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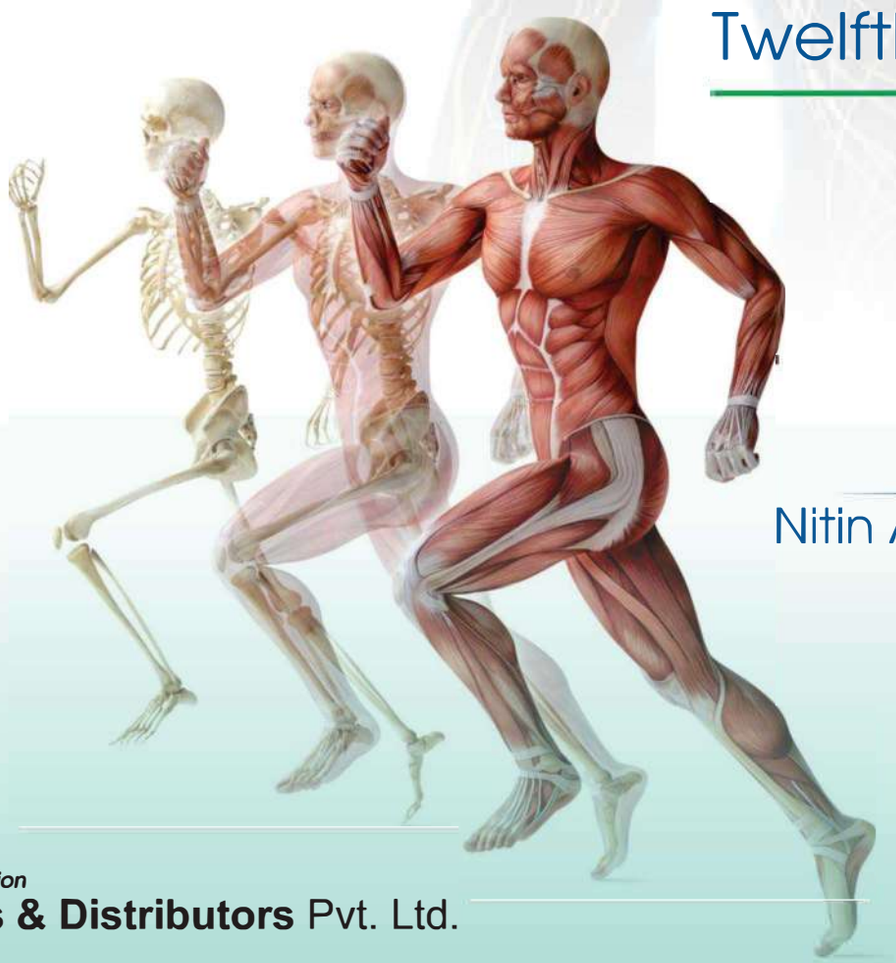
Human Physiology

Twelfth Edition



Editor
Nitin Ashok John

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Human Physiology

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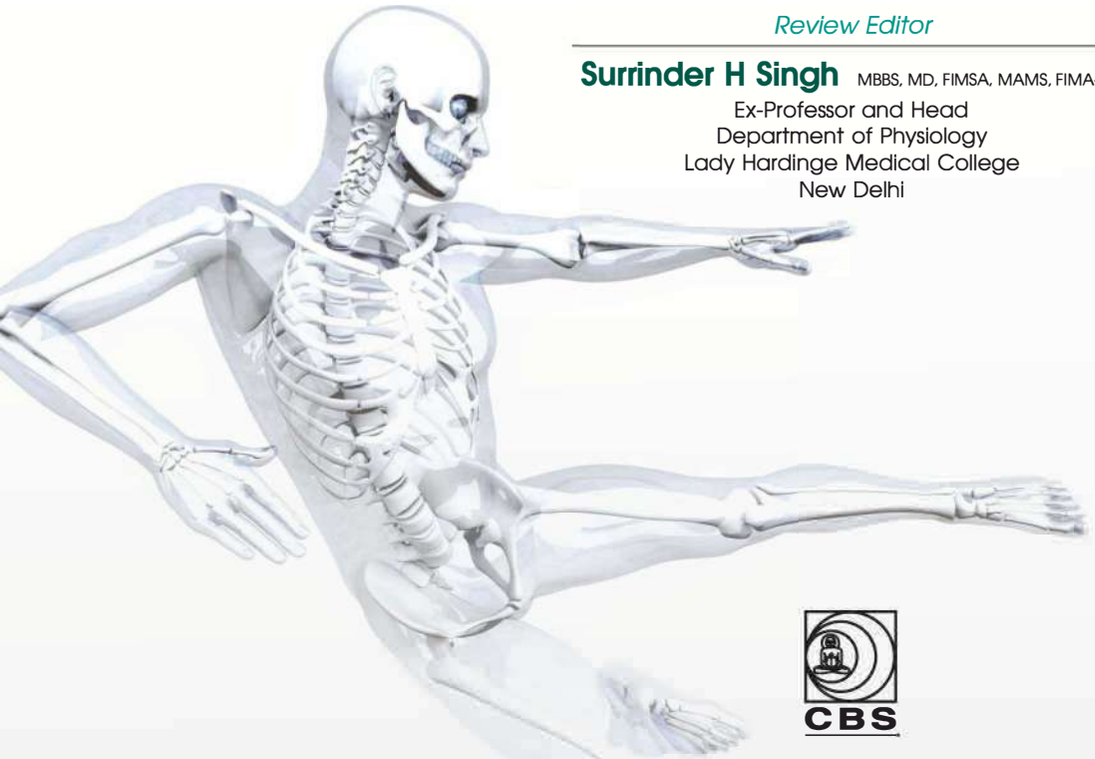

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Preface to the Twelfth Edition

It gives me immense pleasure in writing the Preface to the twelfth edition of CC Chatterjee's *Human Physiology*. This book has been very popular and widely read from its first edition which was published in 1951. Dr CC Chatterjee, a doyen in the field of physiology, was a dedicated academician, devoted teacher, author par excellence, a noble friend, philosopher and a guide to his colleagues and students. He was an enthusiastic physiologist who strived with greatest zeal to give the best integrative knowledge of basic medical sciences, especially that of physiology, to his students.

I express my special gratitude and sincere thanks to Dr Surrinder H Singh, *Ex*-Professor and Head, Department of Physiology, Lady Hardinge Medical College, New Delhi, a renowned teacher of physiology, who provided regular review inputs for updating the book from time to time, and for her devotion in reading the manuscript thoroughly and providing valuable feedback so that no part of the information is left uncovered by oversight.

I express my sincere thanks to my colleagues Dr Neelam Mishra, Professor and Head, Department of Physiology, Government Medical College, Nagpur; Dr MS Phatak, Professor and Head, Department of Physiology, Indira Gandhi Government Medical College, Nagpur; Dr Geeta Kurhade, Senior Lecturer, Department of Physiology, University of West Indies; Dr SV Umadevi and Dr D Niraimathi, Associate Professors, Department of Physiology, Indira Gandhi Medical College and Research Institute, Puducherry; Dr Rakhee Tirpude, Associate Professor, Department of Physiology, NKP Salve Institute of Medical Sciences and LMH, Nagpur, and Dr Sanjay Andrew Rajaratnam, Professor and Head, Department of Physiology, Chettinad Hospital and Research Institute, Chennai, for their valuable suggestions.

As Prof AM Seligman, Dr Barbasa R Betty and Dr Davenport permitted the inclusion of the reference of illustration in the earlier reprint edition and as these are included in this edition too, I extend my gratitude to them. I am also thankful to CBS representatives Mr Ajay (Karnataka), Mr Sarvanan and Mr Jyoti (Chennai) and Mr Ajay Shrivas (Nagpur) for providing constant feedback from various faculty members all over the country for contents to be included in the book and this was immensely helpful.

The twelfth edition of CC Chatterjee's *Human Physiology* is especially designed for undergraduate and postgraduate students of medicine, paramedical sciences and allied health sciences, and will help them in excelling in their examinations and professional career as well.

The key features of this book are the simple language and comprehensiveness which have remained unchanged ever since the first edition. All the topics of physiology are correlated with anatomy, biochemistry, pathophysiology and applied physiology for a thorough integrated learning of the functional aspects of human body. Recent advances have been included to give better insight to understanding the physiological principles. Clinical case scenarios are included to help students in learning of physiological basis of clinical signs and symptoms. Moreover, this book retains the ideas, thought process, knowledge, lucidity and comprehensiveness, original diagrams and intellectual concepts of the doyen physiologist Dr Chandi Charan Chatterjee whose contribution to physiology will always be remembered in the times to come.

In spite of all the untiring efforts, any mistakes or omissions left unknowingly may please be excused, while valuable suggestions are welcome from faculty and students for future printings and editions of the book.

I wish to acknowledge and give special thanks to Mr SK Jain, Chairman and MD, Mr Varun Jain, Director and Mr YN Arjuna, Senior Vice President—Publishing and Publicity for their suggestions and eagerness to make this twelfth edition colourful and informative so that the text is updated with advancements in medical sciences to this day.

I am thankful to Mrs Ritu Chawla AGM—Production, Mr Vikrant Sharma DTP operator, Mrs Baljeet Kaur, Mr Sanjay Chauhan, Mr Neeraj Prasad, Graphic designers, Mr Ananda Mohanty Proofreader, and all publishing team of CBS Publishers & Distributors, New Delhi, for their excellent inputs in shaping the book to its present form.

And last but not the least, I am thankful to my wife Dr Jyoti and my son Joshua for all their support and encouragement.

Nitin Ashok John
Editor

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Preface to the First Edition

At the outset, I would like to pay my humble regards to my revered teacher, Dr Charubrata Ray, MB, BSc, from whose lips I learnt how to 'read' and 'think' Physiology. A quiet unassuming man, a scholar with an inborn spirit of research, a teacher of rare genius—teaching thousands of students throughout his life without the least material interest of his own—Dr Ray represents that long-forgotten school of 'Indian Gurus' with whom teaching was a creed and not a profession. In teaching he sprouts wings. Seldom a teacher could have claimed to have so many students and seldom could he command so much respect from them. There are thousands today who take his name with grateful reverence. May he live long and lead us with his kindly light.

For the last few decades, physiology has been making so rapid progress that it is being increasingly difficult for the average students to manage the subject within the limited period fixed by the universities. Owing to this reason, they are compelled to go in for 'notes', 'synopses', 'made easies' and such other short-cut devices which somehow enable them to squeeze through the examinations but fail to give them a comprehensive knowledge of the subject as a whole. This state of affairs is cutting at the root of medical education and is likely to undermine the standard medical graduates. What is required today is a textbook of reasonable size, including the essentials of histology, biochemistry and biophysics which will give the student a bird's-eye view of the whole subject and at the same time enable him to pass the examination with credit. This book is an attempt in that line.

It has been drawn up to meet the requirements of the preclinical medical students of the different Indian and foreign universities mainly. Advanced and post-graduate students will certainly derive some help from it but should not depend on this book alone. I have no hesitation to say that a good deal of attention has been paid to assure success in examinations. Each system has been divided into a number of problems in such a way that they are usually set or likely to be set as questions by various examining bodies. At the beginning of each system a few introductory lines have been added in which the fundamental principles of that system have been discussed. The students are advised to read these portions carefully and thoroughly to have a better grasp of the subject.

I have tried to avoid as much of the applied aspects as possible because it is my experience that a book meant for the pre-clinical students, should not contain much of applied discussions. The beginner only gets confused and tries to cram up the unnecessary applied details, leaving aside those portions more essential for him. The little 'applied' necessary for them should best be left to the teachers.

18th July, 1951

CC Chatterjee

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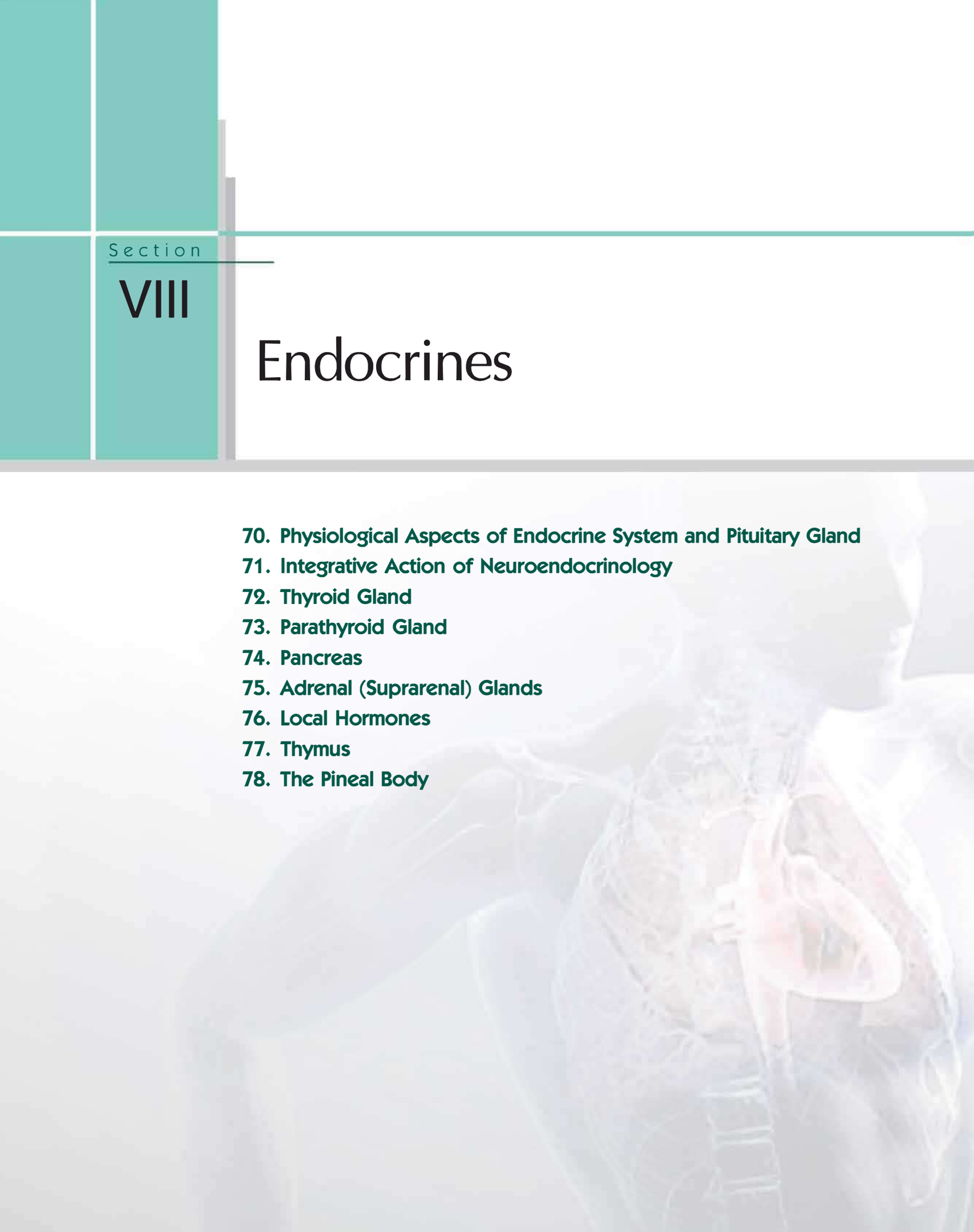
Endocrines



Chapter

70

Physiological Aspects of Endocrine System and Pituitary Gland

INTRODUCTION

The basis of secretions of endocrine gland, mechanism of hormone actions, hormone secretion and actions of hormones secreted by anterior, intermediate and posterior lobe of pituitary gland, hormonal level and hypothalamic control of hormone secretion and pathological diseases related to abnormal hormone secretion will be discussed in the chapter. Detailed account of physiology of growth hormone, vasopressin and oxytocin should be meticulously learned.

The glands of the body may be divided into those with an internal secretion (endocrine glands) and those with an external secretion (exocrine glands). Examples of exocrine glands are the sweat, lacrimal and mammary glands which pass their secretion along ducts to the external surface of the body, and the glands of the mouth, stomach and intestines whose secretions are passed along ducts into the alimentary tract. On the other hand, the endocrine (ductless) glands do not possess any ducts or openings to the exterior.

Two systems are empowered with this act of coordination for body to function as a harmonious unit; they are the nervous and endocrine systems. The endocrine (Greek, *endon* = within; *crinein* = to set apart) system consists of a number of ductless glands (Fig. 70.1) which manufacture certain chemical

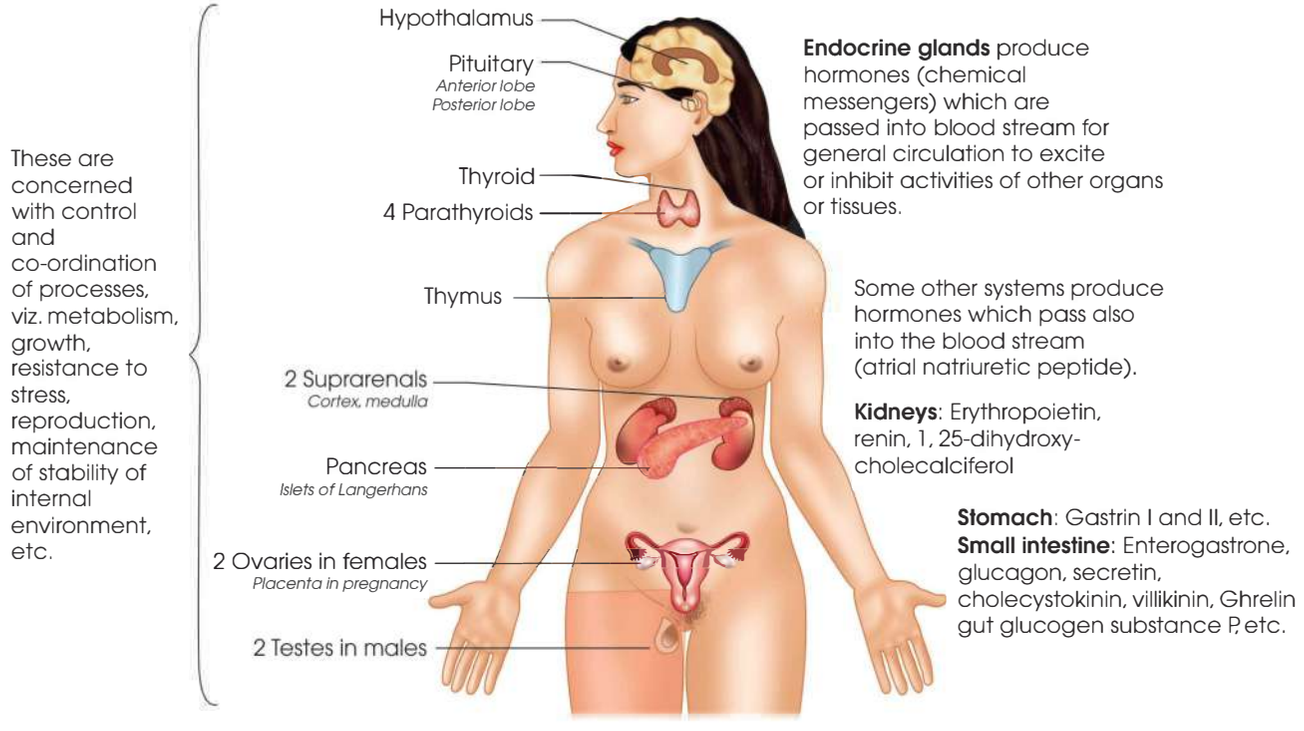


Fig. 70.1: Diagrammatic representation of appropriate anatomical positions of some endocrine glands. Although each endocrine gland has specific functions, but all are interdependent, under activity or overactivity of one tends to affect the whole system

substances that take an essential part in the life processes of the body. In 1902, Starling and Bayliss found that an extract from the intestinal mucosa contains a substance which, when injected intravenously, brought about a secretion of the pancreatic juice. They went on to show that this substance which they termed secretin was released into the blood stream when food entered the small intestine. Following discussions with colleagues at Cambridge in 1905, the word hormone (from the Greek, *hormao*, to excite or arouse or set in motion) was coined for such substances which circulate in the blood and bring about an effect on a distant organ.

The word has tended more recently to be restricted to the substances produced by the endocrine glands, although the digestive tract humoral agents (gastrin, secretin, pancreozymin, etc.) are strictly speaking, hormones. However, these hormones guide and control the growth multiplication, differentiation and metabolic activities of various tissues and systems and thereby bring about a correct physiological balance between them. They also regulate the composition of the various body fluids surrounding the tissue cells and thus establish the normal physiological relation between the cells and the surrounding fluid (internal environment or milieu interne).

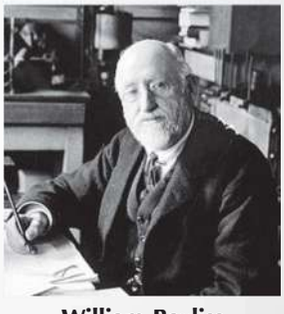
In this way, throughout the whole life—from the early stage of foetal development right up to the moment of death—the endocrine glands exert a profound influence on various bodily activities including the mental and behavioural patterns.

DEFINITION

Starling and Bayliss have defined hormone as a chemical agent which is released from one group of cells and travel via the blood stream to affect one or more different groups of cells. But Huxley (1935) has defined hormones as information-transferring molecules, the essential function which is to transfer information from one set of cells to another, for the good of the cell population as a whole.

Bayliss and Ernest Henry Starling discovered the peptide hormone secretin and peristalsis of the intestines. The Bayliss effect is named after him.

Earnest Henry Starling
1866–1927



William Bayliss
1860–1924

GENERAL CONSIDERATION OF HORMONES

The hormones act as bodily catalysts resembling enzymes in certain aspects and are not used during their catalytic actions. The hormones differ from enzymes in the following ways:

1. The hormones are secreted into the blood stream prior to use, because circulating levels can indicate the activity of endocrine gland and the exposure of target organs.
2. The hormones are produced in an organ other than that in which they finally effect the action.
3. Hormones act in very low concentrations, like the vitamins. Frequently, intravenous injection of a hormone in microgram quantities produces an appropriate measurable change in the variable, controlled by the hormone.

STORAGE, DESTRUCTION AND EXCRETION

Hormones are not ordinarily stored, except in the gland of origin. They do not have any cumulative action, because they are destroyed and excreted as soon as their functions are over. Some hormones work quickly and are destroyed quickly, e.g. epinephrine (adrenaline); others perform their work slowly and are also disposed of slowly, e.g. thyroxine.

MODE OF ACTION

When hormone reaches its target cell, it can affect the intracellular metabolism to modify the cell function. Peptide and protein hormones somewhat being large molecules will not enter cells readily unless specialized transport system is present. For example, insulin may affect cell metabolism by binding to receptors on the surface rather than by entering the cell itself.

When the hormone is restricted to surface binding, there are two mechanisms of action:

1. A hormonally induced change in membrane permeability for ions or substrates.
2. Production of a second messenger within the cell that will transmit the signals of the hormone (Fig. 70.2).

A number of hormones can regulate intracellular metabolism via a second-messenger. Examples are: cAMP, cGMP, IP_3 and DAG (diacylglycerol) and inositol 1, 4, 5-triphosphate (IP_3), Ca^{+2} and PIP_3.

CYCLIC AMP AND HORMONE ACTION

Cyclic AMP (adenosine 3, 5-monophosphate) is a nucleotide. Robinson, Butcher and Sutherland (1971) have described cyclic AMP as a director of foreign

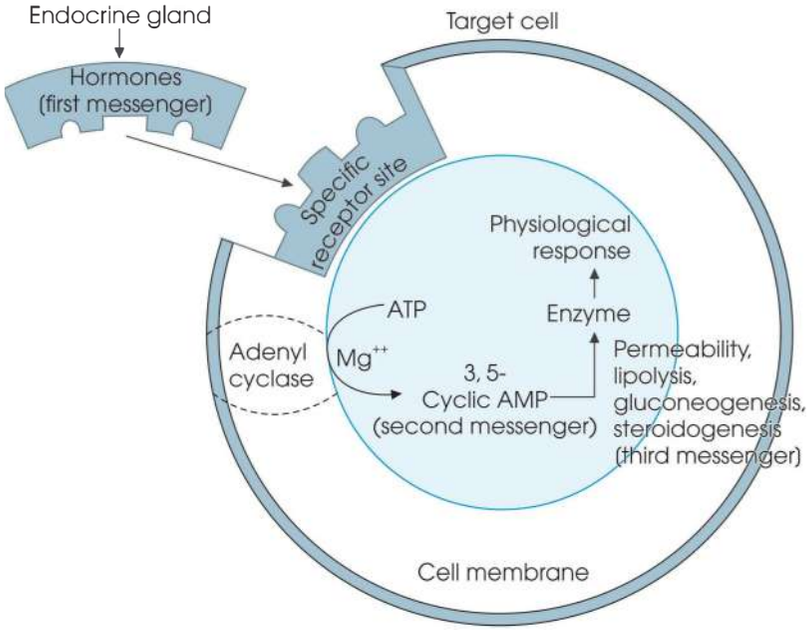


Fig. 70.2: Diagram showing the role of cyclic AMP as a second messenger for hormone action

affairs. In this system (Fig. 70.2), the hormone can bind to a receptor on the cell surface that is a part and parcel of adenyl cyclase involved in the formation of cyclic AMP. As a substrate ATP is used by adenyl cyclase which produces cyclic AMP and inorganic pyrophosphate.

The changes in the activity of adenyl cyclase commonly control the intracellular levels of cyclic AMP. But cyclic levels are affected with the destruction of messenger by phosphodiesterase which is inhibited by methyl xanthines. For example, caffeine intake results in much higher cyclic AMP levels in response to activation of adenyl cyclase.

Effects of the second messenger are:

1. There are changes in membrane permeability to amino acids, water and ions
2. The rate of enzymatic reactions can be modified
3. There is release of stored hormones from endocrine glands
4. Induction of enzyme formation.

A cyclic AMP-dependent protein kinase may be involved in a number of these effects. Cyclic AMP activates protein kinase which catalyses phosphorylation of either enzymes or controls transcription of DNA by histones.

Earl Wilbur Sutherland Jr was an pharmacologist and biochemist. He was awarded the Nobel Prize in Physiology or Medicine for his discoveries concerning the mechanisms of the action of hormones, especially epinephrine, via second messengers, namely cyclic AMP in 1971.

1915–1974

Reference: Sutherland EW. "On the biological role of cyclic AMP". The Journal of American Medical Association 1970;214: 1281–1288.

CYCLIC GUANOSINE MONOPHOSPHATE (cGMP) AS SECOND MESSENGER

Cyclic guanosine monophosphate (cGMP) is derived from guanosine triphosphate (GTP). It acts as a second messenger. It activates intracellular protein kinases in response to the binding of peptide hormones to the external cell surface. The factors that depend on cGMP as second messenger are nitric oxide and atrial natriuretic factor (ANF). The atrial natriuretic factor activates membrane-bound guanylate cyclases while soluble guanylate cyclases are activated by nitric oxide and they further stimulate cGMP synthesis. cGMP phosphorylates a number of smooth muscle proteins mediated via release of nitric oxide producing relaxation of smooth muscle and vasodilatation. cGMP is a known secondary messenger involved in process of photo-transduction in the eye. Similarly, cGMPs are synthesized when olfactory receptors receive odorous input. It is responsible for the long-term potentiation. Atrial natriuretic peptide activates membrane bound guanyl cyclase and produces natriuresis, diuresis, vasodilation, and inhibit aldosterone secretion thereby decreasing the blood volume.

DIACYLGLYCEROL (DAG) AND INOSITOL 1,4, 5-TRIPHOSPHATE (IP_3) AS SECOND MESSENGER

Inositol triphosphate (IP_3) together with diacylglycerol (DAG), is a secondary messenger which plays

Alfred Goodman Gilman was an American pharmacologist and biochemist. He shared the 1994 Nobel Prize in Physiology or Medicine with Martin Rodbell for their discovery of G proteins and the role of these proteins in signal transduction in cells.

1941–2015

Reference: Tang WJ, Gilman AG. Type specific regulation of adenyl cyclase by G protein beta gamma subunits. Science 1991;254 (5037): 1500–3.

important role in signal transduction and lipid signalling in functional cell in human body. The main function of inositol triphosphate is to mobilise Ca^{2+} from storage organelles and this calcium is utilised for regulating cell proliferation and also for other calcium mediated cellular reactions. For example, the increase in concentration of cytoplasmic Ca^{2+} in smooth muscle leads to muscular contraction. It also serves as a second messenger in cerebellum. Cerebellum contains large number of IP_3 receptors and the inositol triphosphate mediated response play an important role in the induction of plasticity in cerebellar Purkinje cells.

Ca^{2+} AS A SECOND MESSENGER

Key Points

1. The intracellular calcium is very low. The common signalling pathway which increases cytoplasmic calcium concentration is the phospholipase C pathway. The intracellular Ca^{2+} via Ca^{2+} binding protein calmodulin bind to target proteins. These target proteins are: Protein kinase, adenyl cyclases, and phosphodiesterases. It affects target proteins by activation of Ca^{2++}/calmodulin-dependent kinase or by directly activating certain enzymes, e.g. phospholipase C.
2. The G protein-coupled receptors and receptor tyrosine kinases are chiefly responsible for activating the phospholipase C enzyme. This enzyme hydrolyses the membrane phospholipid PIP_2 to form IP_3 and diacylglycerol (DAG). The DAG activates protein kinase C promoting its attachment to the plasma membrane. The IP_3 diffuses to the endoplasmic reticulum. Inositol triphosphate binds to an IP_3 receptor which serves as a Ca^{2+} channel, and releases Ca^{2+} from the endoplasmic reticulum to activate protein kinase C.
3. Calcium (as Ca^{2+}) is a very vital second messenger and participates in various physiological mechanisms via protein kinase C such as neuronal transmission, muscular contraction, salivary secretion, cellular motility, cell growth and synaptic plasticity.

Receptor with no enzyme activity but use cytoplasmic tyrosine kinases are (JAK-STATs, e.g. growth hormone) prolactin, cytokines.

SYNTHESIS OF ENZYME AT THE NUCLEAR LEVEL

Key Points

1. The receptors for steroid hormone, thyroid, 1, 25-dihydroxycholecalciferol and retinoid are located in intracellular region; either in cytoplasm or in nucleus.
2. It is enumerated that certain hormones, particularly the steroid hormones are able to penetrate the cell membrane due to their smaller size and lipid permeability. As a result, these compounds can modify intracellular metabolism directly. For example, oestrogen can penetrate the cell membrane and binds to a receptor protein in the cytoplasm. Then it is transported in the nucleus where it is transferred to a nuclear receptor protein.
3. The receptors of steroid hormones resemble the receptors of thyroid, 1, 25-dihydroxycholecalciferol and retinoid. The binding of receptor brings conformational change in receptor exposing the DNA binding domain. The active receptor complex and hormone proceed to DNA and are binded to the enhancer element. Binding thus regulate the transcription of portions of DNA resulting in the formation of messenger RNA. mRNA leaves the nucleus and is translated by the protein synthesis pathway in the cytoplasm.
4. Effect of steroid hormone commonly require 60 minutes or so to be exerted and may be blocked by inhibition of RNA and protein synthesis.
5. Steroid hormones also appear to exert permissive effects on the action of other hormones. The effect of rapidly acting hormones, viz. and glucagon depends upon the presence of normal levels of steroid hormones in order to exert their effects.

Stimulation of Enzyme Synthesis at the Ribosomal Level

It is possible that hormones may alter the rate of synthesis of new enzymes by either activating or inhibiting particular genes directly. Messenger, transfer or ribosomal RNA might be altered. Actinomycin, puromycin, etc. block such synthesis of RNA.

Other Mechanism

Activation of Tyrosine Kinase

The hormones insulin, IGFI, IGFII, growth factors like platelet derived growth factor, endothelial growth factor, etc. bind with receptors having intrinsic tyrosine kinase activity. Binding brings conformational change in the receptor exposing site of autophosphorylation on the receptors. The phosphorylated tyrosine residue

initiate cascade reaction and phosphorylates other enzymes like phosphatase and kinases and thus then regulate or affect cellular function.

Action of growth hormone through **JAK-STAT pathway:** Tyrosine kinase (Janus tyrosine kinase—JAK) phosphorylates signal transducers and activates transcription (STAT) proteins. The JAK-STAT stimulates the transcription and increases mRNA synthesis. And thereby JAK-STAT further activates intracellular enzymatic activity for hormone action.

Dual Control

There are many instances such as regulation of blood sugar, growth, sex, etc. where more than one hormone takes part—some helping the process, others inhibiting it, and thus exerting a dual-control.

Multiple Secretions

A gland may secrete many hormones serving altogether different functions, e.g. pituitary, adrenal cortex, etc.

Chemical Nature

The majority of hormones are peptides, proteins, glycoproteins or amino acid derivatives, steroids. Normally, they are transported in combination with certain fractions of plasma protein.

This is advantageous, in that

1. It increases the solubility of the highly insoluble hormone.
2. It provides a reserve of hormone so that ready supply is available.
3. It may slow the rate of hormone destruction.
4. It determines the rapidity and the onset and duration times of hormonal action.

INTERRELATIONS OF ENDOCRINES

None of the endocrine glands is completely independent. They are closely interrelated and interdependent. The interrelationship may be synergistic or complementary, permissive and inhibitory. They live like a harmonious family, guiding and controlling one another, being complementary to some and antagonistic to others. Consequently, hypoactivity or hyperactivity of a gland will lead to corresponding changes in the other related endocrines. For instance, hyperpituitarism (anterior) may lead to hyperthyroidism. A reciprocal relation is often observed, e.g. if a gland A stimulates another gland B, then B depresses A, directly or indirectly through other glands. For instance, anterior pituitary stimulates thyroid, gonads and adrenal cortex; while the secretion of any one of three glands depresses the particular trophic hormones of anterior pituitary. Hormone levels in circulation are maintained by feedback or push-pull mechanism. This may be a fundamental rule of endocrine regulation.

CONTROL OF ENDOCRINE SYSTEM

The principal function of endocrine system is to maintain the milieu intérieur (milieu interne) constant.

For the maintenance of such constancy many homeostatic mechanisms come into play. Many of such homeostatic processes are of negative feedback type and a few are of positive feedback type. Figure 70.3 demonstrates that A stimulates B, and B stimulates the formation of C. But increased formation of C inhibits B. This is the negative feedback. Figure 70.4 demonstrates the positive feedback. Here A stimulates B, and B stimulates the formation of C and again C stimulates B.

The simplest form of endocrine control that operates in case of secretions of insulin, glucagon, parathyroid, thyrocalcitonin (calcitonin) and also of aldosterone (partly) has been shown in Fig. 70.5. In this systems, endocrine glands secrete hormones which stimulate the target cells. The target cells, on the other hand, release a substance that by negative feedback mechanism decreases the rate of release of hormones. In this system, neural or pituitary control seems to be absent. A and A_1 represent other factors that operates independently of feedback loop and influence respectively the activity of endocrine gland; and target cell.

A more complex system of control operates in the regulation of secretion of aldosterone from the adrenal cortex (Fig. 70.6). Renin plays an important role in such

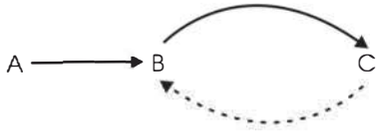


Fig. 70.3: Negative feedback showing when variable A increases, variable B increases leading to an increase in variable C. But an increase in variable C leads to a decrease in variable A, thereby decreasing variable B

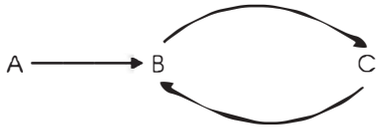


Fig. 70.4: Diagram shows positive feedback

Fig. 70.5: Endocrine control showing action of hormones on specific target cell; the target cells, on the other hand, release a substance that by negative feedback mechanism decreases the rate of release of hormones thus regulating the output of hormones by the end organ

regulation. Renin is a protein-splitting enzyme produced by the juxtaglomerular cells which surround the afferent arteriole just before it reaches the glomerular capillary tuft. Renin converts circulating renin substrate to the decapeptide, angiotensin I. A converting enzyme produced in lungs and blood by removal of two C-terminal amino acids of angiotensin I form biologically active octapeptide, angiotensin II. Angiotensin II has an immediate effect on the peripheral arterioles to cause vasoconstriction and increased systemic blood pressure, and also stimulates secretion of aldosterone by the adrenal cortex and stimulates thirst centre. The renin-angiotensin system is discussed in detail elsewhere.

In next order of complexity, certain endocrine glands (EGs) are under the direct control of hypothalamus.

This type of control system has been described in Fig. 70.7. Adrenaline of adrenal medulla, growth hormone of anterior pituitary and vasopressin of posterior pituitary falls within this control system.

Key Points

1. Hypothalamus controls the endocrine activity either by neural mechanism or by hormonal mechanism. But the activity of the hypothalamus is not controlled by the hormone of the gland itself but indirectly by the change in the plasma constituent occurs due to hormone.
2. The highest complexity in the regulation of endocrine function is observed in case of hormones secreted from the target glands of the anterior pituitary. The general principle of controlling mechanism has been presented in Fig. 70.8. In such system anterior pituitary function is controlled by the hypothalamus through secretion of specific-releasing factors (hormonal). The anterior pituitary hormones are specific for specific target endocrine gland.
3. The normal control of endocrine mechanism is achieved through the negative feedback mechanism at the level of hypothalamus by the product of the final target endocrine glands. TSH and ACTH fall within this category. Sometimes, feedback control is exerted at the level of anterior pituitary by the hormones of the target endocrine gland.

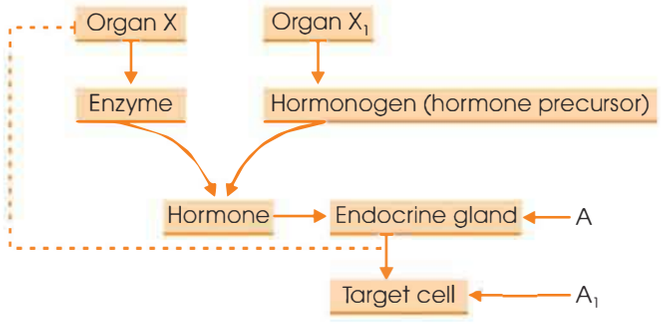


Fig. 70.6: Diagrammatic representation of endocrine control by release of hormonogen (a hormone precursor) from two organs—X and X_1. A and A_1 represent the same function as in Fig. 70.5. Dotted line indicates inhibition

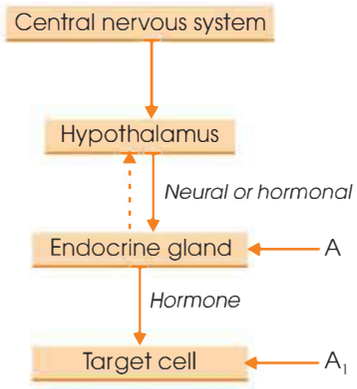


Fig. 70.7: Diagrammatic representation showing the endocrine control achieved by the hypothalamus. A and A_1 indicate the same function as in Fig. 70.5. Dotted line represents inhibition

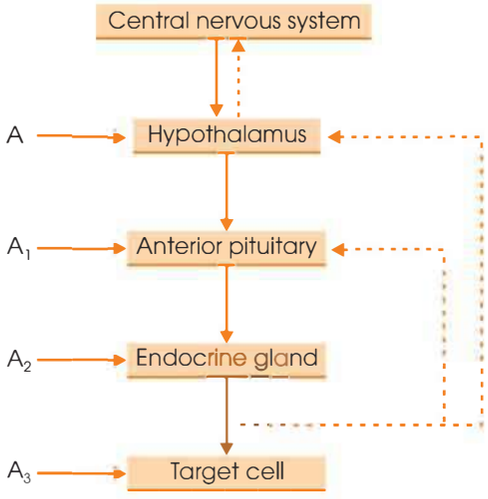


Fig. 70.8: Diagram represents the complex feedback systems that operate in controlling the endocrine function through hypothalamus → anterior pituitary → endocrine gland → target cell. In this system, feedback control is achieved at the level of the hypothalamus and anterior pituitary. A, A_1, A_2, A_3 operate independently of and separately for controlling the function of the hypothalamus, anterior pituitary, endocrine gland and target cell, respectively

DYSFUNCTION OF AN ENDOCRINE GLAND

Effects of Dysfunction

The effects produced by the hypoactivity or the hyperactivity of a particular gland should not be explained by the fault of that gland alone but also (a) by the changes produced in other related glands (central

action) and (b) by the disturbance of the peripheral actions of the other related hormones. As for instance, diabetes mellitus should not be regarded as due to the lack of insulin alone but due to the unopposed activity of the glucagon, etc.

Causes of Dysfunction

The cause of a glandular disturbance may not always lie in the gland itself, but somewhere outside the gland.

The causes may be summarised as follows:

1. The gland itself may be diseased.
2. There may be lack of the raw material with which the hormone is manufactured, e.g. iodine deficiency in goitre.
3. The primary seat of the disease may be in some other gland which normally controls its action, e.g. hyperthyroidism may be secondary to hyperactivity of the anterior pituitary.
4. Overwork of the gland, e.g. excessive carbohydrate feeding is supposed to be a cause of diabetes mellitus. Disturbed nervous system—stress, strain, faulty adaptation, etc. may lead to endocrine troubles.
5. Some of the endocrine disorders are genetic, due to inborn defects. Examples are hereditary diabetes, some types of hypothyroidism, adrenal cortical disturbances, etc.

ENDOCRINE GLANDS

The following is a comprehensive list of endocrine glands in the human body:

Glands with definite endocrine functions:

Pituitary: Anterior lobe and posterior lobe

1. Thyroid
2. Parathyroid

Adrenals: Cortex and medulla

1. Ovary
2. Testes
3. Islets of Langerhans (endocrine pancreas)
4. Placenta—during pregnancy.

Glands with probable endocrine functions:

1. Thymus
2. Pineal body

In addition to above, there are certain other substances which should be regarded as hormones. For instance: (1) Gastrin I and II and the haemopoietic factor-secreted by stomach, (2) secretin, enterogastrone, cholecystokinin-pancreozymin, villikinin, etc. produced by small intestine.

ESSENTIAL PROPERTIES OF A HORMONE

1. **Easy solubility:** Since the hormones are carried in the blood stream, they should be soluble in water or should remain in such a form in which they can be easily carried.
2. **Low molecular weight:** Since they readily pass out of the capillaries, hormones should have small molecular weight.
3. **Easily diffusible:** This is true almost in all cases excepting insulin, thyroglobulin, etc. having comparatively bigger molecules.
4. **No cumulative action:** It must be readily destroyed or inactivated or excreted. This is necessary in order to prevent cumulative or continued action. As soon as their functions are finished they should be disposed of.

MAJOR ENDOCRINE GLANDS AND HORMONES IN CONTROLLING BODY FUNCTIONS

Release of hormones into the blood stream and spread of depolarisation through nerves transmit signals which allows an animal to respond to changes in its environment. Either a nerve impulse or a change in the concentration of some substance into the blood which perfuses the gland may trigger such release (Fig. 70.9). Such a substance called hormone is produced by a gland or specialized neurosecretory cell, is often stored in this cell, and is released into the blood stream in response to some specific stimulus. As soon as the hormone reaches its target cells, it modifies the function of the cell to remove the stimulus that primarily caused the release of the hormone. This negative feedback mechanism operates to maintain homeostasis within the organism.

Signals that are transmitted through nerves possess the advantage of localization and speed to signal cells within a large group of similar cells.

1. **Hypophysis:** ACTH (adrenocorticotrophic hormone), GH (growth hormone), FSH (follicle-stimulating hormone), MSH (melanocyte-stimulating hormone), TSH (thyroid-stimulating hormone), LH (luteinising hormone), prolactin, vasopressin and oxytocin.
2. **Thyroid:** Thyroxine, tri-iodothyronine, calcitonin.
3. **Parathyroid:** Parathyroid hormone.
4. **Adrenal gland:** Glucocorticoids, mineralocorticoids, epinephrine, norepinephrine.
5. **Ovary:** Oestrogen, progesterone.
6. **Testis:** Testosterone.
7. **Islets of Langerhans (pancreatic islets):** Insulin, glucagon.
8. **Skin:** Vitamin D.

Hypothalamus: In response to afferent impulses, chemical or neural, received from all over the body, a different area of the hypothalamus elaborates different neurosecretory-releasing factors. TRF (thyrotrophin-releasing factor), CRF (corticotrophin-releasing factor), GRF (growth hormone-releasing factor), gonadotropin-

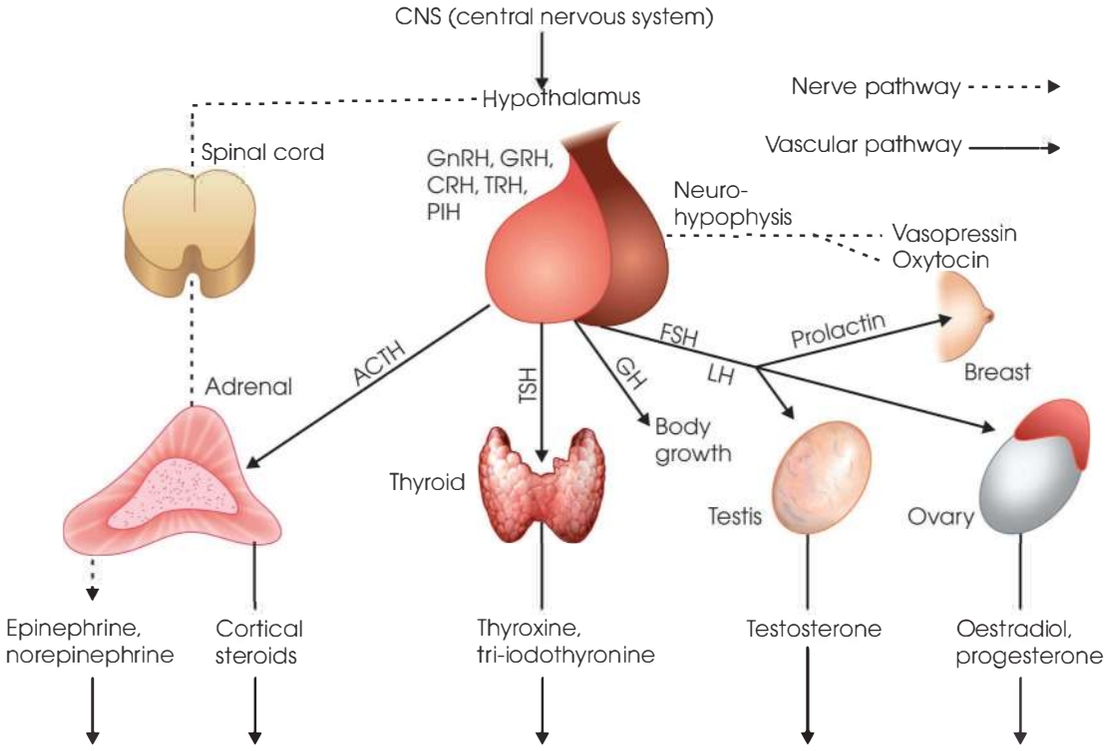


Fig. 70.9: Diagram shows some relationship between the endocrine and nervous system and also shows that neurosecretory structures (i.e. hypothalamus, neurohypophysis and adrenal medulla) are controlled by direct nerve supply and other gland's activity is regulated by hormonal or humoral agents carried in the blood

releasing hormone (GnRH) is responsible for the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary, PIF (prolactin-inhibiting factor), GHIF (growth hormone-inhibiting factor), MIF (melanocyte-inhibiting factor) and somatostatin (which inhibit the release of growth hormone, thyroid-stimulating hormone, adenylyl cyclase in parietal cells and so also inhibits the release of prolactin).

HYPOPHYSIS (PITUITARY GLAND)

In 16th century Vesalius named this gland the pituitary (L. *pituita* = phlegm or mucus) filtered and collected wastes from the brain and these lubricated the nasal and pharyngeal passages. When the true function of the gland was established the term hypophysis (hypo + Gr. *Phyein* = to grow) was substituted. But the gland is still often called the pituitary.

Anatomy

The pituitary gland is a reddish-grey, small oval-shaped structure, situated at the base of the brain, in the sella turcica of the sphenoid bone. It is attached to the floor of the third ventricle by a stalk. The average weight of pituitary gland in adult is 0.5 to 0.6 gm. The weight varies with age, sex and physiological state. It is somewhat

Roger Charles Louis Guillemin received the Nobel Prize for medicine in 1977 for his research on neurohormones. He shared the Nobel Prize with Andrew Schally and Rosalyn Sussman Yalow.

Roger Charles Louis Guillemin
1924

Andrew Schally
1926

Rosalyn Sussman Yalow
1921–2011

Reference: Schlessinger, Bernard S, Schlessinger, June H. The Whos who of Nobel Prize winners, Oryx Press 1901–1995, 1996; p.133.

larger in the females, weighing from 0.6 to 0.7 gm. It increases in size through the fourth decade of life, and then slowly decreases. It also enlarges during pregnancy. Average dimensions are 10 mm (anteroposteriorly) × 6 mm (dorsoventrally) × 13 mm (laterally). Anatomically, it consists of two parts: The anterior lobe and the posterior lobe. But microscopically, it consists of six parts:

1. Pars distalis or pars anterior
2. Pars tuberalis
3. Pars intermedia
4. Pars nervosa (lobus nervosus)
5. Pars posterior (processus infundibuli)—median eminence of tuber cinereum
6. Infundibulum (pituitary stalk).

The pars intermedia are separated from the pars distalis or pars anterior by the interglandular cleft. The first two parts are collectively known as the glandular division or lobus glandularis (adenohypophysis); the last two as the neural division (neurohypophysis) (Fig. 70.10).

Development

The pituitary body develops from two outgrowths. A glandular diverticulum—Rathke's pouch—grows upwards from the primitive buccal cavity (ectoderm) and meets with a similar neural downgrowth from the floor of the third ventricle. The stalk of Rathke's pouch disappears. But that of the neural downgrowth persists and forms the pituitary stalk (infundibulum). From the anterior wall of Rathke's pouch develops the pars distalis or pars anterior; from the top arises the pars tuberalis; from the posterior wall develops the pars intermedia.

The pars intermedia invest the pars posterior or pars nervosa to some extent. The original cavity of Rathke's pouch forms the interglandular cleft. Thus, the so-called **anterior lobe** consists of pars distalis (pars anterior) and pars tuberalis, whereas the **posterior lobe** consists of pars intermedia and the processus infundibuli. Sometimes the term 'posterior lobe' is loosely used as a synonym for the 'pars nervosa'.

Divisions of the pituitary gland as recommended by the International Commission on Anatomical Nomenclature have been presented in Fig. 70.11. Throughout the book this nomenclature will be followed.

The pituitary gland secretes several hormones which have been presented in Table 70.1.

STRUCTURE AND FUNCTIONS OF ADENOHYPOPHYSIS

Adenohypophysis includes pars distalis, pars tuberalis and pars intermedia.

Histology of Pars Distalis (Fig. 70.12)

Pars distalis or pars anterior forms about 75% of the hypophysis and consists of column or masses of epithelioid cells with numerous blood sinuses.

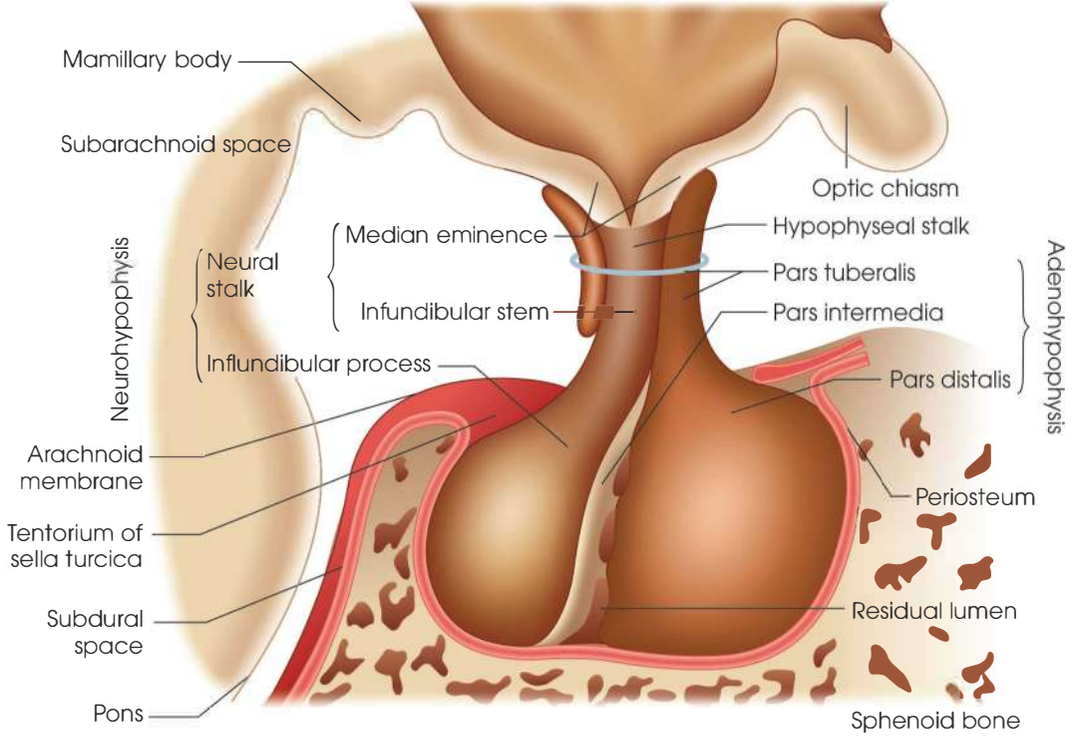


Fig. 70.10: Diagram showing the component structures and systems of nomenclature for the hypophysis and its anatomical position

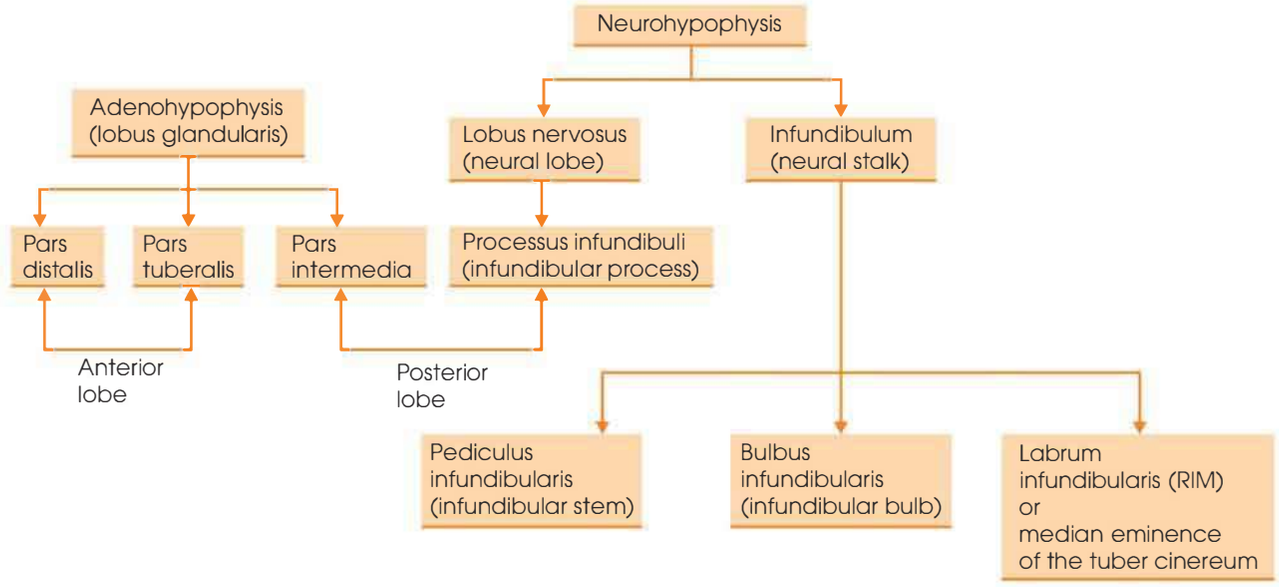


Fig. 70.11: Schematic reproduction of systems of anatomical nomenclature for the hypophysis

Schonemann in 1982 first recorded the diversity of cell types in the anterior pituitary gland. The earlier classification of the cells of pars distalis into acidophils, basophils and chromophobes are inadequate. The present idea is that the different pituitary hormones are liberated by separate cell types. Possibly six kinds of cells secrete six separate hormones. Studies employing histochemical, immunofluorescent and electron microscopic techniques have made such classifications possible.

Chromophobes [C (cheif) cells or reserve cells are 25%] are so named because these cells are not stained with either basic dyes or acid dyes and lack typical secretory granules. Chromophobe cells in general have got less cytoplasm than chromophils.

Chromophil cells (75%) are so named as they have got affinity towards dyes. Early staining methods show only two types of chromophils:

- Acidophil (α-cell or eosinophil or oxyphil, 35%)
- Basophil (β-cell, 15%)

These proportions vary depending upon physiological state, age and sex. The cytoplasm of acidophil is stained with acid dye and that of basophil, with basic dye.

Acidophil cells: The majority of 80% cells are acidophilic. They stain red or orange when stain with acidophilic dyes. The acidophil cell secretes both growth hormone and lactogenic hormone. These hormones are secreted with separate cell types—somatotrophic and lactotrophic.

Somatotrophic cells, orangeophils or α-acidophils: These cell types are stained with orange G of an Azan stain and secrete growth hormone.

Lactotrophic cells, carminophils or α-acidophils: These types of acidophil cells are preferably stained with azocarmine, erythropsin or acid fuchsin. These cells secrete prolactin.

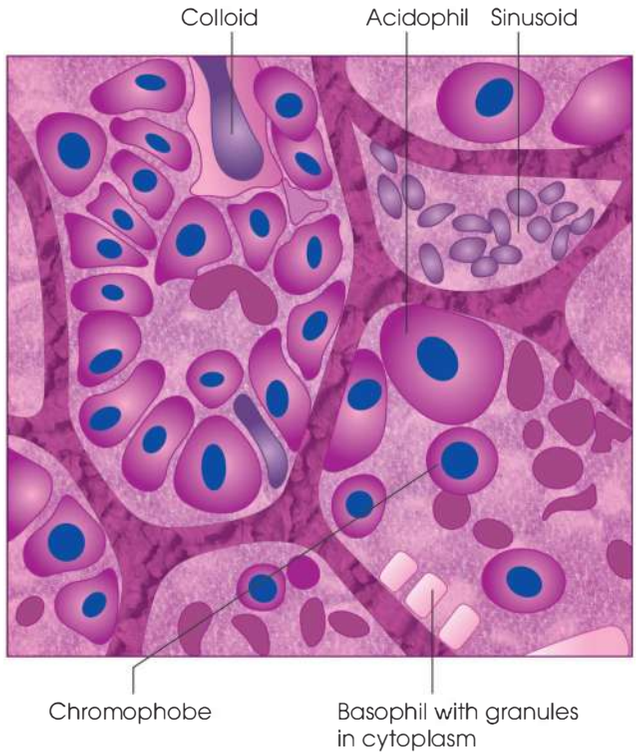


Fig. 70.12: Diagrammatic representation of histological structure of pars distalis only

Basophil or mucoid cells: Nearly 20% of cells are basophilic. There are different kinds of basophil cells secreting different types of trophic hormones like ACTH, TSH, FSH and LH. ACTH is protein whereas the last three hormones are glycoprotein (mucoid cells). Differential staining methods have been able to stain the different basophilic cell types.

Table 70.1: The major hormones secreted by the pituitary gland

Hormones	*Origin*	*Cellular source*	*Chemistry*	*Control*	*Target cell or organs*	*Principal actions*
Growth (GH) or STH	Pars distalis	Acidophils	Protein	Blood sugar hypothalamus	Somatic	Controls growth of bone and muscle; anabolic effect on nitrogen metabolism
Thyroid-stimulating hormone (TSH) or thyrotrophin	Pars distalis	Basophils	Glycoprotein	TRF, thyroxine	Thyroid	Controls rate of iodine uptake by thyroid tissue and influences synthesis of the thyroid hormones
Adrenocorticotrophin hormone (ACTH)	Pars distalis	Basophils	Polypeptide	CRF, cortisone	Adrenal cortex	Stimulates secretion of adrenal cortical steroids by adrenal cortex, certain extracortical actions
Luteinising hormone (LH)	Pars distalis	Basophils	Glycoprotein	LRF, oestrogen and progesterone	Corpus luteum or interstitial cells of testes	*Testis:* Stimulates interstitial cell of Leydig, thus promoting the production of androgen *Ovary:* Ovulation controls formation of corpora lutea, secretion of progesterone; possibly acts in conjugation with FSH
Follicle-stimulating hormone (FSH)	Pars distalis	Basophils	Glycoprotein	GnRH and oestrogen	Graafian follicles	*Testis:* Action on seminiferous tubules to promote spermatogenesis *Ovary:* Controls growth of ovarian follicles; function with ICSH to cause oestrogen secretion and ovulation
Prolactin or luteotrophic hormone (LTH)	Pars distalis	Acidophils	Protein	PIF	Mammary gland	Control proliferation of mammary gland and initiation of milk secretion *Action on gonads*: Stimulating and inhibiting effects on gonads
Melanocyte-stimulating hormone (MSH) or intermedin	Pars intermedia	Basophils and acidophils	Polypeptide	MIF	Megaloblast cells	Controls dispersion of pigment granules in melanophores; darkening of the skin
Vasopressin (antidiuretic hormone—ADH)	Neurohypophysis	Hypothalamic supraoptic and paraventricular nuclei	Polypeptide	CNS	Kidneys, blood vessels, etc.	Elevates blood pressure through action on arterioles; promotes resorption of water by kidney tubules
Oxytocin	Neurohypophysis	Hypothalamic paraventricular and supraoptic nuclei	Polypeptide	CNS	Uterus, mammary glands, etc.	Affects postpartum mammary glands, causing ejection of milk; promotes contraction of uterine muscle; probable action in parturition and in sperm transport in female tract

Thyrotrophic cells: The cell that makes TSH has been termed as thyrotroph and is a large polygonal one with small nuclei, taking PA–Schiff (periodic acid–Schiff) stain combined with aldehyde thionine.

Gonadotrophic or castration or signet ring cells: The gonadotrophic cells are also positive with PA–Schiff stain. They secrete LH and FSH.

Corticotrophic cells: They secrete melanocyte-stimulating hormone (MSH) and ACTH.

Applied Physiology

Pituitary cells and cytokines: Cytokine is one of the peptide mediators of cell growth and differentiation. Cytokines are secreted or expressed on the cell membrane or they may accumulate in the extracellular matrix. The cytokine cell surface receptors via intracellular signal transduction pathways influence the nuclear transcription. The specific receptors for cytokines are expressed in anterior pituitary cells, thus cytokines which occur in different types of pituitary cells act in an autocrine or paracrine manner and help in regulation of hormone secretion and cell growth.

Blood Supply

The anterior lobe of pituitary gland gets blood supply from several **superior hypophyseal arteries** originating from the internal carotid artery and circle of Willis. The

superior hypophyseal arteries supply the anterior lobe through two sets of blood vessels (Fig. 70.13). One set of blood vessels supplies the lobe directly and forms a sinusoid. Another set of blood vessels reaches the capillary plexus of the median eminence and the infundibular stem. This capillary plexus is a spiral structure around the hypophyseal stalk. This capillary plexus is drained by a long portal vein which ultimately ends in the sinusoids of anterior lobe. This second set of blood supply is the **hypothalamo-hypophyseal portal system** and is important for controlling the anterior pituitary secretory function through hypothalamic releasing factors (RF). Vascular connections of the anterior lobe with the hypothalamic nuclei are thus made through this vessel. Inferior hypophyseal arteries give off several end arteries. Venous drainage from the anterior lobe is made through the cavernous sinus.

Nerve Supply

There is definite evidence of a nervous control of the anterior lobe, but only a few fibres either from the hypothalamo-hypophyseal tract of nerve fibres or from the carotid plexus of the cervical sympathetic or from the greater superficial petrosal nerves have been traced to it. They are probably vasomotor nerves.

Functions of the Pars Distalis of Pituitary Gland

Anterior lobe is the master gland of the endocrine system because it produces protein trophic hormones which affect the other ductless glands. This lobe secretes several hormones of which six have been isolated in almost pure forms. The following hormones are secreted by the anterior pituitary:

1. Growth hormone or somatotrophic hormone (GH or STH)
2. Thyrotrophic hormone or thyroid-stimulating hormone (TSH) or thyrotrophin
3. Adrenocorticotrophic hormone (ACTH) or adrenotrophic hormone or adrenocorticotrophin
4. Gonadotrophic hormones or gonadotrophins
5. Follicle-stimulating hormone (FSH)
6. Luteinising hormone (LH) or interstitial cells stimulating hormone (ICSH)
7. Lactogenic hormone or prolactin or mammotrophic hormone (MH) or luteotrophic hormone (LTH) or luteotrophin, which is also gonadotrophic hormone in some species.

A brief description of the hormones is given below.

GROWTH HORMONE OR SOMATOTROPHIC HORMONE (GH OR STH)

It is secreted by acidophil cells.

Chemistry

Human growth hormone has a single straight chain polypeptide structure containing two intramolecular disulphide bridges and molecular weight of 21,500.

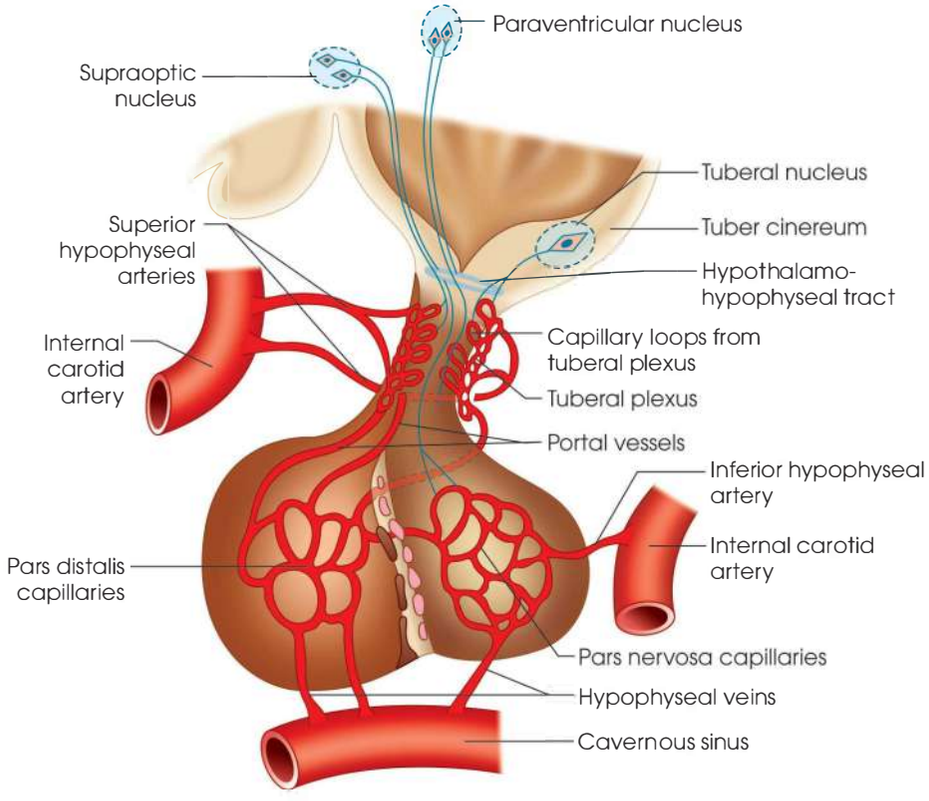


Fig. 70.13: Diagram showing the hypophyseal blood supply

These disulphide bridges are not essential for biological activities. The human growth hormone is composed of 191 amino acids without carbohydrate substituents. It is not effective by oral administration as it is inactivated by pepsin and trypsin. There are two types of growth hormone: 20 K GH has molecular weight of 20,000 and constitutes 10% of the total growth hormone in secretion. The other form 22 K GH has molecular weight of 22,000 constitutes 90% of the circulating growth hormone.

Synthesis of Growth Hormone

The larger prohormone is synthesized in the rough endoplasmic reticulum. The prohormone constitutes 191 amino acids and N terminal signal peptide which while processing through Golgi apparatus is removed. The formed hormones are packed and stored in somatotrophic cells.

GROWTH HORMONE SECRETION

Hypothalamus: The secretion of growth hormone by pituitary acidophil cells is regulated by the hypothalamic hormone, the GHRH (growth hormone-releasing hormone) and GHIH (growth hormone-inhibitory hormone somatostatin). This specific hypothalamic hormone has been isolated and identified as a small acidic peptide of 11 amino acid residues. Lesions in this area arrest growth. It is believed that this releasing factor, GHRH (growth hormone-releasing hormone) or SRH (somatotrophin-releasing hormone), is secreted from the median eminence.

The stimuli which increase GH secretion are: Hypoglycaemia, 2-deoxyglucose, exercise, fasting, protein meal, infusion of amino acid (especially arginine), glucagon, pyrogen, lysine and vasopressin.

1. **Hypoglycaemia:** Insulin-induced hypoglycaemia is considered to be potent stimulus for GH secretion. To have an effective stimulus, blood sugar must fall to 50% or less of the basal level. This effect is not due to direct action of insulin but that of hypoglycaemia.
2. **Fasting:** Fasting causes a rise in plasma growth hormone in humans. In severe malnutrition, plasma GH level is sometimes increased. ACTH and catecholamines may stimulate GH secretion and lipid mobilisation during fasting.
3. **Exercise:** Plasma level of GH is increased even after light exercise. The resultant rise in plasma FFA provides source of energy-sparing glucose.
4. **Amino acid infusion:** Amino acid administration causes an elevation of GH. Rise in concentration of precursor makes condition favourable for protein synthesis.
5. **Stress:** Different stressful stimuli affect the secretion of GH. Surgical stress, emotional stress, bacterial endotoxins stimulate stress. Insulin hypoglycaemia stimulates secretion of human growth hormone (hGH) possibly through stress mechanism. Darkness inhibits growth. Crowding stimulates growth slowly. Exposure to high or low temperature influences growth. Noise sometimes inhibits growth. Gentling or handling stimulates growth. But secretion decreases during REM sleep.
6. **Sleep:** Going to sleep stimulates growth. The young allowed to sleep stimulate growth.
7. **Hormones:** (a) Thyroid hormone stimulates growth through the secretion of growth hormone. (b) Small or large doses of androgens stimulate growth, but on prolonged treatment stops growth by closing the epiphysis. Relation of this hormone with the release of growth hormone has not yet been established. ACTH infusion can stimulate human chorionic gonadotropin (hCG) release during starvation. Ghrelin stimulates secretion of GH.

Following factors may inhibit growth:

1. **Hormonal factors:** Oestrogen and other ovarian hormones have got influence on growth as because females are shorter than the males. It is suggested that ovarian hormones retard growth through inhibition of GH secretion.
2. **Adrenal corticoids:** Corticoids interfere with the growth process. Administration of corticoids causes dwarfism. The corticoids inhibit the stimulating effect of GH on the epiphysis.

