitter in pyramidal cells and stellate cells in the visual cortex.

(III) GABA

1. It is an *inhibitory* transmitter in the spinal cord and to the cells in the cerebral cortex. In the spinal cord it is responsible for presynaptic inhibition (page 857).
2. The Purkinje cells of the cerebellum contain GABA which, when released, hyperpolarizes the cells of Deiter's nucleus and other deep cerebeller nuclei (page 967).
3. It is formed by decarboxylation of glutamic acid by the enzyme *glutamate decarboxylate (GAD)* which is present in nerve endings in many part of the brain.. Pyridoxal phosphate, a vitamin B complex derivative, is a co-factor for GAD. Thus, GABA content of the brain is reduced in pyridoxine deficiency, resulting in neural hyperexcitability and convulsions.

Glutamate $\xrightarrow[PLP]{GAD}$ GABA + CO_2

Note

The autoimmune diseases, *Type I diabetes mellitus* (page 753) and ***Stiffman syndrome*** (SMS) are characterized by formation of antibodies against GAD. SMS is characterized by progressive muscle rigidity and painful muscle spasm secondary to GABA deficiency.

4. It is the major inhibitory neurotransmitter in the brain stem, cerebral cortex and cerebellum. It has both presynaptic and postsynaptic actions.
5. There are three types of *GABA receptors*: $GABA_A$ and $GABA_B$ in the CNS and $GABA_c$ in the retina. Acting via $GABA_A$ and $GABA_c$ receptors (*ligand gated ion channel*), GABA increases cell membrane permeability to Cl^-, whereas via $GABA_B$ receptors (*G-protein coupled receptor*) it produces an increase in K^+ efflux and decrease Ca^{2+} influx. All such changes hyperpolarize neuron producing an IPSP.

Important Note

A number of agents such as benzodiazepines (diazepam) and barbiturates that have marked antianxiety activity and are also effective muscle relaxants, anticonvulsants and sedative binds to $GABA_A$ receptors in the brain neurous to increase Cl^- influx.

Glycine

It is the neurotransmitter formed and released by *inhibitory* interneurons which act on motor neurons in the brain and spinal cord. In the spinal cord it is responsible for direct inhibition (page 856). It acts by increasing Cl^- permeability.

Proof

1. Glycine concentration in the ventral grey matter of the spinal cord is higher than any other amino acid.
2. Strychnine and tetanus toxin produce convulsions and muscular hyperactivity as these agents antagonize the postsynaptic inhibitory action of glycine (page 856).

Notes

1. Strychnine does not antagonize the action of GABA but picrotoxin does.
2. Picrotoxin does not block the action of glycine.
3. Glycine also has *excitatory* effect. For example, it may facilitate pain transmission by binding to the NMDA receptors (page 1048) in the dorsal horn.

Important Note

Alcohols, barbiturates and many inhaled anaesthetics act on ion channel receptors (specially $GABA_A$ and Glycine) to increase Cl^- influx.

LARGE MOLECULE NEUROTRANSMITTERS

A. POLYPEPTIDES AS NEUROTRANSMITTERS

1. Polypeptides are composed of two or more amino acids linked together by peptide bonds and are synthesized in neural tissues. More than 50 polypeptides have been known.
2. Many of the peptides function in communication network within the neural, endocrine and immune systems.
3. *Synthesis and release*
   (i) The polypeptides are derived from large precursor (polyproteins) molecules called *prehormones* or *preprohormones*. These polyproteins in themselves have little inherent biological activity.
   (ii) The synthesis of these precursors is directed by mRNA, located within the cell body and large dendrites of the neuron.
   (iii) In the cell body, the *prohormone* is stored into vesicles, which are then moved by way of axon transport into the nerve terminals where their contents are broken by specific peptidases.

Enkephalins and Endorphins

1. They are of much interest since receptors for these transmitters are the sites of action of the *opiate* drugs such as morphine and codeine.
2. They play an important role in regulating pain, in eating and drinking behaviour, in central regulation of the CVS, and in cell development.
3. There are at least 3 receptor types that respond to the enkephalins, and they occur in discrete locations in the CNS:
   (i) in areas containing pathways that convey pain information;
   (ii) in parts of the brain involved in mood; and
   (iii) in emotions
   (for details, refer to page 900).

Substance P

1. It is transmitter for afferent neurons that relay sensory information into the CNS and is thought to be involved in the transmission of nociceptive (pain producing) stimuli (page 900).
2. It is found in high concentrations:
   (i) in the endings of primary afferent neurons (Aδ and C group of fibers) in the spinal cord;
   (ii) in the nigrostriatal system, and
   (iii) in the hypothalamus, where it plays a role in neuroendocrine regulation.
3. Upon injection into the skin, it causes redness and swelling, and it is the mediator released by nerve fibers that is responsible for the *axon reflex* (page 326).
4. In the intestine, it is involved in the *myenteric reflex* (page 248).

Somatostatin (GHIH)

1. It is a neurotransmitter in many parts of the brain where it modify sensory inputs, locomotor activity and cognitive function.
2. In hypothalamus it function as GHIH (page 662).
3. It inhibit insulin secretion.
4. In GIT, it is an important inhibitory hormone (page 273).
5. Five different somatostatin receptors have been identified, all are G-protein coupled

(IV) ***Hypophysiotropic hormones***

These are releasing and inhibiting hormones/factors from the hypothalamus (page 681). They function as hormones as well as neurotransmitters in different parts of the brain, the retina and ANS.

(V) ***Vasopressin (ADH) and oxytocin***

Besides functioning as hormones (page 670), they are also present in the neurons that project to the brain stem and spinal cord. They appear to be involved in control of CVS.

(VI) ***GIT hormones***

VIP and CCK (page 232) are also found in the brain, the former in the hypothalamus and the latter in the cerebral cortex.

(VII) ***Calcitonin gene related peptide (CGRP)***

It is a product of hormone calcitonin and exists in two forms: CGRPα and CGRPβ; the latter is found in GIT whereas the former in primary afferent neurons which convey taste, and neurons in the medial forebrain bundle.

Note

CGRP has little effect on calcium metabolism.

(VIII) ***Neuropeptide Y***

It is closely related to pancreatic polypeptide and is present in many parts of the brain and the ANS (in noradrenergic neurons). It acts in 8 receptors Y_1-Y_8. It increases the vasoconstrictor effect of NE. Its level in the circulation from sympathetic nerves increases during severe exercise. It play important role in control of food intake (page 1007).

B. PURINERGIC NEUROTRANSMITTERS

1. ***Adenosine***, a purine, binds to four receptors: *A_1 and A_{2A}, A_{2B} and A_3 receptors;* all are coupled to G-protein. The A_1 and A_3 inhibits adenylate cyclase and the A_{2A}, A_{2B} activates adenylate cyclase.
2. A_2 receptors are mainly found in the neostriatum, olfactory tubercle and nucleus accumbens. (page 1028)
3. Adenosine is a CNS depressant, helps in regulation of coronary blood flow (page 361) and has effect on the immune system. Adenosine in the ECF comes from ATP, which itself functions as a neurotransmitter via P_1 and P_2 receptors.
4. ATP mediate rapid synaptic responses in the ANS.

Note

Tea and coffee produce the stimulatory effect on the brain by its caffeine and theophylline contents that blocks the adenosine receptors.

C. OTHER NEUROTRANSMITTERS

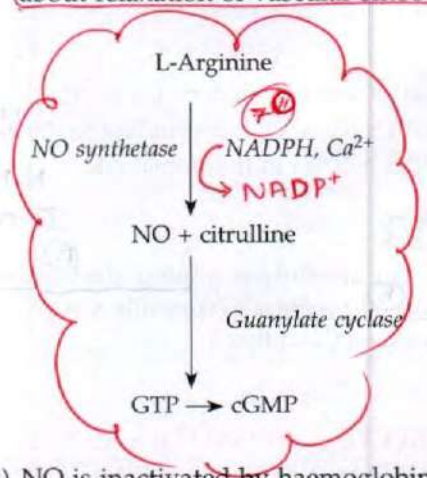
Nitric Oxide (NO)

1. This compound is released by the endothelium of blood vessels as *'endothelium-derived relaxing factor (EDRF)'*. It is also produced in the brain (in the form of a gas) which crosses cell membranes with ease and binds directly to guanylyl cyclase (see below) and is responsible for long-term potentiation-LTP (page 860) and *long-term depression* (opposite of LTP).
   In the cerebellum, simultaneous firing of climbing and parallel fibers causes a long-term depression in conduction of the parallel fiber – Purkinje cell synapses (page 964).

Note

In the cerebellum, nitric oxide (NO) is inhibitory, whereas in LTP (page 860) and in the hippocampus, it is stimulatory (where it plays important role in learning and memory).

2. ***Role of NO in control of vascular smooth muscle***
   (i) NO is synthesized from arginine by action of enzyme *NO synthetase*. It activates guanylate cyclase in cells, producing cGMP which brings about relaxation of vascular smooth muscle.



   (ii) NO is inactivated by haemoglobin.
   (iii) NO is released by variety of agents such as A-ch, sudden increase in tissue blood flow and products of platelet aggregation.
   (iv) NO deficiency produces hypertension, atherosclerosis and impotency.

Prostaglandins

These are fatty acid derivatives found in many cells (details page 763) and also found in the nervous system. They exert their effects as *neuromodulators* (page 1044) via cAMP.

Study Questions

1. **Define and give physiological significance:**
   (i) Neuroeffector communication
   (ii) Neuromodulator.
2. **Differentiate between muscarinic and nicotinic actions of A-ch.**
3. **Name the sites in the nervous system where (i) A-ch and (ii) NE is the major neurotransmitter.**
4. **Give classification of major neurotransmitters in the nervous system. Which one is found in the highest concentration?**
5. **Give the role and physio-clinical significance of the following neurotransmitters in the nervous system:**
   (i) NE (ii) A-ch
   (iii) Dopamine (iv) 5 HT
   (v) Glutamic acid (vi) GABA
   (vii) Substance P (viii) Opioid peptides
   (ix) Nitric oxide.

MCQs

1. ***Not* a feature of neurotransmitters:**
   (a) Influence ion channel by changing the membrane potential
   (b) Changes induced are fast and direct
   (c) Action occurs within milliseconds
   (d) Can activate only postsynaptic receptors
2. **Nor-epinephrine, *not true* is:**
   (a) An inhibitory transmitter in the thalamus, cerebral cortex and cerebellum
   (b) Involved in secretion of ADH from hypothalamus
   (c) Suppress ACTH secretion
   (d) Exert inhibitory action on cholinergic neurons in the caudate nucleus (It itself is cholinergic)
3. **Schizophrenia is due to excess activity of which neurotransmitter?**
   (a) Acetylcholine
   (b) Epinephrine
   (c) Dopamine
   (d) Glycine
4. **In general, serotonin:**
   (a) Has an inhibitory effect on motor pathways
   (b) Has an inhibitory effect on sensory pathways
   (c) Activity is lowest during states of alert wakefulness
   (d) Present in highest concentration in mast cells
5. **Which of the following neurotransmitters plays an important role in regulating pain?**
   (a) Substance P → ↑ ea
   (b) Enkephalin and Endorphin → Regulators
   (c) Glycine
   (d) Neuropeptide Y
6. ***False* about substance P:**
   (a) Involved in transmission of nociceptive stimuli
   (b) Responsible for axon reflex
   (c) Involved in myenteric reflex
   (d) A hypophysiotropic hormones
7. **GABA, *not true* is:**
   (a) An inhibitory transmitter in the spinal cord
   (b) Its brain content is reduced in pyridoxine deficiency
   (c) Acting via $GABA_A$ receptors, it increases all membrane permeability to Cl^-
   (d) Its excess in brain result in neural hyperexcitability and convulsions

Mohammed Siddiq
Motor → Stimulatory
Sensory → Inhib.
"MI" is NOT my mobile
(Inhibitory it is) ⇒ causes muscle relax & sedative effects)

8. **Muscarinic actions of acetylcholine differs from nicotinic actions in that:**
   (a) These actions are slow in onset and prolonged
   (b) They are antagonized by atropine
   (c) These actions are those exerted by acetylcholine in the heart, smooth muscle and exocrine glands
   (d) All of the above
9. **What transmitter substance is released by the spinal nerve ending of the neurons whose cell bodies are located in the raphe nucleus?**
   (a) Endorphin
   (b) Substance P
   (c) Glycine
   (d) Serotonin
10. **Inhibition of the spinal cord may be brought about by:**
   (a) Glutamic acid
   (b) Aspartic acid
   (c) Glycine
   (d) Strychinine
11. **Which of the following neurotransmitters plays an important role in regulating pain?**
   (a) Substance P
   (b) Enkephalin and Endorphin
   (c) Glycine
   (d) Neuropeptide Y

Answers

1. (d) 2. (d) 3. (c) 4. (b) 5. (b) 6. (d) 7. (d) 8. (d) 9. (d) 10. (c) 11. (b)

Unit XII

THE SPECIAL SENSES

Chapter 107: The Smell

Introduction: general versus special sensibility; The common chemical senses; The sense of smell (olfaction): olfactory receptors, olfactory pathways, physiology of olfaction; Applied: Anosmia, Parosmia, Hyposmia; Unitque features

Chapter 108: The Taste

Taste receptors or taste buds; Taste pathways; Physiology of taste; Applied: Ageusia, hypogeusia; dysgeusia..

Chapter 109: The Ear

Physiological anatomy; Auditory pathways; Physical properties of sound; Mechanism of hearing; Electro-physiology of hearing: Electrical activity of cochlea, action potential of the auditory nerve fibers, auditory cortex; Applied aspect: Deafness, tinnitus; Tests for hearing.

Chapter 110: The Eye

Physiological anatomy; Visual pathway and effect of lesions; the image forming mechanisms: Visual acuity, visual reflexes, defects of image forming mechanisms; Photochemistry of vision; Electrophysiology of vision; Physiology of colour vision; Eye movements and Nystagmus

Chapter
107

The Smell

I. Introduction
General versus special sensibility
The common chemical senses

II. The sense of smell: Olfaction
A. Olfactory Receptors
B. Olfactory Pathways
C. Physiology of Olfaction
D. Applied: Anosmia, Parosmia, Hyposmia
E. Unique Features

1 INTRODUCTION

1. Brain receives the information outside the body surface through *five sense organs* viz. nose, tongue, ear, eye and skin. These sensibilities can be classified into two categories: *General* and *Special*. The main differences between general sensibility and special sensibility are given in Table 107.1:
2. The *common chemical senses: Features*
   (i) The capacity to respond to surface application of chemical irritants is called the *common chemical sense.*
   (ii) It contributes to the appreciation of odours, even in non-irritant concentrations.
   (iii) The excessive stimulation of common chemical sense gives rise to pain. For example, the smell of the vapours of onions or ammonia consists of two components:
      (a) one is caused by stimulation of the olfactory apparatus, and
      (b) other arises due to the *irritation* properties of their vapours which stimulate the Vth nerve endings producing pain.
   (iv) In terms of ***threshold concentrations*** of substances required for excitation, smell is the most sensitive of the chemical senses, taste is intermediate and common chemical sensibility is the least sensitive.
   (v) The senses of smell and taste are mainly concerned with nutrition and are closely related to each other.
   (vi) Because smell producing substances are dispersed in the air, the sense of smell can give information about distant objects whereas taste informs only about substances in solution inside the mouth.

2 THE SENSE OF SMELL: OLFACTION

The olfactory sense is highly developed in the rabbit and dog, which are called ***macrosmatic;*** but is much less in man, apes, monkeys (primates), which are called ***microsmatic.***

A. OLFACTORY RECEPTORS

1. The sense of smell arises from stimulation of *receptors* in the yellowish brown *olfactory mucous membrane* located in the roof of the nasal cavity (Fig. 107.1).

Table 107.1: Main differences between general and special sensibility

General sensibility	Special sensibility
1. Its receptors are located throughout the body. Examples include: touch, pain, pressure and temperature sensibility.	1. Its receptors are located at *one* place (in the head) very close to nervous system and are well protected within the skull. Examples: smell, taste, hearing and vision.
2. The receptors get easily stimulated by different stimuli, however, they respond maximally to an adequate stimulus (page 861).	2. The receptors are specialized and respond only to one type of stimulus.
3. The receptor's response is non-specific to different stimuli.	3. The receptor's response is more complex and makes coordination within the CNS.

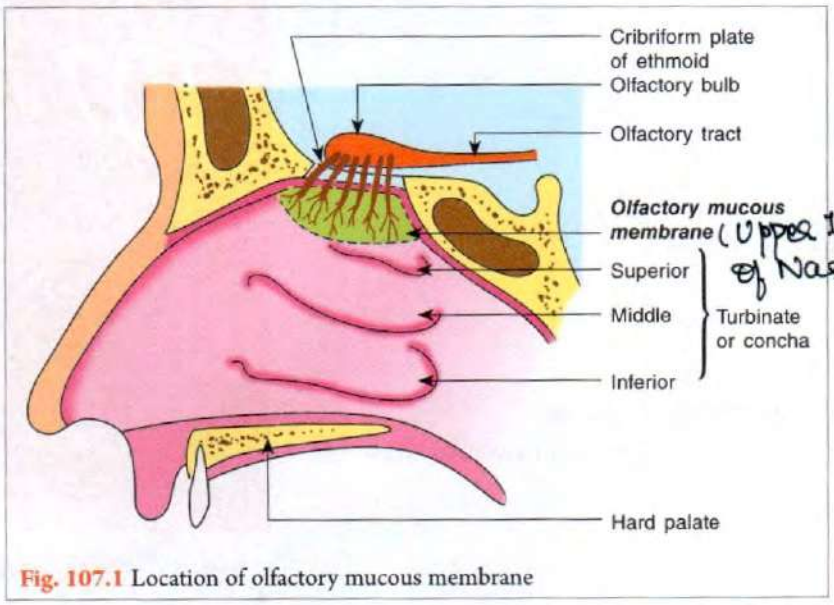


Fig. 107.1 Location of olfactory mucous membrane

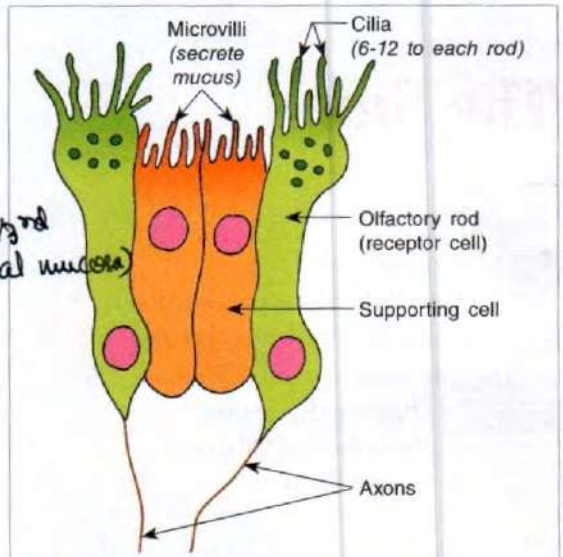


Fig. 107.2 Structure of an olfactory receptor

2. The total area of the olfactory mucous membrane on both sides is 500 mm^2. (In the dog, the area is much larger.) It contains 10-20 million special sensory cells (a bipolar neuron), called ***receptor cells.***)
3. The 'receptor cells' lie between the *supporting cells* and their dendrites extend as naked processes called ***olfactory rods*** which end in fine cilia. There are 6-12 cilia on each rod (2 µm × 0.1 µm) which lie in the mucus covering the olfactory mucous membrane **(Fig. 107.2)**.
   Receptor cells have a short *life span* of about 60 days and get replaced by proliferation of basal cells.
4. The ***supporting cells*** end in *microvilli* which secrete *mucus*. The ***mucus*** is also secreted by Bowman's gland, located just under the basal lamina of the olfactory mucous membrane. It consists of phospholipids, lecithin and their auto-oxidation products. It is necessary for the sense of smell.

Important Note

The olfactory mucous membrane is the place in the body where the nervous system is closest to the external environment.

B. OLFACTORY PATHWAYS

1. The axons from the ***olfactory receptor cells*** are fine unmyelinated fibers, 0.2 µm in diameter which pierce the cribriform plate of ethmoid bone and enter the *olfactory bulb* **(Fig. 107.3)**.
2. Within the olfactory bulb the axons of the olfactory (I) nerve enter the ***glomeruli*** and form synapses with dendrites from ***mitral*** and ***tufted cells***. (These cells form the second order neurons in the olfactory pathway). The glomeruli also contains ***periglomerular short axon cells*** which are *inhibitory neurons* connecting one glomerulus to another **(Fig. 107.4)** and mediate *lateral inhibition* (page 887).
3. Each glomerulus receives impulses from 26000 receptors and passes this information through 24 mitral cells and 68 tufted cells. The arrangement is excellent for *spatial summation* (page 853). [CONVERGENCE]
4. The axons of the mitral cells form the ***lateral olfactory stria*** and run to the *olfactory cortex* on the same side

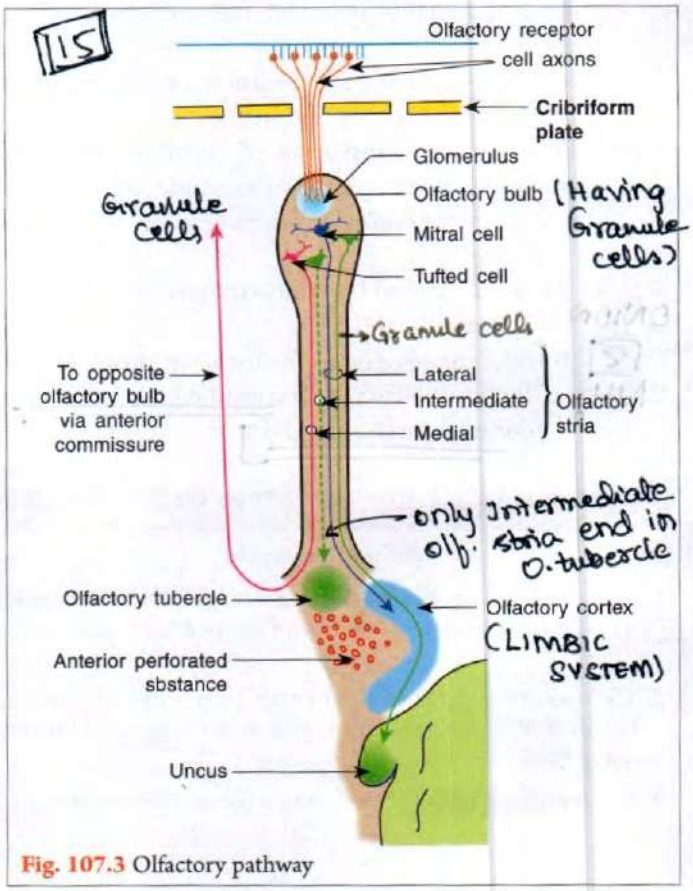


Fig. 107.3 Olfactory pathway

which lies between the anterior perforated substance and the uncus (anterior end of the hippocampal gyrus in the temporal lobe, page 1061). The *olfactory cortex* includes the part of the limbic system viz. anterior olfactory nucleus, piriform cortex, olfactory tubercle, amygdala and entorhinal cortex **(Fig. 107.5)**.

5. Other fibers run via the *intermediate olfactory stria* to connect with the *olfactory tubercle*, and hence with the limbic system.
6. The axons of the tufted cells run in the *medial olfactory stria* and cross the midline in the anterior commissure to form synapses with *granule cells* in the opposite olfactory bulb.

Important Notes

1. **Sectioning of the anterior commissure greatly impairs the sense of smell.**
2. **Destruction of one olfactory bulb produces loss of smell only on the same side.**

7. There is *point to point representation* of olfactory mucous membrane in the olfactory bulb. The upper part of the olfactory epithelium is represented in the anterior part of the bulb while the lower part is represented posteriorly.
8. ***Inhibitory pathways.*** There are *efferent fibers* in the olfactory striae and stimulation of these fibers can depress the electrical activity in the olfactory bulb. These effects are mediated by the *granule cells* (by releasing GABA) that make reciprocal synaptic connections with dendrites of mitral cells **(Fig. 107.4)**.

C. PHYSIOLOGY OF OLFACTION

1. To arouse the sense of smell, molecules of the smell producing *(odoriferous)* substance must come into contact with the receptor cells of the olfactory epithelium. To achieve this the substance first passes through the nasal cavity, which is achieved during the normal quiet breathing; then it gets dissolved in the thin layer of mucus that covers the olfactory epithelium.
2. Deep breathing or the act of *'sniffing'* more effectively brings the substance to the olfactory mucous membrane by producing turbulence in the airflow in the nasal cavity.
3. The substance then penetrates the mucus layer covering the olfactory epithelium, into which the cilia of the receptor cells project and are in constant motion.
4. The odoriferous substance now combines with the receptors on the surface of the cilia. The pattern of induced activity depends on the physical and chemical properties of the stimulant molecules and of the molecules of the receptive substance.
5. The *odour producing molecules* are generally small, containing 4-20 carbon atoms; the substances with strong odours have relatively high water and lipid solubility.

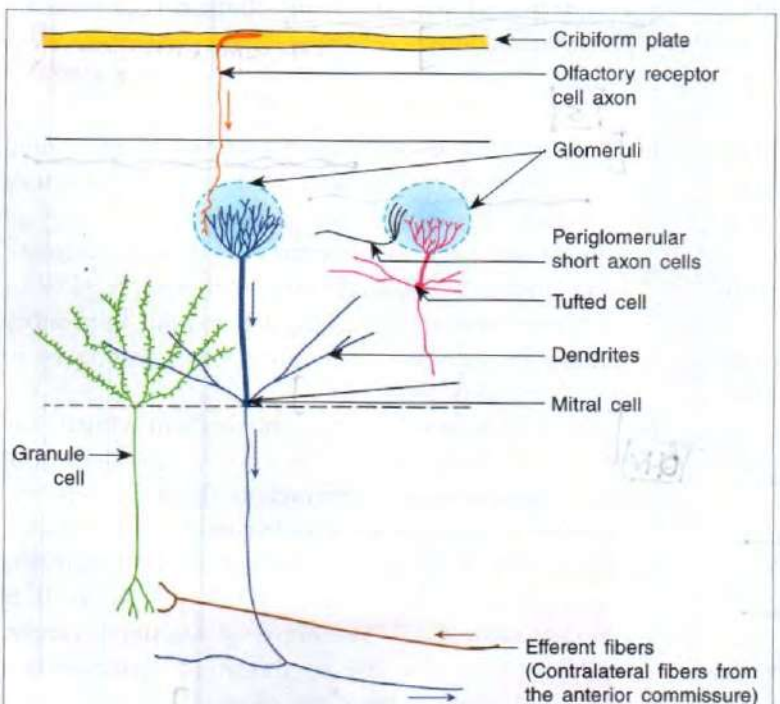


Fig. 107.4 Electron microscopic structure of olfactory bulb

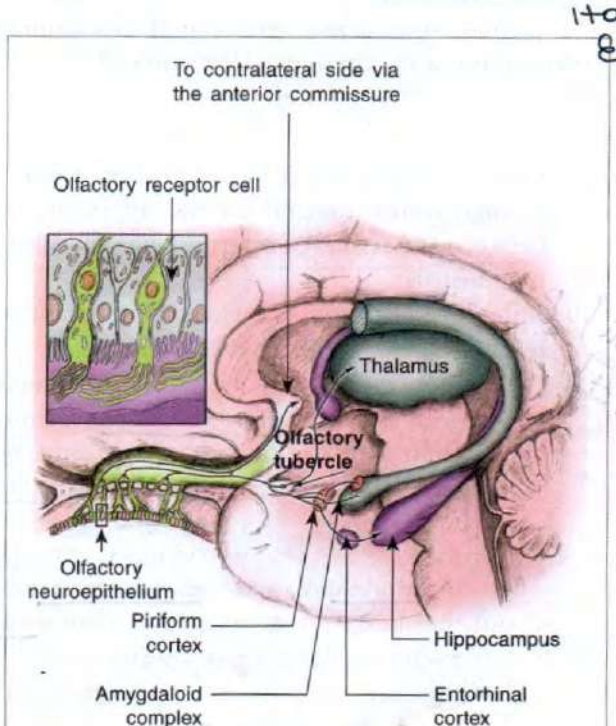


Fig. 107.5 Olfactory cortex

Important Note

The different regions of the olfactory mucous membrane may contain one or more *odorant-binding proteins* that selectively absorb some substances more than others, and in any small area there may be receptors for many different substances.

6. When odour producing substances become attached to the olfactory mucous membrane there develops a ***generator potential*** (page 866) which lasts 4-6 seconds. Action potentials are then set up in the olfactory receptors and are conducted along the axons to the olfactory bulb.
7. The receptors in the olfactory mucous membrane are coupled to G-proteins. Some act via adenylyl cyclase and cAMP, and others act via phospholipase C. All of them are cation channels causing Na^+ and Ca^{2+} influx.
8. Humans can *distinguish between* 4000 and 10000 different odours. This is possible due to presence of different *odorant receptors* and frequency of action potentials in the afferent nerve reaching the brain, *Weber Fechner Law* (page 868).

   The concentration of an odour producing substance must be changed by about 30% before a difference can be detected.

Important Note

To achieve the same, the visual discrimination threshold is a 1% change in light intensity.

9. ***Localization of smell*** i.e. direction from which a smell comes depend on the difference of time between the arrival of odoriferous molecules in the two nostrils.
10. ***Role of higher centres.*** The olfactory cortex also involves the parts of the *limbic cortex:*
    (i) the ***anterior olfactory nucleus*** is concerned with coordination of input from the contralateral olfactory cortex; thus help in transfer of olfactory memories from one side to the other;
    (ii) the ***piriform cortex*** is concerned with olfactory discrimination and conscious perception;
    (iii) the ***amygdala*** is concerned with emotional responses to olfactory stimuli; and
    (iv) the ***entorhinal cortex*** is concerned with olfactory memories.

Important Note

From the region (i to iv above) information travel directly to frontal cortex or via thalamus to the orbitofrontal cortex where conscious smell perception occurs.)

11. ***Individual variations in response.*** Human beings vary in their sensitivity to odoriferous substances. In individuals with apparently normal olfactory sense there are wide differences in sensitivity to different odoriferous substances. Thus individual variations in response are frequent.
12. ***Relation to sex.*** There is a close relationship between smell and sexual functions (specially in animals). The sense of smell is more acute in women than in men, and in women it is most acute at the time of ovulation.

Important Note

In human and other mammals , anterior third of the nasal septum contain another patch of olfactory mucous membrane in a well developed *vomeronasal organ.* This structure is concerned with the percepton of odours that act as *pheromones. Pheromones* are substances produced by animals that act at a distance to produce changes in hormonal, behavioural or other physiological changes in another animal of the same species. *Pheromones* are also used to attract members of the opposite sex for mating purposes. Its receptors project to the areas in the amygdala and hypothalamus that are concerned with reproduction.

13. ***Role of pain fibers.*** Naked endings of trigeminal pain fibers (V cranial nerve) found in the olfactory mucous membrane are stimulated by irritant substances such as peppermint, menthol, chlorine and ammonia. These endings are also responsible for initiating sneezing, coughing, lacrimation, respiratory inhibition (apnoea) and other reflex responses to nasal irritants (page 443).
14. ***Adaptation.*** Adaptation to the smell of odoriferous substances is called *olfactory fatigue.* An odour (foul or pleasant) which at first is quite clearly perceptible, gradually disappears and becomes imperceptible (page 869). It develops within seconds or minutes, depending on the nature of the substance. It is mediated by Ca^{2+}. The *degree of adaptation* can be measured by the rise in threshold concentration required to excite the sense of smell.

Important Notes

(i) Olfactory threshold increases with advancing age.

(ii) Adaptation is selective, therefore, when fatigue has developed to one substance another odoriferous substance produces a normal sensation.

(iii) Adaptation also occurs to 'irritants' which excite the common 'chemical sense' (page 1055). For example, mill workers adapt to the presence of the irritants in the atmosphere and tolerate concentrations which can cause marked sneezing and watering of the eyes in unexposed individuals.

D. APPLIED ASPECT

1. *Anosmia* (complete absence of sense of smell) or *parosmia* (alteration in character of smell) or ***hyposmia*** (reduction of the sense of smell) develops due to damage to the olfactory mucosa or the olfactory pathways by trauma or diseases.
2. Patients with adrenal insufficiency have greatly increased sensitivity for smell.

E. UNIQUE FEATURES

1. All other sensations (general or special) pass through the thalamus and projected to the neocortex, whereas the smell infenation either project directly or via thalamus to the orbitofrontal cortex.
2. Its receptor neurons are in direct contact with the external environment (page 1055).
3. The smell receptors are distant receptors *(telereceptors)* as well as *chemoreceptors;* their adaptation is early and rapid.

Study Questions

1. What special senses are so called?
2. Mention some characteristic features of common chemical senses.
3. How does smell differ from other special sensations?
4. Give the location and functions of olfactory cortex.
5. How does sniffing alters the olfaction?
6. Write short notes on:
   (i) Olfactory receptors (ii) Olfactory mucous membrane (iii) Olfactory cortex
   (iv) Olfactory fatigue (v) Odorant binding protein (vi) Relation between sex and smell.
7. Give the properties of a substance to be effective as an odorant.
8. Mention two components associated with smell of vapours of ammonia.
9. Does advancing age has any effect on olfaction?
10. How humans can distinguish more than 2000 different odours?
11. Define:
    (i) Anosmia (ii) Parosmia (iii) Hyposmia (iv) Telereceptors
12. How can olfactory pathways be inhibited?
13. Give physiological basis of decrease in olfaction:
    (i) if a person suffers from common cold; (ii) in chronic smokers.
14. How can olfactory receptors be distinguished from the surrounding cells?
15. Draw a labelled diagram of olfactory pathway.

MCQs

1. Special sensibility differs from general sensibility in that:
   (a) Its receptors are located together at one place (b) Receptors are specialized and respond only to one type of stimulus
   (c) Receptors lie very close to nervous system (d) All of the above
2. *Not* a feature of common chemical sense:
   (a) It is the capacity to respond to surface application of chemical irritant
   (b) It contributes to appreciation of odour
   (c) Its excessive stimulation gives rise to pain
   (d) Taste is most sensitive of the chemical senses

3. **Smell, *not true* is:**
   (a) It has no relay in the thalamus
   (b) Its receptors are in direct contact with the external environment
   (c) Highly developed in man
   (d) Its receptors are telereceptors as well as chemoreceptors

4. **Olfactory receptor cells, *not true* is:**
   (a) Their dendrites extend as olfactory rods
   (b) Have a short life span of 2-3 days
   (c) Originate from basal cells
   (d) 6-12 cilia are present on each rod

5. ***Not true* of olfactory pathway:**
   (a) Lateral and intermediate olfactory strial are the axons of mitral cells
   (b) Tufted cells axons form medial olfactory striae
   (c) All fibers end in olfactory tubercle
   (d) granule cells depress the activity in the olfactory bulb

6. **Olfactory cortex, *not true* is:**
   (a) Located in the post-central gyrus
   (b) Lies in the limbic system
   (c) Include: anterior olfactory nucleus, piriform cortex, olfactory tubercle, amygdala and entorhinal cortex
   (d) Receives projection from the same side of olfactory mucous membrane

7. **How many different odour a human can distinguish?**
   (a) 1000-2000 (b) 2000-4000 (c) 3000-5000 (d) 5000-7000

8. **The odour discrimination threshold is .... per cent change in odour intensity:**
   (a) 10 (b) 20 (c) 30 (d) 40

9. **Role of higher centres in olfaction is all of the following *except*:**
   (a) Anterior olfactory nucleus transfers olfactory memories from one side to other
   (b) Piriform is concerned with discrimination and conscious perception
   (c) Amygdala is concerned with emotional responses to olfactory stimuli
   (d) Entorhinal cortex is concerned with initiating sneezing → Initiated by pain fibres of Trigeminal N
   → Memory

10. ***Not* a feature of adaptation to smell:**
    (a) Develops within seconds or minutes
    (b) Degree of adaptation cannot be measured
    (c) It is selective to one substance
    (d) Also occurs to irritant chemical sense

11. **Smell receptors are located in:**
    (a) Lower 1/3 of nasal mucosa
    (b) Upper 1/3 of nasal mucosa
    (c) Olfactory bulb
    (d) Cribriform plate

12. **Olfactory receptors are:**
    (a) Sensitive to physical stimuli
    (b) Rapidly replaced
    (c) Slowly adapting
    (d) Bipolar neurons

13. **Type of cells not present in the olfactory bulb:**
    (a) Mitral and tufted cells (b) Granule cells (c) Supporting cells (d) Periglomerular short axon cells

14. **To arouse the sense of smell, odoriferous substance should be:**
    (a) 4-20 carbon atoms
    (b) Relatively high water and lipid solubility
    (c) Volatile
    (d) All of the above

15. **All of the following sensations have 3 chains of neurons *except*:**
    (a) Smell → 2 chains (b) Vision (c) Touch (d) Pressure

16. **Human can distinguish above 2000 different odours. This is possible due to:**
    (a) Presence of different odorant receptors
    (b) Frequency of action potentials in the afferent nerve reaching the brain
    (c) Number of odorant receptors stimulated
    (d) All of the above

17. ***Not* a unique feature of olfaction:**
    (a) Smell pathways have no relay in the thalamus
    (b) Recepts are telereceptors as well as chemoreceptors
    (c) Receptor neurons are in direct contact with external environment
    (d) Receptors do not show fatigue

Answers

1. (d)	2. (d)	3. (c)	4. (b)	5. (c)	6. (a)	7. (b)	8. (c)	9. (d)	10. (b)
11. (b)	12. (d)	13. (c)	14. (d)	15. (a)	16. (d)	17. (d)			

Chapter

108

The Taste = GUSTATION

I. Taste receptors or taste buds

II. Taste pathways

III. Physiology of taste

IV. Applied aspect: Ageusia, hypogeusia, dysgeusia

TASTE RECEPTORS: TASTE BUDS

1. *Flavour* means the complex sensation comprising taste, odour, roughness or smoothness, hotness or coldness, pungent or blandness (non-irritating).
2. The *receptors* for taste are *chemoreceptors* which are stimulated by substances dissolved in the oral fluids. They are located on the edges and dorsum of the tongue, on the epiglottis, soft palate and pharynx.
3. The anterior surface of the tongue is covered with numerous small projections called ***papillae***. The ***taste buds*** **(Fig. 108.1)** are located in the walls of these papillae. There are four types of papillae: **(Fig. 108.2)**
   (i) *Fungiform papillae.* These are rounded structures, most numerous near the tip of the tongue and have about 5 taste buds per papilla usually located at the top of the papilla.
   (ii) *Filiform papillae.* These are small conical papillae that are arranged in diverging rows to the right and left of the midline, and are confined to the back edge of the tongue. They *do not contain taste buds.*
   (iii) *Vallate (or circumvallate) papillae.* These are prominent papillae arranged in a V form at the back of the tongue. Only 10-12 of these structures are present each containing upto 100 taste buds located along the sides of the papillae.
   (iv) *Foliate papillae.* These are found occasionally upon the posteriolateral surfaces of the tongue.
4. In man the total number of taste buds is about 10,000. The number decreases in old age.
5. ***Taste buds*** are oval (egg-shaped) clusters of cells in the epithelial layer with a small pore opening on the

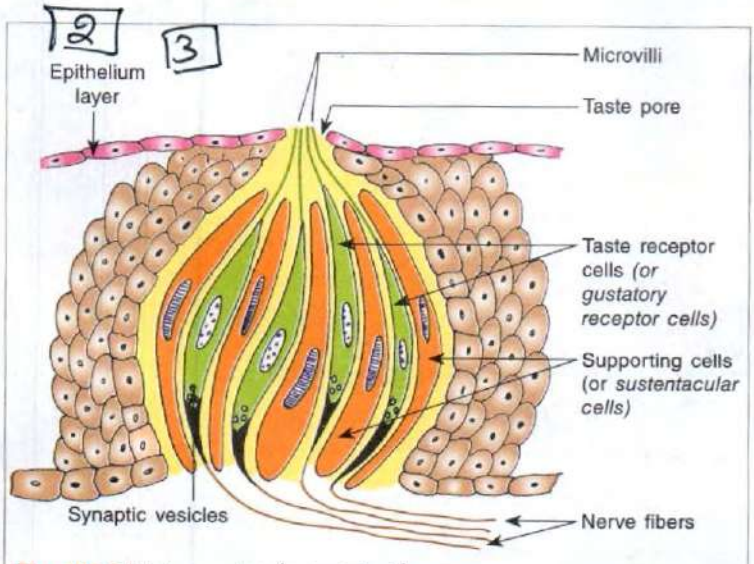


Fig. 108.1 Taste receptor (or taste bud)

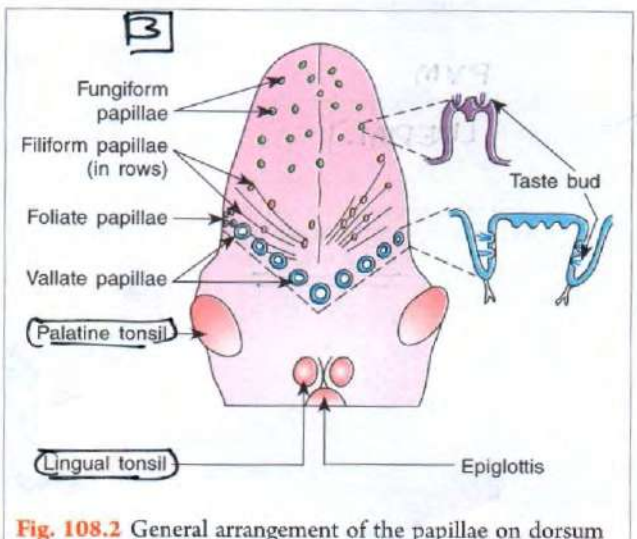


Fig. 108.2 General arrangement of the papillae on dorsum of tongue upon which the taste buds are located

surface that allows substances to reach the interior of the taste bud. It measures 60-80 µm in length and 40 µm in diameter. The cells within the taste buds (*taste cells*) are of *two types: gustatory receptor cells* and *supporting* or *sustentacular cells*. It is presumed that all the cells in the taste bud are sensory but in different stages of development. However, only gustatory receptor cells make synaptic connection to sensory nerve fibers **(Fig. 108.1)**.