Mechanism of Action

1. Growth hormone binds with growth hormone receptor which is a tyrosine kinase associated receptor.
2. Action of growth hormone through JAK-STAT pathway: Jannus kinase (JAK) phosphorylates signal transducers and activator of transcription proteins (STAT) which causes phosphorylation of insulin substrate and further activates intracellular enzymatic activity for hormone action. Growth hormone via the JAK-STAT signalling pathway, stimulates production of insulin-like growth factor 1 which is also known as somatomedin C in the liver which is the principal site of IGF-1 production. IGF-1 which is homologous to insulin has growth-stimulating effects on a wide variety of tissues. It also exhibits stimulatory effects on osteoblast and chondrocyte activity to promote bone growth.
3. The hormone receptor complex also stimulates phospholipases C activity producing DAG; and this DAG brings over or initiates influx of calcium and thus starts the gene transcription in target tissue.

Actions of Growth Hormone (GH or STH)

1. **Skeletal growth:** Stimulates the multiplication of the epiphyseal cartilage and thus increases the length of the cartilage bones. Growth hormone exerts some of

its effects by binding to receptors on target cells, via the mitogen-activated protein kinase (MAPK/ERK) pathway. And it stimulates division and multiplication of chondrocytes of cartilage.

2. **Regulates general body growth:** After administration of this hormone there is an increased body growth due to its direct effect in the tissues. It stimulates the growth of muscles and it also responsible for visceral growth.
3. **Metabolism:** As GH has metabolic effect over and above growth, the secretion of the hormone does not stop at adulthood, but continues throughout the life.

On protein metabolism: GH increases nucleic acid and protein synthesis, decreases nitrogen excretion in the urine and the nitrogen thus retained helps in the synthesis of tissue protein.

a. GH is a protein-anabolic hormone and prevents the catabolism of amino acids. It diminishes the amino acid content of the plasma by transferring it into the tissue and helps in the growth of the tissue.
b. GH increases the transport of amino acids across the cell membrane and thus helps in the synthesis of proteins.
c. GH increases the rate of incorporation of β-amino-isobutyric acid (similar action of insulin on glucose transport).
d. There is also increased serum alkaline phosphatase which helps in the protein synthesis and ossification of bones.
e. On liver protein synthesis: GH increases the synthesis by modifying the activity of ribosomes in the translation of mRNA and also produces marked increase in liver RNA synthesis and content. Eventually GH stimulates liver cell division and increases overall hepatic size. These effects of GH are actually brought about through the mediation of insulin.

On fat metabolism: Growth hormone has got an important effect on fat metabolism.

a. Administration of the hormone causes mobilisation of peripheral fat depot to the liver.
b. The mobilized fat is transported in the plasma as non-esterified fatty acid (NEFA). In human subject plasma level of NEFA increases 2–3 folds after administration of 1–2 mg of primate GH.
c. The alteration of fat metabolism is the primary effect of the GH. Increased oxidation of fat decreases the catabolism of amino acids causing utilisation of amino acids in the synthesis of protein.

On carbohydrate metabolism: The primary effect of GH on carbohydrate metabolism is to stimulate its storage.

a. Administration of growth hormone in human produces hyperglycaemia and glycosuria. The high blood glucose level leads to overproduction of insulin by β-cells and finally to its exhaustion and atrophy. So, the growth hormone is diabetogenic especially in man. The hormone, however, increases in the glycogen content of cardiac muscle. Administration of ACTH produces similar effects as induced by growth hormone.
b. Both GH and ACTH increase gluconeogenesis and diminish the rate of oxidation of glucose. GH and ACTH exert antagonistic actions to those of insulin.

Ion or mineral metabolism: GH (STH) increases intestinal absorption of calcium. In addition to calcium, sodium, potassium, magnesium, phosphate and chloride are also retained.

GH stimulates proliferation of thymic lymphocytes both *in vivo* and *in vitro*.

Applied Physiology

1. Hypopituitarism (atrophy or ill-development of acidophil cells) in infants and children (e.g. before union of epiphyseal cartilage) retards skeletal growth and produces dwarfs **(dwarfism)**.
2. Hyperpituitarism (acidophil tumour) in the young increases skeletal growth producing unusually tall stature (2 to 2.50 meters). This condition is known as **gigantism**.
3. Hyperpituitarism in the adults (e.g. after union of epiphysis) leads to **acromegaly**. Acromegaly is the hormonal disorder due to excessive secretion of growth hormone and characteristic features of acromegaly includes increase thickness of lower jaw, hands and feet, producing a *gorilla-like* appearance, etc.
4. The chief clinical disorders are briefly described below.

DYSFUNCTION OF THE ACIDOPHIL CELLS

Hyperactivity

In adult, it leads to acromegaly.

Hypoactivity

In young, it leads to dwarfism.

Three types:

- Lorain-Levy type.
- Brissaud type.
- Mixed type.

In adult, it leads to acromicria (it is a rare condition).

These conditions are briefly described below.

GIGANTISM (Fig.70.14)

It is caused by hyperactivity of the acidophil cells in the young.

Characteristic Features

1. **Skeleton:** These persons are very tall (up to 7–8 feet).
2. **The muscles and viscera** are proportionally large.
3. **Metabolism:** They present with hyperglycaemia reduced sugar tolerance and may be having glycosuria (due to oversecretion of STH and ACTH). There is increased BMR and increased sweating.
4. **Changes in other glands are similar** as seen in acromegaly.

ACROMEGALY

It is caused by hyperactivity of acidophil cells in the adult.

Characteristic Features

1. **Skeleton**
   - There is overgrowth of the two jaws, the malar bones, the supraorbital ridges, etc.
   - Enlargement of hands and feet (acral parts).
   - There is bowing of the spine (kyphosis). The anteroposterior diameter of the chest is increased.

   The skeletal changes lead to *gorilla*-like appearance of the patient.
2. **Subcutaneous tissues:** The subcutaneous tissues of the hands, feet, scalp, nose, lips and the skin increase in amount, producing deep furrows. Tongue is also enlarged due to same cause.
3. **Metabolism:** Blood sugar level increases leading to hyperglycaemia. There is reduced sugar tolerance and they may present with glycosuria (due to over secretion of STH and ACTH). There is increased BMR and increased sweating
4. **Viscera:** Organs concerned with metabolism are all enlarged, such as heart, lungs, liver, kidneys, pancreas, spleen, etc.

Fig. 70.14A: Patient of acromegaly: Prominent supraorbital ridges, frontal bossing with signs of prognathism (enlargement of jaw)

5. **Other endocrine glands**
   - *Thyroid:* It is enlarged and hyperactive, and may cause Graves' disease.
   - *Adrenal cortex:* It becomes hyperactive and enlarged.
   - *Thymus:* Enlarged.
6. **Reproductive functions**
   - *Gonads:* They are initially they are hyperactive and later they may atrophy (overwork and exhaustion). Almost all patients have increased production of lactogenic hormone.
   - In males, there may be diminished libido and sometimes impotence.
   - In females, they may develop sterility, menstrual disturbances, failure of breast to develop, persistent lactation (lactorrhoea).

Other manifestations are: Lantern jaw, papilloedema, and rhinorrhoea, deepening of voice, visual disturbances, drowsiness and lethargy, complete amenorrhoea, cutaneous pigmentation, concomitant presence of hypertension.

DWARFISM (Fig. 70.15)

It is caused by hypoactivity of the acidophil cells in the young.

Three types: (1) Lorain-Levy, (2) Brissaud, (3) Mixed.

Lorain-Levy Type (Infantilism)

Characteristic Features

1. Stunted growth (adult about 85 cm or 3 feet high.)
2. Sex organs and secondary sex characters do not grow. Hence, an adult man resembles a normal child.
3. Intelligence—normal and proportional to age.
4. Metabolism—normal.

Brissaud Type (Fat Body of Dickens)

The characteristic features are same as Lorain-Levy type plus there is excess deposition of fat in the body, round chubby face, no beard or moustache, sleepy and slothful nature.

Mixed Type

There are mixed histological nature and have the combined clinical manifestations, and may be called dyspituitarism. The subject may be fat and hairless, and yet may have large accessory nasal sinuses, prominent supraorbital ridges, and other stagmata of acromegaly. In some, dysfunction of acidophil cells may develop pressure symptoms on neighbouring structures and behaves like patient of dysfunction of chromophobe cells (hypopituitarism along with acromegaly or gigantism).

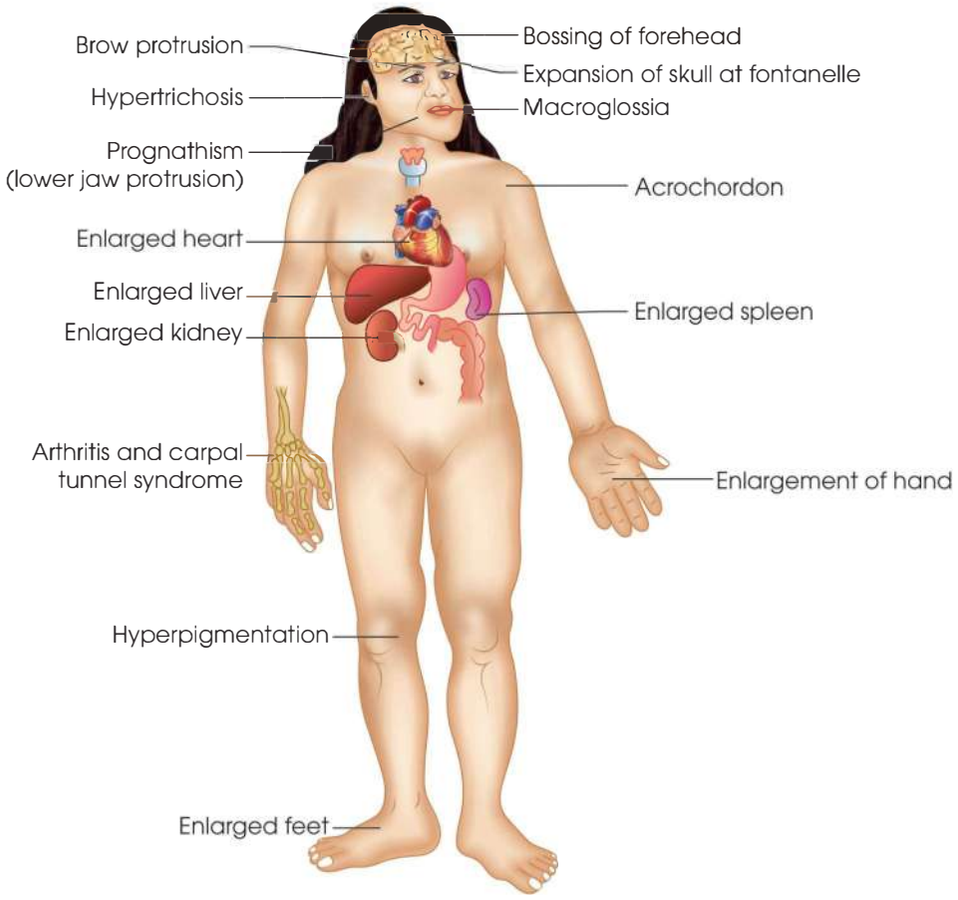


Fig. 70.14B: Features of acromegaly

Fig. 70.15: Dwarfism

ACROMICRIA

It is caused by hypoactivity of the acidophil cells in the adult. It is the anti-thesis of acromegaly. The bones of face, hands and feet are small and there is loss of hair and of sexual function. It is a very rare clinical condition.

Choh Hao Li (1913–1987): He was a US Biochemist of Chinese origin. In 1966 Choh Hao Li discovered that human pituitary growth hormone (somatotropin) is made up of a chain of 256 amino acids. In 1970, he synthesized this hormone.

THYROTROPHIC HORMONE OR THYROTROPIN OR THYROID-STIMULATING HORMONE (TSH)

1. It is a glycoprotein chiefly responsible for secretion of thyroid hormones. It is secreted by the thyrotrops of anterior pituitary. It is a glycoprotein with molecular weight of about 25,000. It has two sub-units α and β. The α unit consists 96 amino acids while β sub-units contains 110 amino acids.
2. **Action:** TSH exerts its action by increasing intracellular concentration of cyclic AMP in the follicular cells. It controls the growth and functional activities of the thyroid gland. Primary physiological action of TSH is to stimulate the release of thyroid hormone from the intra-follicular thyroglobulin. TSH is necessary for coupling of diiodotyrosine to form thyroxine (T_4).

3. **Synthesis:** They are synthesized from prepro-hormone which is transformed to prohormone. The sub-units α and β are synthesized under influence of separate mRNA. The synthesized TSH molecules are stored in thyrotrops cells.

It may be possible that anterior pituitary produces more than one type of thyrotrophin. According to Dobyns and his co-workers pituitary extracts from patients suffering from Graves' disease contain a substance especially capable of producing exophthalmos. This exophthalmos-producing substance (EPS) may not be a separate anterior pituitary hormone but an abnormal variety of TSH. Thyroid hormone which depresses the release of TSH also cures exophthalmos. In man, TSH in the blood is increased in myxoedema, cretinism, etc., but no exophthalmos occurs.

4. **Control of thyrotrophic hormone or thyrotropin or TSH secretion:** Thyrotropin secretion is under the control of hypothalamus and thyroxine level in the blood.

Hypothalamus: Stimulation of the hypothalamus by fine electrodes causes release of a tripeptide humoral factor known as thyrotrophin-releasing factor (TRF) which circulates through the blood stream (hypo-physeal portal system) and helps in the liberation of thyrotrophin from the anterior pituitary.

Control of TSH Output

There are at least two factors:

1. It is inhibited by TH acting directly on the pituitary cells, and
2. The basal levels of TH and TSH are determined by negative feedback mechanism. Any rise in TH depresses TSH output which in turn leads to a fall in TH output. Any fall in TH has the reverse effect. Minute injection of TH into the anterior pituitary or thyroid tissue transplanted there, causes a fall in TSH output. Thus, the negative feedback relationship tends to maintain plasma levels of TH and TSH constant (Fig. 70.16).

Control of TRF Output

Thyroxine Level in the Blood

The rate of the secretion of thyrotrophin is controlled by the thyroxine content of the blood. High thyroxine content in the blood inhibits and low thyroxine content in the blood stimulates secretion. Inhibition of thyro-trophin secretion by thyroxine might possibly be due to its effects both on anterior pituitary and hypothalamus. If the low thyroxine content persists for a prolonged period there will be continuous secretion of a large amount of thyrotrophin which causes thyroid hyperplasia.

Functions

a. It facilitates iodide uptake by follicular cells of thyroid gland.
b. It enhances coupling, organification and synthesis of thyroid hormones.
c. It has stimulatory effect on release of thyroid hormone.
d. It enhances blood flow to the thyroid gland.

Adrenocorticotrophic Hormone (ACTH) or Adrenotrophic Hormone or Adrenocorticotrophin

1. It is secreted by basophil cells under the control of CRF from the hypothalamus, and is subject to indirect (and possibly direct) negative feedback mechanisms involving cortisol. It is polypeptide in nature consisting of 39 amino acid residues and has molecular weight of about 4,500.
2. **Synthesis:** It is synthesized as a preprohormone in the corticotrophs as a larger molecule. This larger molecule pro-opiomelanocortin cleaves to form ACTH and β lipotopin.
3. ACTH controls the growth of adrenal cortex and the synthesis of cortisol and, is therefore, essential to life.
4. **Mechanism of action:** The action of ACTH on adrenal cortex is mediated through cyclic AMP. ACTH in normal subjects produces the same effects as cortisone.
5. **Regulation of secretion:** The hypothalamus is primarily concerned with the synthesis and release of ACTH from the anterior pituitary as the hypothalamus is the area where the CRF is synthesized and stored and released when necessary for activating the anterior pituitary. Besides this, the hypothalamus is the area where the feedback receptors, sensitive to corticoids and to ACTH are predominantly situated. Stress also stimulates ACTH secretion.

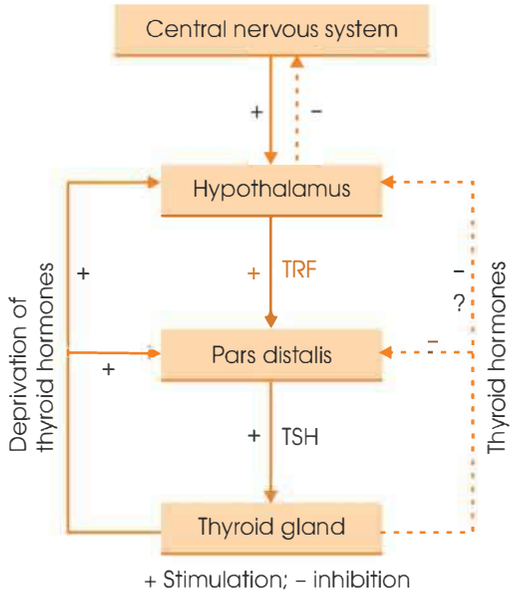


Fig. 70.16: Diagram showing the relationship between hypothalamus, pars distalis and thyroid gland

6. **Function:** It stimulates synthesis of cortisol and other steroid hormones. It controls secretion of cytokines from lymphocytes and thus exerts it influence on immunity and has intrinsic melanocytes stimulating hormone activity.

GONADOTROPHIC HORMONES (GTH) OR GONADOTROPHINS: FSH AND LH

1. The basophil cells secrete gonadotrophins which control the growth and activity of the gonad and indirectly all the other processes connected with it (i.e. growth of sex organs, secondary or accessory sex characters and in females, the phases of menstrual cycle, pregnancy, lactation, etc.).
2. These are two gonadotrophins:
   a. Follicle-stimulating hormone (FSH)
   b. Luteinising hormone (LH) or interstitial cell-stimulating hormone (ICSH).
3. The two gonadotrophic hormones are glycoprotein in nature. The molecular weight of LH is 28,000 and FSH is 38,000. They have α and β units. The unit is nonspecific while β is specific for LH and FSH. FSH is made up of 111 amino acids and LH consists of 121 amino acids.
4. Synthesis: They are produced from same gonadotroph cells. They are separate gene coding for synthesis of α and β units.
5. Control of gonadotrophin secretion: Gonadotrophin secretion is under the control of (1) hypothalamus, and (2) sex hormones.
   a. *Hypothalamus:* Hypothalamic nuclei are known to secrete specific releasing factors for the release of specific gonadotrophic hormones. Luteinising hormone-releasing factor (LRF) for LH (ICSH) and follicle-stimulating hormone-releasing factor (FSH-RF) for FSH are secreted from hypothalamus when they are necessary.
   b. *Sex hormones:* The concentration of sex hormones in blood regulates secretion of gonadotrophins. A high concentration inhibits, whereas a low concentration stimulates secretion.
6. They exert there action by increasing cyclic AMP concentration in the target cells.
7. Functions of gonadotrophins.

Functions of FSH

a. **In females:** Increases the number and size (maturation) of graafian follicles and prepares them for ovulation. After the menopause, the production rate of FSH is increased approximately 15-fold.
b. **In males:** Stimulates spermatogenesis. In old age in the male (as testicular function wanes), the production of FSH increases (due to its action on both male and female gametes, this hormone is also called gametokinetic factor).

Functions of LH

a. **In females:** It regulates the complete development of the ovarian follicles to secretory stage and secretion of oestrogen. The rupture of the follicles and ovulation occurs due to combined action of FSH and LH. It is responsible for appearance, growth and persistence of corpus luteum. In the ovary, LH can stimulate the non-germinal elements to produce androgens, testosterone, etc., giving rise to hirsutism. After menopause a 5-fold increase of LH occurs.
b. **In males:** Luteinizing hormone stimulates the development and functional activity of Leydig (interstitial) cells, and consequently, the production of testicular androgen. Its administration, therefore, produces effects in the organism (except on the testis) similar to those which follow administration of testosterone.

LACTOGENIC HORMONE OR PROLACTIN OR LUTEOTROPHIC HORMONE (LTH) OR MAMMOTROPHIC HORMONE (MH) OR LUTEOTROPHIN

1. It is secreted during pregnancy and lactation in women by acidophil 'pregnancy' cells. It is a peptide hormone, isolated in pure form and contains tyrosine, tryptophan, cystine, methionine, arginine and sulphur.
2. It is made of 198 amino acids and has a molecular weight of 23,000. It is a polypeptide hormone.
3. Synthesis: It is formed from preproprolactin which is converted to preprolactin and finally to prolactin.

Control of Prolactin Secretion

The pituitary prolactin secretion is regulated by endocrine neurons in the hypothalamus. The neurosecretory tuberoinfundibulum (TIDA) neurons of the arcuate nucleus secrete dopamine which is a prolactin inhibitory hormone acts on the D_2 receptors of lactotrophs, and thereby inhibit prolactin secretion. Thyrotropin-releasing factor (thyrotropin-releasing hormone) has a stimulatory effect on prolactin release. TRH is mainly responsible for stimulating prolactin secretion. Prolactin releasing factor, TRH, breast feeding, stress, sleep, etc. enhance prolactin secretion while dopamine, prolactin, somatostatin and GABA inhibit secretion of prolactin.

Reflex Stimulation of Prolactin

Nervous system: Suckling of the baby generates afferent impulses which reflexly stimulate prolactin secretion through hypothalamus (Fig. 70.17). Suckling by the infant stimulates the supraoptic nucleus and paraventricular nuclei in the hypothalamus, which signals to the posterior pituitary gland to produce

oxytocin. Oxytocin stimulates contraction of the myoepithelial cells surrounding the alveoli, and this causes milk to flow through the duct system and be released through the nipple. It is believed that suckling inhibits the median eminence to secrete prolactin-inhibiting factor (PIF) and thus prolactin secretion from the anterior pituitary is increased. Only minute quantities are produced by lactotrophs and released into blood stream. It may regulate its own secretion by a short negative feedback control system.

Evidence: Although nerves play an important role, yet they are not essential, because, denervation of the mammary glands does not stop lactation. Even a grafted mammary gland secretes.

Action of Prolactin

Prolactin acts via JAK-STAT signal induction pathway and influence its effects via cellular actions. It stimulates transcription and increases mRNA synthesis which eventually facilitates synthesis of specific proteins which are required for formation of casein, lipid and lactose.

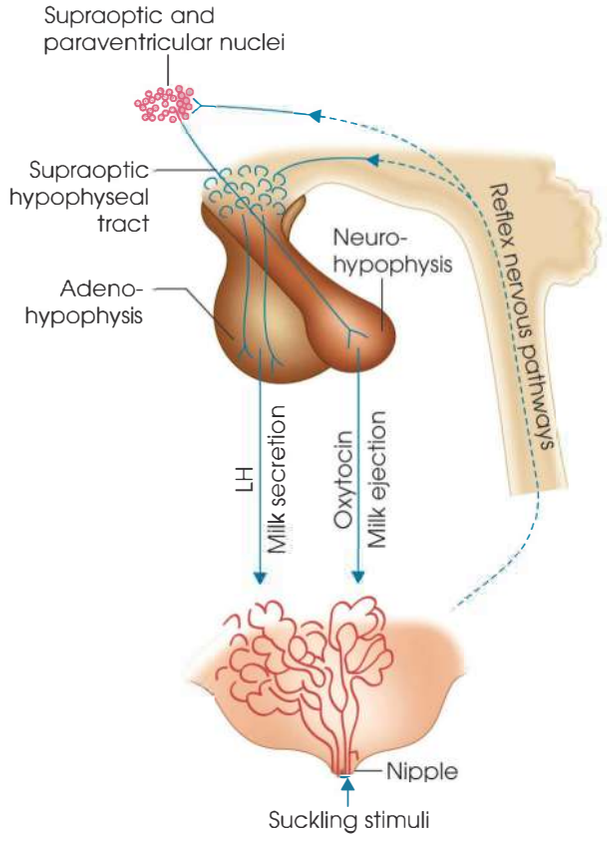


Fig. 70.17: Diagram showing some of the neural and hormonal components involved in controlling lactation (after Harris). Note the luteinizing hormone (LH), follicle stimulating hormone (FSH), and human chorionic gonadotropin (hCG), via control of oestrogen, progesterone, prolactin and growth hormone production favours galactopoiesis

Physiological Functions

A. *Breast Development*

Prolactin (LTH) is responsible for lactation in the postpartum women, the breast having been prepared by oestrogen and progesterone. It helps in initiating (lactogenesis) rather than maintaining milk secretion. Growth or somatotrophic and thyroid hormones help in the maintenance of the secretion of milk (galactopoiesis). The level of prolactin increases during the night. Oestradiol stimulates prolactin release whereas L-dopa inhibits it by promoting the discharge of PIF.

a. It stimulates slightly the proliferation of the glandular elements of the mammary glands during pregnancy and thus helps to complete the development of breasts.
b. If glucocorticoids and insulin as well as prolactin are present during the period of cell division, casein production is observed. Prolactin, insulin and glucocorticoids in combination will induce the synthesis of lactose synthetase system.

B. *Effect on Reproduction*

It helps in maintenance of secretory activity of corpus luteum and secretion of the hormone, progesterone, due to combined action of LH and prolactin.

C. *Effect on GIT*

Prolactin produces growth of oesophagus with histological evidence of epithelial proliferation (human chorionic gonadotrophin) and desquamation. It has metabolic action similar to hCG and HPL (human placental lactogen).

D. *Effect on Milk Secretion*

Ejection of milk: Suckling of the baby not only stimulates prolactin secretion but also stimulates secretion of oxytocin. The afferent impulses after stimulation of the nipple by suckling of the baby reach the supraoptic nuclei of the hypothalamus. From the hypothalamus through the nervous tract the posterior pituitary is stimulated. Oxytocin is released. It circulates in the blood stream, reaches the mammary glands and produces contraction of the myoepithelial cells and helps in the ejection of milk (Fig. 70.17).

E. *Lipotrophin, Lipolytic Hormone (LPH), Fat-mobilising Agent*

Lipotrophin (β-LPH) has been isolated as an adenohypophyseal hormone having chemical and biological characteristics similar to ACTH or MSH, but certain differences exist. All the three hormones have seven amino acids common to their chemical structures and they all stimulate chromatophores. ACTH and β LPH cause lipolysis of rabbit fat pad and β-LPH is named for such lipolytic activity.

CENTRAL AND PERIPHERAL ORGANIZATIONS OF ANTERIOR PITUITARY HORMONES

Figure 70.18 represents of central and peripheral organizations of anterior pituitary hormones. The hypothalamus controls the activity of pars distalis through individual releasing factors corresponding to different trophic hormones. So, there are RF, for gonadotropins and TRF and CRF for the trophic hormones. On the other hand, the hormones elaborated by different endocrine organs named above have inhibitory influence over both the anterior pituitary and hypothalamus in releasing the pituitary trophic hormones and hypothalamic releasing substances respectively. Thus, under normal conditions a perfect optimal endocrine balance in maintained in the body and is detailed in Fig. 70.18.

Mechanism of Releasing Factors

Commonly tissue content of a hormone or hormone level in circulation maintains a balance between rates of synthesis and release of the hormone. Decrease in circulatory hormone levels will influence the hypothalamic nucleus to secrete releasing factor and *vice versa*. An increase in hypothalamic content of releasing factor represents increased synthesis and secretion of the corresponding hormone in the anterior pituitary and this hormone via circulation influences the target gland.

DISORDERS OF PARS DISTALIS (Flowchart 70.1)

Introduction

The following facts will be helpful to understand the clinical manifestations of pituitary disorders

Lesions may be of two types:

1. Hypoactive (degenerative)
2. Hyperactive (tumour, irritation, etc.).

Lesions may affect the:

1. Acidophil cells
2. Basophil cells
3. Chromophobe cells
4. Total gland.

Tumour of a particular type of cell will cause the signs of hyperactivity of those cells plus either the signs of hyperactivity of other neighbouring cells (due to irritation) or the signs of their hypoactivity (degeneration due to pressure).

Anterior lobe, being the leader of endocrine orchestra, any disorder of this gland will lead to

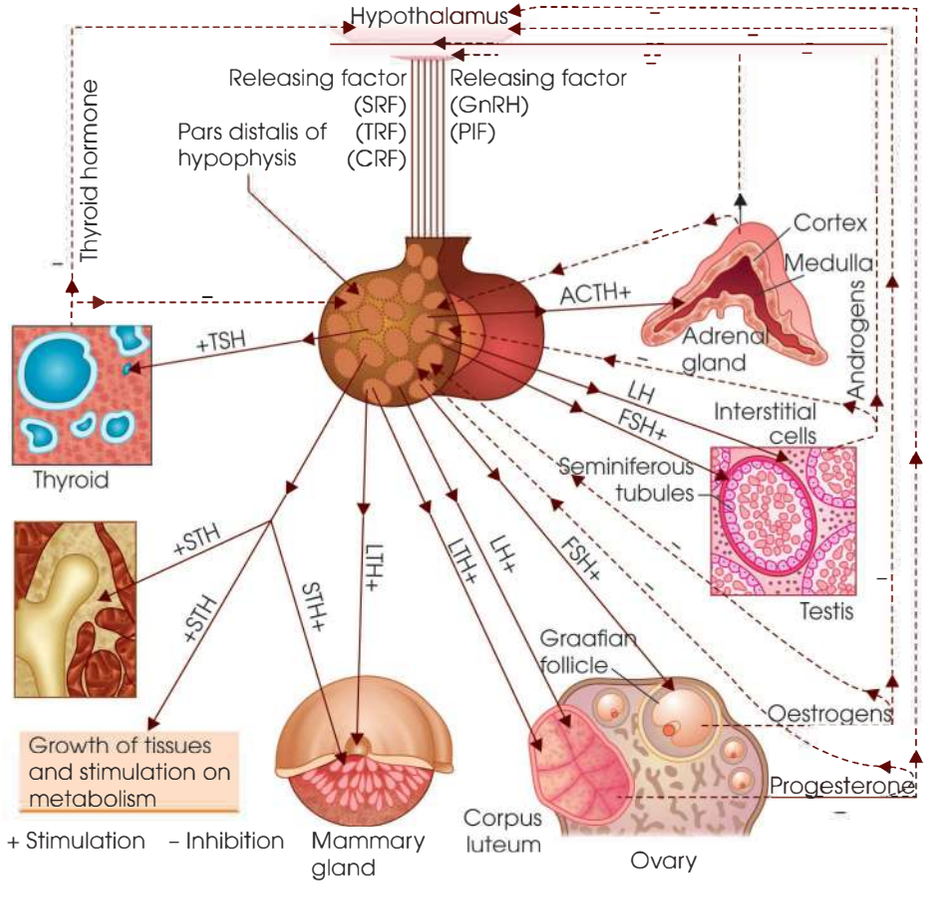
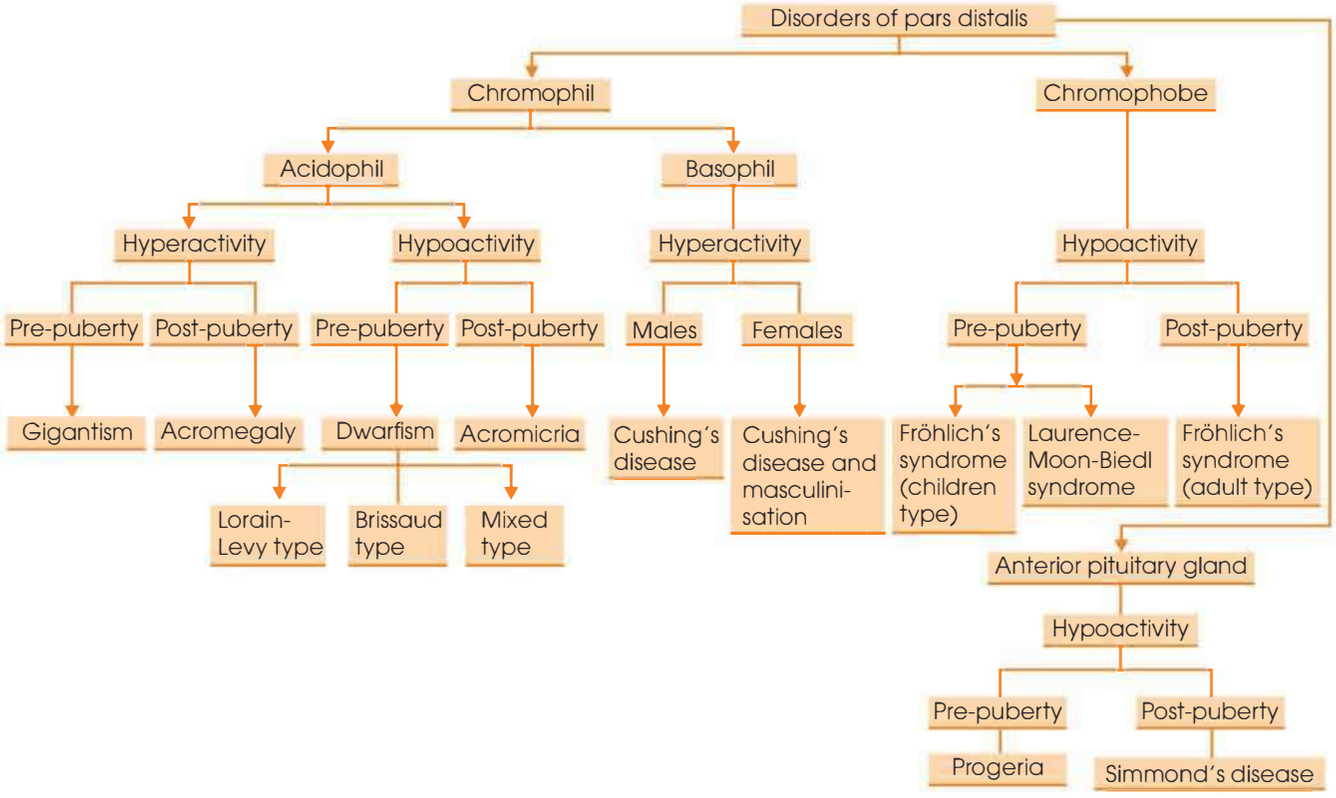


Fig. 70.18: Diagrammatic representation of central and peripheral organizations of anterior pituitary hormones

Flowchart 70.1: Disorders of pars distalis



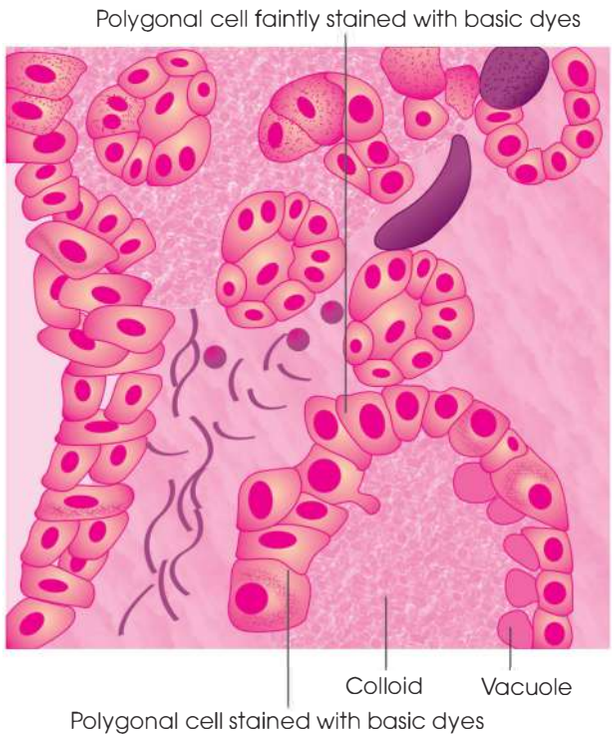


Fig. 70.19: Diagrammatic representation of pars intermedia showing basophilic cells and vesicles with colloid

corresponding changes in the other endocrine glands and the ultimate result will be a pluriglandular dysfunction.

A hyperactive condition may ultimately end in corresponding hypoactive state, possibly due to exhaustion and degeneration.

Hyperactivity lesion: Cushing's disease (pituitary basophilism): Harvey Cushing found out a disease in 1932. This disease is the basophil adenoma of the pituitary gland and is a primary pituitary tumour. This disease was named as Cushing's disease after Harvey Cushing. Similar clinical changes are also found in adrenal tumour and it is called Cushing's syndrome. The signs of hyperactivity develop in this disease due to mechanical pressure on the active cells.

Cushing's Disease

There is excessive deposition of fat over the supracondylar fossae, face (rounded or moon face in a well-developed case), back of the neck and abdomen. Extremities are usually spared. Fatty deposits are tender and painful. Purplish striae are found over the abdomen, thighs, etc. This is due to loss of protein matrix. Women are affected 4 times more than men.

Clinical signs and symptoms observed in this disease are:

1. Masculinisation with growth of beard, moustache, etc.
2. Asthenia and wasting of the muscles of the limbs.
3. Obesity of the trunk but not of the limbs.
4. In males, there is excessive hair growth (hirsutism).

5. Osteoporosis of bones due to decalcification and loss of protein matrix.
6. Hypertension in a few patients.
7. Mental derangement.
8. In males, impotence with atrophy of testis. In females, amenorrhoea, sterility, etc.
9. Hyperglycaemia and glycosuria.
10. Retention of sodium and diminution of potassium level in the plasma.
11. Eosinopenia, lymphocytopenia, and polycythaemia.
12. Increased excretion of 17-oxogenic steroids and 17-hydroxycorticosteroids.

DYSFUNCTION OF THE CHROMOPHOBE CELLS

It is caused by a tumour of the inactive chromophobe cells. Due to mechanical pressure on active cells produces signs of both irritation and hypoactivity. Hence, the following effects are observed in these patients.

In children

Fröhlich's syndrome (adiposogenital dystrophy): The characteristic features of the syndrome are:

1. Stunted growth (dwarfism).
2. Idiotic.
3. Sexual infantilism.
4. Generalized obesity.

Laurence-Moon-Biedl syndrome (often familial): This is same as Fröhlich's syndrome (children type) plus in addition, the patients present with (a) polydactylism, and (b) retinitis pigmentosa.

Clinical Features in Adults—Fröhlich's Syndrome (Adult Type)

In males

1. Adiposity of feminine distribution.
2. Mental disposition and appearance resemble females.
3. Degeneration of sex.
4. Hands and feet are small and pretty, fingers delicate and tapering.
5. Skin of face and body is smooth and hairless.

Harvey Williams Cushing was an American neurosurgeon. He was a pioneer of brain surgery and well known as father of modern neurosurgery. He was the first person to describe Cushing's disease.

1869–1939

Reference: Ellis H. 'Harvey Cushing: Cushing Disease'. Journal of perioperative practice 2012;22(9):298–9.

In females

1. Extreme adiposity.
2. Degeneration of sex.

TOTAL DYSFUNCTION OF THE PARS DISTALIS

Hyperactivity: Not known as a pure clinical type. Often appears in a mixed form.

Hypoactivity (degenerative changes)

- In children: Progeria.
- In adults: Simmonds' disease.
  1. *Progeri:* Appearance of early senility—often seen in pituitary dwarfs.
  2. *Simmonds' disease:* It is due to degeneration of the anterior lobe of the pituitary.

Clinical signs and symptoms include:

1. *Cachexia:* Loss of weight and shrunken appearance.
2. Sexual degeneration: amenorrhoea, sterility, loss of axillary and pubic hairs, impotency (in males), etc.
3. *Asthenia:* Extreme weakness.
4. *Anorexia:* Loss of appetite.
5. *BMR:* Lowered.
6. Mental deterioration.
7. *Atrophy of viscera:* Gonads, thyroid, adrenal cortex, etc. degenerate.
8. Anaemia.
9. Hypoglycaemia.
10. Diminished urinary excretion of 11-oxycorticoids, 17-oxogenic steroids and gonadotrophins. PBI in the blood falls.

PARS INTERMEDIA

The pars intermedia is anatomically associated with the neural lobe and is a thin strip of tissue, separated from the anterior lobe by the interglandular cleft. It invests the pars nervosa and with it, forms the posterior lobe. It develops from the posterior wall of Rathke's cyst.

In man, numerous anastomoses, between superior and inferior hypophyseal arteries, traverse the pars intermedia and it receives some supply from a rich capillary network. The plexus is continuous with the capillary bed of the neural lobe and it possesses some connections with sinusoids of the pars distalis.

Nerve fibres enter the pars intermedia from the neural lobe and ramify among its cells, originated from the hypothalamus. These nerves appear to have mainly inhibitory effect.

Melanocyte-stimulating Hormone

The melanocyte-stimulating principles are distinct for the MSH activity of ACTH and have been referred to

α- and β-MSH. α-MSH is a single chain polypeptide of 13 amino acids and has a C-terminal amide and N-terminal acetyl. As the amino acid sequence of β-MSH is identical to the N-terminal 13 amino acids of ACTH; the ACTH has a little melanin-dispersal activity.

Functions

The pars intermedia secrete a simple polypeptide hormone, called melanocyte-stimulating hormone (MSH) or intermedia which affects the synthesis of melanin. Hydrocortisone and cortisone inhibit the secretion of MSH. Epinephrine and norepinephrine inhibit the action of MSH.

An increase in production of MSH accounts for the increased pigmentation seen in Addison's disease, in some cases of thyrotoxicosis, and in pregnancy. Pigmentation that occurs in human suffering from deterioration for the adrenal cortex (Addison's disease) is mainly due to release by the pituitary gland of excess blood ACTH and urinary MSH. During human pregnancy, the darkening of the skin may result from increased release of one hormone or both ACTH and MSH. Temporary darkening of the skin takes place in humans on administration of MSH.

Pars Tuberalis or Infundibularis

The pars tuberalis develops from the top of Rathke's pouch or cyst. Like the pars intermedia, the pars tuberalis is adjacent to and continuous with the pars distalis. The pars tuberalis is about 25 to 60 nm in thickness and forms a sleeve around the infundibular stalk. The thickest portion is on the anterior surface of the stalk. The pars tuberalis is traversed by the major arterial supply for the pars distalis and the hypothalamo-hypophyseal venous portal system.

STRUCTURE AND FUNCTIONS OF NEUROHYPOPHYSIS

Anatomically the posterior lobe includes the pars nervosa and the pars intermedia. But physiologically the term 'posterior lobe' commonly means the pars nervosa, which is the chief part of the neurohypophysis.

According to the terminology recommended by the International Commission on Anatomical Nomenclature, the neurohypophysis is made up of:

1. Pars nervosa (lobus nervosus): The true posterior lobe.
2. Infundibulum: Pituitary stalk.

PARS NERVOSA

Pars nervosa consists of the following:

Pituicytes: The pituicytes are chief cells and contain fusiform or polygonal supporting neuroglial cells with delicate processes and make up bulk of the gland. They are large, branching, spindle-shaped cells containing yellow-brown granules of neurosecretion due to presence carrier mucoprotein, stained with chrome-alum haematoxylin. The pituicytes consist of adenopituicytes, micropituicytes, fibropituicytes and reticulopituicytes and do not actually secrete any hormone. They also contain non-medullated nerve fibres, mast cells, Herring (hyaline) bodies which are densely staining accumulations of stored neurosecretory substance; and blood vessels (Fig. 70.20).

Pituitary stalk or infundibulum consists of clusters of numerous large sinusoidal vessels which are surrounded by neuroglial tissue, stained with HE. From the hypothalamus neurosecretory cells contain Nissl substance and smaller neurosecretory granules in the axons of the cells (Fig. 70.21); stained with chrome alum haematoxylin.

Blood Supply

The neural lobe (pars nervosa) gets blood supply from inferior hypophyseal arteries which originate from the internal carotid arteries. The vessels while ending in the pars nervosa forms a fine mesh of capillary network.

Nerve Supply

Two tracts of non-medullated nerve fibres (containing at least 1,000,000 fibres in man) arise from the hypothalamus and supply the pars nervosa (Fig. 70.22). They are as follows:

Tuberohypophyseal tract arises from the median eminence of the tuber cinereum which is the protuberance at the floor of the third ventricle near the root of the stalk, passes along the posterior wall of the stalk and enters the gland.

Supraoptic hypophyseal tract arises from the supraoptic and paraventricular nuclei in the hypothalamus, passes down the anterior wall of the stalk, enters the pars nervosa and ends round the blood vessels and cells of

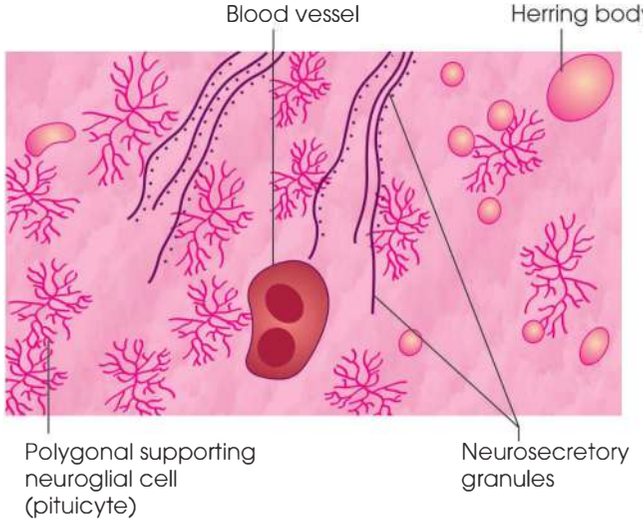


Fig. 70.20: Pars nervosa with nuclei of the pituicytes, neurosecretory granules and Hérring (hyaline) body

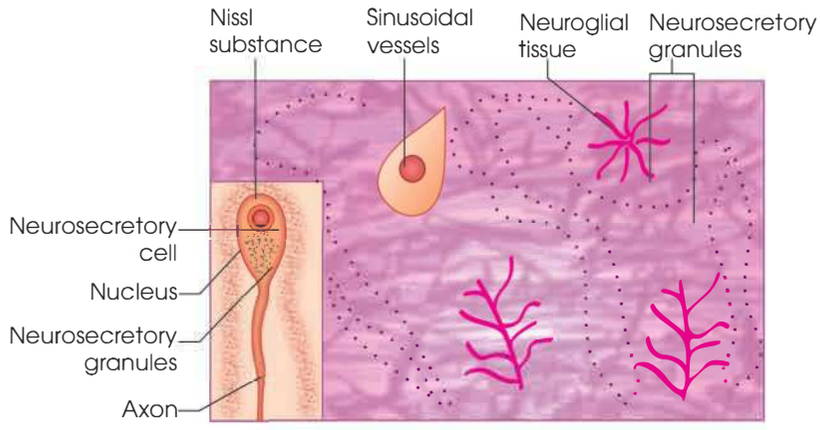


Fig. 70.21: Pars nervosa with nuclei of the pituicytes, neurosecretory granules and Herring (hyaline) body

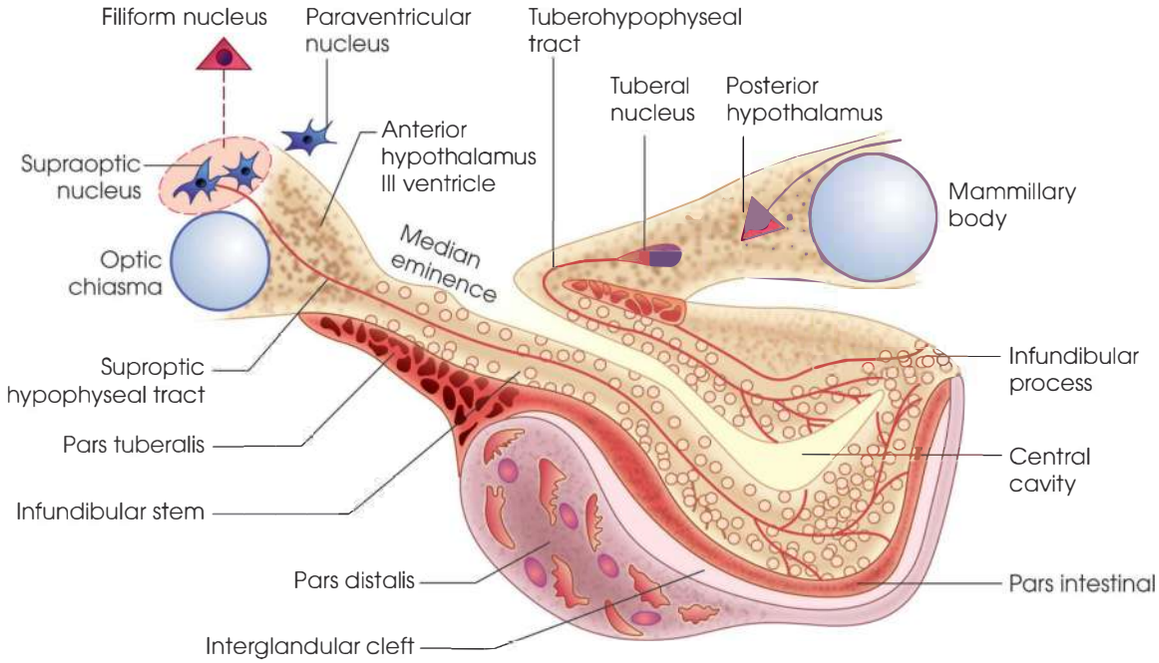


Fig. 70.22: Diagrammatic representation of the hypophysis cerebri and its connections with the hypothalamus (animal)

the gland. A few fibres have been traced to the pars intermedia and fewer still to the pars distalis or pars anterior.

Synthesis, Transport and Storage of the Neurohypophyseal Hormones in the Hypothalamo-hypophyseal System

Vasopressin and **oxytocin** are the two neurohypohyseal hormones. These hormones have been extracted and isolated from the hypothalamic nuclei in higher concentrations than those present in other areas. Both the supraoptic and paraventricular nuclei contain distinctive dense granules.

A supraoptic nucleus mainly forms vasopressin (ADH) while the principal hormone synthesised in the paired paraventricular nuclei and to a lesser extent in the paired supraoptic nuclei is oxytocin. Posterior pituitary hormones are not synthesised in the gland itself, but these are synthesised in the supraoptic nuclei and paraventricular nuclei of the hypothalamus. The hormones are then transported from their origin to the posterior pituitary through axons of the hypothalamo-hypophyseal tracts and stored in association with 2 proteins—neurophysin I (mol wt of 19,000) and neurophysin II (mol wt of 21,000). Either vasopressin or oxytocin can be bound by each neurophysin. When liberated in the blood, vasopressin and oxytocin are transported to the target organs like kidneys, liver, mammary glands, etc. in association with serum proteins (Fig. 70.23).

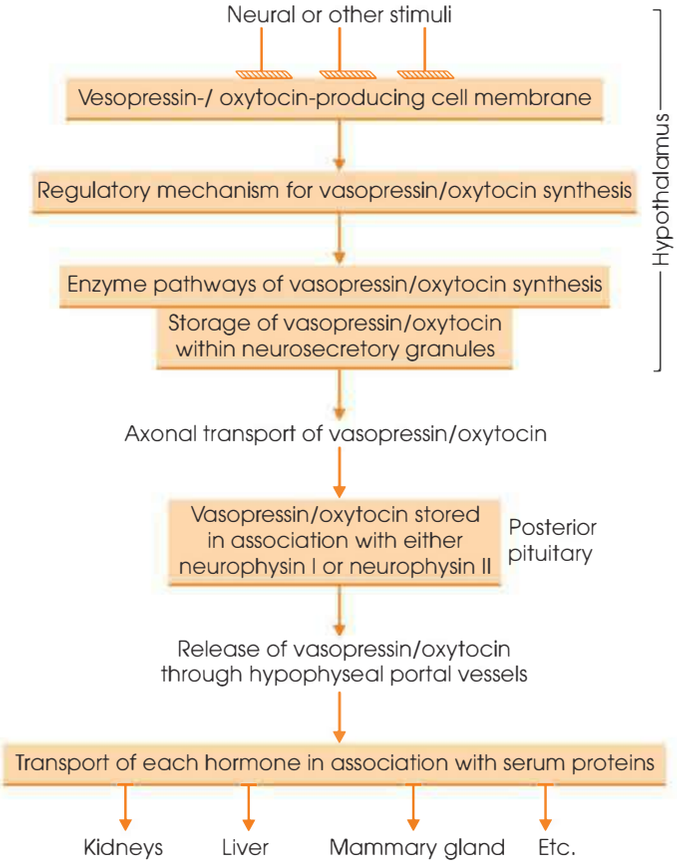


Fig. 70.23: Scheme showing intermediate stages which are involved in the neurosecretory function of the vasopressin-/ oxytocin-producing cells of the mammalian hypothalamo-neurohypophyseal complex

If the posterior pituitary is removed keeping its hypothalamo-hypophyseal tracts intact then hormonal functions remain unaffected and the nerve tracts show accumulations of neurosecretory materials.

Chemistry

Vasopressin and oxytocin, the two secretory hormones of the neurohypophysis, are octapeptide because they consist of 8 different amino acid residues arranged with a five-member S-S-bonded ring and a tail composed of 3 amino acids. The amino acid sequence of oxytocin differs from that of vasopressin in two locations (Figs 70.24 and 70.26), one in the peptide ring (position 3) and one in the tripeptide tail (position 8). There are seven naturally occurring principles in neurohypophysis, which are arginine vasopressin, lysine vasopressin, arginine vasotocin, oxytocin, isotocin (4-serine, 8-isoleucine oxytocin), glumitocin (4-serine, 8-glutamine oxytocin), and mesotocin (8-isoleucine oxytocin).

VASOPRESSIN (PITRESSIN)

Vasopressin has got antidiuretic property and increases facultative reabsorption of H_2O and thus reduces the

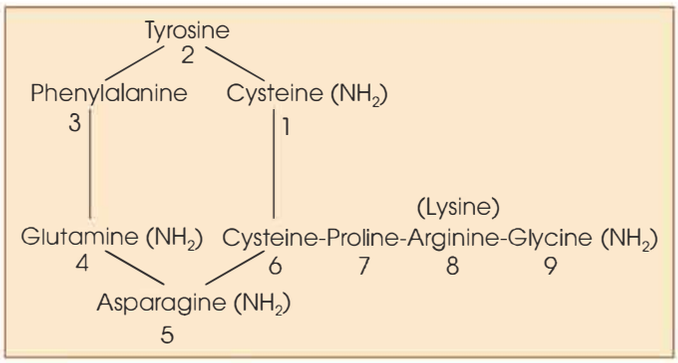


Fig. 70.24: Scheme showing the arrangement of amino acids in a molecule of arginine (beef) vasopressin and lysine (hog) vasopressin

volume of urine formed. Hence, vasopressin is now commonly called antidiuretic hormone (ADH). Vasopressin raises blood pressure by its vasopressor effect on peripheral blood vessels.

Chemistry

It is octapeptide (Fig. 70.26). Vasopressin has molecular weight of about 1100. It contains nine amino acids.

Synthesis

It is synthesized in magnocellular cells of paraventricular nuclei and supraoptic nuclei of hypothalamus. It is formed from preprohormone that is prepropressophysin which form prohormone and finally vasopressin. Neurophysin I carries code for synthesis of oxytocin and neurophysin II for vasopressin.

Regulation of Secretion

Vasopressin (ADH) is released in response to stress, and also in response to dehydration. The factors that increase ADH secretion are increased plasma osmolarity, pain, nausea, emotion, hypoglycaemia, stress and decreased blood pressure and blood volume via renin angiotensin aldosterone mechanism. The factors which decrease ADH secretion are decreased plasma osmolarity, cortisol, ANP, thyroxine, increased extracellular fluid volume, etc.

Units of Vasopressin

The international standard of vasopressin has an activity of 2000 units per gm and the unit is defined as the activity present in 0.5 mg of the dried material.

Mode of Action

1. It stimulates reabsorption of water by the distal convoluted and the collecting renal tubules and thus regulates urine volume. This effect is mediated by insertion of water channels that is aquaphorin-2; into the apical membrane of distal convoluted tubule and collecting duct epithelial cells. Vasopressin acts on

renal collecting ducts via V2 receptors to increase water permeability (it is a cAMP-dependent mechanism: ADH increases the concentration of cyclic AMP in the renal epithelium and its antidiuretic action is mediated through cyclic AMP), which leads to decreased urine formation. The net effect is increases in blood volume and arterial pressure.

2. The receptors for ADH are of two types: V1 and V2. V2 receptors are located in the tubules of the kidney while V1 receptors are located in smooth muscle of blood vessels. ADH which binds to V1 receptors on vascular smooth muscle produces vasoconstriction via the IP_3 signal transduction pathway increasing the arterial pressure. Under physiological conditions the normal concentrations of ADH are lower than its vasoactive range to produce vasoconstrictor effect.
3. It increases urea permeability of the inner medullary portion of the collecting duct and this facilitates urea reabsorption into the medullary interstitium as it moves across the concentration gradient created by water removal from the cortical and outer medullary collecting duct.

Control of the Secretion of Vasopressin (ADH)

1. **Water deprivation:** Moderate or severe dehydration causes increased secretion of vasopressin. In response to water deprivation and to maintain the total plasma volume, vasopressin is liberated from the neurohypophysis.
2. **Plasma volume:** When a large quantity of water is taken, blood becomes diluted and its osmotic pressure falls. This acts through hypothalamus and reduces the secretion of the hormone. Consequently, less water is reabsorbed, urine volume increases and the excess water is got rid of. On the other hand, in conditions of dehydration, the concentrated blood with raised osmotic pressure stimulates the secretion of the hormone by acting on the osmoreceptors, present in the supraoptic nuclei of the hypothalamus and thus increases reabsorption of water. So that, urine volume is reduced and more water is conserved in the body. In such conditions vasopressin may even escape in the urine. Thus, the secretion of this hormone is adjusted according to the water requirements of the body.
3. **Plasma crystalloid osmotic pressure:** Raised crystalloid osmotic pressure of the blood produced either by water deprivation, or increased chloride, urea or glucose concentration in the blood increases secretion of ADH. Lowered crystalloid osmotic pressure produces diuresis by inhibiting the secretion of ADH.
4. **Role of atrial receptors:** Stimulation of atrial receptors causes inhibition of secretion of vasopressin and thus urine flow is increased.
5. **Haemorrhage and other changes in blood volume:** Decrease of blood volume due to haemorrhage causes release of vasopressin. Haemorrhage being as little as 10% of blood volume causes an effect of inhibition of water diuresis due to an increase in the plasma vasopressin level (Fig. 70.25). This response depends upon the degree of blood loss.
6. **Other factors:** Emotional and physical stress, electrical stimulation, nicotine and morphine increase ADH secretion. Alcohol inhibits ADH secretion.

Actions (with a High Dose Level)

1. **On blood vessels and blood pressure:** Constriction of arterioles and capillaries in animals but only of capillaries in man. Generally, it raises blood pressure. But in human beings often a fall is noticed. The fall is due to cardiac depression. The portal venous pressure is reduced due to constriction of the splanchnic vessels.
2. **On heart:** Rate is reflexly reduced due to high blood pressure. Coronary vessels constricted.
3. **On respiration:** Hyperpnoea with occasional apnoea. This is due to changes in blood pressure which reflexly acts on the respiratory centre.
4. **On kidneys:** Due to renal vasoconstriction, urine volume is reduced. In this way it also acts as an antidiuretic.
5. **On muscles:** The muscular walls of the urinary bladder and ureter are stimulated.
6. The intestinal muscles contract and movements of stomach, **large and small intestines** are increased.
7. **Metabolism:** It produces glycogenolysis, hyperglycaemia and glycosuria. Sugar tolerance is reduced. The effect is only a secondary one.

Under physiological conditions, posterior pituitary secretes only small amount of vasopressin which regulates the urine volume only and has no vascular effects. ADH shows pressure effects only at pharmacological dose level, concentration so high that has not been observed in plasma any time.

Clinical: Diseases of the posterior pituitary, hypothalamus or injury to the nerve tracts of the gland produces a condition in which large amount of very dilute urine is produced. The condition is called diabetes insipidus.

Diabetes insipidus is the syndrome which results from the failure of the neurohypophyseal system to produce or to release a quantity of ADH (vasopressin) sufficient to bring about the normal homeostatic renal conservation of free water. The hereditary variant of nephrogenic diabetes insipidus can be caused by mutations in the AVPR2 or AQP2 gene. Both of these genes regulate the production of proteins which determine water excretion in urine. This syndrome is also called vasopressin-sensitive diabetes insipidus to distinguish it from the nephrogenic diabetes insipidus and is characterized by diuresis—up to 28–30 liters of urine per day. Subcutaneous administration or nasal instillation of posterior pituitary extract may control the disease.

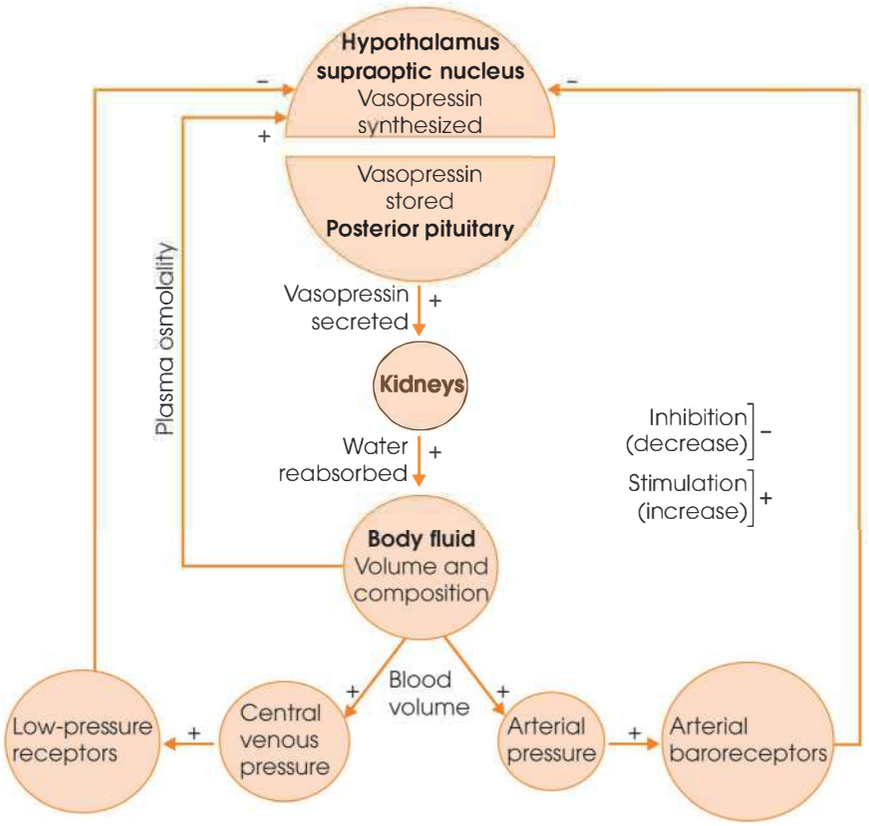


Fig. 70.25: Schematic diagram shows control of vasopressin secretion by plasma osmolality and blood volume (after Share, 1968)

OXYTOCIN (PITOCIN)

It is octapeptide (Fig.70.26). Molecular weight of oxytocin is about 1000.

Source

It is an oligopeptide consisting nine amino acids.

Synthesis

It is synthesized in the paraventricular cells of hypothalamus. It is secreted into posterior pituitary after synthesis.

Unit of Oxytocin

One unit of oxytocin is equivalent to the activity of 0.5 mg of the standard dried posterior lobe, as tested on an isolated guinea pig's uterus under standard conditions. A good preparation may have 225 units per mg. A dilution of 1 in 550 million causes strong contraction of the uterus.

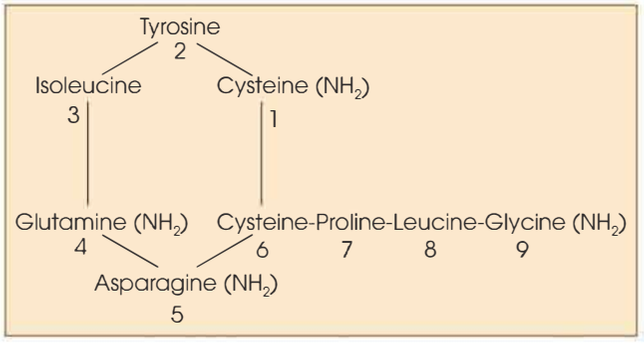


Fig. 70.26: Scheme showing the arrangement of amino acids in a molecule of oxytocin

Regulation of Secretion

Suckling reflex during breast feeding and cervix dilatation during parturition influences oxytocin secretion.

Control of Secretion of Oxytocin

Hypothalamus through supraoptic hypophyseal tracts controls the secretion. It forms the hypothalamo-neurohypophyseal unit.

The mechanism of secretion and the neurosecretory mechanism is decribed as follows:

Key Points

Oxytocin Release during Lactation

1. The major stimuli for release of oxytocin are (i) sucking and (ii) distension of cervix and vagina. Increased milk ejection following administration of oxytocin does not cover increased milk secretion but rather ejection of milk already present in the mammary glands.

2. Oxytocin level is increased after stimulation of nipple by suckling of the baby. Oxytocin is released into the systemic blood stream which causes contraction of the myoepithelial cells surrounding the alveoli of the mammary glands and helps in the ejection of accumulated milk.
3. Tactile stimuli evoked by suckling and milking young from temperature and pressure receptors in the nipple are conducted via afferent nerve fibres to the central nervous system. These impulses compete with those from inhibitory centres for the final common path whose cell bodies are the para-ventricular nuclei of the hypothalamus (Fig. 70.27).

Role of Oxytocin in Labour

Labour is a complicated process which depends upon softening and dilatation of the cervix, loosening of pelvic ligaments and contraction of abdominal muscles. There is no effect of oxytocin in these events. But it has been found that there is an increase of blood levels of oxytocin increases during delivery. The frequency and duration of contraction in myometrial cells of the uterus are stimulated by oxytocin. As engaged head exerts further pressure on cervix along with contraction of myometrial cells of the uterus further promotes oxytocin release and aids in parturition. The effect of oxytocin on myometrium is mediated via its receptor that belongs to the G-protein-coupled receptor superfamily. The second messenger pathway involved in myometerium is via Gq/phospholipase C (PLC)/inositol 1,4,5-triphosphate (P_3). There is up-regulation of oxytocin receptors at the end of gestation and sensitivity to oxytocin-induced contractions is greatly increased. The coordinated synchronous myometrial contractions during labour occur due to the formation of gap junctions among cells. Oxytocin hormone increases connexin-43 levels and upregulates morphological gap junctions. For this reason many of obstetricians frequently give oxytocin in order to induce or intensify contractions of the uterus.

Actions of Oxytocin

1. **Uterus:** The role of oxytocin is vital in normal parturition process. On the virgin uterus its action is negligible.

   Menstruation: There is slight action in the first half of menstruation and a little more in the second half.

   Pregnancy: During pregnancy, the action in the first half is very little. The action increases as pregnancy advances and becomes maximum during labour (2nd stage). Oxytocin thus takes part in the onset of parturition, expulsion of the foetus and placenta. The effect persists to some extent during puerperium and then gradually dies out. Its action is inhibited by progesterone and increased by oestrogens.

   In the later months of pregnancy corpus luteum degenerates. The proportion of oestrogens increases and thus makes the uterine muscles more sensitive

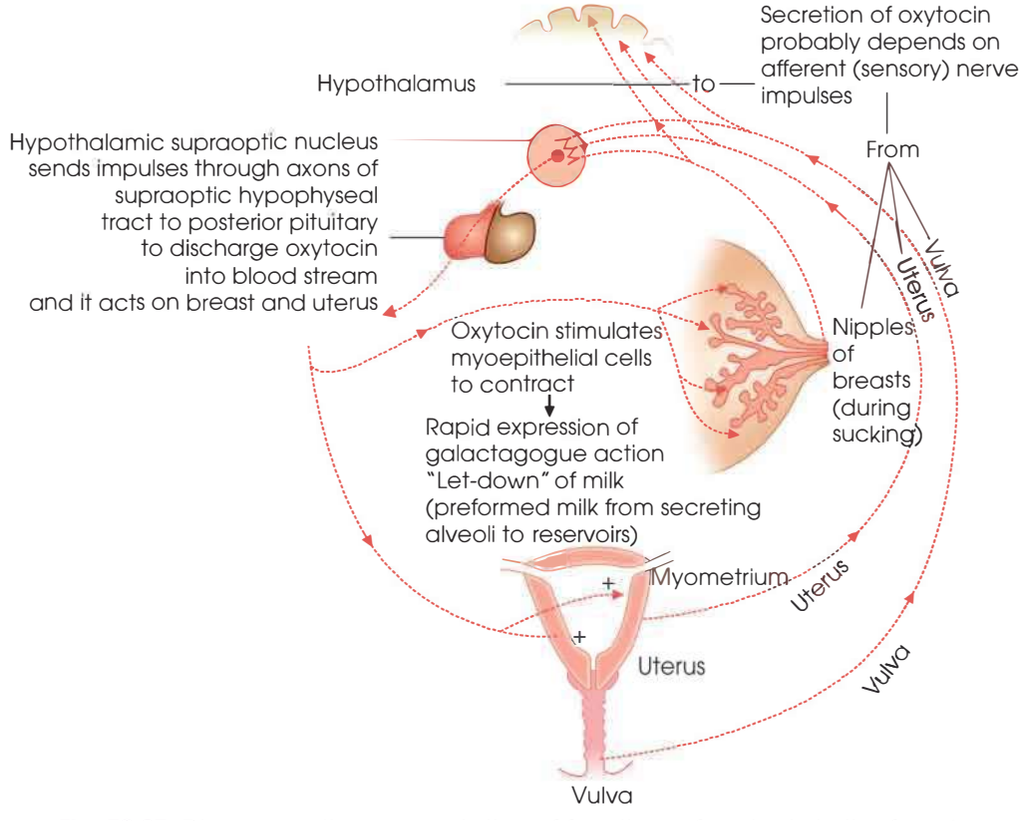


Fig. 70.27: Diagrammatic representation of functions of oxytocin in the female

to circulating oxytocin. This explains why oxytocin acts on uterus in late pregnancy.

2. **Milk ejection:** It causes contraction of the myoepithelial cells around the mammary alveoli. The hormone also is responsible for maintaining the function of such tissue by releasing prolactin from anterior pituitary.
3. **Metabolism:** It produces hyperglycaemia in large doses, especially in dogs.
4. **Sperm transport:** Oxytocin facilitates the transport of sperm in the female genital tract.
5. **Water metabolism:** Oxytocin given in large doses and in abundant fluid volumes may cause water intoxication due to antidiuretic effect of oxytocin on the nephron.

Another action of oxytocin, probably of physiological significance, is to stimulate contraction of gall bladder, intestine and urinary bladder.

DISORDERS OF FUNCTION OF THE POSTERIOR PITUITARY

Destruction of the neurohypophysis causes diabetes insipidus (*insipid* = tasteless). This is a condition in which large quantities of urine of very low specific gravity 1.002 to 1.006 and low chloride content are excreted. But further development of lesion may destroy the pars distalis with amelioration of the diabetes. In diabetes insipidus, fluid intake is increased and thirst is often intense. This condition frequently accompanies tumours of the pituitary or hypothalamic region, and is essentially due to absence of posterior pituitary hormone.

Diabetes insipidus may be controlled with the administration of the hormone vasopressin except some cases. Such individuals may possess an inherent defect of the renal tubules with respect to renal reabsorption of H_2O.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the second messenger mechanism of hormone action.
2. Describe the structure and functions of adenohypophysis.
3. Describe the mechanism of action and function of growth hormone. Add note on acromegaly, dwarfism and gigantism.
4. Describe the mechanism of action and function of vasopressin. Add note on diabetes insipidus.
5. Describe the mechanism of action and function of oxytocin. Add note on milk ejection reflex.

Short Notes

1. Pituitary gland
2. Anterior pituitary hormones
3. Posterior pituitary hormones
4. Thyroid stimulating hormone
5. Adrenocorticotropic hormone
6. Gonadotrophic hormone
7. Melanocyte stimulating hormones

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Chapter

71

Integrative Action of Neuroendocrinology

INTRODUCTION

The subject neuroendocrinology describes the interactions of nervous and endocrine systems. The nervous system is more concerned with adjustments that are rapid, whereas the endocrine system is concerned with slower chronic metabolic adjustments. The chemical substances released at the nerve endings are named as neurosecretions and are of several types.

The effect of the internal secretions on the nervous system can be seen from the following observations:

1. Physiological changes are found in association with changes in reproductive hormone titres during sex cycle.
2. Injection of sex hormones in certain parts of the brain stem changes the behavioural pattern.
3. Hyperactivity and hypoactivity of the thyroid affect brain activity and nervous tissue excitability.
4. Adrenal cortex and parathyroid glands affect nervous tissue excitability indirectly through changes in electrolyte concentration.
5. Anterior pituitary activity is influenced by injections into the hypothalamus of minute quantities of certain hormones of the pituitary target organs.

Hormone secretion at nerve ending: At the nerve endings of synapses, glands (exocrine and endocrine) and in many other organs norepinephrine and acetylcholine are liberated as a result of nerve impulses arriving on them. The above two neurosecretions are responsible for the activity of the organs concerned. Although the different endocrine organs have nerve connections also, they do not have any major control over secretion.

Neurosecretory cells of the hypothalamus: The secretions of the neurosecretory cells of the hypothalamus control the activity of both the anterior and posterior pituitary.

Release of posterior pituitary hormone: The paired supraoptic and paraventricular nuclei of the hypothalamus synthesize the hormones of the posterior pituitary, oxytocin and vasopressin (ADH). The neurosecretory granules which can be stained by suitable staining methods travel via the hypothalamo-hypophyseal tract to pars nervosa. The morphology of neurohypophysis permits a ready release of oxytocin or vasopressin (ADH) into the circulation. Neurovesicles lie very close to the basement membrane of the perivascular space, and the released hormones can generally reach it and enter the capillary bed through its thin fenestrated endothelium. Since processes of neurosecretory cells may reach third ventricle, a direct release of oxytocin and vasopressin in the cerebrospinal fluid (CSF) may also be possible.

Neurosecretory releasing and inhibitory factors: In response to afferent impulses, chemical or neural, received from all over the body, a different area of the hypothalamus elaborates different neurosecretory-releasing factors. The releasing hormones, also called factors, are corticotrophin-releasing factor (CRF), thyrotrophin-releasing factor (TRF), growth hormone-releasing factor (GHRF or SRF), gonadotropin releasing hormone (GnRH) or LH-releasing factor (LHRF), which are responsible for the release of the pituitary trophic hormones: ACTH, TSH, STH or GH, FSH and ICSH respectively. These neurosecretory-releasing factors

Note

1. GnRH is believed to be a single factor/hormone from hypothalamus for secretion of pituitary gonadotropins—both LH and FSH.
2. Hypothalamic factors have also been called hypothalamic hormones. The terms hypothalamic hormones and hypothalamic factors are interchangeable.
3. Hypothalamic hormones are released in pulsatile manner. Constant release downregulates their receptors and hence inhibiting for their effects. Pulsatile secretion of hormones is critical for maintenance pattern and level of secretion of their target pituitary hormones otherwise their receptors are down- or upregulated.

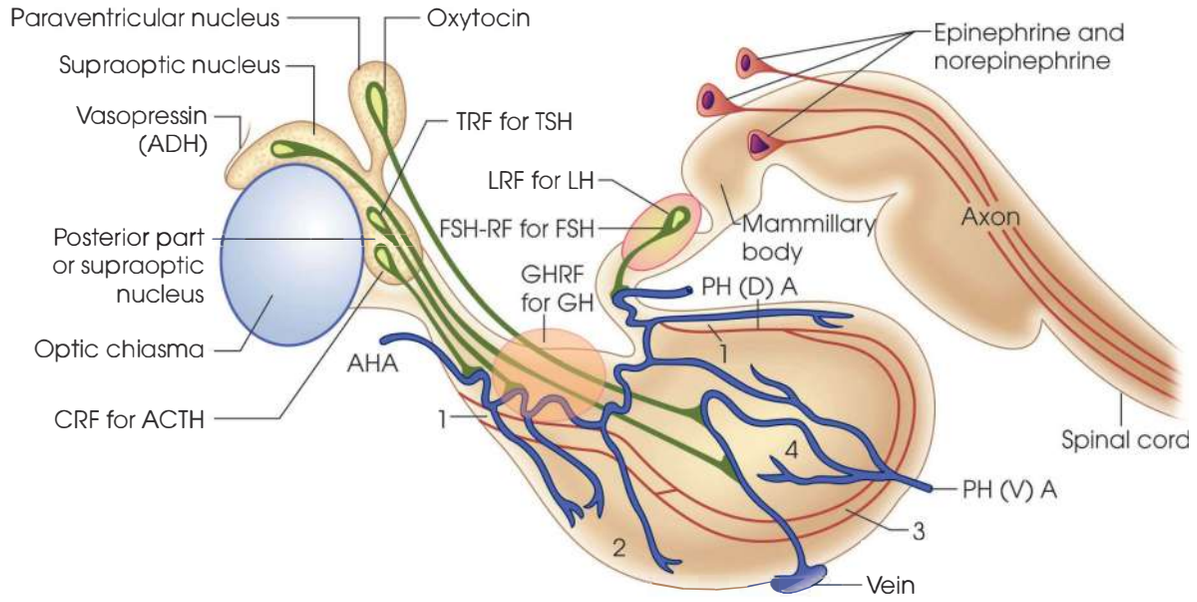

Fig. 71.1: Diagrammatic representation of hypothalamic control areas for the hormone secretions of anterior pituitary and others.
1—pars tuberalis, 2—pars distalis, 3—pars intermedia, 4—pars nervosa. AHA—anterior hypophyseal artery, PH (V) A—ventral branch of posterior hypophyseal artery. PH (D) A—dorsal branch of posterior hypophyseal artery

travel from nerve cells to axons and then to capillaries which drain the sinusoids of the adenohypophysis (Fig. 71.1). Two inhibitory factors: (1) Prolactin-inhibitory factor (PIF) and intermediate-lobe-inhibitory factor (MIF) which inhibit the release of prolactin and MSH respectively, are similarly elaborated by the hypothalamic nuclei. A species specific prolactin-stimulating factor (PSF) is suggested to be present in pigeon hypothalamus. Thus, secretion of prolactin by pigeon pituitary is not inhibited but stimulated by the hypothalamic secretion.

Neuroendocrine Interrelations

The centre of control of the adenohypophyseal functions is in the hypothalamus, and the feedback relationships between peripheral hormone levels and adenohypophyseal secretions are for the most part of trans-hypothalamic, and the hypothalamic control over the pituitary functions is exerted through the secretion of hypothalamic hormones or releasing factors, which may be called hypophyseotrophic substances or hormones.

Hypothalamic Hypophyseal Portal System

Connections between the hypothalamus and the pars distalis are not provided through tracts or nerve fibres (as in the case of hypothalamus to the pars nervosa), but rather through a vascular link in the form of a system of portal vessels. The primary plexus of this vascular system is to be found in a contact area between the ventral hypothalamus and the pituitary stalk (median eminence). Axon terminals from the cells of the hypothalamic nuclei come into close contact with the capillaries of this primary plexus, and perhaps there is passage of the hypothalamic-releasing factors into the blood stream of these capillaries.

The substances are distributed through collecting veins in the pituitary stalk into the adenohypophyseal parenchyma by the secondary plexus of capillaries of the hypothalamo-hypophyseal portal system (Fig. 71.2). The neuroendocrine areas in the hypothalamus appear to be somewhat diffuse if the considerable overlapping of the hypophyseotrophic activities related of one area or another is considered. These hypophyseotrophic areas do not coincide with the classic nuclei of the hypothalamus.

Control Circuits

Hypothalamic feedback: The feedback mechanisms between adrenocortical or ovarian hormones, on the one hand, and ACTH or gonadotrophins (LH, FSH) secretions, on the other, are mediated by the hypothalamus. This feedback effect disappears after placement of the hypothalamic lesions or after peripheral transplantation away from the hypothalamus.

Pituitary feedback: In the case of thyroxine or tri-iodothyronine and TSH secretion, most of feedback effects may take place at the level of the pituitary tissue, increased levels of thyroxine or tri-iodothyronine rapidly inhibiting the secretion of TSH by the isolated pituitary and also inhibiting the stimulation of TSH secretion produced by administration of TRF.

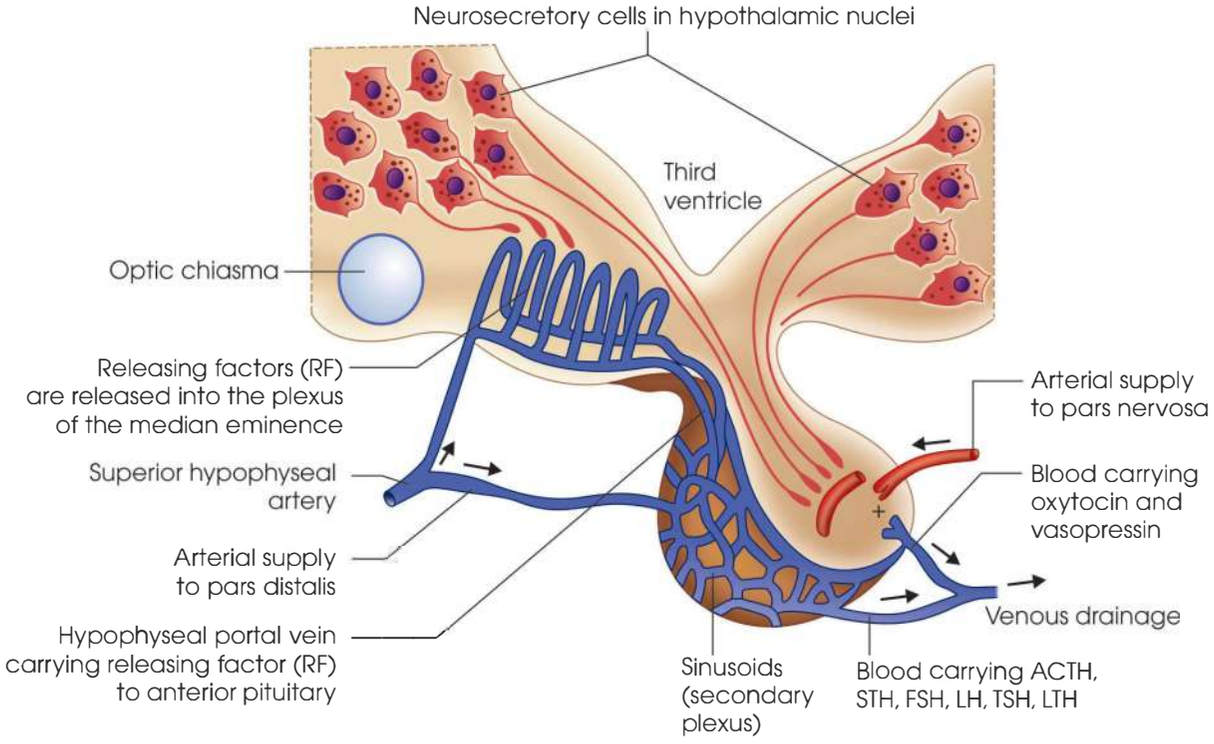

Fig. 71.2: Anatomical organization showing hypothalamic and hypophyseal neurovascular link for the control of hormonal secretion from the hypophysis cerebri

Short-loop feedback: The ACTH, LH and TSH may directly depress their own secretion by acting at the hypothalamic level.

Neuroendocrine Integration

Hypothalamus receives a good number of afferent fibres, and hypothalamo-telencephalic as well as hypothalamo-adenohypophyseal afferents constitutes the basis for reverberating circuits and feedback mechanisms. The hypothalamic afferent fibres come usually from the limbic system (hippocampus and amygdala) and globus pallidus, i.e. from the oldest part of the cortex and the basal ganglia. This system sends fibres into the medial forebrain bundle of the hypothalamus in addition to more certain specific projections upon hypothalamic nuclei. The hypothalamus also has connections with reticular activating substance and midbrain. The integrity of these systems is necessary for a harmonious function of the neuroendocrine mechanisms involved in maintaining homeostasis.

EXAM-ORIENTED QUESTION

Essay

1. Describe the neuroendocrine integration.

Chapter

72

Thyroid Gland

INTRODUCTION

Anatomy

Location: The thyroid situated at the root of the throat, having two fairly symmetrical lateral lobes, each about 5 × 2 × 2 cm, one on either side of trachea, joined by a thin portion of thyroid tissue called the isthmus (middle lobe) crossing in front of the second, third and fourth tracheal rings. As a normal variant the left lobe is often smaller than the right lobe.

Weight in adults: The gland weight in the adult normally varies from 20 to 25 gm but is influenced by age, sex, reproductive state and diet.

Blood supply: Highly vascular-paired superior and inferior thyroid arteries supply the gland with a less

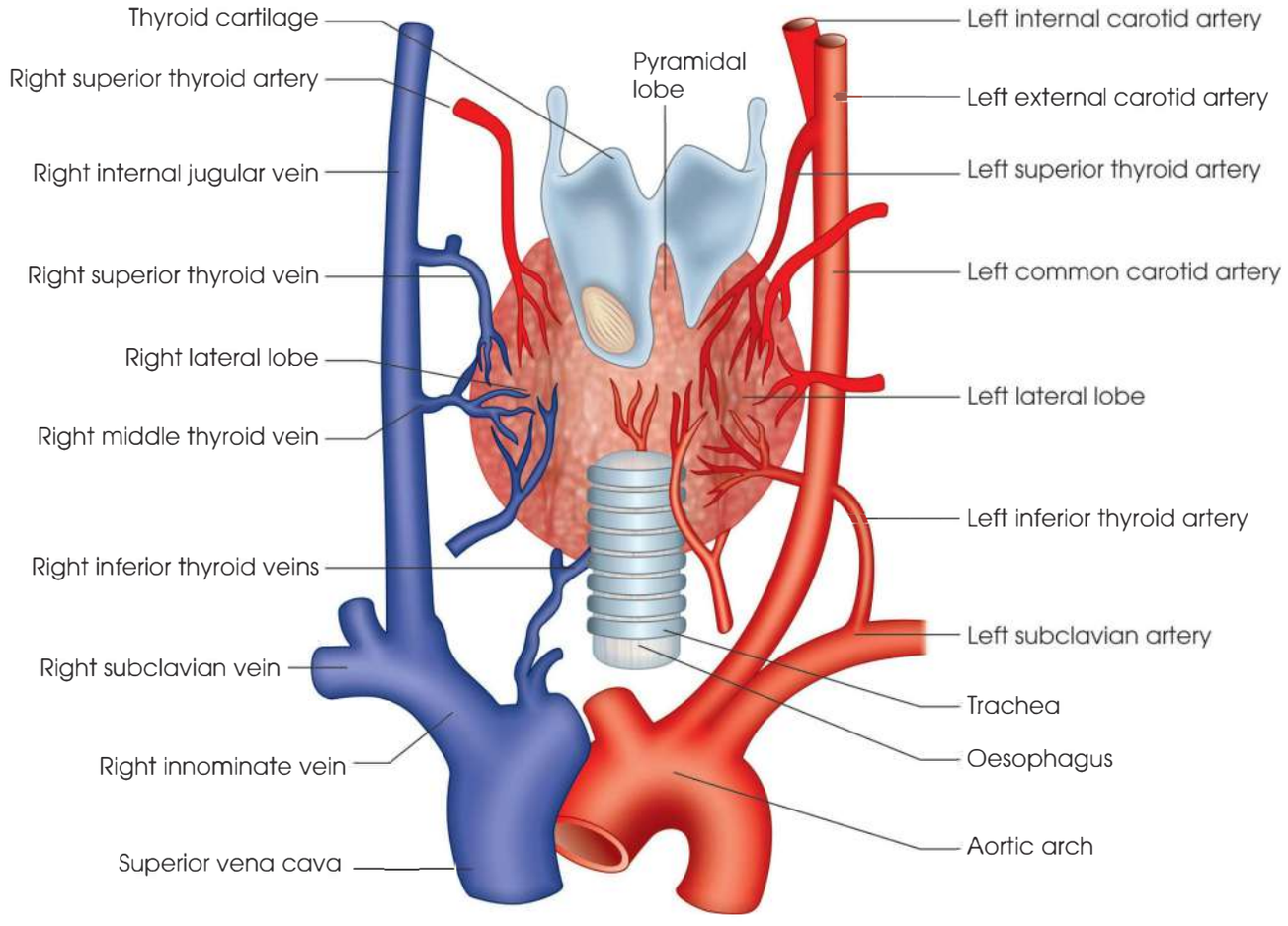

Fig. 72.1: Diagrammatic representation of the anatomical position of the human thyroid in relation to major great vessels

Emil Theodor Kocher was a Swiss physician and medical researcher who did extensive research on understanding thyroid gland in health and disease. He was awarded the Nobel Prize in Physiology or Medicine for his work in the physiology, pathology and surgery of the thyroid in 1909.

1814–1917

important supply directly from the aorta or the innominate artery via the thyroidea ima artery.

Venous and lymphatic drainage: The venous drainage is to the internal jugular and innominate veins and the lymphatic drainage is to the lateral lymph nodes of the neck and anterior mediastinal lymph nodes.

Blood flow: The blood supply to thyroid gland varies from 3.5 to 6.0 ml per gm of thyroid per minute. This high flow rate probably serves to supply the tissue with sufficient inorganic iodide.

Nerve supply: Sympathetic fibres are derived from the superior, middle and inferior cervical ganglia and parasympathetic fibres from the superior and inferior recurrent laryngeal branches of the vagus. They regulate the blood flow rather than secretion of the thyroid gland.

Histology

When the thyroid is examined microscopically it is found to consist of follicles of vesicles lined in the resting slate by a simple cuboidal epithelium cell (Fig. 72.2). The height of this epithelium depends upon the hypo or hyperthyroid state (Fig. 72.3). The follicular cells are arranged as in spherical follicles surrounding colloid. The interiors portion of these follicles forms the follicular lumen. They have thyrotropin receptors on their surface, which are influenced by the thyroid-stimulating hormone. The parafollicular cells (C cells) are scattered along the basement membrane of the thyroid epithelium (Fig. 72.3). Under appropriate stimulation by thyroid-stimulating hormone (TSH) the low cuboidal epithelium may be converted into a tall columnar epithelium.

The thyroid follicles or vesicles-spherical, oval or irregular size and 15–150 µm in diameter, lined by a single layer of granular cubical cells with mitochondria and distinct Golgi apparatus (Fig. 72.3). The bases of the cells are in contact with fine basement membrane which also encircles each follicle. The follicles are filled with a protein material which consists largely of thyroglobulin which, in fact constitutes 75% or more of the soluble proteins of the normal thyroid gland and is the main storage form of the thyroid hormones. The thyroid is unique in this way amongst the endocrine

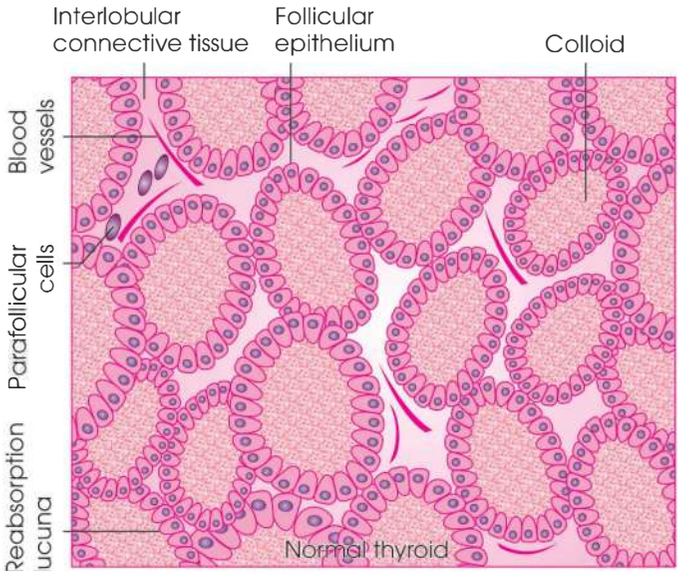

Fig. 72.2: Histological structure of thyroid gland showing normal

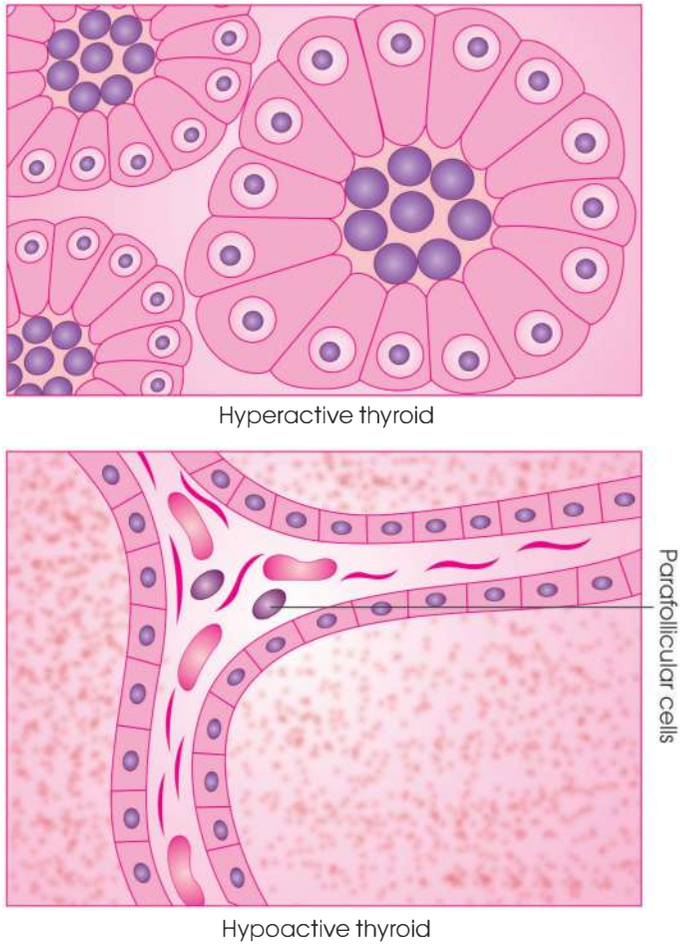

Fig. 72.3: Diagram shows hyperactive, hypoactive thyroid cells and parafollicular cells

glands in having a large store of preformed hormone in the organ. The follicles are surrounded by a very vascular stroma which also contains the lymphatic channels.

The border of the thyroid epithelial cells which impinge on the central colloid of the follicles has a regular formation of microvilli. In addition, within the cell cytoplasmic vesicles are found and many of these at least are absorption vesicles, the colloid being absorbed from the follicles by the process of engulfment by the thyroid cell processes. This mechanism is called pinocytosis. Vesicles are filled up with a colloidal material.

THYROID HORMONES

The thyroid gland produces thyroxine and tri-iodothyronine which are iodine-based hormones.

The hormone thyroxine (T_4) and tri-iodothyronine (T_3) are produced from thyroid follicular cells in the thyroid gland, under influence of thyroid-stimulating hormone secreted by anterior pituitary. The thyroglobulin, the precursor of T_4 and T_3, is produced by the thyroid follicular cells before being secreted and stored in the follicular lumen. Thyroid glands synthesise and release iodinated thyronine molecules. These molecules greatly influence metabolic processes and growth. Within the thyroglobulin molecule, tyrosine residues are iodinated to form MIT and DIT which then combine to form the iodothyronines. Peptide bonds of the thyroglobulin are hydrolyzed by proteolytic enzymes, catheptases, from lysosome and free thyroxine, tri-iodothyronine are released by the thyroid cells, cross them and are ultimately discharged into the capillaries. Mono- and di-iodotyrosines are also released but do not leave the follicle. They are rapidly deiodinated by enzyme, deiodinase or dehalogenase within thyroid cells, and iodine is reutilized for a recycling synthesis of thyroglobulin. MIT and DIT are biologically inactive. Thyroxine is 3,5,3,5′-tetraiodothyronine and tri-iodothyronine is 3,5,3-tri-iodothyronine. These two iodine-containing amino acids are biologically active.

Thyrocalcitonin which is secreted from parafollicular cells (C cells) of the thyroid gland is a polypeptide having molecular weight of about 3600.

SYNTHESIS, STORAGE, RELEASE AND TRANSPORT OF THYROID HORMONES

The thyroid gland is the main iodine-functioning organ in the body. The normal adult takes in about 100–150 µg of iodide per day in food (Fig. 72.4). The iodide is broken down in the gastro-intestinal tract and is commonly absorbed as iodine, which passes into the blood stream where it circulates in the systemic circulation and is actively accumulated by the thyroid from the blood passing through it. The various steps of thyroid hormone synthesis are described as follows.

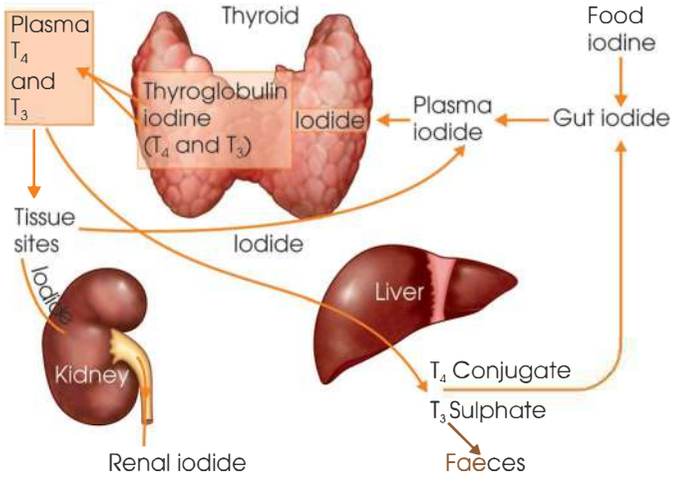

Fig. 72.4: Schematic representation of the iodine cycle

STEPS: SYNTHESIS OF THYROID HORMONE

Synthesis of thyroid hormones involves through several processes, such as:

1. Synthesis of thyroglobulin
2. Trapping of iodide
3. Oxidation (iodination) and coupling (condensation) and organification of iodotyrosine molecules that are attached to thyroglobulin
4. Release of thyroglobulin into the follicular lumen,
5. Reabsorption of thyroglobulin from the follicular lumen into the follicular epithelial cell, and hydrolysis of thyroglobulin to release thyroxine and tri-iodothyronine, MIT and DIT.

1. Synthesis of Thyroglobulin

Thyroglobulin is an iodinated glycopeptide of molecular weight of about 680,000. The polypeptide part of this glycoprotein is synthesised by the rough-endoplasmic reticulum of the thyroid cell. The carbohydrate moiety is added possibly mainly in the Golgi apparatus, which produces the formation of a fully synthesised carbohydrate-containing protein of 17s size (Fig. 72.5). The protein is a precursor of the thyroid hormones; these are produced when thyroglobulin's tyrosine residues are combined with iodine, and the protein is subsequently iodinated by thyroperoxidase in the follicular colloid.

2. Trapping of Iodide

Trapping of iodine: Thyroid gland accumulates inorganic iodide. This is done by an active process which is generally called trapping (Fig. 72.6). For this active transport energy is required. The resting membrane potential of the acinar cell is –50 mV with respect to interstitial fluid and colloid. Iodide pump into the cell occurs against this negative potential and then diffuses down at the electrochemical gradient into

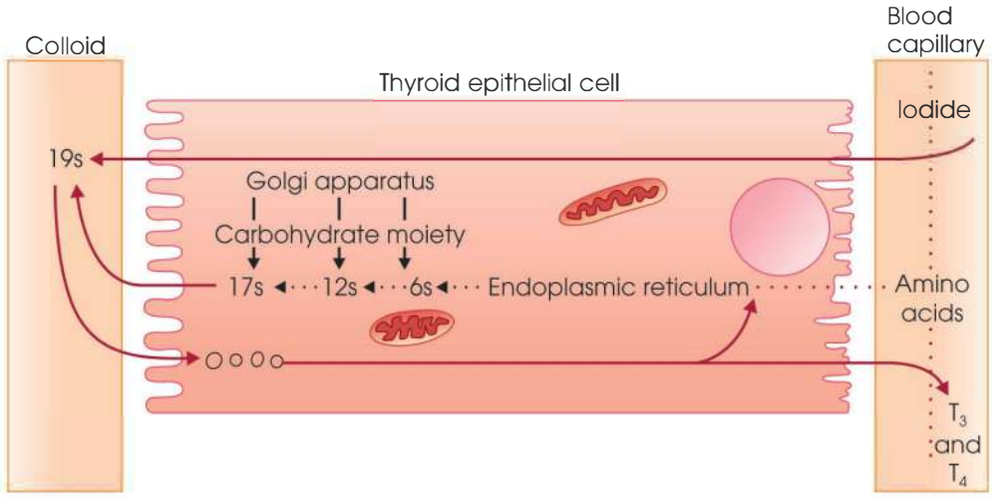

Fig. 72.5: Schematic representation of stages of formation and degradation of thyroglobulin

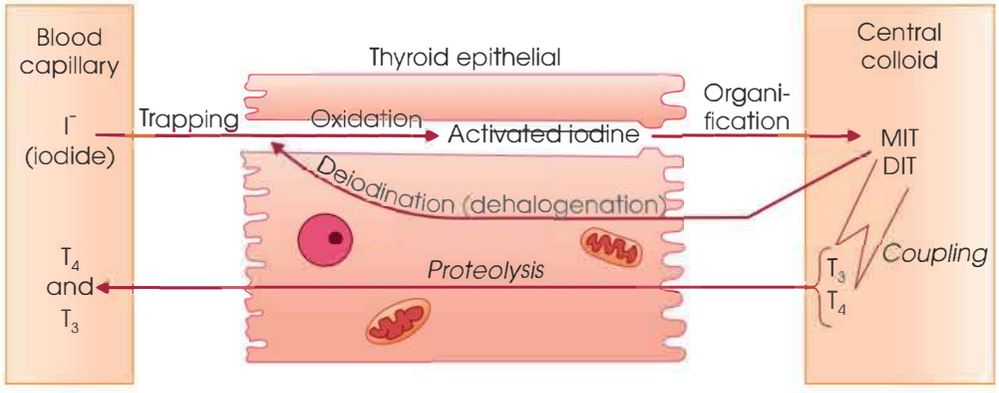

Fig. 72.6: Simplified diagram of the synthesis and degradation of the thyroid hormone

the follicular lumen. The ratio of thyroid iodide to plasma iodide is about 20:1 to 100:1. This iodide pump is also dependent upon ATPase system.

Uptake of iodide can be inhibited by cyanide or dinitrophenol. TSH stimulates iodide uptake by the gland. The normal daily intake of iodide is 100–150 µg and mainly absorbed from the small intestine and subsequently transported in the plasma in loose attachment to protein.

Salivary gland, gastric mucosa, placenta and the mammary glands can transport iodide against concentration gradients but this process is not stimulated by TSH.

3. Oxidation (Iodination) and Coupling (Condensation) and Organification of Iodotyrosine Molecules that are attached to Thyroglobulin (Fig. 72.7)

Oxidation: Once the iodide has been accumulated in the thyroid gland, it undergoes a process of oxidation. Within the thyroid, the iodide that is taken up the follicular cells is quickly oxidized to an active form of iodine, by a reaction, catalyzed probably by a particulate-formed peroxidase in presence of H_2O_2 as a source of oxygen. TSH is active in stimulating this reaction.

Oxidation of iodine to nascent form of iodine:

$$2I^- = I \text{ or } I^o + 2e$$

Peroxidase system

$$H_2O_2 + 2I + 2H \xrightarrow[\text{peroxidase}]{\text{iodide}} 2' \text{ oxidised (active) } I' + 2H_2O$$

The receptors of the activated iodine are the tyrosine residues of the thyroglobulin. Each molecule of thyroglobulin (19s proteins) contains 115 tyrosine residues and consists of four 8s subunits.

1. The iodination of tyrosine in thyroglobulin takes place first at 3 position and then at 5 position of aromatic nucleus, forming respectively the monoidotyrosine and di-iodotyrosine. Simply, the addition of one atom of iodine per tyrosine residue results in increase in the ratio of MIT:DIT and preferential production of T_3.
2. Normally monoiodotyrosine (MIT) and di-iodotyrosine (DIT) molecules are present in equal concentration.

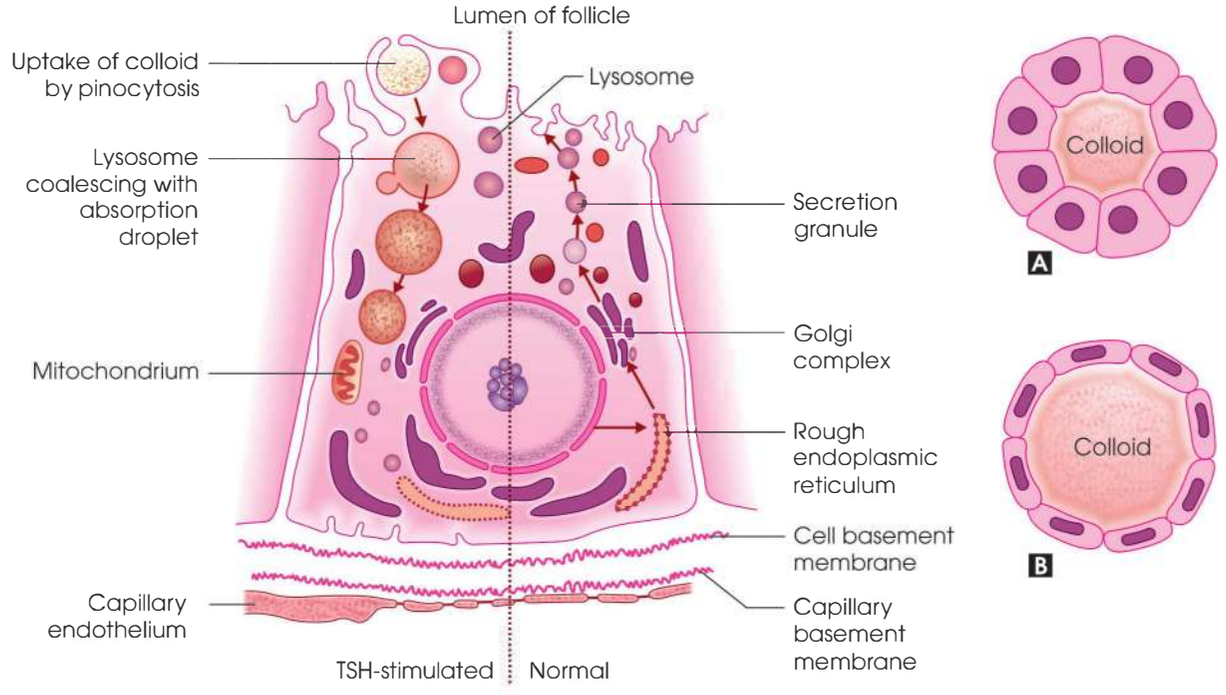

Fig. 72.7: Diagram shows normal thyroid and TSH-stimulated epithelial cells. In the normal cell secretory droplets are formed in the Golgi complex and discharged into the lumen of the follicle. In the TSH-stimulated cell, colloid droplets are taken up by micro-pinocytosis and coalescing with lysosomes. Degradation of TG by hydrolytic

3. Two di-iodotyrosine molecules thus undergo oxidative condensation with the liberation of alanine residue forming thyroxine. TSH is active in stimulating this reaction and the formation of thyroxine (T_4).

Coupling: Tri-idothyronine (T_3) is formed by condensation of monoidotyrosine with di-iodotyrosine. This process of condensation is known as coupling. Under normal conditions, coupling occurs readily between adjacent iodotyrosine residues on the surface of TBG molecules. Loss of iodine atom from thyroxine molecule may possibly produce T_3. Peroxidase necessary for iodination is localised in the cisternae of granular endoplasmic reticulum, perinuclear cisternae, a few Golgi lamellae, apical small vesicles and associated with the external surfaces of the microvilli.

Organification: The next stage of thyroid hormone synthesis is called organification, since it involves attachment of the iodine to tyrosine residues. This is believed to occur on preformed thyroglobulin which has been taken to the full stage of protein synthesis but which has not been iodinated.

4. Release of Thyroglobulin into the Follicular Lumen

Thyroglobulin with thyroid hormones that are formed in the follicular epithelium are discharged within the follicular lumen and stored there until these are required.

5. Reabsorption of Thyroglobulin from the Follicular Lumen into the Follicular Cells and Hydrolysis of Thyroglobulin to Release Thyroxine and Tri-iodothyronine, MIT and DIT

Reabsorption: If TSH is administered then numerous large droplets appear in the thyroid follicular cell. These large droplets have been considered to be the reabsorbed materials from follicular lumen. These droplets are reabsorbed by a micropinocytosis (Fig. 72.8).

Hydrolysis: Final steps in the formation of thyroid hormones are the hydrolysis of thyroglobulin by the proteolytic enzymes from lysosomes or vesicle membranes. It is claimed that lysosomes coalesce with the droplets, releasing hydrolytic enzymes which degrade thyroglobulin to liberate thyroxine (T_4), tri-iodothyronine (T_3), MIT and DIT. Thus "the surface of the cells in contact with the colloid sends off narrow streamers which parcel out small amounts of colloid; the colloid droplets thus formed are then carried into the cytoplasm, where they combine with lysosomes; and under their influence they disintegrate and disappear with the release of thyroid hormones and MIT and DIT". TSH stimulates the process greatly.

MIT and DIT that are released from the thyroglobulin do not escape from the epithelial cells but are deiodinated by a specific deiodinase enzyme that plays a vital role in an intrathyroidal iodine cycle in which iodine and tyrosine are recirculated for fresh hormonal synthesis. This deiodinase has got affinity towards the globulin-bound MIT and DIT.

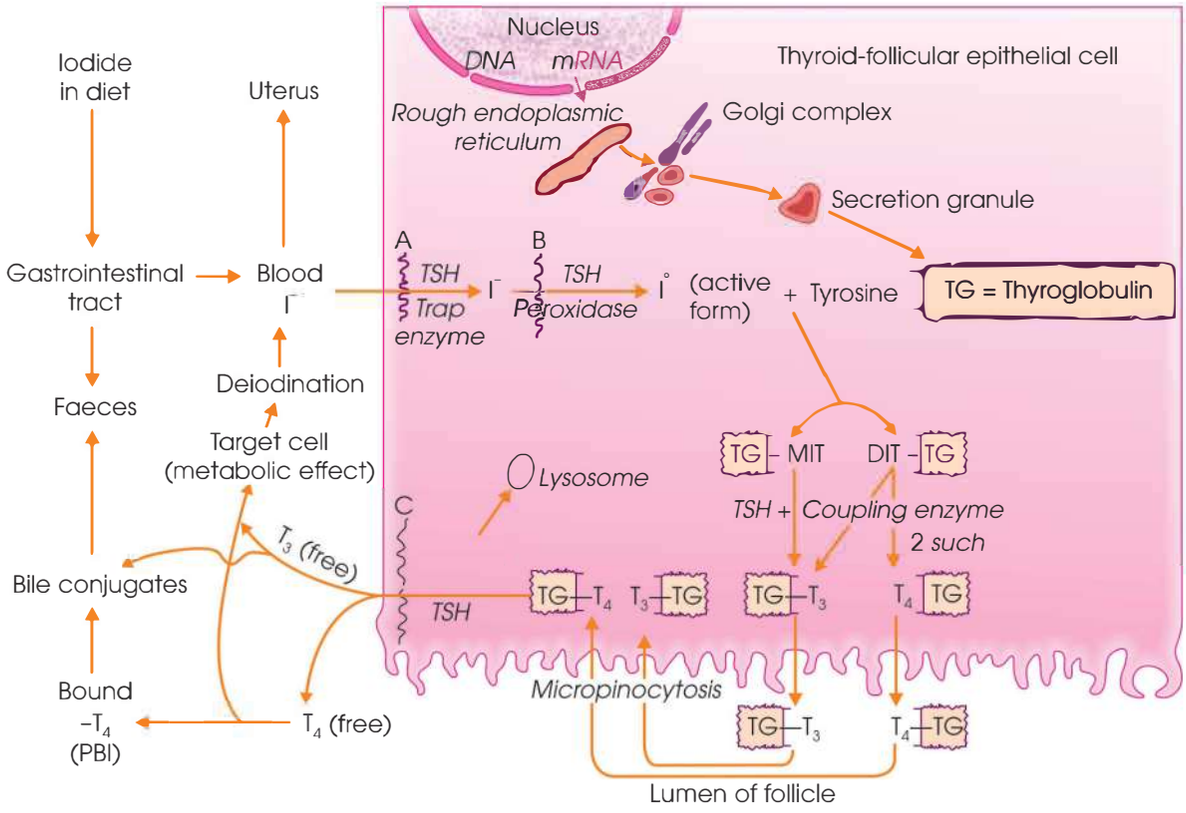

Fig. 72.8: Schematic representation of the metabolism of iodine and synthesis, storage, release and transport of thyroid hormones

TRANSPORT OF THYROID HORMONES

The hormones which are released in the blood are transported as such but in binding with plasma proteins. Thyroxine (T_4) is bound much more firmly than tri-iodothyronine and for this reason tri-iodothyronine is quick acting and short lasting but the thyroxine is slow acting but long acting.

Thyroxine is transported entirely with two plasma proteins: (1) thyroxine-binding alpha-globulin (TBG)—about 60% and (2) thyroxine-binding pre-albumin (TBPA—about 30%). When the binding capacity of these specific carrier proteins is exceeded, thyroxine is bound with serum albumin and approximately about 10% of circulating thyroxine remains in the free and unbound state. This free thyroxine makes up only 0.1% and is the metabolically active hormone. TBG is stable reservoir for both T_4 and T_3. Thyroxine is less tightly bound with TBPA.

DEGRADATION AND EXCRETION OF THYROID HORMONES

Key Points

1. Half-life of 131 iodine labelled thyroxine is about 8 days. In hyperthyroidism the half-life is 3–4 days and in myxoedema it is about 9–10 days. Half-life of T_3 is about 2 days.
2. The deiodination and thyroid hormones occur in all peripheral tissues and probably is the most important degradation process. The iodide released is recirculated and is excreted (urine) or is recycled through thyroid hormone synthesis due to the thyroid iodide-concentrating mechanism. Since the renal tubules reabsorb more than 95% of filtered iodide, thus body economy of iodide is achieved.

> Dehalogenase (iodothyronine-deiodinating enzyme) exists in muscle and other tissues. This enzyme is active only with non-protein (free) material. Thus, cellular protein binding of thyroxine minimises deiodination and in this way provides for some reserve except the cells of the brain, spleen and gonads. Thyroxine dehalogenase activity of human leucocytes is increased in hyperthyroidism and decreased in hypothyroidism.

3. The thyroid hormones deconjugate with glucuronic acid to form β-glucuronide metabolite. Glucuronide derivatives being formed in the liver and passed via bile into gut, where they are reabsorbed after hydrolysis by β-glucuronidase of the intestinal bacteria to be excreted in the faces.

The metabolism of iodine and synthesis, storage, release and transport of thyroid hormones has been presented in Fig. 72.8.

IODINE REQUIREMENT AND ANTERIOR PITUITARY CONTROL IN SECRETION OF THYROID HORMONE

Iodine

The synthesis of thyroid hormones requires a regular and adequate supply of iodine. The daily requirement is about 100 to 150 µg but considerably more may be needed during puberty, pregnancy or stress of any kind and during residence in cold climate. Deficiency of iodine leads to hyperplasia and goitre.

Iodine is taken in with food

1. As the free element
2. As iodide (I^-)
3. As iodine bound to or part of an organic molecule.

As a general rule, ingested iodine must be reduced to iodide before it can be absorbed. Iodide in the blood has a concentration of about 3.5 to 8.0 µg per 100 ml (275.8 to 630.4 nmol/L). In plasma iodine is bound to albumin and called protein-bound iodine or PBI. The normal range of PBI varies from 3.5 to 8 µg per 100 ml. It is a determining factor of thyroid secretion. In hyperthyroidism, the PBI level increases and it may reach to 15 µg and in hypothyroidism (myxoedema), the PBI level falls below 3.5 µg per 100 ml.

Role of Anterior Pituitary

The thyrotrophic hormone of the anterior pituitary controls the synthesis and secretion of thyroxine. It is indicated that the action of TSH is mediated through pentose phosphate pathway is also increased and this helps in hormone synthesis.

PHYSIOLOGICAL ACTIONS OF THYROID HORMONES

The actions of the hormones in different bodily processes are described categorically.

1. **Calorigenic:** Thyroid hormone accelerates energy production, oxygen uptake and basal metabolic rate (BMR). T_3 is 3–4 times more potent than T_4 and increases the oxygen consumption more rapidly. Each milligram raises BMR to about 1000°C and increases the oxygen consumption of all tissues except anterior pituitary, brain, testes, spleen, and uterus. The calorigenic effect of thyroxine is due to its direct effect on the cells.
2. **Metabolism** (*carbohydrate metabolism*): Thyroid hormone
   a. Stimulates absorption of glucose from the intestine
   b. Mobilizes glycogen from liver and heart
   c. Promotes gluconeogenesis
   d. Causes hyperglycaemia
   e. Reduces sugar tolerance

Protein metabolism: In moderate concentrations the thyroid hormone has an anabolic effect, causing an increase in RNA and protein synthesis, an action which precedes increased BMR not only is RNA synthesis increased, but there is increased translation of the message contained in messenger RNA at the ribosome where protein synthesis occurs. In hypothyroidism, the hormone has an anabolic effect on plasma and tissue proteins but catabolic action on extracellular proteins. In high concentrations, negative nitrogen balance is observed and protein synthesis is depressed.

Lipid metabolism: The concentration of most of the lipids of the serum especially cholesterol varies inversely with the level of thyroid activity. The thyroid hormone increases both synthesis and the catabolism of cholesterol and other lipids. The decrease in cholesterol concentration is due to increased formation of LDL receptors in the liver resulting in increased removal of cholesterol from circulation. In hypothyroidism, the balance between the two is disrupted; there is less lipid catabolism, hence serum lipids increase.

Calcium and phosphorus metabolism: Removes calcium and phosphates from the bones leading to osteoporosis. Its action differs from that of parathyroid in causing no rise of serum calcium, and increasing calcium loss both in faeces and urine. Similar changes are seen in Graves' disease.

3. **Kidneys**
   a. Increases nitrogen excretion.
   b. Increases urine volume along with increased elimination of salt probably not by a direct effect on the kidneys but by raising the general metabolism and thus increasing nitrogenous end products which act as diuretics.
   c. Increases the excretion of creatine.
4. **Growth and metamorphosis:** Thyroid is essential for normal growth and also for metamorphosis in tadpoles. In thyroidectomised animals there is retardation of growth. Growth in these animals is again initiated after administration of thyroxine.
5. **Mammary glands:** Increases the output and fat content of milk.
6. **Heart rate:** Thyroxine accelerates the rate of the normal as well as the denervated heart. It acts directly on the heart (SA node). The raised BMR may be an additional factor.
7. **CNS activities:** It is necessary for normal emotional responsiveness, cerebral activity, sensory activity, etc.
8. **Nerves and muscles:** Thyroid hormones influence the levels and activity of the central, peripheral and autonomic nervous systems and of the voluntary muscles. Hyperthyroid patients are nervous and irritable, and exhibit muscular tremors. Catabolism of muscles may cause wasting, weakness and sometimes frank myasthenia. Autonomic stimulation causes sweating, gastro-intestinal hypermotility and vasomotor instability. In hypothyroidism, the patients are apathetic, mentally retarded. Electro-

encephalogram may show slow waves of diminished amplitudes and sometimes absence of waves. Contraction and relaxation of voluntary muscles are delayed and the gut may be sluggish.

9. It increases the tolerance to some type of drugs, e.g. morphine, digitalis.

FUNCTIONS OF THYROID GLAND

1. On Metabolism

General metabolism: Thyroid stimulates the metabolism in the tissues. BMR is increased. O_2 consumption and heat production are also increased. Thyroxine stimulates O_2 consumption of all the tissues except possibly brain, gonads and spleen.

Carbohydrate metabolism: Thyroxine stimulates the absorption of monosaccharides from the intestine. It stimulates glycogenolysis and produces hyperglycaemia. It reduces sugar tolerance. It also stimulates the utilization of glucose in the tissues thus decreasing the hyperglycaemic effect.

Protein metabolism: Thyroxine in physiological doses has a protein anabolic effect including enhancement of growth of all bodily tissues. This effect has been observed in absence of pituitary hormone. Toxic amount does not show such effect. Hyperactive states of thyroid gland increase breakdown of proteins and so elevate nitrogen elimination leading to wasting of tissues.

Fat metabolism: Thyroxine increases synthesis of lipids and also promotes lipolysis by mobilizing and degrading the lipids. It decreases the stores of triglycerides and phospholipids.

Iodine metabolism: Thyroxine helps in the absorption of inorganic iodide from plasma, oxidation of the iodide into iodine, formation of monoiodotyrosine and diiodotyrosine and subsequent transformation into thyroxine. Thyrotrophic hormone of the anterior pituitary controls the formation and the synthesis of thyroxine.

Mineral metabolism: Hyperthyroidism mobilizes Ca and phosphate from bones making them porous. But small amounts of thyroxine increase calcium retention in growing animals as a secondary effect.

2. Relation with Vitamins

Thyroxine helps in the conversion of β-carotene into vitamin A in the body. In hypothyroidism, blood carotene level rises. Thiamine requirements and urinary excretion are increased in hyperthyroidism. Hyperthyroid rats appear to have an increased need for riboflavin. Lack of vitamin B_{12} appears to affect the thyroids of chick embryo. Vitamin C requirement may be increased in hyperthyroidism because urinary vitamin C level is below normal.

3. Growth and Differentiation

The growth of the body is influenced both by somatotrophic hormone (STH) of the anterior pituitary and thyroid hormone or thyroxine but the process of differentiation of tissues is influenced only by thyroid hormones.

Skeletal growth: Somatotrophic hormone helps in general bony growth but thyroxine helps in the maturation and differentiation of the epiphysis, etc. In hypothyroidism before puberty, i.e. in cretinism, there is retardation of skeletal growth.

Muscular growth: In cretinism, there is retardation of muscular growth. In hyperthyroidism, the formation of creatine phosphate is impaired and muscular contraction becomes weak.

Sexual growth: Thyroid controls the normal functions of gonads. In cretins, there is retardation of the gonadal growth and secondary sex characters do not appear. In myxoedema due to hypo-function of the gonads, amenorrhoea occurs in women. It is not definitely clear if gonadal hypo-function during hypothyroidism is due to reduced secretion of pituitary gonadotrophins. Androgens and oestrogens cause alteration of thyroxine-binding globulin (TBG) and thyroxine-binding pre-albumin (TBPA) in the plasma.

Mental growth: Thyroid plays an essential role in mental growth and development of the central nervous system. In cretins, there is retardation of mental growth and development of the central nervous system. The child remains mentally backward and he may be an idiot. Speeches, walking, etc. are all delayed. The development of the cerebral cortex shows various abnormalities, e.g. myelination of axons, arrangement of dendrons, etc. Electroencephalographic study also reveals a lowering of α-waves.

4. Cardiovascular System

During hyperthyroidism a characteristic feature is an increase in systolic blood pressure without any alteration in the diastolic, and also an increase in stroke volume, cardiac irritability and output, heart rate and dilatation of peripheral vessels. Thyroid hormones (T_3 and T_4) increase sensitivity of catecholamines to the tissue. The effect of thyroid hormone on circulation titres of catecholamines may affect the cardiovascular system. In hypothyroid condition, the heart becomes oedematous, sluggish and contracts less forcefully resulting in reduced cardiac output. O_2 consumption of myocardial tissue of experimental animals is increased by thyroid hormones.

5. Nervous System

Thyroid hormone increases the sensitivity of the nervous system. This system is profoundly affected by

deficiency of thyroid function. Deficiency of the hormone in the young animals results in decrease in myelin, neuron size, cerebral water content, number of axons, etc. Thyroid therapy repairs several neural effects of hypothyroidism if begun before a critical period. Effect of thyroid hormone on brain excitability is associated with alteration in electrolyte distribution.

6. Maturation of Red Cells

In hypothyroidism, e.g. in myxoedema, anaemia is a common feature. The anaemia is of megaloblastic type and probably due to deficient absorption of vitamin B_{12}.

7. Heat Regulation

In hypothyroidism, there is an increased susceptibility to moderate cold. The calorigenic effect of thyroxine is due to its direct effect on the cells.

8. Secretion of Milk

Thyroid stimulates galactopoiesis, i.e. it stimulates and maintains the secretion of milk during lactation. It also increases the content of milk.

THYROID DISORDERS

Hypothyroidism

Hypothyroidism produces cretinism in young.

Cretinism (Fig. 72.9)

The symptoms do not appear till after six months of birth, because enough hormones are present in mother's milk.

The chief features are the following:

1. The milestones of child's development such as holding up the head (3 months), sitting and dentition (6–7 months), closure of anterior fontanelle (20 weeks), standing, walking, speech (12–18 months), etc. are all delayed.
2. *Skeleton:* Stunted growth, short club-like fingers, deformed bones and teeth.
3. *Skin:* Rough, thick, dry and wrinkled. Hairs scanty.
4. *Face:* Bloated, idiotic look, thick-parted lips, large-protruding tongue. Saliva dribbling. Broad nose with depressed bridge.
5. *Abdomen:* Pot-bellied, umbilicus often protruding.
6. *Sex:* Sex glands, sex organs and secondary sex characters retarded.
7. *Mental growth:* Idiocy of varying degrees and often deaf and dumb.
8. *Gastro-intestinal tract and metabolism:* Appetite is reduced. Motility of the gastro-intestinal tract is reduced and there is often constipation. BMR lowered by 20 to 40%, low body temperature, and irregular deposit of fat especially above the clavicles.
9. *Blood:*
   - Low blood sugar.
   - High sugar tolerance.
   - High serum cholesterol.
   - Low blood iodine.
10. *Resistance:* Lowered. Susceptible to cold, toxins and intercurrent infection.
11. *Urine:* Creatine excretion less. Normal output (on a meat-free diet with 2 gm of protein per kg) is 0.6–7.8 mg daily. In cretinism, it falls to 0–3.8 mg.
12. *Vitamins:* Carotene accumulates sufficiently to cause yellowing of the skin but not the sclera.

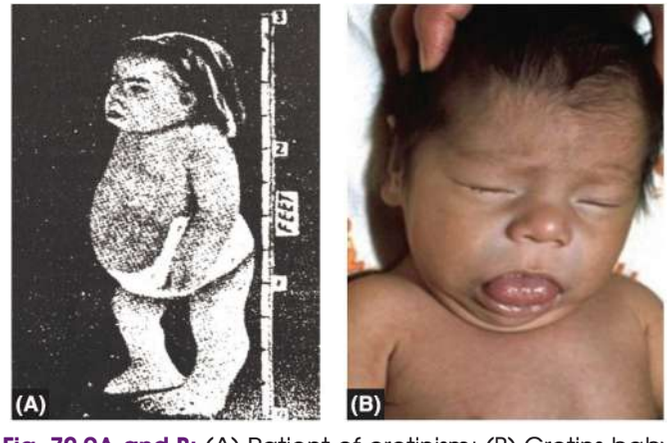

Fig. 72.9A and B: (A) Patient of cretinism; (B) Cretins baby with macroglossia

MYXOEDEMA OR GULL'S DISEASE (Fig. 72.10)

The disease occurs about 7–8 times more frequently in females than in males. Genetic factors (recessive gene)

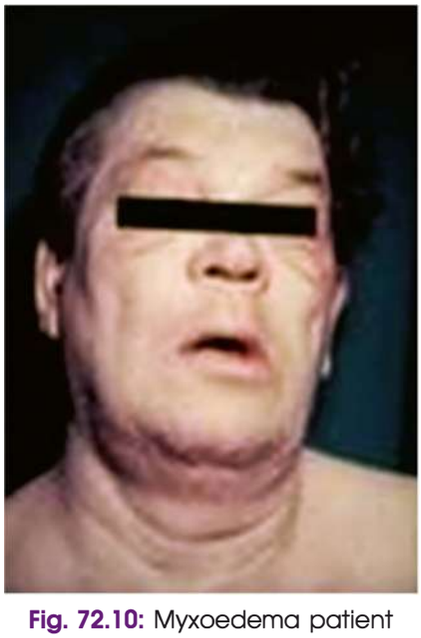

Fig. 72.10: Myxoedema patient

are also of some importance in the genesis of some hypothyroid conditions.

The observed clinical features in myxoedema are:

1. **Face, skin and body**
   - Swollen puffy oedematous look of the face (Mongoloid appearance) and the whole body, due to the deposition of myxomatous tissue.
   - Myxomatous tissue consists of a semi-fluid substance rich in proteins and mucopolysaccharides.
   - Parchment like cheeks, malar flush, hairs fallout from axilla, pubis, head and outer third of the eyebrows.
   - Swelling of the tongue and larynx causing hoarseness and slow-slurring speech.
   - Irregular deposit of fat in the body, etc.
2. **Sex:** Degenerates; impotency, amenorrhoea, etc.
3. **Mental condition:** Impaired; dullness, loss of memory, somnolence, etc.
4. **Gastro-intestinal tract and metabolism**
   - Appetite is reduced. Motility of the gastro-intestinal tract is reduced and there is often constipation.
   - BMR lowered by 30 to 45%.
   - Body temperature low.
   - Increased susceptibility of cold.
   - Body weight increases.
5. **Blood**
   - Low blood sugar and iodine
   - Increased sugar tolerance.
   - Raised serum cholesterol—above 300 mg per 100 ml.
   - Secondary anaemia.
   - Rise of plasma proteins (albumin part).
6. **Heart, circulation and respiration**
   - Slow heart rate.
   - Stroke volume and minute volume is reduced.
   - Transverse enlargement of heart.
   - QRST—low voltage waves are seen on ECG.
   - Fall in cardiac output and blood pressure.
   - Increase in circulation time.
   - Respiratory rates are reduced.
7. **Urine:** Nitrogen, excretion less—similar to cretinism.
8. Thought processes slow down—lethargy, apathy.

GOITRE (Fig. 72.11)

It is non-inflammatory and non-neoplastic enlargement of the thyroid gland. In simple goitre usually there are no constitutional features of hypofunction or hyperfunction of the gland. There may be only pressure symptoms due to enlargement of the gland.

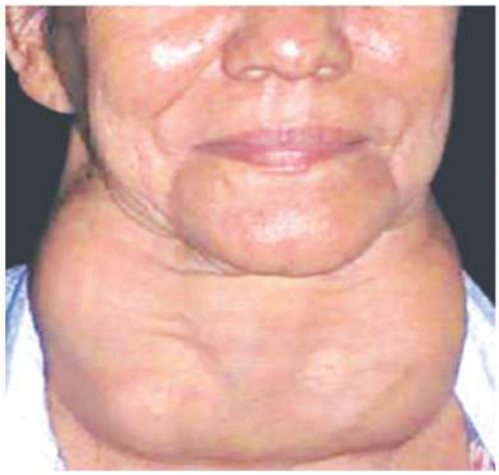

Fig. 72.11: Goitre

The simple goitre may be of the following types:

1. Colloid
2. Diffuse parenchymatous
3. Nodular or adenomatous
4. Toxic goitre.

Colloid goitre (endemic goiter; benign goitre): It is a deficiency disease caused by an inadequate supply of iodine in the diet. The alveoli are distended with colloid lines by cubical or flattened epithelial cells. There is no hypertrophy or hyperplasia. Use of iodised salt reduces the incidence of simple goitre.

In diffuse parenchymatous goitre the alveoli are not distended with colloid like the colloid goitre. The cells lining the alveoli are of columnar type. There is hypertrophy and multiplication of the alveolar epithelial cells. The lumens of some of the alveoli are almost obliterated.

In nodular or adenomatous goitre there is nodular swelling of part of the thyroid gland.

In all these types the iodine content is low.

Causes

1. Iodine deficiency.
2. Presence of goitrogenic substances in the diet, viz. excess of cabbage, brassica seeds, etc.
3. Drugs-like methyl- or propylthiouracil and carbimazole. These drugs inhibit formation of thyroxine, hence used in hyperthyroidism.
4. Faecal contamination of drinking water.
5. Trypanosome infection.

Toxic goitre: Enlargement of the thyroid gland along with excessive secretion of thyroid hormones. The epithelial cells are hypertrophied and hyperplastic. Toxicosis does not mean excessive secretion but toxic symptoms developed due to hyperthyroidism. Graves' disease is always associated with toxic goitre.

Hokkaido goitre: While deficiency of iodine may cause endemic goitre or endemic cretinism, a very high concentration of iodine may also cause hypothyroidism by inhibiting iodine organification—the Wolff-Chaikoff effect.

This may also be named as Hokkaido goitre because in Hokkaido the Japanese people consume large amounts of seaweeds providing 8 to 25 mg of iodine per day or more produced a good number of endemic goitre with hypothyroidism but no case of cretinism. Iodine in high doses may also interfere with release of T_4 and T_3 from the thyroid gland. Parenchymal hyperplasia is very much marked and majority of patients become hypothyroidism.

Hyperthyroidism thyrotoxicosis: Hyperthyroidism is always associated with hyper-secretion of thyroid hormones along with numerous clinical manifestations characterised by weight loss, increased BMR and sensitivity to catecholamines, tremor, increased vascularity of the gland, and also goitre and exophthalmos. More heat is produced and the skin becomes hot and sweaty. The heartbeats at a faster rate and this increase is maintained during sleep. The increased excitability of the heart muscle may result in ectopic pacemakers arising in the atria leading to atrial fibrillation. In this condition, thyroid hormones secretion is tremendously increased sometimes more than 10 times normal. Thyroid gland is enlarged and the enlargement is of nodular (toxic nodular goitre—Plummer's disease) type of more commonly, the diffuse (toxic diffuse goitre) goitre—Graves' disease. Thyroid antibodies have been identified in various thyroid disorders. **Anti-thyroid autoantibodies** such as anti-thyroid peroxidase antibodies (anti-TPO antibodies), thyrotropin receptor antibodies (TRAbs) and thyroglobulin antibodies target the thyroid gland thereby affecting hormone synthesis. The thyrotropin receptor antibodies act via various mechanism such as activating, blocking and neutral antibodies on the TSH receptor. Antibody when binds to the amino terminus of the TSH receptor it shows stimulatory activity, while antibodies binding to residues 261–370 or 388–403 blocks the thyroid activity. TRAbs are present in 70–100% of Graves' disease.

The Graves' disease is always associated with (a) hyperthyroidism, (b) exophthalmos, and (c) goitre.

In thyrotoxicosis, a person with hyperthyroidism becomes clinically ill with the condition. Mental stimulation makes the subject very nervous, irritable and very difficult to nurse. Food is rapidly converted to heat; subjects frequently lose weight although their appetite is still good. Thyrotoxicosis can be treated by medicine and surgery. Carbimazole and methimazole prevent iodine uptake by the thyroid gland and thus may reduce thyroxine formation.

GRAVES' DISEASE (BASEDOW'S DISEASE OR EXOPHTHALMIC GOITRE) (Fig. 72.12)

It occurs due to excessive secretion of thyroxine. Main features are as follows:

1. Enlarged thyroid (hypertrophy and hyperplasia).
2. Increased BMR and increased body temperature.
3. Eye signs
   - Exophthalmos: There is protrusion of eyeball with a 'staring' look—less twinkling of the eyelids due to deposition of fat in the retro-ocular region.
   - Retraction of the upper eyelids is caused by infiltration of fat in the levator palpebral superioris which leads to spasm of this muscle.
   - Opthalmoplegia or weakness of the external ocular muscles: The weakness of the muscles is due to excessive deposition of fat in these muscles. The muscles also show round cell infiltration and degeneration.
4. Body weight: It is decreased. Fat stores are depleted.
5. Mental condition: Sharp, emotional, restless, easy fatiguable.
6. Skeleton: Osteoporosis due to excessive loss of calcium.
7. Skin: It is soft, moist and flushed—due to vasodilatation and this helps in heat loss.
8. Blood:
   - Blood sugar level increased and may lead to glycosuria.
   - Altered lipid profile.
9. Heart and circulation:
   - Heart rate increases—may be up to 140 per minute. Cardiac output is increased. Heart consumes more O_2 and requires more thiamine.
   - Systolic blood pressure increases
   - Fall in circulation time.
10. Voluntary muscle: Fine tremor, increased ankle jerk reflex and muscular weakness.

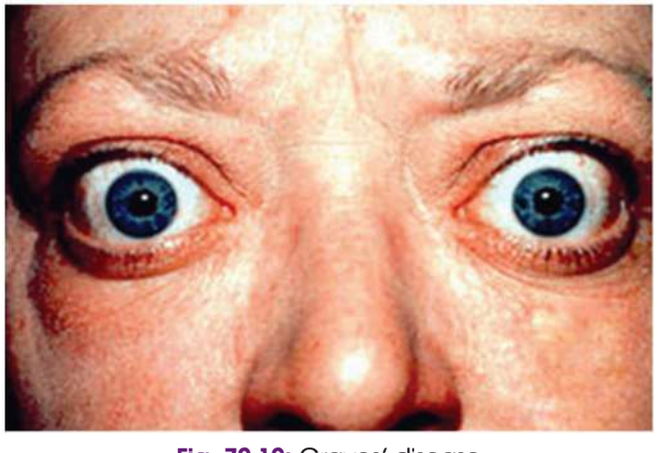

Fig. 72.12: Graves' disease

11. Electroencephalogram: It shows abnormal α-wavers.
12. Increased vitamin need: Due to rise of BMR, vitamin requirement rises—especially for vitamins A, B and C, unless these are supplied in excess amounts, deficiency signs will appear.
13. Sensitive to heat and susceptible to infection (possibly due to increased protein breakdown).

Investigation of Thyroid Activity

1. Since metabolism is affected by thyroid gland activity, the determination of metabolic rate under basal conditions (BMR) gives a guide to thyroid activity.
2. The blood cholesterol level is high in myxoedema and is low in thyrotoxicosis. The normal level of cholesterol is 180 mg per 10 ml of blood. The blood cholesterol level is lowered by thyroxine by increasing the excretion of cholesterol in the bile.
3. Measuring T_3, T_4, TSH and protein bound iodine level. The normal serum T_4 is between 4.6 and 12 µg/dl, the free thyroxine level ranges between 0.7 and 1.9 ng/dl, serum T_3 is 80–180 ng/dl and free T_3 is 230–619 pg/dl. The serum TSH level under physiological condition ranges between 0.4 and 4.2 microunits per milliliter (mcU/ml) or 0.4 and 4.2 milliunits per liter (mU/L). The normal PBI level in serum is between 4 and 8 gamma percent. PBI is low in myxoedema and high in thyrotoxicosis.
4. The use of radio-isotopes of iodine is used greatly to investigate thyroid activity. An oral dose of radio-active iodine gives a measurable concentration in the neck region after 4 hours later and this can be measured using an external radiation counter. The uptake is commonly low in myxoedema and high in thyrotoxicosis.
5. Thyroid activity may be determined by the ankle jerk. In thyrotoxicosis, this reflex is brisk. But in myxoedema this reflex is sluggish and there is a delay before the muscle relaxes.

Pathogenesis of Graves' Disease: Role of Long-acting Thyroid Stimulator (LATS)

Pathogenesis of Graves' disease: There are circulating TSH antibodies which are immunoglobulin and they exerts a prolonged stimulatory effect on the thyroid gland, causing rapid growth of the gland and excess thyroid function, resulting in hyperthyroidism. This stimulator has got long action and is known as long-acting thyroid stimulator (LATS). LATS is γ-globulin and produced by lymphocytes of patients with thyrotoxicosis. LATS biological activity may be transferred through transplacental passage and neonatal hyperthyroidism may be the cause of transfer of LATS from the thyrotoxic mother to the foetus. However, the presence of LATS does not always provide adequate explanation for all aspects of Graves' disease. Neither LATS nor thyroxine is responsible for the aspect of Graves' disease.

Exophthalmos-producing substance (EPS) has been extracted from the plasma of patients with the disease. This EPS is capable of producing exophthalmos experimentally in animals. This substance is not TSH but it may be of pituitary origin and a derivative of TSH.

Treatment of thyrotoxicosis: Thyrotoxicosis can be controlled by blocking thyroid hormone synthesis with anti-thyroid drugs like propylthiouracil and carbimazole (Neo-Mercazole) or by ablation of the hyperactive gland by surgery or radio-iodine. Anti-thyroid drugs block thyroid hormone synthesis and about 50% of patients are cured during a course of anti-thyroid drug treatment for a year. Treatment of thyrotoxicosis through ablation is more effective and rapid but in about 40% of patients it is followed by hypothyroidism associated with hypoparathyroidism. Hypothyroidism seems to be the only complication of radio-iodine therapy, whereas surgery, which is followed less often by hypothyroidism, has other complications such as hypoparathyroidism and damage to the recurrent laryngeal nerves. For rapid symptomatic remission in thyrotoxicosis, treatment with a β-adrenergic blocking agent (propranolol) may be used before treatment with anti-thyroid drugs, radio-iodine or surgery.

CONTROL OF THYROID SECRETION AND ENDOCRINE INTERRELATIONSHIP

Role of Anterior Pituitary (Fig.72.13)

The thyrotrophic hormone of anterior pituitary controls the formation secretion of thyroid hormones. On the other hand, the circulating level of thyroxine controls the secretion of thyrotrophic hormone or thyroid-stimulating hormone (TSH) or thyrotrophin. Rise of thyroxine level in blood depresses, whereas fall of thyroxine level increases secretion of thyrotrophin. After thyroidectomy more thyrotrophin is secreted. In this way, the TSH and thyroxine control each other. In other words, through anterior pituitary, thyroid controls its own secretion. Excess secretion of thyrotrophin stimulates the thyroid hormone formation in the following ways: Increase in the proteolyses of thyroglobulin.

Influence of the Central Nervous System and Role of Hypothalamus

Thyroxine may reach hypothalamus and exerts its inhibitory influence on secretion of pituitary thyrotrophin. Hypothalamus controls the secretion of thyrotrophic hormone or thyrotrophin of the anterior pituitary.

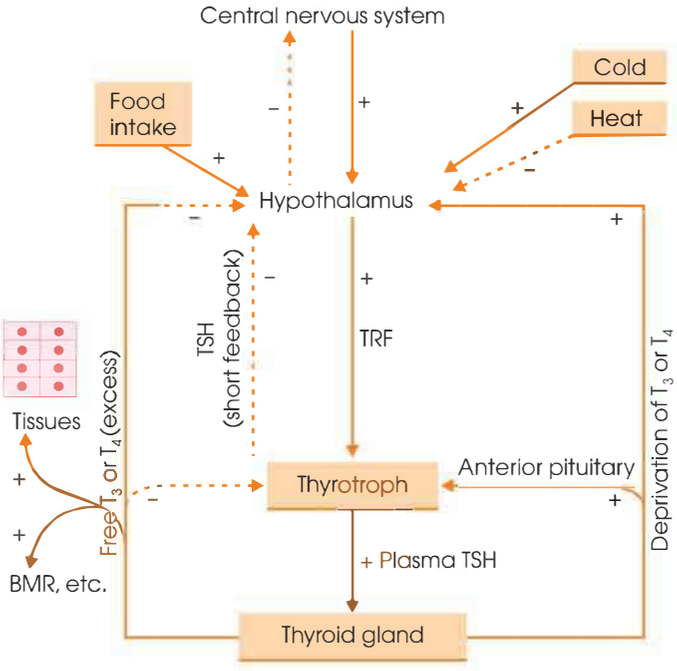

Fig. 72.13: Diagrammatic representation showing interaction of feedback mechanism and neuro-humoral control in the regulation of thyroid hormone secretion

Key Points

1. The neural mechanism which controls TSH secretion is possibly located in the medial eminence of the hypothalamus through liberation of TRF (thyrotrophin-releasing factor) into the hypothalamo-hypophyseal blood vessels.
2. TSH secretion from anterior pituitary is controlled by blood thyroid hormones at dual levels, both pituitary and hypothalamus. The "long-loop feedback" control at the hypothalamic level acts both in an excitatory and inhibitory way and requires the presence of an intact hypophyseal portal system. A direct feedback regulation at the pituitary level is also operative.
3. TSH acts on thyroid gland to stimulate all steps involved in synthesis of thyroid hormone.
4. Rise of thyroxine level in blood depresses, whereas fall of thyroxine level increases secretion of thyrotrophin.