6. The ***taste cells*** are formed from the epithelial cells surrounding the taste bud and migrate towards the centre as they mature and finally degenerate in about 10 days. Each gustatory receptor cell ends in 'microvilli' at the top near the pore. Each taste cell is sensitive to only one of the tastes.
7. The **afferent nerves from the gustatory receptor** cells begin as minute fibers within the cell. These fibers join to form two or three large fibers and each large fiber connects with one or more taste cells. Therefore, each taste bud is innervated by approx. 50 nerve fibers, and each nerve fiber in turn receives input from about 5 taste buds.

Note

Taste buds degenerate and disappear within a week after the afferent nerve to the taste bud is cut.

TASTE PATHWAYS

1. The sensory fibers from the taste buds in the **anterior 2/3rd** of the tongue run in the lingual nerve which branches from the *chorda tympani* nerve (branch of *VII nerve*) **(Fig. 108.3)**.

Note

The *general sensations* of touch, pain, pressure and temperature from this region of the tongue pass first into the trigeminal (V) nerve and then join the chorda tympani nerve.

2. Taste fibers from the **posterior 1/3rd** of the tongue run in the glossopharyngeal **(IX) nerve** and those from the **epiglottis and pharynx** in the *vagus (X) nerve*.
3. The small myelinated taste fibers of all the three nerves run into the ***nucleus of tractus solitarius (NTS)*** in the medulla.
4. The cell bodies of the *second order neurons* are located in NTS and their axons ascend on the same side to join the medial lemniscus (page 892) and terminate with V nerve fibers (carrying touch, pain and temperature fibers) in the posteroventral nucleus of the thalamus.
5. The *third order neurons* arise from here and end in the inferior part of the ipsilateral postcentral gyrus (sensory cortex).

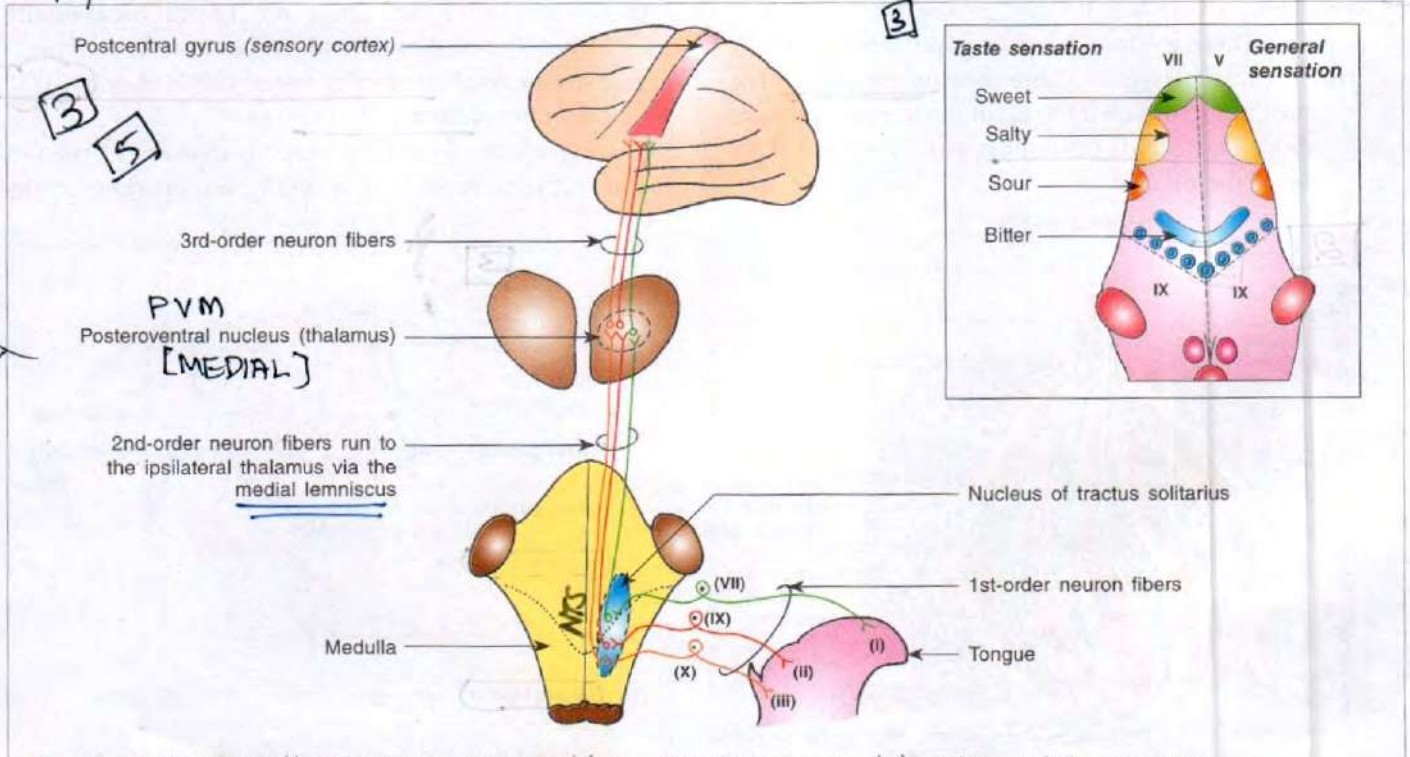


Fig. 108.3 Taste pathway (i) anterior 2/3rd of tongue; (ii) posterior 1/3rd of tongue; (iii) epiglottis and pharynx region
{**Inset**: Sensory innervation of the various regions of the tongue (V, VII and IX: trigeminal, facial and glossopharyngeal nerves respectively)}

Note

All the afferents from the tongue, both of taste and general sensibility, travel along the same pathway to the thalamus and sensory cortex.

PHYSIOLOGY OF TASTE

1. Receptor stimulation

Taste producing substance (*Tastants*) first gets dissolved in the oral fluid and then acts by forming a weak attachment to receptors on the microvilli of the gustatory cells. This combination evokes *generator potential* in the gustatory receptor cells and action potentials are generated in the sensory nerves. The binding of substances to the receptors is *weak* because the taste produced by any substance is abolished by washing the tongue with water.

2. Modalities or qualities of taste

(i) There are *four* basic qualities of taste: *sweet, salt, sour* and *bitter* from which the numerous varieties of tastes of individual substances are made out.

Important Note

Recently, *Umami* (means delicious in Japanese) a fifth taste sense has been added to the four classical taste modalities. This taste is pleasant and sweet but differs from the standard sweet taste. It is mediated by glutamic acid acting on *metabotropic glutamate receptors* (mGlu R4) (located on tongue and stomach). Glutamic acid is abundant in breast milk and is present in most of the natural food (vegetables, specially tomato; cheese; milk; meat and seafood). Glutamic acid is closely involved in smooth digestion and absorption of proteins.

(ii) In the tongue, *sweet and salt* sensitivities are the greatest at the tip, sour at the sides and *bitter* at the back.

Important Note

Salt sensitivity is more homogeneous but the greatest at the tip. However, all four taste modalities can be sensed on the palate, pharynx and epiglottis.

(iii) The *mid-dorsum* is *insensitive* to all tastes.

(iv) Individual taste buds can respond exclusively to salt, sweet, bitter or sour substances or to combination of basic taste modalities.

Important Note

The taste buds selectively sensitive to five qualities of taste show the same histological appearance.

(v) Each taste bud possesses a *cluster of receptors*, the sensitivities of which vary among different taste buds. For example, a nerve discharge from a given receptor cell may be produced by low concentration of NaCl or high concentration of glucose, but in another cell the reverse will hold *i.e.* any one cell reacts to a varying degree to several different chemical stimuli.

Important Note

In man there are no taste receptors which respond to distilled water; whereas in dog, cat, pig and monkey such taste receptors do occur.

3. Substances producing basic taste sensations. There is no clear relationship between chemical composition of a substance and basic taste sensation, *i.e.* the nature of the combination between taste producing substance and specific receptor substance is unknown. Electrophysiological studies have shown the following results:

(i) ***SOUR***

(a) The sour taste is *due to* H^+ (*protons*) and degree of sourness is proportional to the degree of dissociation of H^+ from an acid. This is why *organic acids are often more sour* for a given H^+ concentration than are mineral acids.

(b) Acids which taste sour, depolarize receptor cells by raising intracellular $[H^+]$ by *Na^+ selective channel (ENaC)*. The H^+ can also bind to and block a *K^+ sensitive channel*.

(c) Some acids have other tastes as well; for example:

- citric acid is sweet as well as sour;
- picric acid is bitter and sour; and
- amino acids may taste sour, bitter, sweet or salty depending on the concentration.

(ii) ***SALTY***

(a) Example of pure salty taste is sodium chloride. It is *produced by Na^+*. Salt stimuli depolarize salt receptor cells by influx of Na^+ through *ENaC* channels to trigger release of glutamic acid. (*Proof:* application of Na^+ channel-blocking diuretic amiloride directly to the tongue abolishes the ability to taste salt.)

(b) The anion also contributes to the taste of salts but the *cation can modify the anionic effect;* for example:

- potassium salts tend to be bitter as well as salty and potassium iodide is only bitter;
- salts of heavy metals such as mercury have a metallic taste and lead acetate salt a sweet taste.

(iii) ***BITTER***

(a) Bitter taste is produced by many types of chemical substances such as quinine sulphate, strychnine hydrochloride, morphine, nicotine, caffeine, urea, phenylthiourea, magnesium sulphate etc.

(b) Many sweet substances have an accompanying bitter taste or *after taste*, such as saccharin. This *double taste* is due to the fact that the substance moves from the front of the tongue, where sweet tastes are appreciated, to the back where bitter sensitivity is particularly developed.

(c) The bitter taste is *due to cations*. Substances that taste bitter act via G-protein coupled receptors and phospholipase C to cause release of Ca^{2+} from the endoplasmic reticulum thus raising intracellular $[Ca^{2+}]$.

(iv) ***SWEET***

(a) The sweet taste is *due almost entirely to organic compounds*. Sucrose is the reference substance for the pure sweet taste.

(b) The taste sensation is not the same for all the sugars; for example, fructose is sweeter than sucrose whereas maltose, galactose and lactose are less sweet than glucose.

(c) Synthetic sweetners like saccharin are used as substitutes for sucrose in diabetes and obese persons in whom sugar intake must be reduced.

(d) Substances that taste sweet appear to bind to membrane receptors, via G_S and activate adenylate cyclase with a resulting increase in intracellular cAMP. This leads to the closing of K^+ selective channels.

4. Taste thresholds and intensity discrimination

(i) A 30% change in the concentration of the substance being tested is necessary before an intensity difference can be detected.

(ii) Taste threshold of different substances:

Substance	Threshold concentration (mol/L)
Sour (hydrochloric acid)	0.0001
Salty (sodium chloride)	0.02
Bitter (quinine sulphate)	0.000008 (this provides prevention against poisoning)
Sweet (glucose)	0.08
Sweet (sacchrin)	0.000023

(iii) Women are more sensitive to sweet and salt and less sensitive to sour.

5. Factors influencing taste sensations

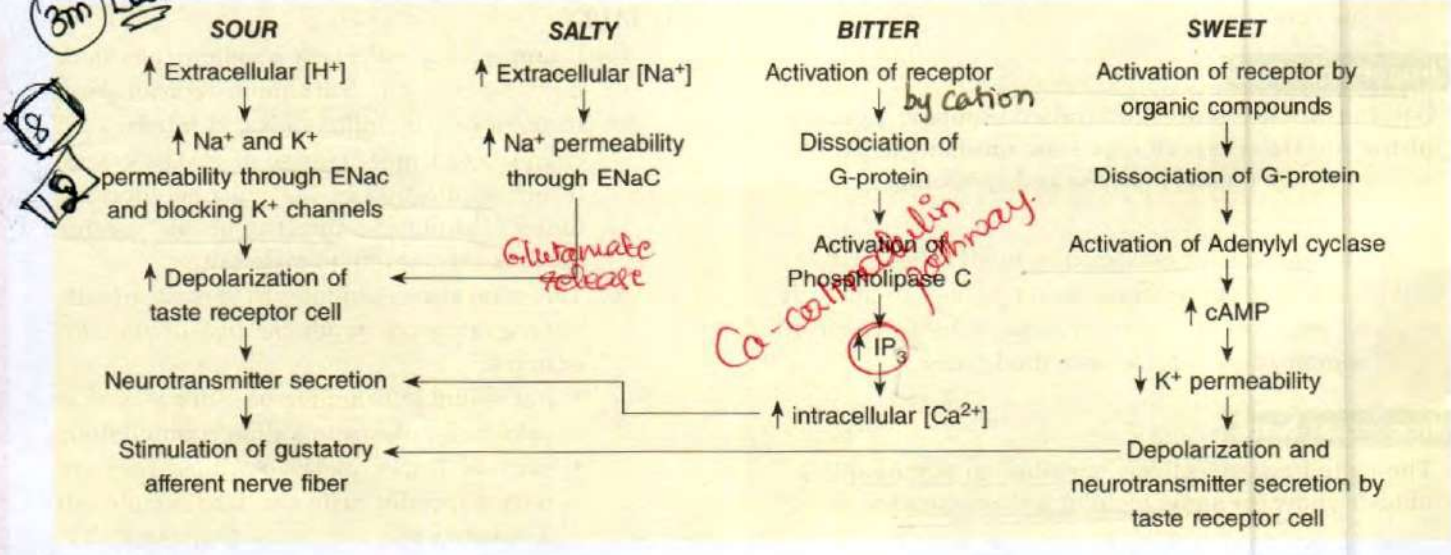
(i) *Area*. The threshold of taste sensation decreases as the area of stimulation increases, therefore, stimulation of a small area of the tongue by one drop of solution produces weaker sensations than does tasting the same solution by the whole mouth.

(ii) *Temperature*. The optimal sensitivity to taste-producing solutions occurs when their temperature is within the range 30-40°C.

(iii) *Individual variations in response*. Variations in sensitivity to taste producing solutions are common, and there is a general decrease in sensitivity in older people. The conditions in which sense of taste is defective are:

(a) ***Familial dysautonomia***. This is a congenital widespread sensory disorder characterized by an inability to recognize by taste even

Summary: The cellular mechanisms of various taste modalities



saturated solutions of reference taste producing substances. The condition is also associated with postural hypotension, absence of lacrimation, hyporeflexia and insensitivity to temperature and noxious stimulation.

(b) ***Selective taste blindness.*** This is an inherited condition in which there is a very marked rise in threshold to the bitter taste of *phenylthiourea* (phenylthiocarbamide). The defect is highly selective since there is no taste blindness to other bitter taste substances or to substances which taste sweet, salt or sour. There is probably a particular receptor protein which is not synthesized in these individuals.

(iv) *Adaptation*

(a) It is a common experience that taste producing substances quickly produce adaptation if kept in one place in the mouth. The adaptation is peripheral.

(b) Interaction between taste-producing substances is a well known phenomenon; the reduction of the sour taste of fruits by sucrose is a good example.

(c) Adaptation to one acid produces adaptation to other acids, because H^+ is the stimulus in all cases.

(v) *Acceptance and rejection of foods*

(a) Taste leads to one of the two reactions, acceptance or rejection. Among the four basic tastes, sweet is the most generally acceptable; bitter quickly becomes unpleasant beyond a small degree; and acids and salts are pleasant initially but moderate concentrations become unpleasant.

(b) Acceptance or rejection is related to the metabolic state; for example, patients with hypoglycemia find strong sugar solution more pleasant to taste than when the blood sugar is normal.

(vi) *A taste modifying protein, miraculin*, has been discovered in a West African plant. This protein itself is tasteless and does not affect the sensation of bitter or salt. However, when applied to the tongue, it makes acids taste sweet.

APPLIED ASPECT

1. *Ageusia* is the absence of the sense of taste. Sulphydryl groups of drugs like captopril and penicillamine or vitamin B_{12} or zinc deficiences can cause temporary loss of taste sensation. It can also be due to damage to the lingual or glossopharyngeal nerve.
2. *Hypogeusia* means diminished taste sensitivity. It is seen with aging and tobacco abuse.
3. *Dysgeusia or Parageusia* (unpleasant disturbed sense of taste) cause a metallic, salty, foul or rancid taste.

Study Questions

1. Define and give physiological significance of:
   (i) Flavour (ii) After taste
   (iii) Dysautonomia and taste blindness (iv) Ageusia, hypogeusia and dysgeusia.
2. Mention functional anatomy of taste buds.
3. Illustrate with the help of diagrams:
   (i) Structure of taste bud (ii) Taste pathways
   (iii) General arrangement of taste papillae over tongue (iv) Distribution of taste modalities on the tongue.
4. Write shorts notes on:
   (i) Sustentacular cells (ii) Gustatory receptor cells (iii) Papillae on tongue
   (iv) Taste modalities (v) Taste adaptation (vi) Mechanism of stimulation of taste receptors
   (vii) Miraculin. (viii) Umami (ix) Taste threshold and factors influencing taste
5. How is taste information conveyed from the tongue to the brain?
6. What will happen to taste bud if its afferent nerve is cut?
7. Comment on taste of distilled water in humans.
8. Mention relation between chemical composition of a substance and basic taste sensations.
9. Why are organic acids more sour than mineral acids?
10. If we have to swallow a medicine, we usually avoid it to touch the tongue. Why?
11. What will happen to taste if both the hypoglossal (XII) nerves are cut?
12. Describe briefly cellular mechanisms of various taste modalities.

MCQs

1. **Taste buds are *not* located on the:**
   (a) Dorsum of the tongue (b) Edges of the tongue
   (c) Right and left of the midline and back edge of tongue (d) Epiglottis, soft palate and pharynx
2. **Which of the papilla *do not* contain taste buds?**
   (a) Fungiform (b) Filiform (c) Vallate (d) Foliate
3. **Taste receptors show the following properties *except*:**
   (a) Non-specificity for various modalities of taste (b) Rapid adaptation
   (c) Rapid renewal of cells (d) Make permanent chemical bond with stimulating substances
4. ***False* statement regarding taste pathways:**
   (a) General sensation from different regions of the tongue run in the corresponding nerves that convey taste
   (b) All afferents from the tongue both of taste and general sensibility, travel along the same pathway to the thalamus and sensory cortex
   (c) A three neuronal pathway
   (d) Destruction of post central gyrus reduces the taste sensibility
5. **Which of the following *do not* depict clear relationship between chemical composition of a substance and basic taste sensation:**
   (a) Sour is due to H^+ (b) Salt is produced by Na^+ (c) Bitter is due to cations (d) Sweet is due to saccharin
6. **Percentage change in the concentration of a substance necessary before an intensity difference in taste can be detected:**
   (a) 10% (b) 20% (c) 30% (d) 40%
7. ***False* statement concerning taste sensations:**
   (a) Women are more sensitive to sweet and salt and less sensitive to sour
   (b) Taste sensitivity decreases in older people
   (c) In women, it is most acute at the time of ovulation
   (d) Optimal sensitivity occurs between temperature range 30-40°C
8. **Among the four basic taste modalities, which one is the most generally acceptable?**
   (a) Salty (b) Sweet (c) Sour (d) Bitter
9. ***Not a correct* match:**
   (a) Ageusia: absence of the sense of taste (b) Hypogeusia: diminished taste sensitivity
   (c) Dysgeusia: disturbed sense of taste (d) Dysautonomia: Increase in taste threshold
10. **Which of the following is *not* a primary taste sensation?**
    (a) Pungent (b) Sweet (c) Salty (d) Sour
11. **Taste buds (or taste receptors) are:**
    (a) Surface epithelial cells (b) Specialised nerve endings (c) Modified epithelial cells (d) Telereceptors
12. **The taste buds are present in all of the following papillae *except*:**
    (a) Fungiform (b) Circumvallate (c) Vallate (d) Filiform
13. **Substentacular cells in taste buds are:**
    (a) Gustatory receptors (b) Taste receptors (c) Supporting cells (d) Taste cells
14. **Bitter taste is felt at the following part of the tongue:**
    (a) Tip (b) Back (c) Mid dorsal (d) Sides
15. ***Not a true* statement regarding taste modalities:**
    (a) Mid dorsum of tongue is insensitive to all tastes
    (b) Individual taste bud can respond exclusively to one primary taste modality only
    (c) In humans there are no taste recep-tors which respond to distilled water
    (d) Taste buds selectively sensitive to four qualities of taste show the same histological structure
16. ***Not a true* match of taste with the substance:**
    (a) Sour: Hydrochloric acid (b) Salty: Sodium chloride (c) Bitter: Nicotine (d) Sweet: Strychinine
17. **Miraculin, a taste modifying protein when applied to the tongue, it makes acids taste:**
    (a) Sour (b) Bitter (c) Salty (d) Sweet

Answers

1. (c) 2. (b) 3. (d) 4. (a) 5. (d) 6. (c) 7. (c) 8. (b) 9. (d) 10. (a)
11. (a) 12. (d) 13. (c) 14. (b) 15. (b) 16. (d) 17. (d)

Chapter
109

The Ear

I. Physiological anatomy
II. Auditory pathways
III. Physical properties of sound
IV. Mechanism of hearing
V. Electrophysiology of hearing:
A. Electrical activity of cochlea
B. Action potential of the auditory nerve fibers
C. Auditory cortex
VI. Applied aspect: Deafness; Tinnitus
VII. Tests for hearing

· Tympanic reflex ·

PHYSIOLOGICAL ANATOMY

The ear is the organ of *hearing* and *equilibrium*. It is divided into *three parts* viz. the *External* ear, the *Middle* ear and the *Internal* ear **(Fig. 109.1)**.

A. THE EXTERNAL EAR

The external or the outer ear includes the *pinna* and the *external auditory meatus*.

1. The ***pinna***. It is a cartilagenous expanded portion covered with skin projecting from the side of the head. It helps to *collect sound waves* and *to localize* the source of sound.
2. The ***External auditory meatus*** or *outer ear canal*. It is 2.5 cm long, runs forwards and inwards (medially), and helps in transporting the sound waves to the middle ear. It is lined with skin which secretes wax (from ceruminous glands) and oil (from sebaceous glands), which by trapping the foreign bodies keep the ear canal clear. It terminates at the ***tympanic membrane*** (ear drum) which covers the opening of the middle ear.

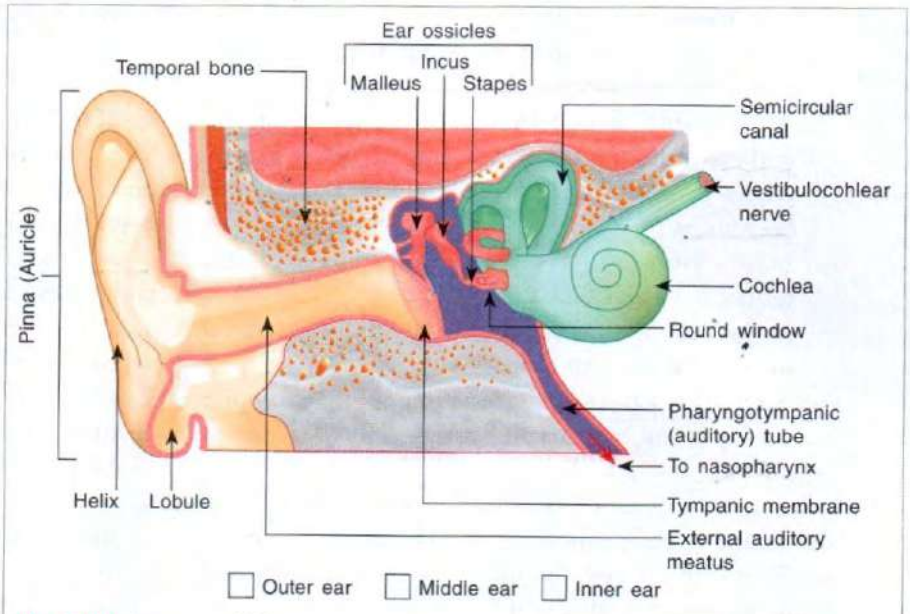


Fig. 109.1 Structure of the ear

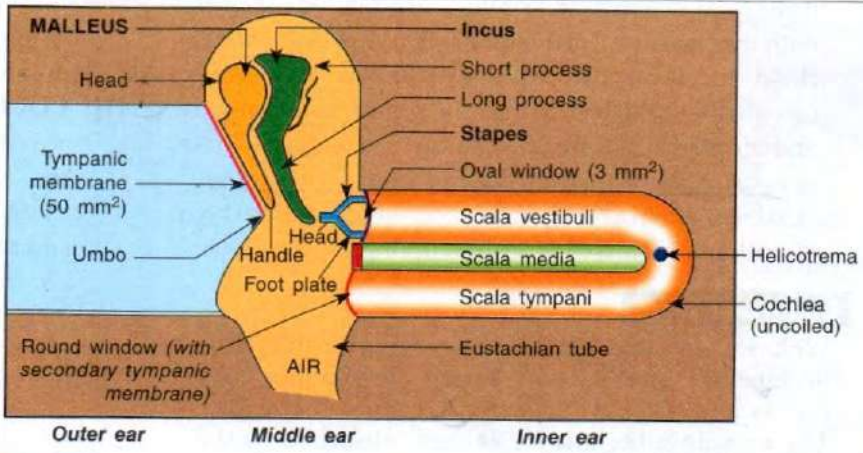


Fig. 109.2 Arrangement of ear (auditory) ossicles in the middle ear and scalae in the cochlea (inner ear)

B. THE MIDDLE EAR

It is *an air filled chamber* and consists of the following parts: **(Fig. 109.2)**

1. ***Tympanic membrane***
   (i) It consists of connective tissue covered with skin on the outside and mucous membrane on the inside.

(ii) It has the shape of a shallow funnel with the centre (UMBO) pointing inwards and is kept in this position by the handle of the malleus.

(iii) The presence of air at atmospheric pressure on both sides of the tympanic membrane enables it to vibrate freely when sound waves strike it, which are then passed on to the *ear ossicles.*

2. ***Ear ossicles or auditory ossicles***

There are *three* minute bony (ear) ossicles, viz. *Malleus* (hammer), *Incus* (anvil) and *Stapes* (stirrup). They extend across the cavity from the tympanic membrane to the *oval window.*

(i) *Malleus* (*hammer*)

(a) its *handle* is attached to the inner side of the tympanic membrane and its tip is situated at the umbo;

(b) its *head* is firmly bound by ligaments to the incus.

(ii) *Incus* (*anvil* – an iron block on which a smith hammers metal into shape).

At one side it is attached to the head of the malleus and on the other side its *long process* passes downwards to articulate with the head of the stapes.

(iii) *Stapes* (*stirrup* – a support for a horse rider's foot).

Its *foot plate* is attached by annular ligament to the margins of the *oval window.*

Function: The ear ossicles function to magnify the *intensity of sound* by 1.2 to 1.3 times. How? (Refer to page 1068).

The opposite wall of the middle ear contains two membrane-covered openings which face the internal ear. They are an ***oval window*** above and a smaller ***round window*** just below it.

3. ***Pharyngotympanic tube or Eustachian tube***

It is 4-5 cm in length and connects the middle ear cavity with the pharynx. Normally its pharyngeal opening is closed but it can be opened by swallowing, chewing or yawning which contracts the tensor palati muscle and air enters into the middle ear. Therefore, it *serves to equalize the pressure on the two sides of the tympanic membrane* when atmospheric pressure decreases (high altitude) or increases (deep sea diving).

Important Note

With the closure of the pharyngotympanic tube by infection such as sore throat or common cold, the swallowing mechanism becomes ineffective. The air within the middle ear gets absorbed by the mucous membrane and its pressure decreases; as a result the tympanic membrane bulges inwards and its vibrations get decreased or abolished, causing discomfort and loss of hearing.

4. ***Two skeletal muscles:*** *Tensor tympani and 'Stapedius'*

(i) *Tensor tympani.* It is attached to the neck of malleus and innervated by trigeminal (V) nerve. Its contraction increases the tension of tympanic membrane by pulling the handle of the malleus medially. Thus it keeps the tympanic membrane firmly attached.

(ii) *Stapedius.* It is attached to the neck of the stapes and to the posterior wall of the middle ear. It is innervated by facial (VII) nerve and on contraction it pulls the foot plate of the stapes out from the oval window.

Function: Both the muscles, the tensor tympani and stapedius can be reflexly activated by loud sounds and this reflexly decreases the amplitude of sound vibration of the tympanic membrane. Thus they serve a protective function by *protection of the internal ear from loud sounds* (also see to page 1074).

LOUD SOUND PROTECTION !!

C. THE INTERNAL EAR

The internal or inner ear consists of *two parts*: the ***bony labyrinth*** and the ***membranous labyrinth.*** The bony labyrinth is a series of channels in the temporal bone which enclose the membranous labyrinth; the latter comprises of:

1. One *vestibule (utricle and saccule).* It is the expanded part very close to the middle ear. (Equilibrium)
2. One *cochlea* (resembles shell of a snail). It is a special tube having a broad base with a narrow apex and is concerned with hearing.
3. Three *semicircular canals* which communicate with the vestibule are arranged at right angle to each other. Together it is called the ***vestibular apparatus*** and is concerned with the equilibrium *i.e.* maintenance of posture and balance of the body (page 941). It detects head motion and position and transfer these informations to a neural signal.

U.S → Static balance; Semicircular canals → Dynamic bal.

THE COCHLEA

1. It is a coiled tube, 35 mm long which makes 2·5 to 2·75 turns.
2. Its lumen is divided throughout the length by two membranes ***(Reissner's and Basilar membranes)*** into three compartments or scalae **(Fig. 109.2 and 109.3)**.

(i) *Scala vestibuli*, a space above the Reissner's membrane and is filled with ***perilymph.***

(ii) *Scala tympani*, a space below the Basilar membrane and is also filled with *perilymph.* (Have / Not)

(iii) *Scala media*, a space between Reissner's and Basilar membranes and is filled with K^+ - rich fluid called ***endolymph.*** It is a closed space and is continuous with the membranous labyrinth.

#: Also contain Ca^{2+}

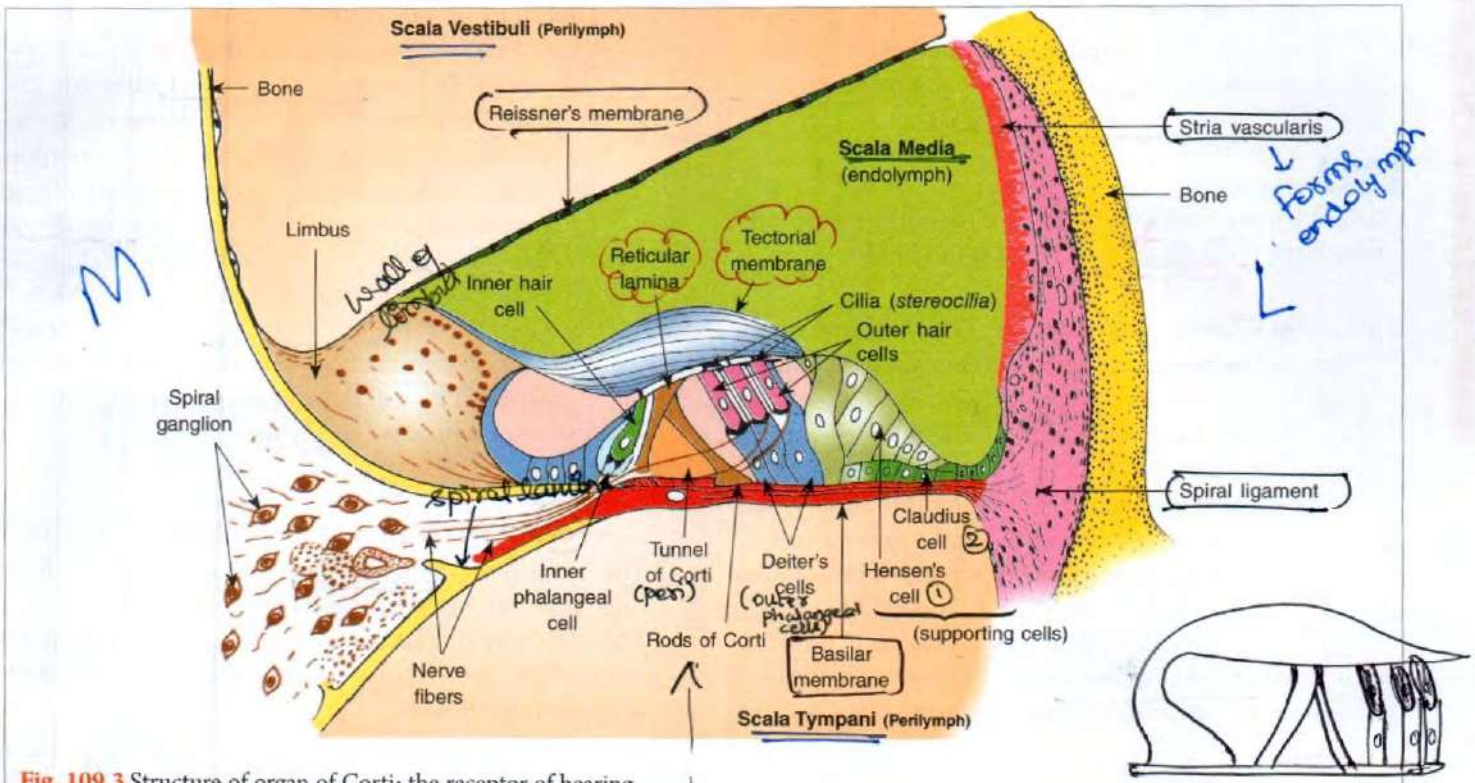


Fig. 109.3 Structure of organ of Corti: the receptor of hearing

3. The basilar membrane is attached medially to the bony spiral lamina and laterally to the fibrous spiral ligament, whereas the Reissner's membrane is attached medially to the wall of the limbus and laterally to the upper margin of the stria vascularis.
4. Scala tympani and scala vestibuli communicate at the apex by a small opening called *Helicotrema*. At the base of the cochlea, the scala vestibuli ends at the oval window which is closed by the foot plate of the stapes. The scala tympani ends at the *round window*, a foramen on the medial wall of the middle ear which is closed by the flexible *secondary tympanic membrane*.
5. *Receptor of hearing:* ***THE ORGAN OF CORTI***
   (i) The primary receptor of hearing is the 'organ of Corti' which is located on the basilar membrane extending from the apex to the base of the cochlea. On this membrane stand two rods (***rods of Corti***) which project into the scala media. In between the two rods is a ***tunnel of corti*** which is filled with *perilymph* (page 1077).
   (ii) Internal (*i.e.* medial) to the inner rod is a single row of ***inner hair cells***, and external (*i.e.* lateral) to the outer rod are three or four rows of ***outer hair cells***. There are in all 3500 'inner' hair cells and 20,000 'outer' hair cells in each cochlea.
   The inner hair cells are supported by inner *phalangeal cells* while the outer hair cells are supported by *Deiter's cells* (outer phalangeal cells).
   (iii) From the upper surface of the hair cell project tiny 'cilia', also called ***stereocilia*** (8-12 µm in diameter, 4 µm long and 0.1 µm thick) which pass through a thin dense granular *Reticular lamina* and get embedded in the *Tectorial membrane*.

Notes

1. The stereocilia which pass through reticular lamina are bathed in endolymph, whereas the bases of the hair cells are bathed in perilymph (also refer to page 1077).
2. The stereocilia of inner hair cells are probably not attached to the tectorial membranes.

   (iv) The ***reticular lamina*** is a tough membrane supported by rods of Corti.
   (v) The ***tectorial membrane*** is a thin but stiff gelatinous (viscous) elastic structure made of glycoprotein material. It is like a spiral ribbon which is attached at one end to the 'limbus', and by one surface and its outer edge to the *Hensen's cells* (supporting cells of organ of corti which lie outside the outer hair cells).
   (vi) ***Innervation***
      (a) ***Afferent innervation.*** The hair cells are innervated by nerve fibers of the cochlear (auditory) division of VIII nerve. These fibers have their cell bodies in the *spiral ganglion*. There are approximately 27,000 fibers in each

a on first order neurons. Most of the fibers, however, supply more than one hair cell and conversely, most hair cells are supplied by more than one fiber.

Note

Although the inner hair cells are less numerous but they have more density (95%) of innervation.

(b) ***Efferent innervation.*** Efferent cholinergic fibers arise from both the ipsilateral and the contralateral superior olivary nucleus via the *olivocochlear bundle.* These fibers descend to join the VIII nerve and end around the bases of 'outer' hair cells (and to some extent to inner hair cells) of the organ of Corti. In general, activity in the efferent fibers causes inhibition of the *afferent fibers* by liberating a hyperpolarizing mediator which is probably acetyl choline (A-ch). It plays an important role in auditory transduction.

(vii) ***Functions of hair cells***

(a) The ***inner hair cells*** are the *primary* sensory cells that *generate action potential* in the auditory nerves and are stimulated by the fluid moving between the tectorial membrane and hair cells. These cell thus besides detecting the sound are also responsible for *fine auditory discrimination.*

(b) The ***outer hair cells*** are responsible for detecting the *presence* of sound and they also *improve hearing* (amplitude and clarity of sound) by influencing the vibration patterns of the basilar membrane.

AUDITORY PATHWAYS

1. The axons of the *spiral ganglion* that innervate the hair cells form the cochlear (auditory) division of VIII nerve. The 'auditory' nerve enters the medulla and ends in *ventral and dorsal cochlear nuclei,* the site of the first synapse **(Fig. 109.4)**.

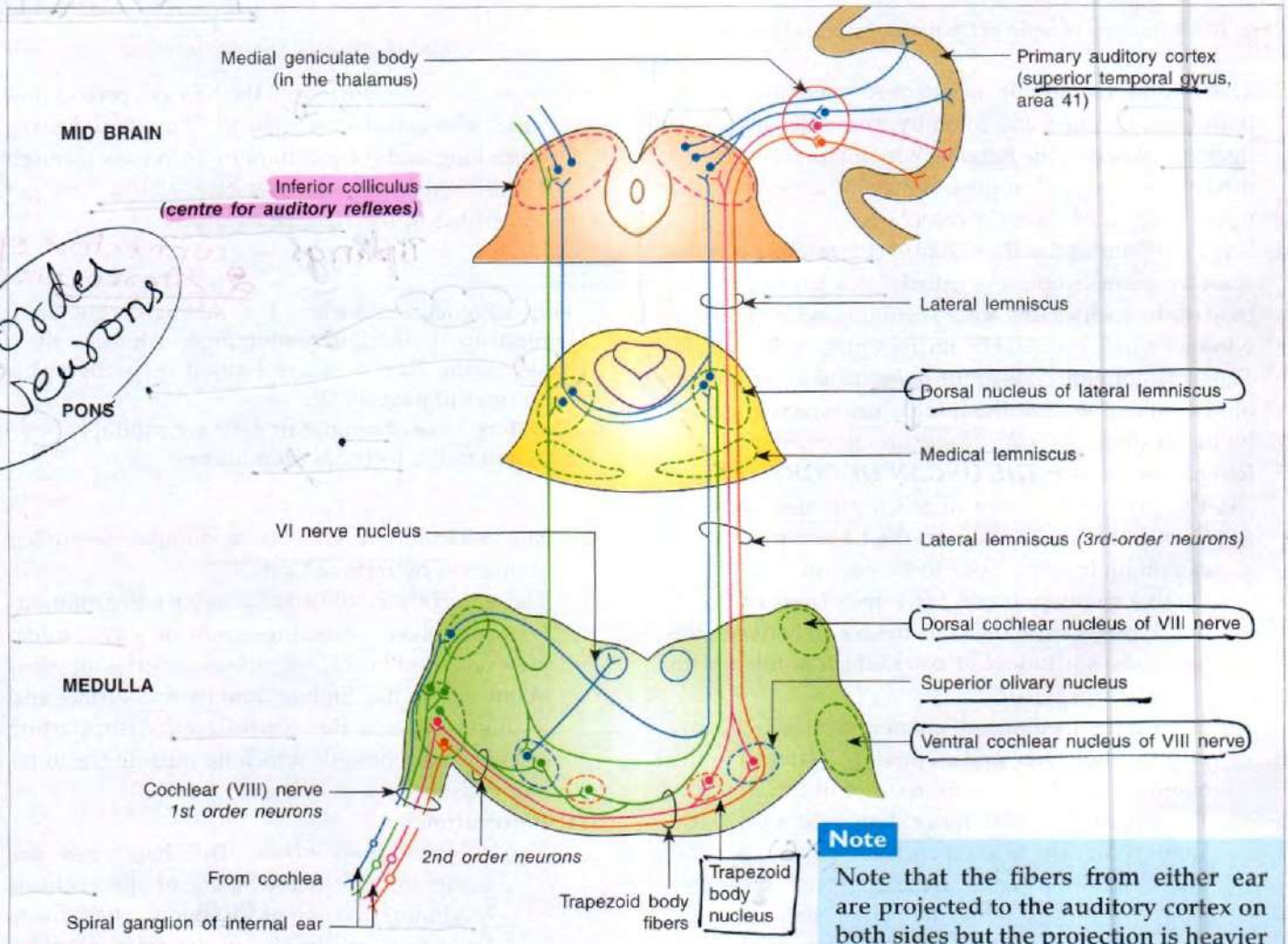


Fig. 109.4 Auditory pathway

Note

Note that the fibers from either ear are projected to the auditory cortex on both sides but the projection is heavier on the contralateral side.

2. Second order neurons from the cochlear nuclei end in *superior olive* and *trapezoid body* on both sides of the brain stem from where third order neurons take origin.

Note

Each superior olivary nucleus receives inputs from both ears.

3. Third order neurons pass up via variety of pathways in the lateral lemniscus to the *inferior colliculi* ***(centre for auditory reflexes)*** of both sides. Some of these fibers also send collaterals to the *reticular formation* and *medial geniculate bodies* in the thalamus.
4. From the inferior colliculi many fibers project and relay in the *medial geniculate bodies;* medial geniculate body neurons finally project to the ***primary auditory cortex (area 41)*** which lies in the superior portion of the temporal lobe located in the floor of the lateral cerebral sulcus. Here nerve impulses are perceived as sound *i.e.* it *receives and perceives auditory informations* such as loudness, pitch, source and direction of sounds.

Note

A portion of the primary auditory cortex called ***planum temporala*** is regularly larger in the left than in the right cerebral hemisphere, particularly in right handed individuals. This is even more larger in musician and other artists who have perfect pitch (page 1073).

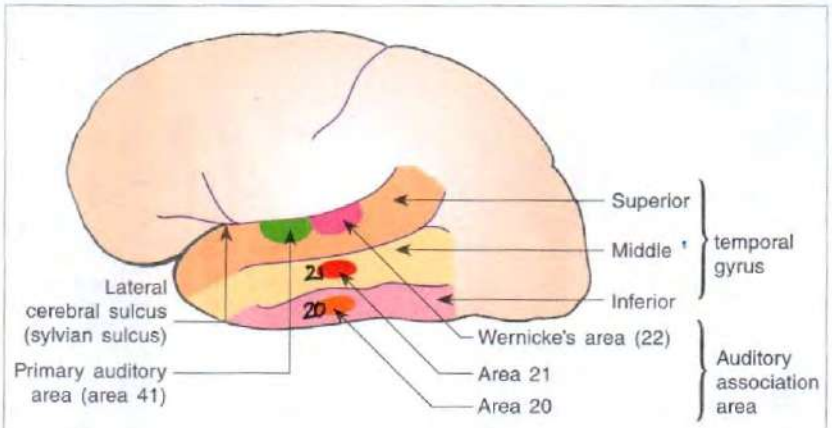


Fig. 109.5 Location of auditory areas

Important Notes

1. Each ear is bilaterally represented in the auditory pathway from the medulla upwards and projects about equally to the two cerebral hemispheres. Thus the removal of one auditory cortex has only a slight effect on *auditory acuity* (sharpness of hearing).
2. Deafness is hardly ever produced by cortical lesions.
3. The auditory pathways are very plastic (page 1073). They are modified by experience. For example:
   (i) individuals who become deaf before language skills are fully developed, viewing sign language activates auditory association areas:
   (ii) individuals who become blind early in life are better at localizing sound than the individuals with normal eye sight.

5. ***Auditory association areas:*** *area* 22, 21 and 20 **(Fig. 109.5)**.
   (i) ***Area 22: Wernicke's area.*** It is located in superior temporal gyrus behind area 41, 42 in the categorical hemisphere *i.e.* dominant hemisphere (page 1031). It is *concerned with* comprehension *i.e.* interpretation and understanding of auditory and visual informations (page 1033). Thus it is concerned with the processing of auditory signals related to speech (spoken or written).

   (ii) ***Area 21 and 20.*** These areas are located in the middle and inferior temporal gyrus and are *concerned with* interpretation and integration of auditory impulses. Lesions of these areas impair auditory short-term memory without impairing visual memory.

3 PHYSICAL PROPERTIES OF SOUND

1. The vibrating objects cause alternating phases of *compression* and *rarefaction* (pressure changes) in the medium surrounding the object. The compressions and rarefactions spread out as sound waves which are perceived by the auditory mechanism as sound **(Fig. 109.6 A)**.
2. Sound *travels in air* at a speed of approximately 330 metres/sec (1100 ft/sec) at 0°C at sea level and increases to 344 metres/sec (1150 ft/sec) at 20°C; while *in water* it travels much faster, at a speed of approx. 1450 to 1500 mts/sec. at 20°C (being greater in salt water as compared to fresh water). The speed of sound *slightly increases with temperature and altitude*.
3. In general *amplitude* (intensity) of sound waves determines the ***loudness*** of a sound while *frequency* of sound waves (number of waves per unit of time) determines the ***pitch*** of the sound. The greater the

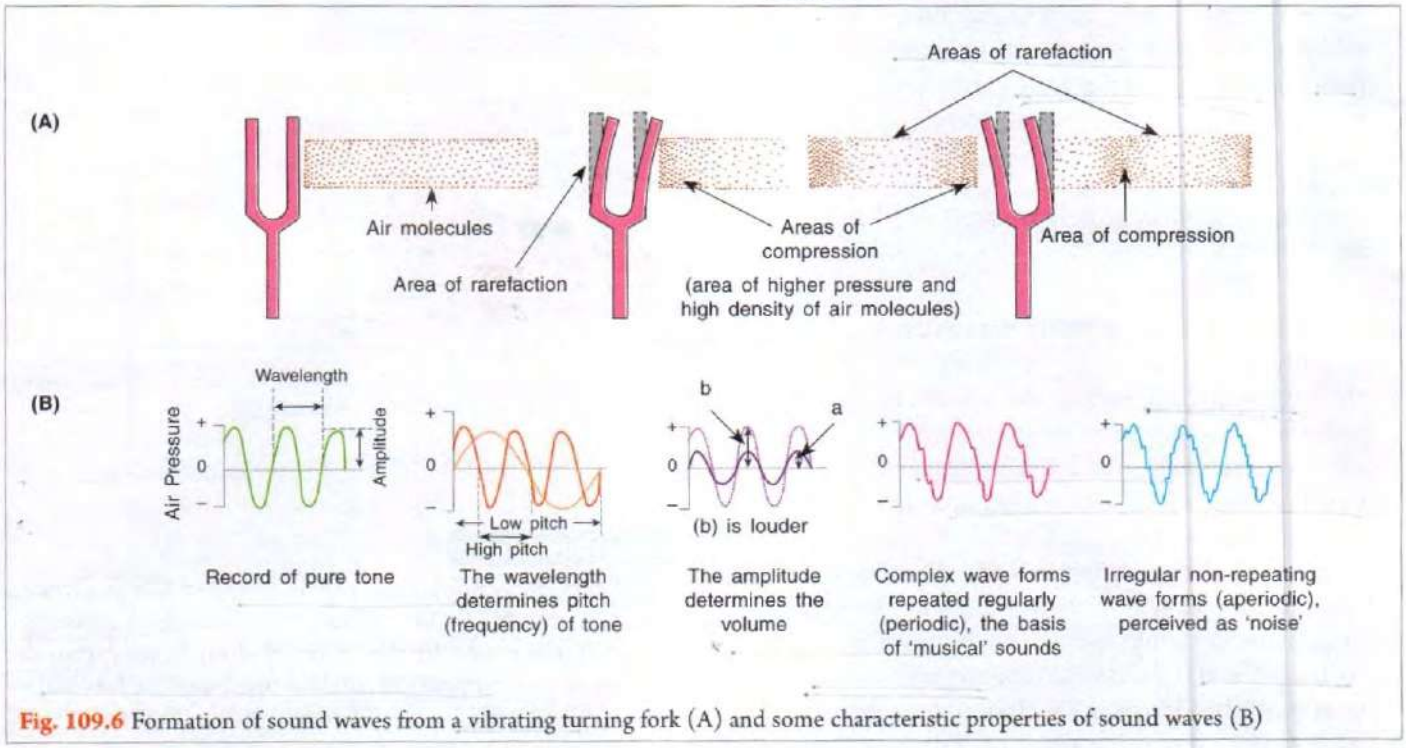


Fig. 109.6 Formation of sound waves from a vibrating turning fork (A) and some characteristic properties of sound waves (B)

amplitude, the louder the sound; and greater the frequency, the higher the pitch.

4. The *wave form* of any periodic vibration (that have repeated pattern) can be resolved into a series of simple waves, of which that with the lowest frequency is called the *fundamental (or primary frequency)*, the others, whose frequencies are multiples of this fundamental, are called *harmonics* or *overtones*. This gives the sound its characteristic *quality*.
5. The ***quality or timbre*** of many sounds are of very complicated 'wave form' but have repeating pattern. These are perceived as ***musical*** sounds **(Fig. 109.6 B)**.

Important Note

Variations in quality (timbre) permit us to identify the sounds of the various musical instruments (such as tabla, sarangi, guitar, etc.) even though they are playing notes of the same pitch.

6. If a sound contains many components which have frequencies that are not simple multiples of the *fundamental*, it is referred to as ***noise***. All noisy sounds are of high amplitude (intensity) and low frequency with completely irregular waves pattern.
7. ***Intensity of sound***
   (i) The intensity (amplitude) of sound is measured in terms of the maximum pressure change at the tympanic membrane, but this is difficult to measure. Moreover, in view of the wide range of intensities involved, a convenient scale of change of intensity is used to describe them. Its unit is ***Bel***. The intensity of a sound in *bels* is the logarithm (log) of the ratio of the intensity of that sound to that of a *reference (standard) sound*. Therefore,

$$1 \text{ bel} = \log \frac{\text{intensity of a given sound}}{\text{intensity of a reference (standard) sound}}$$

Since the intensity of a sound is directly proportional to the square of the sound pressure, therefore

$$1 \text{ bel} = 2 \log \frac{\text{pressure of a given sound}}{\text{pressure of a reference (standard) sound}}$$

Decibel (dB) is more convenient,
1dB = 1/10 bel = 0.1 bel.

(ii) ***'Zero' decibel (dB) = reference (standard) sound.*** It is defined in physical units as 0.0002 dyne/cm^2; such a sound pressure is approximately at the *auditory threshold* for the average human.

Important Note

dB scale is a log scale, therefore, a value of *'zero' dB* does **not** mean the absence of sound but a sound level of an intensity equal to that of the reference (standard).

(iii) **The dB levels of various common sounds are:**

'Zero' dB	: Reference/standard sound
10 dB	: Sound like paper being gently folded
10-30 dB	: Whispering (audible range 2 metres)
30-40 dB	: Normal room noise
40-60 dB	: Normal conversation (audible range 4 metres; intensity of sound approx. 10^6 times as great as 'threshold' of hearing)
60-80 dB	: Heavy traffic noise
80-100 dB	: Loud motor horn; heavy music (intensity of sound approx. 10^{10} times as great as 'threshold' hearing)
100-120 dB	: Noise and discomfort
120-140 dB	: Painful and damaging to the organ of corti (intensity of sound approx. 10^{14} times as great as 'threshold' of hearing)

Important Note

The full range of intensity of sound from the 'threshold' to the loudest tolerable sound can be expressed on the scale between zero and 140 dB. The intensity of sound at the maximum of the scale is actually 10^{14} times that required for 'threshold' hearing. This actually represents a 10^7 fold variation in sound pressure.

8. ***Pitch of Sound***

(i) Human ear can perceive pitch of sound between 16–20,000 cycles per sec or Hertz (Hz). It is *maximally sensitive* to pitch variations in the 1000–3000 Hz range **(Fig. 109.7)**. Why? Refer to page 1074.

(ii) The minimal fractional difference in frequency which is perceptible is 0.3%. Thus a change of 1000 to 1003 and 3000 to 3009 can be detected.

(iii) At very low frequencies (32-64 Hz) the minimal fractional difference in frequency perceptible is 1% and in the upper frequency range (16000 Hz to 20000 Hz) auditory discrimination is very poor.

(iv) *Number of pitches* that can be *distinguished* by an average individual are about 2000 but some individuals like expert musicians violinist can even improve on this by increase in size of the auditory areas activated by musical tone (*An example of cortical plasticity*, page 894).

(v) The pitch of an average male voice during normal conversation is 120 Hz and that of an average female voice is about 250 Hz. 2× ♂ = ♀

4 MECHANISM OF HEARING

The ear converts sound waves in the external environment into action potentials in the auditory (VIII) nerves. How? The sound waves are changed greatly by the tympanic membrane and ear ossicles into movements of the foot plate of the stapes. These movements set up waves in the fluid present in the inner ear. The action of the waves on the organ of Corti generates action potentials in the nerve fibers.

A. ROLE OF EXTERNAL EAR (refer to page 1067)

B. ROLE OF MIDDLE EAR

1. ***Tympanic membrane:*** *Characteristic features*

(i) It acts as a *pressure receiver* *i.e.* it is extremely sensitive to pressure changes produced by sound waves on its external surface;

(ii) it acts as a *resonator* *i.e.* it starts vibrating (in and out movements) freely when the sound waves strike; free vibrator

(iii) it *critically dampens* (stops the vibrations of) the sound waves *i.e.* as soon as the sound waves will stop stretching the tympanic membrane, its vibrations are stopped almost immediately.

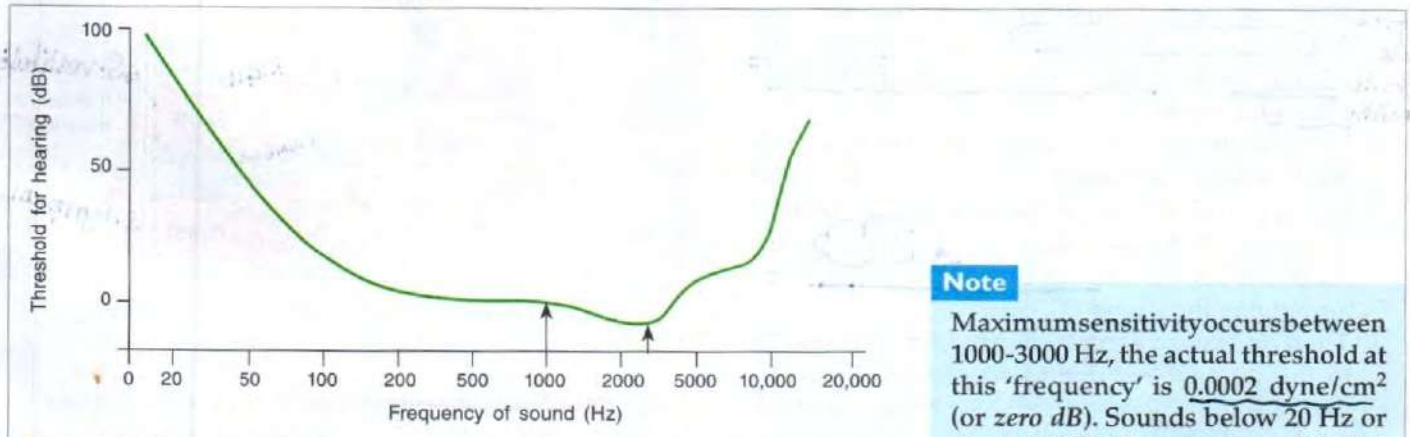


Fig. 109.7 Minimum audibility curve for a normal subject threshold for hearing at different frequencies in the hearing range (also refer to page 1074)

Note

Maximum sensitivity occurs between 1000-3000 Hz, the actual threshold at this 'frequency' is 0.0002 dyne/cm^2 (or *zero dB*). Sounds below 20 Hz or above 20,000 Hz are not amplified at all. Non-amplified sounds

2. *Ear (auditory) ossicles*

(i) The ear ossicles (*malleus, incus, stapes*) ***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.

(ii) The middle ear contains the air, inner ear contains fluid, therefore, *sound is transmitted from the air to the fluid.* As fluid has got inertia, therefore, sound is not transmitted so easily into the inner ear, it is transmitted by increasing the pressure in the middle ear. How?

(a) *The ear ossicles move as a single unit.* Size of the handle of the malleus is less than size of the incus, while size of the stapes is less than the incus; moreover, handle of the malleus is longer than the long process of the incus – all these factors result in *magnification of sound intensity by 1.2–1.3 times*.

(b) The effective surface area of the tympanic membrane is 50 mm^2 and that of the oval window is 3 mm^2, thus reduction of the area is by about 17 times (50/3) at the level of the oval window **(Fig. 109.2)**. This leads to the corresponding increase in pressure at the oval window.

(a) and (b) increase the pressure within the middle ear by 22 times (17 × 1.3). This is referred to as *Impedance Matching*. Thus when the stapes is pressed into the oval window, this pressure is transferred to the perilymph in the scala vestibuli (internal ear).

Important Notes

1. Amplifiction of sound intensity is greatest between 1000-3000 Hz. Sounds below 16 Hz or above 20000 Hz are not amplified at all. This accounts for *minimum audibility curve i.e.* the ability of the middle ear to magnify some sounds better than others **(Fig. 109.7)**.
2. Effective transfer of sound energy from an air to a fluid medium is difficult because most of the sound is reflected as a result of the different mechanical properties of the two media. The middle ear thus functions as an *impedance matching* device by amplifying the sound pressure.
3. There is loss of sound energy from the middle to the internal ear due to resistance offered by the fluid in the internal ear. As a result about *60-70% of the sound energy which falls on the tympanic membrane gets transmitted to the fluid in the cochlea.*

Tympanic Reflex or Acoustic Reflex

A. It is a *protective reflex against the loud sound.* Loud sound initiates a reflex contraction of the middle ear muscles.

(i) Contraction of tensor tympani by causing tensening of the tympanic membrane, decreases its vibrations;

(ii) Contraction of stapedius muscle pulls the foot plate of the stapes out of the oval window.

Thus excessive sound is prevented from going to the oval window.

B. *Reaction time* of this reflex is 40-160 msec *i.e.* it develops in 40 msec and completed in 160 msec. Therefore, a sudden brief extremely loud sound such as due to bomb explosion or gun shot by causing excessive displacement of the hair cells from the tectorial membrane results in deafness.

C. *Role of eustachian tube* (page 1068).

C. ROLE OF INTERNAL EAR

1. *Vibration of basilar membrane: Mechanism*

(i) The movements of the foot plate of the stapes into the oval window set up a pressure in the perilymph in the scala vestibuli. The bony walls of scala vestibuli are rigid but Reissner's membrane is flexible, also the basilar membrane is not under tension; therefore, the basilar membrane is readily depressed into scala tympani by the pressure. Finally, the pressure is transmitted via the scala tympani to the round window, causing secondary tympanic membrane to bulge outwards into the middle ear. Conversely, an outward movement of the stapes and oval window causes an upward movement of the basilar membrane **(Fig. 109.8)**.

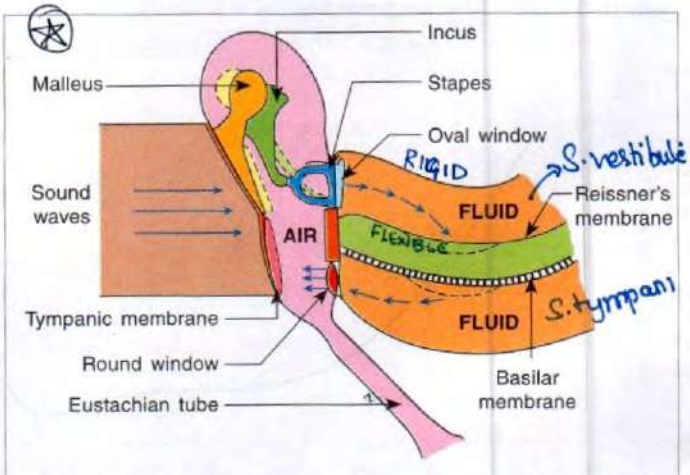


Fig. 109.8 Schematic representation of the way ear (auditory) ossicles movements are transmitted into a wave in the fluid of the inner ear (direction of movements is indicated by dashed lines and arrows)

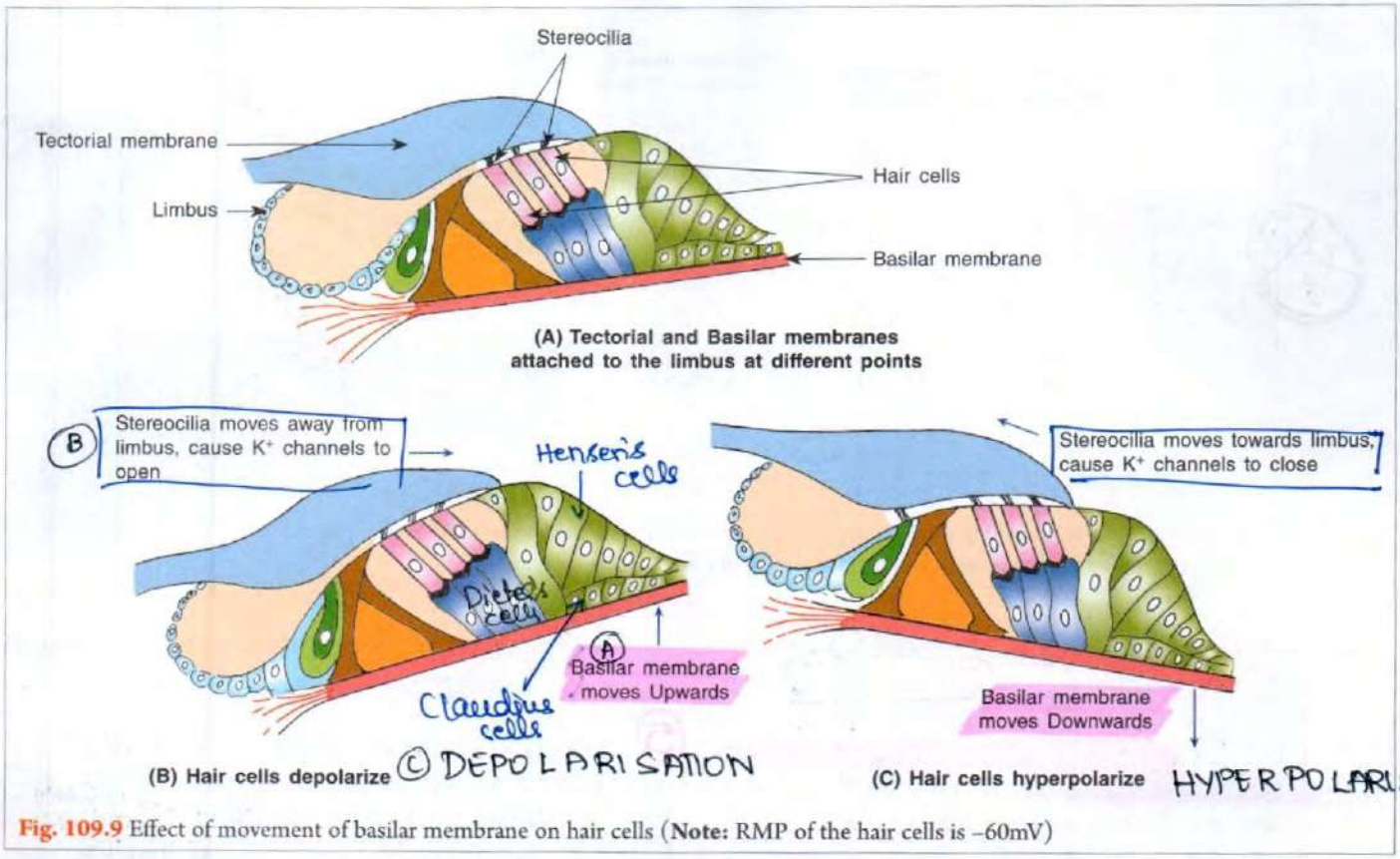


Fig. 109.9 Effect of movement of basilar membrane on hair cells (**Note:** RMP of the hair cells is –60mV)

Secondary tympanic membrane thus plays an important role in proper vibration of the basilar membrane.

(ii) Thus as the stapes rocks to and fro in the oval window it sets up wave motion in the membranous labyrinth. This stimulates movement of the fluid within, causing basilar membrane to vibrate. The site of the membrane at which these vibrations are maximal will be determined by the frequency of the sound waves (see below). [Place theory]

2. ***Stimulation of hair cells: Mechanism.*** The tops of the hair cells in the organ of corti are held rigid by the reticular lamina and their cilia are embedded in the tectorial membrane. The tectorial and basilar membranes are attached to the limbus at different points; therefore, when the basilar membrane moves there is *a sharp motion between two stiff structures, the tectorial membrane and the reticular lamina* **(Fig. 109.9)**. This bends the processes of the hair cells and results in generation of action potential in the auditory (VIII) nerve.
3. ***Functions of the hair cells***
   Refer page 1069.
4. ***Mechanism of pitch discrimination***
   (i) ***Place theory or Bekesy travelling wave theory.*** *Von Bekesy G. (1947)* showed, the basic pattern of movement of the basilar membrane is that of a travelling wave **(Fig. 109.10A)**. As the wave moves up the cochlea, its height increases to a maximum and then drops off rapidly. The distance from the stapes to this point of maximum height varies with the frequency of the vibrations initiating the wave. *High-pitched sounds* generate waves that reach maximum height near the base of the cochlea; *low-pitched sounds* generate waves that reach maximum height near the apex (probably because of the less stiff fibers of the basilar membrane at the apex) **(Fig. 109.10-B)**.

Thus, the apex of the cochlea is affected only by low frequency tones while the base of the cochlea, though responding to low frequencies, is mainly affected by high frequency.

Proof: If hair cells are destroyed at the base of the cochlea, high frequency sound is completely lost; while destroying the hair cells at the apex, high frequency sound is not lost completely but decreases in intensity.

Note

The place theory of coding of sensory information is responsible for the discrimination of sound frequencies only between 2,000 to 20,000 Hz. The sound frequencies below 2000 Hz are discriminated by the volley principle.

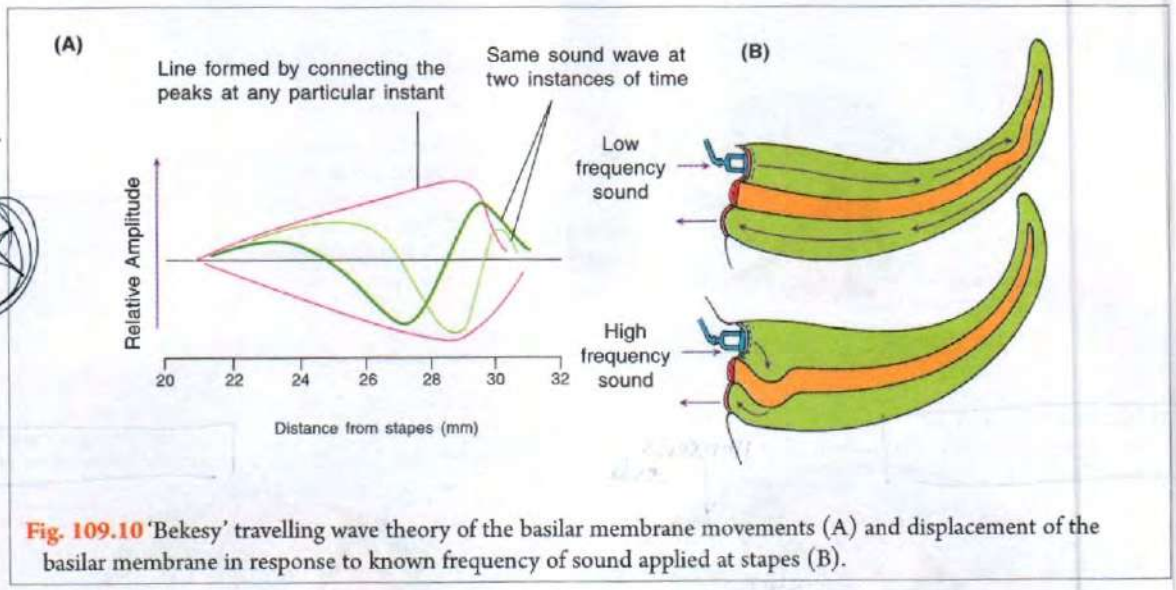


Fig. 109.10 'Bekesy' travelling wave theory of the basilar membrane movements (A) and displacement of the basilar membrane in response to known frequency of sound applied at stapes (B).

(ii) *Volley principle.* The apex of the cochlea contains units which respond to the lower *octaves* i.e. an interval of eight sounds (16-32-64-128-256-512-1024). Thus *pure tones upto 2000 Hz* produce clear synchronous volleys (*i.e.* at the same frequency) of action potentials in the Cochlear nuclei of VIII nerve. This is called the *volley principle* of frequency discrimination.

Important Note

The *place theory* of coding of sensory information is responsible for the *discrimination* of sound frequencies above 2000 Hz (upper limit, 20000 Hz) and the *volley principle* accounts for the coding of sound frequencies upto 2000 Hz. Together it is, called ***Duplex Theory of pitch discrimination.***

(iii) *Factors affecting the pitch of a sound*

(a) *Frequency of the sound wave (page 1073).*

(b) *Frequency* affects loudness: Since the hearing threshold is lower at some frequencies than others (minimum audibility curve, page 1073 and **Fig. 109.7**), therefore, low tones (less than 500 Hz) sound lower and high tones (>4000 Hz) sound higher as their loudness increases.

(c) *Duration:* The pitch of a tone cannot be perceived unless it lasts for more than 0.01 sec. With duration between 0.01 and 0.1 sec pitch rises as duration increases. Refer electrophysiology of pitch discrimination (page 1078).

(d) *Wave form* (page 1072). The pitch of complex wave form of a given frequency can still perceived even when the fundamental frequency is absent.

5 ELECTROPHYSIOLOGY OF HEARING

A. ELECTRICAL ACTIVITY OF COCHLEA

ENDOLYMPHATIC POTENTIAL

1. When two electrodes (one inserted into the scala media containing endolymph and other inserted into the scala vestibuli containing perilymph) are connected through a suitable amplifier to 'CRO', a steady (constant) potential difference of +50 to +100 mV (average +80 mV) is recorded, called the *endolymphatic potential* or *endocochlear potential.* It is written with a 'positive' sign, signifying that *scala media is positive to the scala vestibuli* **(Fig. 109.11)**.
2. The interior of the cells of Reissner's membrane, and of the cells of the organ of Corti and cells of stria vascularis is approx. 30 mV negative to the perilymph in the scala vestibuli. However, there is *no potential difference between the two chambers,* scala vestibuli and scala tympani, both containing the perilymph.
3. *Genesis:* As noted earlier, the cell membrane separates the two fluid compartments (ICF and ECF) having widely different ionic composition with inside (ICF) 'negative' relative to the outside (ECF) (page 29). Likewise, Reissner's membrane separates two fluids (perilymph in scala vestibuli and endolymph in scala media) of widely different composition across the membrane **(Table 109.1)**. Endolymph is formed by stria vascularis and has an electrolyte concentration very similar to that of ICF while perilymph is formed mainly from plasma with very similar in composition to ECF; however, the endolymph potential in scala media is positive with respect to the perilymph in the

scala vestibuli. Therefore, the *endolymphatic potential* cannot be explained on the basis of a $[Na^+]$ or $[K^+]$ difference.

4. *Source:* The *stria vascularis* which covers the lateral wall of the scala media is the source of the endolymphatic potential. Why? The cells in the stria vascularis have a *high* concentration of *Na^+–K^+ ATPase*. In addition, there is a unique electrogenic K^+ pump which accounts for high K^+ concentration of endolymph; as a result the scala media is electrically positive relative to the scala vestibuli and tympani.

   Proof: The endolymphatic potential is directly dependent upon an adequate oxygen supply and it can be abolished by introducing cyanide into any one of the three scalae.

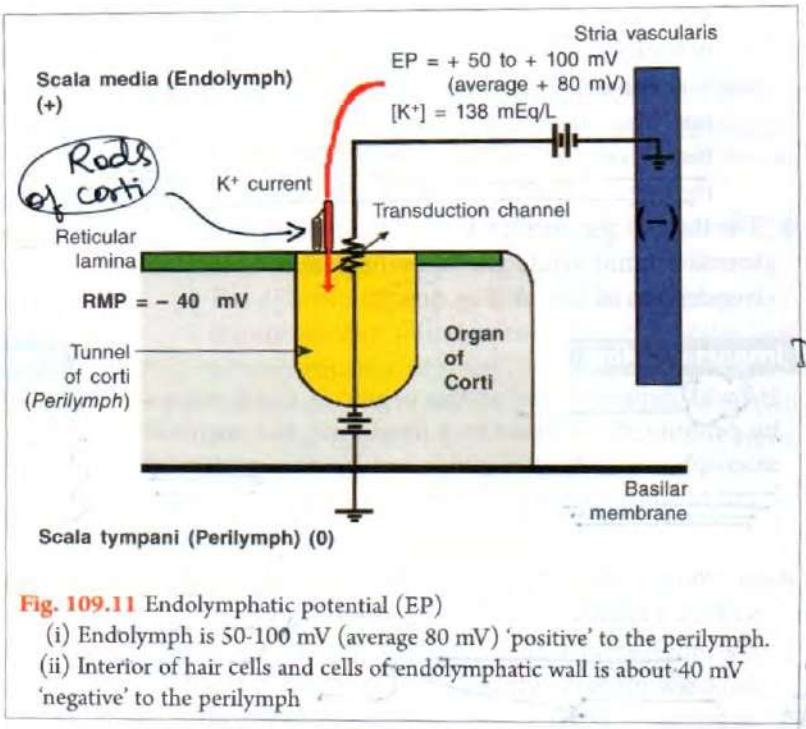


Fig. 109.11 Endolymphatic potential (EP)
(i) Endolymph is 50-100 mV (average 80 mV) 'positive' to the perilymph.
(ii) Interior of hair cells and cells of endolymphatic wall is about 40 mV 'negative' to the perilymph

5. *Factors affecting*
   (i) The *movements of the basilar membrane* affect the endolymphatic potential value by altering the forces on the hair cells which are embedded in the tectorial membrane. It can be *increased by* a downward movement of the basilar membrane, and conversely an upward displacement of the membrane *reduces* it.
   (ii) The *injection of ringer* solution (which has the same composition as that of ECF) into the scala media (composition similar to ICF) abolishes the endolymphatic potential; as expected, it has no effect when injected into the scala tympani (which contains perilymph similar to ECF).
   (iii) The *injection of a potassium rich, sodium poor solution* into the scala media does not alter the endolymphatic potential but abolishes it if the injection is made into the scala tympani or vestibuli.

THE COCHLEAR MICROPHONIC POTENTIALS

1. One of the electrical responses of the cochlea to sound is the *cochlear microphonic potentials*. It is a potential fluctuation that can be recorded between an active electrode placed on or near the cochlea and an indifferent electrode placed anywhere on the body. It is called the *microphonic cochlear potential* because if these potentials are amplified, the loudspeaker records the pure tones (*i.e.* the same frequency and intensity of sounds) fed into the ears as sound waves upto frequencies of 20,000 Hz.
2. These potentials are *similar to the generator potential* (page 866) because:
   (i) they show no latency or refractory period
   (ii) they do not obey all or none law
   (iii) these are resistant to ischaemia and anaesthesia.
3. *Source*
   (i) The cochlear microphonic potentials are produced by transformation of mechanical energy (distortion affecting the 'outer' hair cells) into electrical energy (generator potential).
   (ii) These potentials can be recorded 'optimally' by placing one electrode in the scala media and one in the scala tympani. Thus these potentials

Table 109.1: Ionic composition (in mEq/L) of human body fluids compared

	Endolymph (in scala media)	Perilymph (in scala vestibuli, tympani and tunnel of Corti)	ECF	ICF
K^+	138	5	5	155
Na^+	15	154	145	12
Cl^-	108	120	110	8
Proteins ($Prot^-$)	15	50	15	60

Important Note

Endolymph has an electrolyte concentration very similar to that of ICF (high in K^+ and low in Na^+) while perilymph is very similar in composition to ECF (high in Na^+ and low in K^+).

uniform throughout the frequency range but it is never complete. It is because the skull bones themselves conduct sound to the cochlea (*bone conduction*) and the basilar membrane can be set into vibration.

Causes

(i) Wax or foreign bodies in the external ear.
(ii) Thickening of the tympanic membrane due to repeated infections, therefore, its vibrations decrease.
(iii) ***Otitis media*** *i.e.* middle ear inflammatory disorders which damage the tympanic membrane and/or the ear ossicles.
(iv) ***Otosclerosis*** (ear ossicles sclerosis) *i.e.* pathological fixation of the foot plate of stapes in the oval window.
(v) Blockage of the eustachian tube (page 1068).