Role of Sympathetic and Parasympathetic Nerves (Vasomotor Regulation)

Thyroid is supplied both by sympathetic and parasympathetic nerves. They regulate thyroxine secretion through vasomotor effects only. No direct secretory activity has been observed. Thyroid can secrete thyroid hormones even after complete denervation.

Stress Phenomena

Physical and emotional stress, peripheral electric stimulation, haemorrhage, laparotomy, injection of turpentine, abscess formation, etc.; inhibit the thyroid gland due to a reduction of thyrotrophin output.

Thyroid–Adrenal Interrelationship

Administration of ACTH or cortisone inhibits the thyroidal accumulation and release of radio-iodine. It is probable that TSH secretion is interfere with, since injury to adrenal cortex results in a rise in heat production provided the thyroid is intact. There is a reciprocal relation between ACTH and TSH, and hence between cortical and thyroid hormones effects.

Thyroid–Gonadal Interrelationship

Normal reproductive functions in both the male and the female requires normal amount of thyroid hormones to be present. Female reproductive system: Hypothyroidism results in prolonged to be arrested oestrous cycle, reduced fertility, increased foetal resorption, etc. It is suggested that the placenta secretes a thyroid-stimulating factor which may account for the increased thyroid-stimulating activity of the sera of pregnant women and of patients with tumours of chorionic tissue. Male reproductive system: Adequate thyroid function is presumably necessary for normal development and function of the male reproductive system. Thyroid may exert effects on sperm number and motility and testicular DNA. It is not clear if the abnormal reproductive functions as observed in thyroid hormone deficiency are due to reduced ability of the pituitary to secrete gonadotrophins or defective response of the target organs.

Anti-thyroid Compounds

Anti-thyroid compounds are used experimentally to produce hypothyroidism, and clinically in the treatment of hyperthyroid conditions (Fig. 72.14). The most active group like thiourea, thiouracil, propylthiouracil, etc. and also sulpha drugs, para-aminobenzoic acid (Fig. 72.15), para-aminosalicylic acid, etc. act in a similar manner to produce hyperplastic goitres.

In such condition although the gland can accumulate iodine normally, the synthesis of thyroid hormones does not occur, due to interference in the iodination of tyrosine in the gland, low thyroxine level in blood increases secretion of TSH from the anterior pituitary. The size of the thyroid gland may be reduced by removing the pituitary but such a gland does not produce any hormone. External administrations of thyroid hormones relieve the goitres. The second group of compounds like thiocyanate, periodates, perchlorate, etc. do not block the synthesis of thyroid hormone as in the previous group, but inhibit in the concentration of iodine inside the gland through an unknown mechanism. A high dietary intake of iodine, enough for the synthesis of normal amount of thyroxine prevents the occurrence of such goitre.

Compounds occurring in some natural foods like cabbage, turnips, kale, etc. also produce goitre. They contain a compound progoitrin and an activator which

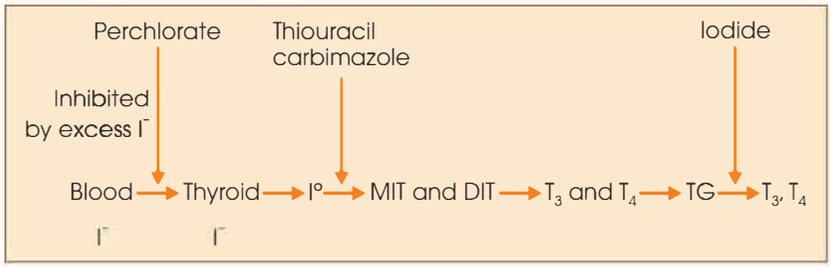

Fig. 72.14: Probable sites of action of anti-thyroid drugs

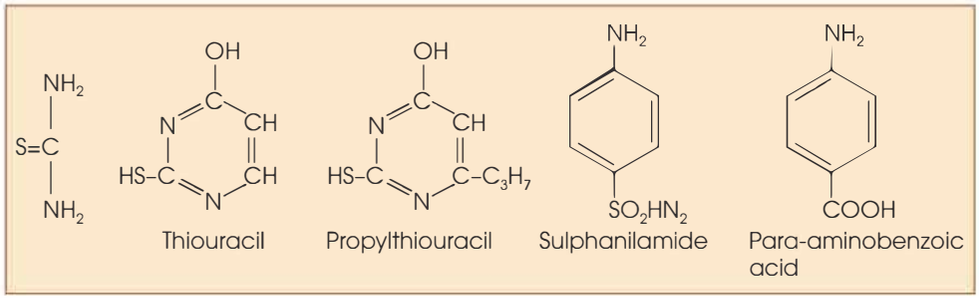

Fig. 72.15: Structural formulae of some anti-thyroid drugs

converts it into goitrin. The activator is also present in the intestine.

EXAM-ORIENTED QUESTIONS

Essay

1. Discuss the physiological action and functions of thyroid gland: Add note on cretinism.
2. Describe the mechanism of secretion and synthesis of thyroid hormone. Discuss the regulation of thyroid hormone secretion.
3. Discuss regarding the synthesis, storage, release and transport of thyroid hormones.

Short Notes

1. Goitre
2. Myxoedema
3. Cretinism
4. Thyroid–gonadal interrelationship
5. Graves' disease
6. Synthesis, storage, release and transport of thyroid hormones

Chapter

73

Parathyroid Gland

INTRODUCTION

Thyrocalcitonin (TCT) is secreted from the mitochondrial-rich parafollicular cells of C cells (C for calcitonin) of the thyroid gland.

Chemistry

Calcitonin is a 32-amino acid linear polypeptide hormone.

Synthesis

It is formed by the cleavage of a larger prepropeptide which is a product of the CALC1 gene (CALCA). The CALC1 gene belongs to a superfamily of related protein hormone precursors calcitonin gene related peptide, islet amyloid precursor protein, and adrenomedullin.

Regulation of Secretion

The blood calcium level controls calcitonin secretion. The normal serum calcium level ranges from 9 to 11 mg/dl. The increase in calcium level will increase the calcitonin secretion from C cells of thyroid gland. The hormone calcitonin inhibits renal tubular cell reabsorption of Ca^{2+} and phosphate and increases the calcium deposition in the bones by inhibiting the osteoclastic activity thereby bringing down calcium level.

Physiology

It is the calcium-lowering hormone of the thyroid. It acts on the circulating calcium levels faster than the parathormone and half-life of thyrocalcitonin is 4–12 minutes, which is shorter than the parathyroid hormone. The hypocalcaemic action of this hormone is due to inhibition of bone resorption and calcium release.

1. It lowers calcium level by inhibiting osteoclast activity in the bones and reabsorption of Ca^{2+} and phosphate in the kidney.
2. *Skeleton-preserving actions of calcitonin:* Calcitonin protects against calcium loss from skeleton during lactation and pregnancy. The protective effect is exerted by calcitonin through the direct inhibition of bone resorption and the indirect effect through the inhibition of the release of prolactin from the pituitary gland. Prolactin stimulates the release of PTH related peptide which promotes bone resorption. Role of prolactin is further being investigated.

It inhibits osteoclastic activities and thus lowers blood calcium and phosphorus. The osteoclast has calcitonin receptors (these are G-protein-coupled receptors) while osteoblasts do not. And since bone resorption and bone formation are interlinked process, the inhibition of osteoclastic activity leads to decreased osteoblastic activity.

THE PARATHYROID

The parathyroids are essential for life, as they are important for the regulation of the concentration of calcium ions in the body fluids. After parathyroidectomy the blood calcium level falls and causes a neuro-muscular irritability—the tetany.

Anatomy

The parathyroid gland consists four small oval bodies (6 × 3 × 2 mm) embedded in the posterior surface of the thyroid—one pair arranged vertically behind each lobe. The total weight of parathyroid gland is about 140 mg. The gland is highly vascular and the blood supply is derived from paired superior and inferior thyroid arteries.

Histology

Histological features reveal masses or columns of epitheloid cells, with large blood sinuses in between them. Two types of cells are:

Chief cells or principal cells: Small faintly staining non-granular cells and completely clear cytoplasm, with comparatively large vesicular nucleus. Sometimes,

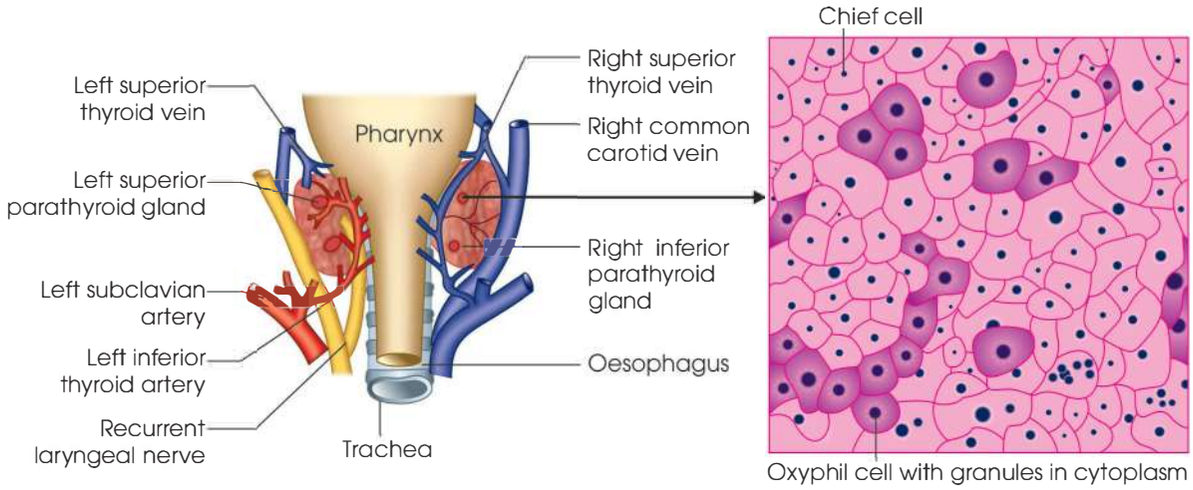

Fig. 73.1: Diagrammatic representation of anatomical position and histological structure of parathyroid gland

these cells enlarge and possess numerous cytoplasmic vacuoles; they are then called water-clear cells. The cells contain glycogen. Majority in number, remain throughout the life.

Oxyphil cells: Large polyhedral granular cells and acidophilic cytoplasm. Granules stain with eosin and other acid dyes. The oxyphil cells are few in number (Fig. 73.1). Both types contain fatty granules or minute spherical globules, increasing in number with age. Principal cells persist up to 10th year of life in human beings. Small colloid vesicles (like those of the thyroid) are also found, but without any iodine. Variable amounts of adipose tissue may be observed within the gland.

Parathyroid Hormone

The parathyroid gland secretes parathormone. PTH is a polypeptide containing 84 amino acids. It is having a molecular weight of 9500. The effective hormone-receptor interaction requires solely the N-terminal amino acids (within amino acids 1–27).

Synthesis

It is synthesized from prepro-PTH containing 115 amino acids. The removal of 25 amino acids in endoplasmic reticulum; forms pro-PTH having 90 amino acids. Final removal of 6 amino acids in Golgi complex forms PTH consisting of 86 amino acids.

CONTROL OF PARATHYROID SECRETION

Secretion of PTH

It is controlled by a negative feedback mechanism, relating to the level of calcium in the plasma (Fig. 73.2). The secretion of parthormone is stimulated by decreased serum [Ca^{2+}], mild decreases in serum [Mg^{2+}] and increase in serum phosphate while increased serum [Ca^{2+}], largely decreased serum [Mg^{2+}] level stimulates calcitriol. Recent advances revealed calcium sensing receptors on membrane of chief cells. Calcium sensing receptors are G protein couple receptors. Receptor attached to phospholipase C binds with calcium forms DAG and IP_3 which via activating protein kinase has inhibitory influence on PTH.

Mechanism of Action

PTH acts via its type 1 receptor (PTH 1R), type 2 receptors (PTH 2R) and type 3 receptors (carboxyl terminal of PTH) activates adenyl cyclase and phospholipase C and via activates DAG and IP_3 to exert its cellular action-mediated functions.

The parathyroid hormone mainly acts on bones intestine and kidney. It releases calcium from the bone, increases absorption of calcium in renal tubule and also enhances absorption of calcium from the gut.

PHYSIOLOGICAL FUNCTIONS OF PARATHYROID GLAND

The physiological functions of the gland are as follows:

1. It regulates serum calcium levels. The active principal of the parathyroid is parathormone (PTH) and acts in response to a lowering of blood calcium by stimulating the osteoclasts to reabsorb bone and free calcium ions from the reserve skeletal depots (Fig. 73.2). In early effect on osteocyte; it leads to release of calcium from crystals of mature bone into blood, this occurs within 15–30 minutes and does not initially depend upon the synthesis of RNA by osteocyte. A slower effect occurs on the turnover of bone and remodeling during maintained hyper-secretion.
2. It directly increases renal tubular reabsorption of calcium. It decreases calcium loss through urine.
3. It regulates the excretion of inorganic phosphate in the urine. PTH increases direct renal excretion of phosphate.

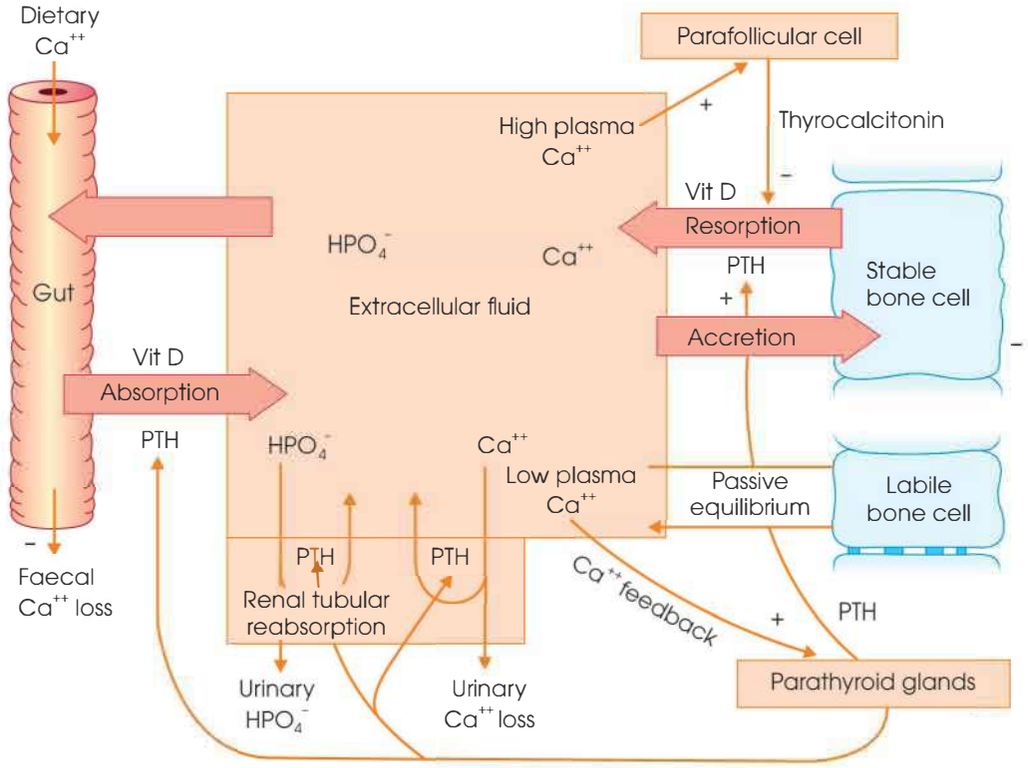

Fig. 73.2: Schematic representation of parathyroid control of extracellular calcium and the sites of PTH action

4. It may increase the rate of calcium ion absorption in the gut and this effect is mediated by calcitriol.
5. PTH may decrease the rate of Ca^{++} secretion by the lactating mammary gland. It also controls the intracellular disposition of phosphate.

These actions enhance the calcium level in circulation.

TETANY IN MAN

It may occur due to removal of the parathyroid during thyroidectomy. The clinical features are:

1. **General convulsion** (children).
2. **Carpopedal spasm** (Trousseau's sign) (Fig. 73.3): Slight pressure on the limbs may elicit this: Elbow and wrist flexed; fingers flexed at the metacarpophalangeal joints but extended at the interphalangeal joints. Thumb in the palm and fignertips drawn together Accoucheur's hand), feet extended and plantar flexed.
3. **Laryngismus stridulus:** Spasm of the glottis with inspiratory stridor.
4. **Chvostek's sign:** Tapping the facial nerve near the styloid process causes facial spasm.
5. **Erb's sign:** Increased excitability of motor nerves to galvanic current.

Causes of Tetany

The lowered ionic calcium in blood and tissue fluid is the immediate cause. Fall of Ca increases the proportion of neuro-excitatory factors, viz. Na, K, etc. and causes tetany. Total calcium has no relation. Lowering of total calcium due to diminished plasma protein does not cause tetany. This shows that calcium which remains bound with protein is not physiologically active.

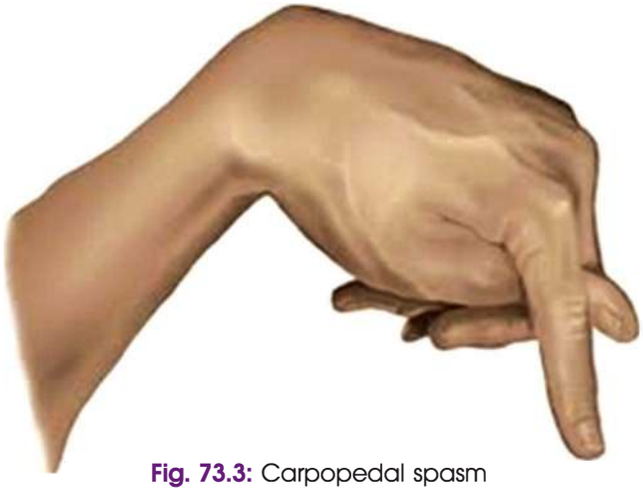

Fig. 73.3: Carpopedal spasm

Other Forms of Clinical Tetany

Apart from parathyroid deficiency, hypocalcaemic tetany is also found in the following conditions:

1. **Tetany from alkalaemia:** Alkalaemia alters ionic balance and decreases the amount of ionic calcium without affecting the total calcium. Alkalaemia increases the proportion of the neuro-excitatory ions, and makes the nerve fibres and centers more excitable.

Alkalaemia may be produced from:
- Excess intake of alkali
- Profuse vomiting
- Increased breathing, etc. It causes tetany without reducing total calcium.

2. **Tetany in rickets (infantile tetany):** Owing to vitamin D deficiency, serum calcium is lowered due to lack of absorption, hence tetany. In osteomalacia (adult rickets), the same thing happens.
3. **Tetany in renal failure:** Reabsorption of calcium by renal tubules is diminished and serum calcium level is lowered.
4. **Tetany due to impaired absorption of calcium** from the intestine as seen in coeliac disease and sprue.
5. **Tetany due to increased alkaline phosphate:** Injection of large amounts of alkaline phosphate lowers serum calcium and produces tetany.
6. **Magnesium deficiency tetany:** It has been produced experimentally in dogs, rats and young cattle by giving magnesium deficient diet. Serum phosphorus and calcium are normal but magnesium is lowered. Not known in man.

DISORDERS OF PARATHYROID SECRETION

This occurs due to parathyroid tumours of diffuse hyperplasia of the parathyroid glands.

Features

1. Weakness, loss of muscular tone, renal disorders (calculi, nephrocalcinosis, and renal failure), nausea, vomiting, reduced appetite, thirst, mental symptoms, polyuria, etc. Polyuria is due to damage of the distal renal tubules inhibiting the reabsorption of water and there is increased excretion of calcium in the urine. Stones, containing calcium salts, are formed in the kidney.
2. Rarefaction of bones (especially subperiosteal resorption) due to increased mobilisation of calcium and phosphate from the bones, sometimes there is also formation of many bone cysts, a disease known as osteitis fibrosa cystica.
3. Increased plasma alkaline phosphatase level.
4. Increased plasma calcium level and reduction of plasma phosphate level. Sometimes only ionic calcium level is raised without increasing total calcium level.

HYPOPARATHYROIDISM

Hypoparathyroidism is uncommon due to idiopathic atrophy (sometimes accompanied by evidence of an autoimmune disorder) of the parathyroids but it occurs most commonly after the surge of the thyroid gland. Hypoparathyroidism causes tetany. When PTH is secreted in excessive amounts; a target-organ resistance to PTH causes pseudoparathyroidism which shows all the features of hypoparathyroidism. There is a defective indication in the membrane-receptor/adenyl cyclase system is a defective indication in the membrane-receptor/adenyl cyclase system in kidneys and bone, and cyclic AMP formation in response to PTH is deficient.

CALCIUM

Calcium is the principal component of the human skeleton and the fifth most common inorganic element of the body. A total calcium content of normal adult humans is 20–25 gm per kg of fat-free body tissue.

Sources

Water especially hard water, eggs, milk (about 1 gm per liter), cheese (5–10 gm per kg) and green vegetables are the chief sources. Fish and meat are poor sources.

Distribution of Calcium in the Body

Total quantity is 2% of the body weight, of which bones and teeth contain 99%. The remaining 1% is distributed in different tissues as follows: Muscles: 8 mg per 100 gm of fresh muscle; plasma or serum: 9–11 mg per 100 ml; RBC—minute traces; lymph and aqueous humour (also ascites and oedema fluid) slightly less than in plasma; cerebrospinal fluid: 5.3 mg per 100 ml. Maternal source in fetal life: Before the fifth month of intrauterine life, very little calcium is found in the foetus, because bone formation is only starting then. During the last two months of intrauterine life, when rapid and extensive ossification takes place, over 60% of the total calcium deposition occurs.

BLOOD CALCIUM

Total quantity (vide above)—varies from 9 to 11 mg (average 10 mg) per 100 ml of blood. This level is kept fairly constant. It remains in the following forms:

1. Diffusible calcium remains in the:
   - Ionised form 4.8 to 6.3 mg per 100 ml of blood and
   - Non-ionised form remains in combination with citrate, bicarbonate and phosphate 0.25 to 0.5 mg per 100 ml of blood.
2. **Non-diffusible calcium** remains in combination with plasma proteins, especially albumin 4 to 5 mg per 100 ml of blood.

The levels of blood calcium depend on the following:

1. **Amount of soluble calcium ingested:** After ingestion of large doses of soluble calcium salts, the serum calcium rises, being maximum in about 2 hours and coming back to normal level in about further 3 hours. It is not possible to maintain a

constantly high calcium level by giving calcium salts alone. Calcium salts, given intravenously, quickly disappear from circulation.

2. **Amount of calcium absorbed by action of parathormone and thyrocalcitonin:** Parathyroid activity increases blood calcium while thyrocalcitonin secretion lowers blood calcium level. Similarly, hydrogen ion concentration of plasma affects calcium levels: A rise of hydrogen ion concentration raises serum calcium whereas alkalaemia, although does not produce a definite decrease in the total serum calcium, yet produces symptoms of hypocalcaemia. Two explanations are advanced:
   - Alkalaemia reduces the amount of active ionised calcium.
   - Alkalaemia excites the nervous system in the same way as low blood calcium.
3. **Concentration of plasma proteins:** Raised concentration of proteins increases blood calcium, because some calcium remains in combination with the proteins. But this is in an inactive form. The variation of the amount of calcium content in different fluids is mainly due to their difference of protein concentration.
4. **Plasma phosphate:** It varies inversely as the plasma calcium. An increase in the phosphate ion causes a corresponding decrease of calcium ion and *vice versa*. The product of calcium and inorganic phosphate of excretion or deposition in the bones.
5. **Sex hormones:** Women during menopause sometimes suffer from negative calcium (and also phosphorus) balance. Either oestrogens or androgens are effective in correcting the above condition; a combination of both hormones is most effective.
6. **Calcium content of lymph and cerebrospinal fluid:** Lymph is having lower protein content, contains less calcium than blood. Cerebrospinal fluid which has traces of proteins contains still less. It contains only about 5.3 mg per 100 ml, but practically the whole of it is in a diffusible active form. Calcium of cerebrospinal fluid is constant and generally runs parallel to the ionic calcium of plasma.
7. **Absorption of calcium from the gut:** It is always incomplete. The ability to utilise calcium of different foods varies greatly. On a high protein diet, 15% of dietary calcium is absorbed; on low protein diet only 5%.

The following facts are important about calcium absorption.

Site of absorption: Absorption takes place mainly from the food (specially dairy products) in the upper part of small intestine (maximal in the duodenum) under the influence of vitamin D (present in food or produced by action of ultra-violet light on 7-dehydrocholesterol in the skin); excess intestinal lipids reduce calcium absorption.

Form of absorption: Soluble inorganic forms are much better absorbed. It is probable that the organic calcium of food is converted into inorganic form, before it can be absorbed. Insoluble calcium compounds are never absorbed. Thus, presence of phytic acid in cereals produces formation of calcium phytate which is insoluble. Oxalates may have a similar effect. Calcium phosphates are not absorbed.

Factors Affecting Calcium Absorption

1. **Role of vitamin D**

   Vitamin D is a group of fat-soluble secosteroids which increases intestinal absorption of calcium. The important compounds in this group are vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Diet and dermal synthesis from sunlight are two important source of vitamin D in humans. Vitamin D is biologically inactive. The conversion of vitamin D to its active metabolite form occurs in liver and kidney which aids in enhancement of intestinal transport of calcium.

   In liver: Cholecalciferol is hydroxylated to 25-hydroxycholecalciferol by the enzyme 25-hydroxylase.

   In kidney: 25-hydroxycholecalciferol in presence of enzyme 1-alpha-hydroxylase, is hydroxylated to form 1, 25-dihydroxycholecalciferol.

   Calcitriol

   Intestine: It increases the plasma calcium levels by increasing calcium absorption in intestine by enhancing the production of calcium carrier protein calbindin D. It also increases the number of Ca^{2+} ATPase in intestinal cells.

   Renal: It also increases calcium absorption from DCT as it enhances the number of calcium pumps in the cells of distal and proximal tubules.

   Bones: Calcitriol increases activities of osteoblast and promotes mineralization of bones.

   Other functions: It aids and stimulate transport of calcium into skeletal and cardiac muscles. It also have promotive role in cell differentiation.
2. **Source of calcium:** Calcium from different sources is differently absorbed. Milk calcium is highly absorbed but vegetable calcium much less. Certain vegetables, such as spinach, owing to its high oxalic acid content, converts soluble food calcium into insoluble calcium oxalates. Hence, these oxalic acid containing vegetables reduces calcium absorption.
3. **Reaction of the intestine:** A high acidity favors calcium absorption, because the calcium salts become soluble in acid medium. Alkalinity produces insoluble calcium salts and reduces absorption. Sugars especially lactose; increases acidity due to its conversion into lactic acid favours calcium absorption. An excess of unabsorbed fatty acids if present in the intestine, converts soluble calcium into insoluble

calcium soaps and reduces absorption. Phytic acid which is commonly present in cereals, precipitates calcium in the bowel as the insoluble calcium phytate, and thus reduces its absorption.

4. **Phosphorus content of diet:** High phosphorus content of food forms insoluble calcium phosphate and reduces calcium absorption.
5. **Bile salts** help calcium absorption by their hydrotropic action on calcium soaps.
6. **Vitamin D:** It is essential for calcium absorption in man but it lowers the renal reabsorption of calcium.
7. **Protein content of diet:** Increased protein intake enhances the absorption of calcium. The amino acids, lysine and arginine are most effective.

CALCIUM EXCRETION

Excretion

It occurs through urine and faeces. With an ordinary diet, the calcium content of human faeces is about 200 mg daily. This is believed to be fully exogenous (i.e. unabsorbed calcium). After intravenous administration of the radioactive isotope 44Ca it is found that about 10% of the amount injected is excreted in the faeces within 8 to 10 days. About 150–200 mg (25% of the total excretion) is excreted through the urine.

Calcium Balance

In the adult, the calcium intake and loss are same. This is called calcium balance. When calcium is retained in the body (i.e. more intake than loss), the balance is called positive. When the loss is more than the intake, the balance is called negative. The positive balance is found during growth, pregnancy, acromegaly, or recovery after calcium starvation. In a growing child, the retention is according to the size of the child and not according to his age (0.01 gm per kg per day). A negative balance is found during hyperactive condition of thyroid and parathyroid, in calcium deficiency and in certain other diseases, such as rickets, sprue, osteomalacia, celiac disease, etc.

Functions

Calcium is of enormous importance for the body. The following is a brief summary:

1. Essential for the formation of bones and teeth.
2. Essential for the coagulation of blood.
3. Essential for the coagulation of milk.
4. Essential for the contraction of the heart muscle and the rhythmicity of heart.
5. Maintains normal neuromuscular excitability. In this respect, it is the reverse of sodium and potassium. These are neuro-excitatory whereas calcium is neurosedative. Consequently, in hypocalcaemia, the action of sodium and potassium becomes unopposed; nervous system becomes highly excitable so that convulsion, tetany, etc. occur.
6. Controls the permeability of the capillary endothelium. High blood calcium diminishes and low blood calcium increases the permeability.
7. Activation of enzymes. Certain enzymes like succinic dehydrogenase, ATPase, lipase, etc. are activated by calcium.

Effects of Deficiency

It may cause rickets, tetany, etc. A deficiency of calcium in the diet on a defective absorption of calcium due to low vitamin D content results in faulty calcification of bones. This condition is known as rickets and is usually found in children maintained on poor diets specially, lacking in calcium and phosphorus content. Renal rickets is caused by a tubular defect in the kidney in which normal reabsorption of calcium from the tubular filtrate is inhibited, and large amounts of calcium are excreted in the urine. As the defect lies in the tubules, vitamin D administration does not correct this phenomenon.

Daily Requirement

1.0–1.5 gm (0.63 gm) per day is the minimum for a subject of 70 kg of body weight. In childhood (from 3 to 14 years) and pregnancy the daily requirement is about 1.5 gm. During lactation the daily requirement is more than 3 gm.

PHOSPHORUS

Sources

1. *Inorganic:* Milk, meat product (muscles), and vegetables.
2. *Organic sources are:* Nucleoproteins, phosphoprotein, phospholipids present in sources such as milk, eggs, brain, liver, yolk of eggs, etc.

Distribution

Total quantity is about 1.1% of the total body weight. It occurs in the form of orthophosphoric and pyrophosphoric acids. It is present in all tissues, both in organic and inorganic forms. In the tissues the concentration of phosphorus is higher than in blood. Bones, brain, liver, pancreas, etc. are very rich in phosphorus.

Blood Phosphorus

1. **Inorganic phosphate:** Distributed equally between plasma and corpuscles: 2.5 to 4.5 mg (average 3 mg) per 100 ml; higher values of phosphorus are found in infants.
2. **Organic phosphate:** Large quantities in the form of phospholipids (lecithin, etc.) and also as ester phosphorus (glycerophosphates, etc.) are found in the red cells.

Calcium/inorganic phosphorus ratio in blood is on the average 2:1. Anything that raises calcium, lowers phosphate and *vice versa*. Their products remain

constant. Inorganic phosphorus is diminished in rickets, hyperparathyroidism and after insulin injections.

Absorption

It is usually incomplete. It is absorbed from the upper part of the small intestine (especially in the jejunum), chiefly in the form of inorganic phosphate. Organic phosphates are believed to be converted into inorganic forms before absorption.

The amount absorbed depends upon the following:

1. Amount of intake of phosphate through diet.
2. Reaction of the intestinal contents. Acidity favours absorption.
3. Calcium/phosphorus ratio of diet. High calcium content diminishes phosphorus absorption. In the diet, the optimum ratio should be 2P:1Ca.
4. Bile salts favour phosphorus absorption by their hydrotropic action.
5. Vitamin D does not appear to stimulate phosphate transport directly. However, dietary level of vitamin D intake does affect phosphate transport indirectly since phosphate appears to be transported in association with calcium. Parathyroid hormone and dihydrocholecalciferol cause a direct stimulation of phosphate transport in the jejunum.
6. Fatty acids in diet. The effect of fatty acids on phosphorus absorption is opposite to that upon calcium. Fatty acids combine with calcium and liberate phosphorus for absorption. Hence, excess fatty acids hinder calcium absorption but favour phosphorus absorption.
7. Excess cereals in diet. The cereals are rich in phytic acid (inositol hexaphosphate) or phytin (Ca-Mg-phytate), which are insoluble, indigestible and hence are not absorbed. In this way large amounts of Ca and P are lost.

Control of Phosphorus Metabolism

1. Endocrines: Probably all the endocrine glands that are mentioned under calcium take part also in the phosphorus metabolism.
2. Kidneys regulate the phosphate buffer system of blood.
3. Vitamin D also takes part in its metabolism.

Excretion of Phosphorus

The total daily output is about 3.5 gm of phosphoric acid. Two-thirds of it (2.5 gm) is passed in the urine and rest in the faeces.

Functions

1. **Essential constituent of all cells,** for instance, nucleoproteins in the nuclei and phospholipids. In these forms they play an essential role in the function of the cells.
2. **Essential for the formation of bones and teeth.**
3. **Phosphoric acid compounds** such as ATP, phosphagen, hexose phosphate, etc. take an essential role in the chemical changes underlying muscular contraction.
4. **Phosphorylation of lipids** is important for:
   - Lipid absorption
   - Lipid transport through blood
   - Lipid metabolism
5. **Phosphorylation of glucose** is essential for:
   - Absorption of glucose from intestine
   - Reabsorption of glucose from kidneys
   - The metabolism of glucose and glycogen.
6. **Takes part in blood clotting.** Kelphalin (cephalin) is a phospholipid which initiates blood clotting.
7. **Regulates H-ion concentration** of cells, blood and urine. In the blood the acid and alkaline phosphates act as buffers. In the urine the relative proportions of these salts are responsible for the reaction of the urine. Inside the cells there are also phosphate buffer systems which regulate intracellular reaction.
8. **Helps in the enzymatic functions of vitamin B complex.** Thiamine, riboflavin, nicotinic acid, etc. act as coenzymes in combination with phosphoric acid.
9. **Other metabolic actions.** Phosphate ion plays a critical role in maintaining an adequate ion solubility product and thereby maintaining sufficient metastability of extracellular fluid to sustain an adequate mineralization of bone. Phosphate ion may also play a role in inhibition of bone resorption. The intracellular concentrations of blood phosphate, particularly in the kidneys, may influence renal transport of calcium. Increased levels of inorganic phosphate in the diet have a direct effect on renal clearance of calcium, as calcium excretion is decreased by a phosphate load.

Daily Requirement

About 1 gm of phosphorus per day is the minimum need for a man of 70 kg. Pregnant and lactating women and growing children require more. On an average, a child requires 1 gm, pregnant female 1.5 gm. Usually enough is present in a normal adequate diet.

Relationship between Plasma Ionized Calcium and Phosphate

When one is increased the other tends to fall, which accounts for the importance of lesions of phosphate metabolism in disorders of calcium utilisation. Bone mineralization does not take place satisfactorily unless the product of calcium and phosphorus is fairly high (normally over 25, but above 60 there is a possibility of metastatic calcification).

CALCITRIOL

It is also known as **1, 25-dihydroxycholecalciferol**

Formation of Calcitriol

The 7-dehydroxycholecalciferol present in the skin under effect of UV radiation from sunlight is converted to vitamin D_3 (cholecalciferol). The Vitamin D is converted in liver to 25-hydroxy cholecalciferol. The 25-hydroxyvitamin D_3, 1-alpha-hydroxylase enzyme catalyzes the hydroxylation of 25-hydroxycholecalciferol (calcifediol) to calcitriol in the proximal tubule of the nephron in the kidneys. The activity of the 25-hydroxyvitamin D_3, 1-alpha-hydroxylase enzyme is stimulated by PTH.

Excretion

Calcitriol is converted to calcitroic acid by enzymatic action of 24-hydroxylase and later excreted in urine.

Action of Calcitriol

Calcitriol increases blood calcium levels by its action on GIT, renal system and bones.

1. It increases the production of carrier protein calbindin thereby enhancing absorption of calcium in small intestines. It increases calcium ATPase activity.
2. It increases reabsorption of calcium in renal tubules.
3. It stimulates osteoblast. It enhances mineralization of bone at physiological levels.

BONE

It is a connective tissue having collagen network and constitutes salt of calcium and phosphate.

Composition of Bone

It consists of inorganic and organic matrix. The bone cells which are osteoblasts, osteocyte and osteoclast are embedded in the organic matrix. The matrix is made up of between 90 and 95% collagen fibres. The inorganic components are hydroxyapatite mainly and calcium and phosphate salts. Nearly 30% of the acellular part of bone is made up of organic components, and salts account for remaining 70%. The hydroxyapatite provides compressive strength to the bone while collagen fibres provide tensile strength. Trace minerals such as magnesium, sodium, potassium and carbonate are also found in bone.

Structure of Bone

Bone is made up of outer layer which is termed as compact bone and inner layer which is trabecular or spongy bone. The compact bone which accounts for 80% of the bone contains mass of bony tissue arranged in concentric layers (Haversian systems). The trabecular or spongy bone which accounts for 20% of the bone is located beneath the compact bone and made of a meshwork of bony bars (are called trabeculae) having interconnecting spaces containing bone marrow. The smaller spaces between the lamellae contain the bone cells and are called lacunae. The minute channels called canaliculi link lacunae together. The nutrients supply and removal of waste product occurs through canaliculi to the osteocytes.

Formation of Bones

1. Bone formation starts during the third week of intrauterine life. Osteoblasts are modified fibroblast and synthesize collagen. The osteoblast which produces new bone invades the cartilage and produces a substance called osteoid. Osteoid is made of collagen and contains sites where calcium phosphate crystals are deposited and this process is called mineralization. The hydroxides and bicarbonates are also deposited in the matrix. This mineralization takes place in the middle of the newly forming bone and this site is known as primary ossification centre. The bone formation progresses from the centre to the ends of the bone. The growth of blood vessels occurs in bone. In newborn, the ends of bones have cartilage. The area at the end of all long bones is the growth plate. This area is the secondary ossification centre and is involved in bone growth and lengthening of bone during childhood. The developing region of bone is the epiphysis and it is separated from shaft by epiphyseal plate. At puberty there is closure of epiphysis and lengthening of long bones ceases then.
2. The bone is composed of various types of cells such as osteoblasts which are involved in the mineralization of bone tissue, osteocytes, and osteoclasts mainly participate in the reabsorption of bone tissue. The osteoblasts further mature into inactive osteocytes. Osteocytes migrated into and are trapped in the bone matrix. The spaces osteoblasts occupy are called as lacunae. Osteocytes through developed processes communicate with osteoblasts and other osteocytes. Osteoclasts are located on bone surfaces in *Howship's lacunae* also known as *resorption pits*. Osteoclasts carry bone resorption and synergistically new bone is then formed by the osteoblasts. The formation and resorption of bones continues throughout the life cycle.
3. The factors stimulating bone formation are growth hormone, vitamin D, oestrogen, testosterone and insulin while parathormone, cortisol, thyroxine, cortisol and prostaglandins stimulate resorption of bones.

Functions of Bones

1. It forms the skeleton framework of the body.
2. The skeleton which is formed of bones provides mechanical protection to the internal organs of body Example: Cranial bones envelope the brain and prevent it from injury, vertebrae provide protection to the spinal cord, etc.

3. They aid in body movements and participate in maintenance of posture.
4. The bone contains marrow in which blood cells are formed.
5. Bones store minerals such as calcium, phosphate and magnesium.
6. The red marrow is converted to yellow marrow with aging and it contains adipose cells which contain chemical energy reserve.

Effects of Deficiency

Phosphate diabetes is one of the most common forms of osteomalacia. Hypophosphatasia is a recessive disorder with deficiency of alkaline phosphatase in tissues and serum, which interferes with the calcification of osteoid tissue. Renal tubular dysfunction is usually a low serum phosphate due to reduced renal tubular reabsorption of phosphate and generally a genetically determined primary defect of the renal tubule.

EXAM-ORIENTED QUESTIONS

Essay

1. Discuss the mechanism of action and secretion of parathormone. Discuss the functions of parathyroid gland.
2. Describe the calcium balance. Factors affecting calcium absorption. Add note on tetany.
3. Discuss the phosphorus metabolism. Add note on hypophosphatasia.

Short Notes

1. Relationship between plasma ionized calcium and phosphate
2. Rickets and osteomalacia
3. Control of phosphorus metabolism
4. Tetany
5. Factors affecting calcium absorption
6. Hypoparathyroidism
7. Factors affecting phosphorus absorption.

Chapter

74

Pancreas

INTRODUCTION

Endocrine Pancreas

The human pancreas is a large retroperitoneal gland and is both exocrine and endocrine in its secretory functions. The exocrine cells of the pancreas responsible for the enzyme-rich pancreatic secretion are the pancreatic acinar cells. The endocrine cells of the pancreas are found in scattered groups throughout the organ and are commonly designated as the islets of Langerhans, or simply as pancreatic islets or small island. The endocrine tissue of the pancreas makes up about 1–2% of the total gland. In 1869, Langerhans demonstrated that the islets were unconnected with the duct system of the pancreas.

Histology

1. Pancreatic tissue exhibits endocrine and exocrine functional role. The lightly-stained clusters of cells, called pancreatic islets which are also called islets of Langerhans are responsible for endocrine functions. Islets of Langerhans are groups of epithelioid cells, situated between the pancreatic alveoli or acini pervaded by large tortuous blood vessels and having no duct. Islets are more numerous in the tail of the pancreas than in the head and body. The number of islets in the adult human beings varies from about 200,000 to 2,000,000 and in the newborn infant from 100,000 to 500,000.
2. The darker-staining cells form clusters called acini. The acini are arranged in lobes and are separated by a fibrous barrier. The secretory cells of each acinus contain small granules of zymogens (secretory in nature) and they surround a small intercalated duct. The intercalated ducts drain via larger ducts into interlobular ducts. The ducts are lined by a single layer of columnar epithelium.
3. Adult human pancreas has about 1.7 units of insulin per gram. Islet tissue contains about 150 units/gram of it.
4. There are four distinct islet cell types and these are (i) A or α cells secreting glucagon; (ii) B or β cells, secreting insulin; (iii) D or δ cells secreting somatostatin; (iv) F cells secrete pancreatic polypeptide. Pancreatic peptide is probably concerned primarily with regulation of ion transport in intestine.

Canadian physician Frederick Banting (1891–1941) and John Macleod (1876–1935) were awarded the 1920 Nobel Prize for Physiology or Medicine for the discovery of insulin.

Sir Frederick Banting

John Macleod

Alpha cells (15–20%): Opaque and spherical granules are relatively uniform in size, are distributed throughout the cytoplasm, enclosed in a smooth membranous sac, stained red with Mallory-Azan, insoluble in alcohol. Alpha cells contain high electron density of secretory granules. **Glucagon** is secreted from the cells which have got hyperglycaemic effect.

Beta cells (70–80%) are granular but basophilic. They are stained orange with Mallory-Azan. Granules are generally similar in size but less opaque than those of α cells. They are soluble in alcohol. The β cells are smaller in size, remain in the periphery and secrete insulin. The granules in them represent stored insulin which produces hypoglycaemia.

Delta cells (1–8%): The δ cells secrete somatostatin. In the Zollinger-Ellison syndrome the non-δ cells (β cells) appear to secrete gastrin. The syndrome is due to a tumour or hyperplasia arising in the islets, which certainly does not secrete insulin and glucagon, but does produce enormous amount of gastrin.

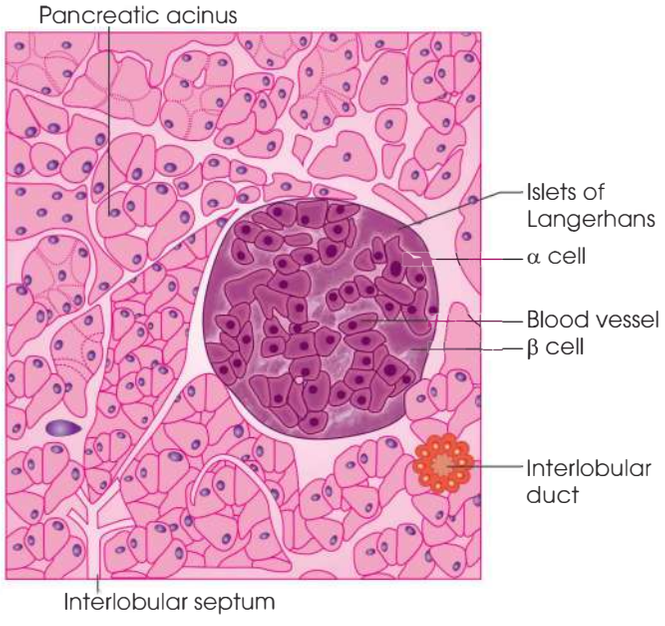

Fig. 74.1: Histological features of pancreas

Pancreatic polypeptide (PP cell) or F cells: The F cells secrete pancreatic polypeptides which are influenced by sympathetic and parasympathetic nerve activities. These nerve endings lie in close proximity to that of alpha and beta cells.

Nerve Supply

It is richly supplied with branches of the right vagus (secretomotor) and stimulation of the right vagus causes increased secretion of insulin.

INSULIN

Insulin is hypoglycaemic anti-diabetic factor and the protein hormone which regulates the blood glucose. It increases the deposition of glucose in the liver and muscles as glycogen. It also increases the oxidation of glucose to CO_2 in the tissues and depresses gluconeogenesis, i.e. formation of glucose from sources other than carbohydrates.

The β cells of the islets produce an antidiabetic hormone, called insulin.

Unit of Insulin

The insulin content of blood is expressed in international units, such as molar concentration, such as pmol/L or μIU/ml where 1 μIU/ml equals 6.945 pmol/L. The physiological level of insulin is 10–50 μIU/ml (7–350 pmol/L).

Chemistry

Various attempts were made to extract the principle from the pancreas, and the first potent extracts were obtained by Banting and Best in 1922. Crystalline insulin was obtained by Abet et al in 1926. Insulin is a large polypeptide or small soluble protein which has a molecular weight of 6000 and is made up of 51 amino acids. It consists of two open polypeptide chains (A and B). There are 21 amino acids in the A chain and 30 amino acids in the B chain. The two chains are interlinked by disulphide bridges. There is, in addition, a disulphide bridge between the 6th and 11th amino acid residues of the A chain. The complete unit contains 51 amino acids (Fig. 74.2). Breaking the disulphide bonds inactivate insulin.

Synthesis, Storage and Release of Insulin

Biosynthesis of insulin in β cells of the islets of Langerhans is presumably similar to protein synthesis in other cells. At first, raw material such as amino acid must be ingested into the islet cells from blood penetrating through some barriers, i.e. endothelial cells of blood capillary, two basement membranes and plasma membrane of the islet cell (Fig. 74.3).

Synthesis: Insulin is synthesized by the ribosomes of the granular endoplasmic reticulum (GER) under the control of triplet nucleotide sequences of mRNA. It is known that the amino acids participating in the

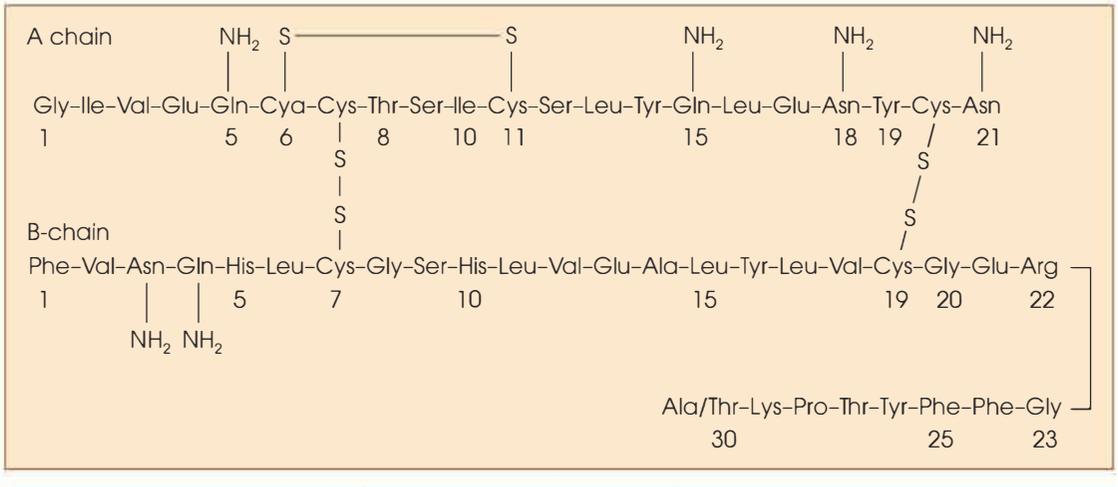

Fig. 74.2: Amino acid sequence of human insulin

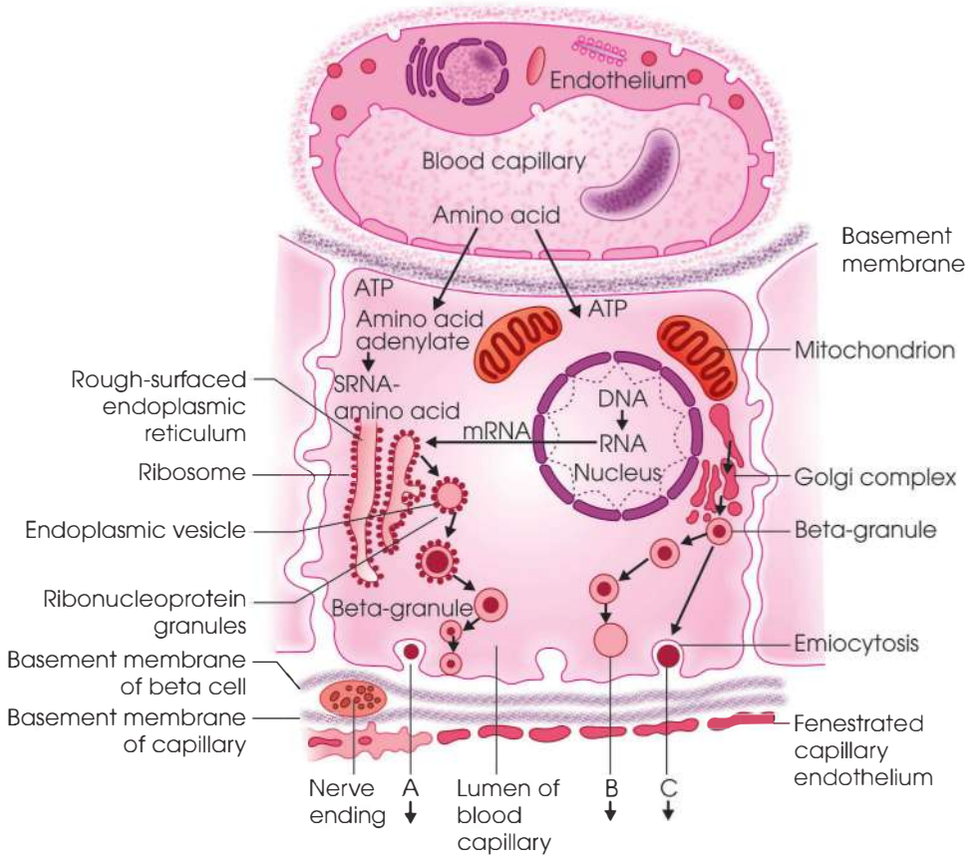

Fig. 74.3: Diagrammatic representation of course of granular synthesis, storage and extrusion in the pancreatic β-cell. A and C denote eruptocrine mechanism, whereas B denotes diacrine process (read mitochondrion for mitochondrion)

synthesis of insulin are apparently activated by an enzyme system requiring ATP and go with the soluble RNA constituents, where through the influence of mRNA and enzyme systems, they are arranged in proper amino acid sequences. The proteinous secretory substance is condensed into a visible core within the cisternae of granular ER and studded ribosomes are released from the outer surface of the cisternae with the formation of endoplasmic vesicle (EV) and surrounded by ribonucleoprotein granules (RNG). Eventually β-granules (BG) are then formed from EV in the region of Golgi bodies and RNG disappears.

Steps in Synthesis of Insulin

1. The preproinsulin is formed in the ribosomes.
2. Preproinsulin gets cleaved in endoplasmic reticulum to form proinsulin. The proinsulin contains A, B and C chains of peptides.
3. The proinsulin is cleaved then with Golgi apparatus to form insulin. Insulin contains A and B chains which are linked by C chain peptides and the disulfide.

Storage: The β-granules become dense and remain enclosed within the smooth membranous sacs.

Transport of insulin: Insulin binds with circulating protein synalbumin in circulation and is carried to the target tissue. Insulin which does not bind with the receptor is degraded by the enzyme insulinase.

Glucose Transporters (Table 74.1)

Glucose enters cells by facilitated diffusions or in the intestine and kidney by secondary active transport with sodium. There are number of glucose transporters in the cell membrane of different tissues by which glucose enters the cells by facilitated diffusion. GLUT-4 is the transporter which is insulin sensitive and is present in the muscle and adipose tissue where it is stimulated by insulin. Most of the other glucose transporter are not insulin sensitive. In muscle, adipose and some other tissues insulin stimulate glucose entry by increasing the number of transporters into the cell membrane. A pool of GLUT-4 is maintained in the vesicles in the cytoplasm of insulin sensitive cells (Fig. 74.4). When the insulin receptors of these cells are activated vesicles move rapidly to the membrane and fuse with it inserting transporter into the cell membrane. When insulin action ceases patches of membrane are endocytosed and vesicles stored again.

Insulin also increases entry of glucose into liver cells but does not exert the effect by increasing the number of GLUT-4 transporters into the cell membrane instead induces glucokinase that increases phosphorylation of glucose that lowers glucose concentration in the cell

Table 74.1: Glucose transporters

Glucose transporter	*Function*	*Main sites of expression*
Secondary active transport (Na^+ glucose cotransport)		
SGLT 1	Absorption of glucose	Small intestine, renal tubules
SGLT 2	Absorption of glucose	Renal tubules
Facilitated diffusion		
GLUT 1	Basal glucose uptake	Placenta, blood–brain barrier, brain, red cells, kidneys, colon, many other organs
GLUT 2	"B" cell glucose sensor; transport out of intestinal and renal epithelial cells	"B" cells of islets, liver, epithelial cells of small intestine, kidneys
GLUT 3	Basal glucose uptake	Brain, placenta, kidneys, many others organs
GLUT 4*	Insulin-stimulated glucose uptake	Skeletal and cardiac muscle, adipose tissue, other tissues
GLUT 5	Fructose transport	Jejunum, sperm
GLUT 6	None	Brain, spleen, leucocyte
GLUT 7	Glucose-6-phosphate transporter in endoplasmic reticulum	Liver, other tissues

*The major insulin responsive glucose transporter.

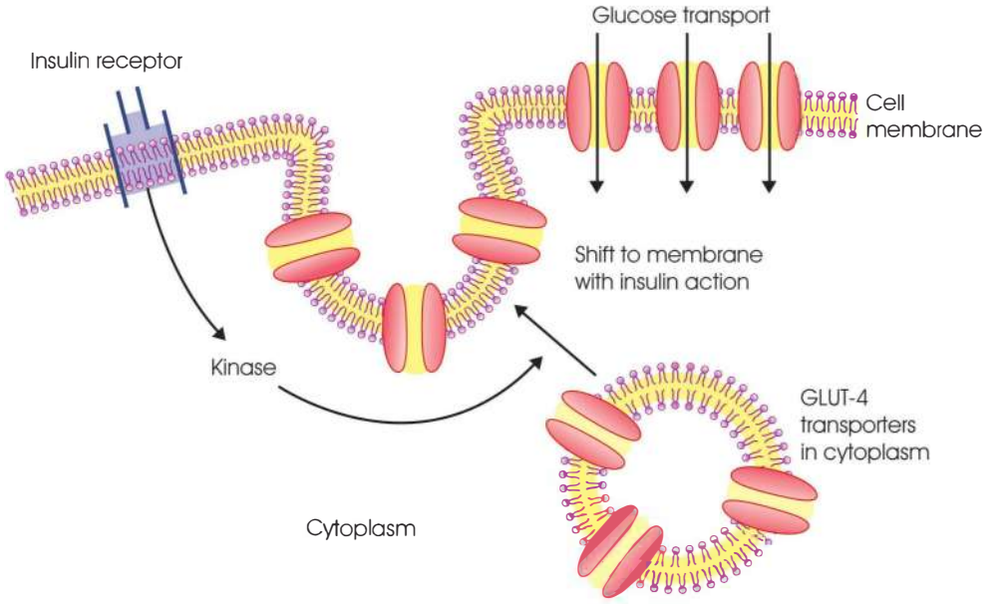

Fig. 74.4: Activation of the insulin receptor causes movement of the GLUT-4 into the cell membrane. The GLUT-4 transporters then mediate glucose transport into the cell

and so facilitates entry of glucose into the cell. In tissues in which insulin increases the number of GLUT-4 in the cell membrane the rate of phosphorylation of glucose is regulated by other hormones.

Insulin sensitive tissues contain a population of GLUT-4 vesicles that move into the cell membrane in response to exercise, process is independent of insulin.

Insulin Secretion

Glucose acts directly on pancreatic B cells to increase insulin secretion.

Sequence of Events

1. A specific glucose transporter (GLUT-2) facilitates diffusion of glucose into β cells. Helps to maintain glucose concentration in the cell at level equal to interstitial fluid.
2. Glucokinase enzyme functions as glucose sensor that controls subsequent β cells response to phosphorylation of glucose and subsequent yield of pyruvate. Subsequent rate of insulin secretion parallels that of glucose oxidation.
3. Oxidation of glucose leads to rapid increased in intracellular ATP concentration.
4. ATP sensitive K^+ channels close efflux of K^+ from β cells is suppressed and cell depolarises, that opens volate-gated Ca^{2+} channel, rasing intracellular Ca^{2+} concentration. Which activates mechanism for secretory granular movement and fusion of granules with the membrane, exocytosis of insulin follows.

Fate and Degradation of Insulin

1. Insulin administered from external source or released internally undergoes the same fate like other proteins.
2. It is destroyed in blood and tissues by degradation process. Mostly all the tissues can degrade insulin. Liver, kidneys, pancreas, testes and placenta can degrade the insulin greatly.
3. Nearly 80% of insulin is degraded in liver and kidney by hepatic glutathione insulin transhydrogenase.
4. 20% of insulin is degraded by enzymes insulin proteases in other tissues of body.
5. There are certain compounds which inhibit degradation of insulin such as β-corticotrophin, growth hormone, oxytocin, vasopressin, prolactin, insulin itself, glucagon, etc.

Secretion of insulin: The plasma glucose level influences the secretion of insulin in circulation. The elevated blood glucose level stimulates insulin sectretion. The other factors which influence insulin secretion are discussed as follows.

Factors Influencing Insulin Secretion

The islets secrete insulin continuously. That the hormone is secreted continuously is proved by the fact that the removal of pancreas is always followed by hyperglycaemia. In normal individuals about 50 units of insulin are secreted by the pancreas daily. Numerous factors influence the secretion of insulin. These are discussed below:

1. **Control by blood sugar level:** It has been shown that excess sugar of arterial blood entering the pancreas controls the rate of insulin secretion. The rate of insulin release by the pancreatic β cells is controlled mainly by the glucose concentration of the fluids that bathe the β cells.
   High blood sugar stimulates (Fig. 74.5), whereas low blood sugar depresses it. This action is directly on the islet tissues independent of nerves. Blood sugar level also acts on the central nervous system (hypothalamus, pons and medulla) and adjusts insulin secretion by modifying the vagal tone. Thus blood sugar controls insulin secretion in two ways: (a) by directly acting on the pancreatic islets and (b) through the right vagus. In addition, glucose also stimulates insulin synthesis, an effect which requires a longer period.
2. **Control by anterior pituitary:** Anterior Pituitary exerts an important influence on the secretion of insulin through the effects of growth hormone, Somatostatin, ACTH and TSH. The growth hormone increases insulin secretion by stimulating β cells. Somatostatin inhibits β cells and decreases insulin secretion, in physiological level ACTH and TSH increases blood glucose levels.

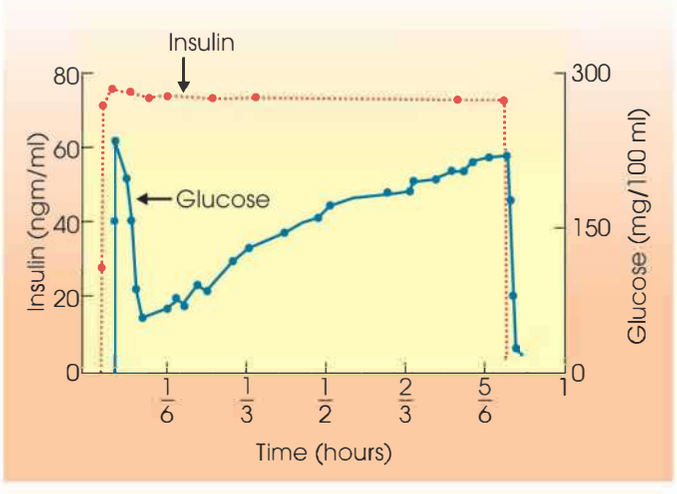

Fig. 74.5: Effect of glucose infusion on insulin release

Excess of the growth hormone and glucocorticoids may exhaust the β cells. This is not due to any direct action on the β cells but to hyperglycaemia caused by their demand of more insulin.

74

3. **Control by adrenal cortex:** Glucocorticoids of adrenal cortex also stimulate the secretion of insulin. Glucocorticoids prevent the utilization of glucose in the muscle and adipose tissue and stimulate gluconeogenesis in the liver and thus they oppose the action of insulin. But these corticoids and insulin have got some similar functions, i.e. both of them promote glycogenesis.
4. **Glucagon,** secreted by α cells of the islet tissue has got antagonistic effect against insulin. It produces hyperglycaemia, which is responsible again for increased secretion of insulin. Glucagon seems to have a direct stimulatory effect on insulin release through activation of adenyl cyclase. But at times it helps insulin in the uptake of glucose by the peripheral tissue.
5. **Thyroxine** has got hyperglycaemic effect and thus opposes the effects of insulin. It stimulates the secretion of insulin. The thyroid effects are probably related to the effects of thyroid hormone on carbohydrate metabolism:
   - Acceleration of glucose oxidation in tissues, and
   - Increase in gluconeogenesis.
6. **Epinephrine, norepinephrine, and role of β and β-adrenergic receptors:** Catecholamines like epinephrine and norepinephrine. Activation of α-adrenergic receptors by epinephrine lowers the cyclic AMP in the β cells. Thus, epinephrine inhibits glucose-induced insulin release possibly through lowering of the cyclic nucleotides. Whereas β-adrenergic receptors of the β cells when activated, cause increased liberation of insulin. This effect is possibly mediated through

the activation of adenyl cyclase of β cells resulting increased concentration of cyclic AMP. Monoamine oxidase inhibitors stimulate insulin release through activation of β-adrenergic receptors.

7. **Oestrogen** also stimulates secretion of insulin.
8. **Gastrointestinal hormones.** Secretin, pancreozymin and gastrin stimulate insulin secretion.
9. **Neural factors.** Stimulation of the right vagus increases insulin secretion. Normally, blood sugar level adjusts the vagal tone and modifies insulin secretion. High blood sugar stimulates and low sugar depresses the vagus. But nerves are not essential for the process. The vagal mechanism represents a 'fine adjustment'.*
10. **Serotonin** inhibits insulin release indirectly by glucose.
11. **Vasopressin and oxytocin** do not exert any marked influence on insulin release.

Other factors

- Factors that stimulate insulin secretion are fatty acids, ketone bodies, insulin antibodies, calcium, magnesium (low concentration), potassium, adenosine triphosphate, cyclic AMP.
- Factors that inhibit secretion are insulin itself, starvation, hypoxia, glucosamine, phenethyl-biguanide, diazoxide and magnesium (high concentration).

Above factors affecting insulin secretion has been presented in the following ways (Table 74.2).

Table 74.2: Factors affecting insulin secretion

Stimulation	*Inhibition*
Glucose	α-adrenergic stimulators
Fructose	Insulin
Mannose	Starvation
Ribose	Hypoxia
Amino acids	2-Deoxyglucose
(leucine, arginine, others)	Mannoheptulose
Ketones	Diazoxide
GH	Vagotomy
ACTH	Phenethylbiguanide
Glucosteroids	Glucosamine
T4	Hypoxia
Glucagon	Serotonin
Placental lactogen	Magnesium (high conc.)
Oestrogen	K^+ depletion
Magnesium (low conc.)	β-adrenergic blockers
Insulin antibodies	Thiazide diuretic
Potassium	
ATP	
Cyclic 3, 5-AMP	
Vagal stimulation	
GLP-I (7–36)	
Secretin	
Pancreozymin	
Gastrin	
Sulphonylureas	
β-adrenergic stimulators	
Phentolamine	
Monoamine oxidase inhibitor	

Insulin Receptors

The insulin receptor has been identified as transmembrane receptor which is activated by insulin. The receptor of insulin consists of two alpha units and two beta units linked by disulphide bonds. The alpha chains are extracellular while beta chain peneterates the plasma membrane. The receptor is a tyrosine kinase. When insulin binds with alpha units, it phosphorylates beta unit; and stimulates catalytic activities of the receptor. The receptor on activation phosphorylates number of intracellular protein altering there activity and generates physiological action response.

Functions of Insulin

On carbohydrate metabolism

Insulin increases glucose upatake by most of the cell

1. It stimulates glycogen synthesis in skeletal muscle, liver and adipose tissue. Note that the decrease levels of insulin otherwise causes liver cells to convert glycogen to glucose and excrete it into the circulation.
2. It increases glucose uptake in muscle and adipose tissue increasing peripheral utilization of glucose. It facilitates transport of glucose in adipose tissue and skeletal muscle by activating hexokinase and GLUT-4 receptor activity.

   Insulin increases the activity of UDGP-transglucosylase enzyme also known as synthetase to synthesize amylase, the acceptor being glycogen. Insulin promotes the uptake of glucose inside the cells and the intracellular phosphorylation of glucose to glucose-6-phosphate (Fig. 74.6). Glucose-6-phosphate itself also appears to be a specific activator of glycogen synthetase.
3. It decreases gluconeogenesis (enhanced production of glucose from noncarbohydrate substrates in liver) and inhibits hepatic glycogenolysis.

On protein metabolism

1. It increases amino acid uptake by the cells. Insulin increases the synthesis of messenger RNA. It increases the translation of messenger RNA.
2. As a prolonged action it also increases the rate of transcription of selected DNA sequence thus promoting protein synthesis. It increases protein synthesis especially in the muscle.

*Role of sino-aortic nerves. It may be that the sino-aortic nerves reflexly adjust the rate of insulin secretion through the vagus, just as they regulate epinephrine secretion through the sympathetic.

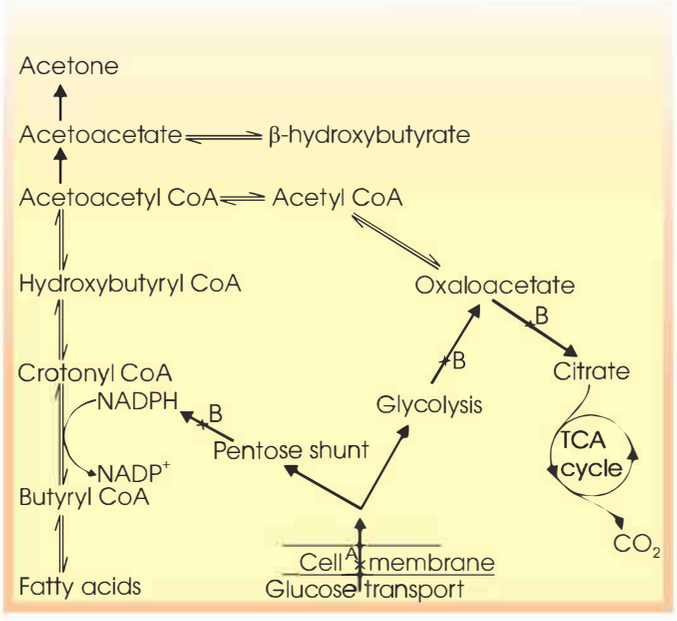

Fig. 74.6: The scheme represents influence of insulin deficiency on carbohydrate metabolism, lipogenesis and ketone body formation showing primary influence at A and secondary influence at B

3. Insulin inhibits protein breakdown. It inhibits protein catabolism by suppressing lysosomal activities.
4. It decreases degradation of RNA.
5. Insulin stimulates protein synthesis (proteogenesis) and growth, e.g. nitrogen retention, bone formation, etc. It increases the incorporation of amino acids into peptides.

On fat metabolism

1. It stimulates lipogenesis. It increases synthesis of triglycerides and free fatty acids in liver, muscle and adipose tissue. As it inhibits hormone sensitive lipase in adipose tissue. Insulin stimulates lipoprotein lipase activity thereby braking down triglycerides.
2. It decreases the mobilization of lipid into circulation from liver.
3. It regulates the free fatty acid concenteration
4. It decreases lipid and fat breakdown for energy sources.
5. It decreases the formation of ketone body (anti-ketogenic): In advanced diabetes, excess ketone bodies are formed in the liver, due to incomplete combustion of fatty acids. Insulin helps in the deposition of lipids (lipogenesis) in adipose tissue from glucose. It inhibits lysis and mobilisation of depot lipids (anti-lipolysis). On diabetic subjects due to lack of insulin, lipid deposition is markedly decreased. Insulin decreases the cholesterolaemia and lipaemia. It also prevents accumulation of excess lipid in the liver and breakdown of lipid in adipose tissue.
6. Potassium absorption: Insulin increases potassium uptake by stimulating the cells synthesizing glycogen to absorb potassium from the extracellular fluids lowering potassium levels in plasma. This effect is mediated via insulin-induced translocation of the Na^+/K^+-ATPase to the surface of skeletal muscle cell.

Note

In condition of insufficient insulin, there are increased gluconeogenesis, glycogenolysis, hyperglycaemia, hyperosmolalaemia, ketogenesis, polyuria, etc. (Fig. 74.7).