2. **Nerve (or Sensori neural) Deafness**

It is due to either defects of the internal ear (hair cells) or damage of neural pathways. Therefore, it is *characterized by complete loss of hearing.*

Causes

(i) ***Aging:*** Hearing gradually decline with age, called ***Presbycusis.*** It is probably due to gradual cumulative loss of hair cells and cortical neurons.
(ii) Hereditary.
(iii) Injury to VIII nerve (acoustic trauma).
(iv) Hazards of industrial noises (prolonged exposure to noise damages the hair cells, initially it manifests as loss of sensitivity of hearing in 300-3000 Hz range resulting in the impairment of the subject's understanding of conversation).
(v) Toxic degeneration of VIII nerve such as due to streptomycin injection, quinine, measles, meningitis, etc.
(vi) Tumours of VIII nerve (*acoustic neuroma*).
(vii) Vascular damage in medulla which leads to destruction of the auditory pathways.

B. TINNITUS

It is a ringing sensation in the ears by irritative stimulation of either the internal ear or the auditory (VIII) nerve.

TESTS FOR HEARING

INTRODUCTION

1. ***Masking*** *(means a covering)*
   (i) It is a common experience that the voice must be raised when conversing in noisy surroundings *i.e.* quiet conversation conducted at an intensity level of 60 dB has been masked.
   (ii) It represents the inability of the *auditory mechanism* to separate the total stimulation into the separate components. This is due to the *property of refractoriness* (non-responsiveness).
   (iii) Masking tends to be greater for tones of approximately similar frequency than for tones widely different in frequency.
   (iv) Low frequency tones mask high-frequency tones more easily than the reverse.
   (v) Masking raises the auditary threshold (page 1072).
2. ***Conduction of Sound Waves***
   (i) The main pathway for normal hearing *i.e.* conduction of sound waves to the fluid of the inner ear via the tympanic membrane and the ear ossicles is called ***Air or Ossicular Conduction.***
   (ii) The transmission of vibrations from the bones of the skull to the fluid of the inner ear is called ***Bone Conduction.***
      (a) Considerable bone conduction occurs when tuning forks or other vibrating objects are applied directly to the skull.
      (b) This route also plays a role in transmission of extremely loud sounds.

HEARING TESTS

A. Use of the human voice

A conversational voice (60 dB) which should be heard at 3.5 mts (12 feet) in each ear separately; if extends to 6 mts (20 feet) it can be presumed that the subject has normal hearing. Lists of ***spondee*** (phonetically balanced) words are used for this test, which should be repeated using the whispered voice.

B. Tuning fork tests

The most widely used for these tests to distinguish between conductive and nerve deafness are forks vibrating at 256 or 512 Hz (why? page 1076). These tests are summarized in **Table 109.2** and **Fig. 109.15.**

C. Audiometry

Auditory acuity *(sharpness of hearing)* can be measured with the help of an ***audiometer.*** The device consists of the following parts:

1. *Electronic oscillator,* it can generate pure tones that range from low to high frequencies.
2. *Intensity dial,* it helps to adjust the threshold intensity of hearing (page 1072) for each tone.
3. *A headphone.*

Procedure

(i) The test is conducted in a sound-proof room. Each ear is tested separately. The subject wears a headphone. This device presents the subject with pure tones of various frequencies through the headphone. He flashes a light whenever he hears the sounds. At each frequency, the threshold intensity is determined

Table 109.2: Tuning fork tests (Fig. 109.15)

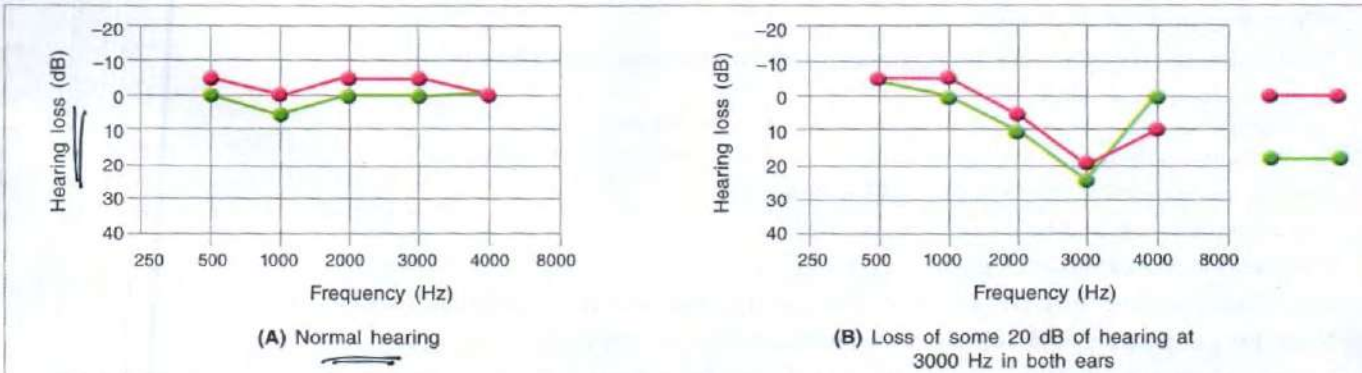
Test	Method	Normal	Conductive deafness	Nerve deafness
1. Rinne test	Base of the vibrating tuning fork is placed on the mastoid process until subject no longer hears it (*bone conduction*), then it is held in the air, next to ear (*air conduction*).	Subject hears vibrations in air after bone conduction is over. Air conduction is better than bone conduction (*Rinne test – positive*).	Vibrations in air not heard after bone conduction is over *i.e.* bone conduction is better than air conduction (*Rinne test – negative*).	If **partial** nerve deafness: *Rinne test is 'positive'*. If **complete** nerve deafness, both air conducted and bone conducted sounds are not perceived.
2. Weber test	Base of the vibrating tuning 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*** because 'masking' effect of environmental noise is absent on the affected side.	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 the examiner 'hear' the sound equally well.	Subject's bone conduction is better than the examiner's.	Subject's bone conduction worse than the examiner's.

(A) *Rinne's Test* (B) *Weber's Test* (C) *Schwabach Test*

Fig. 109.15 Tuning fork tests.

and plotted on a graph as a percentage of normal hearing. This provides an objective measurement of the degree of deafness and a picture of the tonal range most affected.

(ii) ***Hearing loss*** is determined by increasing the intensity until threshold audibility is achieved for each tone tested; the corresponding dB increase on the intensity dial is noted **(Fig. 109.16)**.



(A) Normal hearing (B) Loss of some 20 dB of hearing at 3000 Hz in both ears

Fig. 109.16 Audiograms showing hearing loss against frequency. A hearing loss of 'zero' dB implies normality (standard used in the calibration). A negative loss (above zero line) indicates an auditory threshold lower than normal.

Significance of the test

1. To assess the degree of the deafness, and
2. To assess the frequency range in which deafness is most affected. Thus ***hearing aids*** can be designed to overcome some of the hearing problems of the individual patient.

Hearing aids are for: Conductive (or) Sensorineural?

Study Questions

1. **Define and give physiological significance:**
   (i) Quality (or timbre) of sound
   (ii) Fundamentals and harmonics
   (iii) Reference (or standard) sound and Auditory threshold
   (iv) Impedance matching
   (v) Presbycusis.
2. **Write short notes on:**
   (i) Organ of corti (ii) Auditory association areas (iii) Tympanic reflex
   (iv) Role of eustachian tube in hearing (v) Mechanism of pitch discrimination (vi) Role of middle ear in hearing
   (vii) Endolymphatic potential (viii) Sound localization (ix) Cochlear microphonic potential
   (x) Audiometry (xi) Tuning fork tests and its significance (xii) Otosclerosis.
   (xiii) Factors affecting pitch discrimination
3. **Name the muscles present in the middle ear. Give their innervation and function.**
4. **What will happen and why to hearing:**
   (i) If someone suffers from sore throat?
   (ii) If air within the middle ear gets absorbed?
   (iii) If one auditory cortex get damaged?
5. **Draw a well-labelled diagram:**
   (i) Location of auditory areas
   (ii) Auditory pathways
   (iii) Structure of organ of corti
   (iv) Movements of ear ossicles transmitted into a wave in the fluid of the inner ear
   (v) Maximum audibility curve
   (vi) Effect of movement of basilar membrane on hair cells
   (vii) Bekesy travelling wave theory of basilar membrane movements
6. **Give the innervation of outer and inner hair cells and give their function.**
7. **Differentiate between:**
   (i) Primary and secondary tympanic membrane
   (ii) Outer and inner hair cells
   (iii) Place theory and volley principle of pitch discrimination
   (iv) Conductive and nerve deafness
8. **Give relationship between frequency of sound and threshold of hearing.**
9. **Why is there need for two ears?**
10. **What makes the tympanic membrane vibrate freely when sound waves strike it?**
11. **Give the physiological basis of:**
    (i) Musical sound (ii) Noise perception
    (iii) Minimum audibility curve (iv) Endolymphatic potential.
12. **Give the mechanism of vibration of basilar membrane.**
13. **Can perception of sound be possible in vacuum?**
14. **Give the common causes of conductive deafness.**
15. **Should ear plugs ever be worth for prolonged period to overcome noise pollution? Explain.**
16. **Name the components of middle ear. Give the functioning of each component.**
17. **Describe physical properties of sound. How sound intensity is measured? Give various intensity levels of common sounds.**
18. **Describe briefly the mechanism of hearing.**

MCQs

1. **A structure *not* present in the middle ear:**
   (a) Tympanic membrane
   (b) Three ear ossicles: malleus, incus and stapes
   (c) Eustachian tube
   (d) Membranous labyrinth

2. **The arrangement of three minute bony (ear) ossicles across the cavity from tympanic membrane to oval window is:**
   (a) Stapes, incus, malleus
   (b) Incus, malleus, stapes
   (c) Malleus, stapes, incus
   (d) Malleus, incus, stapes

3. **The cochlea, *not true* is:**
   (a) 35 mm long coiled tube which makes $2^1/_2$ turns
   (b) lumen is divided throughout the length by 2 membranes into 3 compartments
   (c) It is a receptor of hearing ⇒ Hair cells
   (d) It has a broad base with a narrow apex

4. ***False* statement for hair cells in organ of Corti is:**
   (a) There are 3-4 rows of inner hair cells and a single row of outer hair cells
   (b) Its bases are bathed in perilymph
   (c) Stereocilia that project out from its upper surface are bathed in endolymph
   (d) Inner hair cells are more densely innervated as compared to outer cells

5. **If a person can perceive sound informations but fails to understand the meaning of sound, the lesion is most likely in:**
   (a) Primary auditory cortex
   (b) Auditory association areas
   (c) VIII nerve
   (d) Inferior colliculus

6. **Bilateral destruction of primary auditory cortex causes:**
   (a) Difficulty in interpretation of sound
   (b) Difficulty in hearing
   (c) Complete loss of hearing
   (d) Vertigo → sensation of whistling & loss of balance

7. **Sound travels at a speed of:**
   (a) 330 mts/sec in air at 0°C
   (b) 344 mts/sec in air at 20°C More temp. is good!
   (c) 1500 mts/sec in water at 20°C
   (d) All of the above are true

8. **Quality or timbre of a sound is determined by its:**
   (a) Fundamental
   (b) Overtones
   (c) Primary frequency
   (d) Pitch

9. **Sound of minimal intensity which the human ear may perceive is:**
   (a) Zero decibel
   (b) 20 decibel
   (c) 40 decibel
   (d) 60 decibel

10. **The sound becomes painful above decibel of:**
    (a) 70
    (b) 80
    (c) 140
    (d) 160

11. **Ear is most sensitive to frequency (Hz) of:**
    (a) 300-500
    (b) 1000-3000
    (c) 10000-20000
    (d) 16-20000

12. **Number of pitches that can be distinguished by an average individual are about:**
    (a) 500
    (b) 1000
    (c) 2000
    (d) 3000

13. **During transmission of sound from the middle to inner ear, pressure within the middle ear increases by:**
    (a) 1.2-1.3 times
    (b) 12-13 times
    (c) 17 times
    (d) 22 times (17 × 1.3)

14. **Tympanic reflex or acoustic reflex, *not true* is:**
    (a) A protective reflex against the loud sound
    (b) It develops in 40 msec and completed in 160 msec
    (c) Occurs due to contraction of middle ear muscles
    (d) More effective to a prolonged loud sound than to a sudden loud sound

15. **Secondary tympanic membrane:**
    (a) Covers the oval window
    (b) Limits the movements of the Reissner's membrane
    (c) Plays an important role in proper vibration of basilar membrane
    (d) All of the above are true

16. **Stimulation of the hair cells in the cochlea is caused by:**
    (a) Compression of the hair cells by the sound waves
    (b) Vibration of the hair cells by the sound waves
    (c) Bending of the hair cells by sharp motion between the tectorial membrane and reticular lamina
    (d) The electrical current generated by potential differences between the endolymph and the perilymph

17. **Duplex theory of pitch discrimination is:**
    (a) Volley principle and place theory together
    (b) Apex of cochlea respond to octaves
    (c) Responsible for discrimination of sound frequencies above 2000 Hz
    (d) Coding of sensory information upto 2000 Hz

18. **Regarding primary auditory cortex, *not true* is:**
    (a) There is an orderly tonotropic representation
    (b) Anterior part receives only low frequency tone
    (c) Posterior part of the gyrus receives impulses arising from the base of the cochlea
    (d) Concerned with integration of auditory impulses

19. **Deafness:**
    (a) Associated with paralysis of vocal cords
    (b) Bone conduction more than air conduction seen in VIII nerve damage
    (c) For high tones more than for low tones is a typical result of working for years in a very noisy environment e.g. above 85 dB
    (d) Due to nerve damage is, in general, more improved by a hearing aid than is obstructive deafness

20. **Deafness:**
    (a) It means inability to hear either wholly or partly
    (b) Conductive deafness is more common than nerve deafness
    (c) Most common cause is hereditary
    (d) Hearing aids can overcome all forms of deafness

21. ***Not* a feature of external ear:**
    (a) Pinna helps to collect the sound waves and to localize the source of sound
    (b) External auditory meatus (EAM) is 2.5 cm long and runs forward and medially
    (c) EAM is lined with skin which secrete wax from ~~sebaceous gland~~ ceruminous gl.
    (d) EAM helps transporting the sound waves to middle ear and protects tympanic membrane from injuries

22. ***False* statement regarding three compartments (or scalae) in the cochlea:**
    (a) Scala vestibuli, a space below the Reissner's membrane
    (b) Scala tympani is filled with perilymph
    (c) Scala media is a closed space and is filled with endolymph
    (d) Scala tympani and scala vestibuli communicate at the apex by a small opening, helicotrema

23. **Which one of the following statements is *incorrect* about impulses in right auditory nerve?**
    (a) Are initiated by distortion of hair cells in organ of corti
    (b) Are carried to the cochlear nuclei of medulla
    (c) Result in stimulation of 4th order neurons in thalamus
    (d) Finally result in stimulation of auditory area in temporal cortex

24. **The auditory pathway passes via all *except*:**
    (a) Cochlear nuclei
    (b) Superior olivary nucleus
    (c) Trapezoid body
    (d) Superior colliculus

25. **Final projection of auditory pathways to cerebral cortex takes place in:**
    (a) Superior temporal gyrus
    (b) Middle temporal gyrus
    (c) Inferior temporal gyrus
    (d) Superior and middle temporal gyrus

26. **Removal of one auditory cortex results in:**
    (a) Complete loss of hearing
    (b) Impairs auditory short term memory
    (c) Only a slight effect on auditory acuity
    (d) Loss of interpretation and understanding of auditory informations

27. **The amplitude and frequency of sound waves determines respectively ..... and ..... of a sound:**
    (a) Speed and loudness
    (b) Loudness and speed
    (c) Loudness and pitch
    (d) Pitch and speed

28. **A sound with many components which have frequencies that are *not* simple multiples of the fundamental, is referred to as:**
    (a) Noise
    (b) Musical sound
    (c) High pitch sound
    (d) Loud sound

29. **Optimal frequency for transmission of sound waves is:**
    (a) 32-64 Hz
    (b) 1000-3000 Hz
    (c) 16000-20000 Hz
    (d) 16-20000 Hz

30. **In general, the minimal fractional difference in frequency, which is perceptible, is:**
(a) 0.1% (b) 0.3% (c) 1.0% (d) 3.0%

31. **Percentage of loss of sound energy from the middle to the internal ear is:**
(a) 10-20 (b) 20-30 (c) 30-40 (d) 40-50

32. **Why is a sudden loud sound more likely to damage the cochlea than a prolonged loud sound?**
(a) The basilar fibers are sensitive to sudden sounds but adapt to prolonged sounds
(b) A sudden sound carries more energy
(c) The tympanic membrane becomes flaccid during prolonged loud sounds
(d) There is a latent period before the tympanic reflex can occur

33. **The hair cells depolarize when:**
(a) Stereocilia moves away from limbus
(b) Stereocilia moves towards limbus
(c) Basilar membrane moves downwards
(d) Cl^- moves out of the hair cell membrane

34. **Scala media is filled with:**
(a) Fluid having electrolyte concentra-tion very similar to that of ECF
(b) Perilymph
(c) Endolymph
(d) Fluid rich in Na^+ and low in K^+

35. ***Not* a feature of conductive deafness:**
(a) Complete loss of hearing
(b) Hearing loss is fairly uniform throughout the frequency range
(c) Rinne test-negative
(d) Subject bone conduction is better than the examiner's

36. **Masking, *not true* is:**
(a) Means a covering
(b) Inability of auditory mechanism to separate the total stimulation into separate components
(c) Greater for tones of approximately similar frequency
(d) High frequency tones mark low frequency tones more easily than the reverse

Answers

1. (d)	2. (d)	3. (c)	4. (a)	5. (b)	6. (c)	7. (d)	8. (b)	9. (a)	10. (c)	11. (b)	12. (c)	13. (d)	14. (d)	15. (c)
16. (c)	17. (a)	18. (d)	19. (c)	20. (a)	21. (c)	22. (a)	23. (c)	24. (d)	25. (a)	26. (c)	27. (c)	28. (a)	29. (b)	30. (b)
31. (c)	32. (d)	33. (a)	34. (c)	35. (a)	36. (d)									

Cytokines, IL1, (Endogenous Pyrogens)

Chapter 110

The Eye

I. Physiological anatomy: Photoreceptors (rods and cones)
II. The visual pathways and effect of lesions
III. The image forming mechanism
Visual Acuity; visual reflexes; defects of image forming mechanisms
IV. Photochemistry of vision
Photopic and scotopic vision; Visibility (or sensitivity) curve; photosensitive pigments; adaptation; night blindness
V. Electrophysiology of vision: Genesis of electrical activity of retina
VI. Colour vision: colour blindness
VII. Eye movements and nystagmus

PHYSIOLOGICAL ANATOMY

The eye is a special organ of the sense of *sight*. The adult human eyeball is a hollow, spherical structure, 24 mm in diameter and situated in the orbital cavity. *Only 1/6th of the eyeball is visible outside.* The walls of the eyeball contain *three* principal layers: the *outer* fibrous layer; the *middle* vascular layer; and the *inner* nervous layer, the *Retina*. In addition, it also contains the *Lens*, the *Aqueous humour* and *Vitreous humour* **(Fig. 110.1)**.

1. ***The outer layer, SCLERA***
   (i) It is a tough, fibrous opaque coat made up of dense connective tissue and is white in colour. It *provides shape* to the eyeball and is *protective* in function.
   (ii) It gets modified in the central portion of the eye to form a clear transparent and *avascular cornea.*
2. ***The middle layer, CHOROID***
   (i) It is bluish in colour as it contains numerous blood vessels, therefore, also called the *uveal layer*. It

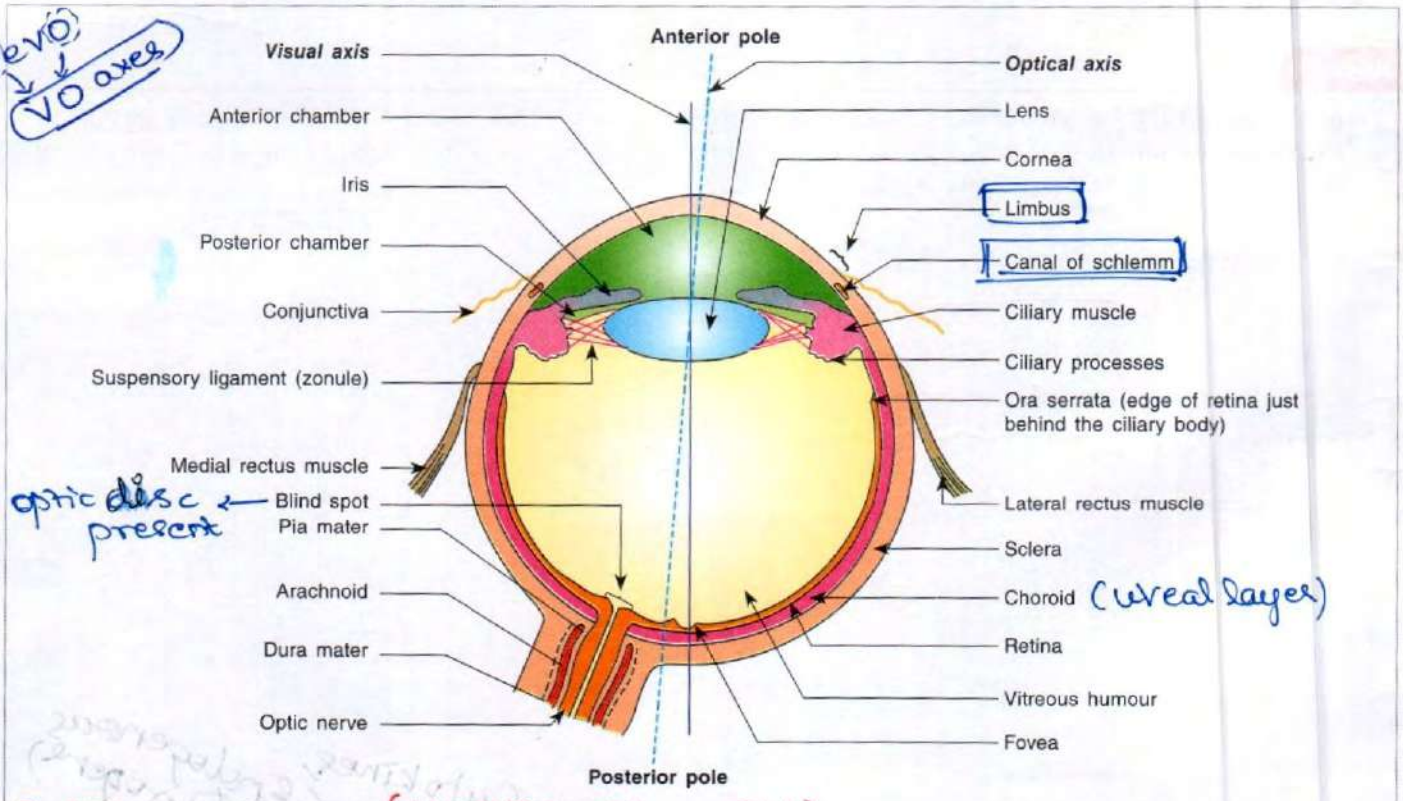


Fig. 110.1 Structure of the right eye

optic disc → marks BLIND SPOT AREA

nourishes the structures in the eyeball. It is thin over the posterior 2/3rd of the eyeball and is called the ***choroid***; but in front it thickens to form the *ciliary body*. It also contains pigmented granules supported by loose connective tissue, this provides a dark background to *absorb extra amount of light* entering the eye.

(ii) **The ciliary body**

(a) It is attached to the ***suspensory ligament*** (or *zonule*); the other end of this ligament is joined to the capsule enclosing the crystalline *lens*. The ciliary body itself continues forward to form the *iris*.

(b) It contains two types of smooth muscle fibers, circular and longitudinal that attach near the corneoscleral junction. The ciliary muscle plays an important role during *accommodation* for near vision (page 1100).

(iii) **Iris**

(a) It is a *pigmented and opaque* muscular structure which gives *colour to the eye* (black, brown or blue eyes).

(b) In the centre, it has an aperture known as *pupil* through which light reaches the interior of the eye.

(c) It contains two types of muscle, ***sphincter pupillae*** (circular muscle fibers) and ***dilator pupillae*** (radial muscle fibers). These muscles determine the size of the pupil (page 738).

(d) It divides the space between the posterior surface of cornea and anterior surface of lens into *anterior* and *posterior chambers*. The space enclosed behind the cornea and in front of the iris is the *anterior chamber* and the space in front of the lens and behind the iris is the *posterior chamber* of the eye. Both the chambers are filled with ***aqueous humour*** (page 1088).

(e) *Functions*

- *Regulates the intensity of light* entering the eye either by constriction or dilatation of the pupil. In addition, pigmented layer of the iris *absorbs the extra amount of light*.

Important Note

Variations in the diameter of the pupil can produce upto five-fold changes in the amount of light reaching the retina.

- Prevents entry of light through the periphery of the lens, thus prevents spherical and chromatic aberrations (page 1102).
- Increases the *depth of focus* by constriction of the pupil (page 1101).

3. ***The inner layer***, the ***RETINA***, it contains:

(i) an outer pigmented layer of epithelial cells which is firmly attached to the whole of the inner surface of the choroid; and

(ii) an inner layer of nerve cells and nerve fibers which contains the ***photoreceptors*** (light sensitive receptors), the *rods* and *cones* (page 1088).

4. ***Crystalline lens***

(i) It is a circular biconvex transparent body enclosed within a capsule. It lies immediately behind the pupil and is held in position with the help of suspensory ligaments (or zonule), the other end of which is attached to the ciliary bodies.

(ii) It helps in the formation of image on the retina by altering the curvature of its anterior surface (page 1099). The *'central core'* of the lens *possesses a higher refractive index* than does the remainder.

(iii) The lens ***has no blood*** supply but satisfies its low metabolic requirements by taking up substances from the aqueous humour. Glucose is taken up by the lens substance and is metabolized (mainly anaerobically) to lactic acid (glycolysis); the lactic acid diffuses into the aqueous humour.

5. All nerve fibers from the retina converge to form the ***optic nerve*** to finally reach the brain. The small area of retina where optic nerve leaves the eyes is called the ***optic disc***. It lies 3 mm medial to and slightly above the posterior pole of the eye ball. It contains no light sensitive receptors (rods and cones), as a result vision is not possible over this area. Therefore, this spot is called the ***blind spot***.

6. At the posterior pole of the eye there is a yellowish pigmented spot, called the ***macula lutea (or yellow spot)*** which marks the location of ***fovea centralis***. The fovea is 1.5 mm in diameter, situated 3 mm temporal to the optic disc. It is thinned out, *rod-free portion* of the retina where the cones are densely packed and there are very few cells and no blood vessels overlying the receptors. It is the point of *greatest* ***visual acuity*** (sharpness of vision) and is highly developed in humans.

Important Note

The line joining the anterior pole to the posterior pole of the eyeball is called the *optical axis* while the line joining the fixation point to the fovea centralis is called the *visual axis*. (The fixation point is the point over the object at which eye is fixed for viewing.)

AQUEOUS HUMOUR

1. It is a thin watery fluid (pH 7.1–7.3; SG 1002–1004) contained in the anterior and posterior chambers of the eye. It is formed from the *capillaries of the ciliary processes* @ 2 µL/min.
2. *Composition*
   (i) *Low in protein*, as it is an *ultrafiltrate* (page 516) and is formed by diffusion from capillaries and by active transport of components from the plasma.
   (ii) *High* content of *Vitamin C*, this helps in glucose metabolism.
   (iii) High concentration of *NaCl* because Na^+ ions are actively transported from the plasma and Cl^- ions follow them passively; accumulation of these ions results in passive transport of water due to osmosis.
   (iv) *Low* in *glucose* but *high lactic acid* content because glucose is utilized by the avascular cornea and lens anaerobically.
   (v) *High* amounts of *hyaluronic acid* which is kept in the fluid state by hyaluronidase present in the ciliary body. Therefore, the viscosity of the aqueous humour is low.
3. *Circulation*. Aqueous humour once formed from the ciliary processes passes from the posterior chamber, then via pupil into the anterior chamber, then it passes across the corneal endothelium lining, the *canal of schlemm* (at the *limbus i.e.* junction of cornea with sclera) into the intrascleral venous plexus, which finally drains the fluid into the anterior ciliary veins **(Fig. 110.2)**.
   Normal pressure in the *anterior chamber* is 13-18 mmHg while in the *venous plexus* it is 10-15 mmHg, thus helps in continuous drainage of aqueous humour into venous plexus.

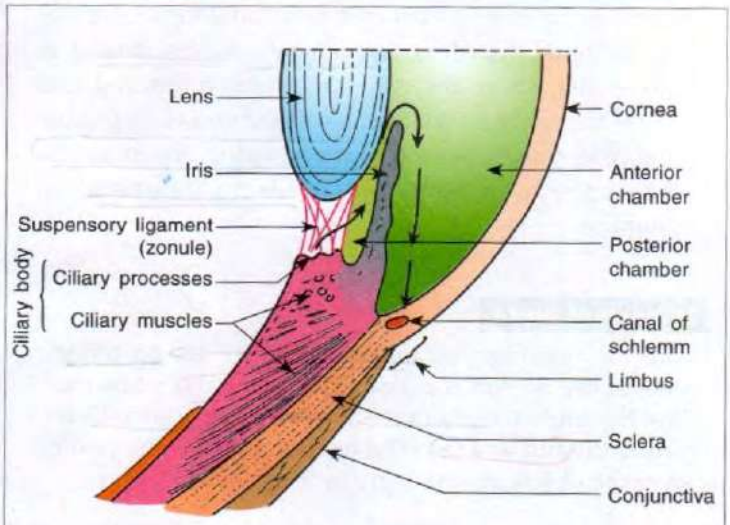


Fig. 110.2 The Circulation of aqueous humour

Important Note

Blockage of the canal of schlemm leads to an increase in intraocular pressure above 80 mmHg so the eyball on palpation feels as hard as a stone. This condition is called *Glaucoma*. *Acute glaucoma* produces severe pain while *chronic glaucoma* by constant pressure over blood vessels of the retina and choroid leads to their degeneration and finally produces blindness.

4. Lipid soluble substances such as chloramphenicol and sulphonamides can enter the aqueous humour while proteins (*e.g.* insulin) cannot enter, this shows there is a barrier between the blood and aqueous humour (***blood-aqueous barrier***).
5. *Functions*
   (i) *Provides nutrition* to all the avascular structures of the eye *i.e.* the cornea and the lens.
   (ii) *Maintains intraocular pressure* at a constant level, thereby helps in normal image forming mechanisms.

VITREOUS HUMOUR

The interior of the eyeball between the lens and the retina is filled with a clear amorphous (shapeless) transparent gel, containing albumin and hyaluronic acid. The latter is responsible for the high viscosity of the vitreous.

Functions

1. It *prevents* the walls of the *eyeball from collapsing*.
2. It *maintains intraocular pressure* and keeps the intraocular structures in position, thus helps in normal focusing of the image over the retina.

Applied Aspect

1. Decrease in intraocular pressure (*Normal* 13-18 mmHg) results in loosening of the suspensory ligaments with bulging of lens, therefore, image is formed in front of the retina (Hypermetropia)
2. Increase in intraocular pressure prevents contraction of the ciliary muscles, therefore, near objects cannot be seen clearly *i.e.* accommodation becomes defective (page 1099).

LAYERS OF RETINA AND PHOTORECEPTORS (RODS AND CONES)

1. The retina contains **10** layers *except* in optic disc and fovea centralis. The *photoreceptors* (rods and cones) are placed outermost towards the choroid. The layers of retina from outwards to inwards are: **(Fig. 110.3)**
   Layer 1: Pigmented epithelium. It contains melanin pigment which along with the pigmented choroid absorbs extra amount of light, thus preventing the

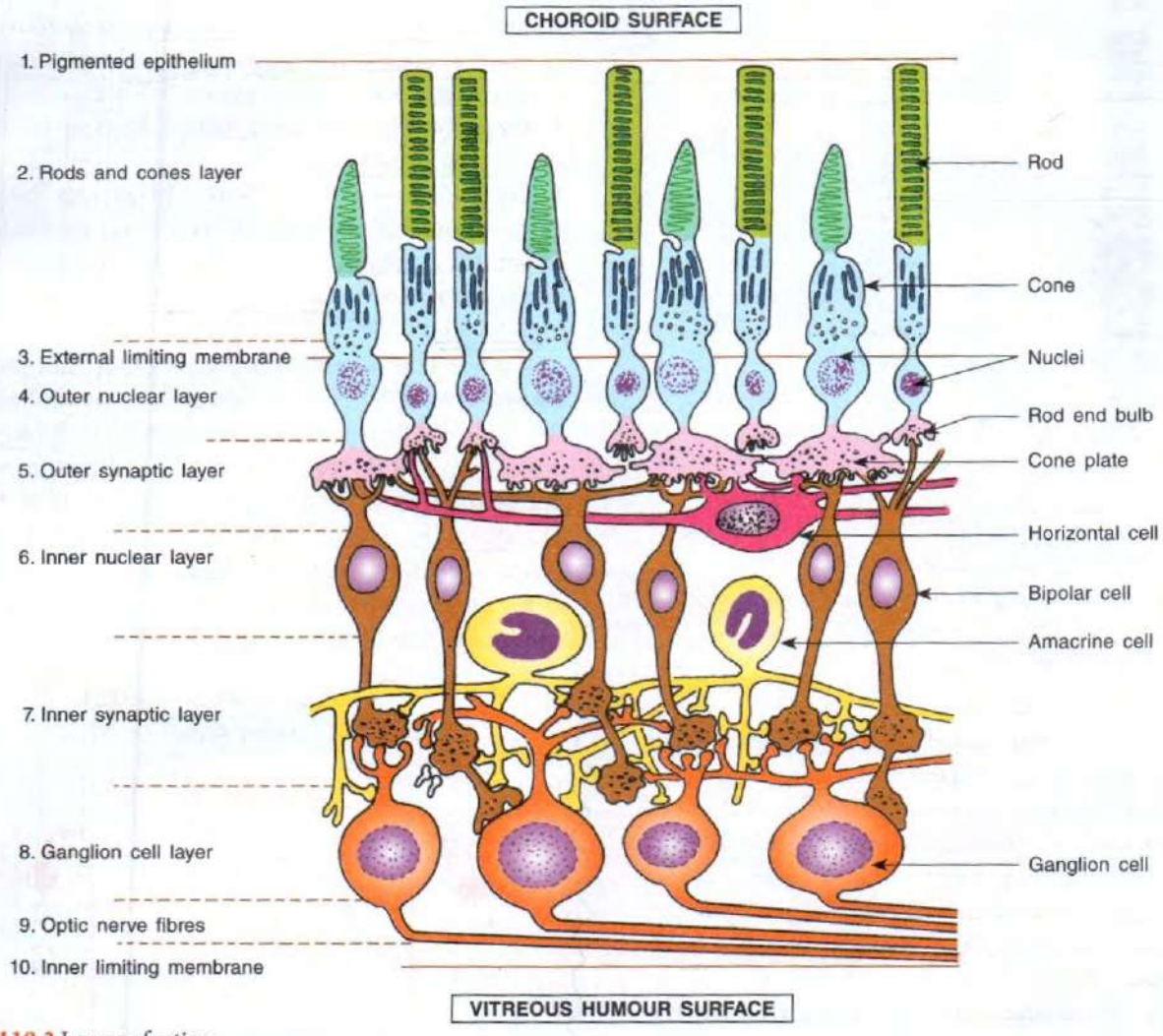


Fig. 110.3 Layers of retina

reflection of rays back through the retina. If this light gets refracted back, it would result in 'blurring' of vision (objects will not be seen clearly). It also has phagocytic function (see below).

Layer 2: Rods and cones layer – photoreceptors. Each rod and cone is divided into outer segment, inner segment and a synaptic zone. The outer and inner segments form the layer of rods and cones.

(i) **The outer segment**

(a) These are modified cilia and are made up of regularly arranged piles of flattened discs or saccules composed of membrane. In cones, the *saccules* are formed by infolding of the cell membrane but in rods, the discs are separated from the cell membrane.

(b) The discs or saccules contain the *photosensitive pigment* (***Rhodopsin*** in rods and ***Iodopsin*** in cones). The rods are *extremely sensitive to light* and are receptors for *dimlight* (***Scotopic***) *vision;* while the cones are responsible for *bright light* (***Photopic***) *vision* (page 1105), high visual acuity (page 1097) and for colour vision (page 1112).

(c) *Rods* are named for the thin, rod like appearance of their outer segments. Its outer segments are being constantly renewed by formation of new discs at the inner edge of the segments and phagocytosis of old discs from the outer tip by cells of the pigment epithelium **(Fig. 110.4)**.

Important Note

In *retinitis pigmentosa* the phagocytic process is defective and a layer of debris accumulates between the receptor and the pigment epithelium finally producing blindness.

(d) *Cones* generally have conical outer segment, its renewal is more diffused process and appears to occur at multiple sites in the outer segment.

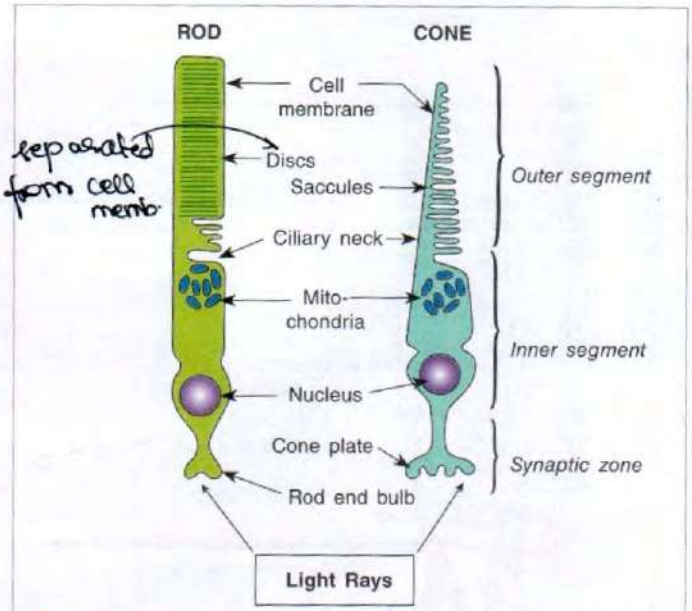


Fig. 110.4 Electron microscopic appearance of photoreceptors, rod and cone

(ii) *The inner segment*

(a) It is rich in mitochondria. Cone's inner segment is thick, oval in shape and is larger.

(b) Towards the inner side both rods and cones pierce the 'external limiting membrane', then enlarge to form rod and cones nucleus respectively and finally enlarges into *rod end bulb* (knob like fashion) and *cone plate* respectively.

Layer 3: *External limiting membrane.* It is formed by the glial tissues, it is the continuation of internal limiting membrane and is pierced by the rods and cones.

Layer 4: *Outer nuclear layer.* It is formed by the nucleus of rods and cones.

Layer 5: *Outer synaptic layer.* It is formed by synapse between the ends of rods and cones with dendrites of 'bipolar' cells and 'horizontal' cell processes (see below).

Layer 6: *Inner nuclear layer.* It contains:

(i) ***Bipolar cells;***

(ii) ***Horizontal cells*** which connect one receptor cell to other receptor cell; and

(iii) ***Amacrine cells.*** Its processes make synaptic contacts with dendrites of both ganglion and bipolar cells, and connect ganglion cells to one another (page 1110).

Layer 7: *Inner synaptic layer.* There is a considerable overall *convergence* of photo-receptors (rods and cones) on bipolar cells and that of bipolar cells on ganglion cells. The synapse between the axons of bipolar cells with the dendrites of ganglion cells occur in this layer. It is the *site of major processing of the visual image.* The selective responsiveness to motion or direction of motion is a function of the amacrine cell system. Their horizontal inter-connections cause a sharpening of the edges of any stimulated field on the retina.

Layer 8: *Ganglion cell layer.* It is a single layer of cell containing round cells.

Layer 9: *Optic nerve.* It is formed by joining the axons of ganglion cells; here all the axons run parallel.

Layer 10: *Internal limiting membrane.* It separates the retina from the vitreous humour. It is formed by the glial tissues.

2. The retina comprises several layers in which the *light sensitive receptors* (*rods and cones*) *are outermost towards* the choroid. The light rays transmitted through the cornea have to traverse the ganglion and bipolar cells before finally reaching the photoreceptors **(Fig. 110.5)**. The ganglion cells and their fibers cannot themselves function as light receptors, since the point of entrance of the optic nerve (optic disc) is insensitive to light and constitutes the ***blind spot*** (page 1087).

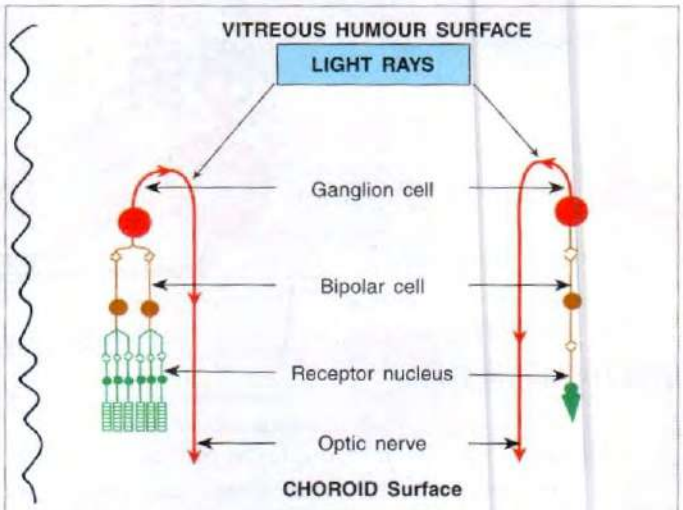


Fig. 110.5 How the light rays reach the photoreceptors?

Note

One optic nerve fiber is serving several rods units (on the left) while serving a single cone (on the right)

3. The *fovea* contains ***no rods***, and each foveal cone has a single bipolar cell connecting it to one ganglion cell. Thus each foveal cone is connected to a single fiber in the optic nerve. In peripheral portion of retina rods predominate; rods and cones often converge on the same ganglion cell **(Fig. 110.6)**.

4. There are about 6-7 million cones and 120-125 million rods in each human eye, but only 0.8-1.2 million nerve fibers in each optic nerve; therefore, overall *convergence of receptors* through bipolar cells on ganglion cells is approximately 105-165 : 1.

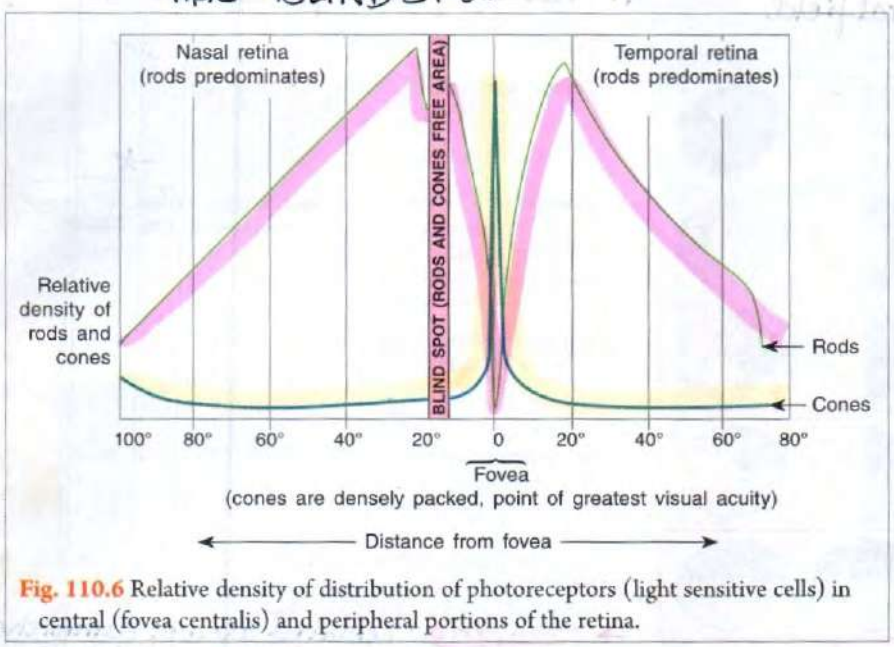


Fig. 110.6 Relative density of distribution of photoreceptors (light sensitive cells) in central (fovea centralis) and peripheral portions of the retina.

Important Notes

1. The retinal blood vessels supply the bipolar and ganglion cells, but the photoreceptors (rods and cones) are nourished for the most part by the capillary plexus in the choroid. This is why *retinal detachment* is so damaging to the receptor cells and leads to the blindness.
2. The arteries, arterioles and veins in the superficial layers of the retina can be seen through the *ophthalmoscope*. This is the one place in the body where arterioles are readily visible, thus ophthalmoscopic examination is of great value in the diagnosis and evaluation of diseases that affect blood vessels such as diabetes mellitus, hypertension.

THE VISUAL PATHWAYS

The visual fibers arise in the layer of nerve cells *(bipolar and ganglion cells)* in the retina. Sensory pathway from the eye to the cerebral cortex is a 3-order neuron pathway viz. primary, secondary and tertiary neurons.

1. First-order neurons or *primary neurons.* These are the *bipolar* cells whose dendrites synapse with photoreceptors (rods and cones); and its axons synapse with dendrites of ganglion cells **(Fig. 110.5)**.
2. Second-order neurons or *secondary neurons* **(Fig. 110.7)**. These are the *ganglion* cells.
   (i) The axons of the ganglion cells pass backwards along the *optic nerve* to the *optic chiasma* where partial crossing of the fibers takes place. The fibers from the temporal side of the retinae remain 'uncrossed' and those from the nasal retinae 'cross' to the opposite side.

Important Note

The fibers from the macula lutea (location of fovea) behaves in exactly the same way.

   (ii) Thus two *optic tracts* are formed, the left optic tract conveys fibers from the left halves of both retinae and the right optic tract from the right halves of both retinae.
   (iii) The optic tract passes in between crura ciberium and ends in two main areas:
      (a) majority of fibers end in the *lateral geniculate body (LGB)*, a part of thalamus; and
      (b) few fibers enter the *superior colliculus* (in mid brain); these fibers synapse with pretectal nucleus and serve as a centre for *visual reflexes* (page 1099).

Important Note

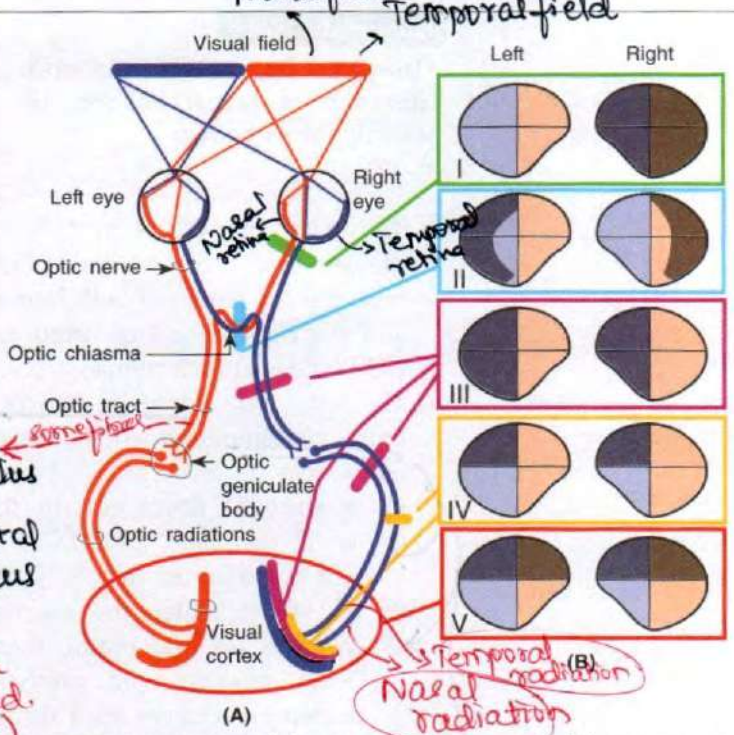
Some axons of the ganglion cells pass directly from the optic chiasma to the suprachiasmatic nuclei in the hypothalamus, where they form connections that mediate a variety of endocrine and other *circadian rhythm* with the light-dark cycle (page 1003).

   (iv) In the *lateral geniculate body (LGB)*, there is an orderly point to point (*topographical*) representation of retina.
      (a) The grey matter of the LGB shows six clear-cut layers numbered 1 to 6. The fibers from the retina to the *contralateral* (opposite) side end in *layers 1, 4 and 6*; the fibers from the *ipsilateral* (same) retina end in *layers 2, 3 and 5*. **(Fig. 110.8)**
      (b) Similarly, the visual fibers from the *upper* retinal quadrants terminate in the *medial halves* of the LGB, while the fibers from the *lower* retinal quadrants terminate in the *lateral halves*.

Important Note

About 1/3rd of the fibers in the optic tract and LGB are derived from the maculae.

3. Third-order neurons or *tertiary neurons.* These are the neurons located in the LGB. Its axons form the *geniculo-calcarine tract* which passes to the *occipital lobe* of the cerebral cortex.



I. ***Complete blindness*** right eye

II. ***Bitemporal hemianopia***, i.e. loss of temporal field of vision in both the eyes (or ***Heteronymous hemianopia*** - since right half of visual field is lost in right eye and left half of vision is lost in the left eye

III. ***Left homonymous hemianopia***, i.e. loss of left halves of visual fields in both the eyes

IV. ***Left quadrantanopia***, i.e. loss of left 1/4th of the visual field in both the eyes

V. ***Discrete quandrantic visual field defects*** (called Scotoma) because of specific anatomic arrangement of the optic nerve fibers in the occipital cortex

Fig. 110.7 Visual pathway (A) and effect of lesions on it (B). **Note:** For further details also refer to pages 1095

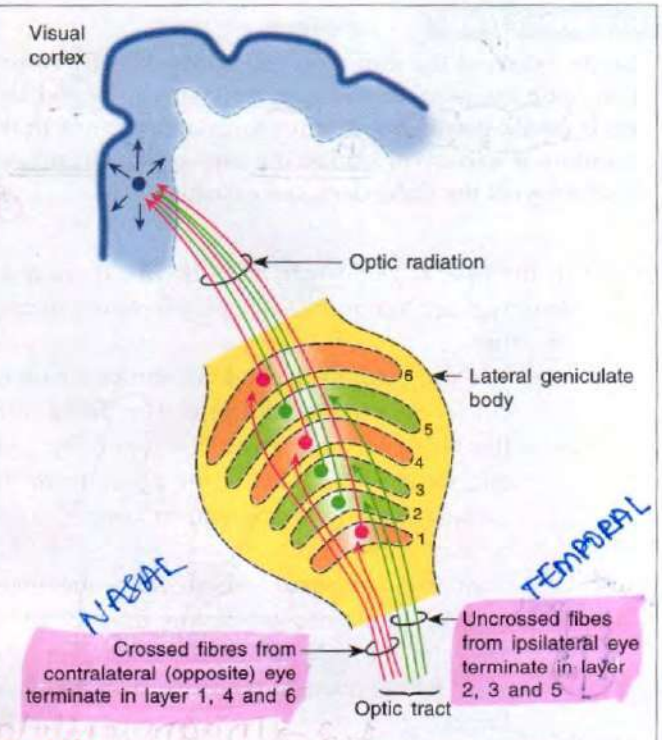


Fig. 110.8 Mode of termination of fibers of optic tract in six layers of lateral geniculate body and further course to visual cortex

4. ***Visual Cortex***

(i) *Optic radiations* from the LGB pass through the internal capsule via geniculo-calcarine tract to the ***primary visual area***, also called ***visuo-sensory area*** (*V – 1*) (area 17). It is the highest area for the perception of visual sense and is located on the medial surface of the occipital lobe, above and below the calcarine fissure **(Fig. 110.9)**. Here, again there is an orderly *point to point* representation of the retina.

(ii) The geniculo-calcarine fibers from *medial halves of LGB (i.e. upper retinal quadrants)* terminate on the ***superior lip of*** the calcarine fissure, while those from the *lateral halves (i.e. lower retinal quadrants)* terminate on the ***inferior lip***.

(iii) Furthermore, the fibers from the LGB which subserve ***macular vision*** separate from those that subserve peripheral vision and *end more posteriorly* on the lips of the calcarine fissure. *Thus the macula has a very large central representation and that of peripheral retina is small.*

(iv) Results have been obtained by studying the evoked potentials in the occipital cortex resulting from stimulation of separate part of retina. It has been seen that 1 mm of *fovea* retina is represented by about 16 mm in the cortex, whereas more peripheral parts of the retina receive only approximately 1/60th of this representation per mm.

Note

There are twice as many fibers in the geniculo-calcarine tract as in the optic nerves, and in the visual cortex the number of neurons concerned with vision is 1000 times the number of fibers in the optic nerve (*Divergence* of output - page 858)

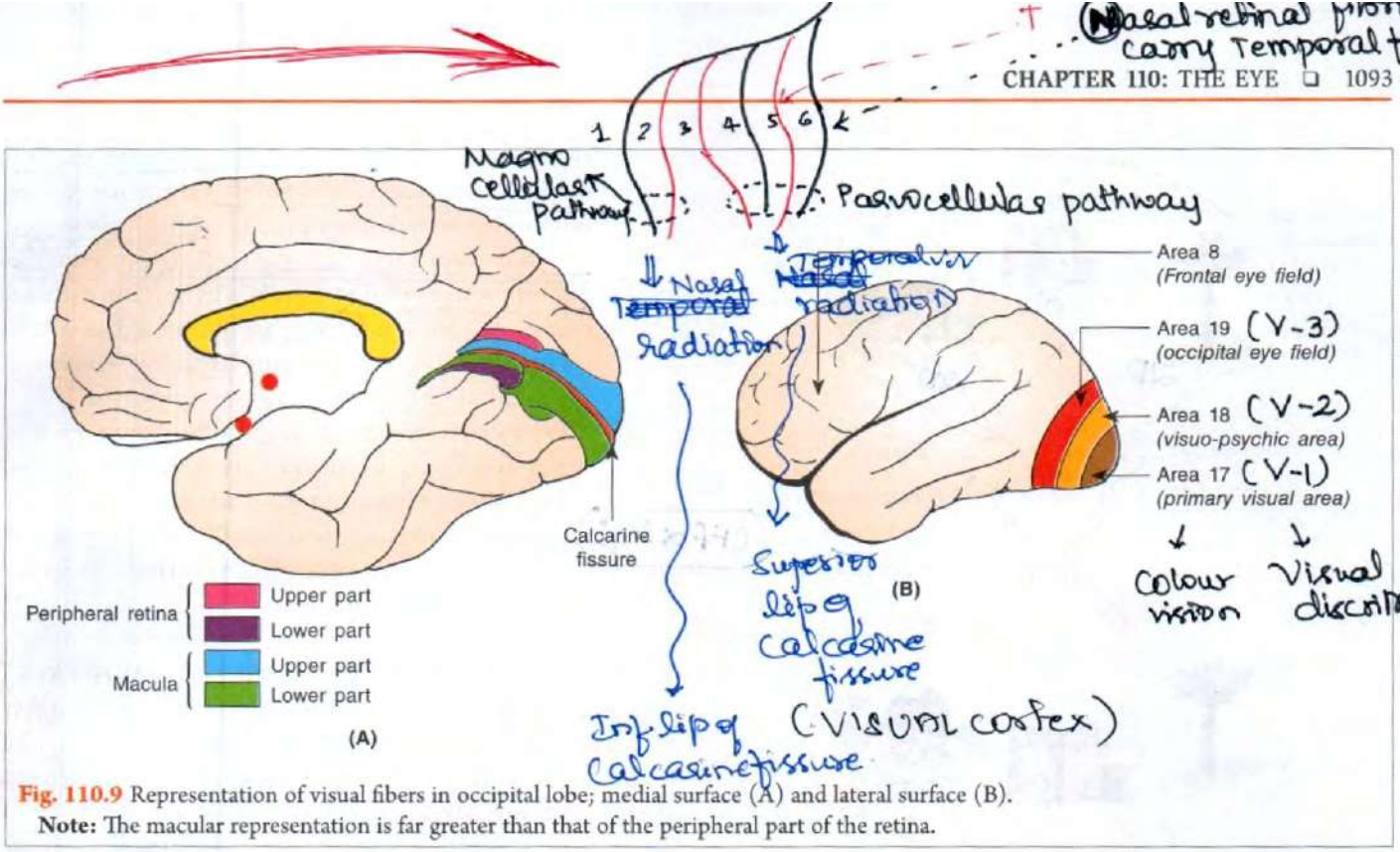


Fig. 110.9 Representation of visual fibers in occipital lobe; medial surface (A) and lateral surface (B).
Note: The macular representation is far greater than that of the peripheral part of the retina.

(v) Each half of the retina receives light rays from the opposite half of the field of vision; therefore, each visual cortex is called ***half visual centre***, as one half of the visual cortex represents half visual field in one eye.

(vi) Like the rest of the neocortex, the visual cortex has six layers (page 1014). The axons from the LGB neurons end on pyramidal cells in layer 4 which in turn project primarily to more superficial layers (layers 2 and 3). These layers contain 'clusters' of cells, called ***blobs*** which contain high concentration of the mitochondrial enzyme cytochrome oxidase. These are concerned with ***colour vision***. The primary visual area (area 17) also plays a role in ***visual discrimination***. (For details, refer to page 1110)

5. ***Visual Association Areas***

(i) Area 18, ***visuo-psychic area*** *(V – 2)*. It is located on lateral surface of occipital lobe above and anterior to area 17.

(a) It is concerned with higher visual functions such as ***visual orientation, depth perception*** and relay of information from visual cortex to other parts of the brain.

(b) It is the area where visual senses are interpreted and integrated in the light of *past experience*. It also enables *assessment of distance* and *orientation of an object in space*. For example, there is a light and area 17 sees the light. It is the area 18 which interprets that the light is from a candle stick. Thus area 18 is homologue of *stereognosis* (page 901).

(c) After destruction of this area, an individual will fail to recognise nature of objects but can see the objects.

(ii) Area 19, ***occipital eye field***. It is located anterior to area 18 on the lateral surface of occipital lobe. It is the centre *concerned with deviation and movements of eyeball*. Stimulation of this area produces conjugate deviation of eyes to the opposite side and *visual hallucinations* (false belief of seeing something).

(iii) Area 8, ***frontal eye field***. It is located in the middle frontal gyrus. Fibers from this area pass back to area 18, therefore, stimulation of this area also *produces conjugate deviation of eyes to the opposite side*.

6. ***Field of Vision (Visual Field)***

(i) ***Definition:*** The visual field of each eye is the area visualised on the screen when the *gaze* (look far and steadily) is fixed at an object.

(ii) ***Binocular vision*** – the central parts of the visual fields of two eyes coincide; therefore, anything in this portion of the field is seen with both the eyes, called binocular vision **(Fig. 110.10)**.

(a) The impulses set up in the two retinae by light rays from an object are ***fused*** at the cortical level into a single image. The points on the retina on which the image of an object must fall if it is to be seen binocularly as a single object are called ***corresponding points***.

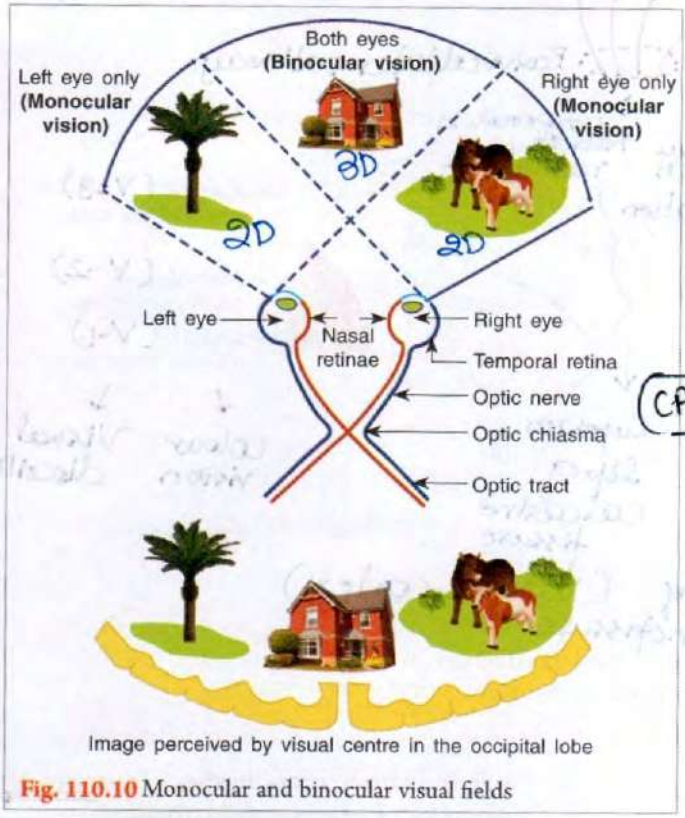


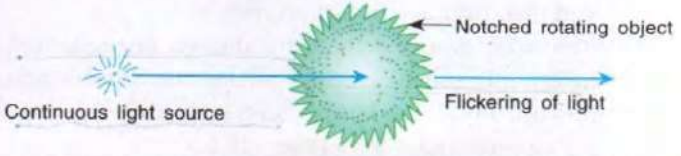
Fig. 110.10 Monocular and binocular visual fields

Important Notes

1. If one eye is gently pushed out of the line while gaze is fixed at an object in the centre of the visual field, double vision (*diplopia*) results; the image on the retina of the eye that is displaced no longer falls on the corresponding point.
2. When visual images chronically falls on *non-corresponding points* in the two retinas in children below 6 years of age, one is eventually *suppressed* and diplopia disappears. This is a cortical phenomenon and it usually does not develop in adults.

(b) Binocular vision plays an important role in appreciation of perception of depth and proportion of objects.

7. ***Flicker Sensation of Light***



(i) It is a common experience that when the light continuously falls on a notched slowly rotating object, a flickering sensation of light is felt. However, if the rotational frequency is increased, the flicker sensation disappears. How?
The time-resolving ability of the eye is determined by measuring the *critical fusion frequency (CFF)* i.e. the rate at which stimuli can be presented and still be perceived as separate stimuli. Frequency of light where flicker will disappear *i.e.* stimuli presented at a more rapid rate than the CFF are perceived as a continuous stimulus. This is why motion pictures move because the frames are presented at a rate above the CFF and it begins to flicker when the projector slows down.

(ii) ***Ferry porter law.*** According to this law CFF is a direct function of log of intensity of light. Therefore, if the CFF has been obtained for one intensity of illumination, the sensation of flicker reappears if the intensity is increased. The periphery of retina is more sensitive to flicker.

EFFECTS OF LESIONS OF THE VISUAL PATHWAYS

The effect of lesions of the visual pathways are *described in term of field of vision* (or visual field, page 1093). The following definitions will help to understand these defects **(Fig. 110.11 and 110.12)**.

(1) ***Anopia.*** It means complete loss of visual field in an eye *i.e.* blindness. *Hemianopia* refers to blindness of half of the visual field.

(2) ***Homonymous hemianopia.*** When the same halves of field of vision in both eyes are lost. For example, loss of the right or the left halves of fields of vision in both the eyes.

(3) ***Heteronymous hemianopia.*** When different halves of field of vision are lost in two eyes. For example, loss of right half of visual field in one eye and loss of left half of visual field in the other eye. Therefore, it is of two types, either *'bitemporal' or binasal.*

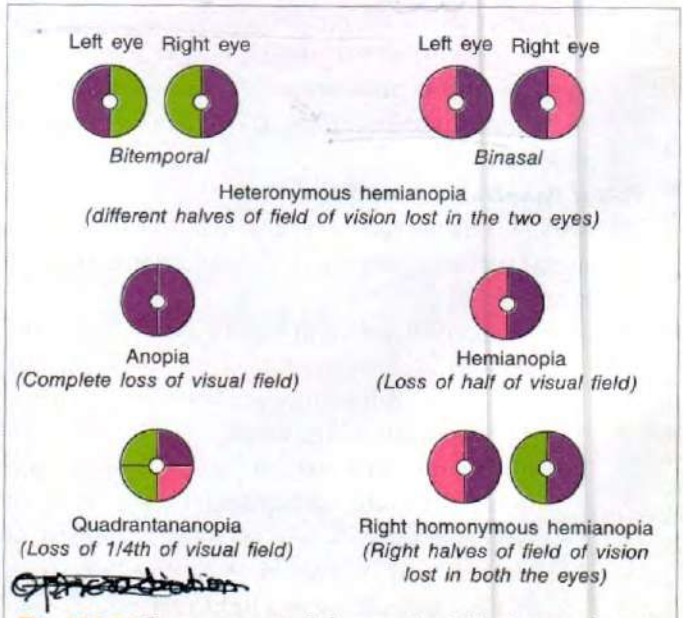
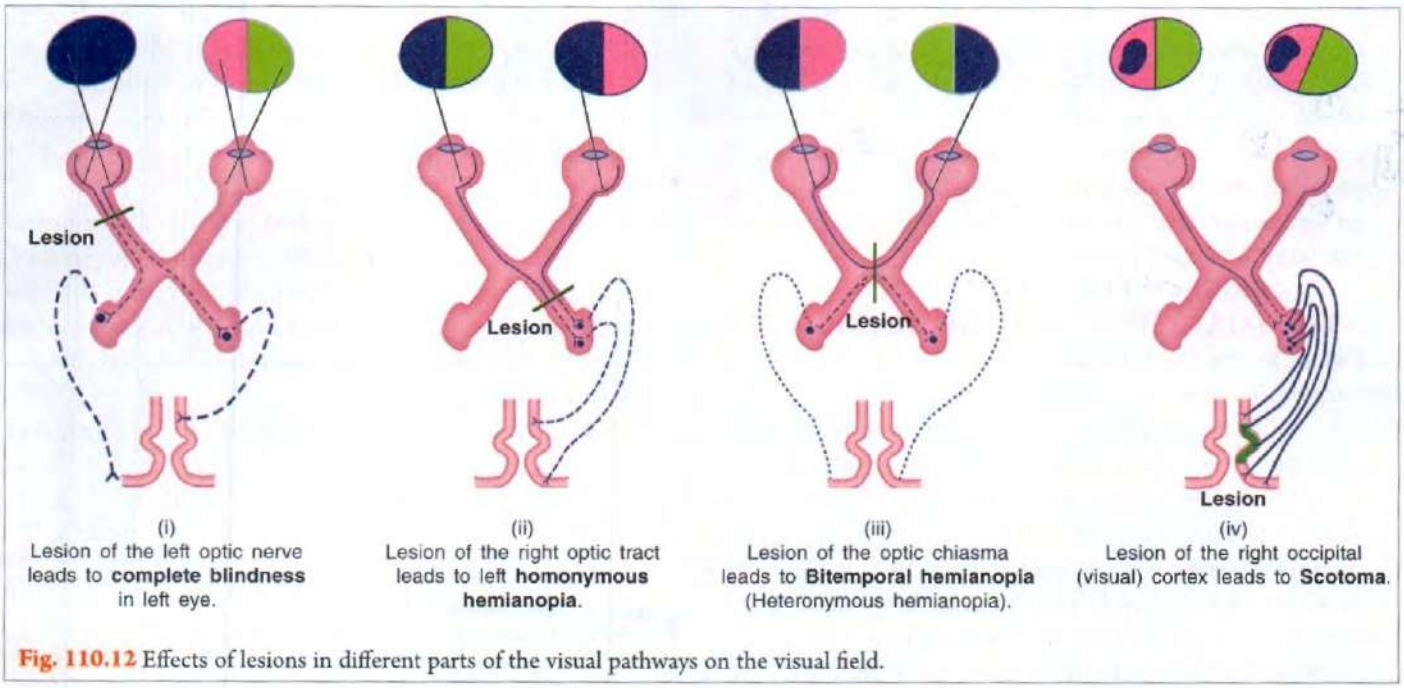


Fig. 110.11 Some common defects in the field of vision (visual field) (**Note:** purple colour indicate loss of visual field)



(i) Lesion of the left optic nerve leads to **complete blindness** in left eye.

(ii) Lesion of the right optic tract leads to left **homonymous hemianopia**.

(iii) Lesion of the optic chiasma leads to **Bitemporal hemianopia** (Heteronymous hemianopia).

(iv) Lesion of the right occipital (visual) cortex leads to **Scotoma**.

Fig. 110.12 Effects of lesions in different parts of the visual pathways on the visual field.

(4) *Quadrantanopia.* When 1/4th of visual field is lost in an eye.

(5) *Scotoma.* It is the loss of vision in an eye which is confined to the centre of the visual field.

EFFECT OF LESIONS (Fig. 110.7 page 1092)

(Also see **Fig. 110.12**)

1. *Lesion of the optic nerve.* It is seen following increased intracranial tension or injury to the optic (I) nerve. It leads to atrophy of optic nerve and causes ***complete blindness*** and loss of direct light reflex (page 1099).
2. *Lesion of optic chiasma.* It occurs due to aneurysm of internal carotid artery or tumours of anterior pituitary. This causes damage of the fibers from both sides of nasal retinae and produces ***Bitemporal hemianopia.*** This is also called, ***heteronymous hemianopia*** since right half of visual field is lost in one eye and left half of vision is lost in the other eye.

Important Note

Since the fibers from the macula are located posteriorly in the optic chiasma, hemianopic scotomas develop before there is complete loss of vision in two hemiretinae.

3. *Lesion of outer margins of the optic chiasma.* This damages the fibers from both sides of temporal retinae and causes ***binasal hemianopia.***
4. *Lesion of optic chiasma and its right outer margin.* This damages the fibers from both sides of nasal retinae and that of right temporal retina; and causes 'blindness' in right eye with 'temporal hemianopia' in the left eye.
5. *Lesion of optic tract.* It causes ***homonymous hemianopia*** (loss of same halves of the visual fields in both the eyes) with hemianopic pupillary responses (page 1099) If the light reflex fibers are partially damaged (depending on the site of lesion), it results in ***Wernicke's pupillary reflex*** *i.e.* when light is focused on the blind retina, light reflex is lost and if light is focused on the sound retina, light reflex persists.
6. *Lesion of lateral geniculate body or optic radiations.* It causes ***homonymous hemianopia*** with normal pupillary reaction to light.

Important Note

Blindness with preservation of the pupillary light reflex usually is due to a lesion behind the optic tracts.

7. *Lesion of occipital cortex,* primary visual area (area 17). Its lesion produces only discrete *quadrantic visual field defects* (page 1094) because of specific anatomic arrangement of the optic nerve fibers in the occipital cortex (page 1093).

Important Note

A common finding with most of the occipital lesions is loss of peripheral vision with normal and complete macular vision, called *Macular Sparing.* This is because the macular representation in occipital lobe is separate and far greater than peripheral part of the retina. Therefore, occipital lesions must extend for considerable distances to destroy macular as well as peripheral vision.

8. ***Lesions of the visual association areas, area 18 or 19.*** This leaves visual sensibility intact but causes disturbance of higher visual functions, such as loss of visual orientation of localization of space, impaired perception of depth and distance, loss of visual attention and inability to recognize visually the common everyday objects, a phenomenon called ***visual agnosia*** (also see to page 1021).

THE IMAGE FORMING MECHANISM

A. PRINCIPLES OF OPTICS

Refraction by spherical lenses.

(1) The light rays are refracted (bent) when they pass from one medium into a medium of a different density, *except* when they strike perpendicular to the interface. Thus the light rays get refracted *towards the centre* when they enter from low density medium to the high density medium; and *away from the centre* when they move from high to low density medium.

(2) A ***lens*** is a piece of transparent glass bounded by two spherical surfaces. There are three types of lenses: convex, concave and cylindrical.

(i) A *convex* lens is thick at the centre but thinner at the edges.

(ii) A *concave* lens is thin in the middle but thicker at the edges.

(iii) A *cylindrical* lens is one in which one surface is plain and other surface is either concave or convex.

(3) The centre point of a lens is known as its ***optical centre*** or ***nodal point***. It has a property that a ray of light passing through it does not suffer any refraction (deviation) and goes straight **(Fig. 110.13)**.

(4) The ***principal axis*** of a lens is a line passing through the optical centre of the lens and perpendicular to both the faces of the lens.

(5) The ***principal focus*** of a *convex lens* is a point on its principal axis to which light rays parallel to the principal axis converge after passing through the lens. Thus a convex lens is also known as a ***converging lens*** because it converges a parallel beam of light rays.

(6) The principal focus of a *concave lens* is a point on its principal axis from which light rays, originally parallel to the axis, appear to diverge after passing through the concave lens. Thus a concave lens is also known as ***diverging lens*** because it diverges a parallel beam of light rays.

(7) The ***focal length*** of a lens is the distance between optical centre (nodal point) and principal focus of the lens.

(8) The light rays from a ***distant object*** *(more than 6 metres or 20 feet)* that strike a lens are approximately parallel. The light rays from an object closer than 6 mts are 'diverging', and are thererfore brought to focus farther back on the principal axis than the principal focus.

(9) ***Power of a lens***

(i) The power of a lens is defined as the reciprocal of its focal length in metres.

$$\text{Thus, power of a lens} = \frac{1}{\text{focal length of the lens (in metres)}}$$

Important Note

Since the power of a lens is inversely proportional to its focal length, a lens of short focal length has more power whereas a lens of long focal length has less power.

(ii) The S.I. unit of the power of a lens is ***dioptre*** which is denoted by the letter 'D'. One dioptre is the power of a lens whose focal length is 1 metre.

(iii) A ***convex lens*** has a *positive* focal length, so the power of a convex lens is positive (and written with a '+' sign). A ***concave*** lens has a *negative* focal length, so the power of a concave lens is negative (and written with a minus '–' sign).

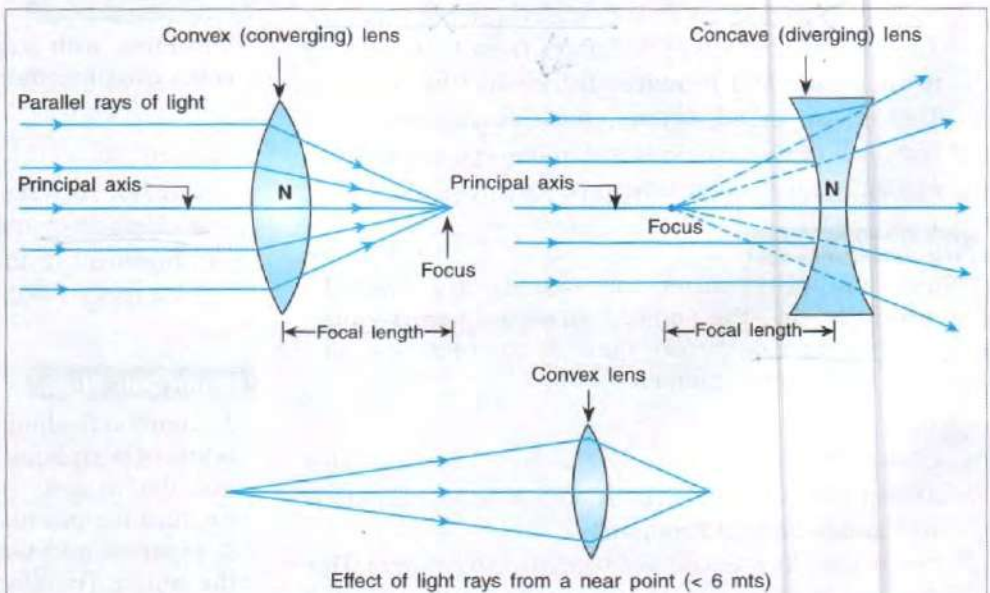


Fig. 110.13 Refraction (bending) of light rays by convex and concave lens (N: optical centre or nodal point)

(10) ***How to distinguish between a convex and concave lens without touching them?***

Keep the lens close to the page of a book and see the image of the writing of the book through it. If the letters of the book appear enlarged, it is a convex lens; and if the letters appear diminished, it is a concave lens. This is due to the fact that when an object is within the focus of a convex lens, it produces an enlarged image. But a concave lens produces a diminished image for all positions of the object.

B. REDUCED or SCHEMATIC EYE

1. ***Refractive index*** of a transparent substance:

$$= \frac{\text{Velocity of light in air}}{\text{Velocity of light in that substance}}$$

Velocity of light in solids and liquids is less than in air, therefore, velocity of light in air is taken as 1. The *lens system* of the eye is composed of four refractive interfaces. The refractive indices of various structures in the eye are as under:

	Eye structure	Refractive index
(i)	Cornea	1.37
(ii)	Aqueous humour	1.33
(iii)	Crystalline lens	1.42
(iv)	Vitreous humour	1.34

For practical purposes, the refractive index of cornea, aqueous and vitreous humour is same. However, the crystalline lens has a refractive index of 1.42; therefore the *light rays suffer refraction at the cornea and at the surface of the lens.*

2. The first refraction occurs at *air-corneal surface* (this being the ***greatest***); the lens contributes less. Therefore, any defect of cornea will lead to refractive errors.

Important Notes

(i) When a person is in water, no refraction occurs at cornea because refractive index of water and the cornea becomes the same, thus producing *blurring of vision.*

(ii) Variations in lens curvature, such as seen with optical aberration (page 1102) are of great importance in vision.

3. Due to the differences in the refractive indices of the eye structures, the refraction of light is 'complex' at different surfaces. Therefore, 'compound' eye refraction can be simplified as ***reduced*** or ***schematic eye.***
4. The reduced (*or schematic*) eye has a single spherical surface (the lens) of radius 5.6 mm separating two media of refractive indices 1 and 1.33, situated 1.4 mm behind the cornea in the aqueous humour. The 'nodal point' (or optical centre, page 1136) of this eye is situated 7 mm behind the anterior surface of the cornea **(Fig. 110.14)**.

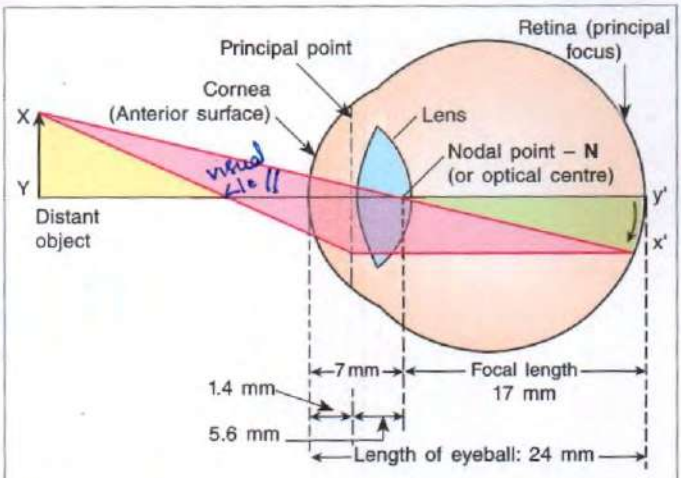


Fig. 110.14 The reduced or schematic eye (∠XNY is 'visual angle')

5. The human eye is about 24 mm in length, so the focal length is 24 – 7 = 17 mm. Therefore,

Refractive power of the lens of the reduced eye (in dioptres)

$$= \frac{1}{\text{Focal length (in mts)}}$$

$$= \frac{1000}{17}$$

= 59D (approx.)

6. The normal human eye also has almost identical refractive power of 59D; thus it also behaves as the reduced eye.
7. The angle subtended by any object at the nodal point is called the ***visual angle*** (significance see below).

Important Note

After removal of the lens, the dioptric power of the eye is reduced by 16D, therefore, the *cornea is responsible for 43D* (59 – 16) of the refractive power of the eye. The refractive power of the cornea is lost when the head is immersed in water (see above) and no refraction occurs at the cornea; this is why blurring of vision occurs when water enters the eye.