Mechanism of Action of Insulin

Key Points

1. Insulin promotes the transfer of glucose, amino acids and electrolytes across cell membranes, the target tissues being hepatic, muscle and fat cells. The cell membrane has got a specific transport system. This transport system helps in the transfer of glucose across the cell membranes into the interior. Insulin helps this transport system.
2. Insulin helps glucose uptake in muscle and adipose tissue due to its influence on the specific transport system, cell permeability and phosphorylation process. The transport system in the neurons and erythrocytes does not require the help of insulin. Intestinal absorption or renal reabsorption is not affected by this hormone. In liver, it stimulates uptake of amino acids and their incorporation into protein by hepatic cells.
3. Insulin activates the intracellular enzymes. It antagonizes the phosphorylase activation in response to glucagon and epinephrine and increases the muscle and hepatic glycogen synthetase activity.
4. Insulin inhibits the action of the growth or somatotrophic hormone of anterior pituitary and glucocorticoids of adrenal cortex. The latter hormones enhance the release of fatty acids from depot lipid and inhibit the uptake of glucose in muscle and adipose tissue whereas insulin produces opposite effect.
5. It is also known that some effects of insulin are the result of a fall in the level of cyclic AMP. Cyclic AMP decreases glycogenesis, proteogenesis and lipogenesis. All these processes are stimulated by insulin. Under normal physiological conditions, insulin apparently exerts a continuous damping effect on hepatic level of cyclic AMP.
6. The affinity or number of insulin receptor may change, e.g. obesity and persistent hyperglycaemia decreases number of insulin receptors while exercise and starvation increases number of insulin receptors. Similarly affinity of receptor decreases when glucocorticoid levels are increased and affinity increases on exposure to decrease amount of insulin.

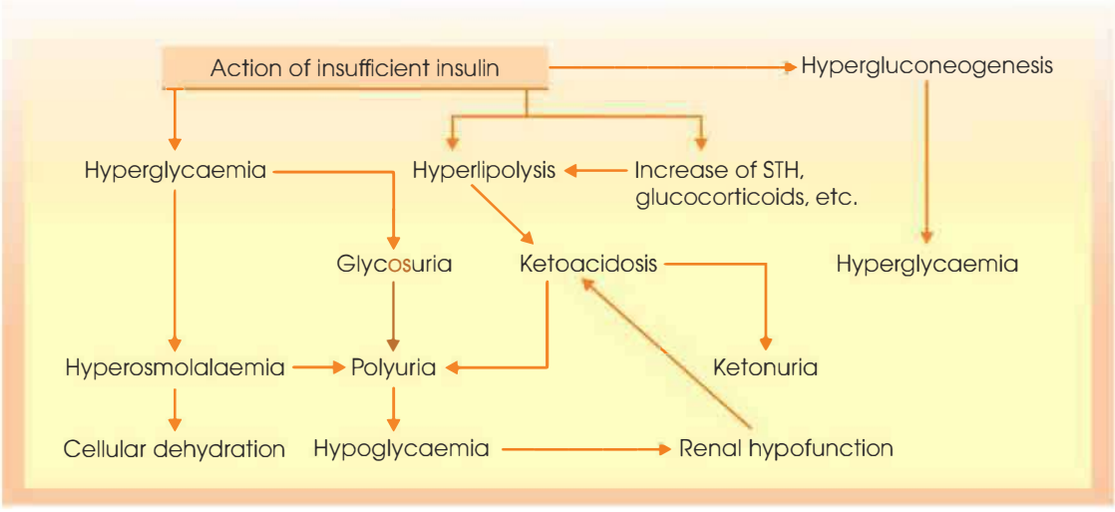

Fig. 74.7: Diagram shows the different metabolic derangement in the liver due to insufficient insulin

Insulin hypersensitivity: It is found in Addison's disease and Simmonds' disease. The dose of insulin which produces slight fall of blood sugar level in normal subjects causes severe fall of blood sugar level in these diseases.

Glucose Tolerance Test

A zero time (baseline) blood sample is withdrawn and blood sugar levels are calculated. The subject is administered 75 gm of glucose. As a standard dose of glucose is ingested by mouth and blood levels are checked two hours later. The standard two-hour GTT (glucose tolerance test) is effective for evaluation and to diagnose or exclude all forms of diabetes mellitus at the earliest stages of development. It is called an oral glucose tolerance test (OGTT)

Interpretation

Normal GTT: The fasting plasma glucose should be less than 6.1 mmol/L(110 mg/dl).

Impaired GTT: Fasting levels between 6.1 and 7 mmol/L (110 and 125 mg/dl).

Diabetic: The fasting levels repeatedly at or above 7 mmol/L (126 mg/dl) are considered to be having diabetes.

SOMATOSTATIN

It is a growth hormone inhibitory factor synthesized from delta cell of islets of Langerhans and also secreted in antrum of stomach and hypothalamus. It has inhibitory effects on synthesis and release of growth hormone. It inhibits gucagon, insulin and gastrin secretions. It reduces the motility activities in stomach, duodenum and gall bladder. The increased level of blood glucose, amino acids, free fatty acids and cholecystokinin increases secretion of somatostatin.

Pancreatic Polypeptide

It is secreted from F cells of islets of Langerhans. It decreases food intake and also decreases the absorptive rate of food from gastrointestinal tract.

GLUCAGON

Glucagon (also known as hyperglycaemic-glycogenolytic factor—HGF) is secreted by the α cells (A cells) of the islets of Langerhans. It is a polypeptide hormone with 29 amino acids having molecular weight of 3,485 (Fig. 74.8). This polypeptide has been completely synthesized.

Function and Mechanism of Action

1. **Carbohydrate metabolism:** It increases glucose levels by promoting gluconeogenesis, stimulate glycogenolysis, decrease conversion of glucose to glycogen, and decreases glucose breakdown for energy purposes.
2. **Protein metabolism:** It increases protein catabolism.
3. **Fat metabolism:** It has ketogenic effect: It increases breakdown of lipids and fats and thereby increases production of ketone bodies.

Summarised action: Glucagon on carbohydrate, fat and protein metabolism (Fig. 74.9)

a. Glucagon causes glycogenolysis liver by stimulating the enzyme adenyl cyclase and thus activating inactive phosphorylase. The action is similar to that of epinephrine. The enzyme cyclase, activated by glucagon and catecholamines, causes an accumulation of cyclic 3, 5-AMP by catalyzing the cyclisation. The cyclic 3, 5-AMP in turn activates the kinase system.

b. Glucagon also increases breakdown of amino acids and increases gluconeogenesis form the deaminated part.

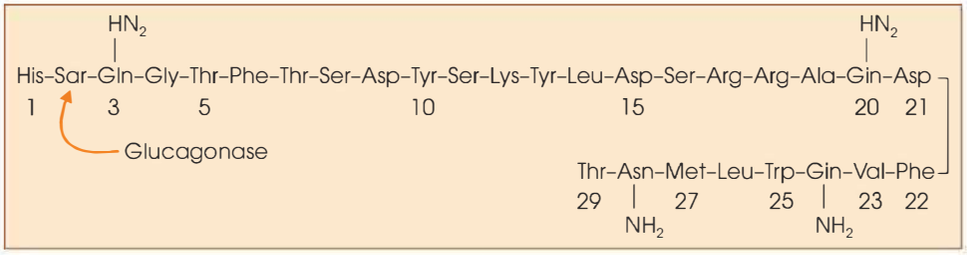

Fig. 74.8: Amino acid sequence of glucagon

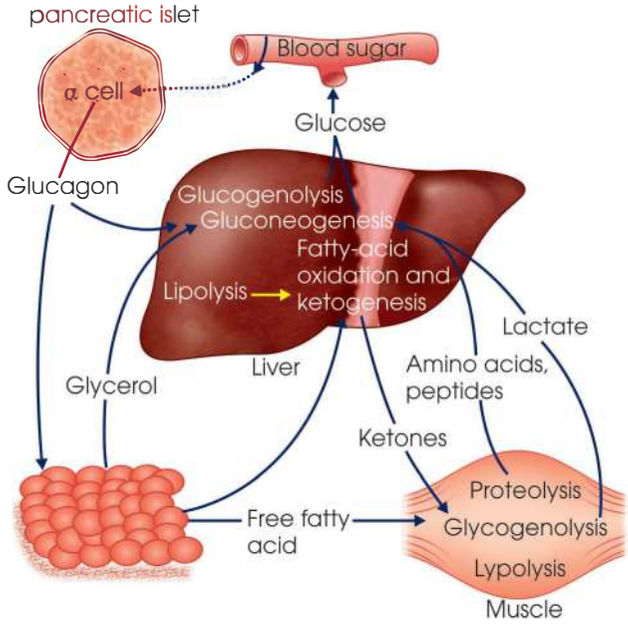

Fig. 74.9: Diagram shows the effects of glucagon on metabolic changes involving adipose tissue, muscle and the liver

c. Glucagon mediated gluconeogenesis and ketogenesis are stimulated by enhanced rate of lipolysis within the liver causing increased levels of short- and long-chain fatty acid CoA ester.
d. It has been considered further that these esters possibly provide the basis for the gluconeogenic action of glucagon since they stimulate indirectly the carboxylation of pyruvate to oxaloacetate and inhibits the conversion of pyruvate to acetyl CoA.

Factors Influencing Secretion

1. Glucagon secretion is regulated by the blood sugar level. Hypoglycaemia stimulates and hyperglycaemia inhibits release of glucagon from the islets of Langerhans. This hormone is also secreted in increased amounts during muscular activity.
2. Growth hormone has been implicated as an agent capable of stimulating glucagon release.
3. Pancreozymin also stimulates release of glucagon.
4. Glucagon secretion is also enhanced by protein meals and amino acids.
5. Amino acids also stimulate insulin and hypoglycaemic action of insulin is prevented by concomitant release of glucagon.

Glucagon and Cyclic AMP

1. The hyperglycaemic response to glucagon resembles that of epinephrine. Cyclic AMP acts as a second messenger for both hormones.
2. Glucagon stimulates the adenyl cyclase activity. Glucagon causes a prompt increase in the intracellular level of cyclic AMP. It has been observed that for any given effective concentration of glucagon, the level of cyclic AMP in the liver remains high so long the glucagon is present in the perfusing medium, and begins to fall as soon as the hormone is removed.
3. It also increases inositol triphosphate in the cell.
4. Accumulation of cyclic AMP by glucagon precedes glycogenolysis, gluconeogenesis, amino acid uptake, urea formation and the increase in tyrosine aminotransferase activity.

74

REGULATION OF BLOOD SUGAR LEVEL

Key Points

Normal blood sugar level varies from 80 to 100 mg per 100 ml (fasting) to 100–120 mg per 100 ml (after meal). Large quantities of sugar are constantly entering the blood stream (absorption, glycogenolysis and gluconeogenesis) and are constantly being removed from it (glycogenesis, oxidation of sugar, synthesis of lipids, etc.). In spite of those opposing forces, blood sugar level remains fairly constant within this limited range. This indicates that there must be strong machinery for blood sugar regulation.

The mechanism involves the following factors.

1. Alimentary Mechanism

Assimilation limits of glucose

When glucose is given by mouth up to 200 gm, no sugar is found in the urine in the next 24 hours. When given up to 300–500 gm, a large amount of water is osmotically drawn in and stomach becomes distended. Its movements are inhibited and consequently, it slowly empties into the small intestine. In this way, rapid absorption causing a very high rise of blood sugar is prevented. Blood sugar rises to some extent but as a rule, does not go beyond the renal threshold. Yet, some subjects develop a little glycosuria. This is probably due to the fact that, kidneys being unaccustomed to work

under such high sugar pressure; fail to reabsorb glucose completely from the renal tubules and consequently, a small amount leaks out. If more than 500 gm be given at a time, the subject develops nausea and the glucose is vomited out.

2. Digestion of Starch

It is a slow and long process. Necessarily, absorption becomes slow. So that, a sharp rise of blood sugar is prevented.

3. Rate of Absorption

It is believed that there is a maximum limit of glucose absorption. It is about 1.84 gm per kg per hour. Whatever is the amount of sugar given, the rate of absorption does not go beyond it, and hence blood sugar cannot have a sharp rise. It is interesting to note that utilisation of sugar by tissues has also nearly the same rate.

4. Role of Liver

This organ takes an important part in blood sugar regulation. It helps in two opposite ways, e.g. (a) when blood sugar tends to rise, liver stores it as glycogen and thus rise of blood sugar is checked, (b) when blood sugar tends to fall, liver mobilizes its glycogen store and speeds up the rate of gluconeogenesis (other than carbohydrates) and thus restores the level to normal. Both these processes are under the control of hormones as described already.

5. Role of Muscles

Muscles also help in the same two ways as liver. It draws in glucose from the blood stream and stores it as glycogen, thus tending to reduce blood sugar. When blood sugar becomes low (hypoglycaemia) or after severe muscular exercise, lactic acid is mobilised from the muscles, converted first into glycogen and then into glucose in the liver and discharged into the blood stream. Thus, blood sugar is raised. Through this 'Cori cycle' (Fig. 74.10) liver and muscle co-operate in maintaining blood sugar.

6. Role of Endocrines

Endocrines are the chief regulators of blood sugar level. The following endocrine glands and secretion take part in controlling glucose metabolism.

A. *Insulin*

It is the strongest blood sugar-reducing factor. It lowers blood sugar in three ways:

1. By increasing glycogenesis.
2. By promoting glucose uptake in muscles and adipose tissue due to its influence on the cell permeability and phosphorylation process and by stimulating glucose combustion.
3. By preventing gluconeogenesis.

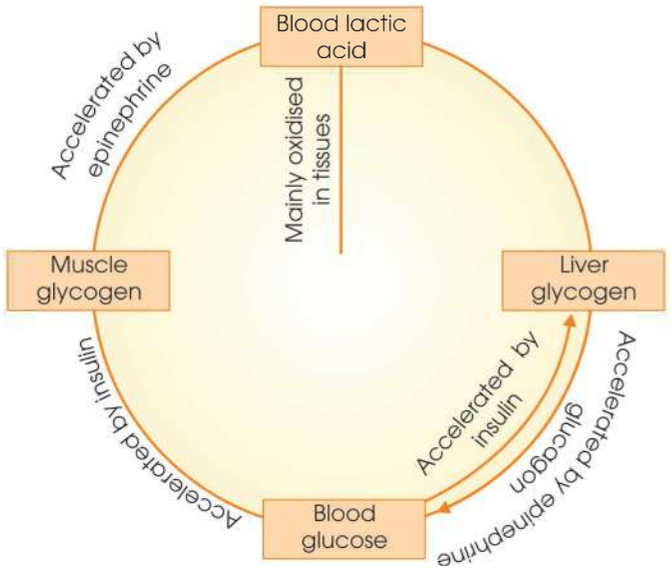

Fig. 74.10: Cori cycle

B. *Anterior Pituitary*

A number of anterior pituitary hormones increases blood sugar:

a. Growth hormone decreases peripheral utilisation of glucose and the resulting hyperglycaemia stimulates the β cells to over-production of insulin.
b. Growth hormone also has lipolytic action.
c. Adrenocorticotrophic hormone (ACTH) through adrenal cortex.
d. Thyrotrophic hormone (TSH) through thyroid, increase blood sugar level.
e. GH, ACTH and TSH have got opposing actions to that of insulin.

C. *Posterior Pituitary*

A large dose of vasopressin and oxytocin raise the blood sugar level temporarily. In rabbits, vasopressin is more effective in raising the blood sugar level, whereas in dogs, oxytocin has greater hyperglycaemic effect.

D. *Adrenal Cortex*

Glucocorticoids work in the following ways:

a. Depress the peripheral utilisation of glucose due to retardation of phosphorylation.
b. Increase gluconeogenesis in the liver due to retarded amino acid incorporation into protein, thus making more gluconeogenic material available. Administration of glucocorticoids produces temporarily diabetes in a number of animal species. Partially pancreatectomised animals may be made permanently diabetic by administration of cortisol or cortisone.

Epinephrine and Norepinephrine

These raise blood sugar by:

a. Stimulating glycogenolysis in liver

b. Converting muscle glycogen into lactic acid, which, through Cori cycle (Fig. 74.9), increases the blood sugar level. Epinephrine increases basal metabolic rate (BMR) by 20%, and increases the oxidation of glucose in the tissues. Norepinephrine has similar effects, although to a much lesser degree.

E. *Thyroid*

The following effects are exhibited by thyroxine on carbohydrate metabolism:

a. Increase in the peripheral utilisation and combustion of glucose in the tissues.
b. Stimulation of glycogenolysis and gluconeogenesis.

On continued administration the animals become resistant to epinephrine and more sensitive to insulin. Severity of diabetes increases in hyperthyroidism.

F. *Glucagon*

Glucagon increases blood sugar due to glycogenolysis in liver and gluconeogenesis.

Thus, one will find that, almost all the important endocrine glands take part in blood sugar regulation. Insulin tries to reduce blood sugar, whereas the other glands try to raise it. The normal sugar level is the optimum balance between these two opposite forces.

7. Role of Nervous System

Hypothalamic lesion causes disturbances of carbohydrate metabolism, namely hypoglycaemia, increased sensitivity to insulin, etc. Autonomic nervous system takes a great part in blood sugar regulation. For instance:

a. Stimulation of the right vagus reduces blood sugar level by increasing insulin secretion.
b. Stimulation of the sympathetic increases blood sugar level by mobilising liver glycogen (direct action on liver) and by stimulating epinephrine secretion. Autonomic action is controlled by blood sugar level.

8. Role of Blood Sugar

Blood sugar regulates its own level. Hyperglycaemia stimulates insulin secretion by:

a. Directly acting on the β cells
b. Stimulating the right vagus.

It also increases the rate of oxidation of sugar in the tissue independent of hormones and probably depresses the secretion of growth hormone. In this way, the raised blood sugar is brought down to normal.

On the other hand, hypoglycaemia depresses insulin secretion by:

a. Directly action on the pancreatic islet tissues, and inhibiting the right vagus.
b. It stimulates epinephrine secretion, and that of the growth hormone. In this way, the low sugar level is raised to normal. In this way, blood sugar level controls itself.

9. Role of Tissues, Tissue Fluid and Skin

The tissue fluid (nearly 30 litres), having nearly the same glucose content as plasma, can store a large amount of glucose. Any rise or fall of blood sugar is at once compensated by appropriate exchange with tissue fluid. The skin and subcutaneous tissue can store a large amount of glucose temporarily.

The tissues in general use up sugar in a number of ways such as conversion into lipids (adipose tissue), synthesis of other substances, oxidation of glucose and so on. The rate of oxidation is controlled by endocrines, blood sugar level, vitamins, etc. The tissues can remove sugar from the blood stream at a maximum rate of 2 gm/kg/hour (nearly the same as the maximum rate of sugar absorption from the intestine).

10. Role of Kidneys

Kidneys act as the last outposts. When blood sugar goes above the renal threshold (180 mg per 100 ml), it leaks out through the kidneys. It is an obvious attempt on the part of the kidneys to check further rise of blood sugar.

From the above considerations, it will be seen that, glucose being the ready source of energy, the body has developed a very elaborate and an efficient machinery to control its supply, storage and utilisation.

74

APPLIED PHYSIOLOGY

Hypoglycaemia

Hypoglycaemia is a condition in which blood sugar level is present below the normal level, i.e. below 80 mg per 100 ml. Generally, hypoglycaemic symptoms start somewhere between 70–50 mg per 100 ml. In diabetic subjects whose tissues are accustomed to high blood sugar, hypoglycaemic symptoms may start at a blood sugar level much above normal. Hypoglycaemic symptoms depend on three factors:

1. The actual blood sugar level.
2. The rapidity of blood sugar reduction.
3. The previous blood sugar level, i.e. that level with which the tissues were accustomed. Since nerve cells have very little stored food and since they use sugar mostly as the sole source of energy.

Hypoglycaemia will, therefore, affect the nerve cells first. Hence, the earliest manifestations will be nervous in origin. For instance:

1. A feeling of fatigue, weakness and hunger.
2. Extreme anxiety and irritability.
3. Abnormal behavior as in alcohol poisoning.
4. Tremors develop and fine movements are not possible.
5. Vasomotor disturbances such as flushing or pallor, perspiration and chilliness.
6. Later on, there may be delirium, diabetic coma and convulsions and loss of deep reflexes.

Hypoglycaemic symptoms are relieved by the administration of glucose. Other monosaccharides are less effective.

Hyperinsulinism

A rare clinical condition associated with hyperfunctioning of islet tissues (tumours) due to excessive production of insulin of β cells. The symptoms are those of paroxysmal attacks of typical hypoglycaemia. Only a few cases have been recorded uptill now.

Compensatory reactions of hypoglycaemia: Hypoglycaemia stimulates hypothalamus which in its return promotes the secretion of ACTH and other hormones which oppose the actions of insulin and restore the blood sugar level to normal. Hypoglycaemia also stimulates the secretion of epinephrine which stimulates glycogenolysis and raises the blood sugar level.

Hyperglycaemia

Hyperglycaemia is a condition in which blood sugar increases above the normal level, i.e. above 120 mg per 100 ml. When the blood sugar level exceeds the renal threshold (180 mg per 100 ml), sugar appears in the urine. Persistent hyperglycaemia occurs when there is diminished utilisation of glucose, and discharge of excess sugar from the liver. Hyperfunction of some of the endocrine glands, viz. anterior pituitary, adrenal cortex, etc. causes hyperglycaemia. Lack or diminished secretion of insulin is the main factor which produces hyperglycaemia and glycosuria as in diabetes mellitus (vide below).

Glycosuria

Glycosuria is a condition when the blood glucose level exceeds 180 mg glucose per 100 ml blood above the normal blood glucose level (60–100 mg) glucose per 100 ml blood. At this time the renal tubule cells are not able to reabsorb all the glucose. Some glucose reaches the urinary bladder and glycosuria results. In normal condition, the renal tubule cells are able to transfer all the glucose back into the blood by active transport, and no glucose passes to the urinary bladder. But the tubule cells are limited in the quantity of glucose that they can transport back to the blood in a given time (tubular maximum for glucose).

Diabetes Mellitus

The term diabetes means that a large volume of urine is passed. The term mellitus (= sweet) dates from the time when the urine was tested by tasting and the urine in this condition is sweet to the taste. Hyperglycaemia, glycosuria, ketosis, acidosis, diabetic coma (unconsciousness), polyuria, weight loss in spite of polyphagia (condition of increased appetite) and polydipsia (condition of increased thirst) are the abnormal characteristics of diabetes. But the principal abnormalities are an increased liberation of glucose in circulation from the liver and a reduced entrance of glucose in peripheral tissues due to deficiency of intracellular glucose and excess of extracellular glucose. Diabetes mellitus is a disorder of metabolism characterised by high blood sugar level and excretion of sugar in urine. The diabetes mellitus are mainly of two types: Type I—insulin dependent diabetes mellitus and Type II—non insulin diabetes mellitus.

Causes of Diabetes Mellitus

Due to insulin lack:

1. Juvenile diabetes has its onset in childhood or adolescence—frequently complicated by ketoacidosis.
2. Maturity onset diabetes is mild, develops late in life and occurs much more frequently in obese persons. Ketoacidosis is uncommon. Reduction of weight improves glucose tolerance.
3. In juvenile diabetes β cell pathology is observed and the insulin content of the pancreas is low. On the other hand, maturity onset diabetes (adult type)—β cell morphology and the pancreatic insulin content are generally normal.
4. Hyperpituitarism—gigantism and acromegaly (due to hypersecretion of GH).
5. Hyperthyroidism—Graves' diseases.
6. Hyperfunction of adrenal cortex—Cushing's syndrome (due to hypersecretion of adrenal glucocorticoids).

Metabolism in Diabetes Mellitus

Diabetes mellitus is a condition of glycosuria accompanied with hyperglycaemia, primarily due to lack of insulin, caused by the degeneration or hypoactivity of the β cells of the islets of Langerhans. Serious derangement of carbohydrate, fat and protein metabolism takes place. Almost all the ill effects can be explained from two standpoints:

1. Absence of insulin.
2. Unopposed activity of the insulin antagonists.

The metabolic disturbances (Fig. 74.11) are briefly described below.

Carbohydrate Metabolism

Glycogen Metabolism

Insulin stimulates glycogenesis and prevents glycogenolysis. Absence of insulin, in this disease, will, therefore, cause reverse effects, viz. glycogen content of liver will be low and glycogen formation depressed. In the muscles, glycogen content diminishes and its synthesis during recovery is depressed. Curiously enough, in the heart, the glycogen content increases. Insulin rectifies all these defects.

Combustion of glucose: Insulin stimulates oxidation of glucose. Hence, in diabetes mellitus, glucose,

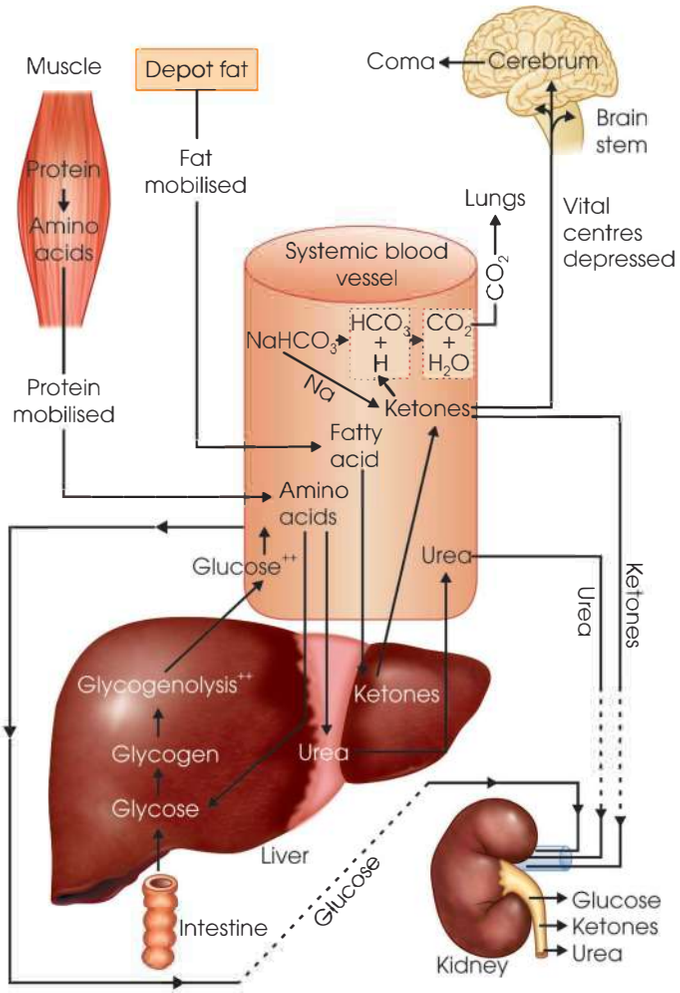

Fig. 74.11: Diagrammatic representation of the metabolism in diabetes mellitus in the body

combustion will be depressed. There is an impairment of glucose oxidation, not a complete interruption. This is shown by the following facts:

1. RQ falls to about 0.7 and arteriovenous glucose difference is low. This shows that tissues are utilising very little glucose and fats are being burnt.
2. Isolated organs or limbs, if perfused with glucose plus insulin, remove glucose much more quickly than when perfused with glucose alone. Studies after administration of glucose labeled with radioactive 14C have shown that insulin directly increases the rate of glucose oxidation.

Gluconeogenesis: Normally insulin checks this process. In diabetes mellitus the rate of gluconeogenesis increases, because insulin is absent. The activity of this group of enzymes, called transaminase, which are responsible for the conversion of glucogenic amino acids to carbohydrate intermediates, is increased in the liver of a person suffering from diabetes. The liver helps in the formation of more glucose and hyperglycaemia is enhanced.

Glucose tolerance: Lowered.

Fat Metabolism

The following changes occur:

1. Depot fats mobilised.
2. Liver loaded with fats.

There is formation of excess ketones due to lack of insulin. In the liver, fatty acids are converted into active acetate units—acetyl CoA. Under normal condition, these two-carbon units pass through Krebs cycle for oxidation and are completely oxidised. In diabetes mellitus carbohydrate metabolism is deranged and all the two-carbon units do not pass through the Krebs cycle, rather they condense with each other and form four-carbon aceto-acetic acid. Ketone bodies are produced at a faster rate than can be used up by the tissues causing ketosis. (They can be used up by the tissues even in absence of insulin.)

> Hence, ketosis is due to overproduction of ketone bodies and not due to their non-utilisation. Increase in blood ketone bodies leads to metabolic acidosis which causes deep and rapid breathing; a characteristic feature of diabetic acidosis and finally ketotic (diabetic) coma (unconsciousness) and death. It should be noted that the chief danger in diabetes mellitus comes from the derangement of fat metabolism and consequent ketosis.

Glycerol quantitatively converted into sugar. Blood cholesterol rises. It is due to active acetate being converted into more cholesterol instead of fatty acids. The increased cholesterol level of blood produces atherosclerotic condition of the blood vessels in diabetic subjects. RQ: Since glucose is not burning, energy is derived chiefly from the combustion of fats. Hence, RQ falls to about 0.7. After administration of insulin it rises to normal (fall of RQ may also mean conversion of fats into glucose).

Protein Metabolism

This is also seriously disturbed. Insulin stops gluconeogenesis. In diabetes mellitus, insulin being absent, the growth hormone acts unopposed. Hence, glucose is formed from the non-carbohydrate sources at a faster rate in the liver. About 60% of the non-nitrogenous residue of protein is converted into sugar. If enough protein is not given in the diet, the tissue proteins will be mobilised, deaminated in the liver and be converted into sugar. That this sugar is coming from proteins, is proved by the fact that, in a starving diabetic, D/N ratio is constant and is about 3.6, showing that both dextrose (D) and nitrogen (N) are coming from the same source—the protein. There are certain amino acids, called anti-ketogenic amino acids which are all converted into sugar. In juvenile diabetes there is marked loss of weight and protein synthesis is impaired leading to negative nitrogen balance.

Blood Changes

Blood sugar rises due to 4 causes:

1. Increased glycogenolysis.

2. Lack of glycogenesis.
3. Increased glyconeogenesis.
4. Depressed sugar combustion: When it goes beyond 0.18%—glycosuria results. Increased blood lipids (lipaemia), may go up to 12–24%. The blood cholesterol increases even up to 350 mg per 100 ml.

Ketosis and acidosis—alkali reserve lowered. Blood phosphates—rise.

Haemoconcentration: Decrease in blood volume peripheral circulatory failure and the resulting reduction in O_2 supply to tissues in general.

Urine Changes

1. Presence of sugar and acetone.
2. Increased urine volume—diuresis. Presence of sugar increases osmotic pressure, retards water absorption, hence polyuria. (Consequently, increased thirst—polydipsia.)
3. Loss of electrolytes—dehydration.
4. Increased loss of nitrogen
5. Raised ammonia coefficient (acidosis).
6. Increased PO_4 excretion.

Infections

Characteristically, there is reduced resistance to infections. It is probably related to altered immunological response circulating impairment, altered metabolism, etc.

Action of Insulin in Diabetes Mellitus

When insulin is given, reverse changes will take place and the condition will be restored to normal.

1. The rate of dissimilation of glucose becomes normal.
2. Blood sugar comes down to normal level and glycogenesis is stimulated.
3. Excess of gluconeogenesis is checked.
4. Ketosis disappears and ketone formation in the liver stops.
5. RQ becomes normal.
6. Sugar and ketone bodies disappear from the urine.
7. Rate of protein synthesis augmented.
8. Increased conversion of glucose to fat.
9. Fall in blood, the level of potassium and inorganic phosphate.

Oral Anti-diabetic Agents

In recent years, several hypoglycaemic agents effective orally, have been used in the treatment of diabetes, as a substitute for insulin. These agents include the sulphonylureas drugs, glybenzcyclamide, tolbutamide and chlorpropamide. Sulphonylureas act by stimulating the production of insulin and so their activity depends on the presence of functional β cells. Action of exogenous insulin is also potentiated by these agents possibly due to inhibition of insulinase, an enzyme responsible for degradation of insulin. Sulphonylureas and biguanides may destroy the A cells decreasing the production of glucagon. It has also been suggested that they reduce glycogenesis by the liver.

1. Stage I: **Prediabetes.** It is observed from birth. These patients are considered to have occult, potential or suspected diabetes.
2. Stage II: **Latent chemical diabetes,** subclinical diabetes or latent diabetes. Glucose tolerance of this subject is mostly normal but under stress (pregnancy or major disease) abnormalities of carbohydrate metabolism becomes precipitated.
3. Stage III: **Overt diabetes.** In this type of diabetes, full-fledged syndrome of clinical diabetes is present.
4. Stage IV: **Chromic diabetes.** Members of this group show abnormal glucose tolerance test and abnormal fasting blood sugar. Symptoms of different clinical manifestations are encountered. Vascular lesions are also observed.

Heredity and Diabetes

Considering the greater incidence of diabetes in the same family generation after generation thorough analysis has been made. It has been described by Joslin that 41% of diabetics have a definite family history of disorder. It has been observed that diabetics are homozygous for a recessive gene. The children of two diabetics (parents) are always potent diabetics. Even diabetes may appear simultaneously in monozygotic twins.

Metabolic syndrome: It is characterised by elevated blood pressure, dyslipidaemia, and increased waist circumference. The basic underlying cause may be the insulin resistance that precedes type 2 diabetes.

EXAM-ORIENTED QUESTIONS

Essay

1. Discuss the physiological action and functions of insulin. Add note on insulinoma.
2. Describe the mechanism of secretion and synthesis of insulin. Discuss the role of insulin in regulation of blood glucose.
3. Discuss the role of insulin and glucagon in regulation of blood glucose.
4. Describe the factors affecting insulin secretion and functions of insulin.
5. Describe the factors affecting glucagon secretion and functions of glucagon.

Short Notes

1. Metabolic syndrome
2. Hypoglycaemia
3. Diabetes mellitus
4. Oral anti-diabetic agents
5. Hyperinsulinaemia
6. Glucose tolerance test
7. Synthesis of insulin
8. Insulin receptor
9. Glucagon secretion
10. Fcators affecting insulin secretion

Chapter

75

Adrenal (Suprarenal) Glands

ANATOMY

Two in number, roughly triangular in shape, one situated on the upper pole of each kidney (hence, the name suprarenal). The right gland is smaller and looks like a cocked hat; and the left one is roughly crescentic and usually larger.

Each gland in the adult usually measures about 50 × 30–40 × 10 mm. The average weight of each gland is about 5–9 g in adults (medulla being one-tenth of the total weight). It consists of two parts (Fig. 75.1): (a) Outer part—the cortex, (b) inner part—the medulla. Whole enclosed in a capsule. The two parts are structurally, functionally and in embryological aspect different. At birth, the adrenal glands weigh about 8 gm, which is proportionately 16–20 times greater than in the adult. They gradually decrease in size.

BLOOD SUPPLY

It is one of the most vascular organs of the body, receiving 6–7 ml of blood per gm per minute. Blood vessels enter the gland through the surface and form a rich vascular plexus in the cortex. From these plexuses blood runs into dilated sinuses in the medulla. The latter join up to form the central vein which passes out through the hilus of the gland. Thus, blood passes, first to the cortex and then to the medulla. A few arterioles pass direct to the medulla through the cortex (Figs 75.2 and 75.3).

Fig. 75.1: Diagram shows section through adrenal gland

NERVE SUPPLY

The nerve supply to adrenal gland is from the greater splanchnic nerves. Fibres pass through the suprarenal plexus, pierce the surface of the gland, pass through the cortex and end in the medulla. They are medullated fibres without any cell station in their course. In other words, they are entirely preganglionic; the medullary

Edward Calvin Kendall was awarded the Nobel Prize for Physiology or Medicine along with Swiss chemist Tadeus Reichstein and Mayo Clinic physician Philip S. Hench, for their work with the hormones of the adrenal gland. Tadeus Reichstein, They studied the hormones of the adrenal cortex, their structure and biological effects, biochemistry, and endocrinology.

Edward Calvin Kendall
1886–1992

Tadeus Reichstein
1897–1996

Philip Showalter Hench
1896–1965

Reference: Stevcowicz S, 'Taudeus Reichstein', Prezeglad lekarski 56(3): 245–246.

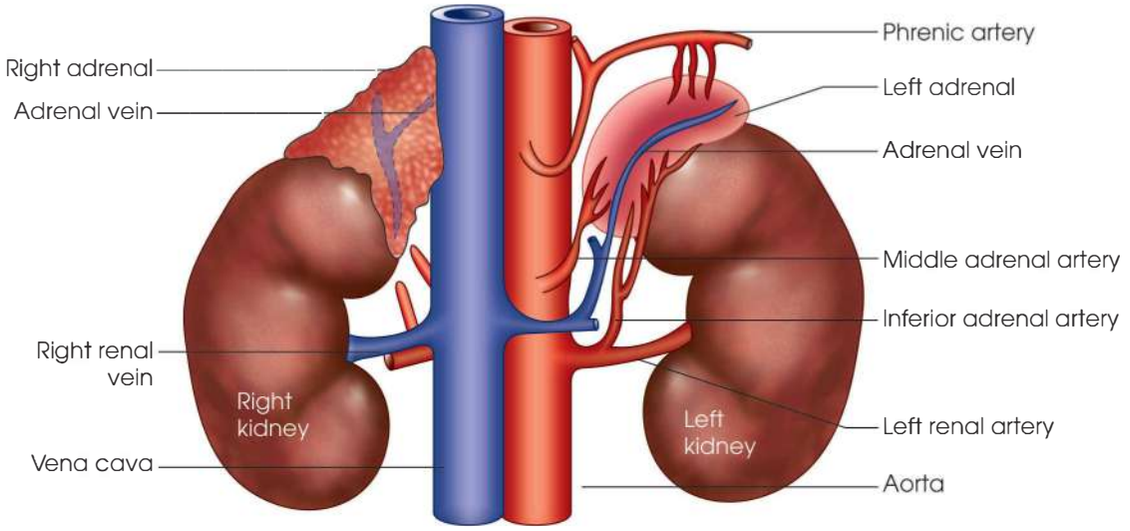

Fig. 75.2: Diagram shows major arterial supply and venous drainage of the human adrenal gland

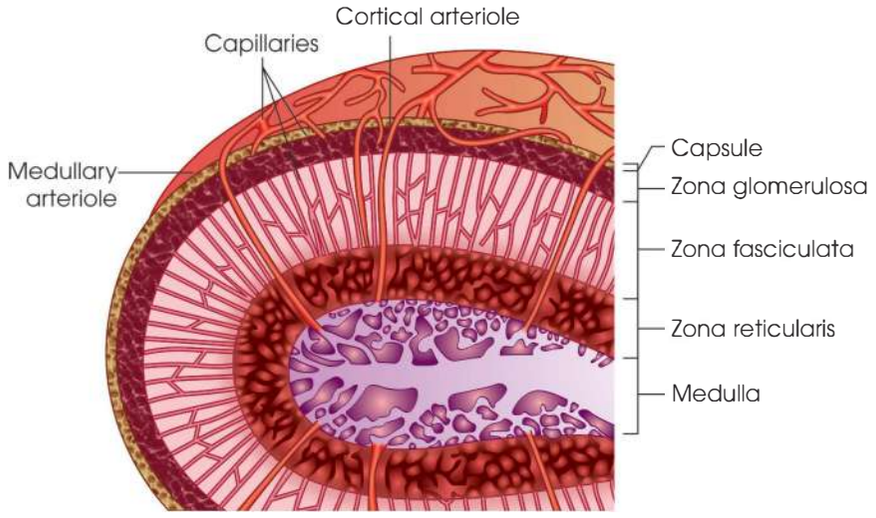

Fig. 75.3: Schematic representation of the circulation in a mammalian adrenal gland

cells representing the whole of the third neurons of the sympathetic ganglia. These nerves control adrenal medulla only. They are believed to have no action on the cortex.

ADRENAL CORTEX

Histology

It is divided histologically into three zones:

The adrenal cortex is covered by a capsule from which trabeculae pass into the gland, carrying blood vessels and nerves. The cells are arranged in the following three layers from outside inwards (Figs 75.4 and 75.5).

Zona glomerulosa (outer): There are groups of columnar cells which are comparatively small and thickly set with their long axis parallel to the surface. Zona glomerulosa secretes mainly aldosterone.

Zona fasciculata (middle): It is the widest layer. The polyhedral cells present in this layer are proportionally larger, containing pigment granules upon which the brownish-yellow colour of the cortex depends.

This layer secretes predominantly glucocorticoids. The cells of both the zona glomerulosa and zona fasciculata contain large amounts of smooth surfaced endoplasmic reticulum, which are supposed to be related to the synthesis of steroid hormones.

Zona reticularis (inner): Made up of an irregular network of rows of cells. The cells contain lipid droplets. The meshes of the network are filled up with sinusoids lined by reticulo-endothelial cells. Zona reticularis secretes sex hormones.

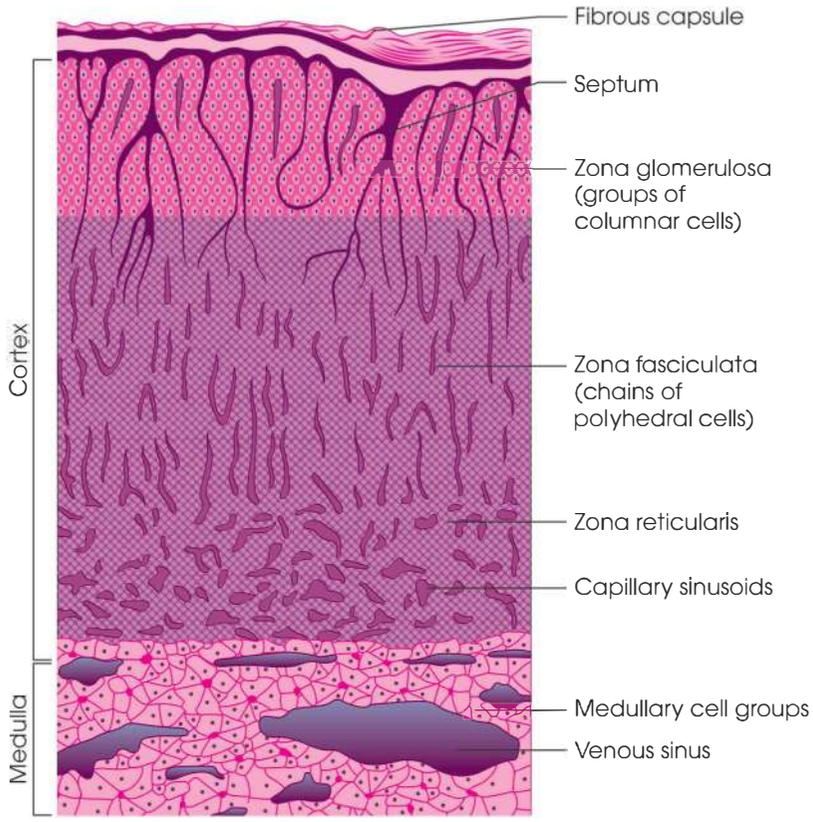

Fig. 75.4: Diagrammatic representation of section of adrenal (suprarenal) gland showing arrangement of cells in three layers of the cortex and part of medulla at the bottom

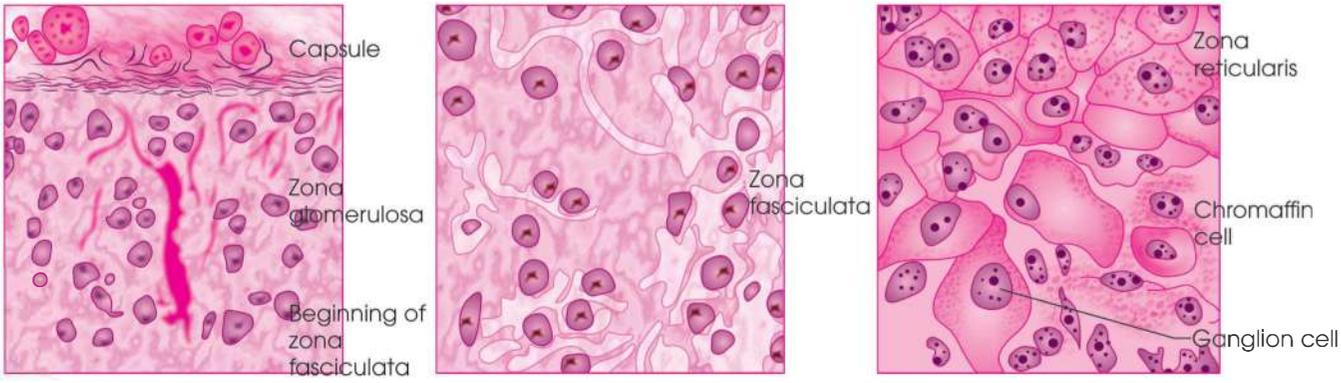

Fig. 75.5: Diagrammatic representation of histological structure (magnified) of zona glomerulosa, zona fasciculata and zona reticularis of cortex of the adrenal gland

ACTIVE PRINCIPLES OF ADRENAL CORTEX AND THEIR FUNCTIONS

Active Principles

The crude extract cortin contains a number of steroids. It can keep up an adrenalectomised animal in normal health. About 50 steroids have been isolated from adrenal gland of which only 7–8 have physiological activity. Although numerous variations of structures occur in the precursors and metabolites of active steroid hormones; the configurations of major steroids are relatively few and quite well-defined (Fig. 75.6).

The active substances can be divided into: Adrenal corticoids (glucocorticoids and mineralocorticoids) containing 21 carbon atoms and sex steroids containing 19 such atoms are as follows.

Adrenal Corticoids

Glucocorticoids (C_{21}): Steroids with = O or –OH at the 11C position.

1. *11-Dehydrocorticosterone* (= *O at the 11C position*): Compound A of Kendall.
2. *Corticosterone* (*–OH at the 11C position*): Compound B of Kendall.

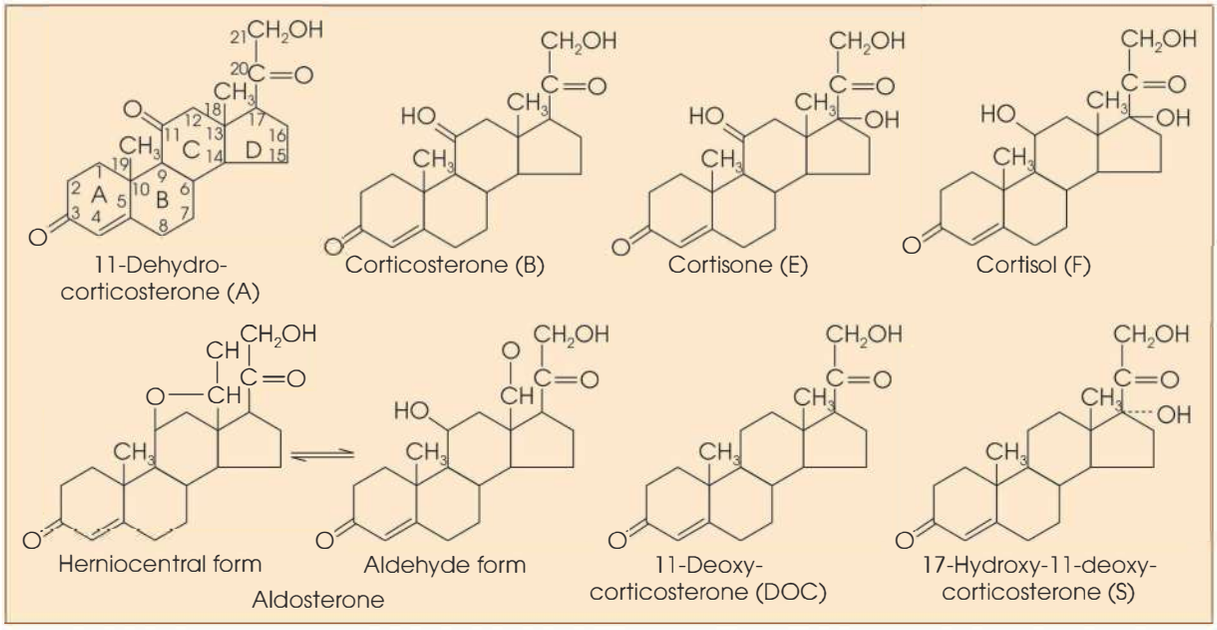

Fig. 75.6: Structural formulae of adrenal corticoids (as described by Kendall)

3. *Cortisone* (= *O at the 11C position*): 17-Hydroxy-11-dehydro-corticosterone compound E of Kendall.
4. *17-Hydroxycorticosterone* (*–OH at the 11C position*): Hydrocortisone or cortisol or compound F of Kendall.

Mineralocorticoids

1. Steroid with –OH or = O at the 11C position: Aldosterone (18-aldocorticosterone)–(18-aldehyde form and 11-hemiacetal form). Characteristic feature—the methyl group at 18C position is replaced by an aldehyde group. It can remain both as aldehyde and hemiacetal forms in solution.
2. Steroid without = O or –OH at the 11C position: Deoxycorticoid-11-deoxycorticosterone (DOC)* or deoxycortone.
3. 17-Hydroxy-11-deoxycorticosterone (–OH at the 17C position)—compound S of Reichstein.

Sex steroids (C_{19}) with = O or –OH or a side-chain $COCH_3$ at the 17C position:

1. Androgen—androsterone
2. Dehydroepiandrosterone (DHEA)
3. Oestrogen—oestradiol
4. Progesterone.

Biosynthesis of Adrenal Steroid Hormones

Adrenal corticosteroids are synthesized from cholesterol or from acetate. There is good evidence that mineralocorticoid secretion is largely confined to the zona glomerulosa and glucocorticoids secretion to the zona fasciculata. It has been observed in some species that the androgen synthesis occurs predominantly in the zona reticularis.

It is suggested that the several steps of biosynthesis in adrenal steroid formation take place in the mitochondria.

Transport, Metabolism and Excretion

Transport: Normally steroid hormones circulate in association with the specific binding proteins and only a small quantity is free. In man, daily secretion rate of cortisol is about 14–15 mg, of 17-ketosteroids (17-oxosteroids) 18–20 mg and of aldosterone 50–200 µg according to Na^+ balance. About half of the hydroxy-corticosteroids are transported in the blood, bound loosely to plasma proteins, glucocorticoids are bound specifically to β-globulin corticosteroid-binding globulin (CBG) or transcortin which binds cortisol and corticosterone and β-globulin-sex hormone-binding globulin (SHBG) or gonadal steroid-binding globulin (GBG) which transports oestradiol and testosterone.

GBG binds steroids with δ4-3-ketone and 20-ketone groups, while SHBG or testosterone-oestradiol binding globulin binds oestrogen and androgens with a 17β-OH group. A minor degree of binding to albumin also takes place. The bound hormone is essentially inactive. Normally, very little 'free' cortisol is present in plasma, but if secretion increases, there is rise in unbound fraction (Fig. 75.7).

Synthesis: CBG and SHBG are synthesised in the liver and are increased by oestrogen. CBG and SHBG levels are elevated during pregnancy and depressed in cirrhosis, nephrosis, etc. When CBG level rises, more cortisol is bound, producing a decrease in free cortisol level, which results in ACTH secretion. Normally

*Aldosterone is the chief mineralocorticoids secreted from the adrenal cortex. Deoxycorticosterone seems to be secreted in abnormal situation.

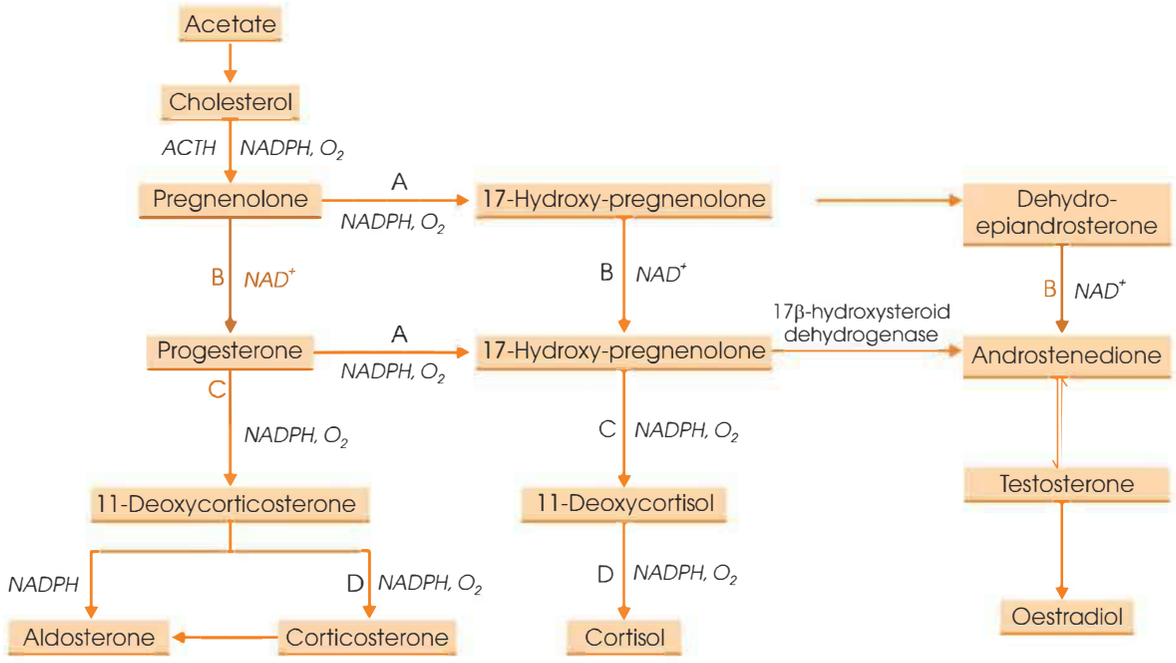

Fig. 75.7: Diagram shows biosynthetic pathways in the adrenal gland to the major steroid hormones. D is blocked by metyrapone causing transient fall in glucocorticoids like corticosterone and cortisol. A = 17α-hydroxylase (zona glomerulosa and zona reticularis), B = 3β-dehydrogenase-δ5, δ4-isomerase, C = 21β-hydroxylase, D = 11β-hydroxylase

plasma contains 5–15 µg/100 ml of cortisol. Aldosterone content is 3–15 ng/100 ml. The cortisol level is higher in early morning (6–8 a.m.) and very low near midnight in man.

Metabolism: Major metabolites of adrenal steroid hormones are formed in the liver, kidneys and in the gut (Fig. 75.8). Adrenal corticoids are inactivated mostly in the liver very rapidly.

Excretion: They are conjugated with glucuronic acid and the inactivated and conjugated products are excreted in the urine as tetrahydroforms coupled to glucuronide, DHEA as sulphate, progesterone as pregnanediol, testosterone as reduced compound such as androsterone and etiocholanolone which appear in the urine with a large quantity of 17-ketosteroids (recently called 17-oxosteroids, 17-OS) secreted by the adrenal, oestradiol as conjugated form after hydroxylation to oestriol or oxidation to oestrone.

Mechanism of Action of Adrenal Steroids

1. The receptors for steroid hormone, located intracellularly.
2. It is enumerated that certain hormones, particularly the steroid hormones are able to penetrate the cell membrane due to their smaller size and lipid

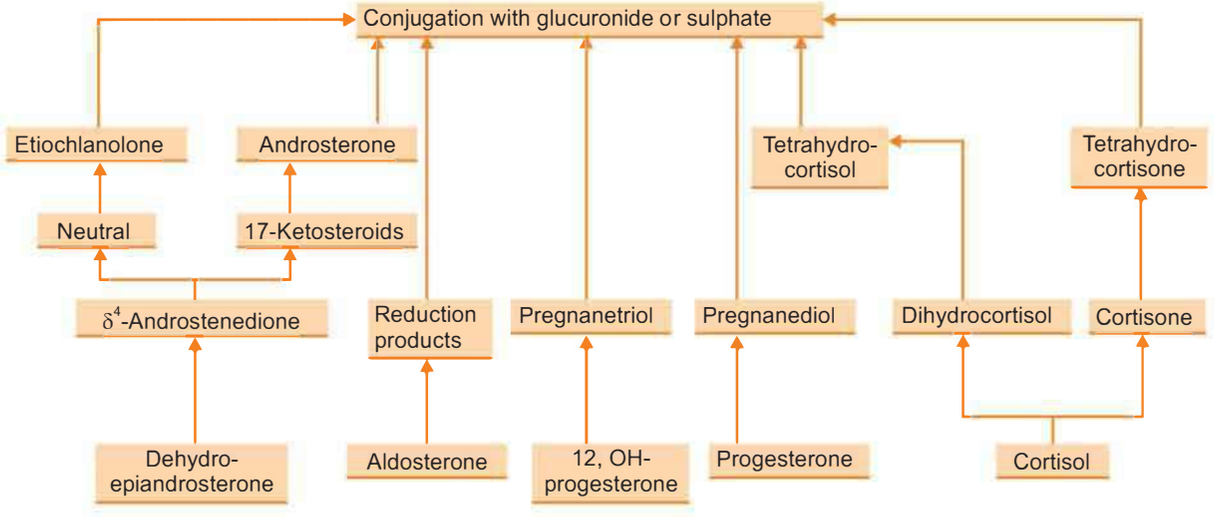

Fig. 75.8: Diagram shows routes of major adrenocorticoid inactivation

permeability. As a result, these compounds can modify intracellular metabolism directly.

3. The receptors of steroid hormones are monomeric phosphoproteins and resemble the receptors of thyroid, 1, 25-dihydroxycholecalciferol and retinoid. The binding of receptor brings conformational change in receptor exposing the DNA binding domain. The active receptor complex and hormone proceed to DNA and are binded to the enhancer element. Binding thus regulate the transcription of portions of DNA resulting in the formation of messenger RNA. mRNA leaves the nucleus and is translated by the protein synthesis pathway in the cytoplasm.
4. Effect of steroid hormone commonly require 60 minutes or so to be exerted and may be blocked by inhibition of RNA and protein synthesis.
5. Steroid hormones also appear to exert permissive effects on the action of other hormones. The effect of rapidly acting hormones, viz. and glucagon depends upon the presence of normal levels of steroid hormones in order to exert their effects.
6. *Non-genomic action of corticosteroids:* The corticosteroids exert non-genomic effects on the excitability and activation of neurons in the prefrontal cortex, hypothalamus, amygdala and hippocampus. The corticosteroids also influence and affect cognition, adaptive behaviour and neuroendocrine output faster. The nongenomic steroid actions are mainly mediated via the classical steroid receptors, or modified classical receptors.

Functions of Adrenal Hormones (Table 75.1)

The chief functions of the active principles of adrenal cortex are briefly described below.

Functions of Adrenal Cortex

From clinical and experimental studies, functions seem to be as follows:

1. **Control of mineral metabolism:** Mineralocorticoids, e.g. deoxycorticosterone, aldosterone, etc. increase reabsorption of NaCl and depress that of potassium and phosphates by renal tubules. Thus, by controlling the excretion of these salts, the mineralocorticoids keep an adequate balance of inorganic ions in blood, other body fluids and tissue cells.
2. **Control of water balance:** Adrenal corticoids stimulate water absorption by the renal tubules and thus regulate water balance. Aldosterone increases sodium reabsorption and an increases potassium and hydrogen excretion in the renal tubule. Aldosterone activates mineralocorticoid receptors in the distal tubules of the kidney, leading to increased permeability of the apical membrane of the cells to sodium. It also upregulates within minutes the sodium–hydrogen exchange apart from mineralocorticoid receptors mediated sodium absorption. It also increases the activity of the sodium/potassium adenosine triphosphatase (ATPase) in the serosal membrane. The glucocorticoids increase glomerular filtration rate, renal plasma flow and may produce water diuresis. Cortisol increases sodium retention and potassium excretion.
3. **Control of carbohydrate, protein and fat metabolism**

   Carbohydrate metabolism: Glucocorticoids produce the following effects:

   a. Stimulate formation of glycogen in the liver.
   b. Increase gluconeogenesis in the liver, especially from the protein (antagonistic to insulin).
   c. Depress glucose uptake and oxidation by tissues. The action of glucocorticoids to decrease oxidation of glucose by tissues is possibly mediated through its inhibitory action (along with STH) on glucose phosphorylation (antagonistic to insulin).
   d. Cortisol raises the blood pyruvate level and helps in the synthesis of glucose from pyruvate in the liver.
   e. Excess of cortisol produces hyperglycaemia and depresses sensitivity to insulin. Deficiency of cortisol produces hypoglycaemia and increases sensitivity to insulin. The release of glucose from glycogen by epinephrine or glucagon depends on the presence of cortisol. This effect of cortisol is known as the permissive action.
   f. Consequently, the action is partly similar and partly antagonistic to insulin. Aldosterone has got very little effect on carbohydrate metabolism.

   Protein metabolism: Glucocorticoids

   a. Increase the rate of deamination and breakdown of tissue proteins to amino acids indicating increased liver transaminase activity. Body proteins are lost, increasing nitrogen excretion. Synthesis of protein is also reduced.
   b. Stimulate gluconeogenesis from the amino acids.
   c. They by antagonizing the effect may be mediated through the metabolism of nucleic acids.
   d. Excess of cortisol causes wasting of muscles, osteoporosis, dissolution of lymphoid tissues and increased excretion of creatine and uric acid in the urine. Aldosterone has got very little effect on protein metabolism.

   Fat metabolism: Glucocorticoids

   a. Stimulate fat absorption from the intestine.
   b. Stimulate mobilisation of lipid from the depots and its disintegration in the liver to form ketone bodies through their ability to mobilize free fatty acid (FFA).

Table 75.1: Functions of adrenal hormones

Active principles	*Chief physiological functions*
Adrenal corticoids • **Glucocorticoids—steroids with = O or –OH at the 11C position** Cortisol Cortisone Corticosterone 11-Dehydrocorticosterone	• *On carbohydrate metabolism—chief action*. Hence, called **glucocorticoids**—(a) stimulate formation of glycogen in the liver and muscles (same as insulin), (b) increase gluconeogenesis in the liver (specially from proteins), (c) depress glucose uptake and oxidation by tissues (anti-insulin), the enzyme hexokinase helps in the phosphorylation of glucose to glucose-6-phosphate. Glucocorticoids together with STH interfere with the phosphorylation of glucose. (d) Help absorption of sugar from the intestine and possibly from renal tubules. (e) Cortisol raises the blood pyruvate level and helps in the synthesis of glucose from pyruvate in the liver. (f) Deficiency of cortisol produces hypoglycaemia and increases sensitivity to insulin. Excess of cortisol produces hyperglycaemia and depresses sensitivity to insulin. • *On protein metabolism*: Glucocorticoids (a) increase the rate of deamination and breakdown of tissue proteins to amino acids. Body proteins are lost, increasing nitrogen excretion. They also decrease protein synthesis which might be due to interference in nucleic acid metabolism. (b) Increase gluconeogenesis in the liver (anti-insulin). (c) Excess of cortisol causes wasting of muscles, osteoporosis, dissolution of lymphoid tissue and increased excretion of creatine and uric acid in the urine. • *On lipid metabolism*: Glucocorticoids (a) stimulate lipid absorption from the intestine, (b) mobilise lipid from the depot and disintegrate to form ketone bodies in the liver. (c) Excess of cortisol causes redistribution of lipid in the body, increased lipid and cholesterol level in the blood. (d) Depress the synthesis of lipid from carbohydrate. • *On mineral metabolism*: *Minimum action*. There may be some retention of NaCl and water, and the increased excretion of K and PO_4. • *On muscle*: Cortisol and cortisone relieve muscular weakness found in hypofunction of adrenal cortex. • *Blood*: Anti-lymphocytic and anti-eosinophilic action—causes dissolution of lymphocytes in blood and lymphoid tissues, producing (a) lymphopenia in blood, (b) involution of thymus, lymph gland, spleen, etc. (c) eosinopenia in blood. • *Blood pressure*: Hypotension found in deficiency of the adrenal cortex is rectified after administration of cortisol. • Protect the body against stress. • *Bones*: Excess of cortisol causes osteoporosis due to decalcification and interference in formation of protein matrix.
• **Glucocorticoids**	• *Central nervous system*: In hypofunction of the adrenal cortex, e.g. in Addison's disease, the function of the central nervous system is deranged. It is rectified after administration of cortisol. • *Cortisone* has a special action in curing certain types of arthritis. [ACTH has same action probably through cortisone.] • *Anti-inflammatory effect*: At high concentrations, glucocorticoids decrease cellular protective reactions and in particular, retard migration of leucocytes into traumatised areas. • *Immunosuppressive effect*: Cortisol also decreases immune responses involved in infections, allergic states and anaphylactic shocks. There is decreased synthesis of DNA and DNA-dependent RNA polymerase in lymphocytes. The action may be thus at the sites of nucleic acid and protein synthesis in immunologically active cells.

(*Contd.*)

Table 75.1: Functions of adrenal hormones (*Contd.*)

Active principles	*Chief physiological functions*
• **Mineralocorticoids** – **Steroid with –OH or = O at the 11C position, and presence of a aldehyde group at the 18C position** Aldosterone – **Steroid without = O or –OH at the 11C position** Deoxycorticoid Deoxycorticosterone or Deoxycortone	• *Exocrine secretory effect*: Chronic treatment with glucocorticoids causes increased secretion of HCl and pepsinogen by the stomach and trypsinogen by the pancreas. • *On mineral and water metabolism*: *Greatest action*. Hence, called **mineralocorticoids:** (a) Retention of NaCl and water, (b) increased excretion of K, and (c) intracellular K lowered and Na raised. • On *carbohydrate and protein metabolism*: *Little action*. • More effective in protection against stress. • Does not inhibit the secretion of ACTH. [No reciprocal relation.]
• **Sex steroids with = O or –OH or a side-chain $COCH_3$ at the 17C position** Androgen—androsterone Oestrogen—oestradiol Progesterone	• *On mineral and water metabolism*: *Ponounced action, but less than aldosterone. Also named as* **mineralocorticoids:** (a) Retention of NaCl and water, (b) increased plasma volume, (c) increased excretion of K, and (d) intracellular K lowered and Na raised. • *On carbohydrate and protein metabolism*: Action much less than glucocorticoids. • Regulates renal function. • Most potent in maintaining life of adrenalectomised animals. • Action on sex organs and secondary or accessory sex characters similar as sex steroids.

c. The glucocorticoids influence the redistribution of body fat in hypercorticism; but they also facilitate lipolysis. Excess of cortisol causes redistribution of fat in the body with increased deposits on the trunk and shoulders at the expense of fat in the extremities while the fat in the arms and legs is diminished. There is increased lipid from carbohydrate. Chronic overproduction of cortisol causes lipolysis, hyperlipidaemia and hypercholesterolaemia and increases the incidence of atheroma.

d. It also stimulates the mobilisation of fatty acids and glycerol from adipose tissue in the blood.

Control of phosphorylation: Glucocorticoids help in the action of phosphatase, phosphorylase, etc. and thus control all the processes involving phosphorylation. The metabolic function of adrenal cortex, especially on carbohydrates and fats are supposed to be due to its influence on phosphorylation.

4. **Relation with digestive functions:** Cortisol is concerned in the secretion of hydrochloric acid and pepsin by the stomach. It stimulates oxyntic cells of stomach for secretion of HCl. It also stimulates secretion of trypsinogen and pepsinogen. It inhibits absorption of calcium from small intestine.
5. **Control of basal metabolic rate:** In some way adrenal corticoids control BMR; a fall even 25% below normal has been noted in adrenal cortical deficiency.
6. **Anti-lymphocytic and anti-eosinophilic action:** Cortisone, cortisol, etc. cause decreased lymphocyte mitotic activity and rapid destruction of lymphocytes and eosinophil in the blood, increased sequestration of eosinophils in spleen and lungs and also cause involution of thymus and other lymphoid structures. The certain lymphocytes also undergo glucocorticoid-induced apoptosis. Thus, glucocorticoid causes immunosuppression, thereby decreases the function and/or number of lymphocytes (B cells and T cells) and the size of lymph nodes and thymus by inibiting lymphocyte mitotic activity. They reduce secretion of cytokines and reduced secretion of IL-2 lead to reduced proliferation of lymphocytes. Hypofunction of adrenal cortex is generally associated with lymphocytosis, eosinophilia, neutropenia and anaemia. In tropical eosinophilia treatment with adrenocortical steroids is indicated. Glucocorticoids have potent anti-inflammatory and immunosuppressive properties. Hence, glucocorticoids are widely used in treating arthritis, dermatitis, and autoimmune diseases.

   Aldosterone has about half eosinophilic activity.
7. **Control of normal composition, volume and pressure of blood:** Adrenal corticoids regulate the volume, composition and pressure of blood. In adrenal deficiency:

a. *Blood volume and pressure fall:* Myocardial weakness develops. In hyperfunction of the adrenal cortex the blood pressure rises.
b. Haemoconcentration takes place—specific gravity, cell count, percentage of haemoglobin and concentration of plasma proteins in blood—increase. Both (a and b) are due to increased water loss by the kidneys and passage of more water from the blood stream into the tissue spaces.
c. Retention of nitrogen, increased excretion of potassium and PO_4, reduced NaCl and bicarbonate occur.
d. Vascular reactivity: Glucocorticoids restore the vascular reactivity. It is essential for physiological action of certain hormones, e.g. catecholamines. This supportive action of cortisol is known as permissive action. The vasopressor effect of catecholamines is potentiated by glucocorticoids.

8. **Control of kidney function:** Adrenal corticoids help to regulate normal kidney function. After adrenalectomy kidney function is depressed. At first, excretion of water increases, then urine volume diminishes. This is partly due to low renal circulation and partly to a direct depression of kidneys. Due to low renal circulation and fall of glomerular pressure there is less glomerular filtration and diminution of the quantity of urine. Renal efficiency falls; nitrogen retention takes place, leading to uraemia. Diuretic response to water drinking is not seen after adrenalectomy.
9. **Effects on nervous system:** Adrenal corticoid hormones especially glucocorticoids influence mood and behavior in an individual. In deficiency personality changes and slower EEG waves have been noted. Both excess and deficiency of cortisol may cause mental depression and psychosis.
10. **Relation with sex:** Sex hormones of the adrenal cortex are believed to control the differentiation of sex in the foetus, and growth of sex glands, sex organs and secondary sex characters after birth. Proof: (1) Cortical tumours cause: (a) pseudohermaphroditism in foetal life, (b) precocious sexual development in children, (c) reversal of sex characters, adrenal virilism in adults. (2) In Addison's disease—depression of sex. (3) Cortex produces sex hormones. (4) Sex hormones in large doses exert similar actions as corticoid sex hormones. (5) Adrenal cortex and gonads develop from the same parent tissues. (6) Persistence of 'libido' after castration is supposed to be, at least partly, due to the sex hormones from the adrenal cortex.
11. **Provides resistance against various stress:** Adrenal corticoids help the body to resist against various physical and mental stress, viz. exposure to low temperature, low oxygen pressure, mental and physical strain, etc. Subjects with Addison's disease easily succumb under such conditions. The glucocorticoids are effective in protecting the body against stress.
12. **Relation with melanin formation:** Under physiological condition cortisone and hydrocortisone inhibit the release of the melanocyte-stimulating hormone (MSH). In Addison's disease, excess melanin is deposited leading to bronzing of skin and mucosa. It is due to increased secretion of the melanocyte-stimulating hormone from the pars intermedia of the pituitary gland.
13. **Storage of vitamin C:** The cortex is very rich in vitamin C—about 200 mg per 100 gm of cortical tissue; it is stored here. When cortical secretion is stimulated its ascorbic acid content (also cholesterol content) falls. This is used as an index for stimulated cortical secretion.
14. **Bone metabolism:** Excess cortisol impedes the development of cartilage and causes thinning of the epiphyseal plate and interruption of growth in children. Cortisol being antagonistic to vitamin D prevents absorption of calcium from the gut, when given in excess. There is also decreased deposition of calcium in protein matrix of bone.
15. **Effects on cardiac and skeletal muscle:** Glucocorticoids and mineralocorticoids have a positive inotropic effect on cardiac muscle *in vitro*, but it is not known whether this digitalis like action is effective *in vivo*. The P-R interval of ECG is prolonged in adrenal insufficiency. In adrenalectomised animals, skeletal muscles become fatigued rapidly and glucocorticoids treatment is necessary for restoration of muscle to normal.
16. **Anti-pyretic effect:** Cortisone as well as ACTH is anti-pyretic in that, they reduce an elevated body temperature to a normal level and reduce any toxemia that may be present. They are particularly effective in inhibiting the effects of the endotoxins of gram-negative organisms. The mode of operation is not known as yet.
17. **Anti-inflammatory and anti-allergic response:** Glucocorticoids have an effective therapeutic influence against any type of inflammatory and allergic syndrome. These glucocorticoids have profound effects on allergic and immune responses triggered by foreign antigens such as those in pollen or bacteria; because, glucocorticoids suppress the formation of antibodies and reduce the response to histamine and other inflammatory agents.

HYPOFUNCTION OF ADRENAL CORTEX

Acute insufficiency of adrenal corticoids sometimes occurs when the subject is exposed to sudden stress or failure of secretion of ACTH after prolonged administration of glucocorticoids. In acute phase adrenal cortex fails to secrete cortisol. Chronic insufficiency of adrenal corticoids occurs in Addison's disease.

Addison's Disease (Fig. 75.9)

Addison's disease is usually due to tuberculosis of the gland, involving both cortex and medulla. But the effects are mainly due to cortical damage and consequently, insufficient secretion of cortisol and aldosterone.

Clinical Features

1. *Muscular weakness and easy fatigability:* Muscular weakness is due to loss of sodium chloride and defective power of glycogen formation.
2. Vomiting, anorexia, hypochlorhydria and gastrointestinal disturbance.
3. Low blood pressure: The systolic blood pressure remains at about 90 mm Hg, and the diastolic, at 60–65 mm Hg.
4. Pigmentation (bronzing) of the skin (especially in the exposed areas) and mucous membrane: Catecholamine production is deranged with the formation of the dark pigment melanin instead of adrenaline and noradrenaline. The skin becomes pigmented. It is attributed to an increased secretion of MSH or probably by excess ACTH (by feedback mechanism) possessing the melanocyte-stimulating property.

Fig. 75.9: John F Kennedy: A patient of Addison's disease
Reference: Brauer, Carl M. 'John F Kennedy': In Graff Henry. The President: A Reference History. 2002;7th Edition: 481–498.

5. *Low BMR* and subnormal temperature.
6. *Disturbed ionic balance*, viz. (a) increased excretion of NaCl and decreased excretion of potassium in the urine. This leads to (b) fall of NaCl (and bicarbonate) and rise of K in the plasma. The primary action is on the renal tubules.
7. *Decreased blood volume and haemoconcentration:* Sodium in the extracellular fluid falls. The cell membranes are impermeable to Na^+. The crystalloid osmotic pressure inside the cells thereby becomes relatively higher than the extracellular fluid. Water is withdrawn from the extracellular into intracellular fluid. Due to all these changes the blood cell count, percentage of haemoglobin and concentration of plasma proteins increase.
8. *Increased capillary permeability:* More water passes out of the capillaries and accumulates in the tissues, causing oedema.
9. *Deficiency of kidney function:* Glomerular filtration is decreased causing low urine volume, nitrogen retention and ultimately uraemia. Large intake of NaCl and restriction of potassium improve the condition. Disturbance of carbohydrate metabolism: (a) Absorption of sugar from the small intestine (and probably from the renal tubule) is slowed down, due to depressed phosphorylation. (b) Glycogenesis (from glucose or lactate) and gluconeogenesis (especially from proteins) in the liver are depressed. (c) Hypoglycaemia may occur. Hypoglycemic unresponsiveness is also seen. (d) Skeletal muscles show defective power of glycogen formation. (e) There may be glycosuria (uncommon) due to depressed reabsorption of sugar (defective phosphorylation).
10. Absorption of lipid from the intestine and its metabolism is diminished.
11. Restlessness, insomnia, lack of mental concentration, etc. also occur.
12. Excretion of 17-ketosteroids (17-oxosteroids) in urine is much reduced and in females it almost becomes nil.
13. Depression of sex functions.

HYPERFUNCTION OF ADRENAL CORTEX

1. Cushing's syndrome.
2. Hyperaldosteronism.
3. Adrenogenital syndrome.

Cushing's Syndrome (Fig. 75.10)

Cushing's syndrome is found in adrenal tumour or adrenal hyperplasia and there is excessive secretion of cortisol. Pituitary tumours causing excess secretion of ACTH may be the reason of this syndrome.

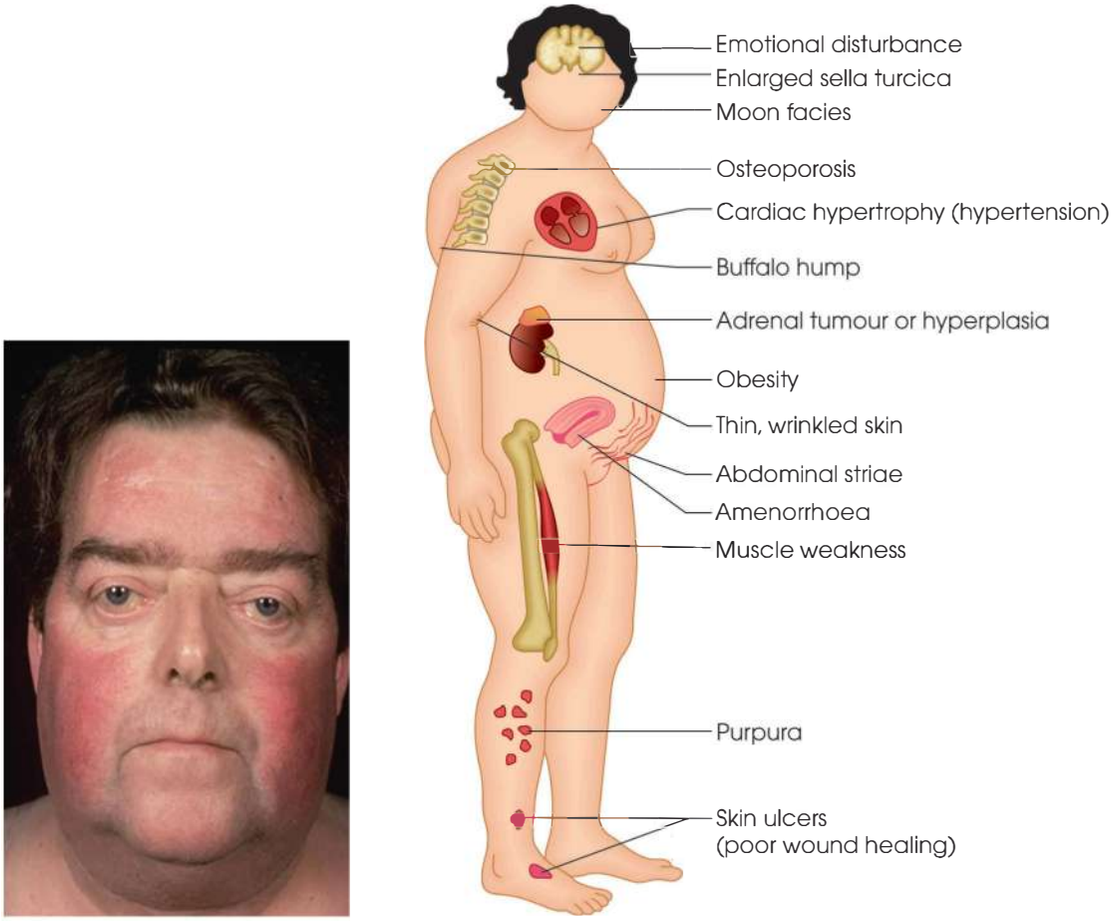

Fig. 75.10: Features of Cushing syndrome

Clinical Features

There is an increased deposition of fat on the trunk (but not the limbs), face (rounded or moon-face—the plethoric moon-face of the textbook is often absent in Cushing's syndrome, although a thick neck and fat below the chin is usually seen), characteristic pad of fat at the back of the neck (a buffalo hump) and abdomen. Extremities are usually spared. Fatty deposits are tender and painful. The skin bruises easily and shows purple striae with hirsutism in the female. Purple striae are usually found over the abdomen, thigh, etc. This is due to loss of protein matrix. In males, excessive hair-growth (hirsutism). In females, masculinisation with growth of beard, moustache, etc. The patient presents with asthenia and wasting of the muscles of the limbs. The wound healing is poor and minor injuries cause bruises and ecchymoses. There is osteoporosis of bones due to decalcification and loss of protein matrix. These patients may develop hypertension and mental derangement; in male's impotency with atrophy of testis occur while in females there is amenorrhoea, sterility, etc.

Biochemical analysis reveals:

1. Hyperglycaemia and insulin-resistant diabetes with glycosuria.
2. Retention of sodium and diminution of potassium level in the plasma.
3. Eosinopenia, lymphocytopenia, and polycythaemia.
4. Increased excretion of 17-ketosteroids (17-oxosteroids) and 17-hydroxycorticosteroids.

Hyperaldosteronism

Hyperaldosteronism may be primary or secondary. An excessive production of aldosterone commonly due to tumour of the zona glomerulosa tissue of the adrenal cortex is termed Conn's disease or primary aldosteronism. Hypertension, muscular weakness, retention of sodium, alkalosis, etc. are found. There is no oedema. The potassium depletion damages the kidneys, resulting in polyuria. The potassium depletion causes muscle weakness, metabolic alkalosis which may lower ionised calcium level resulting in tetany. Secondary hyperaldosteronism occurs in congestive cardiac failure, cirrhosis of liver with ascites, etc.

Adrenogenital Syndrome

The main characteristic of adrenogenital syndrome is the overproduction of adrenal androgens. It is associated with tumours of the adrenal cortex.

Clinical Features

In foetal life: Produces pseudohermaphrodite (eunuchs). Both male and female sex characters are present in the same subject, but both incomplete.

In childhood

1. *Females:* Precocious sex development, viz. early menstruation, breast formation, etc.
2. *Males:* Precocious growth of sex (puberty) and body-producing the so-called 'Pocket Hercules' or 'Infant Hercules'.

In adults: Reversal of sex characters is the main feature.

- In females—virilism. Female changes into male. Face, body appearance, voice—become of male type. Beard and moustache grow. Menstruation stops. Uterus and ovaries degenerate. Clitoris enlarges.
- In males—feminization may occur (but not common).

Similar changes may also result from congenital inborn errors of metabolism which derange the production of cortisol by the gland.

Laboratory Studies for Adrenocortical Functions

A urinary 17-hydroxycorticosteroid: The level of urinary 17-hydroxycorticosteroid gives an indication about the functional status of the adrenal cortex. The normal twenty-four-hour excretion of these corticosteroids in adult males is 10 ± 3 mg (approx) and in adult females is 7 ± 2 mg. The level of this urinary 17-hydroxycorticosteroid (17-OHCS) is increased after administration of ACTH. If it is abnormally increased then it strongly suggests that the patient has got hyperactive adrenal cortex.

Urinary aldosterone: Determination of urinary aldosterone level is of a great importance in the diagnosis of mineralocorticoid activity of the adrenal cortex.

CONTROL OF CORTICAL SECRETION

Hormonal Control

Anterior pituitary: ACTH is the chief controller.

Feedback control: There is evidence to prove that the concentration of cortical hormones (glucocorticoids) in blood regulates ACTH formation. This is the feedback mechanism. Rise of cortical hormones depresses, whereas a fall stimulates ACTH secretion by anterior pituitary. In the hypothalamus, secretion of CRF is influenced by negative feedback control from the plasma-tree cortisol level, a mechanism imposing diurnal variation, and stressful stimuli mediated by CNS. There is presumably also direct feedback control by cortisol to the corticotrophin-producing cells in the anterior pituitary. The 39-amino acid ACTH peptide chain is secreted by specific basophil cells in response to these stimuli and combines with membrane receptors on the zona fasciculata cell, leading to the formation of cyclic AMP. This cyclic AMP stimulates pregnenolone synthesis in the mitochondria.

In such feedback control, cortisol and cortisone are most effective; aldosterone regulates the secretion to some extent whereas deoxycorticosterone (DOC) has only one-tenth activity. Hyperplasia of the gland occurs after repeated injections of ACTH (Fig. 75.11).

Nervous Control

Stimulation of the hypothalamus (stress, excitement, cold, etc.) releases a chemical mediator, corticotrophin-releasing factor (CRF), which is carried through local blood circulation to the anterior lobe of the pituitary gland and stimulates secretion of ACTH which in its turn causes secretion of adrenal cortical hormones (Fig. 75.12).

Inorganic Control

Diet low in sodium or high in potassium stimulates secretion of aldosterone.

Blood Volume

Diminished blood volume increases the section of aldosterone whereas increased blood volume produces opposite effect.

Renin-angiotensin Mechanism

The main regulatory control of aldosterone secretion is mediated through renin (mol wt 57,000) liberated from juxtaglomerular cells. These cells respond to changes in the diameter of the renal arteriole and the renin liberated, converts into plasma β-globulin ultimately to angiotensin II and angiotensin III (half-life in the circulation of only one minute). The latter compound stimulates zona glomerulosa cells to release aldosterone and also other adrenal cortical hormones to some extent (Fig. 75.13).

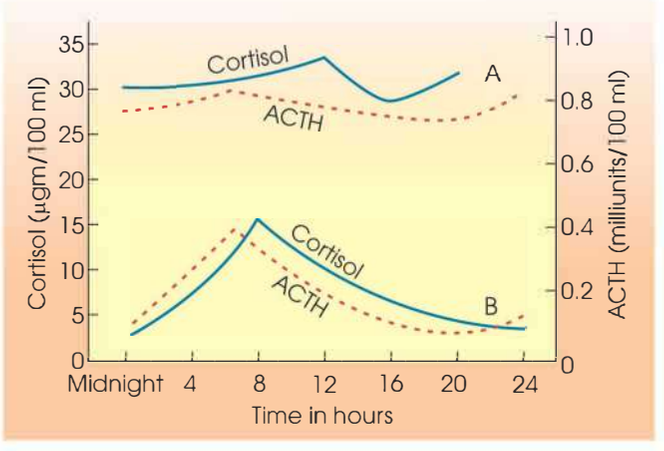

Fig. 75.11: Diagram shows plasma cortisol and ACTH levels at B in a normal subject and a patient with Cushing's syndrome at A

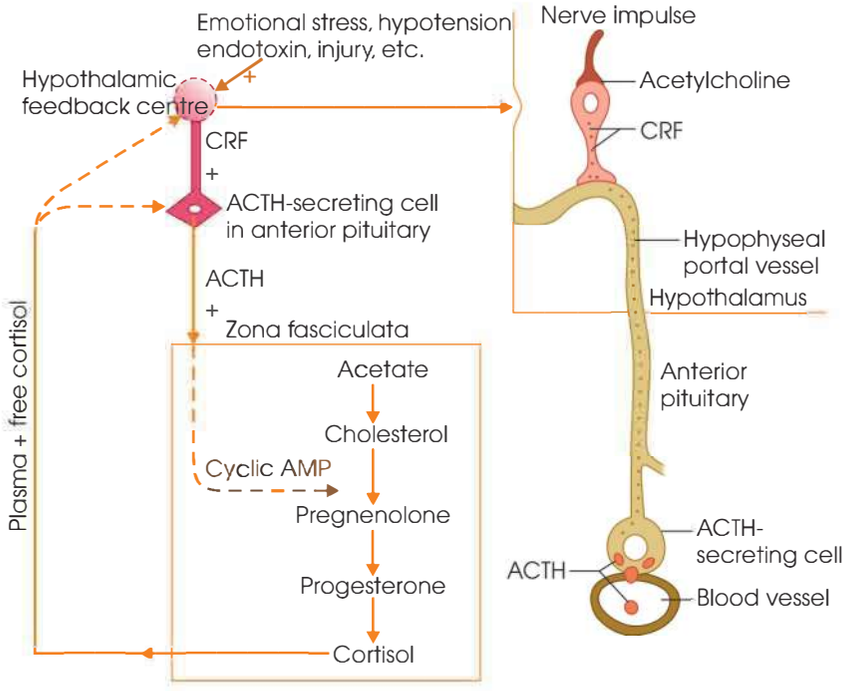

Fig. 75.12: Scheme shows pathways for secretion of cortisol. It shows those factors which can affect the hypothalamus directly to bring about the secretion of cortisol. It also shows that the increased secretion of cortisol in response to injury comes about as a consequence of nerve impulses from the injured area to the hypothalamus where CRF is released and carried to the anterior pituitary via the hypophyseal portal system

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GENERAL ADAPTATION SYNDROME

Experimental studies: It is known that after adrenalectomy or in adrenal deficiency (Addison's disease) the animals fail to react quickly and effectively to environmental changes. They easily succumb under stress and strain, viz. infection, toxin, cold, anoxia, etc. which a normal animal can easily withstand. Experimental study by Selye has shown that if the strain be continued for some length of time certain morphological and functional changes take place in various glands and tissues which enable the animal to adapt itself successfully to the changed environment, and that, adrenal cortex takes a prominent role in the process. It is no wonder that adrenal cortex, with its immense influence on organic and inorganic metabolism, on kidney functions, on sex, on immunity mechanism, etc. will play an essential role in the process of adaptation. After all, adaptation means the calling-up of the reserves of the body and to set up a new metabolic balance at a new gear and if that be so, then adrenal cortex, with its all-abiding influence on ovary cell of the body must naturally play a very prominent role.

The process of adaptation is called by Selye as general adaptation syndrome. The mechanism as to how the stress and strain, e.g. exposure to cold, etc. bring physiological adaptive changes as described further. When an animal is kept in cold, three stages are described during adaptation.

Alarm reaction: This is the first stage and comes within 6–24 hours. The stress is at first too severe and the animal seems to bend under the below.

a. General changes—fatigue, loss of muscle tone, diminished urine.
b. Blood changes—fall of NaCl and sugar, and lymphopenia.
c. Changes in glands. (A) Adrenal gland—both medulla and cortex—shrunken. Granules disappear from the cells. (B) Thymus and lymphoid tissues—involution. If the strain be too severe the animal may die in shock. If not, the second stage appears.

Stage of resistance: The animal recovers and gains back a good deal of its normality. Blood sugar and chloride become normal. Urine output increases and there are large amounts of adrenocorticoid hormone in it. The adrenal cortex enlarges and granules reappear in the cells. Other organs and glands regain their normal structure and functions. Thus, the animal gradually adapts itself against stress. Such adaptive mechanism may, on the other hand, induce a number of pathological changes like arthritis, arteriosclerosis, ulceration of digestive tract, etc. Excess of ACTH and adrenocortical steroids produced as a result of such stress causes such "adaptation disease" described by Seyle.

Stage of exhaustion: If the stress is maintained and increased further, the resistance gradually fails after one or two months. All the signs of failure as described under first stage reappear and the animal dies in prostration.

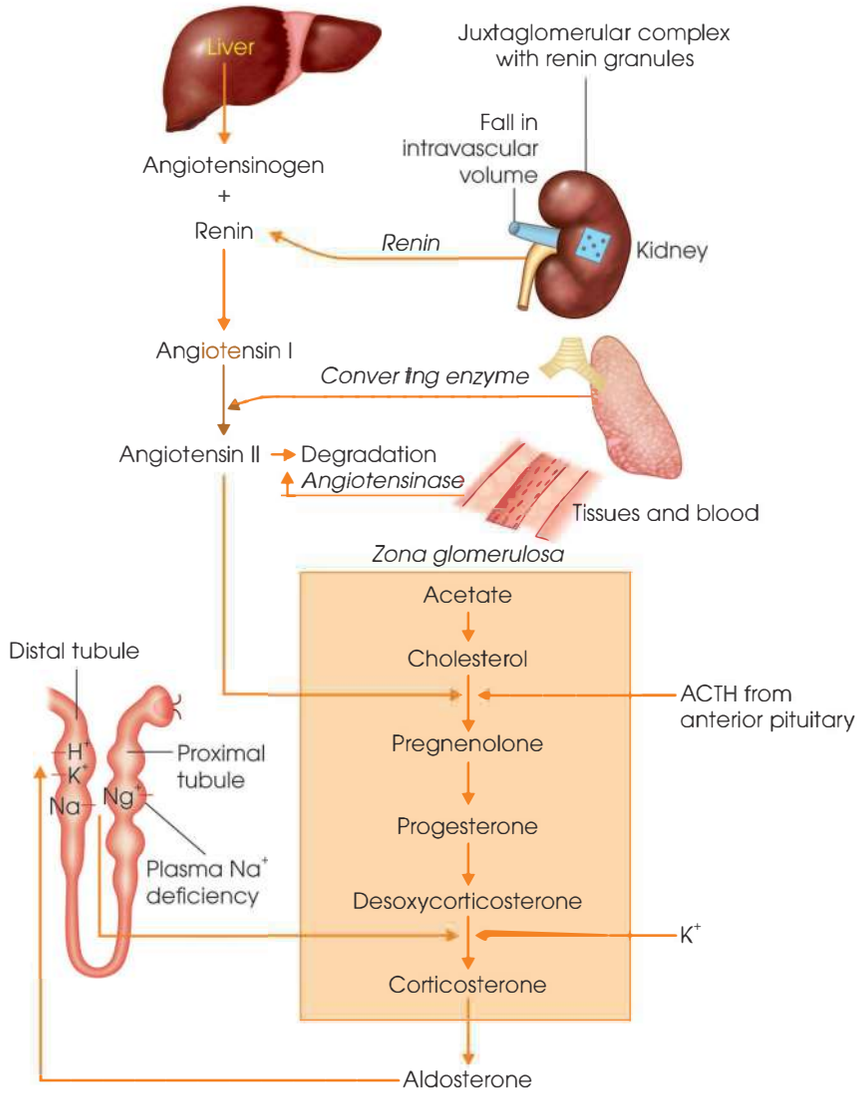

Fig. 75.13: Schematic representation of factors stimulating aldosterone secretion in the zona glomerulosa

ADRENAL MEDULLA

Histology

Adrenal medulla consists of irregular masses of polyhedral granular cells, surrounded by blood sinuses. Granules represent stored adrenaline, disappearing during secretion and reappearing after rest. They stain black with osmic acid, green with iron salts and brown with chromic acid, for the last property, they are called chromaffin (glanglion) cells. Some of the chromaffin cells secrete epinephrine and some norepinephrine. Small lymphocyte-like cells with dark nucleus and scanty cytoplasm, called sympathogonia are also present. Staining reactions help to determine the limit between cortex and medulla (Fig. 75.14).

Electron Microscopic Structure of Adrenal Medullary Cells (Fig. 75.15)

It showed dark granules. Each granule is enclosed by a smooth-surfaced membrane and is denser in its core than in its periphery. Average diameters of the granules are about 200 nanometres. Number of granules in different cells may vary probably in different stages of secretory activity.

Besides this, there are two types of cells: One is specialised to secrete norepinephrine and the other to secrete epinephrine.

Adrenal Medullary Hormones

Adrenal medulla produces catecholamines, e.g. epinephrine, norepinephrine or levarterenol and dopamine.

Biosynthesis of Adrenomedullary Hormones

The principal catecholamines (Fig. 75.16), found in the body, are norepinephrine, epinephrine and dopamine. These catecholamines are formed from amino acids, tyrosine and phenylalanine by hydroxylation and decarboxylation. Steps and enzymatic processes involved in the synthesis of catecholamines from phenylalanine and tyrosine have been presented in Fig. 75.17.

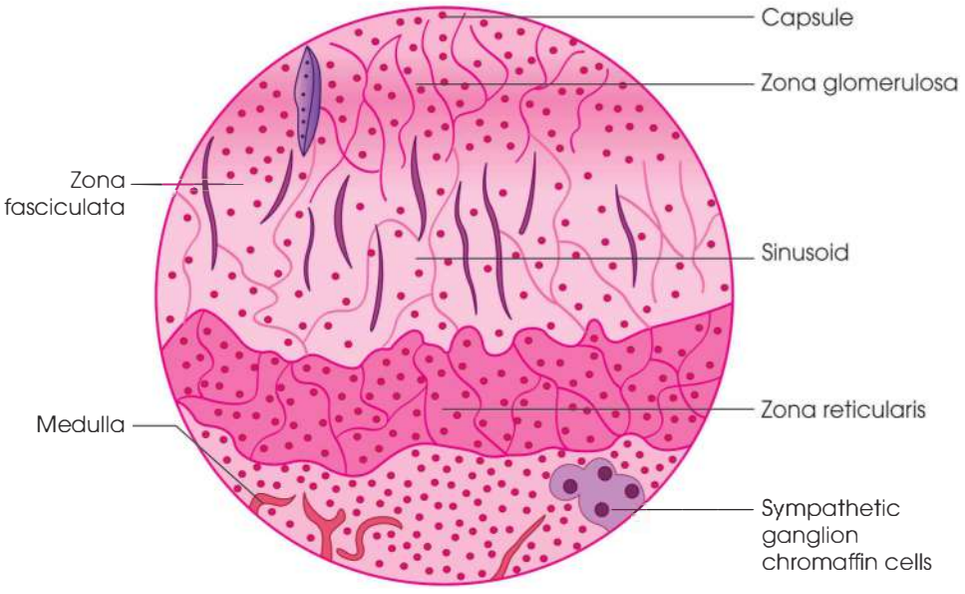

Fig. 75.14: Diagrammatic representation of histological structures (magnified) of adrenal medulla of the suprarenal gland

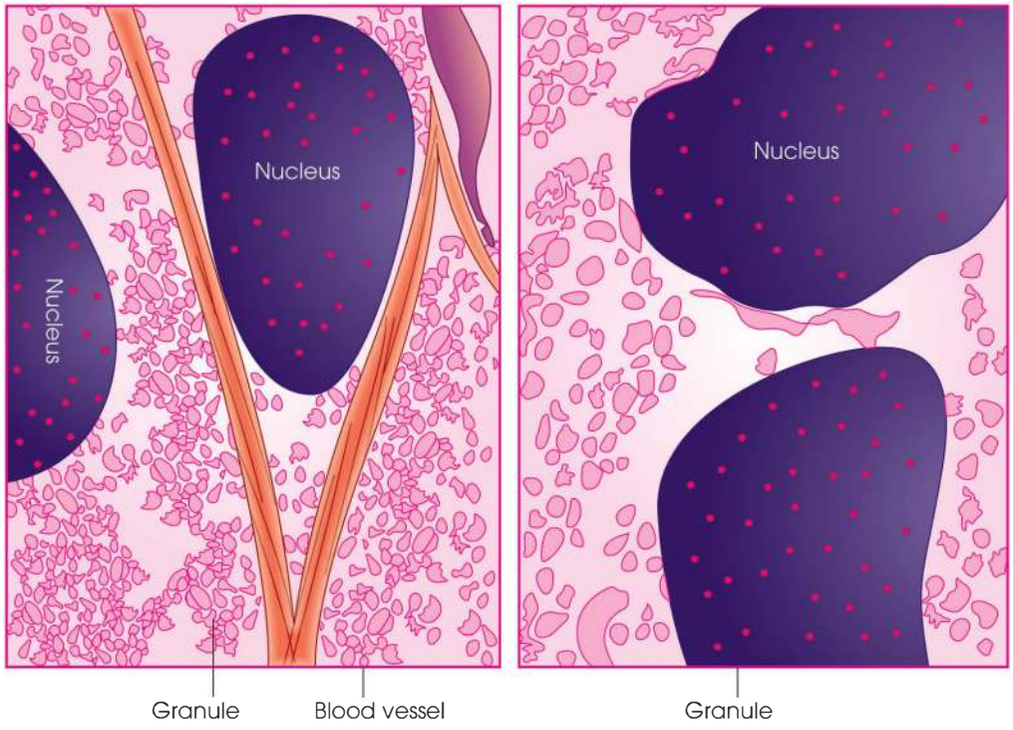

Fig. 75.15: Diagrammatic representation of electron micrographs of adrenal medullary cells showing abundant membrane-limited dense granules which are sites of storage of catecholamines

Phenylalanine hydroxylase takes place in the conversion of phenylalanine to tyrosine, which is formed in the liver because this specific enzyme is present in the liver. Tyrosine thus formed from phenylalanine and also of the dietary sources is transported to the adrenal medulla. There it is converted to DOPA by tyrosine hydroxylase. DOPA on decarboxylation by enzyme aromatic L-amino acid decarboxylase, dopamine is formed. Dopamine thus formed enters the granulated vesicles (storage vesicles), within which it is converted to norepinephrine by the enzyme dopamine β-oxidase. The rate-limiting step in the synthesis of catecholamines is the conversion of tyrosine to DOPA. Synthesis in adrenergic nerve endings is similar up to this stage. In the adrenal medullary cells there is cytoplasmic enzyme phenylethanolamine-N-methyl transferase (PNMT) in high concentration (Fig. 75.17). This enzyme converts the norepinephrine to epinephrine. Thus, appreciable amount of epinephrine is formed in the adrenal medulla. The amines are held in the storage vesicles by

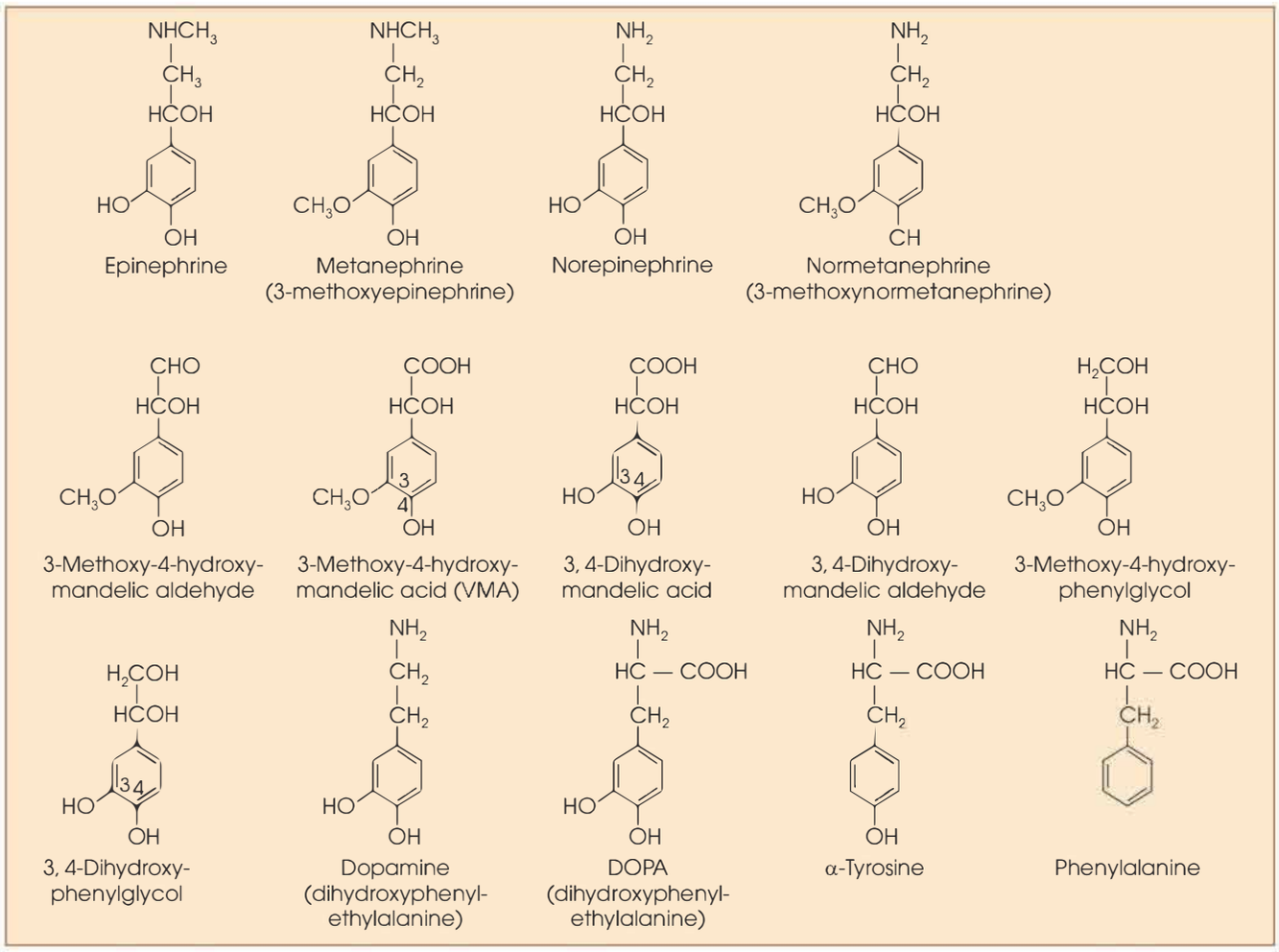

Fig. 75.16: Chemical structures of catecholamines

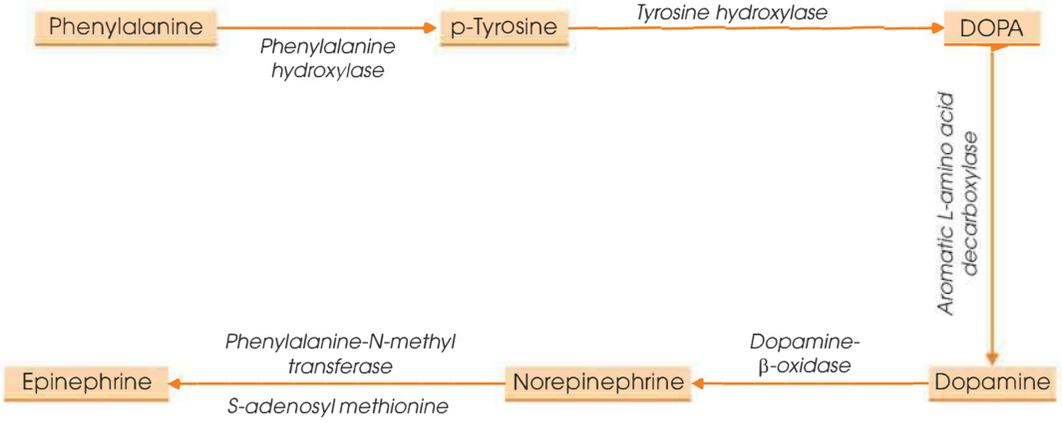

Fig. 75.17: Schematic representation of biosynthesis of catecholamines. PNMT is only present in high concentration in the adrenal medulla. That is why excess amount of adrenaline is being formed in this organ

an active transport system. In the storage vesicle norepinephrine and epinephrine are bound to ATP and protein.

RELEASE OF CATECHOLAMINES

Catecholamines are released from the adrenal medulla by a process known as exocytosis. After chemical stimulation, followed by membrane depolarisation, the chromaffin granules discharge catecholamines including ATP and specific proteins.

MECHANISM OF ACTION OF CATECHOLAMINES

Catecholamine responses are mediated via cAMP, G proteins and phosphatidylinositol and are associated with α- and β-adrenergic receptor responses.

The catecholamine response through β_1, β_2, and β_3 receptor is mediated via increase cAMP in cells, α_2 receptors bind to inhibitory G protein and thereby action is mediated by decreased cAMP in the cells while α_1 receptors are coupled with phosphatidylinositol and action is mediated via DAG and IP_3 as second messengers.

Alpha and Beta Receptors

It is possible that there are two types of receptor substances in the target organs that respond differentially to epinephrine and norepinephrine. The alpha receptor in the cells responds more to norepinephrine and both alpha and beta receptors to epinephrine. The β-receptor and β-receptor functions of the two catecholamines can be studied by using respective blockers (Fig. 75.18 and Table 75.2).

Recent advances in receptor studies have revealed there are three types of β receptors β_1, β_2, and β_3 and two types of α receptors α_1 and α_2. The β_1, β_2, and β_3 receptors are coupled with adenyl cyclases and there action is mediated by increasing cyclic AMP level in the cell. The α_1 receptor is coupled to inhibitory G protein and mediates the catecholamine action on binding by decreasing cyclic AMP. α_2 receptor is coupled with phospholipase C and its effects are mediated via DAG and IP_3.

Catabolism of Catecholamines

Catecholamines, released from the adrenal medulla or from the sympathetic neurons, are metabolised in the liver by two enzymes—monoamine oxidase (MAO) and catechol-*O*-methyl transferase (COMT) (Fig. 75.19).

Epinephrine and norepinephrine of blood are for the most part methylated by COMT and then oxidised in the liver by MAO. Epinephrine on methylation by COMT gives rise to metanephrine, whereas norepinephrine on methylation by COMT gives rise to normetanephrine. Both metanephrine and normetanephrine are ultimately converted into 3-methoxy-4-hydroxymandelic aldehyde by MAO. 3-methoxy-4-hydroxymandelic aldehyde is excreted as 3-methoxy-4-hydroxymandelic acid or vanil (vanillyl) mandelic acid (VMA) (Fig. 75.20).

Table 75.2: Principal actions of some drugs which affect sympathetic activity

Nature of action	*α-receptors*	*β-receptors*
Stimulation	Norepinephrine Epinephrine Metaraminol Methoxamine Phenylephrine	Isoproterenol Epinephrine Norepinephrine
Inhibition	Phenoxybenzamine Phentolamine Ergot alkaloids	Dichloro-isoproterenol Pronethalol Propranolol

Principal metabolic product either of epinephrine or of norepinephrine that is excreted through urine is the VMA. Normetanephrine and metanephrine are also excreted. All these metabolic products are excreted as sulphate or glucuronide. Preferably sulphate of the products is excreted through the urine.

In sympathetic neuron, norepinephrine is constantly oxidised by MAO into 3, 4-dihydroxymandelic acid and its corresponding glycol. These two inactive products thus formed, enter the general circulation and then subsequently are converted into their corresponding, O-methyl derivatives, the VMA and 3-methoxy-4-hydroxyphenyl glycol (Fig. 75.21).

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EPINEPHRINE (ADRENALINE)

Epinephrine is one of the active principles of adrenal medulla. Epinephrine content of the resting gland is about 0.1 mg% of its moist weight. Total store in both glands is about 10 mg in man. Epinephrine is a tyrosine derivative. In the adrenal medulla, the epinephrine is stored in granules bound to ATP and protein. Its

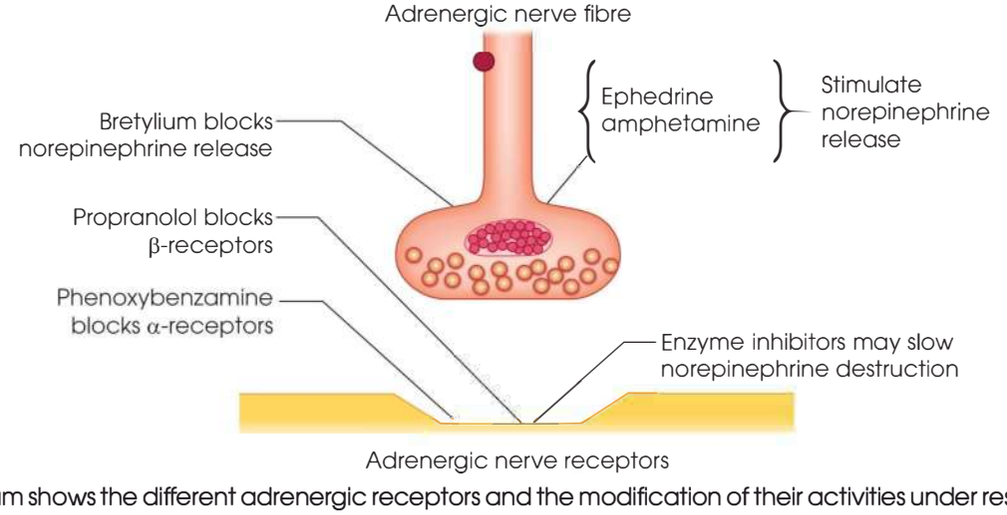

Fig. 75.18: Diagram shows the different adrenergic receptors and the modification of their activities under respective blockers

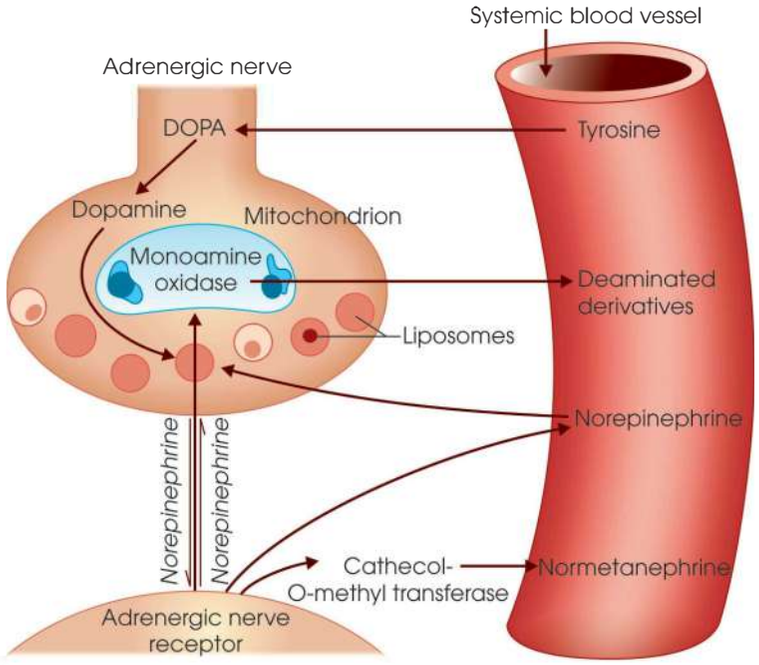

Fig. 75.19: Schematic representation of formation uptake and metabolism of norepinephrine at the adrenergic nerve ending (read *catechol* for cathecol)

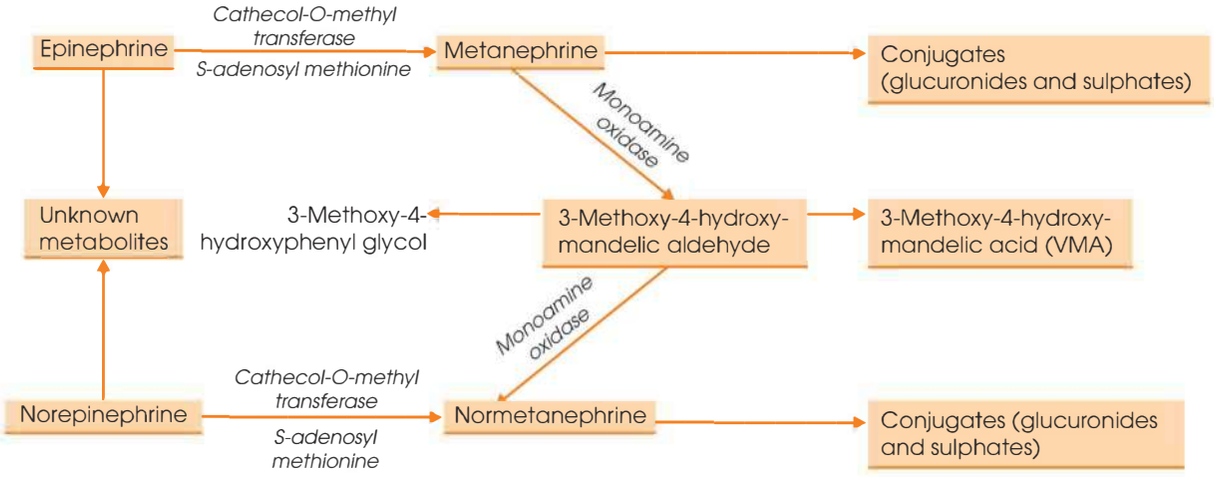

Fig. 75.20: Scheme shows catabolism of circulating epinephrine and norepinephrine. The chief site of catabolism is the liver. The conjugates are mainly glucuronides and sulphates (read *catechol* for cathecol)

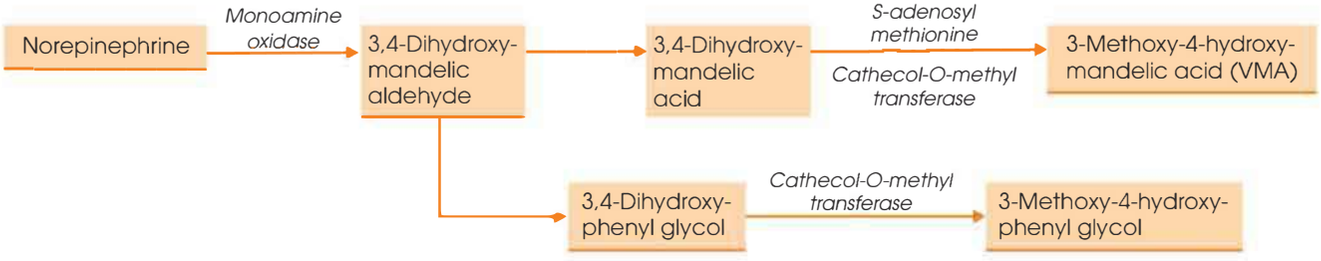

Fig. 75.21: Schematic representation of catabolism of norepinephrine in the adrenergic nerve endings. The acid and glycol enter general circulation

secretion is initiated by acetylcholine, released from the preganglionic neurons that innervate the secretory cells. The acetylcholine increases the permeability of the cells and the Ca^{++} entering the cells from ECF triggers exocytosis. Natural epinephrine is levorotatory and is about 12–15 times stronger than the dextro form. Both forms have been synthesized. It is rapidly oxidised on exposure to light producing a brown substance.

Mode of Action

Epinephrine is a sympathomimetic hormone, exerting the same effects as sympathetic stimulation throughout the body. The exact nature of action on a particular tissue (viz. stimulation or depression, constriction or relaxation) will be same as the local sympathetic effect. The strength of action on a particular tissue will depend on the richness of sympathetic supply.

Urinary products of epinephrine are

1. Metanephrine	40%
2. VMA	41%
3. 3-methoxy-4-hydroxyphenyl glycol	7%
4. 3,4-dihydroxymandelic acid	2%
5. Unchanged epinephrine	6%
6. Miscellaneous	4%

Site of Action

Site of action of epinephrine is on the α-receptors and β-receptors of effector organs. Due to the β-receptor activity of epinephrine, blood pressure is raised; cardiac muscle is excited, smooth muscle of spleen and epididymis of rat contracted and so on. But due to the β_2-receptor activity, blood pressure is decreased (vasodilatation), bronchial muscle is relaxed, force of contraction and frequency of heartbeat are increased. The main effects of β-receptors are excitatory, whereas those of α-receptors are inhibitory.

Action of Epinephrine

Its action on different tissues and systems are briefly summarised below.

On circulation

1. **Heart**
   - Rate, force and output increase (in the intact body, the rate may be slowed down by sino-aortic reflex—caused by raised blood pressure).
   - Myocardium—excitability increased.
   - Bundle of His—conductivity raised.

   The enzyme tyrosinase can convert tyrosine into DOPA (dihydroxyphenylalanine). In the animal body, ascorbic acid or ultra-violet rays, in presence of Fe, can convert tyrosine into DOPA. The rich ascorbic acid content of adrenal cortex may have some part of play.

2. **Blood vessels.** All constricted except coronary vessels and those of skeletal muscles. Although splanchnic vessels constrict, yet the intestinal vessels are believed to dilate.
3. **Blood pressure:** Rises sharply and comes down slowly and even below the basal level. Systolic blood pressure rises. Diastolic blood pressure may fall. But mean arterial blood pressure is raised. Total peripheral resistance is increased due to vasoconstriction in the skin and splanchnic area—causing decrease of total vascular capacity of the body.
4. **Respiration:** Bronchial muscles relax causing dilatation of bronchioles and cause shrinkage of the mucosa and diminution of secretion of mucus (hence, its therapeutic use in asthma). The rate and depth of respiration are increased. The metabolic rate is accelerated, hence RQ is increased.

   Epinephrine apnoea: This is not seen in man. In animals, respiration becomes shallow and even may cease at the height of raised blood pressure following epinephrine injection.

5. **Anterior pituitary:** Epinephrine stimulates anterior pituitary to liberate ACTH, which again helps in the release of glucocorticoids mainly. Glucocorticoids increase blood sugar through a process of gluconeogenesis. The stimulation of anterior pituitary might either be a direct one or mediated through the hypothalamus.
6. **Skeletal muscles:** Excitability and contractility is raised. The onset of fatigue delayed.
7. **Liver:** Glycogen is mobilised due to increased breakdown of liver, glycogen.
8. **Blood**
   - Blood sugar is increased due to: (1) Glucogenolysis from liver, (2) formation of glucose from lactic acid of muscles through Cori cycle, (3) increased gluconeogenesis due to epinephrine mediated release of glucocorticoids.
   - Blood lactate increases due to breakdown of muscle glycogen. Coagulation time is reduced.
   - A rise in serum potassium.
   - Red cell, white cell, platelet count, percentage of haemoglobin, as also blood volume is increased due to contraction of spleen. It causes a fall in the number of circulating eosinophils (indirectly through ACTH).
   - The increased cell count is usually believed to be due to mobilisation from the depots, especially due to contraction of spleen. But small changes occur after splenectomy. Since, plasma proteins are also concentrated to the same degree, it is more likely that the haemoconcentration is due to increased filtration of fluid from the blood stream into the tissue spaces—caused by raised blood pressure.
   - Plasma proteins concentrated.
9. **Kidneys**
   - Urine volume is reduced.
   - Renal circulation diminished (caused by constriction of renal vessels, specially the efferent glomerular vessels).

- May cause glycosuria (due to hyperglycaemia).
- Even if renal circulation is cut down, the volume of glomerular filtrate remains the same. This is because, plasma is more extensively filtered. In other words, filtration fraction (i.e. glomerular filtrate/plasma flow) increases. These facts prove that epinephrine selectively constricts the efferent glomerular vessels, thus reducing the glomerular flow but increasing the glomerular pressure. Consequently, filtration increase. But in spite of it, urine volume is reduced. This is because rate of reabsorption of water by the renal tubules increases.

10. **Metabolism**
    - Basal metabolic rate is increased by moderate doses of epinephrine, large doses cause a fall.
    - *Respiratory quotient:* O_2 consumption rises by 20–40% and CO_2 production by 30–50%. Hence, respiratory quotient rises.
    - *Carbohydrate metabolism:* Blood sugar is raised due to breakdown of glycogen (glycogenolysis) in the liver and muscles (through Cori cycle). Epinephrine activates phosphorylase in the liver and skeletal muscles, and hence blood sugar rises. The blood lactic acid also rises. Plasma potassium rises coincident with the glycogenolysis. The primary effect is probably due to increase in cyclic AMP by activating the enzyme adenyl cyclase. Cyclic AMP in turn activates the phosphorylase. This effect is similar to that of glucagon but the latter is only effective in the liver tissue. Epinephrine also stimulates ACTH release and thus indirectly raises blood sugar by gluconeogenesis. Depressed utilisation of glucose by the tissues is another causative factor for hyperglycaemia.
    - *Adipose tissue:* Causes hydrolysis of neutral lipid through cyclic AMP.
11. **Smooth muscle**
    - *Intestine:* Movements inhibited, sphincters closed.
    - *Gall bladder:* Contraction of gall bladder.
    - *Urinary bladder:* Relaxation of bladder and constriction of sphincter. *Uterus:* Effects not uniform. In labour and puerperium, inhibited. *Spleen:* Contraction (smooth muscles in the capsules contract).
    - *Eye:* Dilatation of pupils, due to contraction of dilator papillae muscle and retraction of the lids due to contraction of the smooth muscle of the lids.
12. **Skin**
    - It leads to contraction of arrector pili causing standing of the hairs. Other smooth muscles of the skin also contract (the spreading of bird's feathers, peacock's plumes, porcupines 'thorns', etc. are due to epinephrine secretion during excitement).
    - *Sweet gland:* In human beings sweating can be induced by intradermal administration of epinephrine in small amount. But in some animals, through the glands are innervated by sympathetic nerves, yet sweating cannot be induced.
13. **Nervous system:** Epinephrine but not norepinephrine produces a sense of restlessness, anxiety and fatigue.
14. **Spinal cord:** Large doses of epinephrine diminish muscle tone and somatic reflexes (knee jerk, etc.). This is due to a direct depressant action of the cord, independent of any circulatory or other changes.
15. **Salivary gland:** Salivary glands have got both sympathetic and parasympathetic innervations. The two nerves act synergistically and for the same reason their respective neurohumours, norepinephrine, likewise epinephrine and acetylcholine have got synergistic effects on the secretion of salivary glands. Epinephrine or norepinephrine stimulates thick mucinous secretion and acetylcholine stimulates profuse watery secretion. Thus, total volume of salivary secretion is increased when epinephrine and acetylcholine are administered at a time.
16. **Lacrimal gland:** Lacrimal glands receive secretory fibres from the parasympathetic but not from the sympathetic. Stimulations of the parasympathetic always cause secretion, but sympathetic stimulation has got no such effect. Epinephrine likely has got no effect on lacrimal secretion.
17. **Melanophores:** The effects of MSH on the dispersion of melanin granules within melanophores are antagonised by catecholamines through adrenergic β-receptors. This effect seems to be mediated through the decreased level of cyclic AMP.

Control of Epinephrine Secretion

Nervous Control

Hypothalamus is the higher centre which controls the sympathetic and epinephrine secretion. This centre may be affected in two ways: (a) Directly, and (b) reflexly.

The following factors affect the centre directly:

1. **Higher centre:** Excitement generally stimulates secretion.
2. **O_2 lack, CO_2 excess, increased H ion concentration,** etc. stimulate secretion.

3. **Blood sugar level:** Hypoglycaemia stimulates, hyperglycaemia depresses the centre.

The following factors affect the centre reflexly:

1. **Sino-aortic reflexes:** Raised blood pressure depresses, lowered blood pressure (haemorrhage, etc.) increases epinephrine secretion.
2. **O_2 lack, CO_2 excess, increased H ion concentration**—stimulate.

These sino-aortic nerves exert a tonic inhibitory control over adrenal medulla. Section of these nerves stimulates secretion.

1. **Exposure to cold** stimulates epinephrine secretion reflexly. This helps in two ways: (a) Vasoconstriction of the skin-reducing heat loss. (b) Increased metabolic rate—raising heat production. Thus, in cold climates, epinephrine plays a great part in heat regulation.
2. **Any acute sensation**, viz. pain, heat, etc. stimulate reflexly.

Norepinephrine (Noradrenaline) or Levarterenol or Levophed

Norepinephrine is another hormone of adrenal medulla. It is the immediate precursor of epinephrine. It is supposed to be the actual sympathetic transmitter produced at the endings of the adrenergic fibres.

Commercial epinephrine, as usually extracted from the adrenal medulla, contains about 18% norepinephrine. Hence, the effects of the commercial epinephrine are due to the presence of both. Normally, when adrenal medulla secretes, it liberates both the hormones. Consequently, the effects of stimulation of adrenal medulla (or sympathetic) in the body is due to both the hormones. Paroxysmal hypertension, due to tumour of adrenal medulla is believed to be due to an increased secretion of norepinephrine.

Action

Except for a few instances, the actions of epinephrine and norepinephrine are very similar (Table 75.3). Norepinephrine is more closely sympathomimetic than epinephrine. When norepinephrine is infused slowly in normal animals or humans the systolic and diastolic blood pressure increases. This hypertension stimulates the carotid and aortic pressoreceptors, producing reflex bradycardia which overrides the direct cardio-accelaratory effect of norepinephrine.

Site of Action

Site of action of epinephrine is on the α-receptors and β-receptors of effector organs. Its actions are mediated via α- and β-receptors. Norepinephrine acts on the heart via β_2-receptors increasing heart rate and force of cardiac contraction and increases the systolic blood pressure. It acts via α_1-adrenergic receptor of blood vessels producing vasoconstriction and increasing diastolic blood pressure. The other actions on various visceral organs and metabolism have been discussed with that of epinephrine. The hormone epinephrine is nearly three times potent then norepinephrine in raising blood sugar, increases lactic acid levels and oxidation of lactic acid leads to increase glycogen synthesis in liver, increases oxygen consumption by tissue producing calorigenic effect, and decreases muscle glycogen.

Table 75.3: Action of epinephrine and norepinephrine

Human systems	*Epinephrine*	*Norepinephrine*
• Heart		
– Rate	Increased	Slightly increased
– Output	Raised	No change
– Blood pressure		
Systolic pressure	Raised	Raised
Diastolic pressure	No change	Raised
Mean arterial pressure	Increased	Raised
• **Vessels**	Dilator for some (muscle), constrictor for others	Entirely constrictor
• **Respiration**	Stimulated	Stimulated
• **Kidney**	Constrictor of renal vessels	Constrictor of renal vessels
• **Uterus**	Inhibited	Inhibited
Non-pregnant in rat or cat		
• **Central nervous system**	Increased mental anxiety	No effect
• **Metabolism**		
– O_2 consumption	Increased	Increased
– Blood sugar	Increased	Increased
– Free fatty acid release	Increased	Increased
• **Intestine**	Inhibited	Inhibited

Control of Norepinephrine Secretion

Adrenergic endings continuously secrete norepinephrine which is essential for the normal control of vascular tone and so, blood pressure. It is believed that changes in the blood pressure level regulate the liberation of norepinephrine from both the adrenergic endings and the adrenal medulla. The increased liberation of this hormone in emergent condition is not of primary importance.

Functions of Adrenal Medulla

Norepinephrine which is liberated after stimulation of sympathetic nerves plays an important role in the regulation of circulation, whereas epinephrine which is secreted mostly from adrenal medulla is mainly concerned in metabolic adjustments. Both hormones are involved in emotional expression. Presence of normal amount of adrenocortical hormones is necessary for majority of actions of catecholamine.

Developmentally, medullary cells represent the nerve cells of sympathetic ganglion. Functionally, they also resemble each other by secreting epinephrine. The only difference is that, the ganglion cells secrete norepinephrine at the nerve endings whose effect is limited to a particular locality. While the medullary cells secrete the epinephrine and norepinephrine directly into the blood stream and thus affect the whole body. Thus, adrenal medulla and the sympathetic ganglia should be regarded as the two divisions of a common sympatho-epinephrine mechanism—one division reinforcing the activity of the other.

Methods of Functional Study of Adrenal Medulla

Summary of the Functions of Adrenal Medulla

From the above observations, functions of adrenal medulla can be summarised as follows:

1. Reinforce sympathetic action (sympathomimetic).
2. Helps to keep the normal resting blood pressure at a steady level by adjusting the rate of epinephrine secretion. Fall of blood pressure stimulates, rise of blood pressure depresses secretion via sino-aortic nerves. Secretes more epinephrine during emergency and enables the subject to fight out the situation successfully.
3. Takes part in heat regulation.
4. Takes an important part in metabolism—especially in carbohydrate metabolism.

Hyperfunction of Adrenal Medulla

Pheochromocytoma is catecholamine-producing tumours that arise from chromaphin cells most of the adrenal medulla.

Clinical Manifestations

1. Paroxysmal or permanent hypertension: Excessive effects of epinephrine or norepinephrine.
2. Spells or crises.
3. Extreme elevations in blood pressure associated with headache, angina pectoris or blanching of face and extremities—these reflect primarily α-receptor stimulation.
4. Facial flushing or sweating, rapid palpitations, fever and, sometimes, hypotension (α-receptor effects seem to dominate).
5. There may also be nervousness or anxiety, diabetes mellitus, thyrotoxicosis, various types of emotional disturbance, primary haemorrhagic lesions of GI tract, biliary colic, primary renal disease, acute adrenal insufficiency, toxaemia of pregnancy, hyperglycaemia along with transient glycosuria, a high haematocrit, weight loss, anorexia, increased BMR, increased O_2 consumption, etc. Myocarditis is sometimes observed; the cause is unknown.

EXAM-ORIENTED QUESTIONS

Essay

1. Discuss the physiological action and functions of glucocorticoids. Add note on Cushing syndrome.
2. Describe the mechanism of secretion and synthesis of cortisol. Discuss the functions of glucocorticoids.
3. Discuss the role of mineralocorticoids and glucocorticoids on metabolism.
4. Discuss the functions of mineralocorticoids. Add note on Addison's disease.
5. Describe the mechanism of action and functions of epinephrine and norepinephrine.
6. Discuss the mechanism of action of ACTH. Discuss the regulation of ACTH secretion.

Short Notes

1. Phaeochromocytoma
2. Addison's disease
3. Cushing syndrome
4. General adaptation syndrome
5. Functions of adrenal medulla
6. Mechanism of action of catecholamines
7. Epinephrine
8. Mineralocorticoid
9. Glucocorticoids and immunity
10. Addison's crisis

Chapter

76

Local Hormones

INTRODUCTION

The local hormones are produced by local action and are endogenous substances with known biological activity. They are not released or stored in blood. The important local hormones are erythropoietin, renin, histamine, serotonin, prostaglandins, bradykinin, atrial natriuretic peptides, endothelin, adrenomedullin, etc. Most of these are not released into circulation Gastrointestinal hormones have been discussed in GIT.

ERYTHROPOIETIN

Erythropoietin is a polypeptide hormone. It acts on bone marrow. It stimulates the production of red blood cells, but unlike haemopoietin, does not affect the white blood cells or platelets.

Physiological Basis

Erythropoietin is a glycoprotein hormone. It is a protein signaling molecule for red blood cell precursors in the bone marrow. It has a molecular weight of 34 kDa. It is produced by the interstitial fibroblast in the peritubular capillary bed of the kidney and the perisinusoidal cell in the liver. Its production predominates in liver in the fetal and perinatal life while renal production is predominant during adulthood. Its synthesis is regulated by the feedback mechanism measuring blood oxygenation and iron availability. The transcription factors for EPO, known as hypoxia-inducible factors, are hydroxylated and proteosomally digested in the presence of oxygen and iron.

Action

Erythropoietin acts on the bone marrow to promote the development of the erythroblast stem cells, which then mature into reticulocytes and red blood cells without the need for further hormonal action. It can augment the production of haemoglobin within red cells, increasing cell volume and haemoglobin content.

Interrelationship

Hypophysectomy causes anaemia which may be reversed probably by GH, ACTH and TSH, by stimulating an increase in erythropoietin secretion. Androgens increase erythropoiesis in a variety of disorders. Cobalt, thyroid hormones and adrenaline enhance erythropoietin production. Oestrogens impair the bone marrow's response to erythropoietin. Erythrocytaemia results from increased erythropoietin secretion. Hypoxia and anaemia are the main factors known to increase erythropoietin secretion.

The exogeneous source for erythropoietin is recombinant human erythropoietin (rhEPO) is produced by recombinant DNA technology.

RENIN

Renin also known as an angiotensinogenase is an enzyme that plays a key role in activating the renin-angiotensin-aldosterone system (RAAS). The renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS) is a hormone system which regulates the plasma sodium concentration and arterial blood pressure. Renin has been discussed along with renal system.

HISTAMINE AND HEPARIN

It is a nitrogenous compound involved local immune response. Histamine and heparin are synthesised by the tissue mast cells, stored there and released under certain circumstances. If the mast cells belong to the APUD series which shows a high amino content, amine precursor uptake, amino acid decarboxylase and marked metachromia and are described widely in tissues close to the walls of small blood vessels. In some species, but probably not in man, the mast cells also contain 5-HT.

Synthesis

Histamine is derived from the decarboxylation of the amino acid histidine. This reaction is catalyzed by enzyme L-histidine decarboxylase.

Action

Histamine binds to histamine receptors which are located on the surface membrane of cells. Histamine receptors are of three types H1, H2, and H3.

Histamine is probably responsible for some of the effects of the atypical carcinoid syndrome and both are probably involved in the mastocytosis syndrome which proliferates mast cells giving rise to diffuse or nodular infiltration of many organs including the skin, liver, spleen, bone marrow, lymph nodes, pancreas, thymus, lungs, meninges, etc. Excessive release of histamine causes urticaria pigmentosa, dermographism, duodenal ulceration and pyrexia. Heparin may cause defects of coagulation. The histamine action can be blocked by antihistaminic drugs. Antihistamines are used for treatment of allergies and H1 receptor blocker drugs are prescribed for the same. H2 antagonists' drugs, such as cimetidine that inhibits gastric acid secretion and is used for treating peptic ulcers.

THE PROSTAGLANDINS

Prostaglandin was the name given by von Euler in 1935 to a substance isolated from human seminal fluid and thought to be secreted by the prostate gland. The name prostaglandin given by him was a lipid-soluble, acidic compound, which lowered blood pressure and stimulated various isolated smooth muscle preparations. The prostaglandins and related compounds are recognized as eicosanoids. The examples of eicosanoids are prostaglandins, prostacyclins, thromboxane, leukotrienes and epoxyeicosatrienoic acids. The eicosanoids are considered local hormones and there special characteristics are that they have specific effects on target cells close to their site of formation and are rapidly degraded, so they are not transported to distal sites within the body. They are participating in intercellular signaling as well as in intracellular signal cascades. Within recent years, thorough chemical analysis of the prostaglandins has been made and as many as 14 types of naturally occurring prostaglandins have been isolated. Among the fourteen, eight are metabolites of the remaining six and 13 of the 14 are found in human. The prostaglandin endoperoxides have a very brief existence and are rapidly hydrolyzed into more stable metabolites, such as PGD_2, PGF_2, PGE_2, PGI_2 (prostacyclin), thromboxane A_2, thromboxane B_2 (TXB_2), and HHT (hydroxyheptadecatrienoic acid). The formation of prostaglandin is tissue specific. Platelets synthesize TXA_2 which is a vasoconstrictor and platelet-aggregating substance. The arterial wall, corpus luteum, follicle, uterus, and ductus arteriosus produces PGI_2, a vasodilator and inhibitor of platelet aggregation. PGE_2 and PGF_2, are produced in nearly all tissues, including the uterus, follicle and brain. $PGF_{2\alpha}$ and PGE_2 have both antagonistic and agonistic interactions. In the oviduct, $PGF_{2\alpha}$ promotes smooth muscle contraction, whereas PGE_2 promotes smooth muscle relaxation. Both $PGF_{2\alpha}$ and PGE_2 promote contractions in uterus.

Chemistry

Prostaglandins are a class of C_{20} fatty acids containing cyclopentane ring. These biologically active lipids are derivatives of a hypothetical fatty acid—the prostanoic acid (Wolfe, 1970). All natural prostaglandins with the exception of certain metabolites contain a hydroxyl group at C-15 (R) and a transdouble bond at C-1314 (δ13). The chemical name of PGE is 9-keto-11 (α), 15(R)-dihydroxy-prost-13 (tr)-enoic acid, PGR is 9(α), 11(α), 15(R)-trihydroxy-prost-13 (tr)-enoic acid, etc. Structural configurations of certain prostaglandins have been shown in Fig. 76.1.

Distribution

Prostaglandins are widely distributed. Almost each tissue contains small amount of prostaglandin. Seminal plasma and seminal vesicles, menstrual fluid, endometrium, amniotic fluid, decidua, placenta, spleen, skin, iris, lung, thyroid, thymus, submaxillary salivary gland, gastro-intestinal tract, pancreas, kidney, adrenal medulla, cerebrospinal fluid (CSF), brain, spinal cord, phrenic nerve, vagus, etc. contain prostaglandins.

Mode of Action

Prostaglandins act via increasing the cAMP levels. The secreted prostaglandins also bind to specific cell surface G-protein coupled receptors, and increase cAMP levels. Prostaglandins may also bind to nuclear receptors and alter gene transcription. The different types of prostaglandins have different functions (sometime it acts as agonist as well as antagonist) depending on tissue location. The prostaglandins increase cAMP in many endocrine glands; such as pituitary, thyroid and parathyroid; leading to increased hormone production respectively. While they decrease formation of cAMP in some tissues such as:

1. Adipose tissues leading to decreased lipolysis
2. Pancreas leading to reduced insulin secretion
3. Stomach leading to decreased gastric HCl secretion

Synthesis of Prostaglandins

Prostaglandins along with prostacyclins and thromboxanes are synthesized from arachidonic acid (Fig. 76.1). The hormones such as epinephrine,

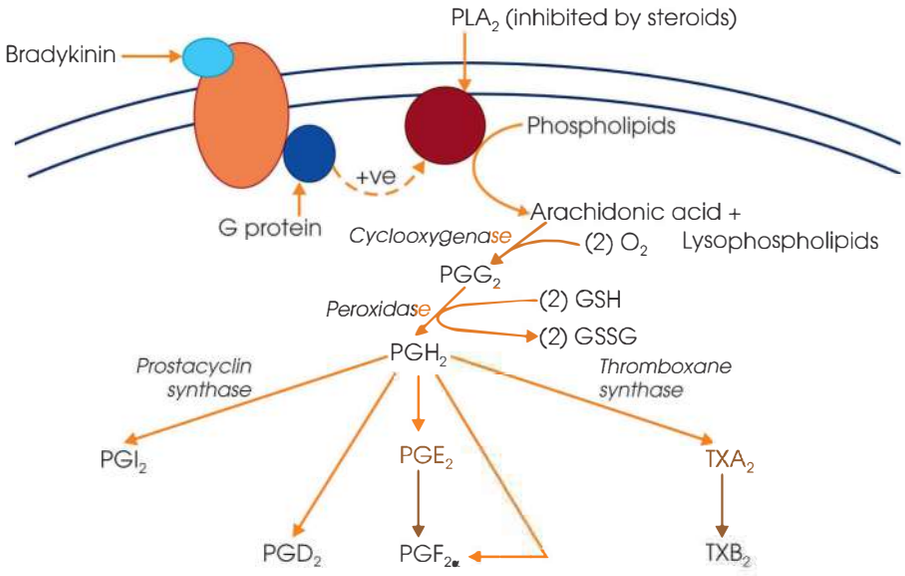

Fig. 76.1: Synthesis of prostaglandins

thrombin and bradykinin activate phospholipase A_2 which hydrolyzes arachidonic acid from membrane phospholipids to form prostaglandin.

Functions

Variation in Functions of Prostaglandins

The prostaglandins may carry a particular function in one tissue while in some other tissue it may oppose the same. *For example:* Some prostaglandins cause relaxation of smooth muscles; especially of bronchi and blood vessels (vasodilatation decreases blood pressure); while others cause muscle contraction (stimulates uterine contraction, helps in parturition)

The various functions of prostaglandin include:

1. *Prostaglandins in Reproduction*

Prostaglandins have got significant role in sperm transport. Prostaglandins deposited in the vagina during coitus may act locally on the cervix and body of the uterus so as to help in sperm transport.

Menstruation: There is some evidence that certain prostaglandins ($F_{2\alpha}$ and E_2) are related with the onset of menstruation.

Parturition: Prostaglandin $F_{2\alpha}$ possibly takes part during labour as evident from high concentration of prostaglandin $F_{2\alpha}$ in amniotic fluid during labour.

Placental blood flow: As umbilical cord contains high concentration of prostaglandins, it is suggested that prostaglandins may have some role in regulation of placental blood flow.

2. *Central Nerve Transmitters*

There are certain evidences suggesting the role of prostaglandins as neurotransmitters in the CNS. When administered by microelectrophoresis on to nerve cell, they alter the firing rates of neurons. But more work is required for substantiating this postulation.