C. VISUAL ACUITY

1. It is the degree to which the details and contours of objects are perceived; it is expressed in terms of ***visual angle***. We can resolve two points or parallel lines and recognise them as two only when the visual angle is 1

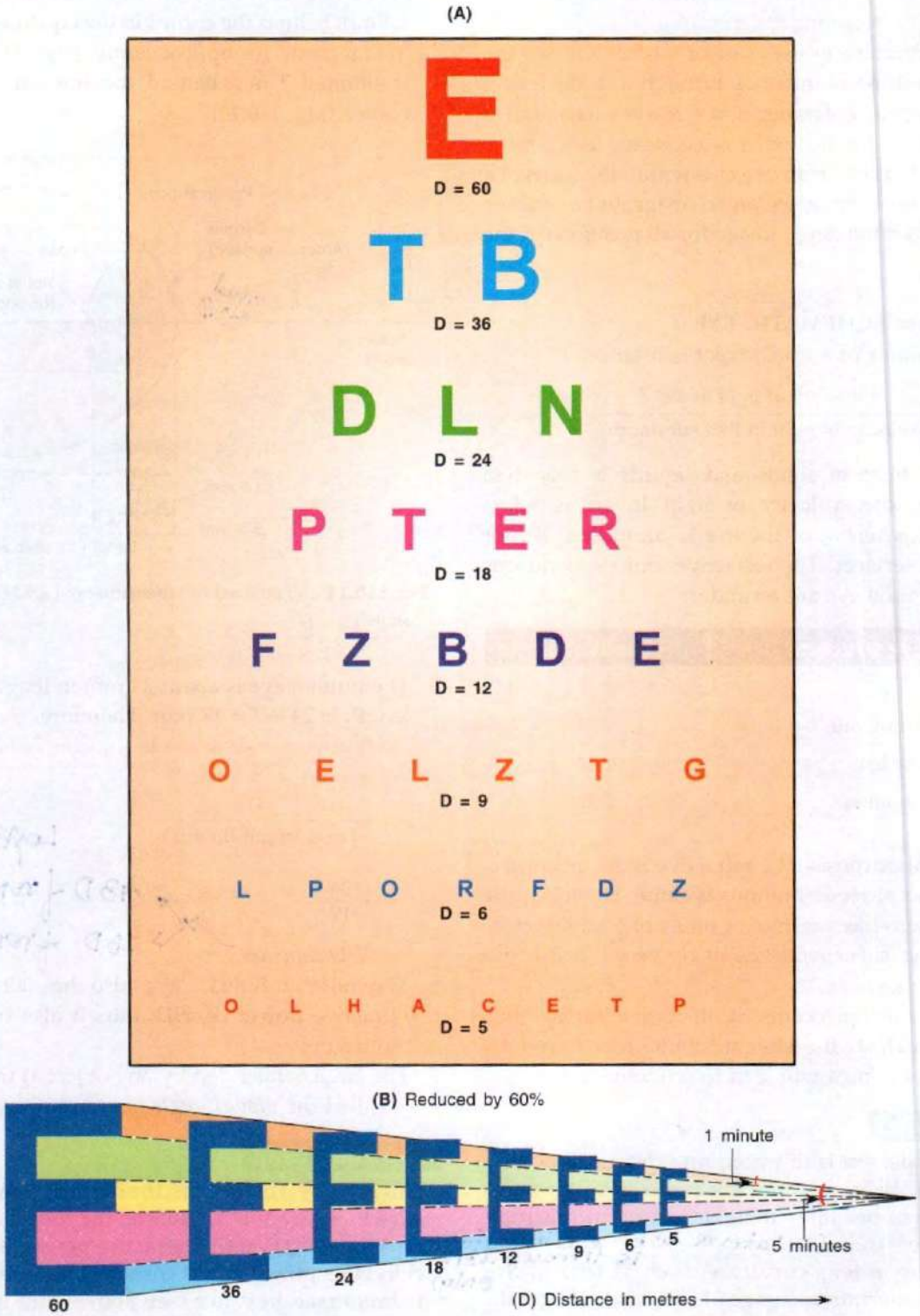


Fig. 110.15 Snellen chart for testing the visual acuity (above) and basis of designing of 'test' letters (below)

minute (1° = 60 min). It is different from *visual threshold* (page 1105).

2. Visual acuity is usually defined in terms of ***minimum separable*** *i.e.* shortest distance by which two lines can be separated and still be perceived as two lines or power determining the shape, outline etc. of surroundings. The space on the retina separating the two images is calculated to be approximately 4.5 μm.
3. 'Clinically' visual acuity is tested with the help of *Snellen Chart* by the ability of the subject to recognise ***test letters*** when illuminated suitably **(Fig. 110.15)**.
   (i) The test 'block' letters which are black on a white

background are of different sizes. Each line of letters has a figure of 60, 36, 24, 18, 12, 9, 6 and 5 metres noted beside it. The chart is so designed that each letter a normal individual can read at a required distance, *subtends a visual angle of 5 minutes.*

(ii) The *width of each stroke* of the letter being *1 minute* and the lines in the letter are also separated by 1 min of arc. Thus the *minimum separable* in a normal individual corresponds to a visual angle of approx. 1 min.

(iii) If the subject, who stands at 6 metres (20 feet) distance reads the chart with one eye at a time and can read no further than the '24 metres' line, his visual acuity is 6/24. It means a letter which can be read by a normal individual at 24 metres is being read at a distance of 6 metres only.

(iv) *6/6 or 6/5 is regarded as* ***normal*** *visual acuity.*

4. ***Factors affecting visual acuity***

(i) ***Optical factors*** such as the state of the image forming mechanisms of the eye. Thus the visual acuity is low in optical aberrations and in defects of image forming mechanisms (page 1102).

(ii) ***Retinal factors.*** Visual acuity is maximal at the fovea centralis where the cones are closely packed and each has connections with a single ganglion cell. The periphery of the retina has a visual acuity of less than 1/30th of that of the fovea.

(iii) ***Stimulus factors*** such as size and colour of the object and its distance from the eye; illumination, brightness of the stimulus, contrast between the stimulus and background, and the length of time the subject is exposed to the stimulus.

(a) *Size of the object and its distance from the eye.* Visual acuity is directly proportional to the visual angle.

$$\text{Visual angle} = \frac{\text{Size of the object}}{\text{distance of the object from the eye}}$$

(b) *Colour of the object.* Coloured object means a weak stimulus. Visual acuity is thus less for coloured objects as compared to white object.

D. VISUAL REFLEXES

PUPILLARY LIGHT REFLEX

Shining of light in one eye leads to constriction of the pupil in the same eye (*Direct Light Reflex*); in addition it also results in constriction of the pupil in the other eye (*Indirect* or *Consensual Light Reflex*).

***Pathway* (Fig. 110.7 and 110.16):** The afferent nerve fibers that carry the visual information travel in the 'optic nerve' and 'optic tract' to end in the 'superior colliculus' or the adjacent pretectal nucleus. From here 'colliculonuclear fibers' arise which cross both in front and behind the aqueduct of sylvius and relay in both sides of 'III nerve (Edinger-Westphal nuclei)'. The fibers of the III nerve relay in the 'ciliary ganglion' and pass in the 'short ciliary nerves' to the 'sphincter pupillae'.

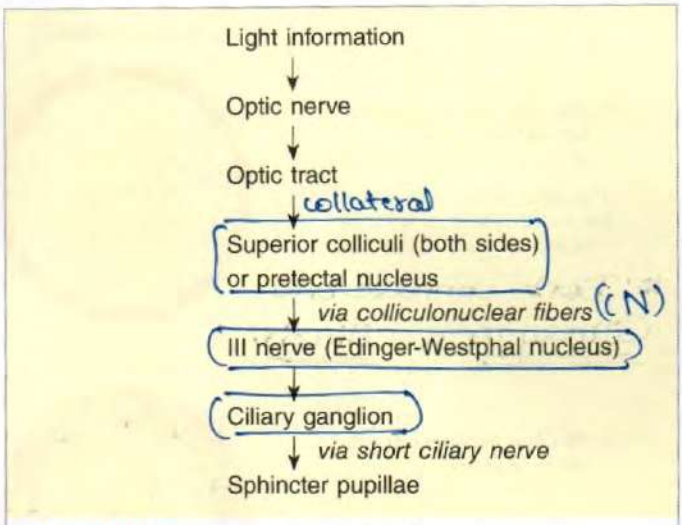


Fig. 110.16 Summary: Pathways for light reflex (direct and consensual)

As the fibers from each retina reach both optic tracts and both superior colliculi, shining of light in one eye leads to the constriction of both the pupils.

ACCOMMODATION

1. ***Definition.*** The ability of the eye to focus an object at varying distances is called *accommodation*. It is due to a mechanism which brings about the change of curvature of the anterior surface of the lens. This is because the lens capsule is thinnest in the central part on the anterior surface.

Note

By increasing its convexity the lens increases its refractive power by 12 D.

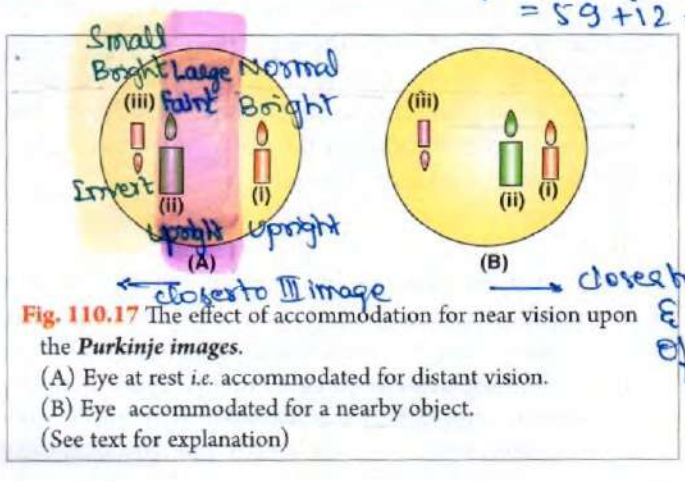


Fig. 110.17 The effect of accommodation for near vision upon the ***Purkinje images.***
(A) Eye at rest *i.e.* accommodated for distant vision.
(B) Eye accommodated for a nearby object.
(See text for explanation)

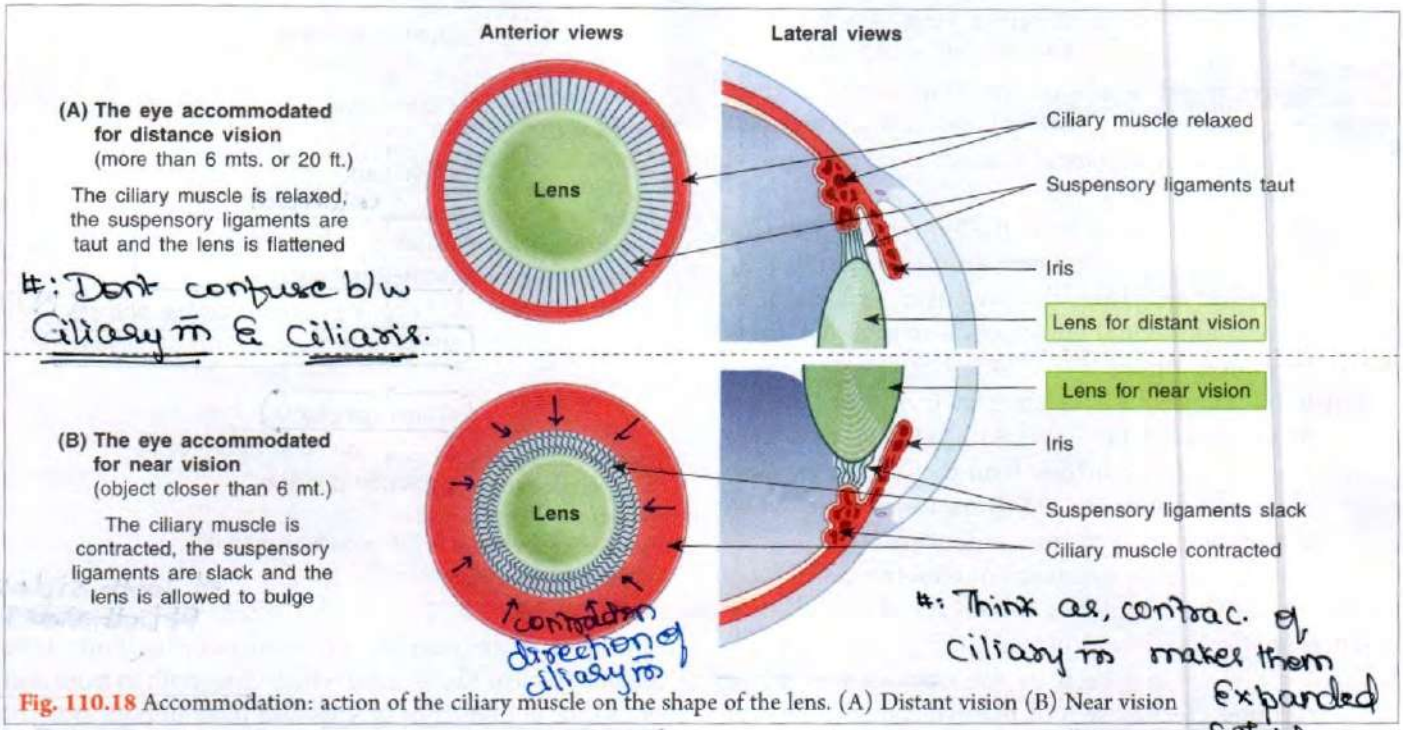


Fig. 110.18 Accommodation: action of the ciliary muscle on the shape of the lens. (A) Distant vision (B) Near vision

The change in the curvature of the lens during accommodation for near vision can be demonstrated by observing the *Purkinje images* in a normal human subject when the eye is relaxed *i.e.* focused at distant object (more than 6m), and when it is focused upon a nearby object.

In a darkened room, a candle is held to one side of the head of the subject and three images will be seen by the observer **(Fig. 110.17)**.

(i) A bright ~~upright~~ reflection of the candle from the convex surface of the cornea;

(ii) A second larger and fainter image of the candle reflected from the convex anterior surface of the crystalline lens; and

(iii) A much smaller inverted but brighter image reflected from the posterior surface of the lens.

Now, if the subject focuses his eye upon a nearby object, the first and third (i and iii) images do not change much; however, the second image (ii) moves significantly closer to the first and also becomes somewhat smaller. This result signifies that during the process of accommodation the anterior surface of the lens assumes a greater convexity.

2. *How anterior curvature of the lens is increased?* **(Fig. 110.18)**

(i) At rest the lens is held under tension by the suspensory ligaments. When the eye is directed at near object, the ciliary muscle contracts.

(ii) The ciliary muscle consists of *two types of fibers*, circular and radial; the former lies in the centre while the latter originates near the corneo-scleral junction and are inserted posteriorly into the choroid. Therefore, when ciliary muscle contracts it pulls the ciliary body forwards and inwards towards the lens causing laxity of suspensory ligaments.

(iii) The tension exerted by the suspensory ligament on the lens is reduced, as a result the elastic lens bulges forwards and its anterior surface increases.

3. *Accommodation Reflex or Near Response*

It is a *three-part* response when an individual looks at a near object, therefore, also called ***near response***. It *consists of:* contraction of ciliary muscles, constriction of pupils and convergence of visual axes.

(i) *Contraction of ciliary muscle* via III nerve. As a result anterior curvature of lens increases (see above).

(ii) *Constriction of pupil* due to contraction of sphincter pupillae. This allows the light to fall only on the centre of the lens in which the accommodation changes are maximum. Constriction of pupils also helps:

(a) to decrease spherical and chromatic aberrations (page 1102);

(b) to decrease intensity of light entering into the eye; and

(c) to increase the *depth of focus*. (How? **Fig. 110.19**).

(iii) *Convergence of visual axes* due to contraction of medial rectus muscle. This helps in focusing the image of an object on fovea centralis. If convergence of visual axes fails, *diplopia* (double vision) occurs.

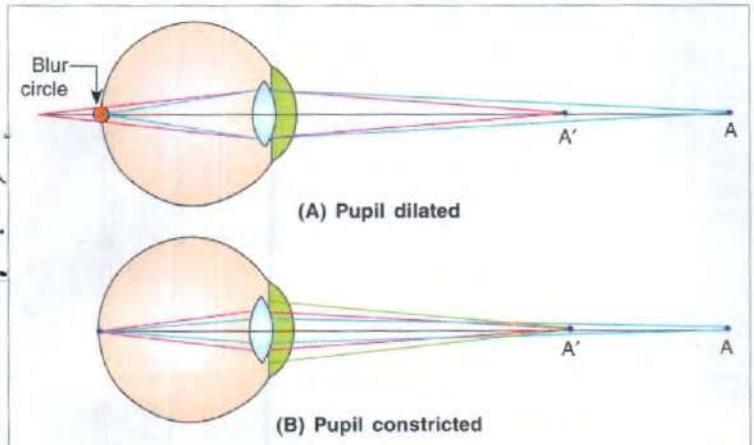


Fig. 110.19 Depth of focus: Role of pupil during accommodation
(A) When object moves from A to A', the latter image produces 'blur circle' as image is falling on more than one receptor. Therefore, one particular point is perceived as more than two points (***blur image***).
(B) By pupillary constriction, extra peripheral light rays are cut off, and hence **no** 'blur circle' forms, thus increases 'depth of focus'

(Soln. to blurred image)

Important Notes

1. Accommodation reflex is bilateral *i.e.* if we close one eye and look at the near object with the other eye, both the eyes show constriction of the pupil.
2. Accommodation is an active process which requires muscular effort. Therefore, watching television or reading for a long period can be tiring and may produce severe headache due to muscular fatigue.

4. *Accommodation pathway*

The visual information passes to the 'primary visual area', area 17 (page 1093) and are relayed to the 'frontal eye field', area 8. 'Corticonuclear fibers' from here pass in the anterior limb of the internal capsule to reach the 'III nerve nucleus' which supplies all the three muscles viz. ciliary muscle, sphincter pupillae and medial rectus **(Fig. 110.20)**.

Visual information
↓ *via visual pathway*
Primary visual area, area 17
↓
Frontal eye field, area 8
↓ *via corticonuclear fibers*
III nerve (Edinger-Westphal nucleus)
↓
Ciliary muscle; sphincter pupillae and medial rectus

(In light reflex, Corticonuclear fibres)

Fig. 110.20 Summary: Pathway for accommodation reflex
(**Note:** Effects of ANS activity - see page 926-927)

Applied aspect

(i) *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*. It is associated clinically with lesions in or near the aqueduct of Sylvius and the superior colliculi which interrupt the pathway of light reflex only **(Fig. 110.16)**. This sign is very frequently found in syphilis of CNS which affects this region.

(ii) *Reverse Argyll-Robertson pupil*

This is reverse of (i) above; here pupillary constriction in *response to light is present* while the *response to accommodation is absent*. This is due to bilateral damage of frontal lobe or damage of its descending fibers to III nerve nucleus.

(frontal eyefield damage)

5. *Amplitude of Accommodation*

(i) *Definition.* This is the difference in refractive power of the eye between the two states, complete relaxation and maximal accommodation.

(ii) *'Far point' of vision.* Under resting condition (*i.e.* when the eye is adapted for *'distant' vision*, the ciliary muscle is relaxed) parallel light rays from distant object (more than 6 metres) are brought to a focus on the retina **(Fig. 110.21)**. In this state the 'resting power' of eye is 59D which is taken as 'Zero' and the position of the object is referred as the 'far point' of vision.

(iii) *'Near point' of vision.* When a person focuses clearly, on a near object, in addition to this *resting power*, an extra amount of refractive power is required to focus the image on the retina. Thus the nearest point to the eye at which object can be clearly seen with maximum accommodation is called the 'near point' of vision.

Important Note

The near point recedes (moves away) slowly as age increases due to loss of elasticity of the lens.

(iv) The *'extra' amount of refractive* power required to focus the images of near objects on the retina is called the *Amplitude of Accommodation*. Thus for an object at a distance of 10 cm, if refractive power of the eye is 69D (10D above the 'resting' power of 59D), the amplitude of accommodation is 10D.

69 = 59 + 10

Important Note

As near point increases with age, amplitude of accommodation decreases with the age.

Table 110.1: Near point and amplitude of accommodation at different ages

Age (years)	Near point of vision (cm)	Amplitude of accommodation (in dioptres)
10	9 cm	11 D
20	10 cm	10 D
30	12.5 cm	8 D
40	18 cm	5.5 D
50	50 cm	2 D
60	85 cm	1.5 D
70	100 cm	1 D

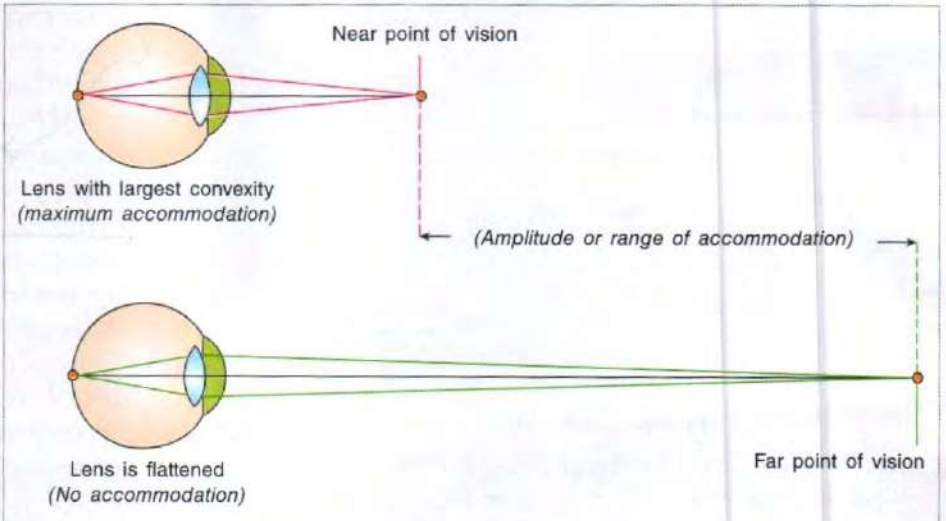


Fig. 110.21 Amplitude of accommodation

Important Note

Accommodation can increase in a young adult by approx. 12D; by the time a normal person reaches 40 years of age, the loss of accommodation is sufficient to make reading and close work difficult.

E. OPTICAL ABERRATION

Aberration means deviation from what is normal. Even in the normal (*emmetropic*) eye, 'optical defects' may be present (although they may be minimal) which prevents the light rays converging to a point producing blurring of vision. These aberrations are of two types: *spherical* and *chromatic aberration* **(Fig. 110.22)**.

1. *Spherical Aberration.* It is due to the biconvex eye lens in which the refractive power at the periphery and central part of the lens is **not** the same. Normally refractive power at the periphery is less and that of the centre is more, therefore, light rays are more divergent the periphery. However, the iris which covers the outer part of the lens, functions to reduce any spherical aberration **(Fig. 110.18)**.
2. *Chromatic Aberration.* It is due to the different refraction suffered by the colours comprising white light which depends on their wavelength.
   (i) Red light with a longer wavelength is refracted the least and thus focused little farther away while the blue light with the shortest wavelength is refracted the most and is focused little earlier.
   (ii) Normally no such chromatic aberration occurs (why? not known). However, when pupil dilates or if the eye looks at bright light the middle wavelengths are focused, the blue rays meet in front of the retina and the red rays behind and none is brought to a point focus, producing chromatic aberration.

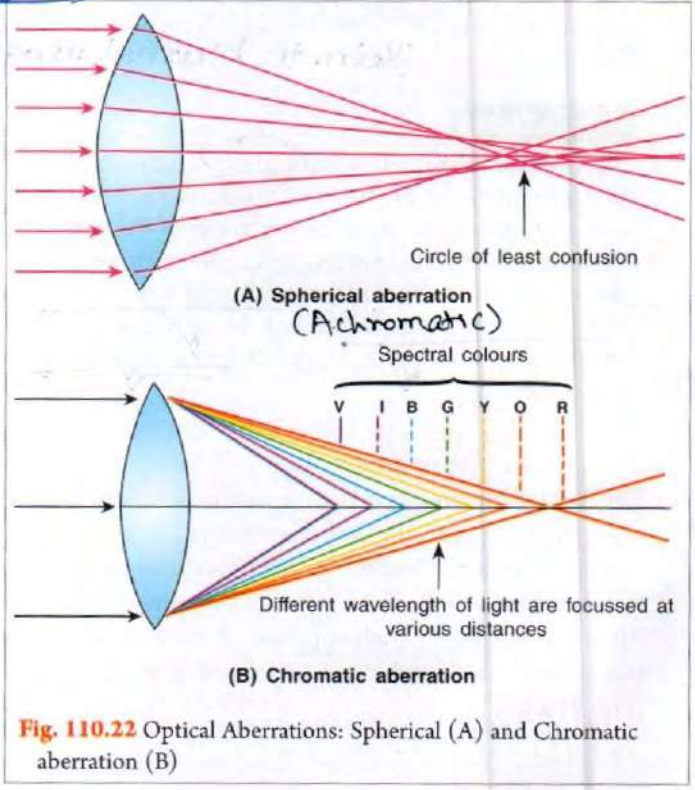


Fig. 110.22 Optical Aberrations: Spherical (A) and Chromatic aberration (B)

F. DEFECTS OF IMAGE FORMING MECHANISM

1. *Presbyopia* (*means loss of accommodation*)
   (i) The ability of the eye to accommodate decreases with advancing age (see above) due to increasing sclerosis (hardening) of the lens substance. As a result the near and far points of vision become so close to each other that reading becomes difficult. Thus the aging can no longer accommodate for both far and near vision **(Fig. 110.23A)**.
   (ii) The loss of elasticity of lens is *due to* denaturation of its proteins by the ultra violet rays which are being absorbed by the lens. As a result of such

irradiation the protein agglutinate and coagulate in the presence of Ca^{2+}. Eventually, the lens becomes swollen, hard and opaque (called *Cataract*).

Important Notes

1. If ultra violet rays are not absorbed by the lens, these rays will reach the retina and damage it.
2. The high incidence of cataract in diabetes mellitus is due to an action of glucose which makes the proteins more easily coagulable by light.

(iii) It can be *corrected by* wearing glasses with *bifocal lens* (The upper segment focussed for distant objects and the lower segment for near vision).

2. ***Myopia*** or ***short-sightedness***

In this condition *(genetic in origin)* the parallel rays of light from distant object are focussed in front of the retina **(Fig. 110.23 B)**. It is because:

(i) either length of the eyeball is too long (*Axial myopic eye*), or

(ii) refractive power of lens increases (*Refractive myopic eye*).

Characteristic features

(i) A person ***cannot see the distant object***, thus called near-sightedness or short-sightedness.

(ii) *Far point* of vision is at a definite distance from the eye; may be less than 1 metre in severe myopia. Normally it is at infinity, more than 6 metres (20 feet).

(iii) *Near point* of vision becomes nearer (close to the eye) as axial length of eyeball increases.

(iv) As a result of (ii) & (iii), 'far point' and 'near point' of vision are closely approximated, therefore, the *range of accommodation* decreases.

(v) Presbyopia gets corrected by myopia because in myopia near point decreases. Thus myopia patients do not need treatment for presbyopia.

(vi) *Correction:* it can be corrected by *concave glasses* which causes divergence of the incident rays. The power of the lens required gives a measure of the degree of myopia **(Fig. 110.23 C)**.

Important Note

The aged myopic subject may never need glasses for reading fine print, as his 'near point' in youth is so close to the corneal surface that even in old age his 'near point' may be at a distance which is normal for a young subject.

3. ***Hypermetropia (or Hyperopia)*** or ***long-sightedness***

In this condition parallel light rays from distant object are focussed behind the retina **(Fig. 110.24 A)**. It is because:

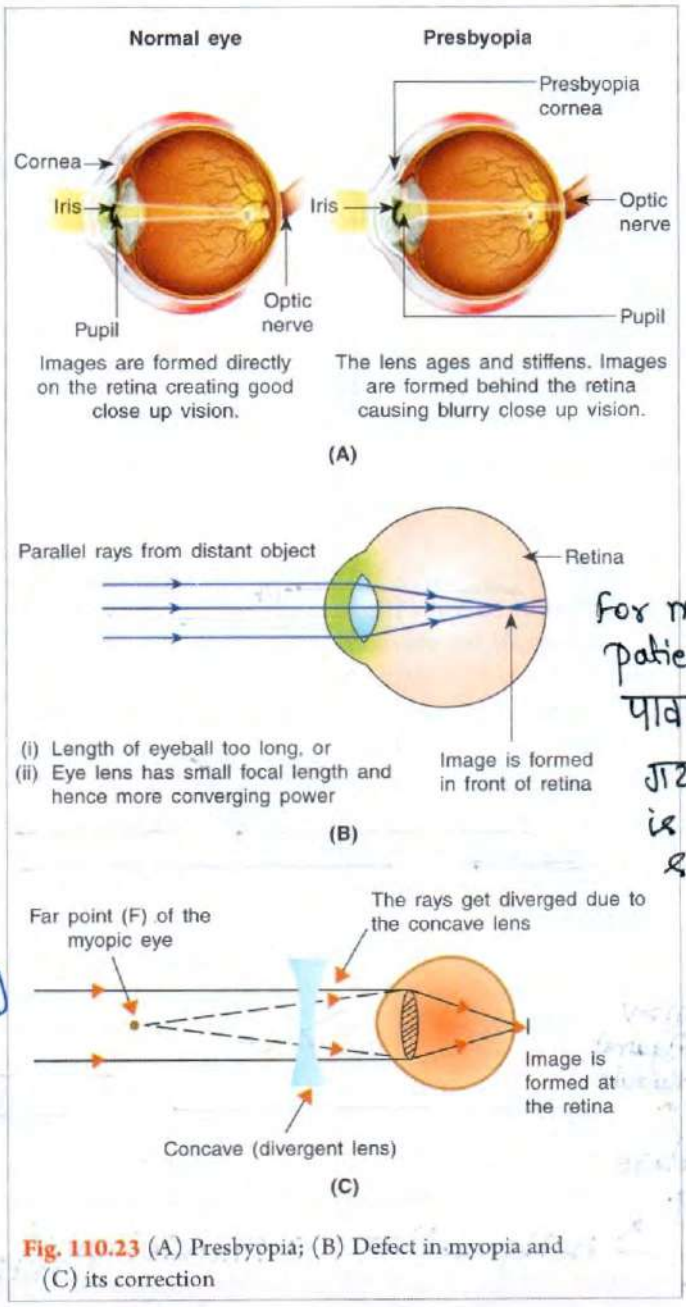


Fig. 110.23 (A) Presbyopia; (B) Defect in myopia and (C) its correction

(i) either length of the eyeball is too short (*Axial hypermetropic eye*) or

(ii) refractive power of the lens decreases (*Refractive hypermetropic eye*).

Characteristic features

(i) A person can see the 'distant' objects clearly only while using some accommodation, thus called 'far-sightedness' or 'long sightedness'.

(ii) *Hypertrophy of the ciliary muscles* occurs because individual will be using the accommodation all the times for seeing the far object. Sustained accommodation (*i.e.* prolonged muscular effort) is tiring and may cause severe headache and blurring of vision.

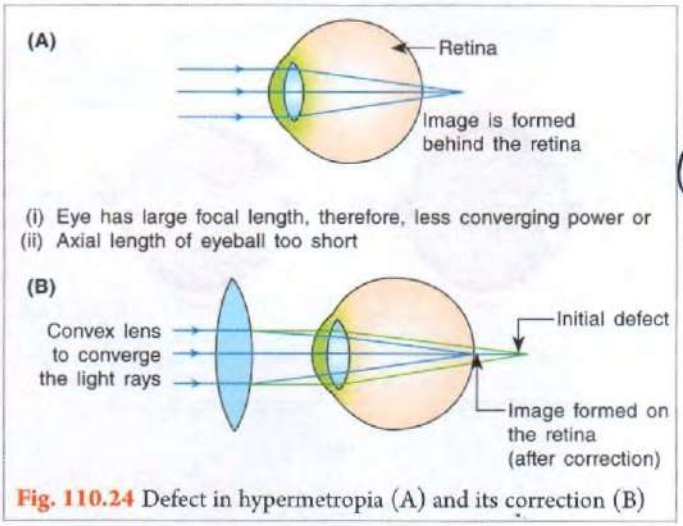


Fig. 110.24 Defect in hypermetropia (A) and its correction (B)

(iii) The prolonged convergence of the visual axes associated with the accommodation, finally leads to ***squint (strabismus).***

(iv) The *near point* of vision moves farther away as the axial length of the eyeball is too short. It can be corrected by *convex* glasses which cause convergence of the incident rays **(Fig. 110.24 B)**.

(v) If hypermetropic individual suffers from presbyopia, he requires correction at an early age than does the normal subject.

4. ***Astigmatism***

(i) *Stigma* means a *point*, therefore, astigmatism is an error of vision in which the light rays are not brought to a 'point' focus on the retina **(Fig. 110.25)**. This is most commonly *due to* a difference in horizontal and vertical curvature of cornea or lens occasionally it may be due to similar defect in the lens. Therefore, the focus of vertical image is not the same as the focus of horizontal image. Thus an astigmatic subject will find *difficult to focus all the lines of a graph paper.*

(ii) Even in normal individuals *'small' vertical astigmatism* is present, called *Physiological Astigmatism*. This is because even in normal eye vertical curvature of the cornea is greater due to pressure of the upper lid or that of the eyeball during growth.

(iii) It is of two types: *'curvature'* and *'index' astigmatism.*

(a) ***Curvature astigmatism.*** It is said to be present when the defect lies in the curvatures of the cornea. If the vertical curvature is greater, astigmatism is said to be ***with the rule***; if the horizontal curvature is greater, the astigmatism is ***against the rule.***

(b) ***Index astigmatism.*** When refractive indices of different parts of lens are different due to malposition of lens, it is called index astigmatism.

(iv) *Correction:* Astigmatism can be corrected with cylindrical lens (page 1136) placed in such a way so that the refraction from all the meridians becomes equal.

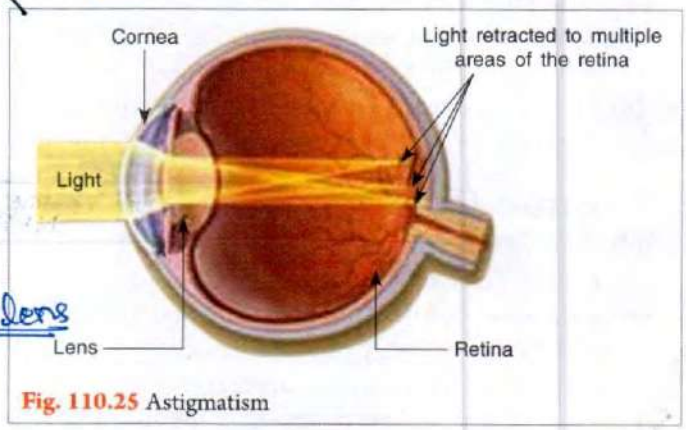


Fig. 110.25 Astigmatism

Table 110.2: Summary: Comparison between normal, myopic and hypermetropic eye

	Normal eye (emmetropia)	Myopic eye	Hypermetropic eye
1. Parallel rays of light from distant object	Focused on the retina	Focused in front of the retina	Focused behind the retina
2. Primary defect	Nil	Either axial (antero-posterior) length of eyeball is too long or refractive power of lens increases	Either axial length of eyeball is too short or refractive power of lens decreases
3. Far point of vision	At infinity (>6 mts *i.e.* 20 feet)	Decreases; it is at a definite distance from the eye (<6 mts.)	At infinity
4. Near point of vision at 20 years of age	10 cm	Close to eye, less than 10 cm	More distant, more than 10 cm
5. Whether accommodation is used for distant objects or not	No	No	Yes
6. If associated presbyopia occurs	Correction required; convex lens	No need for correction	Needs correction at an early age
Correction	Nil	Concave (divergent) lens	Convex (convergent) lens

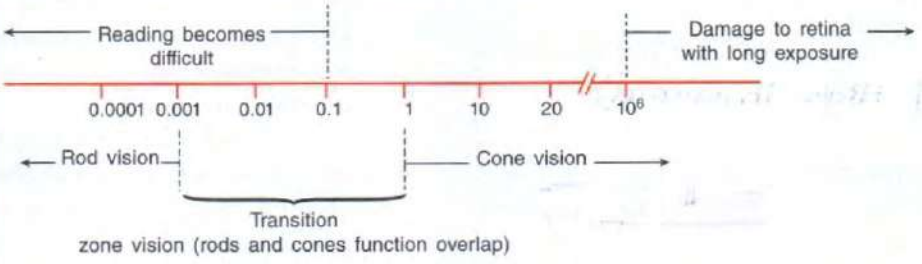


Fig. 110.26 Response of the human eye to different levels of brightness (values in millilamberts)

PHOTOCHEMISTRY OF VISION

A. PHOTOPIC AND SCOTOPIC VISION

The range of luminance to which the human eye responds is described in Fig. 110.26.

1. ***Photopic vision.*** It is daylight vision due to *cone* receptor mechanism. It operates at higher intensity of light, brightness level above 1 millilambert (mA). The cones have a much *higher threshold* but have a much 'greater' acuity (page 1097) thus responsible for vision in bright light and for colour vision.

Note

The minimal amount of light that produces a sensation of light is referred as *visual threshold*.

2. ***Scotopic vision.*** It is dim light vision and is a function of the ***rods***. It is incapable of resolving the details of the objects or determination of their colours. It operates below 0.001 mA intensity of brightness since rods have much *'lower' threshold* and are extremely sensitive to light.
3. ***Mesopic vision.*** It is full moon light vision with brightness level 0.01 mA; below 0.1 mA intensity of brightness, reading becomes difficult.
4. Between 0.001 to 1.0 mA is ***transition zone*** of vision because function of cones overlaps the rods.
   There are thus two kinds of inputs to the brain from the eye; input from the rods and input from the cones. The existence of these two kinds of input, each working maximally under different conditions of illumination is called the *Duplicity Theory of Vision*.

B. VISIBILITY or SENSITIVITY CURVE

1. The eye responds to light of wavelengths (λ) between 400 nm and 750 nm, called ***visibility or sensitivity range of vision*** (Fig. 110.27).
   (i) below 400 nm *(ultraviolet light rays)*, get absorbed by the choroid; and
   (ii) above 750 nm *(infrared light rays)*, get absorbed by the cornea.
   This is why the photoreceptors (rods and cones) are not stimulated by the ultraviolet and infrared light rays and thus these light rays are not perceived by the human eye.
2. The **wavelengths of spectral colours** (VIBGYOR) are: violet (400 nm), blue (450 nm), bluish-green (500 nm), green (550 nm), greenish-yellow (560 nm), orange (600 nm) and red (650-750 nm).
3. The ***sensitivity of vision*** is measured in terms of *energy of light* to produce sensation of vision when low intensity of light is focused. Therefore, high energy of light is less sensitive while low energy is more sensitive. Thus the 'sensitivity' of photoreceptors (rods and cones) to different wavelengths of light can be expressed as a reciprocal of the energy required to produce a standard visual sensation of equal brightness.

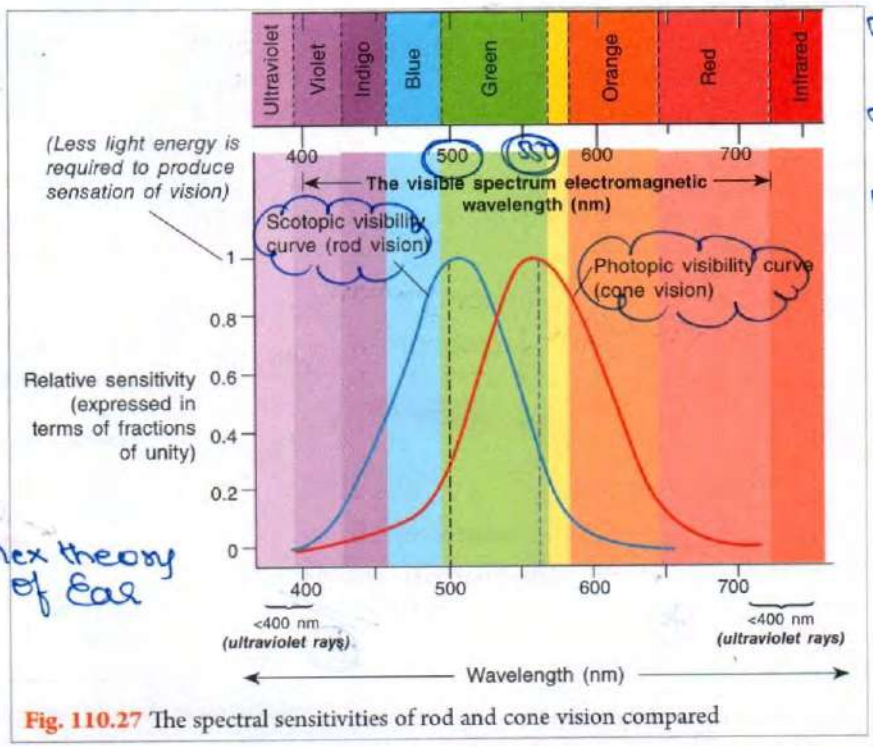


Fig. 110.27 The spectral sensitivities of rod and cone vision compared

Important Note

The cone vision sensitivity is 1/100th – 1/1000th that of rod vision.

4. The *maximum sensitivity of scotopic (rods) vision* (page 1106) is approx. 500 nm *i.e.* for bluish green light. This shows that *red* colour (λ : 650-750 nm) is **not** *at all sensitive to dim light*. Thus in dim light, if blue and red colours need to be compared, blue can be made out easily.
5. Likewise *maximum sensitivity of photopic (cones) vision* (page 1106) is about 560 nm *i.e.* for greenish yellow light.
6. The shifting of sensitivity of eye from photopic to scotopic vision *i.e.* from cones vision to rods vision is known as *Purkinje Shift* or *Purkinje phenomenon*. (This was first noted by *J.E. Purkinje*, the Czech physiologist). This phenomenon is normally seen towards the evening.

Important Note

It is a common experience, the flowers of different colours of similar brightness during the day, change their 'appearance' towards the evening so that the blue appears to glow, whereas the red become almost black.

C. PHOTOSENSITIVE PIGMENTS: RHODOPSIN AND IODOPSIN

1. ***Rhodopsin – rod pigment***
   (i) It is purplish red protein, a photo-sensitive pigment contained in rods discs and coupled to G-protein, therefore, also called ***Visual Purple***. It gets bleached (becomes white) by light **(Fig. 110.28)**.
   (ii) The pinkish protein is made up of an 'opsin', called ***scotopsin*** combined with retinene$_1$, which is the aldehyde of vitamin A_1.
   (iii) *In the dark*, the retinene$_1$ in rhodopsin is in the 11-*cis* form which gets converted to *long-trans* form in the presence of light with formation of a series of intermediates, one of which is metarhodopsin II or prelumirhodopsin. This is the main compound that initiate the closure of Na^+ channels (page 1109).
   (iv) The final step is, separation of retinene$_1$ from the opsin, *scotopsin i.e.* rhodopsin gets bleached.
   (v) Some of the rhodopsin is regenerated directly from retinene$_1$ so formed, while some of the retinene$_1$ is reduced by the enzyme *alcohol dehydrogenase* in the presence of NADH to vitamin A_1; this in turn reacts with scotopsin to form rhodopsin.
   (vi) All of above reactions *except* the formation of *long-trans* form are independent of light, proceeding equally well in light or darkness. The amount of rhodopsin in the receptors, therefore, varies inversely with the incident light *i.e.* when light falls, rhodopsin synthesis amount will be less, and in dim light rhodopsin synthesis increases.
   (vii) *Rhodopsin* (rod pigment) has a maximum sensitivity to light at the wave length of 505 nm, i.e. far bluish-green light.
2. ***Iodopsin – cone pigment***
   (i) There are *three types of cones*, each possessing its own characteristic photosensitive substance. These receptors subserve colour vision and respond maximally to light at wavelength 430 nm (blue colour or ***cyanolabe***); 535 nm (green or ***chlorolabe***) and 575 nm (red or ***erythrolabe***) **(Fig. 110.29)**.

Note

The maximal absorption of light by the 'red' cones actually lies in the orange colour band of the spectrum.

   (ii) The different colour sensations are supposed to be caused by stimulation of various combinations of these three types of receptors.

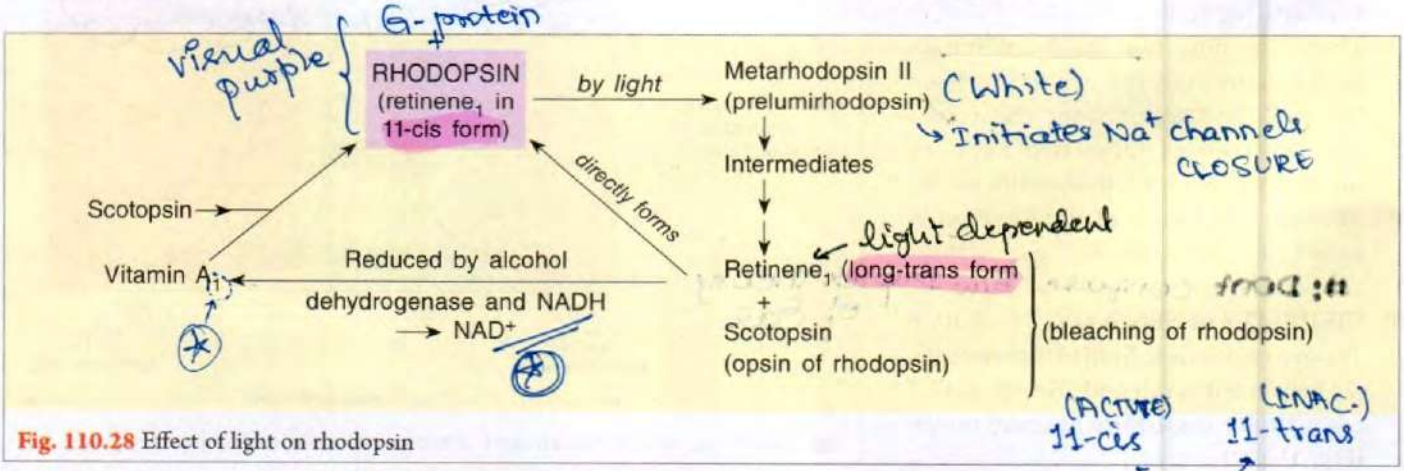


Fig. 110.28 Effect of light on rhodopsin

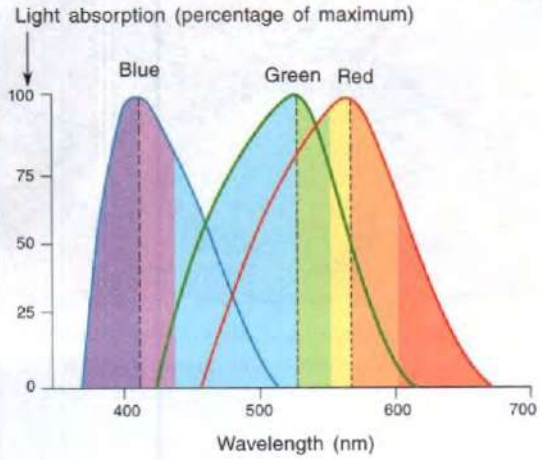


Fig. 110.29 Absorption spectra of the three cone pigments plotted as the percentage of the maximum absorption against the wavelengths of the light

(iii) Only one cone pigment has been isolated from the human retinae, called ***Iodopsin***. It is *maximum sensitive i.e.* absorbs light maximally at about 560 nm (*i.e.* for greenish-yellow light).

(iv) Iodopsin contains the same protein as rhodopsin-retinene$_1$ and opsin (or photopsin); therefore, in the presence of light, all reactions are the same as above.

$$\text{Iodopsin} \xrightarrow{light} \text{Retinene}_1 + \text{opsin (photopsin)}$$

Result of various *experimental analysis* which show that the rods are responsible for the 'scotopic' vision and cones for 'photopic' vision.

1. In vitro, solution of rhodopsin absorbs maximum light at wavelength of 500 nm. The curve relating to the sensitivity in dim light of the intact eye to light of different wave-lengths (*scotopic visibility curve*) also reaches a maximum at 500 nm (page 1105).
2. The low intensity of light cannot be seen on fovea centralis which contains only cones, while same intensity of light on the periphery can be seen because of presence of the rods. Thus it can be said that the rods are responsible for the dim light vision.
3. In chicken eye, only cones are present and they suffer from *night blindness*.
4. 'Night animals' such as rat, owl, mainly have rods while 'day animals' like pigeon have no rods.

D. ADAPTATION

Adaptation means accustomed to or used to new conditions.

DARK ADAPTATION

It is a common experience that entering a dimly lit room, such as a cinema hall, one finds it initially difficult to see. However, visual perception improves quickly at first and then more slowly thereafter. This decrease in *visual threshold* or increase in sensitivity of eye to light, is called ***Dark Adaptation***. There are two components of dark adaptation response: *fast* and *slow response*.

(i) ***Fast response:*** Initially, the first drop in visual threshold is rapid but small in magnitude. It is due to dark adaptation of the cones, called ***paradoxical adaptation***. It *occurs over a period of 4-5 minutes* **(Fig. 110.30)**.

Proof: When the *visual threshold* stimulus (minimum effective stimulus) is tested only over fovea centralis (rods free portion of retina), the drop in the threshold stimulus stops at 4 minutes adaptation.

(ii) ***Slow response:*** Later, a further drop in visual threshold *occurs slowly over a period of 25 minutes*. It is due to adaptation of the rods in peripheral portion of the retina. Because initially, there is less 'rhodopsin' store and time is required for synthesis of rhodopsin, therefore, the time of dark adaptation will be equal to the time required for the rhodopsin synthesis.

The changes which occur during dark adaptation are:

(a) Mydriasis (dilatation of pupils);
(b) Change over of the photoreceptor function from the cones to rods; and
(c) Resynthesis of rhodopsin.

Important Note

With the completion of dark adaptation, visual sensitivity is increased 10,000 fold.

Physiological significance

Radiologists, aircraft pilots who need maximal visual sensitivity in dim light can avoid having to wait for 20 minutes in the dark to become dark adapted. This can be achieved if they wear red goggles when in bright

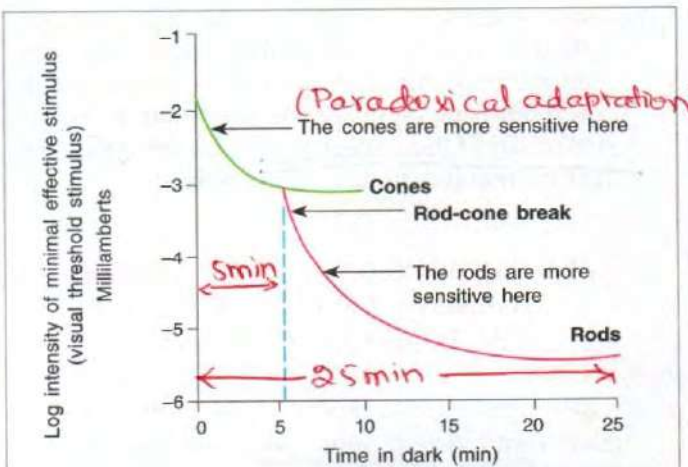


Fig. 110.30 Dark adaptation curve

light. *Mechanism:* The wavelength of red coloured light stimulates the rods to only a slight degree, and simultaneously allowing the cones to function. Therefore, a person wearing red goggles can see in bright light during the time it takes for the rods to become dark adapted.

LIGHT ADAPTATION

When one stays in dark for some time and passes suddenly to brightly lighted surroundings, the light is felt strong and may be uncomfortably bright. This persists until the eyes adapt to this increased illumination and *visual threshold* increases. This is called *light adaptation* and *occurs over a period of about five minutes.* It is merely the disappearance of dark adaptation.

Applied Aspect:

Night Blindness (or Nyctalopia)

1. Night blindness *means* blindness in dim light. This condition is *characterized by* decreased sensitivity (*i.e.* increase in *visual threshold*) of the eye to light *due to* vitamin A deficiency. Since vitamin A is required for the synthesis of retinene$_1$, vitamin A deficiency produces visual abnormalities; the earliest to appear is night blindness (Also refer to page 630 and **Fig. 110.31**).
2. In daylight, even when intensity of light is less, sufficient light is present to excite the cone pigments; therefore, visual abnormalities remain confined at night only.
3. Prolonged vitamin A deficiency is associated with anatomic changes in the rods and cones followed by degeneration of the neural layers of the retina.

Important Notes

(i) Treatment with vitamin A can restore retinal function if given before the photoreceptors are destroyed.

(ii) Nicotinamide is a part of the nicotinamide adenine dinucleotide (NAD^+) which helps in the interconversion of vitamin A and retinene in rhodopsin cycle. Therefore, other vitamins (specially of B-complex group) are necessary for the normal functioning of the retina.

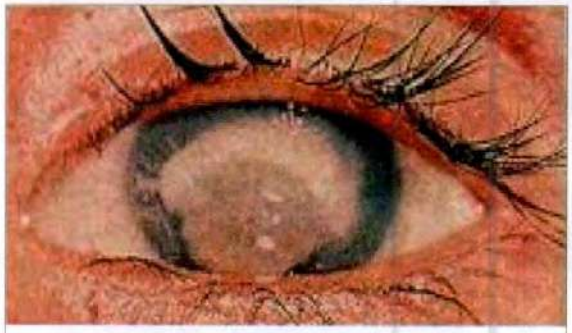
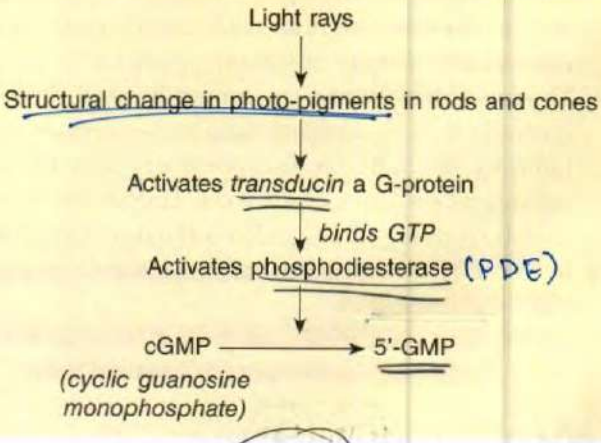


Fig. 110.31 Keratomalacia (dry eye) due to severe Vitamin A deficiency (details refer to page 630)

ELECTROPHYSIOLOGY OF VISION (GENESIS OF ELECTRICAL ACTIVITY OF RETINA)

A. GENERAL

1. *Visual images* have different *characteristics*, such as colour, form, depth, movement and texture; each processed simultaneously by a separate channel in the visual system, called *parallel processing of visual informations.*
2. The processing of visual information in the retina involves the generation of electrical activity at *three places:* the *first* activity is generated by the action of light on the photoreceptors, the *second* in the bipolar cells and a *third* electrical activity is generated in the ganglion cells.
3. The electrical activity in the bipolar cells and ganglion cells is altered by the horizontal cells and amacrine cells respectively. There is a little change in the impulse pattern in the lateral geniculate bodies, which finally reaches the occipital cortex.
4. The potential changes that initiate action potentials in the retina are generated by the action of light on photo-sensitive pigment in the rods and cones. When light is absorbed by these pigments, they trigger a sequence of events that initiate neural activity (*phototransduction*).
5. Sequence of events in phototransduction in photoreceptors (rods and cones) (Also see to page 23).



B. PHOTO RECEPTOR POTENTIALS

1. *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 and probably of the cones (**Fig. 110.32**). The

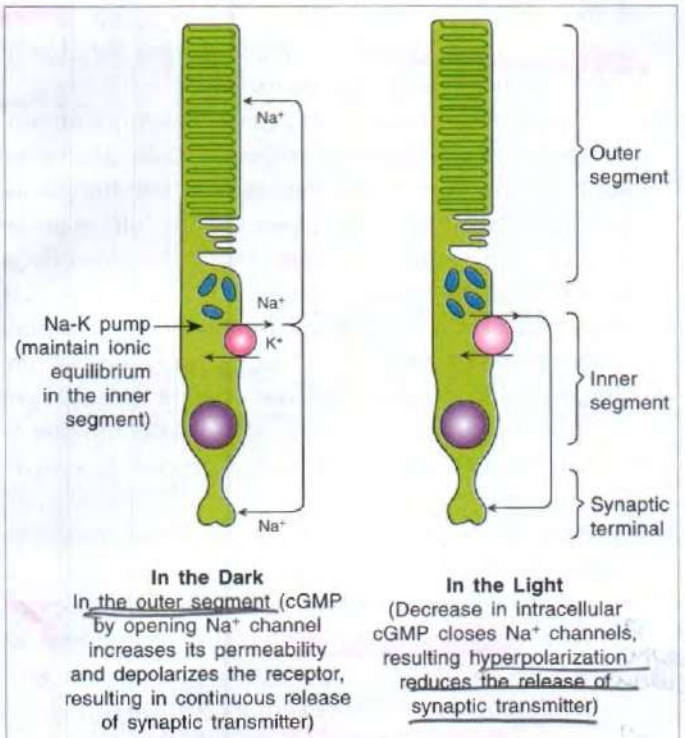


Fig. 110.32 Effect of light on current flow and release of synaptic transmitter in photoreceptors.

Important Note

Resynthesis of cGMP: Light decreases the concentration of both Na⁺ and Ca2+ within the photoreceptors; the resulting decrease in [Ca2+] activates guanylate cyclase, which generates more cGMP. It also inhibits the light activated phosphodiesterase thereby restoring cGMP and eventually Na^+ channels open.

steady current also flows in the synaptic ending of the photoreceptors. Light by decreasing intra-cellular cGMP closes these Na^+ channels that decreases the current flow; and the resulting hyperpolarization generates local graded potentials (*generator potential*) (page 859) in the synaptic terminal of the photoreceptor.

2. *Mechanism of development of hyperpolarization*. Exact mechanism is not known; probably straightening of retinene (metarhodopsin II, page 1106) decreases Na^+ permeability in the outer segment due to release of a substance that blocks the Na^+ channels in the membrane of the saccules.
3. The receptor potentials of both rods and cones are preceded by an earlier biphasic electrical response, called *early receptor potential*, its amplitude indicates accurately the concentration of photopigment.
4. The rods and cones (RMP: -40 mV) do not generate action potential; their response to adequate stimulus (light) is *hyperpolarization* rather than depolarization. The *cone receptor potential* has a sharp 'onset' and a sharp 'offset', whereas the *rod receptor potential* has a sharp 'onset' and a slow 'offset'.
5. Rod responses are proportionate to stimulus *intensity* at levels of illumination that are below the threshold for cones; while cone responses are proportionate to stimulus intensity at high levels of illumination. This is why *rods detect absolute illumination whereas cones generate good responses to change in light intensity.*

C. RESPONSES OF BIPOLAR, AMACRINE AND HORIZONTAL CELLS (Fig. 110.33)

1. The *'bipolar' cells do not generate action potentials*, instead they generate relatively steady hyperpolarizing or depolarizing potentials upto 10 mV.
   (i) In some cells, hyperpolarizing potentials are produced by a spot light, whereas depolarizing potentials are produced by an *annulus (ring) of light* around the centre. Cells with opposite patterns are also observed (*'on' and 'off' centre cell response*, see below).
   (ii) Thus the *receptive fields* (page 886) of the bipolar cells are organised into central and peripheral portions which generate opposite reactions.

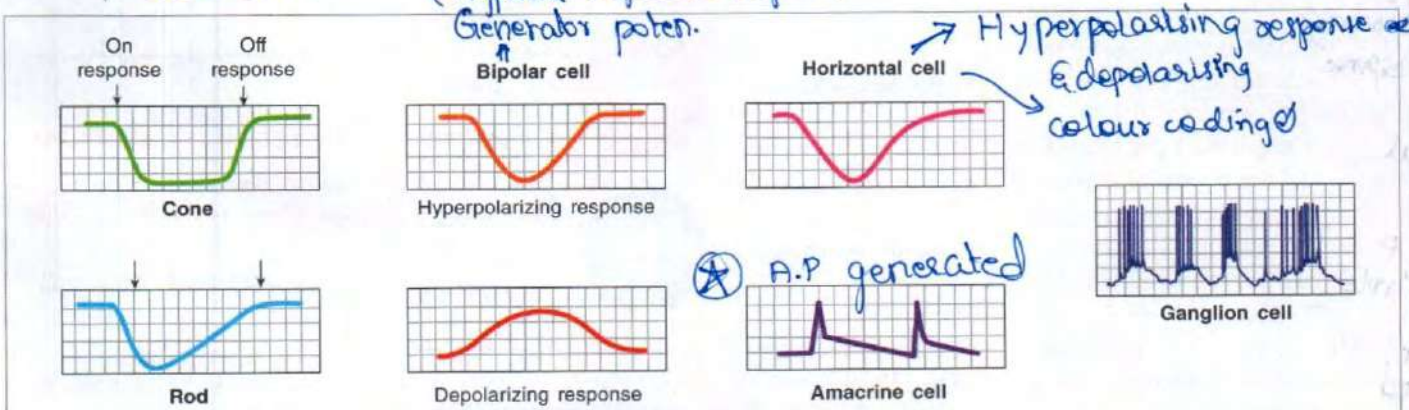


Fig. 110.33 Intracellular recording of potential changes from different cells in the retina to light

(iii) If the periphery and the centre are stimulated at the same time, the activities tend to cancel each other.

2. The *'Horizontal' cells produce only graded hyperpolarizing and depolarizing responses.* They appear to play a role in colour coding and also increase retinal sensitivity by improving contrast.
3. The *'Amacrine' cells* (page 1090) *produce transient depolarizing potentials and spikes* at the 'onset' and 'offset' of visual stimulus. These are the *first cells in the visual pathway capable of generating impulses*, which are initiated during depolarization. Thus they are concerned with recording changes in illumination rather than steady levels of illumination.

D. RESPONSE PATTERN OF GANGLION CELLS

1. These cells *generate 'action potential'* **(Fig. 110.33)** which is transmitted along their axons to the lateral geniculate bodies. They discharge steadily at a slow rate even in the absence of input from the rods and cones, called ***resting discharge***. This discharge can be increased or decreased by shining light on a small circular region of the retina (*receptive field*) (page 886).

Note

It is only in the ganglion cells that *all or none* action potentials transmitted over appreciable distances are generated.

2. There are ***two types*** of ganglion cells: *'on' centre cells* and *'off' centre cells* **(Fig. 110.34)**.
   (i) ***'On' centre cells:*** They respond with increased discharge (burst of impulses) when a small circular beam of light is shone on their 'receptive' field, called ***on discharge***; while illumination (shining of light) of the surrounding zone inhibits discharge but a burst of impulses follows when the light is switched off, called ***off response***.
   (ii) ***'Off' centre cells:*** In these cells light falling on the centre of their 'receptive' field causes *'off response'* and on the surrounding zone produces *'on discharge'*.
3. The form of inhibition in which activation of a particular neural unit is associated with inhibition of the activity of surrounding units is called ***lateral or afferent inhibition.*** *This helps to sharpen the edges of a stimulus and improve discrimination.*
4. Two spots of light shone on separate parts of an 'on' area induced a bigger 'on response' than did either alone; if one part of an 'on' area is stimulated by light simultaneously with a point in the 'off' area the ganglion cell response is very weak, the two effects tend to neutralize each other.
5. Some ganglion cells respond to steady illumination; others respond only to changes in illumination. Moreover, the ganglion cell response to diffuse light affecting the whole retina is much less as compared to a small circular spot covering the precise 'receptive' field centre.
6. Different types of ganglion cells have been found to have different *functional properties.*
   (i) *Large ganglion cells* ***(Y-cells or M-cells)*** are concerned with movement and ***stereopsis*** (equivalent to astereognosis, page 933).
   (ii) *Small ganglion cells* ***(X-cells or P cells)*** are concerned with colour, texture and shape of visual images.

Neurotransmitters within retina

1. Cones release ***glutamic acid:***
   (i) it has *inhibitory effect* on bipolar cells ('on' centre cells) produced by opening K^+ channels and closing Na^+ channels; both being operated via G-protein;
   (ii) it has *excitatory effect* on bipolar cells ('off' centre cells) produced by opening of K^+ and/or Na^+ channels.
2. Horizontal cells release ***GABA***. It produces both its inhibitory effect (on 'on' centre cells) and its excitatory effect (on 'off' centre cells) by depolarizing cones.
3. Amacrine cells release ***A-ch*** to produce the effect (see below).

Type of ganglion cell	Part of 'receptive field' stimulated	Light: Off	Light: On	Light: Off
(A) *'On'-centre cell*	centre / periphery			
(B) *'Off'-centre cell*	centre / periphery			

Fig. 110.34 Record of type of discharge (burst of impulses) from two main types of ganglion cells: 'on' centre cells (A) and 'off' centre cells (B) in response to illumination (shining of light) and otherwise (light off).

E. RESPONSES OF NEURONS IN LATERAL GENICULATE BODIES (LGB) AND VISUAL CORTEX

1. The six layered *lateral geniculate bodies (LGB)* contain two types of cells:
   (i) layers 1 and 2 have large cells and are called ***Magnocellular***. It receive input from M (or Y) ganglion cells.
   (ii) layers 3 to 6 have small cells and are called ***Parvocellular***. It receive input from P (or X) ganglion cells.
2. LGB carry signals for detection of movement, depth and flicker ***(magnocellular pathway)***, and signals for colour, shape and fine details of vision ***(parvocellular pathway)***. Its function is to separate and relay these different kinds of informations from the retina to different cortical zones.
3. Like the ganglion cells, neurons in LGB and in layer 4 of the visual cortex respond to stimuli in their 'receptive' fields with 'on' centres (and inhibitory surrounds) or 'off' centres (and excitatory surrounds) (page 1110).
4. The responses of the neurons in other layers of the visual cortex respond to lines and edges in their 'receptive' fields rather than to circular spots. They are classified into two main groups: *simple* and *complex cells.*
   (i) ***Simple cells:*** They respond best to a *linear stimulus* such as bars of light, lines or edges, but only when they have a particular position. For example, when a bar of light is rotated as little as 10 degrees from this particular position, the firing rate of these cells is decreased; and if the stimulus is rotated much more, the response disappears.
   (ii) ***Complex cells:*** They also require a particular position of a linear stimulus but are less dependent upon the location of a stimulus in the visual field than the simple cells. *They often respond maximally when a linear stimulus is moved laterally without a change in its position.*
5. In the ***visual cortex*** there are many neurons associated with each fiber projected from the LGB.
   (i) Most neurons in one subdivision of the visual cortex are responsive only to stimuli oriented in a particular direction in the visual field. This is important in the detailed description of the form of an object.
   (ii) Some neurons in another subdivision are most responsive to movements of an object across the visual field.
   (iii) Some neuronal groups may respond best to colour (page 1093).
   (iv) Some neurons respond only to input from both eyes, and provide important clue to depth perception.

F. ELECTRORETINOGRAM (ERG)

1. At rest, the potential difference between the front and the back of the eye is 6 mV (with front positive). When light falls on the eye it produces series of potential changes which can be recorded by placing one electrode on the cornea and other indifferent electrode in the mouth or forehead. The record of this sequence is known as ***electroretinogram (ERG).***
2. The *sequence of potential changes* which occur are: **(Fig. 110.35)**
   (i) When the light stimulus is turned 'on' it produces, 'A', 'B' and 'C' waves; while when the stimulus is turned 'off', a small negative 'off' deflection is produced ***(off-response).***

SUMMARY

Organization and function of visual pathways

Ganglion cells	M (or Y) cells	P (or X) cells
	↓	↓
Lateral geniculate body	Large cell layers 1 and 2	Small cell layers 3 to 6
	↓	↓
	via magnocellular pathway	*via parvocellular pathway*
	↓	
Visual cortex	Superficial layer 4	Deep layer 4
	↓	↓
Function	Detection of movement, depth and flicker	Detection of colour, shape and fine details of vision.

(a) **'A' wave** is the first sharp negative deflection due to rods and cones potential.

(b) **'B' wave** is a positive wave which follows the 'A' wave and results from activity in the bipolar cells or glial cells.

(c) **'C' wave** is due to activity in the pigmented epithelium of the retina. It is so slow that with short stimulus its peak occurs after the end of the stimulus. {*Proof:* If retina is removed except the pigmented layer, still 'C' wave can be recorded or if iodate is injected which damages the pigmented layer, 'C' wave disappears.}

(ii) When the light stimulus is turned 'off', a small negative 'off' deflection is produced, called *'off' response*. They appear as a 'slow' decay in predominately rod retinae, called *Remnant Negativity*; and appear as a 'faster' decay from retinae containing only cones. Sometimes neural component summate to give a positive deflection ('D' wave) in pure cone ERG.

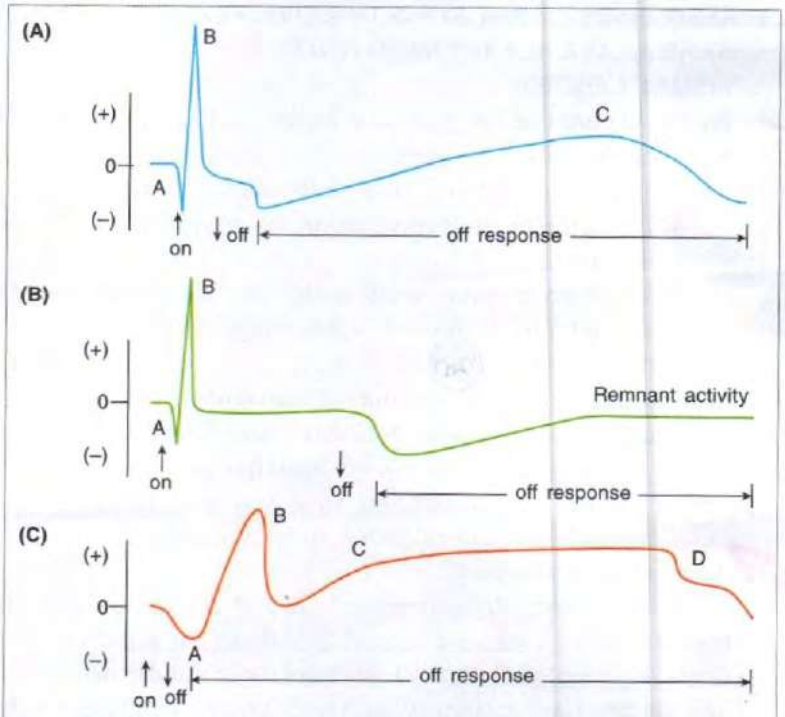


Fig. 110.35 ERG from retinae containing both rods and cones (A), only rods (B) and only cones (C).
↑: stimulus applied; ↓: stimulus terminated.

3. *Uses*

(i) Helpful in the diagnosis of diseases in which visualization of the retina is difficult because the ocular fluids are cloudy.

(ii) Helpful in cogenital retinal dystrophies in which the retina appears normal by ophthalmoscopy.

COLOUR VISION

A. GENERAL

1. Vision is of two types: *Achromatic* and *chromatic*.

(i) *Achromatic* is sensation of white vision and no colour has been assigned to it.

(ii) *Chromatic* is:

(a) spectral colours vision (page 1105); and

(b) extraspectral colour vision *i.e.* mixing of two ends of spectrum such as blue and red produces carbon colour.

Important Note

Blind eye does not 'see black', it 'sees nothing'.

2. *Complementary colour* – When two colours are mixed in appropriate amounts it leads to cancellation of colour sensation producing sensation of 'white'. Thus for any colour there is a 'complementary' colour that when properly mixed with it, produces a sensation of 'white'.

3. *Primary colours* – Red, green and blue are called the primary colours; each responds maximally to light of certain wavelength (page 1105). A spectral or extraspectral sensation of which can be produced by mixing varying proportions of these three primary colours.

B. THEORIES OF COLOUR VISION

1. *Thomas Young and Von Helmholtz's Theory.* According to this theory, the basis of three primary colours (Red, Green, Blue) is three types of cone receptors, each containing a different photosensitive pigment and maximum sensitivity to 'one' type of primary colour. By mixing three primary colours in different proportions, any type of colour sensation can be produced. When three receptors are stimulated equally, sensation of 'white' is produced.

Evidences which show that cones are responsible for the colour vision.

(i) Intensity of light less than 0.001 mA, when only rods are functioning shows 'achromatic' vision *i.e.* sensation of white light.

(ii) Spectral sensitivities analysis has shown that there are *three types of cone system* (page 1106).

2. *Muller's Doctrine of Specific Nerve Energy Theory* (also see to page 869)

(i) There are specific nerve fibers with specific ganglion cells resonding to three primary colours, which in

turn send information to the primary visual cortex (page 1093) which identifies the colour. Recently it has been shown that there is an electrical activity of the retina which in some unknown way converts this colour phenomenon due to 'off' or 'on' response (page 1110), therefore, with green 'on', red is 'off'. In this way it leads to the perception of complementary colour. For example:

(ii) If we see one colour and close the eye, still that colour can be seen. This is called *positive after image*. As red plus bluish green produces sensation of white, while seeing red colour if we look at white colour, complementary colour, bluish green is seen. This is called *negative after inhibition*. This is due to adaptation to red colour.

3. ***Granit's Theory***

Granit studied the electrical activity of a single ganglion cell with the help of microelectrode. He *concluded* that:

(i) The range of wavelengths of light to which the visual mechanism responds is between 395 and 700 nm.

(ii) Some cones have wide spectrum of sensitivity and described them as *dominator receptors*; while some cones respond maximal to narrow range of spectrum, either to blue, green or red colour, called *modulator recptors*.

(iii) In dark adapted eye, the 'sensitivity' corresponds with the 'scotopic' vision; and in light adapted eye to that of the 'photopic' vision.

C. COLOUR BLINDNESS

1. ***Definition:*** Insensitive to colours *i.e.* inability on the part of an individual to recognise the colours is called colour blindness.
2. ***Classification:*** Based on *John Dalton's (1798)* three receptor theory, colour blindness is classified into three heads: *Tri-*, *Di-* and *Monochromats*.

I. *Trichromats*
- (a) Protanomaly
- (b) Deuteranomaly
- (c) Tritanomaly

II. *Dichromats*
- (a) Protanopia
- (b) Deuteranopia
- (c) Tritanopia

III. *Monochromats*

3. (i) *Suffix* ***anomaly*** means colour weakness and suffix ***anopia*** means colour blindness.

(ii) *Prefix* ***Prot***, ***Deuter*** and ***Trit***, refer to Red, Green and Blue colour defected cone system.

Thus the term *protanopia* refers to inability to appreciate red colour and *protanomaly* means weakness (less sensitivity) to red colour.

4. The individuals with normal colour vision, and those with 'protanomaly' or 'deuteranomaly' or 'tritanomaly' are called *Trichromats i.e.* they have all the three cone systems but one may be weak.
5. *Dichromats* are the individual with only two cone systems present, thus they may have either 'protanopia'; 'deuteranopia' or 'tritanopia'.

Important Note

Example of ***physiological Dichromatic vision*** is at fovea centralis where only blue and red cones are present.

6. *Monochromats* are the individuals with only one cone system present (rare occurrence).
7. *Dichromats* can match their colour spectrum by mixing only two primary colours; and 'monochromats' match theirs by varying the intensity of only one. Apparently monochromats see only black and white and shades of gray.
8. ***Common defects of colour blindness*** (in order of occurrence) **(Fig. 110.36 A)**.
   (i) Deuteranomaly
   (ii) Deuteranopia
   (iii) Protanopia
   (iv) Protanomaly
   (v) Tritanomaly

Important Note

This explains the reason behind the traffic lights (Fig. 110.36 B).

9. ***Inheritance of colour blindness***

(i) Like hemophilia (page 102), colour blindness is also an inherited sex linked anomaly due to abnormal gene on X-chromosome. The gene responsible for colour blindness is present on the arm of the X-chromosome and females are the carriers **(Fig. 110.37)**. Females will suffer only when both X-chromosomes carry the defective gene. (Also see to page 24)

(ii) Protanomaly, protanopia, deuterano-maly and deuteranopia are examples of X-linked inheritance.

(iii) *Incidences:*

(a) In males: red-green defect occurs in about 2–2.5% of the population; deuteranomaly accounts for 50% of the total cases of these defects.

(b) In females the defect is present in only 0.4% of the population.

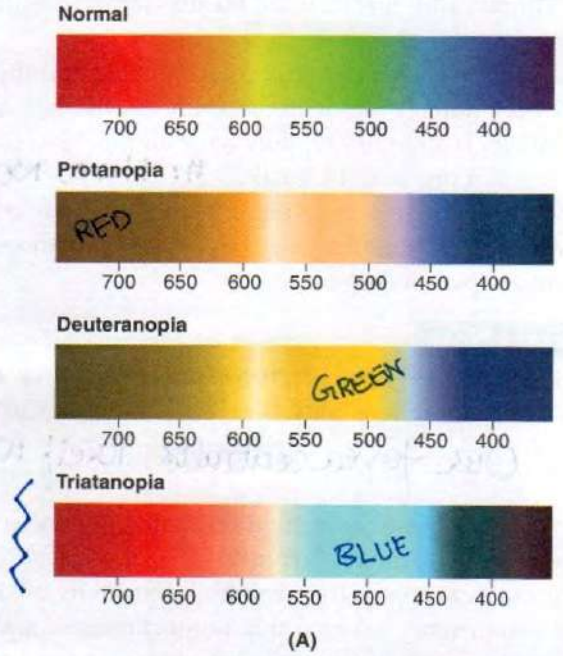


Fig. 110.36 (A) Common defects of colour blindness; (B) Traffic light perception in a deuteranope

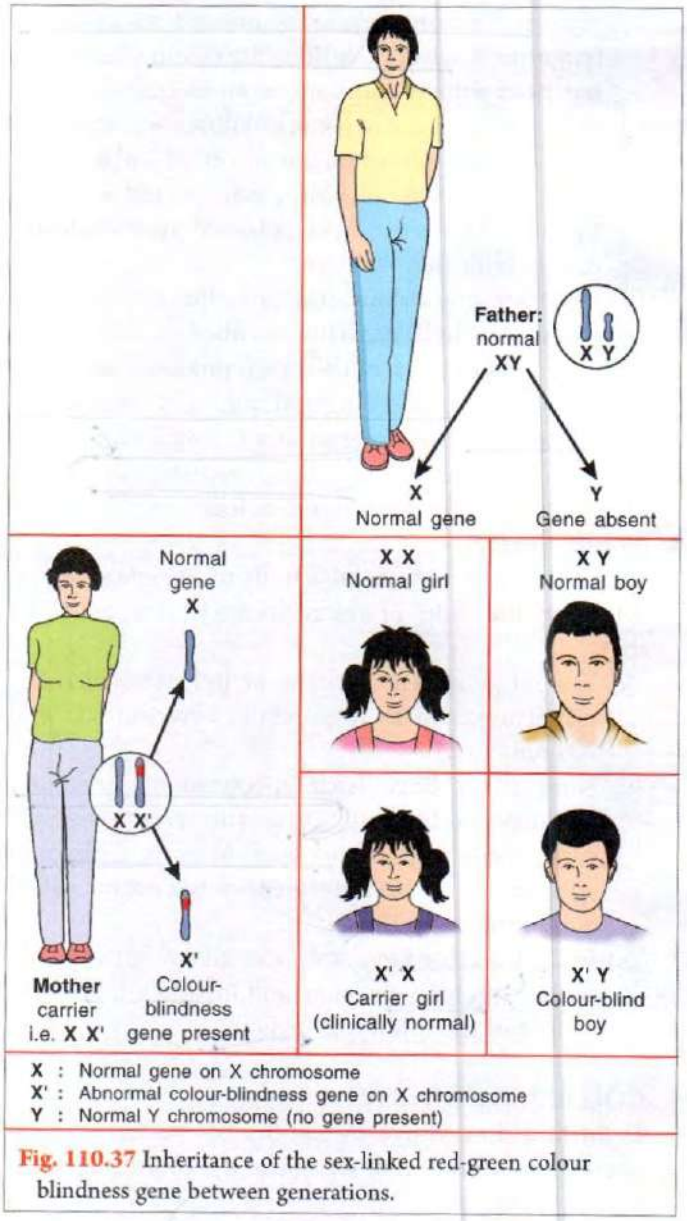


Fig. 110.37 Inheritance of the sex-linked red-green colour blindness gene between generations.