3. *Lipolysis*

Prostaglandin is potent inhibitor on lipolysis. Lipolytic effects of catecholamines, ACTH, glucagon, TSH, vasopressin, sympathetic nerve stimulation, cold stress, etc. are reduced by prostaglandin E_1. Lipolytic actions of epinephrine, vasopressin, LH and gastrin are due to formation of cyclic AMP through the activation of adenyl cyclase on ATP. It is claimed that prostaglandin E_1 behaves like a competitive inhibitors of the different hormones that increase lipolysis. As antilipolytic actions of prostaglandin E_1 may result from inhibition of adenyl cyclase (Fig. 76.2), it has been suggested that the apparent competitive antagonism of adenyl cyclase by prostaglandin E_1 may be due to an action in preventing the adsorption of ATP by the enzyme.

4. *Gastric Secretion*

Considering the involvement of cyclic AMP in gastric secretion in response to a variety of secretagogues, it is predicted that prostaglandins must inhibit gastric secretion. This has been observed true in rats. Oral administration of prostaglandin E_1 causes inhibition of gastric secretion.

5. *Permeability to Water*

Water permeability of the isolated toad bladder and tubule by vasopressin can be inhibited by prostaglandin E_1 through acting on the adenyl cyclase.

6. *Steroidogenesis*

Prostaglandins E_1 and E_2 do not inhibit the increased secretions of progesterone and dihydroprogesterone in

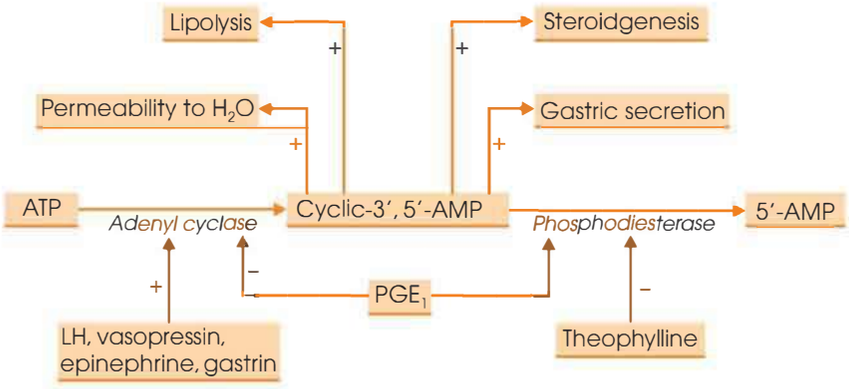

Fig. 76.2: It represents lipolytic effects of PGE through inhibition of adenyl cyclase activity

response to gonadotrophins release. Prostaglandin E_2 potentiates the formation of dihydroprogesterone in response to gonadotrophins.

7. *Vascular Smooth Muscles*

Prostaglandins (E and A group) are potent vasodilators. This action is not abolished by atropine.

8. *Respiratory Smooth Muscle*

Human bronchial smooth muscle *in vitro* is relaxed by prostaglandins E_1 and E_2 but contracted by $F_{2\alpha}$.

9. *The Clinically Important Prostaglandin Mediated Functions*

1. PGD_2 secreted primarily from the mast cells inhibits platelets aggregation and produces vasodilatation.
2. PGE_2 secreted by most cells especially the kidney, the platelets and the heart increases cAMP production. They produce vasodilatation, and platelet aggregation. They are used in obstetric practice for inducing uterine contraction and labour.
3. $PGF_{2\alpha}$ secreted by the lung, spleen, uterus, heart and many other cells produces vasoconstriction, bronchoconstriction and smooth muscle contraction, e.g. uterine contractions.
4. Prostacyclin [PGI_2 is secreted primarily by vascular endothelial cells (especially heart)]; increases cAMP in platelets, and inhibits platelets aggregation, it also prevents platelets adherence to vessels wall, and produces vasodilatation, lowering the blood pressure.

SEROTONIN

Serotinin also known as 5-hydroxytryptamine are found in GI enterochromaffin cells, platelets and brain. It is synthesized from tryptophan (in diet) in two steps. There is active uptake process of serotonin in platelets and nerve terminals.

Serotonin receptors, also known as 5-hydroxy-tryptamine receptors or 5-HT receptors, are a group of G protein-coupled receptors. These are ligand-gated ion channels found in the central and peripheral nervous systems. The serotonin receptors are of 15 types and subtypes. The main subtypes are 5HT-1A, 5HT-2, 5-HT, etc.

Synthesis

Tryptophan is the precursor to serotonin. Tryptophan is taken up by serotonergic neurons in restricted brain areas such as the raphe nucleus. As it enters the neurons, an enzyme tryptophan hydroxylase adds the hydroxyl group to form 5-HTP (short for 5-hydroxytryptophan). 5-HTP is decarboxylated by aromatic L-amino acid decarboxylase to produce serotonin.

Actions

1. **Respiratory system:** Respiratory blood vessels muscles affected.
2. **GI tract:** It produces intense rhythmic contractions in small intestine and may produce diarrhoea. It also stimulates vomiting.
3. **Cardiovascular system:** It produces vasoconstriction by the direct effect on arteries.
4. It plays important role in pain perception and sleep/wakefulness cycle.
5. It is involved in neuroendocrine regulation—controls hypothalamic cells involved in release of several anterior pituitary hormones.

BRADYKININ

It is an endogenous locally produced endogenous vasodilator. It is a non-apeptide and is formed from plasma globulins called kininogens.

Synthesis

Protease kallikrein acts upon high molecular weight kininogen precursor in response to infection or injury leading to hydrolysis of plasma kininogen to produce

bradykinin. There are of the plasma and tissue kallikreins.

Functions

1. Cardiovascular action: It via nitric oxide release produces vasodilatation.
2. It increases the capillary permeability and lead to accumulation of fluid in interstitium producing localised oedema.
3. Bradykinin via its direct effect on heart increases rate and force of contractions. It elicits also a coronary vasodilation.
4. It increases salivary secretion and leads to hyperaemia of salivary glands.
5. It produces visceral smooth muscle contraction.
6. It stimulates the release of antidiuretic hormone and produces natriuresis.

ENDOTHELINS

They are polypeptides containing 21 amino acids. There are three types of endothelin: Endothelins, I, II and III. They have different amino acid sequence in their chemical structure. Endothelin 1 (ET-1) is the most active out of the three endothelins. They are found in the vascular endothelium apart from kidney, brain, adrenal gland and intestine.

Synthesis

Endothelins are synthesized from prepropeptides, preproendothelin. This is hydrolyzed by enzyme endopeptidases into pro-endothelins (39 amino acids). The endothelin converting enzyme acts upon pro-endothelin to form endothelins.

Functions

1. Endothelins via action on ETA and ETB receptors produce general vasoconstriction especially in coronary and pulmonary arteries.
2. They increase the rate and force of contraction of heart.
3. They produce bronchoconstriction.
4. They by a mitogenic effect may induce changes in musculature of heart such as cardiac hypertrophy and also produce atherosclerotic changes in blood vessel.

ATRIAL NATRIURETIC PEPTIDE

The family of endogenous polypeptide which are known to be of cardiac origin are Natriuretic peptides, (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Atrial myocytes when get stretched due to increase volume load, it produces vasodilator effect and natriuresis.

Synthesis

ANP is a polypeptide made up of 28-amino acid and is secreted by atrial myocytes on distension. BNP is a 32-amino acid secreted from ventricles in response to stretch. The CNP is a 22-amino acid polypeptide formed in vascular endothelium and brain. The chemical structure of ANP, BNP and CNP is signified by ring formation of a disulfide bond admixed between 2 cysteine residues.

Functions

1. *Renal:* It increases glomerular filtration rate and produces diuresis.
2. *Heart:* It produces vasodilation and thereby decreases arterial pressure. It also reduces vascular reactivity to vasoconstrictive agents.
3. *Hormonal:* It stimulates lipolytic action, inhibits aldosterone and renin secretion and perhaps of antidiuretic hormone and opposite effects to angiotensin II. It also reduces the feeling of thirst and appetite for salt.

ADRENOMEDULLIN

It is a 52-amino acid peptide present in adrenal medulla. It is also found in intestine heart and kidney. It has vasodilator and natriuretic effects.

Neurotransmitters

Epinephrine and Norepinephrine

The Nobel Prize in Physiology or Medicine in 1970 was awarded to **Julius Axelrod** (1912–2004) along with Bernard Katz and Ulf von Euler for their research findings on the release and reuptake of catecholamine (epinephrine and norepinephrine) in the brain.

Julius Axelrod

Acetylcholine

The Nobel Prize in Physiology or Medicine in 1936 was awarded to **Otto Loewi** (1873–1961) along with Sir Henry Dale (1875–1968) for discovery of acetylcholine.

Otto Loewi

Sir Henry Dale

Jôkichi Takamine

Japanese chemist **Jôkichi Takamine** (1854–1922) isolated and purified the hormone adrenaline from animal glands in 1901. He received the first patent ("Process of Making Diastatic Enzymes") on a microbial enzyme in the United States in 1894.

EXAM-ORIENTED QUESTION

Short Notes

1. Serotonin
2. Bradykinin
3. Prostaglandin
4. Atrial natriuretic peptides
5. Endothelins

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Chapter

77

Thymus

INTRODUCTION

Anatomy

Thymus is partly an endocrine gland and partly a lymphoid structure. It is located in the anterior and superior mediastinum of the thorax behind the sternum. It extends from the pericardium into the neck to the lower border of the thyroid gland. The thymus consists of two fused asymmetrical, elongated and flask-shaped lobes. The left lobe is smaller than the right. Each lobe is composed of innumerable lobules. Each lobule is made up of small follicles of about 1 mm in diameter. Thymus is largest relative to body weight in the foetus and in childhood up to the age of puberty, after which it undergoes gradual and continuous involution (Fig. 77.1).

This process may be greatly accelerated in the course of many infections and in wasting disease (accidental involution). During regression the thymic tissue is generally replaced by fat, so that the adult thymus is composed largely of fat and connective tissue.

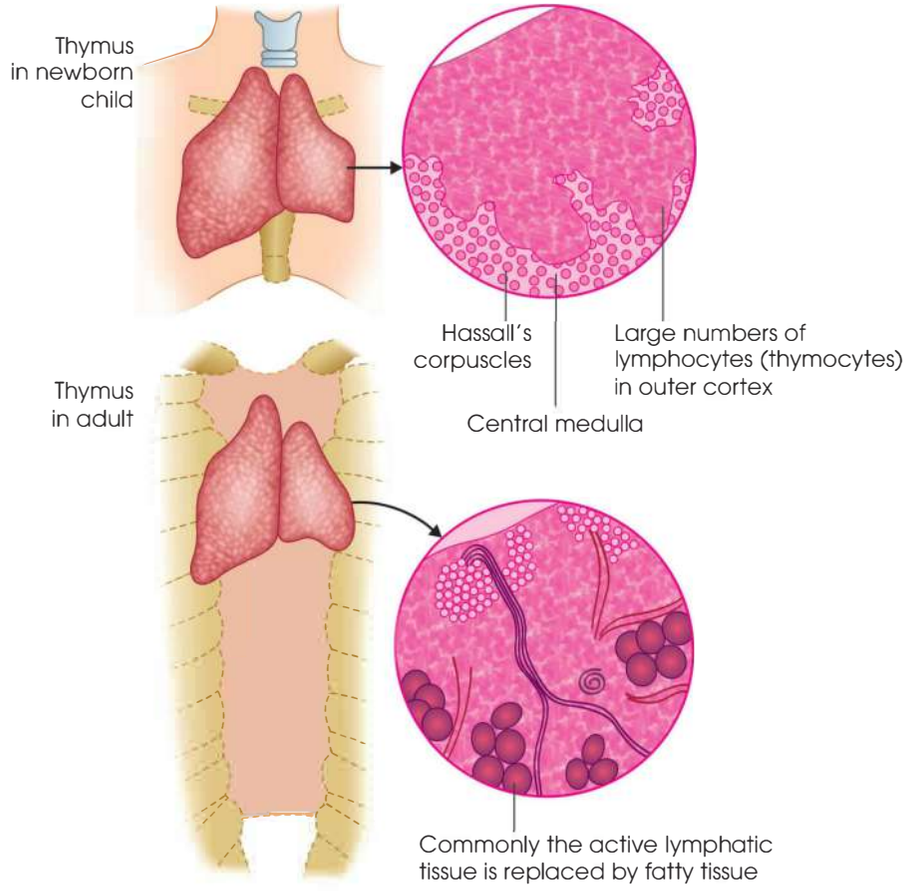

Fig. 77.1: Diagrammatic representation of involution of the thymus

Development

The thymus develops from the endoderm of the third and probably of the fourth branchial clefts on both sides, and in mammalian embryos it is the primordial lymphoid organ, in which lymphocytes can first be identified. The outgrowths coalesce to form a single mass in the midline. Later on, these endodermal elements become secondarily invaded by surrounding mesodermal tissues from which the lymphoid tissues develop. **Hassall's corpuscles** (Fig. 77.2) develop from the remnants of the original endoderm. In birds there is a second primary lymphoid organs, the **bursa of Fabricius**, situated near the cloaca but also arising from the epithelial tissue. The thymus is probably the main source of lymphocyte production in mammalian embryonic life; the rudimentary spleen, for example, does not contain the primordial cells necessary for lymphoid differentiation. At birth, when the spleen and lymph nodes are still poorly developed, the thymus is already a prominent lymphoid organ.

The weight at different ages is as follows (Hammar): At birth—13 g; 1–5 years—23 g; 6–10 years—26 g; 12–15 years—37 g; (maximum); 16–20 years—25 g; 21–25 years—25 g; 26–35 years—20 g; 35–45 years—16 g; 46–55 years—13 g. In old age it decreases to 3–6 g.

Histology

The organ has a connective tissue capsule and consists of two lobes—each with numerous lobules. Each lobule has a dense, darkly-staining peripheral cortex and a looser lightly-staining central medulla (Fig. 77.2).

Capsule

It is dense white connective tissue variably rich in macrophages, plasma cells, mast cells, granular leucocytes, and fat cells. The connective tissue continuous with the capsule dips into the organ separating lobes and lobules, and forms a trabecular or septal system. Large blood vessels, lymphatic vessels and nerves run in the capsule and septa. When the thymus ages and undergoes involution, lobes diminish in size, and the septa and capsule become correspondingly broader and fatty.

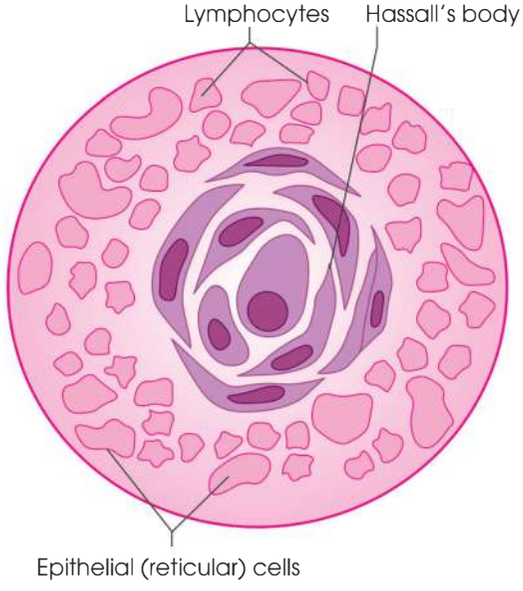

Fig. 77.2: Diagram shows thymic medullary tissue

Cortex

It looks very similar to the lymphoid tissue of the ordinary lymphatic nodes, but lack of primary follicles. The cortex consists of densely packed masses of cells that morphologically look like lymphocytes. Of the lymphocytes in mouse thymus, according to Metcalf's report, about 1% has cell diameter more than 11 µm (large lymphocytes), about 10% have cell diameter about 7 to 11 µm (medium-sized lymphocytes) and the rest are small lymphocytes (also called thymocytes) having cell diameter less than 7 µm. The large lymphocytes transform into the medium and the latter in turn into small lymphocytes. The large and medium lymphocytes probably undergo 3–4 cycles of cell division a day, fulfilling the role of primitive lymphoid cells actively engaged in lymphopoiesis. Scattered among these cells, are elongated reticular cells with pale nuclei. Cyclic AMP appears to stimulate the rate during which time DNA synthesis takes place. These cells are certainly of epithelial origin.

Medulla

It is a broad, branched band of thymic tissue. The medullary branches provide the lobar and lobular patterns of the organ. The medulla consists of epithelial (reticular) cells like those in the cortex. These cells are easily visible due to much less numerous lymphocytes than in the cortex. There are variable numbers of plasma cells, mast cells, eosinophil cells and melanocytes, generally near blood vessels. Hassall's concentric corpuscles or thymic corpuscles are organization of flattened epithelial (reticular) cells and are the characteristic features of the thymus. They are formed from hypertrophied and degenerating reticular cells, concentrically arranged cells of Hassall's bodies stain with acid dyes. The innermost cells show signs of degeneration and hyalinization (Fig. 77.3). Central cells may degenerate completely and cysts or calcareous deposits appear.

BLOOD VESSELS AND NERVE SUPPLY

The thymus receives arterial supply from the internal thoracic and the inferior thyroid arteries. Large venules arise in the medulla, and then combine with larger veins which empty into the left innominate and thyroid veins. The thymus itself is not the site of antibody formation. Epithelial reticular cells in the thymic vessels constitute

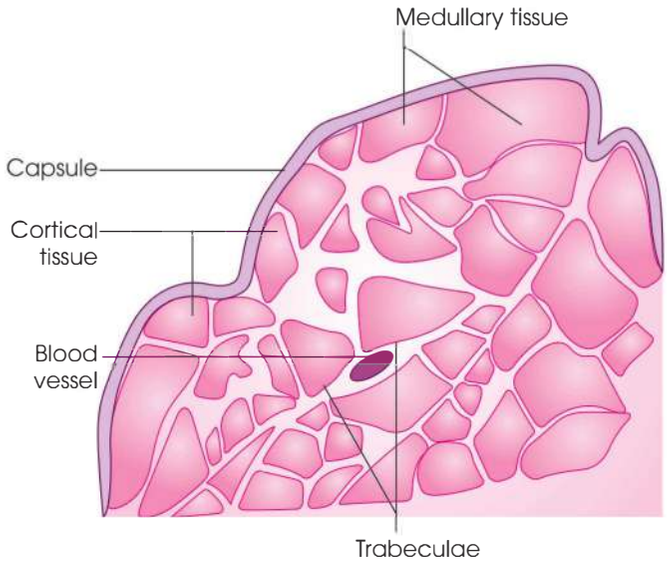

Fig. 77.3: Diagrammatic representation of histological structure of the thymus

an element in the blood-thymus barrier just as the glial cell contributes to the blood–brain barrier. In the thymus the antigen appears to be unable to pass through the blood-thymus barrier to reach to the lymphoid tissue from the blood vessels. The thymic capsule is moderately rich in small unmyelinated and myelinated nerve fibres from the vagus, cardiac plexus, first thoracic ganglion, and ansa hypoglossal. Unmyelinated fibres enter the organ with blood vessels and are probably of vasomotor nature.

EXPERIMENTAL AND CLINICAL EVIDENCES OF THYMIC FUNCTION

Effects of Extirpation

In young animals:

1. At first adiposity, then cachexia and coma.
2. Defective deposition of mineral salts on the bones.
3. A wasting disease with a great fall in blood and tissue lymphocytes and interference in immunity reactions.

Clinical Evidences

1. In myasthenia gravis, thymus enlarges. Thymectomy often improves.
2. In Graves' disease, Addison's disease and acromegaly, thymus enlarges.
3. In eunuchs or after castration in young, thymus does not involute. Sex hormones or maturation of gonads cause thymic involution.
4. In cancer thymus, features almost same as Cushing's syndrome.
5. Status thymicolymphaticus—slight injury, infection, anaesthesia, etc. causes sudden death in many young people. In such cases, enlarged thymus and swelling of the lymphoid structure of the body are found at autopsy. It is held that the thymic enlargement is somehow related to the occurrence of sudden death. Since subjects of status thymicolymphaticus die during anaesthesia, operation, etc., and since adrenal cortex protects against such stress and strain, it seems all the more reasonable that the fundamental defect in status thymicolymphaticus may be an adrenocortical dysfunction. It has also been observed that either any kind of stress or administration of adrenal cortical steroids causes shrinkage of the thymus in young animals or human beings.

THYMOSIN OR THYMIN

A polypeptide, thymosin has been isolated from the thymus gland. This substance has been shown to increase the number of lymphocytes in the circulation and accelerate rejection of skin grafts from other mammals.

Control of Thymus

Anterior pituitary—stimulates. After administration of growth hormone of anterior pituitary in experimental animals; enlargement of thymus has been observed. In Graves' disease thymus is enlarged. Gonads inhibit, and this is possibly the cause of reduction in the size of the organ at sexual maturity. Adrenal cortex also causes inhibition and was used as an assay method of corticosteroids. In Addison's disease thymus is enlarged.

Thymic Disorders and Genesis

In the neonatal myasthenia, the thymus-stimulating antibody passes through the placenta and acts of the foetal thymus. This is responsible for excessive production of thymosin. The pattern and the genesis of neonatal myasthenia gravis resemble neonatal thyrotoxicosis, as a result of the action of LATS (long-acting thyroid stimulator) transferred to the foetus from the blood of the thyrotoxic mother.

EXAM-ORIENTED QUESTION

Short Notes

1. Functions of thymus
2. Thymic disorders

Chapter

78

The Pineal Body

INTRODUCTION

Anatomy

The pineal body (epiphysis cerebri or conarium) of the human brain is a somewhat flattened, cone-shaped, grey body measuring about 5–8 mm in length and 3–5 mm in breadth. It is attached by a short hollow stalk (Fig. 78.1) to the roof of third ventricle. Pia mater covers the body (except where it is attached to the habenular and posterior commissures) and gives rise to connective tissue septa that carry numerous blood vessels into the organ. These septa separate cellular element into cords.

Histology

The cells of the pineal are neural in origin, but bear a little semblance to nerve cells when fully differentiated. There are at least two types of major cells: (i) Parenchymal or chief cells (pinealocytes) have large irregular nuclei and a moderately basophilic cytoplasm. Under E/M, the cytoplasms of chief cells are rich in microtubules which penetrate to the tips of the extended cell processes. A moderately well-developed endoplasmic reticulum and Golgi apparatus and dense membrane-bounded vesicles also typify these cells (Fig. 78.2). Lipid droplets, lipochrome pigment droplets and lysosome-like structures are often present, (ii) Interstitial or supportive cells. Pineal interstitial cells (Fig. 78.3) are markedly stellate in appearance and lie between the clusters of pinealocytes and in perivascular spaces. The cytoplasm is somewhat more basophilic. These cells have a denser nucleus, fewer mitochondria, granular reticulum, and free ribosomes. There are occasional deposits of glycogen.

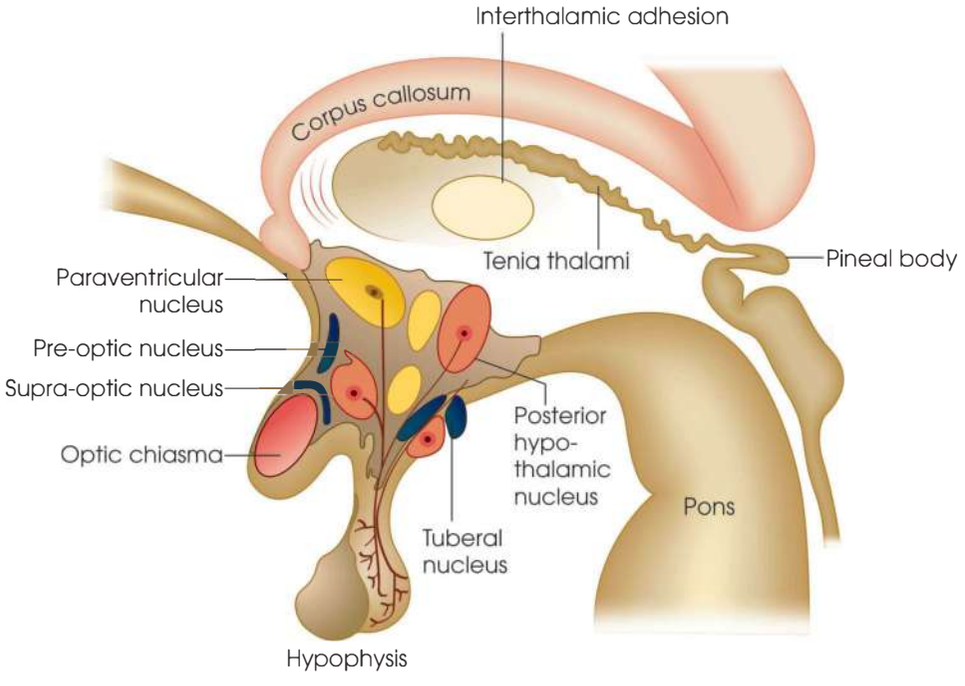

Fig. 78.1: Sagittal section of human brain stem showing the anatomical position of pineal body

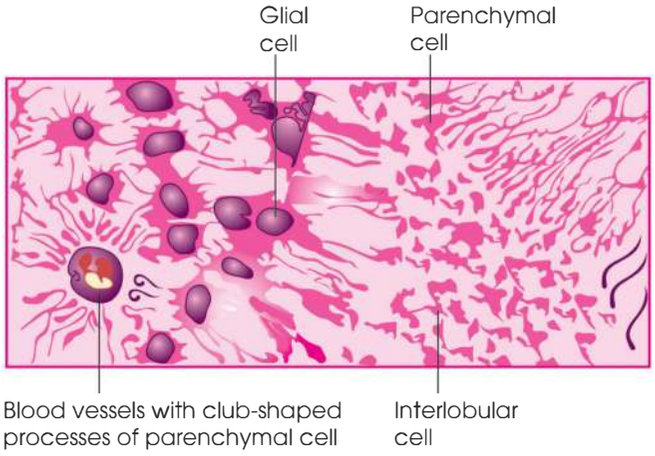

Fig. 78.2: Semi-diagrammatic representation of an adult human pineal body showing two lobules

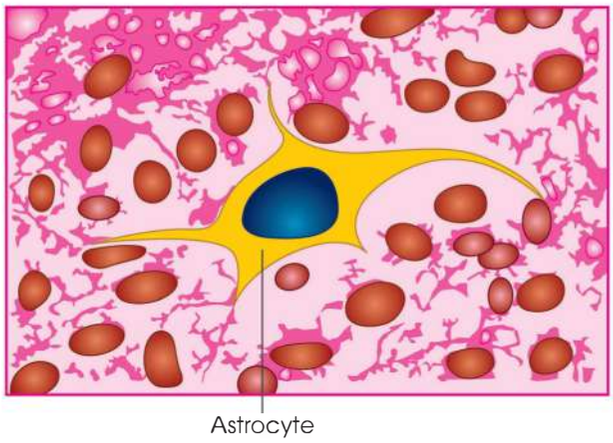

Fig. 78.3: Diagram shows astrocyte in lobule of an adult human pineal body

These cells constitute approximately 5% in the pineal. These cells are regarded by many authorities as atypical glial elements. Some species variation exists in the form and number of interstitial or supportive cell elements. Connective tissue cells, mast cells, Schwann cells, and axons of autonomic nerves are also present in the pineal.

Concretions

The human pineal body shows the presence of extracellular concretions known as corpora arenacea (acervuli cerebri, or brain sand). These concretions are composed of a mineralized organic matrix and usually appear in the capsule and septa. They consist of laminated calcareous nodules (carbonates and phosphates of calcium and magnesium).

Changes with Age

The pineal body first appears at about 36 days of gestation in the posterior region of the roof of the diencephalon. This body attains its maximum development by about 7 years of age and then undergoes a very slow involution. This involution continues to about 14 years of age and is characterized by a relative increase of interstitial tissue, and by hyaline changes in the septa and in the cells. Brain sand increases as involution proceeds.

MELATONIN

Pineal gland contains high concentration of melatonin.

1. It is N-acetyl-5-methoxytryptamine. It has been named melatonin because it lightens the skin of tadpoles by an action on the melanophores.
2. Melatonin is synthesised from 5-hydroxytryptamine—the serotonin.
3. The synthesis of serotonin from tryptophan requires two enzymes—the tryptophan hydroxylase and aromatic L-amino-acid decarboxylase. These two enzymes are present in high concentration in this gland.
4. For melatonin synthesis, serotonin is first acetylated by acetylating enzymes into N-acetyl serotonin. N-acetyl serotonin is converted into melatonin in presence of s-adenosylmethionine and enzyme HIOMT (hydroxyindole-O-methyl transferase) (Fig. 78.4). HIOMT is only present in the pineal gland.
5. High concentration of HIOMT in the tissue serves as a good indicator for pineal tissue.
6. In mammals the melatonin is released as hormone and acts at the level of brain and other tissues so as to influence the development and functional activity of the gonads, pituitary, thyroids and other organs.

Control of Synthesis and Release of Melatonin

1. Exogenous norepinephrine and other catecholamines or the sympathetic nerve fibres increase the melatonin content in the pineal body. This effect is

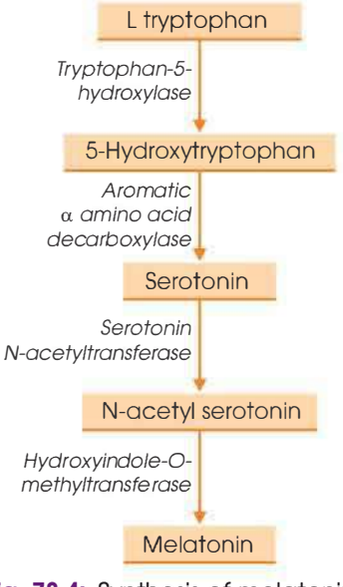

Fig. 78.4: Synthesis of melatonin

brought about from the stimulating rate of melatonin synthesis from serotonin and of serotonin synthesis from tryptophan. Since catecholamines stimulate adenyl cyclase in the pineal gland and since dibutyryl derivative of cyclic AMP can mimic these effects of catecholamines on the synthesis of serotonin and melatonin, so these effects are mediated by cyclic AMP.

2. But that effect of norepinephrine is not mimicked by exogenous cyclic AMP in the pineal body, leads to an increase in the rate of tryptophan uptake. It is suggested that cyclic AMP stimulates melatonin synthesis not by changing the properties of HIOMT but rather by making more substrate available to it.
3. β-receptors can only block the stimulation of pineal adenyl cyclase but not the α-adrenergic blocking agents. Norepinephrine (or perhaps some other factors) released from sympathetic nerve endings normally acts to inhibit the synthetic rate of adenyl cyclase.
4. Environmental lighting affects the melatonin formation and its release from the pineal body and these effects of light are mediated by the sympathetic nervous system. It is proved that the level of melatonin and the activity of enzyme HIOMTs rise during periods of darkness and fall during periods of light.
5. According to Wurtman et al, the inhibitors of protein synthesis do inhibit the increase in HIOMT activity which normally responses in continuous darkness.

Functions

1. The pineal body shows a quick phosphorus metabolism as measured by the uptake of radio-active phosphorus.
2. As photic stimulus relayed for optic pathways to the pineal via sympathetic nerve fibres is translated by pineal activity into humoral gonadal control, melatonin plays an active role in the light-influenced reproductive cycle of rodents and birds.
3. The HIOMT is responsible for the production of a number of hydroxyindoles. This specific enzyme possesses a photoreceptor-type pineal system in the brain and retina of lower vertebrates. But the activity of HIOMT is reduced in constant light.
4. Histochemically pineal phospholipid content is highest during dioestrus and lower during oestrus. During the oestrus cycles, serotonin content and HIOMT activity of the pineal fluctuate. Injections of melatonin and other methoxyindoles reduce ovarian weight and alter the stages of oestrus.
5. The ability of melatonin to modify gonadal function suggests that its secretion is associated with the timing of the oestrus and menstrual cycles, probably mediated through the decrease in gonadotrophic releasing factor of the hypothalamus.
6. It is postulated that adenoglomerulotrophin of the pineal may regulate the secretion of aldosterone and it also liberates an anti-ACTH factor. It is a source of growth-inhibiting factor.
7. Pineal tumour in children generally is concerned with delayed puberty as a result of increased pineal activity. The pineal body seems to have a neuroendocrine function, although the physiology of this gland is a subject of intensive investigation. The pineal seems to participate in the regulation of the rhythmic activity of the endocrine system, by the elaboration of specific hormone or compounds such as methoxyindoles. The prime stimulus for this secretion may well be mediated by visual reflexes.
8. It is a source of a compound that cures schizophrenia.

EXAM-ORIENTED QUESTION

Short Notes

1. Functions of pineal glands
2. Melatonin

CLINICAL CASE SCENARIO

Q1. Describe the characteristic feature of pituitary dwarfism.

Ans. The characteristic features of pituitary dwarfism are immature child like facial features, plump face, delayed skeletal and dental growth and delicate extremities.

Q2. A 48-year-old male was diagnosed as a case of bronchogenic carcinoma and he developed syndrome of inappropriate ADH (SIADH) secretion. Enlist the effects of excessive ADH secretion on physiological functions.

Ans. The increased ADH secretion in syndrome of inappropriate ADH (SIADH) secretion leads to increase water reabsorption across the tubules, increase in circulatory blood volume, decreases plasma osmolality and fluid leaks into the interstitial spaces producing oedema. There is associated hyponatremia with increased excretion of sodium in urine.

Q3. A 27-year-old female presented with complaints of enlarged swelling in the neck region puffiness of face and peri-oribtal swelling. Blood investigational revealed TSH secretion and decreased T_3, T_4 secretion. What is the diagnosis? What are the other characteristic features in the condition?

Ans. The patient is suffering from myxoedema. The other characteristic features in the condition are hoarsening of voice, loss of scalp hair, drooping of upper eyelid, dry, thick, rough and yellow skin, lethargy, inability to concentrate, loss of memory, menstrual disturbances, etc.

Q4. A 5-year-old patient of rickets was brought in hospital with complains of deformed bones and softness of bones. What is the pathophysiology for the cause?

Ans. It is deficiency of vitamin D which leads to rickets. The deficiency of vitamin D leads to poor absorption of calcium and this result in poor mineralization of the protein in the bone. The matrix in-between new bone and cartilage cells are inadequately impregnated with lime salt leading to softness of bone.

Q5. A 32-year-old male reported with complains of marked muscular and generalised weakness. Investigation revealed elevated plasma and urinary aldosterone levels. What are the other characteristic features of this disease?

Ans. The patient is suffering from primary hyperaldosteronism. This is also termed Conn's syndrome. The other characteristic features in Conn's syndrome are muscular weakness, hypernatraemia, hypokalaemia, loss of urine concentrating ability of kidney, increased blood pressure and metabolic alkalosis.

Q6. A 46-year-old female was diagnosed as a case of primary adrenocortical insufficiency? What are the causes for the same? What deficiency leads to manifestation of the condition?

Ans. The common causes for primary adrenocortical insufficiency are tuberculosis, autoimmune diseases and carcinoma. There is deficiency of glucocorticoids and mineralocorticoids.

Q7. A 43-year-old male patient reported to hospital with characteristic features of centripetal distribution of body fat with characteristic buffalo hump, muscular atrophy and thinning of skin of subcutaneous tissue. Diagnose the condition. What is the cause for the same?

Ans. The diagnosis is Cushing syndrome. It is due to excessive glucocorticoids secretion. It is the ACTH secreting tumour of anterior pituitary.

Q8. Describe the cause of characteristic of carcinoid syndrome.

Ans. Carcinoid tumour leads to endogenous secretion of kallikrein and serotonin. Flushing of skin, diarrhoea, nausea, vomiting, secondary restrictive cardiomyopathy; bronchoconstriction and abdominal pain are characteristic signs and symptoms of carcinoid syndrome.

Q9. Explain in brief the following endocrine emergencies.

Ans. Thyroid storm: It is also known as thyrotoxic crisis due to overactivity of thyroid gland and it occurs in patient of hyperthyroidism or in patients of untreated mild hypothyroidism who have developed an infection. The characteristic features observed in this condition are high fever, tachycardia, vomiting agitation and diarrhoea. The patient may develop myocardial infection or heart failure.

Hypercalcaemic crisis: It occurs when there is increased serum calcium level above 14 mg/dl. The signs and symptoms of this crisis include anuria or oliguria, and a stage of somnolence or comatose state.

Myxoedema coma: Any stressful stimuli such as infections or episode of myocardial infarction may precipitate hypothyroid state leading to myxoedema coma. The characteristic features of this condition include hypotension, bradycardia, decreased body temperature, hyponatraemia, hypercapnia and hypoxia.

Pituitary apoplexy: It occurs in disorder such as tumour of pituitary in which there is impaired blood supply or bleeding into pituitary gland. The patient may present with headache, diplopia and visual field defect.

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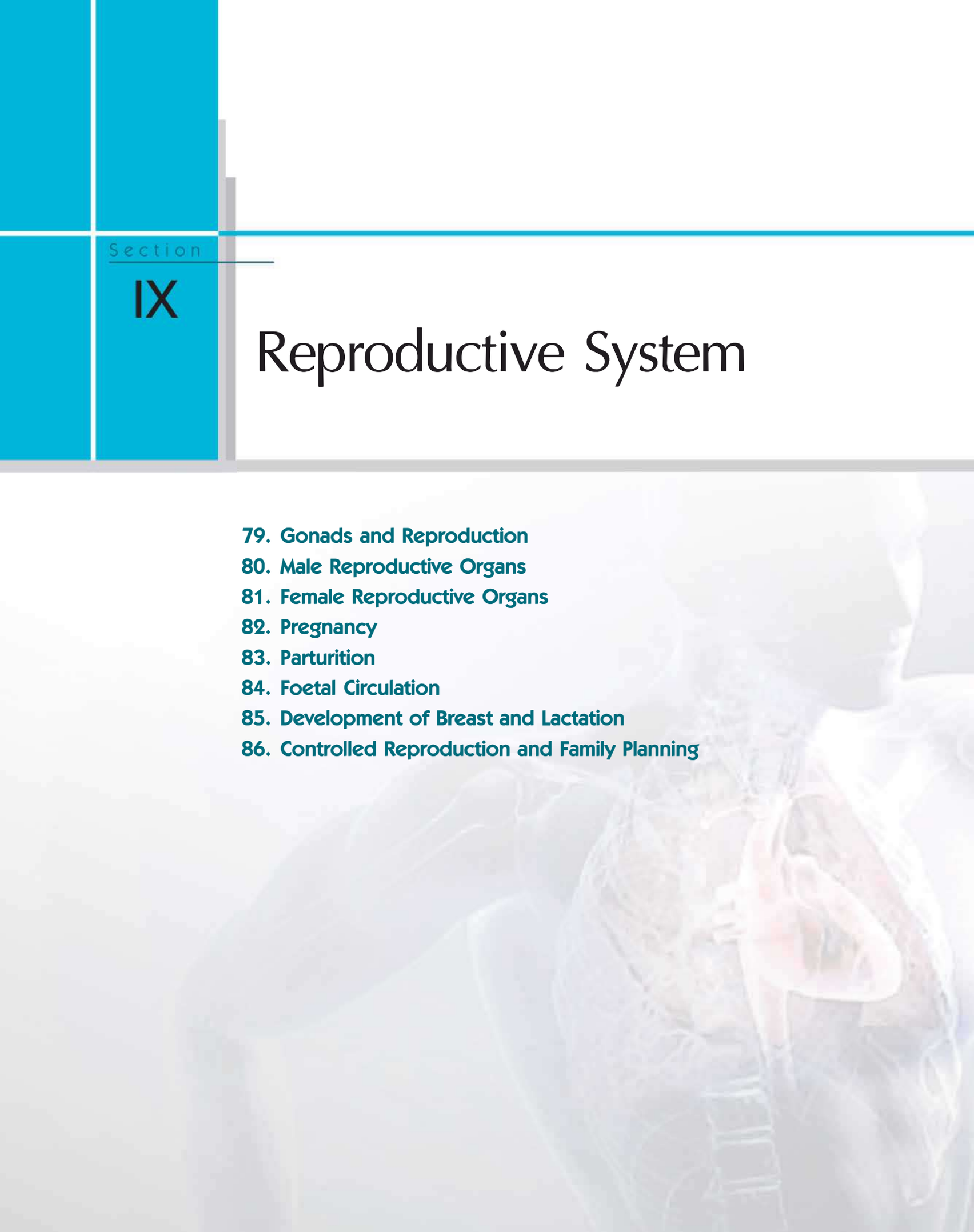
Section

IX

Reproductive System



Chapter

79

Gonads and Reproduction

INTRODUCTION

The male generative organs consist of testes, epididymis, vas (ductus) deferens, seminal vesicles, ejaculatory ducts, prostate, Cowper's (bulbo-urethral) glands and penis. The female reproductive organs include ovaries, Fallopian tubes, uterus, Bartholin's (greater vestibular) glands, vagina and breasts. Of these, testes and ovaries are called the primary sex organs or the gonads. The remaining structures are collectively known as the secondary or accessory sex organs.

It should be noted that both males and females are fundamentally bisexual. In males, the masculine features predominate, the feminine features remain rudimentary. In females, it is just the reverse. The urine of both sexes contains both male and female hormones but in different proportions. It is more than probable that the physical and mental get-up of the male or female does not depend on the activity of the male or female hormone only—but on the combined action of both the hormones. It seems that an optimum balance of these two hormones is the more important factor than any one of them.

GONADAL FUNCTION

Testis and ovary possess two functional components. One component secretes hormones and other produces gametes. Interstitial cells of Leydig produce testosterone in the male; and in the female follicles of the ovary secrete oestrogen, 17β-OH progesterone, and variation of progesterone secretion depends upon the time of the ovarian cycle. This small amount of progesterone which is present in the female blood is formed mostly by peripheral conversion from precursors, e.g. androstenedione which is secreted by the ovary. The steroids which are formed in the gonads and adrenals follow a common biosynthetic pattern except 11β-hydroxylation characteristic of corticosteroid synthesis in the adrenal gland.

REPRODUCTION

It depends upon hormonal control in all aspects. Gonads fail to develop completely without pituitary gonadotrophin and in the adult removal of the pituitary causes the failure of reproduction. Most of the functioning of the hypothalamic pituitary system controls the gonadal development and generation of reproductive rhythms. Pituitary gonadotrophin secretion makes gonadal differentiation and development, maturation of germ cells and gonadal steroid secretion. In turn, gonadal steroid hormones lead to genital development and appropriate libido regulating a cyclic fashion in the female. This cyclic fashion provides conditions suitable for conception and implantation. Moreover, when the function of placenta is established, the fetal development becomes independent of pituitary and ovarian support. But ovulation, implantation and early development of zygotes are controlled by the hormones.

PUBERTY

The onset of reproductive life is called puberty. It is the time when the gonads develop both endocrine and gametogenic functions. It occurs about two years earlier in females. The usual age of onset lies between 12 and 16 years. In old age, reproduction ceases. In females, the limits of reproductive life are very sharp. It begins with the first appearance of menstruation (menarche) and ceases with menopause female (climacteric). Menopause occurs between 45th and 55th years of life and at this stage, both the primary and the secondary sex organs degenerates. In males, the limits of sex life are not so sharp. Its beginning and termination are gradual and indefinite.*

Puberty Changes

At puberty, the following changes take place:

1. **Physical changes:** In the males, the voice breaks, beard and moustache grow. The body becomes taller

*Testosterone levels peak during puberty and declines markedly by seventh decade of life.

and more muscular, assuming the 'male type'. In the females, breasts develop. In both the sexes axillary and pubic hairs grow (in females, the pubic hairs are concave forwards, in males convex forwards).

2. **Sexual changes:** The gonads develop, producing mature gametes. The secondary sex characters appear. In the females, the most characteristic feature is the appearance of menstruation.
3. **Mental changes:** The appearance of sexual desire, etc.

From puberty to menopause, the human female is a continuous breeder. But in the lower mammals there are definite reproductive periods—the mating or breeding season—during which only conception is possible. The duration of the season and its recurrence in the year, vary in different species. It may come once or twice a year (dogs—spring and autumn) or more frequently.

DEVELOPMENT OF GONADS

They arise from two sources: (1) Germinal epithelium; (2) Mesoblastic genital ridge. The former is derived from that part of coelomic epithelium which covers the inner surface of the wolffian body. The latter originates from a mesoblastic thickening lying just underneath the germinal epithelium. Both these structures send finger-like processes into each other in an interlocking manner. Those from the germinal epithelium are called the genital cords. They gradually become cut off from the surface and give rise to the seminiferous tubules of the testes. In the females, the proliferating sex cords are less prominent and the germ cells are larger and arranged in clusters, giving rise to the graafian follicles of the ovaries. The stroma cells and probably the interstitial cells develop from the mesoblastic genital ridge.

APPLIED PHYSIOLOGY

Delayed puberty: In some individuals there is failure of development of accessory sex organs and also lack of development of secondary sex characters though the puberty age is already attained. This condition if occurred in males is called eunuchoidism and in females is called primary amenorrhoea. This condition may occur primarily due to pituitary disorder or due to hypofunctioning in either of the gonads.

Precocious puberty: In some individuals there may earlier appearance of secondary sexual characteristics earlier to nine years of age. The precocious puberty is of two types—true puberty and pseudo-precocious puberty. True puberty is the presence of gametogenesis with earlier development of secondary sexual characters. The common causes for true puberty are damage and interruption of neural pathway which inhibits gonadotrophin releasing hormones due to cerebral infection and cerebral tumours involving posterior hypothalamus, pineal tumours infiltrating the hypothalamus, etc. The pseudo-precocious puberty is a condition in which the secondary sexual characteristics appear earlier but there is failure of gametogenesis. The common causes of pseudo-precocious puberty are interstitial cell tumours of testis, granulosa cell tumours of ovary, congenital virilizing adrenal hyperplasia, androgen secreting tumours in males and oestrogen secreting tumours in females.

GENETIC BASIS OF SEX DIFFERENTIATION

Similar to somatic cells, the male spermatogonia and the female oögonia also contain 23 pairs of chromosomes. Of the 23 pairs of chromosomes observed in human beings, 22 pairs are autosomes which do not play any part in the determination of sex. The last pair is named as sex chromosomes as they have a major contributor role in sex determination. The sex chromosomes in women are homologous because of having two X chromosomes (XX pattern), whereas in men they are of a heterologous type, consisting of one X and one Y chromosome (XY pattern), the last one being smaller in size (Fig. 79.1).

During meiosis or reduction division of the primary spermatocytes or oocytes, half of the number of chromosomes passes to the daughter cell. As a result of this, each daughter cell contains 22 autosomes and one sex chromosome. In the female, the sex chromosomes in all the daughter cells are X chromosomes, but in the male half of the normal sperms will contain an X chromosome and the other half will contain a Y chromosome. Hence, each daughter cell (gamete) will possess either X or Y sex chromosomes (Fig. 79.2).

In the process of fertilization between sperm (22 autosomes and either X or Y sex chromosome) and ovum (22 autosomes and X sex chromosomes); the resulting zygote would contain 23 pairs of chromosomes, of which 22 pairs are autosomes. The remaining 23rd pair determines the sex character of the offspring. If the sperm containing X sex chromosome unites with ovum (X), the two sex chromosomes would be identical (X and X) and the resulting sex will be a female offspring. But if Y sex chromosome of the male unites with ovum (X), the two sex chromosomes will be different (X and Y) resulting in a male offspring. In the process of oogenesis (maturation of ovum) the germinal cell is differentiated into primary oocytes which contain diploid number of chromosomes (44 XX). Primary oocytes thus enters into the meiotic division and separates into (i) first polar body (22 X-haploid) and (ii) secondary oocytes (22 X-haploid). Secondary

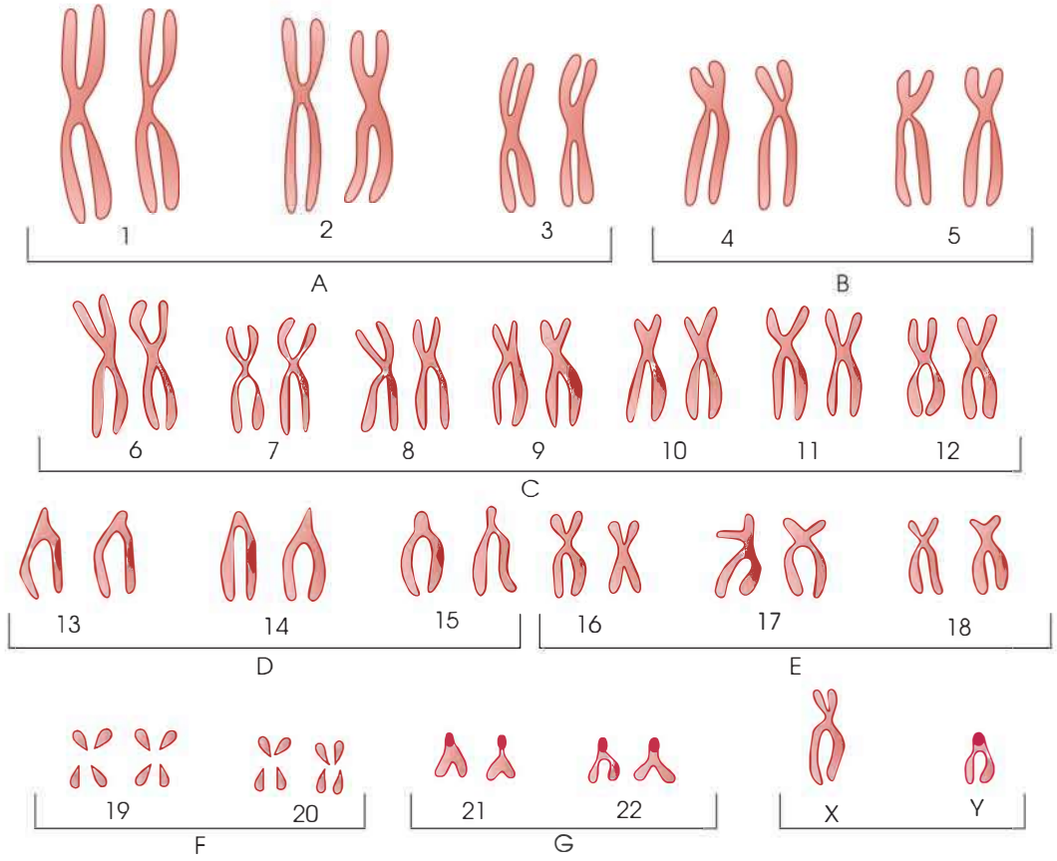


Fig. 79.1: The present-day conception of shape and size of chromosomes and their classification was accepted in Paris Conference of 1973. Autosomes in A to G groups and sex chromosomes XY are shown separately. The Y chromosome and X chromosome will be in G group and in C group respectively. In females, both X chromosomes will be in G group

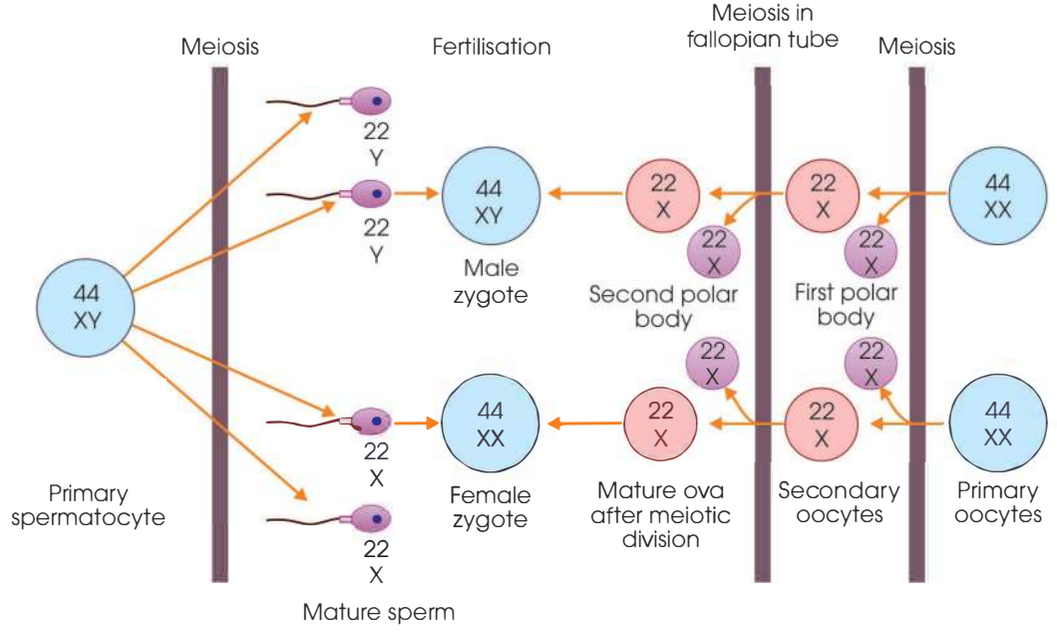


Fig. 79.2: Schematic representation of the genetic basis of the sex determination

oocyte then undergoes second meiotic division only after being fertilized (after penetration of zona pellucida by the sperm) within the fallopian tube. Under this meiotic division the chromosomes split longitudinally, the cytoplasm divides unequally and the nucleus divides equally so that the secondary oocytes are transformed into (i) matured ovum (22 X) and (ii) second polar body (22 X).

In case of spermatogenesis, the epithelium lining the seminiferous tubules undergoes series of mitotic division to give rise to spermatogonial cells. The spermatogonial cell then divides further mitotically into two resting primary spermatocytes (44 XY). The primary spermatocytes then undergo first meiotic division (heterotypical) to give rise to two secondary spermatocytes (22 X and 22 Y). Secondary spermatocytes then undergo second meiotic division (phonotypical) to give rise to two spermatids (22 X and 22 Y). The spermatid then is simply transformed into mature sperms (22 X and 22 Y) (Fig. 79.2).

SEX CHROMATIN

Cells of individuals who have two X chromosomes contain an extra bit of chromatin, the 'sex chromatin' or 'Barr body'. It is seen in the nuclei, usually attached to the nuclear membrane. In almost all cells of females except the ova, an X chromosome is partially inactive and condensed and it is this which is visible as the sex chromatin (Fig. 79.3). It is easily visible in over 25% of the cells in smears of the buccal mucosa and skin biopsies, and is well-developed in many other cells as well. There is also a small drumstick of chromatin (Fig. 79.4) projecting from the nuclei of 1–15% of the polymorphonuclear leucocytes in females but not in males. Normal females thus have sex chromatin and are said to be chromatin positive.

Chromosomal Abnormalities in Sex Differentiation

The major defect in chromosomal abnormalities is non-disjunction, a phenomenon in which sex chromosomes fail to separate; one gamete gets both sex chromosomes, but the other gets none.

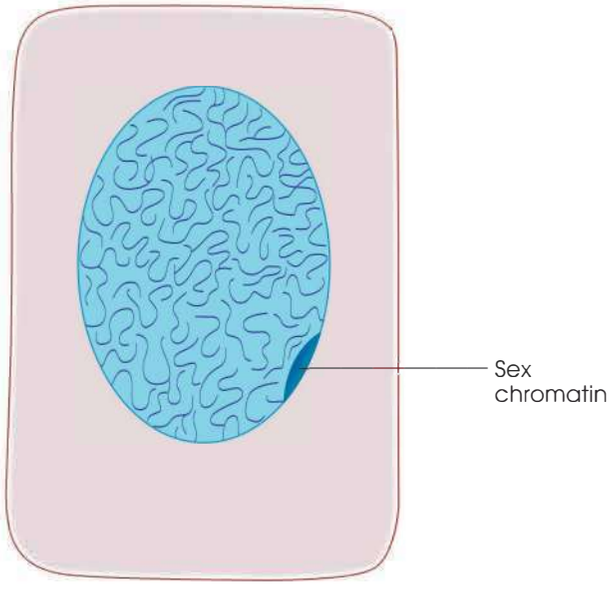


Fig. 79.3: Sex chromatin in a cell from a buccal smear

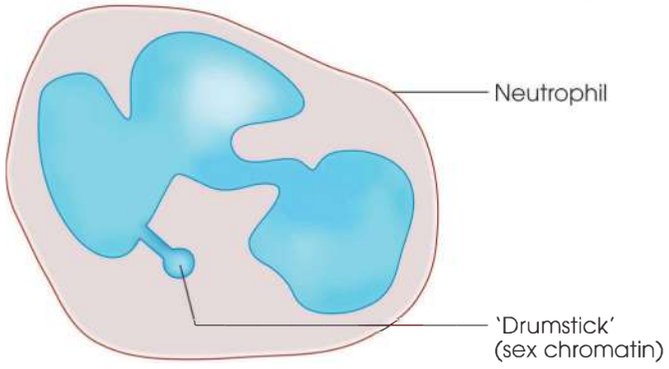


Fig. 79.4: Drumstick sex chromatin in a polymorphonuclear leukocyte

Abnormalities due to Maternal Non-disjunction

Due to maternal non-disjunction during oogenesis four abnormal zygotes may be formed following fertilization with sperm having either 'X' or 'Y' chromosome. These are as follows.

Gonadal dysgenesis (44 XO chromosomal pattern): Due to union of female gamete having no sex chromosome with male gamete having X chromosome. In this chromosomal defect, gonads are rudimentary or absent. Because normal number of sex chromatin is absent. This syndrome is known as ovarian agenesis or Turner's syndrome (Fig. 79.5) or gonadal dysgenesis. The affected female is sterile, does not menstruate, is short of stature, and often has various congenital abnormalities such as a web of skin on either side of the neck, coarctation of the aorta, and when the arm is extended the forearm tends to be displaced outward away from the body (cubitus valgus).

'Super-females' (44 XXX) is due to union of female gamete having XX chromosomes with male gamete having X chromosome.

Klinefelter's syndrome or seminiferous tubule dysgenesis (44 XXY) is due to union of female gamete having XX chromosomes with male gamete having Y chromosome. In this pattern seminiferous tubules are not developed and there is defect in gametogenic function of the testis. In this syndrome, affected men are sterile, have very small testes, sometimes have gynaecomastia, and are often mentally defective. They are sterile because their testes fail to produce spermatozoa (Fig. 79.6).

44 YO pattern: It is mostly lethal and caused by fusion of male gamete having Y chromosome with female gamete having no chromosome.

Abnormalities due to Paternal Non-disjunction

Due to the paternal non-disjunction during spermatogenesis, two abnormal zygotes may be formed following union with ovum having X chromosome:

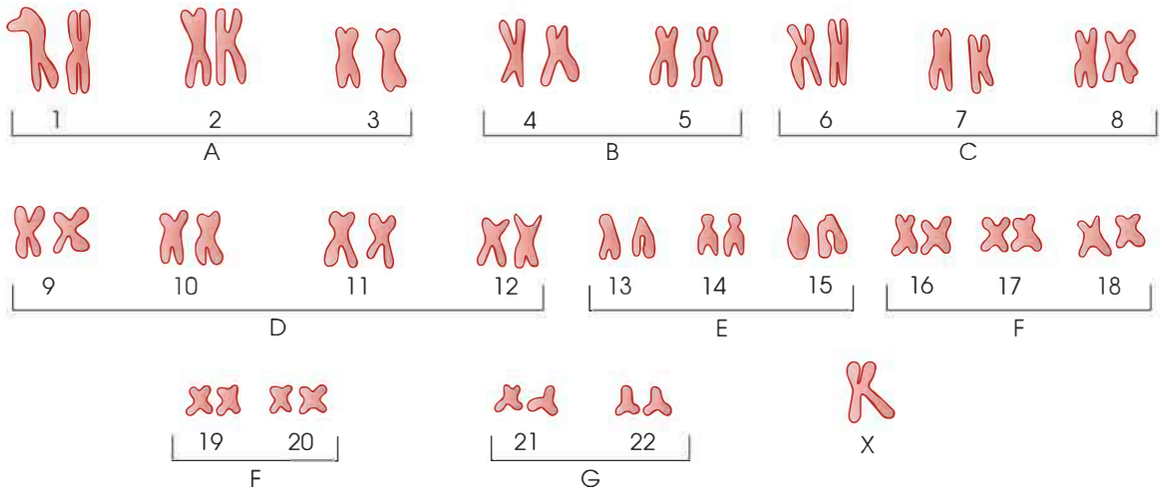


Fig. 79.5: Karyotype with Turner's syndrome (45 XO)

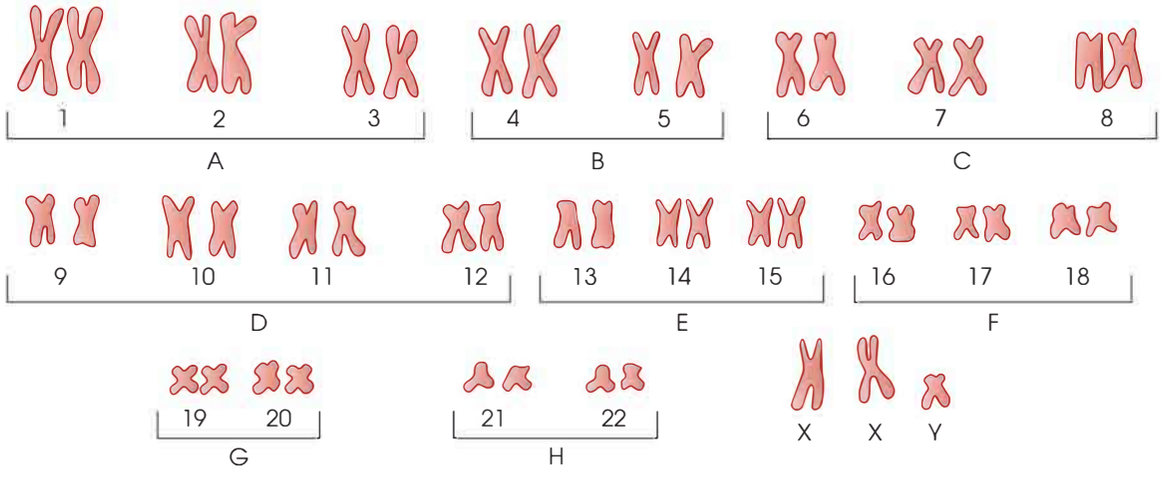


Fig. 79.6: Karyotype with Klinefelter's syndrome (47 XXY)

Klinefelter's syndrome or seminiferous tubule dysgenesis (44 XXY): If male gamete having XY chromosome units with female gamete having X chromosome, then this type of syndrome may occur. This type of syndrome is also observed due to defect in female non-disjunction.

Gonadal dysgenesis (44 XO): Gonadal dysgenesis also occurs due to abnormalities in disjunction of chromosomes in male gamete. Here male gamete having no sex chromosome unites with female gamete having X chromosome.

Abnormalities due to Mosaicism

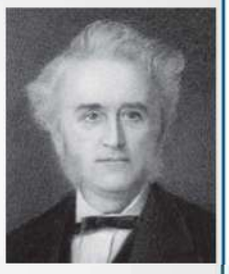
Chromosomal abnormalities are also observed due to defects in the separation of sex chromosome during mitosis after fertilization of the ovum. This type of defect in the separation of chromosome is known as mosaicism and these abnormalities are very common. True hermaphroditism, in which the individual has both ovaries and testes, is probably due to XX/XY mosaicism and related mosaic patterns, although other genetic aberrations are possible.

Down Syndrome or Mongolism

The term mongolism is commonly obsolete and Down's syndrome has replaced this. In this syndrome there are 47 chromosomes instead of normal 46 chromosomes. The extra-chromosome is small acrocentric chromosome similar to chromosome 21. This syndrome is usually detected autosomal disorders. Down's syndrome is trisomy 21. Down's syndrome is generally common in children with mental retardation. Flattened head becomes anterior and posterior. There is an upward slant of eyes and bony orbit becomes smaller than the normal. There are speckling of iris (Brush-field spots) and conspicuously small external ears. The younger child possesses an epicanthic fold. The nose becomes short with flat bridge and tongue protrudes from a small mouth. The foot is broad with a deep grove on

John Langdon Haydon Down, DS, was a British physician best known for his description of a relatively common genetic disorder, now known as Down syndrome, which he originally classified in 1862.

Reference: JLH DOWN. "Observations on 9th ethnic classification of idiots". Clinical Lecture Report, London Hospital 1866;3:259–262.



1828–1896

the sole of the foot between 1st and 2nd toes. The most characteristic features are palmar and plantar dermatoglyphic analyses. There is an incidence of leukaemia (10–20% more than normal). There is rudimentary condition in the second phalanx of the fifth finger. In Down's syndrome there is a transverse simian crease on the palm of the hand. There is furunculosis, skin infection and incidence of congenital heart disease. Hypotonia of abdominal muscles is frequently seen. Other defects may be observed in the children with extra-chromosomal numbers 13, 14, 15, 17 and 18.

Sex Differentiation due to Hormones

Though the sex differentiation is taken place genetically, yet several factors may alter the embryonic sex development. The gondas are developed from the mesodermal primordia in the genital ridges, which are biopotential organs up to sixth week of development. The Y chromosome in humans and many other mammals is necessary and sufficient for the production of testes and in it the testes determining gene product is called SRY (for sex determining region of Y chromosome). SRY is a DNA-binding regulatory protein. It binds the DNA and acts as a transcription factor thal initiates transcription of number of genes necessary for testicular differentiation including gene for müllerian inhbiting substance (MIS). The gene for SRY is located near the tip of short arm of human Y chromosome. In genetic males the medulla develops during the seventh and eighth week in testes and the cortex regresses and Sertoli cells appear and testosterone and MIS are secreted. In genetic females the cortex developes in ovary and medulla regresses. The embryonic ovary does not secrete hormones. Hormonal treatment of mother has no effect on gonadal development (as opposed to ductal and genital). The Leydig cells of the fetal tests secrete testosterone and the Sertoli cells secrete MIS (also called müllerian regression factor, or MRF) MIS is a member of transforming growth factors β (TGF-β), superfamily of growth factors.

Sex hormones, the androgens and MIS have got immense role in sex differentiation and subsequent development in mammals. In their effects on internal as opposed to external genitalia MIS and testosterone act unilaterally MIS causes regress of the müllerian ducts by opoptosis on the site it is secreted and testosterone is responsible for the development of vas deferens and related structures from the wolffian ducts. The testosterone metabolite the dihydro-testosterone induces the formulation of male external genitalia.

Male differentiation of the external genitalia occurs in response to androgen secreted by the Leydig cells in the embryonic testes. This effect is bilateral unlike the effect on internal genitalia which is unilateral.

Applied Physiology

Male pseudo-hermaphroditism: If the functional status of the embryonic testes is defective then female internal genital organs are developed in genetic male. The syndrome that results in the genetic male is known as male pseudo-hermaphroditism. In this syndrome female internal genital organs along with testes (rudimentary) are present in genital male.

Female pseudo-hermaphroditism: In female pseudo-hermaphroditism, ovaries only are present and it shows male genital development. Sex chromosomes are female type (genetic female XX). The female pseudo-hermaphrodite is the cause of excessive androgenic activity in embryonic life due to adrenal virilism in the mother. This type of syndrome is also observed in some cases where the mother is treated with excessive androgens. In true hermaphroditism, both the testes and ovaries are present and secondary sexual characters are variable. This syndrome is generally due to defect in the separation of the chromosomes during mitosis after fertilization of the ovum (mosaicism).

EXAM-ORIENTED QUESTIONS

Essay

1. Discuss the genetic basis of sex differentiation.

Short Notes

1. Delayed puberty
2. Precocious puberty
3. Klinefelter's syndrome
4. Down syndrome
5. Male pseudo-hermaphroditism
6. Female pseudo-hermaphroditism

Chapter

80 Male Reproductive Organs

INTRODUCTION

Male reproductive system is the vital human visceral part which by spermatogenesis provides normal sperms for uniting and fertilizing ovum for production of progeny. The study of anatomical and functional physiology will help in understanding reproductive physiology.

TESTIS

Anatomy (Fig. 80.1)

The testis consists of two somewhat flat, oval bodies, one on each side, remaining inside the scrotum. In early foetal life, they remain within the abdomen. During the foetal life, the testes move caudally from their position high in the abdomen, then gradually migrate and descend in the scrotum by the time the child is born. The exact cause of descent is not known, but it is suggested that the hypophyseal hormones probably initiate the process. Failure of descent results in the testes being retained somewhere along the route of descent and the condition is known as cryptorchidism (hidden testes). This produces sterility as spermatogenesis do not occur at the higher temperature of the abdominal cavity.

The testis is covered by a tough, compact, fibrous capsule (tunica albuginea) from which trabeculae descended divide the gland into a number of pyramidal lobules. The lobules are filled up with convoluted seminiferous tubules, each about 500 mm long. Several tubules unite to form a straight tubule which again unites forming the rate testis. These join up to form the vasa efferentia which finally combine to form the duct of epididymis. The whole epididymis consists of a single convoluted tube about 6 metres long remaining coiled up together with the entwining connective tissue and surrounding tunic (Fig. 80.2) at the back of the testis

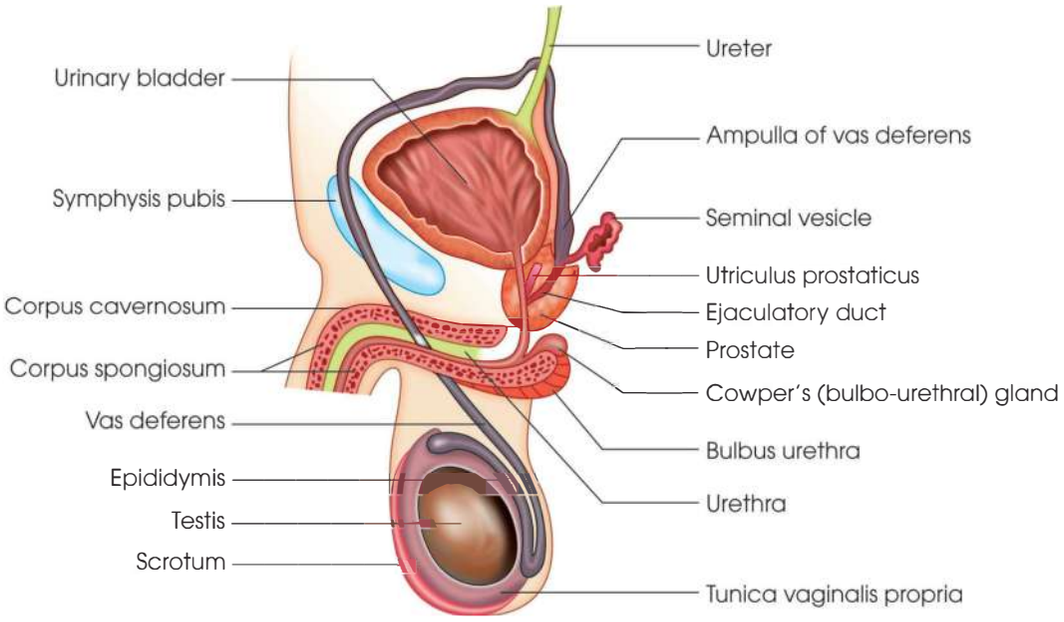


Fig. 80.1: Diagrammatic representation of the anatomical organization of the male reproductive organs (median view)

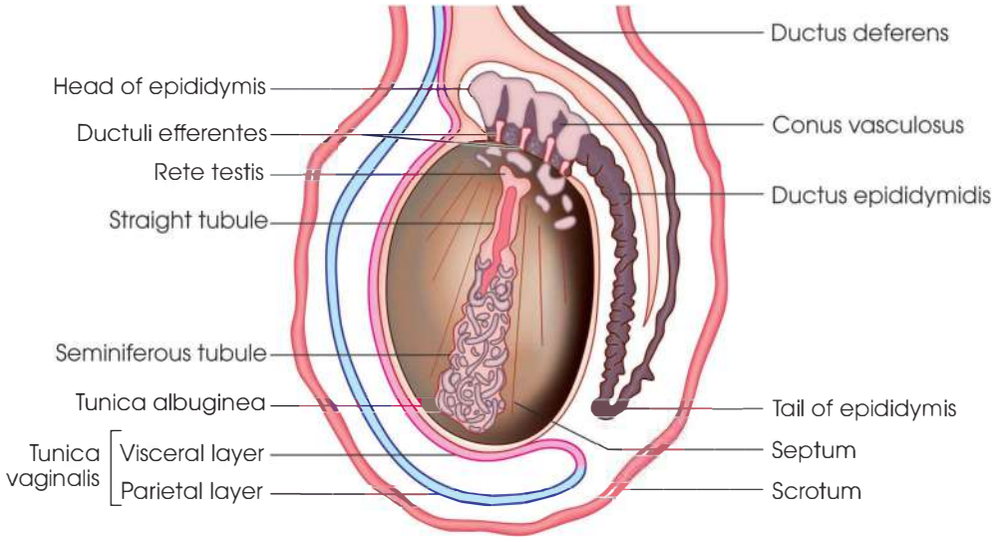


Fig. 80.2: The vertical view of the testis showing arrangement of ducts and the scrotal relation

and is ultimately continued as the vas deferens. The epididymis is lined with pseudo-stratified epithelium with tall columnar cells and rounded basal cells (Fig. 80.3). The surface cells contain secretory granules and, sometimes, pigment. The epididymis acts as a storehouse for spermatozoa until ejaculation occurs. Spermatozoa are produced whether ejaculation takes place or not, those not ejaculated are reabsorbed in the vas deferens. The vas deferens is joined by the duct of the seminal vesicles—a musculoglandular sac—to form the ejaculatory duct which opens into the prostatic urethra.