D. TESTS FOR DETECTING DEFECTS OF COLOUR VISION

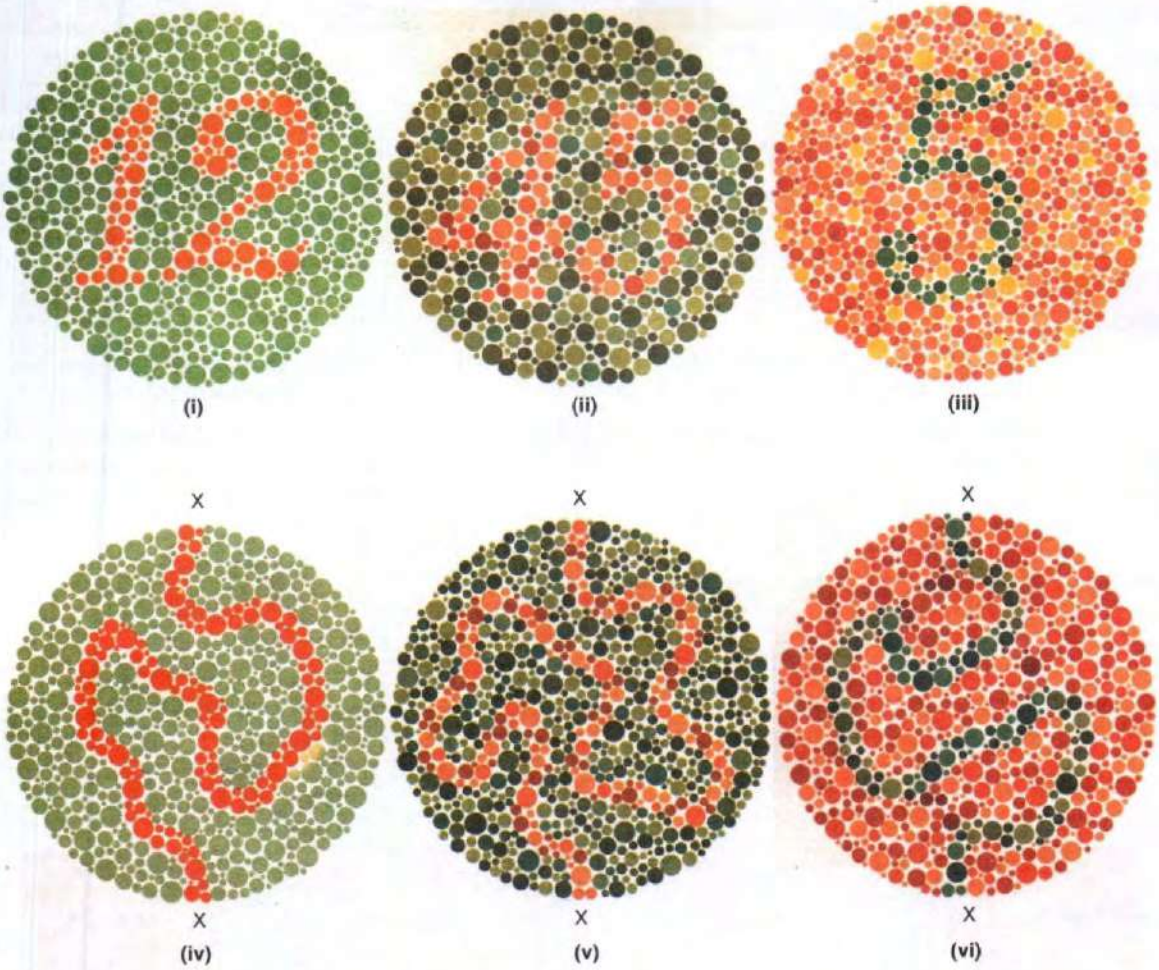
1. *Yarn (spun thread) matching test or Holmgren's skeins of coloured wool test* (Holmgren's wool test)
The subject is asked to match a piece of wool from the collection of skeins (bundle of yarn) of various colours **(Fig. 110.38)**.

Fig. 110.38 Yarn (spun thread) matching test

2. *Ishihara charts* → It comes with a key to identify types...
The Ishihara charts and similar poly-chromatic plates are plates which are printed with figures or designs in coloured circles on a background of similarly shaped colour circles **(Fig. 110.39)**. The figures are intentionally made up of colours that are likely to look the same as the background to an individual who is colour blind.
3. *The Edridge Green Lantern*
This device is used by the medical board to test would-be engine drivers etc. for evidence of colour defective vision. Here subject has to identify the colour of a small illuminated area, the size of which can be varied **(Fig. 110.40)**.
• Drivers test.
• Painter's & Artists

EYE MOVEMENTS

The eye is moved within the orbit by six external muscles of the eye. The muscles and their details are summarized



The plates are designed to be appreciated when held 75 cm from the subject in natural daylight. The numbers which are seen on plates (i), (ii) and (iii) are stated and each answer should be given without more than three seconds delay. If the subject is unable to read the numbers, plates (iv), (v) and (vi) are used and the winding lines between the two X's are traced with a brush. Each tracing should be completed within ten seconds.

Fig. 110.39 Ishihara's series of Plates designed as a test for Colour-blindness

Fig. 110.40 Edridge green lantern

in Table 110.3 and Fig. 110.41. Normally the movements of the two eyes are symmetrical, so that the visual axes meet at the point at which the eyes are looking. This is called as ***conjugate movement*** of the eyes. It is necessary since much of the visual field is binocular (page 1094)

Important Note

Formula for remembering the innervation of external ocular muscles: $ER_6(SO_4)_3$. External (lateral) rectus (supplied by VI); SO_4 is superior oblique (supplied by IV) and the remaining all eye muscles (by III nerve).

There are *four* types of eye movements: *saccadic, smooth pursuit, vergence* and *vestibular.*

1. *Saccadic movements*
   (i) These are very rapid jerky movements and occur when gaze is moved on an object. The eyes move in a conjugate fashion. Thus they bring the object to focus on the fovea and decreased adaptation in the visual pathway that would occur if the gaze were fixed on a single object for long periods.
   (ii) Normally the movements are voluntary but can be aroused by peripheral visual or auditory stimuli by

Table 110.3: Action, innervation and effect of paralysis of external ocular (eye) muscles

Muscle	Action	Innervation	Effect of paralysis
1. Lateral rectus	Rotate the eyeball laterally (*abduction*)	Abducens (VI) nerve	(i) Affected eye turning medially due to unopposed action of the medial rectus. (ii) *Strabismus* (squint, page 1104). (iii) *Homonymous diplopia* (double vision, page 1092).
2. Medial rectus	Rotate the eyeball medially (*adduction*)	Oculomotor (III) nerve	(i) Lateral deviation of the eye due to reason as above (ii) Heteronymous diplopia
3. Superior oblique	Pulls the eyeball downwards, outwards and rotates it inwards	Trochlear (IV) nerve	Patient cannot move his eye downwards and suffers diplopia
4. Inferior oblique	Rolls the eye outwards and pulls it upwards	Oculomotor (III) nerve	Paralysis of individual muscle is rare, however, these muscles get involved during lesion of III nerve; as a result eye is displaced downwards and outwards.
5. Superior rectus	Upward movement of the eye with adduction	-do-	
6. Inferior rectus	Downward movement of the eye with adduction	-do-	

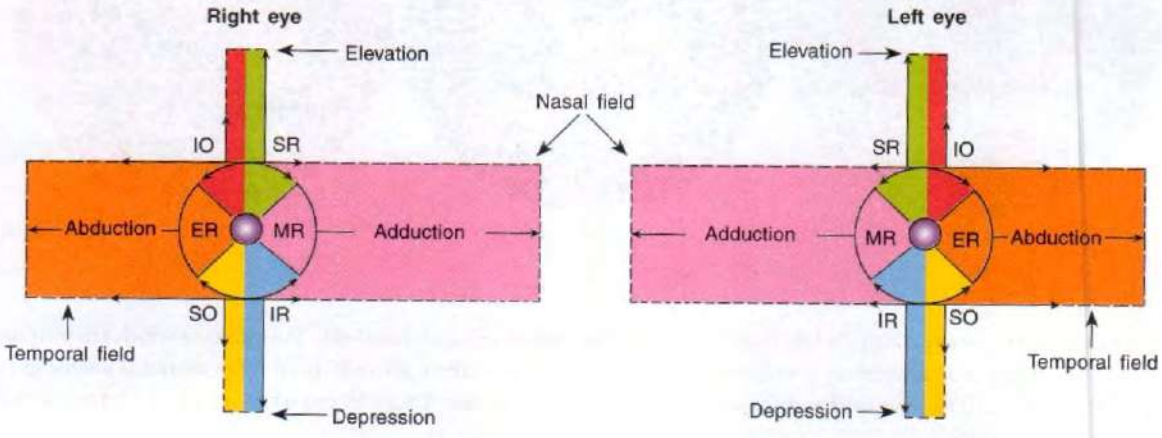


Fig. 110.41 Movements of the eyeball induced by contraction of the individual extraocular muscles
(I.O.: inferior oblique; E.R.: external or lateral rectus; MR: medial or internal rectus; S.R.: superior rectus; S.O.: superor oblique; I.R.: inferior rectus)

stimulation of the frontal eye fields (area 8). Thus these movements are programmed in the frontal cortex.

(iii) *Function:* They help to prevent sensory adaptation to the visual image.

2. ***Smooth pursuit movements***

(i) Pursuit means following or chasing; these movements occur voluntarily when the eye follows moving objects but occur involuntarily if a repetitive visual pattern is displayed continuously.

(ii) They involve conjugate displacement of the two eyes and depend on visual information from area 17, 18 and 19 and from superior colliculi.

3. ***Vergence movements.*** These movements allow focusing of an object which moves away from or towards the observer or when visual fixation shifts from one object to another at a different distance. *Divergence* or *convergence* occurs accordingly.

4. ***Vestibular movements***

(i) These movements help in compensating for the effects of head movements in disturbing visual fixation such as when the head is tilted sideways.

(ii) They involve eyes rotation around their antero posterior axes, so that their vertical axes are kept in a line with the direction of gravity.

(iii) The afferent nerves responsible for these movements have their receptors in the vestibular saccule, hence called *vestibular movements.*

NYSTAGMUS

(i) When a subject's gaze is fixed at a stationary object, the eyeballs are not still (without motion), there are continuous jerky movements. This is called *physiologic nystagmus*.

(ii) ***Significance:*** When the image of an object is fixed, it falls steadily on the same point on the retina and the object disappears from the view. This is because of the fact that for continuous visualization of objects, the retinal images must be continuously and rapidly shifted from one receptor to another.

Note

Individual visual receptors do not adapt rapidly to constant illumination, their neural connections do.

(iii) However, when the body is rotated at great speed round a vertical axis (*e.g.* merry go-around ride; a skater performing a spin), there occurs a slow motion of the eyes in the opposite direction to that of the rotation. It is followed by a quick jerky binocular 'return' movement in the direction of rotation. This sequence is repeated as long as the *angular acceleration* lasts. This is initiated by the vestibular mechanism and is called *oculovestibular nystagmus*.

Study Questions

1. **Define and give physiological significance of:**
   (i) Anterior and posterior chamber (ii) Depth of focus (iii) Photoreceptors
   (iv) Limbus (v) Glaucoma (vi) Retinitis pigmentosa
   (vii) Ultrafiltrate (viii) Blood aqueous barrier (ix) Visuo-psychic area
   (x) Field of vision (xi) Corresponding points and diplopia
   (xii) Homonymous and heteronymous hemianopia and quadrantanopia (xiii) Scotoma
   (xiv) Nodal point (xv) Depth of focus (xvi) Focal length
   (xvii) Dioptre (xviii) Optical centre (xix) Minimum separable
   (xx) Amplitude of accommodation (xxi) Mesopic vision (xxii) Sensitivity of vision
   (xxii) Protanomaly (xiv) Trichromats.

2. **Differentiate between:**
   (i) Rods and cones (ii) Optical and visual axis (iii) Aqueous and vitreous humour
   (iv) Central and peripheral retina (v) Primary visual area and visual association area
   (vi) Binocular and monocular vision (vii) Curvature and index astigmatism (viii) Convex and concave lens
   (ix) Visual acuity at the periphery of retina and at fovea (x) Direct and consensual light reflex
   (xi) Argyll-Robertson pupil and its reverse (xii) Far and near point of vision
   (xiii) Spherical and chromatic aberration (xiv) Visual threshold and visual acuity (xv) Photopic and scotopic vision
   (xvi) Rhodopsin and iodopsin (xvii) Dark and light adaptation (xviii) Achromatic and chromatic vision
   (xix) Primary and complementary colour (xx) Physiological and oculovestibular nystagmus.

3. **Write short notes on:**
   (i) Binocular vision (ii) Critical fusion frequency (iii) Macular sparing
   (iv) Wernicke's pupillary reflex (v) Visual agnosia (vi) Presbyopia
   (vii) Myopia and hypermetropia (viii) Factors affecting visual acuity (ix) Near response
   (x) Role of pupil in accommodation (xi) Light reflex pathway (xii) Duplicity theory of vision
   (xiii) Visibility curve (xiv) Accommodation pathway (xv) Purkinje shift
   (xvi) Photosensitive pigment (xvii) Effect of light on rhodopsin (xviii) Dark and light adaptation
   (xix) Night blindness (xx) Inheritance of colour blindness (xxi) Colour vision theories
   (xxii) Physiological nystagmus (xxiii) Conjugate movement of eye (xxiv) Photoreceptor potentials.

4. **Illustrate with the help of diagrams/draw well labelled diagrams:**
   (i) Structure of eye (ii) Circulation of aqueous humour (iii) Layers of retina
   (iv) How the light rays reach photoreceptors (v) Visual pathways (vi) Myopia and its correction
   (vii) Reduced eye (viii) Defect in hypermetropia (ix) Basis of designing test letters
   (x) Mechanism of accommodation (xi) Spectral sensitivity of rods and cones (xii) Purkinje images
   (xiii) Type of discharge from two main types of ganglion cells.

5. **Give physiological basis of:**
   (i) Vision is not possible over the optic disc
   (ii) Visual acuity is maximum over fovea
   (iii) Retinal detachment is damaging to photoreceptors
   (iv) Diplopia

(v) Reading newspaper or magazine in a moving bus is so difficult
(vi) Central part of lens has the maximum refractive power
(vii) Blurred vision following installation of homatropine into the eye.
(viii) Watching TV for long periods may produce severe headache.
(ix) Argyll-Robertson pupil.
(x) Reading or close work becomes progressively difficult with advancing age.
(xi) Ultraviolet and infra-red rays are not perceived by the human eye
(xii) Radiologist wears red goggles when in bright light
(xiii) How sensation of white light is produced.
(xiv) Cones are responsible for colour vision.
(xv) Physiological dichromatic vision.
(xvi) Reason behind the traffic light.

6. **What will happen and why.**
   (i) If intraocular pressure alters (falls or rises)?
   (ii) If choroid fails to absorb extra amount of light entering into the eye?
   (iii) to vision if occipital lobe gets damaged?
   (iv) If hypermetropic individual suffers from presbyopia.?
   (v) to refractive power of eye if water enters the eye?
   (vi) If fovea gets damaged?
   (vii) If ciliary muscles get temporarily paralysed?
   (viii) If pupil fails to constrict during accommodation?
   (ix) to accommodation if medial rectus gets paralysed?
   (x) to near point of vision with advancing age?
   (xi) If one stays in sun for some time and then suddenly enters a dark room?
   (xii) to vision if one suffers from deficiencies of vitamin A and B-complex?
7. **What gives colour to the eye? Which colour is scientifically the best and why?**
8. **What determines the size of pupil? Give its significance.**
9. **Name avascular structures of the eye. From where they get their nutrition?**
10. **Give the composition of aqueous humour. Why is it called ultrafiltrate?**
11. **Name the types of neurons present in the retina. Give their functions.**
12. **What is physiological astigmatism? Does it need correction?**
13. **Which portion of retina possesses maximum visual acuity and why?**
14. **Mention the factors on which visual angle depends.**
15. **How is the anterior curvature of lens increased during accommodation?**
16. **How much refractive power of lens can be increased during maximum accommodation?**
17. **Name the receptors subserving colour vision. Give their spectral absorption.**
18. **Give the role of vitamins for normal functioning of the retina.**
19. **List common defects of colour blindness. Which one is the commonest?**

MCQs

1. **Scientifically which colour of the eye is the best?**
   (a) Brownish-black (b) Blue (c) Green (d) All of the above
2. **Variations in diameter of pupil can produce ..... fold change in the amount of light reaching the retina:**
   (a) 2 (b) 3 (c) 4 (d) 5
3. ***Not* a function of iris:**
   (a) Absorbs extra amount of light entering into the eye
   (b) Nourishes the structures in the eyeball
   (c) Regulates the size of pupil
   (d) Increases the depth of focus
4. **The lens:**
   (a) Is a transparent biconcave structure
   (b) Is held in position with the help of ciliary body
   (c) Has no blood supply
   (d) Possesses higher refractive index at the periphery than at the centre

5. **Visual acuity is greatest in the retinal fovea because of all *except*:**
   (a) Only cones are present in the fovea
   (b) Each foveal cone has its own optic nerve fibre
   (c) Blood vessels and ganglion cells do not cover foveal cones
   (d) The fovea has a greater surface area than the surrounding retina
6. **Aqueous humour differs from plasma in that it:**
   (a) Is high in protein
   (b) Has high content of vitamin C and NaCl
   (c) Has high glucose but low lactic acid
   (d) Has high viscosity
7. **Decrease or increase in intraocular pressure results in:**
   (a) Bulging of lens
   (b) Prevents contraction of ciliary muscle
   (c) Defective image formation
   (d) Damage to retina
8. **In what layer of the retina is a large store of vitamin A found?**
   (a) Choroid (b) Pigment layer (c) Outer nuclear layer (d) Photoreceptors layer
9. **In retinitis pigmentosa, *not* seen is:**
   (a) The phagocytic process is defective
   (b) A layer of debris accumulates between the receptor and pigment epithelium
   (c) Blindness
   (d) Retinal degeneration
10. **In the lateral geniculate body, *false* statement is:**
    (a) There is topographical representation of retina
    (b) Approx. 1/3rd of fibers come from the maculae
    (c) Fibers from contralateral retina end in layer 1, 4 and 6
    (d) Fibers from upper retinal quadrants terminate in lateral halves
11. **Which of the following is *not* a correct match?**
    (a) Primary visual area (area 17), highest area for perception of light
    (b) Area 18, visuo-psychic area, homologue of stereognosis
    (c) Occipital eye field is area 19
    (d) Area 8 is concerned with depth perception
12. **The centre point of a lens is known as:**
    (a) Nodal point
    (b) Principal axis
    (c) Principal focus
    (d) Visual point
13. **Loss of right half of visual field in one eye and loss of left half of visual field in the other eye is referred as:**
    (a) Heteronymous hemianopia
    (b) Right homonymous hemianopia
    (c) Left homonymous hemianopia
    (d) Quadrantanopia
14. **Most of the refraction that occurs 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
15. **Blurring of vision occurs when water enters the eyes because:**
    (a) Corneal surface becomes irregular
    (b) No refraction occurs at water layer formed in front of cornea
    (c) No refraction occurs at cornea
    (d) Water is poor medium for transmission of light
16. **After removal of the lens, the dioptric power of eye is reduced by:**
    (a) 4 Dioptres (b) 8 Dioptres (c) 16 Dioptres (d) 32 Dioptres
17. **Visual acuity decreases with:**
    (a) Decrease in size of the object
    (b) Decrease in distance of object from the eye
    (c) White object as compared with coloured object
    (d) Portion of retina where cones are densely packed
18. **Contraction of ciliary muscle results in increase of anterior curvature of the lens by:**
    (a) Pulling ciliary body forwards and inwards
    (b) Causing laxity of suspensory ligaments
    (c) Reducing tension on the lens
    (d) All of the above
19. **To view a near object, if refractive power of the eye is 69D, the amplitude of accommodation is:**
    (a) 10D (b) 20D (c) 59D (d) 69D
20. ***Not* a feature of myopia:**
    (a) Far point of vision is at a distance from the eye
    (b) Near point is close to the eye
    (c) Range of accommodation increases
    (d) No need of correction, if associated presbyopia occurs

21. **Duplicity theory refers to:**
(a) Photopic and scotopic vision (b) Double pain
(c) Diplopia (d) Two point discrimination

22. **Which of the following is *not* important in dark adaptation?**
(a) Conversion of retinene into rhodopsin (b) Conversion of vitamin A into retinence
(c) The pupillary dilatation (d) Conversion of retinene into lumirhodopsin

23. **With completion of dark adaptation, visual sensitivity is increased by ..... folds:**
(a) 10 (b) 100 (c) 1000 (d) 10000

24. **Achromatic vision:**
(a) Sensation of white (b) Spectral colour vision
(c) Extraspectral colour vision (d) Black and white vision

25. **Thomas Young and Von Helmholtz Theory of colour vision states:**
(a) There are three kinds of cones in the retina responding to the three primary colours
(b) There are two kinds of cones called dominators and modulators
(c) There is only one kind of cone and the colour is recognised only in area 17
(d) There are seven types of cones responding to the seven colours of the spectrum

26. **Trichromats are individuals with:**
(a) Two normal and one weak cone systems (b) Normal colour vision
(c) 3 cone system (d) Deuteranomaly

27. **Best test for detecting defects of colour vision is:**
(a) Yarn matching test (b) Ishihara charts
(c) Edridge green lantern (d) Snellen's chart

28. **The adult human eyeball, *not true* is:**
(a) 24 mm in diameter
(b) Only 1/6th is visible outside;
(c) Its walls from outer to inner are; sclera, choroid and retina
(d) Retina is highly vascular layer

29. ***False* about sclera:**
(a) Tough, fibrous and opaque (b) Modified in front to form trans-parent vascular cornea
(c) Provides shape to eyeball (d) Protective in function

30. **The colour of the eyes is due to:**
(a) Sclera (b) Cornea
(c) Pupil (d) Iris

31. ***False* about blind spot:**
(a) Also called optic disc (b) Lies 3 mm medial to the posterior pole of eyeball
(c) Vision is not possible over this area (d) With anterior pole of eyeball forms the optical axis

32. **The fovea centralis is point of greatest visual acuity because:**
(a) Rod free portion of retina
(b) Avascular
(c) Highly developed in humans
(d) Each foveal cone is connected to a single fiber in the optic nerve

33. **The visual axis:**
(a) Is the line joining the fixation point to the fovea centralis
(b) Is the shortest distance between the anterior and posterior poles of the eyeball
(c) Is the longest distance between the anterior and posterior poles of the eyeball
(d) It is perpendicular to both the faces of the lens

34. **Intraocular fluid, *not true* is:**
(a) Formed from capillaries of ciliary process (b) Reabsorbed into intrascleral venous plexus
(c) Maintains intraocular pressure (d) Provides nutrition to choroid

35. **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 dose of vitamin C (d) Bright sunlight

36. **Decrease or increase in intraocular pressure results in:**
(a) Bulging of lens (b) Prevents contraction of ciliary muscle
(c) Defective image formation (d) Damage to retina

37. **Which of the following is *wrong*?**
    (a) Rods are named for their thin, rod like appearance of their outer segment
    (b) Fovea lies on the temporal side of optic disc
    (c) Cones are more sensitive to light than rods
    (d) Rhodopsin and iodopsin are photo-sensitive pigments in rods and cones respectively.

38. **Colour perception is a function of:**
    (a) Rods (b) Cones (c) Primary auditory cortex (d) Visual association area

39. **Horizontal cells in the retina, *not true* is:**
    (a) Connect ganglion cells to one another
    (b) Connect one receptor cell to other receptor cells
    (c) Produce only graded hyperpolariz-ing and depolarizing response
    (d) Play a role in colour coding and improve contrast

40. **Overall convergence of photoreceptors through bipolar cells on ganglion cells is:**
    (a) 1 : 100 (b) 1 : 105-165 (c) 105-165 : 1 (d) 1 : 1

41. **Sensory pathway from the eye to cerebral cortex is:**
    (a) 3-order neuron pathway (b) Disynaptic
    (c) Monosynaptic (d) Variable

42. **The area visualised on the screen when gaze is fixed at an object is called:**
    (a) Field of vision (b) Binocular vision (c) Monocular vision (d) Diplopia

43. **Loss of right half of visual field in one eye and loss of left half of visual field in the other eye is referred as:**
    (a) Heteronymous hemianopia (b) Right homonymous hemianopia
    (c) Left homonymous hemianopia (d) Quadrantanopia

44. **Pick the *incorrect* statement about lens:**
    (a) A piece of transparent glass bounded by two spherical surfaces
    (b) A convex lens is thick at the centre but thinner at edges
    (c) A concave lens is thin in the middle but thicker at edges
    (d) Lens in which one surface is convex and other surface concave is a cylindrical lens

45. **Highest refractive index is that of:**
    (a) Cornea (b) Aqueous humour (c) Lens (d) Vitreous humour

46. **Visual angle is the angle subtended by an object at the:**
    (a) Cornea (b) Lens (c) Nodal point (d) Fovea

47. **The accommodation reflex includes:**
    (a) Relaxation of ciliary muscles (b) Dilatation of pupil
    (c) Decrease in field of vision (d) Diplopia

48. **During accommodation reflex, constriction of pupil decreases *all except*:**
    (a) Spherical and chromatic aberrations (b) Intensity of light entering into the eye
    (c) Depth of focus (d) Size of pupil

49. ***Not* a part of accommodation reflex:**
    (a) Area 19 (b) Area 8 (c) III nerve nucleus (d) Ciliary muscle

50. **For normal eye of a 20 year old individual, near point is situated at .... cm:**
    (a) 9 (b) 10 (c) 18 (d) 50

Answers

1. (a)	2. (d)	3. (b)	4. (c)	5. (d)	6. (b)	7. (c)	8. (d)	9. (d)	10. (d)
11. (d)	12. (c)	13. (a)	14. (a)	15. (c)	16. (c)	17. (a)	18. (d)	19. (a)	20. (c)
21. (a)	22. (d)	23. (d)	24. (a)	25. (a)	26. (c)	27. (c)	28. (d)	29. (b)	30. (d)
31. (d)	32. (d)	33. (a)	34. (d)	35. (a)	36. (c)	37. (c)	38. (b)	39. (a)	40. (c)
41. (a)	42. (a)	43. (a)	44. (d)	45. (c)	46. (c)	47. (c)	48. (c)	49. (a)	50. (b)

Appendix 1

Commonly Used Abbreviations and Symbols in the Book

↑	:	Increase
↓	:	Decrease
→	:	Leads to/produces
(+)	:	Stimulation
(–)	:	Inhibition
≥	:	More than or equal to
≤	:	Less than or equal to
@	:	At a rate of
+	:	Mild
++	:	Moderate
+++	:	Severe
[ ]	:	Concentration of
Δ	:	Change in (example: ΔP: change in pressure)
α	:	Alpha
β	:	Beta
γ	:	Gamma
δ	:	Delta
ε	:	Epsilon
η	:	Eta
θ	:	Theta
κ	:	Kappa
λ	:	Lambda
μm	:	Mu, micrometer; 10^{-6} meter
π	:	Pi
σ	:	Sigma
ρ	:	Rho
ϕ	:	Phi
Å	:	Angstrom units, 10^{-10} mt; 0.1 nm
A^-	:	General symbol for anion
A^+	:	General symbol for cation
A-ch	:	Acetylcholine

ACTH	:	Adrenocorticotropic hormone
Acyl-CoA	:	Coenzyme A ester
ADH	:	Antidiuretic hormone (vasopressin)
ADP	:	Adenosine diphosphate
AMP	:	Adenosine 5′-monophosphate
ANP	:	Atrial natriuretic peptide
Approx.	:	Approximately
ATP	:	Adenosine triphosphate
ATPase	:	Adenosine triphosphatase
A-V difference	:	Arteriovenous concentration difference of a substance
AVN or AV Node	:	Atrioventricular node
Av	:	Average
AV valves	:	Atrioventricular valves
BBB	:	Bundle branch block
BER	:	Basic electrical rhythm
BMR	:	Basal metabolic rate
BMT	:	Basal myogenic tone
BP	:	Blood pressure
bpm	:	Beats per minute
2,3-BPG	:	2,3-biphosphoglyceric acid (same as 2,3-DPG)
CA	:	Carbonic anhydrase
CAI	:	Carbonic anhydrase inhibitor
cal	:	The calorie (gram calorie)
Cal	:	1000 calories; kilocalorie (capital 'C' is used)
CCF/CHF	:	Congestive cardiac (heart) failure
cAMP	:	Cyclic adenosine 3′,5′-monophosphate
CBF	:	Coronary blood flow
CC	:	Cubic centimeters
CCK; CCK-PZ	:	Cholecystokinin-pancreozymin
cGMP	:	Cyclic 3′,5′-guanosine monophosphate
cm	:	Centimeter(s)
CmH_2O	:	Unit of pressure, cm of water
cmm/cumm (or µL)	:	Cubic millimeter (or microlitre)
CNS	:	Central nervous system
CO	:	Cardiac output; also carbon monoxide
CoA	:	Coenzyme A
COHb	:	Carbon monoxy haemoglobin
COP	:	Colloidal osmotic pressure
cps	:	Cycles per second; also called hertz

Cr	:	Creatinine
CSF	:	Cerebrospinal fluid; also colony-stimulating factor
CT	:	Collecting tubules
CVC	:	Cardiac vagal centre
dB	:	Decibel
dL	:	Decilitre
DBP	:	Diastolic blood pressure
DCT	:	Distal convoluted tubules
DNA	:	Deoxyribonucleic acid
Dopa	:	Dihydroxyphenylalanine, L-dopa
2,3-DPG	:	2,3-Diphosphoglyceric acid
ECF	:	Extracellular fluid
ECFV	:	Extracellular fluid volume
ECG	:	Electrocardiogram
EDV	:	End diastolic volume
e.g.	:	For example
EPSP	:	Excitatory postsynaptic potential
Eq	:	Equivalent(s)
ERPF	:	Effective renal plasma flow
FAD(N)	:	Flavin adenine dinucleotide
FFA	:	Unesterified free fatty acid; also called NEFA: non-esterified free fatty acid
FSH	:	Follicle-stimulating hormone
Gm	:	Gram(s)
GABA	:	Gamma aminobutyric acid
GFR	:	Glomerular filtration rate
GH	:	Growth hormone
GHIH	:	Growth hormone inhibiting hormone
GIP	:	Gastric inhibitory peptide
GIT	:	Gastro intestinal tract
GM	:	Grey matter
GMP	:	Guanosine monophosphate
GTP	:	Guanosine triphosphate
gm/dL	:	Grams per 100 ml of solvent/blood
GnRH	:	Gonadotrophin releasing hormone
GHRH	:	Growth hormone release hormone
Hb	:	Reduced/deoxygenated haemoglobin
HbA	:	Adult haemoglobin
HbF	:	Foetal haemoglobin
HbO_2	:	Oxyhaemoglobin

HbOH	:	Methaemoglobin
HCG	:	Human chorionic gonadotrophin
HDL	:	High density lipoprotein
HP	:	Hydrostatic pressure
Hr	:	Hour(s)
HR	:	Heart rate
5-HT	:	5 Hydroxytryptamine (serotonin)
Hz	:	Hertz, unit of frequency; 1 cps = 1 Hz
ICF	:	Intracellular fluid
ICFV	:	Intracellular fluid volume
i.e.	:	That is
I.F.	:	Intrinsic factor
Ig	:	Immunoglobulin(s)
I.V.	:	Intravenous
IVC	:	Inferior vena cava
JGA	:	Juxtaglomerular apparatus
JG cells	:	Juxtaglomerular cells
Kcal	:	Kilocalorie (1000 calories)
Kgm	:	Kilogram (10^3 grams)
L	:	Litre(s)
LA	:	Left atrium
LDL	:	Low density lipoprotein
LH	:	Luteinizing hormone
LRH/LHRH	:	Luteinizing hormone releasing hormone
LV	:	Left ventricle
MAO	:	Monoamine oxidase
MBP	:	Mean blood pressure
mEq	:	Milliequivalent(s)
mg% (or mg/dL)	:	Milligram per 100 ml (or milligram per decilitre)
MI	:	Myocardial infarction
min	:	Minute(s)
ml	:	Millilitres (10^{-3} L)
mm	:	Millimeters (10^{-3} mt)
mmHg	:	Millimeter of mercury
mol	:	Mole, gram molecular weight
mosm	:	Milliosmole(s)
mt, mts	:	Meter(s)
msec	:	Millisecond(s)
mV	:	Millivolt(s)

MW	:	Molecular weight
nm	:	Nanometer (10^{-9} mt)
NA	:	Nucleus ambiguus; also called cardiac vagal centre
NAD^+	:	Nicotinamide adenine dinucleotide
NADH	:	Dihydronicotinamide adenine dinucleotide
$NADP^+$	:	NAD phosphate
NADPH	:	NADH phosphate
NEFA	:	Nonesterified free fatty acid, same as FFA
NREM sleep	:	Non rapid eye movement sleep
NTS	:	Nucleus of tractus solitarius
osm	:	Osmole(s)
pCO_2	:	Partial pressure of CO_2
PCT	:	Proximal convoluted tubules
pg	:	Picogram; μμgm (10^{-12} gm)
pH	:	Negative logarithm of H^+ concentration of a solution
P or Pi	:	Inorganic phosphate
PG	:	Prostaglandin(s)
pO_2	:	Partial pressure of O_2
PP	:	Pulse pressure (systolic minus diastolic BP)
PR	:	Peripheral resistance
RA	:	Right atrium
RBC	:	Red blood cell(s)
RBF	:	Renal blood flow
RES	:	Reticulo endothelial system, also called tissue macrophage system
RMP	:	Resting membrane potential
RNA	:	Ribonucleic acid
RPF	:	Renal plasma flow
RV	:	Right ventricle
S	:	Serum
SAN or SA Node	:	Sinoatrial node
SBP	:	Systolic blood pressure
sec	:	Second(s)
SG	:	Specific gravity
SV	:	Stroke volume
T_3	:	3,5,3′–Triiodothyronine
T_4	:	Thyroxine
TBW	:	Total body water
Tm	:	Renal tubular transport maximum
TPR	:	Total peripheral resistance

TRH	:	Thyroid releasing hormone
tRNA	:	Transfer RNA
TSH	:	Thyroid stimulating hormone
µL	:	Microlitre (or cumm)
VIP	:	Vasoactive intestinal polypeptide
VLDL	:	Very low density lipoprotein
VMC	:	Vasomotor centre
V_{O_2}	:	Oxygen consumption per unit time (dot over a symbol indicates rate)
$V_{O_2\ max}$	:	Maximal oxygen consumption per unit time
VR	:	Venous return
WBC	:	White blood cell(s)
WM	:	White matter

Temperature

(i) To convert celsius degrees (°C) into Fahrenheit (°F), multiply by 9/5 and add 32.

(ii) To convert °F into °C, subtract 32 and multiply by 5/9.

Prefix	Abbreviation	Magnitude
mega-	M	10^6
kilo-	K	10^3
hecto-	h	10^2
deca-	da	10^1
deci-	d	10^{-1}
centi-	c	10^{-2}
milli-	m	10^{-3}
micro-	µ	10^{-6}
nano-	n, µµ	10^{-9}
pico-	p, µµ	10^{-12}
femto-	f	10^{-15}
atto-	a	10^{-18}

Appendix 2

Ranges of Normal Values in Human Whole Blood (B), Plasma (P) or Serum (S) (As laid down by WHO)

Parameter			Traditional Units
ACTH(P) (morning, resting)			25 pg/mL
Aldosterone (P)			3-10 ng%
Alkaline phosphatase (S)			5-13 kÅ units
Amino acid (B)			30-65 mg/dL
Ammonia (B)			20-80 µgm/dL
Amylase			50-120 units/litre
Bleeding time (Duke method)			2-6 min
Bicarbonate (S)			25-30 mEq/L
Bilirubin (S)			Total (conjugated plus free): 0.2-0.8 mg/dL conjugated (direct): upto 0.4 mg/dL
Blood (Specific gravity)			1050-1060
Calcitonin (S)			0-2 ng/mL
Calcium (S)			9-11 mg/dL
Catecholamines (P)		Epinephrine	300 pg/mL
(free levels)		Nor-epinephrine	30 pg/mL
		Dopamine	35-40 pg/mL
Ceruloplasmin (S)			25-40 mg/dL
Chloride (S)			100-110 mEq/L
Cholesterol (P)			120-200 mg/dL (free 28%; esterified 72%)
Clotting time (capillary tube method)			3-8 min
Copper (S) Total			70-150 µg/dL
Cortisol (P) (6 a.m. fasting)			5-25 µg/dL
Creatine			1-2 mg/dL
Creatinine (S)			0.6-1.2 mg/dL
Dihydroepiandosterone, DHEA (P)			150-200 µg/dL
Folic acid			3-20 ng/mL
Growth hormone (P)			3 ng/mL
Glucose, fasting (B)			70-90 mg/dL
Haematocrit (PCV) (B)			45%; 5-8 mg/mL in children
Haptoglobin (S)			0.12 gm/dL
Haemoglobin (B)	at birth		23 gm/dL
	Adults	Males	14-18 gm/dL
		Females	12-15.5 gm/dL
	Iron content		0.33%

Appendix 3

Contribution of Scientists to Physiology

1. Sir Acharya patanjali, 486 

2. Sir Angustus D. Waller, 150 

3. Sir Babinski Joseph, 928 

4. Sir Bainbridge Kenneth, 331 

5. Sir Banting Frederick, 743 

6. Sir Bayliss Frank, 231 

7. Sir Bayliss-Folkow, 367, 511 

8. Sir Bernoulli Daniel, 349 

9. Sir Bohr Neil, 430 

10. Sir Breuer E, 442 

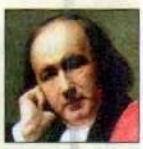
11. Sir Brodmann K, 893, 1013 

12. Madam Bucy P, 1021 

13. Sir Burnet F M, 125 

14. Sir Cannon W B, 3, 50, 928 

15. Sir Charles Best, 743 

16. Sir Claude Bernard, 3, 28 

17. Sir Dalton John, 403 

18. Sir Davenport H.W., 218, 552 

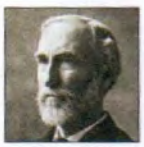
19. Sir Erlanger J, 146 

20. Sir Fechner, 867 

21. Sir Fick A, 342 

22. Sir Frank C, 182 

23. Sir Gasser H.S., 146 

24. Sir Gibbs F.G., 34 

25. Sir Goldblatt David, 394 

26. Madam Goldman-Hodgkin, 37 

27. Sir Granit J, 1113 

28. Sir Hagen L, 315 

29. Sir Haldane, 434 

30. Sir Hamburger, N 435

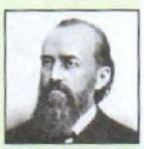
31. Sir Hans Berger, 981 

32. Sir Harvey Cushing, 722 

33. Sir Heidenhain, 216 

34. Sir Henry, 403 

35. Sir Hensen J, 161 

36. Sir Hering E, 442 

37. Sir Heymans C, 444 

38. Sir Holmgren, 1114 

39. Sir Huxley A F, 165 

40. Sir Huxley H E, 166 

41. Sir Ishihara, 1114 

42. Sir J. N. Donnan, 34 

43. Sir James Parkinson, 995 

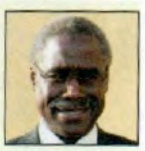
44. Sir John Dalton, 1113 

45. Sir Jouvet M, 987 

46. Sir Katz B, 37 

47. Sir Kluver, 1021 

48. Sir Landsteiner Karl, 106, 107 

49. Sir Lewis T, 376 

50. Sir Macfarlane R G, 95 

51. Sir Marcello Malpighi, 502 

52. Sir Melzack R, 898 

53. Sir Muller R, 901, 1112 

54. Sir Neil E, 444 

55. Sir Nernst W, 36 

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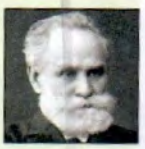
58. Sir Pavlov I P, 217, 1020, 1035 

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