The secretion of the prostate and seminal vesicles makes up a considerable part of the semen. The seminal vesicles do not store spermatozoa but act as an activator for them. The secretion of seminal vesicles contains fructose, ascorbic acid, citric acid, inorganic phosphorus, acid-soluble phosphorus, electrolytes, protein, and trace amounts of ergothioneine, among other constituents and a number of enzymes like creatine phosphokinase. These vesicles contribute about 60% of total volume of human semen. The secretion of prostate contains spermine, citric acid, cholesterol, phospholipids, fibrinolysin, and fibrinogenase and has important functions for the nourishment of the sperms. The prostate contributes about 20% of total volume of human semen (*vide* prostate).

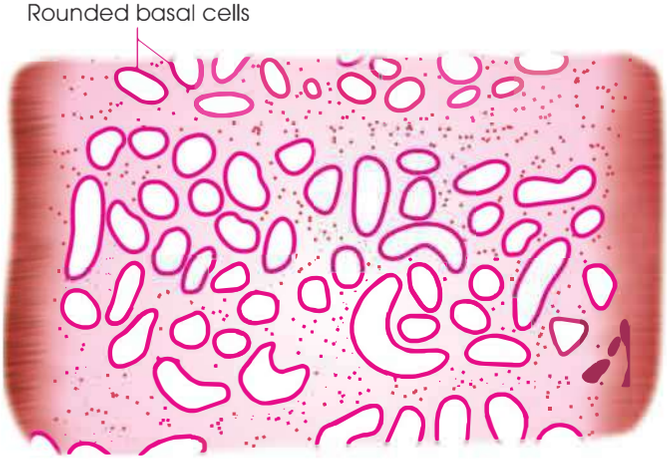


Fig. 80.3: Vertical section through body of human epididymis (diagrammatic)

Histology (Fig. 80.4)

The testis is composed of three elements:

1. The fibrous covering, **tunica albuginea**, from which trabeculae descend. Tunica albuginea is composed of collagenous connective tissue with an admixture of elastic tissue. There is a thin layer of squamous cells on the outer surface of this coat, which is mesothelial lining of scrotal sac reflected over the testes. The tunica vasculosa is the inner aspect of the tunic and contains a number of blood vessels. The tunic becomes thickened at the posterocephalic margin of the testis; forming mediastinum testis. Duct, blood vessels and nerves enter or leave the testes through the mediastinum.

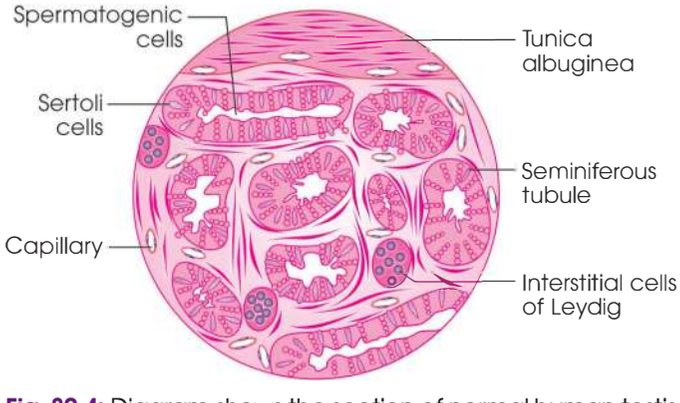


Fig. 80.4: Diagram shows the section of normal human testis

2. **Seminiferous tubules,** where spermatogenesis takes place.
3. **Interstitial cells** of Leydig, which secrete the male hormone. The last two essential elements are briefly described below.

Johannes Peter Müller was a German physiologist, comparative anatomist, ichthyologist, and herpetologist and müllerian duct is named after him.

Reference: Berrios GE. On the fantastic apparitions of vision by Johannes Muller. History of Psychiatry 2005:16:229–46.

1801–1858

Seminiferous Tubules

1. In humans, the combined length of seminiferous tubules is estimated at about 200–400 metres. They are ensheathed by a heavy basement membrane.
2. Each testicular lobule contains one to three greatly convoluted, sperm-producing tubules, seminiferous tubules. These exist mainly in the form of arches (Fig. 80.5) which connect at each end with a space in the mediastinum, the rete testis.
3. They are lined by four to eight layers of cells, each layer representing a particular stage in the development of spermatozoa (sperma). From outside inwards the following five layers are found: The spermatogonia, primary spermatocytes, secondary spermatocytes, spermatids and spermatozoa (Fig. 80.6).

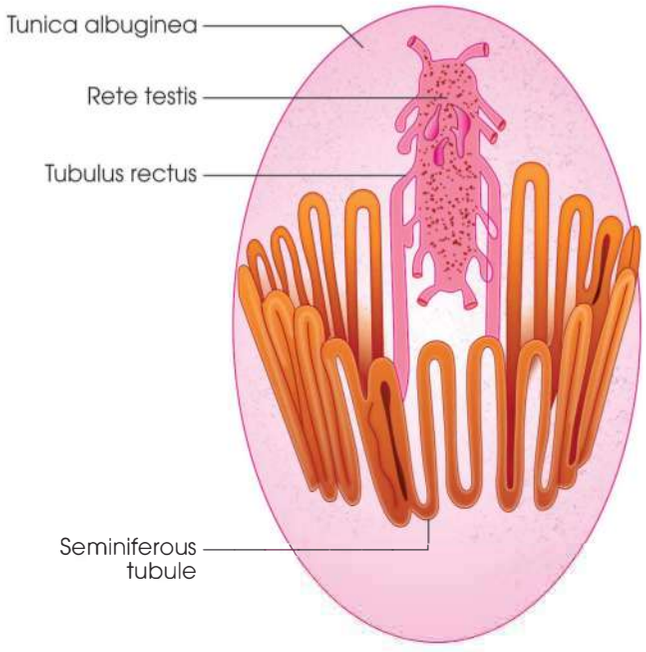


Fig. 80.5: Schematic representation of arched nature and connections of the seminiferous tubule with the rete testis

4. Elongated supporting cells are found in the outermost layer among the spermatogonia. They are called the cells of Sertoli (*L. sustento*-I support) in which sperms bury their heads.
5. These glycogen-containing cells (sustentacular cells) can be distinguished by the presence of lipid droplets, small fibrils, elongated mitochondria and reticular cytoplasmic appearance.
6. The maintenance of the structure and the spermatogenic function of the seminiferous tubules depend upon the action of FSH. FSH stimulates the

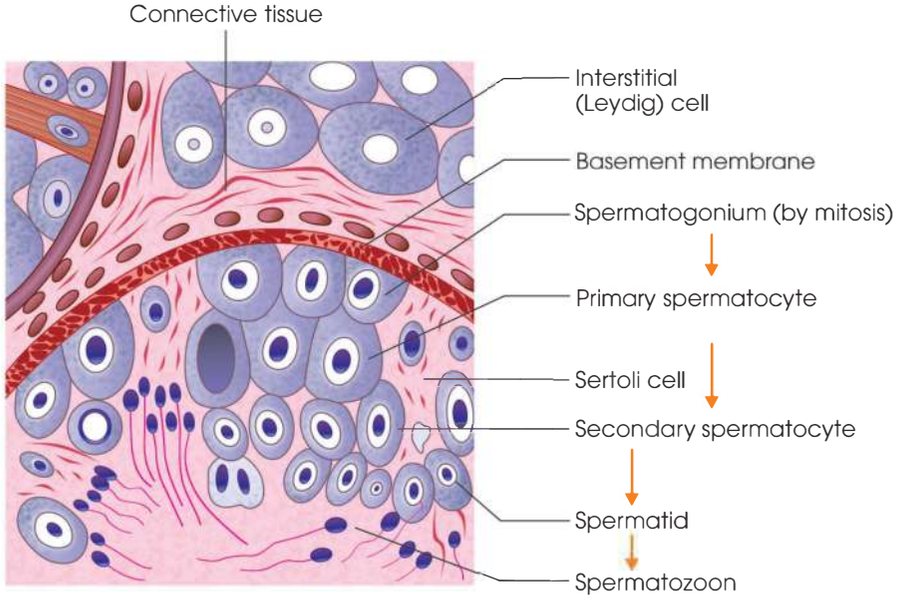


Fig. 80.6: Portions of two seminiferous tubules, stages of spermatogenesis and group of Leydig (intestinal) cells

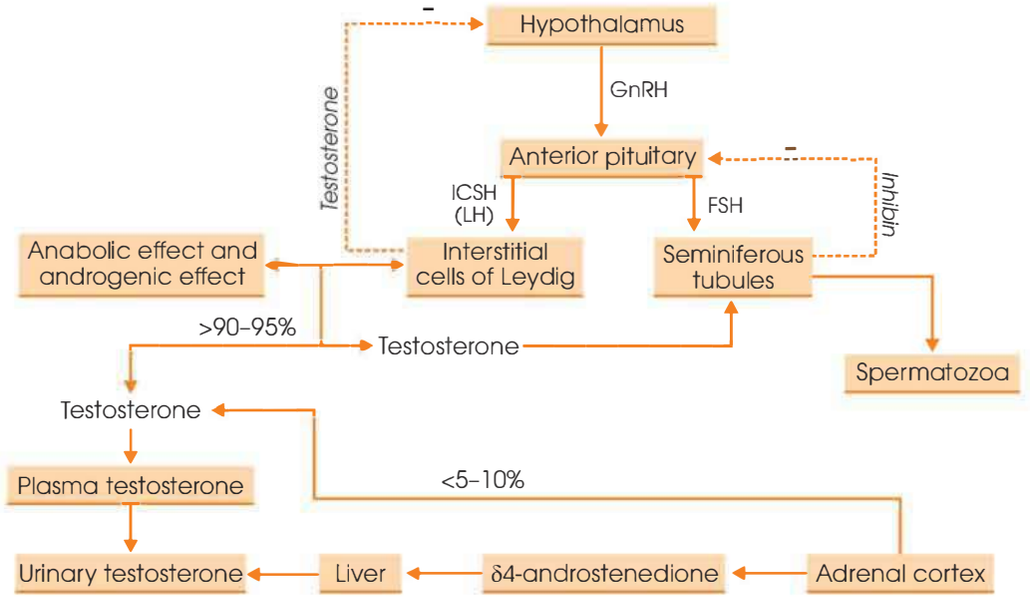


Fig. 80.7: Schematic representation of pituitary-gonadal axis of normal male

metabolic activity of Sertoli cells. FSH secretion is controlled by the feedback of a hypothalamic substance (inhibin) which is secreted by Sertoli cells in seminiferous tubules (Fig. 80.7). These cells may also secrete oestrogens. The release of spermatozoa from the Sertoli cells is known as spermiation.

Interstitial Cells (Cells of Leydig)

Inside the stroma and between the seminiferous tubules, groups of polyhedral cells are found which are called interstitial cells of Leydig. They are abundant in early foetal life, then gradually diminish during childhood, increase again at puberty and diminish in old age. These cells are large, ones with an eccentric nucleus contain one to three nucleoli and possess scanty, poorly staining cytoplasm. They contain abundant agranular endoplasmic reticulum (rich in ascorbic acid), vacuoles containing fats, phospholipids and cholesterol, resembling in such features, the interstitial cells of the ovary, the luteal cells of the corpus luteum and cells in the adrenal cortex, and mitochondria, Golgi apparatus, pigment granules, many lysosomes, refractile globules, protein crystals of Reinke. Cells are arranged around the blood vessels.

Functions of Leydig Cells

Leydig cells comprise less than 10% of the testicular volume and secrete about 7–8 mg of testosterone per day.

1. At puberty, the rising secretion of pituitary ICSH (identical with LH) favours the transformation of androstenedione to testosterone. Testosterone is known to be converted in certain androgen responsive tissues to a more potent androgen, dihydrotestosterone, which is localized in the nuclei of target cells and appears to be active intracellular androgen.
2. ICSH stimulates development and differentiation of Leydig cells at puberty, leading to about 20-fold rise in plasma testosterone level. ICSH secretion is suppressed, rather slowly, by the feedback effects of testosterone and oestradiol on the hypothalamus (Fig. 80.7).
3. The prominent effect of ICSH on the synthesis of steroid hormones is a rapid increase in testosterone secretion, mediated by cyclic AMP and apparently due to accelerated conversion of cholesterol to pregnenolone in the mitochondria of Leydig cells.
4. The interstitial cells of the testis not only secrete testosterone but also oestrogens such as oestradiol. They are themselves stimulated into the activity by the interstitial cell-stimulating hormone (ICSH identical with LH) and GnRH of the anterior lobe of hypophysis cerebri.

Functions of Testis

1. **Spermatogenesis:** This takes place at the seminiferous tubules.

Evidence

- In a histological section of the testis, the process of spermatogenesis can be seen in the seminiferous tubules (Fig. 80.6).
- Degeneration, hypoactivity or malformation of these tubules disturbs the production of spermatozoa.

2. **Secretion of testosterone:** The interstitial cells, which represent the endocrine tissue of the testis, synthesize the hormone.

Cryptorchidism (undescended testis). The tubules in the undescended testis are non-functioning. Spermatogenesis fails to occur. If the condition is bilateral, the subject is sterile but the accessory sex organs and the secondary sex characters are fully developed, indicating normal production of the hormone. The high abdominal temperature inhibits spermatogenesis, but not hormone synthesis is inhibited.

3. Testes secrete testosterone which is required for the growth of secondary sex characters.

ANDROGENS

Androgens are substances having masculinising properties. Administration of androgens causes

1. Growth of the accessory sex organs in the castrated males,
2. Growth of the comb, wattles and the ear lobules of the castrated male birds. These methods are employed for assaying the androgenic potency of an unknown substance.

The testis secretes androgens and these are: Testosterone, androstenedione, and dihydrotestosterone.

Chemistry and Varieties

Androgens are C-19 sterol compounds. Their structures are shown in Fig. 80.8 and two varieties are as follows:

Natural and Synthetic

1. The chief natural androgen is called testosterone.
2. Of the synthetic products, methyl testosterone and testosterone propionate are important members.
3. Synthetic androgens are effective by mouth being freely absorbed and unaffected by liver. Natural androgens are mostly inactivated by liver.
4. The chief degradation products of androgens are the 17-ketosteroids (17-KS), androsterone and dehydroepiandrosterone (DHEA).
5. The peripheral conversion of testosterone to oestrogen accounts for a large proportion of oestradiol production in the male.
6. Testosterone originates almost entirely in the testis; small amounts of ketosteroids secreted by the testis do not possess significant activity, either directly or as precursors of testosterone. However, testosterone, ketosteroids and much greater quantities of DHEA secreted by the adrenal gland after puberty contribute substantially to urinary 17-ketosteroid excretion.

Sources

Two sources of secretion:

1. Testis—the Leydig cells secrete testosterone. The testosterone is synthesized from the cholesterol ester content of these cells.

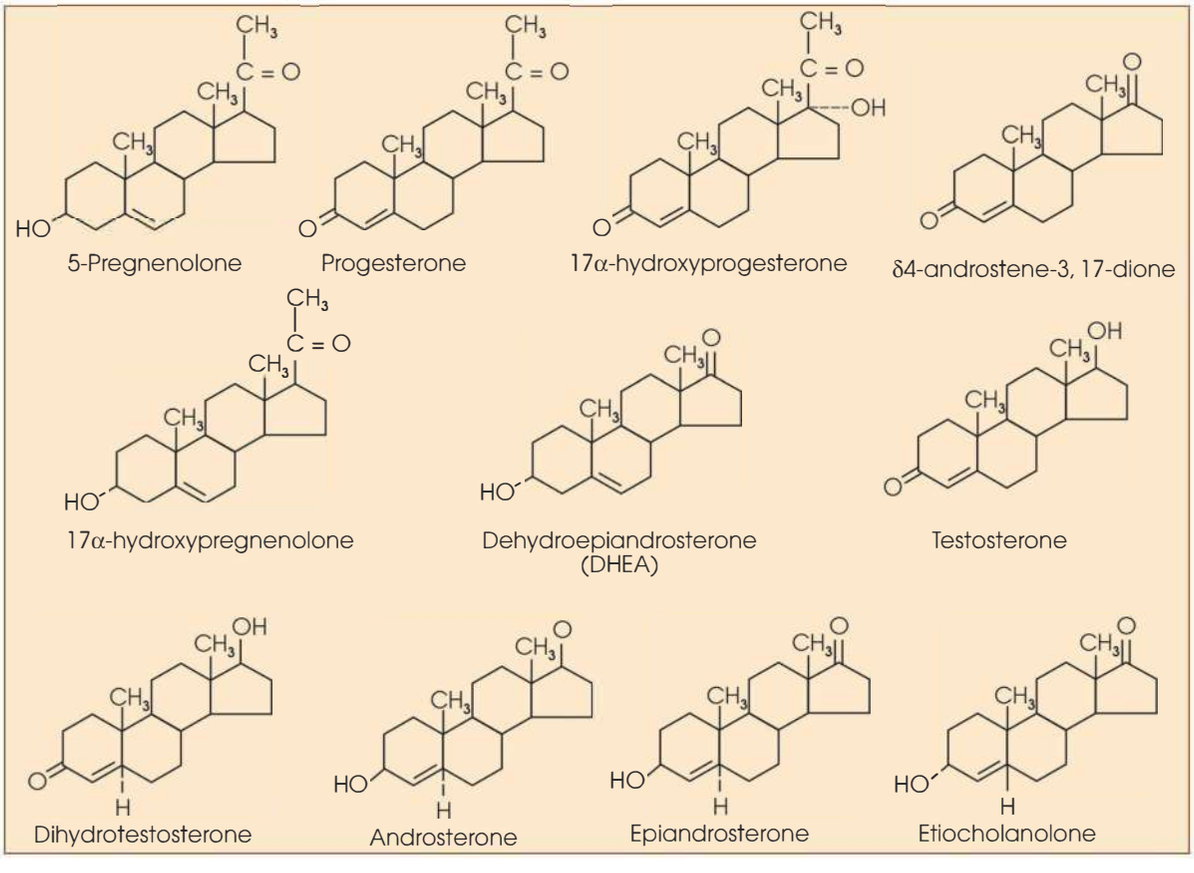


Fig. 80.8: Chemical structures of naturally occurring androgens

2. Adrenal cortex—it secretes testosterone in traces.
3. Testosterone is also secreted from adrenal cortex, ovaries and placenta.

International unit for androgens is defined as the activity of 0.1 mg of androsterone. Since pure androgens are available, one can use and express activity on a weight (mg) basis.

Plasma levels of testosterone: The normal plasma concentration of testosterone is 300–1000 ng/dl in adult male and 30–70 ng/dl in females. The plasma estradiol levels in males are 20–50 pg/ml.

Biosynthesis of Androgens in the Testis

1. Interstitial cells of Leydig are the target cells that are stimulated by gonadotrophin for an increased synthesis of androgens. The chief products which are secreted into the spermatic venous blood of adult testes are testosterone and smaller quantities of δ4-androstenedione and dehydroepiandrosterone (DHEA). Major pathways for synthesis of androgens are presented in Fig. 80.9.
2. The major route for the formation of androgens from 5-pregnenolone is 17α-hydroxypregnenolone to DHEA and thence to δ4-androstenedione and is the same as for reactions in the ovary and in adrenal cortex. The other pathway is 5-pregnenolone to progesterone and thence to δ4-androstenedione.
3. There is an increase in activity and amount of 17-dehydrogenase in the male at puberty. This enzyme leads to a marked increase in the formation of testosterone from δ4-androstenedione. Normally, the testis and the adrenal possess similar qualitative capacities to synthesis androgens.
4. In the Leydig cells, 11- and 21-hydroxylases are absent and pregnenolone is hydroxylated in C-17. Side-chain cleavage forms 17-ketosteroids and these ketosteroids are converted to testosterone.
5. Testosterone is also secreted from adrenal cortex. The sex steroids secreted from adrenal cortex are C (19) steroids and is responsible for formation of Dehydroepiandrosterone (DEA/DHEA). There activity competency is less than 20% of that of testosterone.

MODE OF ACTION OF TESTOSTERONE AND OTHER ANDROGENS

1. Testosterone directly binds with cytoplasmic nuclear receptors. They activate the DHT pathway and testosterone pathway. The enzyme 5α-reductase converts testosterone to dihydrotestosterone (DHT). The DHT binds to receptor located in the nucleus and initiates formation of mRNA and promotes protein synthesis and the formed proteins help in sexual maturation and external virilization.
2. Testosterone directly binds to testosterone receptors and initiates mRNA activity and regulates spermatogenesis, gonadotrophin secretion and maintains sex drive.
3. Androgens promote protein synthesis is the male accessory glands by direct stimulating effect on DNA and RNA polymerase by increasing the synthesis of mRNA in the nucleus and increased amino-acyltransferase at the ribosomal level. Androgens increased the activities of glycolytic enzymes, phosphofructose kinase and of the mitochondrial level to increase respiration rate, synthesis of

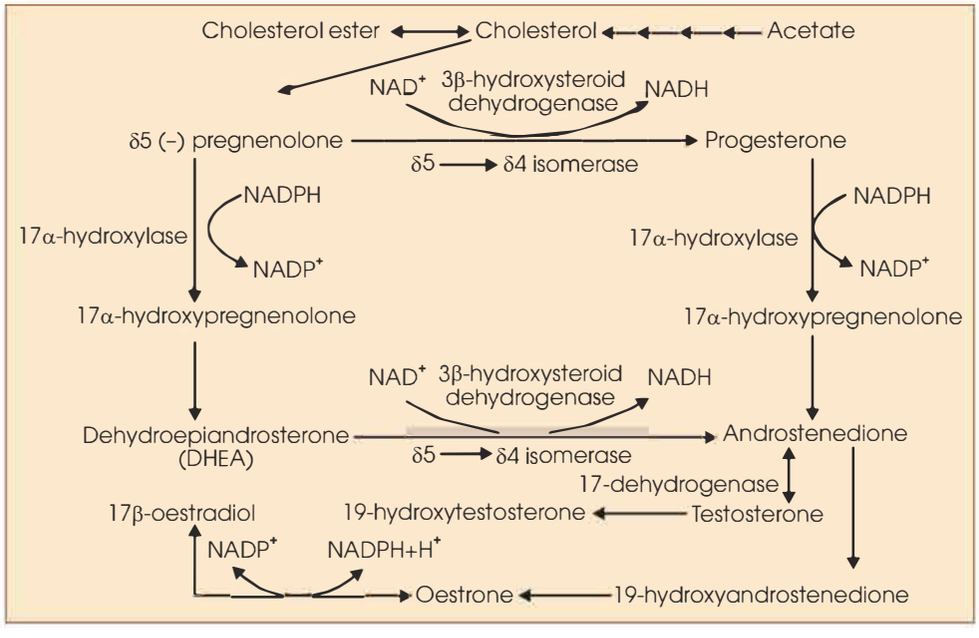


Fig. 80.9: Steroids synthesis in the testis. Although about 95% of testosterone is secreted from Leydig cells, some of the intermediates may be in the circulation

mitochondrial membranes and number of mitochondria.

TRANSPORT, METABOLISM AND EXCRETION OF TESTOSTERONE

1. **Transport:** About 60–65% of testosterone in plasma is bound to albumin and β-globulin. The latter protein binds also oestradiol and hence is known as testosterone-oestrogen-binding globulin (TEBG), sex-hormone-binding globulin (SHBG) or gonadal-steroid-binding globulin (GSBG). Free and bound testosterone levels in plasma are about 0.6 mg/100 ml in normal men and 0.1 g/100 ml in normal women. In men it somewhat declines with age.
2. **Metabolism:** Large amounts of secreted testosterone are converted in the liver in 17-ketosteroids and a small amount of secreted testosterone is converted to oestrogen. About 98% of testosterone binds with plasma protein and 2% is free in plasma. The free testosterone enters the target tissue and is converted to dihydrotestosterone (DHT) by 5α-reductase. The testosterone is a pro-hormone and DHT is the active form of it. They have affinity to bind with receptors then testosterone.
3. **Excretion:** Principal metabolites of testosterone are androsterone and etiocholanolone and the major 17-ketosteroids (17-oxosteroids: 17-OXOS) in urine. In addition, a small quantity of DHEA is also excreted as sulphate (Fig. 80.10). Androsterone and DHEA are weaker than testosterone. About 60–65% of urinary 17-ketosteroids (17- OXOS) have adrenal origin and the rest are of testicular origin. But not all 17-ketosteroids are androgens and not all androgens are 17-ketosteroids.

Notes

Mitochondrial conversion of cholesterol to 5-pregnenolone is a rate-limiting step, especially 20-hydroxylation reaction of cholesterol for the adrenal cortex and the ovary (Fig. 80.11). Gonadotrophins may also influence this step.

FUNCTIONS OF ANDROGENS: TESTOSTERONE

1. Testosterone is responsible for growth of accessory male sex organs, the seminal vesicles, prostate, epididymis, vas deferens, penis, etc. and maintenance of the morphological and functional activity of the seminal vesicles.
2. Testosterone brings over the normal development of male secondary sex characters.

   The development of the following secondary sexual characteristics in males occurs under influence of testosterone:

   a. The growth of hair on the face, in the axilla, on the chest and in the pubic region at puberty, and also responsible for the upward growth of hair towards the umbilicus in the midline (male escutcheon: δ).
   b. Development of typical masculine voice.
   c. Enlargement of penis and scrotum and enhances male sex drive and libido.
   d. Activity and emotional make-up of characteristic male. In the female, androgens cause the growth of sexual hair and may influence other aspects of sexual activity and libido.
   e. It is responsible for fusion of epiphysis in long bones and thereby halts linear growth.
   f. It brings over temporal hair line recession in males.
3. **Maintenance of spermatogenesis.** Effect on sperm production: Androgens facilitate spermatogenesis. Due to absence of blood vessels at the germinal epithelium, androgens produced by the Leydig cells under the influence of ICSH diffuse inside the tubules and exert their action. There is also a possibility that androgens may be produced by the Sertoli cells regulated by FSH. Androgens have a direct stimulating effect on DNA and RNA polymerase and increase the synthesis of mRNA and the incorporation of amino acids into protein.
4. **Protein anabolic action:** Testosterone is a protein anabolic hormone (nitrogen-retaining effect). It causes increased passage of amino acids inside the cell and positive nitrogen balance. This effect is a direct one, independent of the presence of endocrine organs.
5. **Muscular development:** Testosterone has myotrophic effect and is responsible for well developed skeletal musculature in males at puberty. Testosterone increases synthesis and protein deposition in skeletal muscle which enhances strength of muscles.
6. **Effect on growth of bone:** Due to the protein anabolic nature of testosterone it causes increase in bone matrix and thus increases deposition of calcium salts. It also leads to closure of epiphyses of long bones, thus arrests growth.
7. **Effect on BMR:** Testosterone increases BMR. This effect might also be secondary to the protein anabolic nature of the hormone.
8. **Effect on RBC:** Total number of RBC in males is higher than in females. Castration causes reduction

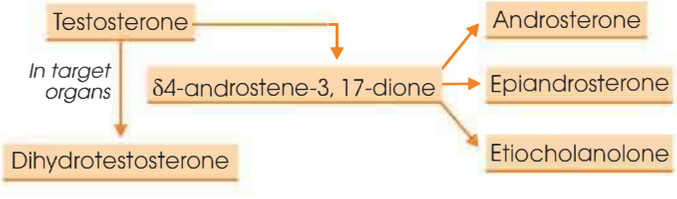


Fig. 80.10: Schematic representation of metabolic pathway of testosterone

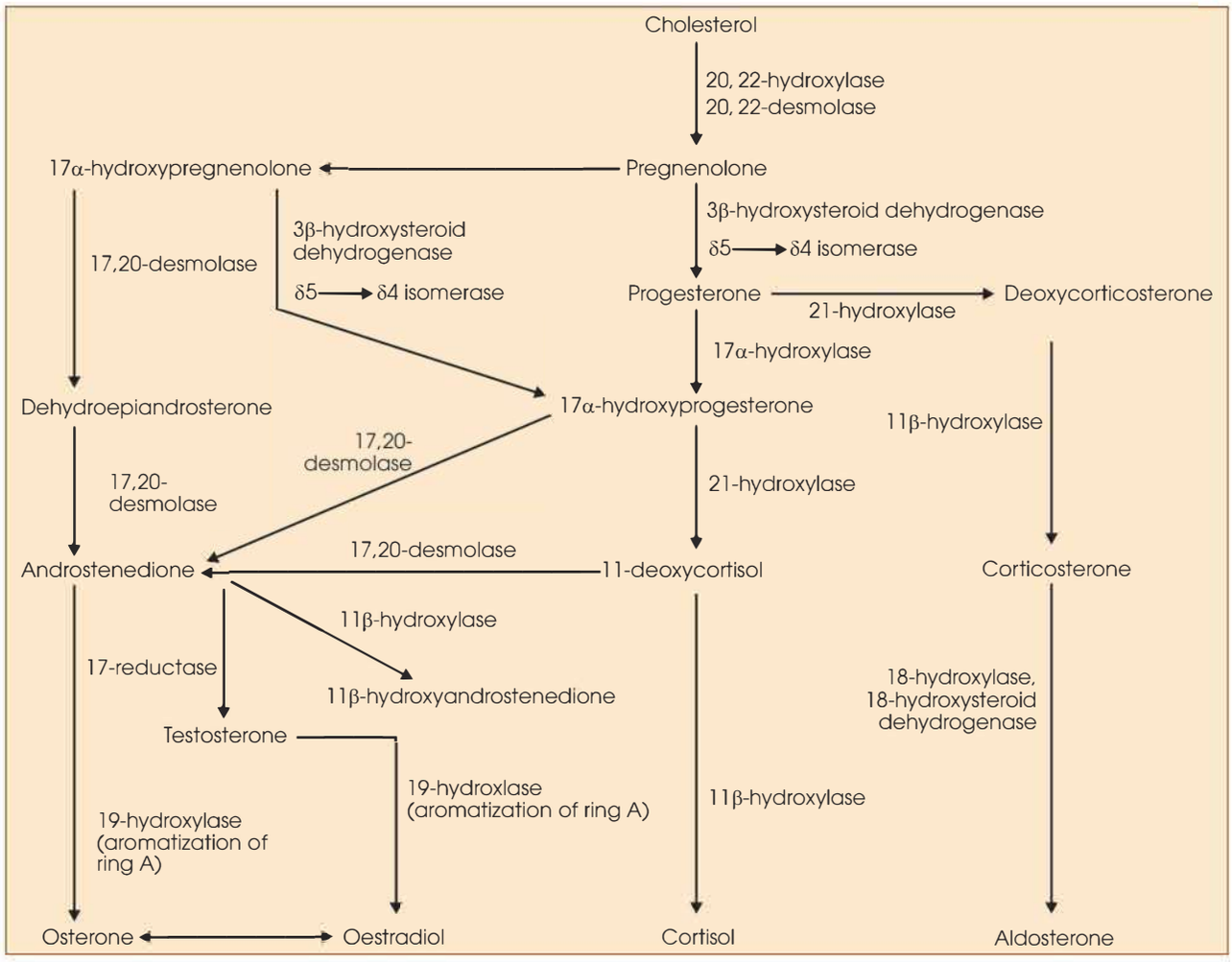


Fig. 80.11: Biosynthesis of main steroids from cholesterol in testis, ovary and adrenal. The enzymes 20, 22 desmolase and 11β-hydroxylase are situated in the mitochondria, whereas 3β-hydroxysteroid dehydrogenase, 17β-hydroxylase and 21-hydroxylase are microsomal in origin. Isomerase is contained in the cell cytoplasm. The sequence of events resulting in the production of the individual steroid depends on the enzymes being attached in the correct order on the mitochondrial surface within the cell

of RBC which comes back to control level on androgen treatment.

9. **Effect on water and mineral metabolism:** Testosterone causes retention of sodium, potassium, calcium, phosphate and water to some degree. This is probably related to increased protein anabolism.

Note

The biosynthesis of oestradiol, cortisol and aldosterone from cholesterol occurs in testis, ovary and adrenal gland (Fig. 80.11).

HORMONAL AND NEURAL CONTROL OF TESTOSTERONE SECRETION

1. Hormonal and Neural Control

A. **Anterior pituitary** (Fig. 80.12): Anterior pituitary releases the gonadotrophins: Follicle stimulating hormone (FSH), luteinizing hormone (LH) or ICSH and prolactin

a. Of these FSH controls spermatogenesis and ICSH or LH initiates and maintains the activity of the interstitial cells and controls the secretion of androgens and the latter activate the seminiferous tubules.

b. Prolactin is reported to have synergistic action with androgens in stimulating growth of male accessory sex organs.

c. FSH is also called 'gametokinetic' as it controls formation and maturation of gametes, i.e. sperm in males and ovum in females. FSH not only helps in the formation of spermatozoa to complete maturation, but androgens which are secreted by interstitial cells under the influence of ICSH are also required.

d. ICSH stimulates the interstitial cells to produce androgens which are responsible for the maturation and activity of secondary or accessory sex organs and characters.

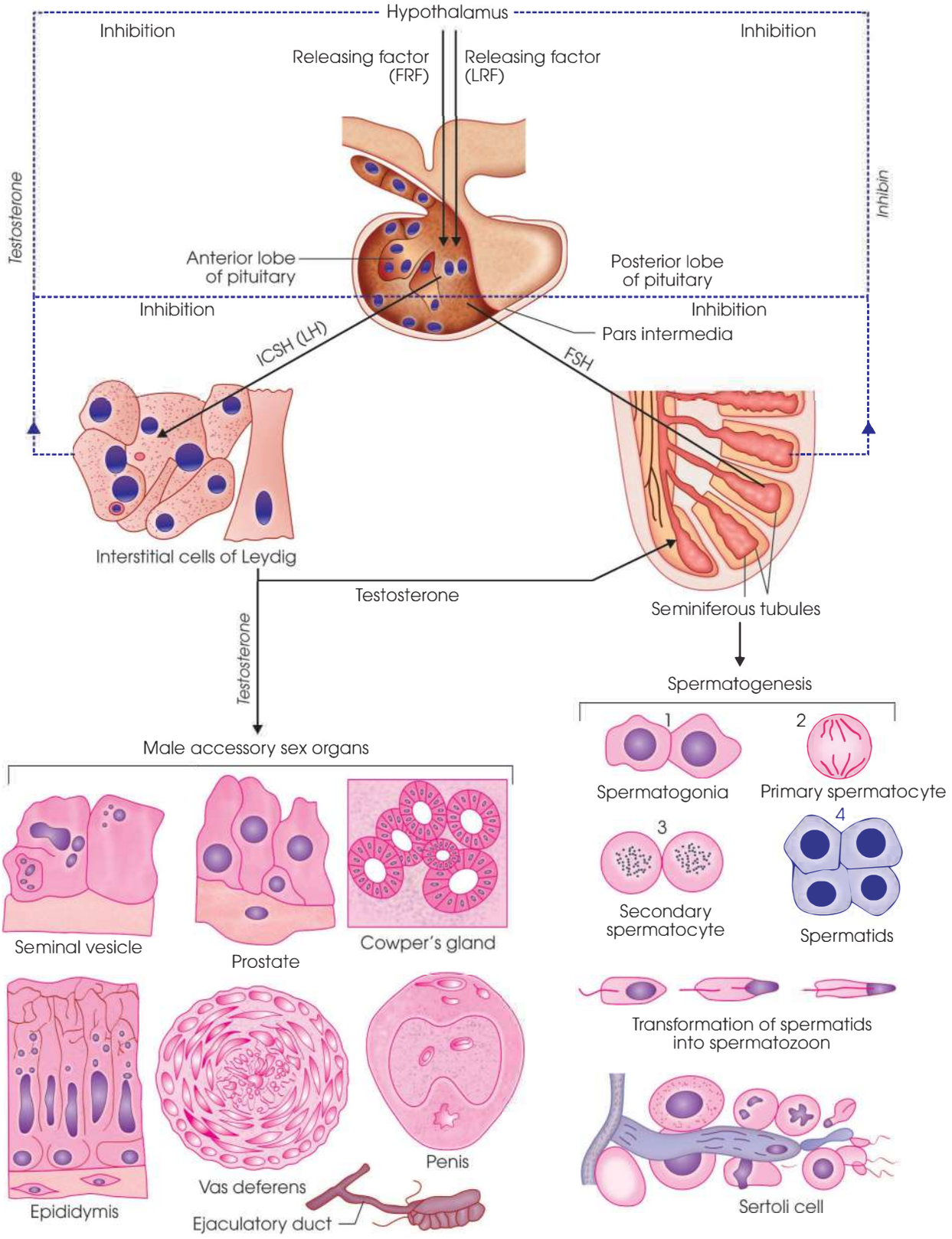


Fig. 80.12: Diagrammatic representation of the hormonal control of testicular activity

e. The mechanism by which LH stimulates the Leydig cells appears to involve increased formation of cyclic AMP and increased protein synthesis.

f. There is reciprocal relation between testis and anterior pituitary. Testosterone inhibits the secretion of ICSH (LH). Secretion of FSH is possibly controlled by the feedback of a substance

called inhibin or X-hormone which is secreted by Sertoli cells in the seminiferous tubules. Oestrogen inhibits gonadotrophin (LH) and thus reduces androgen level. Female hormone oestrogen secreted from testis also takes part in the regulation of FSH secretion.

B. **Hypothalamus:** The release of pituitary gonadotrophins is regulated by the releasing factors GnRH (LHRF) liberated from hypothalamus. Hypothalamic disorder causes testicular degeneration. It has also been established that the feedback inhibition of gonadotrophin released by testosterone is at the hypothalamic level.

C. **Adrenal cortex:** The sex steroids secreted from adrenal cortex are C (19) steroid and is responsible for formation of dehydroepiandrosterone (DEA/DHEA).

D. **Thyroid hormone:** It maintains libido and features of loss of libido and impotency seen in patients of hypothyroidism.

E. **Thymus:** Testosterone depresses thymus and compromises immunity response. At puberty it involutes.

2. Temperature Control

Higher temperature inhibits spermatogenesis (*vide* cryptorchidism).

> Undescended testis, being under higher abdominal temperature, is sterile, scrotum, with the help of dartos muscle, adjusts its own surface area and therefore, the heat loss. In this way it maintains an optimum temperature in the sac and acts as a perfect incubator for the testes. Impairment of testicular function has been noted in febrile condition, when testes are subjected to higher temperature.

3. Dietetic Control

Malnutrition has a deleterious effect on testicular physiology. Insufficient intake of calorie, protein of vitamins affects adversely the accessory sex organs and also somniferous epithelium. The androgen under influence of pituitary gonadotrophins is able to restore them to normal condition. This indicates the primary defect to be in gonadotrophins. Vitamins and mineral supplementation has added advantages. Some type of infertility in adults might result from malnutrition during prepubertal life.

Other Testicular Hormones

Inhibin: It is secreted from Sertoli cells of testis in males and from granulosa cells of ovary in case of females. The inhibin A and inhibin B are its two types. Inhibin B inhibits FSH secretion via feedback mechanism.

Activin: It is secreted from Sertoli cells and it stimulates FSH secretion.

Follistatin: They bind with activin and inhibit FSH secretion. It facilitates spermatogenesis.

LIFE HISTORY OF SPERMATOZOA (SPERMS)

Histology

Head and Neck

The mature spermatozoon can be commonly divided into head and tail. The tail again consists of a neck, middle piece or engine room or body, main piece and end piece on the basis of slight differences in thickness along its length. There are significant differences in the internal structure of these segments. The head of the human spermatozoon is oval on surface view and pear-shaped on side view (Figs 80.13 and 80.14). It is elastic and measures about 4–5 µm in length and 2.5 to 3.5 µm in diameter. The head is a condensed nucleus and contains about 40% of DNA and is rich in arginine. The nucleus is covered on its anterior two-thirds by acrosome (galea capitis) or head cap proper. The head cap has anterior and posterior parts in most animals. But the posterior head cap is said to be absent in the human spermatozoon. The posterior head cap, known as post-nuclear part, lies behind the nucleus. The acrosome is formed out of the Golgi apparatus of the spermatid and can liberate a chemical substance which enables the sperm to pierce the zona pellucida of the

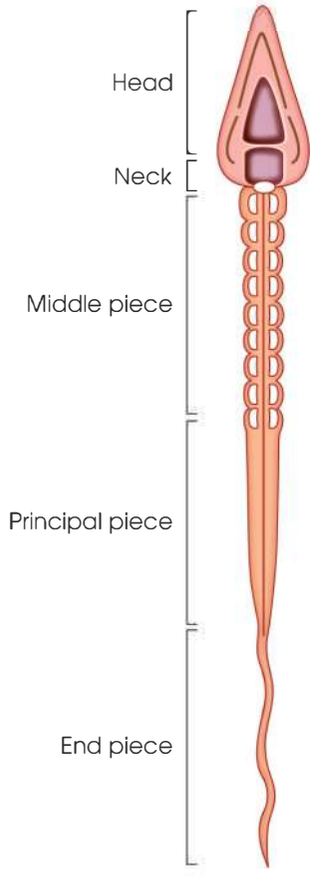


Fig. 80.13: Diagram of spermatozoa

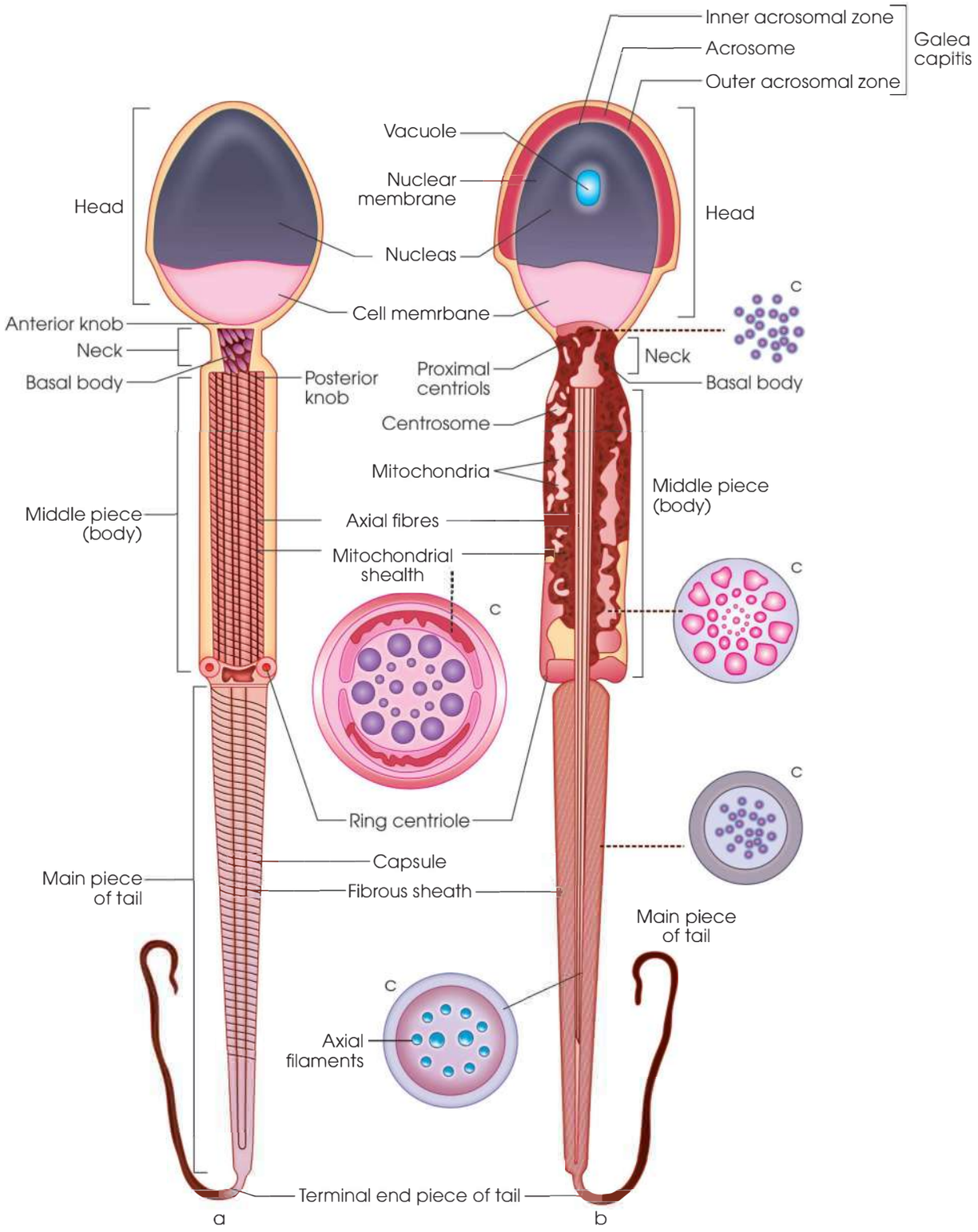


Fig. 80.14: Diagrammatic representation of spermatozoa: a—front view; b—longitudinal section; c—cross-section of the respective parts

ovum. The neck is a short, weak segment and connects the head with the middle piece (body). The proximal centriole (anterior knob) fits in the depression in the head and is the junction of the head and neck, whereas distal centriole (posterior knob) lies between the neck and the middle piece. In the neck the axial filaments consist of three bundles of fibrils being connected with the three basal granules in the anterior centriole.

Middle Piece or Body

It is the engine room of the spermatozoon and is cylindrical in form. It has a length of 5 to 7 µm and a

thickness of somewhat more than 1 µm. It extends from a slender connecting piece immediately behind the posterior pole of the head to a ring-like structure called the annulus or terminal ring. In the middle piece the helical mitochondrial sheath consists of 10–14 turns in which cisternae mitochondrial is found to be fused with its limiting double membrane with lipid-rich substance. The axial fibre bundle is the central filamentous body which begins from the proximal centriole and ends in the end piece. Except in the endpiece the axial filaments are surrounded by the axial sheath which is formed out of condensation of a thin layer of the cytoplasm.

Main Piece of Tail

It is about 45 µm long and about half a micrometer thick at the base, gradually tapering towards the end piece. The main piece consists of a core of axoneme of longitudinal filaments surrounded by a fibrous sheath of circumferentially oriented dense fibres. The ATPase is present throughout the whole length of the tail. This enzyme helps in the movement of spermatozoon.

Endpiece of Tail (Flagellum)

It consists of the terminal portion of the axial filament and is about 5 µm long. Its axial filament is embedded in a minimum matrix of the cytoplasm being enclosed only by the plasma membrane that invests the entire sperm. The total length is about 60–62 µm. There are 100,000 *sperma* per cu mm in healthy semen.

SPERMATOGENESIS

Before puberty, mature spermatozoa are not formed. It takes place actively following puberty and is maintained with the advancing age, although the same is slowed gradually. There is no such clear-cut male menopause (male climacteric) as it is characterized in women with advancing age. In many species, it occurs during the breeding season only. At other times, development remains suspended at the spermatocytes stage.

Key Points

Spermatogenesis is the process of formation of spermatozoa including spermatocytogenesis and spermiogenesis.

1. The spermatocytogenesis is the first stage of the formation of spermatozoa including spermatogenesis and speriogenesis. The spermatogonia develop into spermatocytes and then into spermatids, whereas the spermiogenesis is that stage in the formation of spermatozoa in which spermatids transform to spermatozoa.
2. The seminiferous tubules, which are long, convoluted structures about 150 to 200 µm in diameter and 30 to 70 cm in length, are responsible for the main bulk of the organs. There are several hundreds of them in each testis. The tubule is surrounded by a thin basement membrane where lies a compound epithelium composed of supporting cells and spermatogenetic or germ cells. Each supporting cell (cell of Sertoli) extends from the basement membrane to the lumen. Between the Sertoli lie the spermatogenetic cells in a series of development, i.e. spermatogenesis.
3. Near the basement membrane occurs the most immature of the male germ cells known as the spermatogonia or parent cells which are capable of a limitless number of mitotic divisions. Occasionally, a daughter cell, formed as a result of one of these mitoses is pushed towards the lumen of the seminiferous tubules and enters a growth phase to become primary spermatocytes. At this stage this germ cell reaches its greatest size.
4. The primary spermatocytes undergoes a meiotic cell division whereby the number of chromosomes in the nucleus of each daughter cell becomes half that of the parent cell. After exchanging components, however, they do not split lengthwise as in mitosis, but separate, one from every pair passing to each daughter cell. The secondary spermatocytes, which are formed as a result of meiosis of the primary spermatocytes, are smaller than their parent cell and lie nearer the lumen.
5. Secondary spermatocytes are very short-lived, since after their formation they pass through mitosis to produce cells, known as spermatids which the till smaller.
6. The spermatids are converted, without further division, into spermatozoa. Spermatogenesis proceeds in waves along each tubule, so that not all stages are seen in any one cross-section. The Sertoli cells are larger than the spermatogonia and rest on the basement membrane. They project towards the lumen of the tubule, tapering as they do so. As the spermatids are formed they become attached in clusters to the Sertoli cells and actually penetrate into their cytoplasm, where they develop into spermatozoa. The fully formed germ cells are then displaced into the lumen by the immature cells passing between them. The Sertoli cells aid the development of the spermatozoa and may also have an endocrine function.

The mechanism of their release from the Sertoli cell is unknown; when first liberated they are non-motile. As there is no muscle in the wall of the seminiferous tubule, passage along the lumen towards the rete testis is probably attribute to fluid currents caused by the tension of the fibrous capsule of the testis and passive, induced by the pressure of the new spermatozoa behind and possibly by the actions of the cilia and smooth muscle in the walls of the efferent ductules.

7. The spermatozoa pass down the seminiferous tubules, through the network of the rete testis, along the efferent ductules and into the duct of the epididymis.

During their passage through the epididymis, however, they become activity motile and attain their maximum capacity for the fertilization of ova. When they enter the vas deferens they are ready for ejaculation. The fluid part of the semen is contributed by the seminal vesicle, prostate and bulbo-urethral glands.

Stages of Spermatogenesis

Spermatogonia → primary spermatocytes → secondary spermatocytes → spermatid → (maturation) → spermatozoon. In man, this process begins during adolescence. On an average, the maturation process takes about 74 days—from a primitive germ cell to a mature sperm.

Control of Spermatogenesis

The following factors regulate it:

1. FSH and LH of anterior pituitary. LH stimulates Leydig cells to stimulate spermatogenesis. FSH facilitates last stage of spermatid maturation.
2. Temperature: The process of spermatogenesis takes place at a temperature which is considerably lower than that of the body. Normal position of the testes in scrotum ensures this lowered temperature. The temperature within the scrotum is 1.5° to 2°C below that in the abdomen, and normal development and function of the seminiferous tubules can take place only at this lower temperature. Nowadays adopting methods of preservation and storage for artificial insemination in cases of infertile human marriage are utilized. Human semen can be stored at a temperature of –70°C for weeks and months. The motility and fertility of the suspended spermatozoa reappear when the frozen suspension is unfrozen.
3. Vitamins E, A, ascorbic acid and several members of vitamin B complex enhances process of spermatogenesis.
4. Thyroid influence and enhances process of spermatogenesis.
5. Adrenal cortex hormones also promote spermatogenesis
6. Testosterone secreted from interstitial cells of testes also has regulatory control on spermatogenesis.

It is inhibited by deep X-ray, radium, alcoholism, etc. Close confinement also inhibits the process in animals. Wild animals do not breed in captivity. Probably mental depression may inhibit anterior pituitary through hypothalamus. But these factors do not affect the secretion of testosterone from interstitial cells.

Motility, Span of Life and Fertilizing Power

1. The motility of the spermatozoa depends upon undulatory and tortional movements of the tail of spermatozoon of which tortional movement are attributable to the unequal size of the coarse fibrils of the tail.
2. In the seminiferous tubules and the proximal part of epididymis, the spermatozoa are not motile and their fertilizing power is low.
3. In the distal end of the epididymis motility develops and the fertilizing power becomes double.
4. The secretion of the epididymis has got spermatotrophic effect. If the epididymis be tied at the both ends, the spermatozoa inside remain alive for 60 days but their fertility lasts only for 30 days. If the same experiment is repeated after castration, both the periods are reduced by half. This proves that the internal secretion of the testes increases both span of life and the fertilizing power of the spermatozoon.
5. Full fertilizing power of the sperm is achieved only after travelling within the uterine tube. This power is known as capacitation. This capacitation is acquired only after staying in the uterine cavity for a few days because freshly ejected sperm into the vagina has got a little fertilizing power.
6. The spermatozoa swim through the vas deferens aided by the ciliary movement of the vas epithelium and probably by the contraction of its muscular wall. In the female genital tract the spermatozoa do not live more than 72 hours.

Fate of Spermatozoa

After their entry into the vagina, the spermatozoa travel at the rate of about 1–3 mm per minute and takes about 45 minutes to pass from the opening of the cervix to the ovarian end of the fallopian tube (about 16–20 cm). The onward progress of the male gametes in the female genital organ is helped by the following factors:

1. The inherent movement of the gametes.
2. The positive chemotaxis exerted by the alkaline secretion of the cervix, and the negative pressure created due to contraction of the uterus during coitus.
3. Prostaglandin present within seminal plasma helps in the movement of sperms. The cervical opening dilates and the uterus moves making its axis parallel to vaginal canal—thus facilitating the entry of the gametes in the cervix.
4. After traversing the body of the uterus the gametes enter the fallopian tube, where if the ovum be present fertilization takes place. Otherwise, the spermatozoa die, degenerate and disappear generally after 72 hours.

Metabolism of Spermatozoa

While the spermatozoa are present inside the epididymis, they are metabolically inactive due to the absence of O_2 and sugar to be metabolized. After ejaculation they normally metabolize fructose in contrast to other tissues which use mainly glucose.

Fructose is present in the accessory sex glands and regulated by androgens. Under anaerobic conditions fructose is broken down to lactic acid which is oxidized with liberation of energy in presence of O_2. Sperm motility depends upon the breakdown of ATP which provides energy for contraction of the fibrils present in the tail. Fructolysis helps in the regeneration of ATP. For maximum motility of sperm, both fructose and O_2 should be present.

Hyaluronidase

Although fertilization is done by a single spermatozoon, yet the presence of myriads of spermatozoa in the seminal fluid appears to be an apparent prodigality of Dame Nature. But it is seen that, if the semen contains spermatozoa less than 20 million per ml, the subject is usually sterile. In other words, the enormous number is an essential factor for successful fertilization. The explanation of this curious paradox is that the ovum remains covered up by a layer of cells (corona radiata) derived from the discus proligerus. These cells remain cemented together by hyaluronic acid*. Unless this cell layer penetrate, the spermatozoon cannot reach the ovum.

Fertilization of the Ovum

1. During the chemical warfare for removal of the corona radiata a large number of spermatozoa die and only the strongest survivor ultimately reach the ovum.
2. One sperm, the strongest one enters the zona pellucida of the ovum by side-to-side jerky movements.
3. The physical characteristics of the zona pellucida are changed due to direct contact with the sperm. Here the sperm loses its head cap (acrosome) which contains an enzyme that depolarizes the zona pellucida in a very restricted zone.
4. The penetration in the zona pellucida is taking place by a specific mucolytic enzyme present in the sperm and for penetration in this layer capacitation is required by the sperm.
5. As soon as one spermatozoon enters the ovum, a stiff membrane develops around the latter preventing the entrance of any other spermatozoon.
6. After crossing through the zona pellucida layer and the perivitelline space, the sperm touches the vitelline membrane. At this stage the second meiotic division of the secondary oocytes takes place (Fig. 80.15).
7. The sperm penetrates vitelline membrane by flagella like movement of its tail. As the point of contact of the vitelline membrane with the sperm head, an outward bulging in the ooplasm occurs which helps in the sperm penetration. However, the head and probably a part of the neck enter the ovum. The rest of the gamete drops out and degenerates.

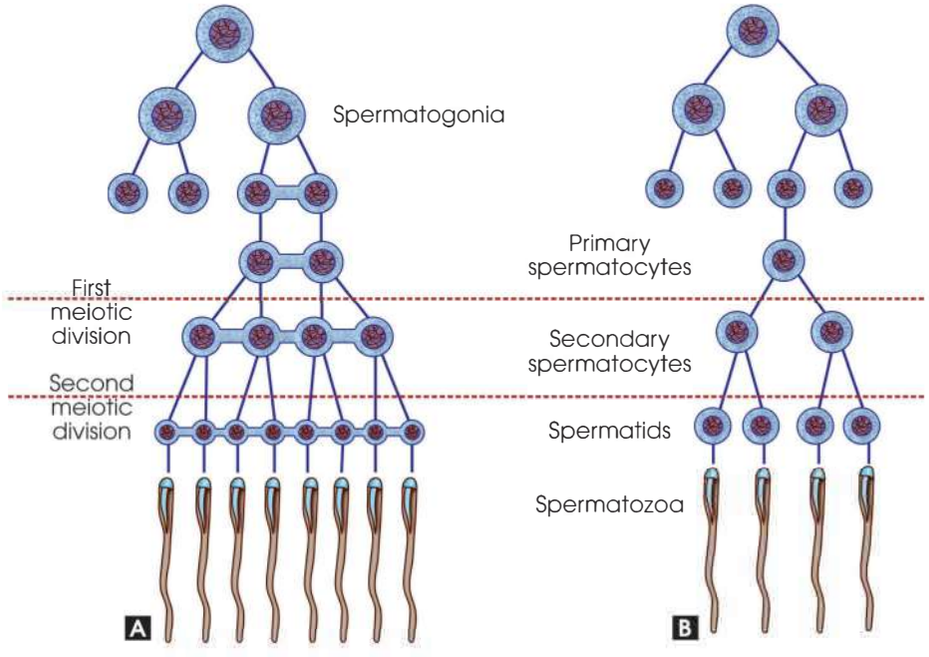


Fig. 80.15A and B: Diagram of mammalian spermatogenesis. (A) Showing as revised on the basis of electron microscopic observations of intercellular bridges connecting the developing germ cells. In most species primary and secondary spermatocytes and spermatids seem to be joined by bridge. Late in their differentiation the spermatids separate to produce individual spermatozoa. (B) Shows conventional spermatogenesis (DW Fawcett)

*Hyaluronic acid molecule is made up of acetyl glucosamine and glucuronic acid with molecular weight 200000–400000. The viscosity of the vitreous humour, synovial fluid, Wharton's jelly of the umbilical cord, etc. is chiefly due to hyaluronic acid. Hyaluronic acid gel serves as the cementing material by which cells are held together.

8. Fusion of the male and female pronuclei takes place (syngamy) and these acts as a powerful stimulus for multiplication.
9. The fertilized ovum starts multiplying at a terrific speed. The mass of cells thus formed (Morula) is carried slowly along the fallopian tube by the ciliary movement of this epithelium and reaches the body of the uterus in about eight days. At this time it has a diameter of about 0.2 mm. The fertilized ovum is embedded in the already prepared decidua and pregnancy starts.

SEMEN (SEMINAL PLASMA OR FLUID)

1. Semen is a suspension of spermatozoa in the secretion of the epididymis, prostate, seminal vesicle, Cowper's glands.
2. Volume at each emission is about 2–4 ml containing 100–200 million spermatozoa, 80% of which should remain actively motile for 45 minutes but not later than 3 hours. They should not contain more than 20% abnormal forms. Volume and sperm count in semen are decreased with repeated ejaculation.
3. About 5% of men contain 20 to 40 million sperm/ml of semen but those containing less than 20 million/ml are termed sterile.
4. Semen contains fructose, orbital, spermine, citrate, acid phosphates, lipids, fibrinolysin and prostaglandins.
5. Its specific gravity is 1.028 and pH 7.35–7.50. Seminal suffers (phosphate and bicarbonate) serve to protect the sperm against low pH of the vagina.
6. Its colour is highly viscid opalescent, greyish white. Prostaglandins possibly help in the movement of spermatozoa to be fallopian tube through uterus.
7. Human semen after ejection coagulates immediately due to conversion of fibrinogen into fibrin, but after 15 to 20 minutes there is liquefaction by the enzyme fibrinolysin of plasmin contained in it.
8. The substrate for gel formation (coagulation) is the protein-like material which is secreted by seminal vesicles, whereas the gelatin enzymes take contact with the substrate only during ejaculation, being elaborated distally to the seminal vesicles by the prostate.

Functions of the Constituents of Seminal Fluids

Fructose

Seminal vesicles are the chief site of fructose formation in men. As the storage capacity of seminal vesicles on men is small, consecutive ejaculations within several days result in low semen fructose content. About 2–4 days are required for replenishment.

Phosphatases

Human semen contains a high amount of acid phosphatases that arise from prostatic secretion. Alkaline phosphatase is also present in low concentration in human semen.

Spermine

It is a nitrogenous base secreted by the prostate and found in large amounts in human semen. When human semen is allowed to stand for a short period, crystals of spermine phosphate begin to appear. The presence of spermine distinguishes semen from other body fluid. At ejaculation, acid phosphatase liberates orthophosphate from phosphoryl-choline which reacts with spermine. The reaction of spermine with picric acid is the basis of a test of diagnostic value in forensic medicine (Barberio test).

Choline

It is also nitrogenous base and is found in high concentration in human semen. Physiologic functions of choline in semen involve lipotrophic activity, stimulation of phospholipid turnover, transmethylation and possibly an acetylcholine-like activity.

Ergothioneine

It is also a nitrogenous base and is found in the semen of certain forms, including humans. It ensures sperm motility and fructose utilization by protecting essential sulphydryl groups in the sperm from sulphydryl group-binding substances and agents which are capable of oxidizing the sulphydryl groups. These sulphydryl-reducing groups of ergothioneine act as protection.

Citric Acid

Citric acid which is found in human semen is derived from prostatic secretion. Citric acid content in human semen is influenced by androgenic level, being increased by androgen and decreased after castration.

Lipid

It is found in the semen and derived from prostatic secretion. This lipid is composed mainly of phospholipids and cholesterol. Lipid globules (not lecithin), macrophages containing lipid granules and corpora amylacea, being prostatic origin, account for opalescence of semen.

Protein Materials

Seminal plasma of the male contains about 3.5–5.5 g of protein-like substance/1100 ml. This substance is responsible for the coagulation of semen being acted upon by the gelatin enzyme doing contact during ejaculation.

Hyaluronidase

It is commonly associated with the sperm. It is also found in semen as a consequence of this release from the sperm and is derived from the tubule area of testes. It is mucolytic enzyme which depolymerized and hydrolyses hyaluronic acid. Although hyaluronidase is involved in the process of spermatogenesis, yet it may facilitate fertilization by liquefying a passage for each sperm through cumulus cells which surround the ovum.

Other Substances

These include creatine, creatinine, epinephrine, norepinephrine and inositol. These substances have been identified in the semen of experimental forms. Their function in seminal fluid is not clear.

APPLIED PHYSIOLOGY: IMPOTENCE

Impotence may be defined as the failure to achieve or to maintain an erection sufficient to accomplish intromission and coitus. If an erection is achieved it usually subsides without ejaculation. Primary impotence implies that a male has never been successful in any attempt at intromission. Impotence may be 'constitutional', 'organic' or 'psychogenic' (Cooper). Constitutional impotence is associated with a defective sexual drive without evidence of organic disease. Organic impotence develops in a previously normal subject and is the result of some pathological process. Psychogenic impotence implies that there is no organic basis for the condition and that it results from psychological causes. Patients with endocrine disorders rarely complain of importance unless questioned directly. Those with hypogonadism have diminished libido as well. In humans, various degrees of importance are commonly found, but it is rare to find definite organic cause for the complaints. The development of the male sexual attitude and power depends upon the presence of normal androgenic secretion at the tide of puberty and the development of a male-oriented sexual attitude based on sociologic and psychogenic influences.

Male Sexual Act

Coitus

Coitus, by which the sperms are introduced into the vagina, depends upon the presence of testosterone and on the integrity of many parts of the nervous system. The higher centers usually initiate the act, but may also inhibit it. Erection and ejaculation, however, can be induced reflexly in a paraplegic man.

Erection

This function is initiated by psychic or local influences. Erection of the penis is brought about by the distension with blood of venous sinuses in the erectile tissue, in response to sexual excitement. Afferent stimuli pass from the glans penis, via the parasympathetic pudendal nerve (S2–S4), and from other areas to the spinal cord. A centre for erection in the lumbosacral part of the spinal cord sends impulses, via the nervi erigentes (S2–S3) which cause vasodilatation of the arterioles of the corpora cavernosa and spongiosa of the penis to relax and constriction of the main dorsal vein and the blood pressure within them approaches that of the carotid arteries. The corpora cavernosa and spongiosa of the penis fill with blood under high pressure and the penis changes from a small flabby organ to a rigid elongated organ. If the sacral parasympathetic outflow is interrupted such as will occur after a bilateral lumbar sympathectomy operation, ejaculation no longer occurs although the quality of erection of the penis is still present. Lack of psychic stimulus can impair the quality of erection.

Emission

Emission is the movement of the semen into the urethra and is a sympathetic response. Secretory nerve impulses from the glans penis reach the sacral cord and travel to the integrating centre in the upper lumbar segments of the spinal cord. These impulses set off a massive stimulus through the hypogastric sympathetic nerves with the contraction of smooth muscles of the vasa differentia and seminal vesicles. These nerves cause secretions from the prostate, seminal vesicles and ejaculatory ducts to enter the prostatic urethra. Interruption of these nerves may preclude emission.

Ejaculation

Ejaculation proper is the propulsion of semen out of the urethra at the time of orgasm. The centre or ejaculation is in the upper lumbar region of the spinal cord. It sends impulses, via the lumbar sympathetic trunks (L1–L2), which cause the muscles of the vasa deferentia, the seminal vesicles and the prostate to contract rhythmically and eject the semen into the urethra. At the same time sympathetic impulses relax the detrusor muscle and cause the internal sphincter to contract, thus inhibiting micturition and preventing the reflux of semen into the bladder. Ejaculation from the urethra is effect by rhythmic contractions of the perineal muscles, which are supplied by the perineal branch of the pudendal nerve (S2–S4). Hence, a lower motor neuron lesion in this zone could impair ejaculation and the sensation of orgasm.

APPLIED PHYSIOLOGY: HYPOGONADISM

Male hypogonadism is a clinical condition in which the removal of testis is carried out prior to onset of puberty. The person become completely sterile and develops eunuchoidism. The secondary sexual characteristics fail to develop in this condition and there is failure of complete maturation and development of penis, seminal vesicle and prostrate to adult size and they appear to be

prematurely small. The outward appearance is of female type and the person may be very tall due to delayed union of epiphysis. If hypogonadism occurs after puberty there is atrophy of prostrate and seminal vesicle, the secondary sexual characteristic are normally developed but the individual may develop loss of libido-erectile penile dysfunction.

PROSTATE

Histology (Fig. 80.16)

Prostrate is a male accessory sex organ. It surrounds the first part of urethra, and is covered by vascular capsule. It is composed of fibroelastic tissue, plain muscles and mucosal glands. The glands are tubulo-alveolar, containing a low cubical or pseudo-stratified columnar epithelium, highly folded upon itself. The cytoplasm of the cells has a high amount of acid phosphatase activity. The cells shrink and become non-secretory in deficiency of androgens.

Functions

The secretion of the prostatic glands increases the volume of semen. Probably, it acts as a nutritive fluid for the male gametes, prolonging their life and helping their function. The prostatic fluid is acid in reaction contributes 20% of total volume of human semen, and contains citric acid, spermine, phospholipids, fibrinolysin, fibrinogen, thromboplastin, cephalin and cholesterol. In addition, prostatic secretion contains epithelial cells, a few leucocytes, protein and electrolytes. It is rich in enzyme fibrinogenase and acid phosphatase which hydrolyses organic phosphates (glycerophosphate, hexose phosphate, etc.) in an acid medium and liberates inorganic phosphates. [Bones contain alkaline phosphatase, being active in alkaline medium.] The acid phosphatase content in the prostatic fluid is a measure of its activity. This enzyme probably helps and nutrition and function of the spermatozoa. A small amount of the enzyme enters the blood stream, where the upper normal limits and below 3.25 units percent. Its level fluctuates according to the degree of activity of prostate. In cancer of prostate the figure goes above 10 units % (diagnostic). The prostatic secretion is opalescent and has an approximate pH of 6.4 in human.

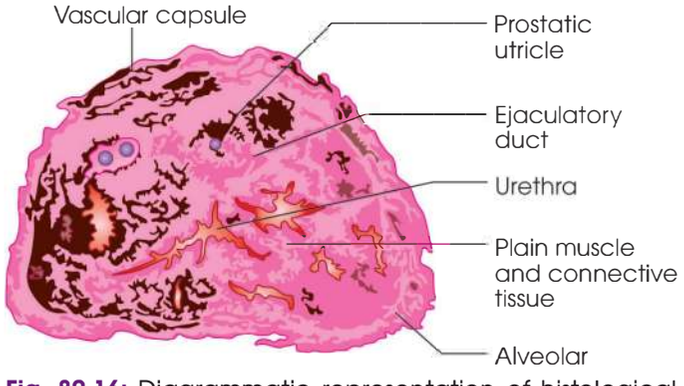


Fig. 80.16: Diagrammatic representation of histological structure of prostate gland

Control of Prostate

Prostate is under the dual control of both androgens and oestrogens (both present in the male body).

Proof

Castration causes atrophy of the prostate with degeneration of the glands. Injection of androgens restores it to normal, showing that optimum androgen level is necessary for prostatic activity.

Injection of oestrogens causes degeneration and keratinisation of the glandular epithelium (same as vaginal epithelium), but enlarges the non-glandular part of prostate. This shows that prostate is controlled by both the hormones—an optimum balance between them is responsible for its normal structure and functions.

Applied Physiology: Prostatic Hypertrophy

In old age, prostate hypertrophies with the degeneration of its glands. This is believed to be due to the decline of androgens and relative rise of the oestrogens. In simple senile prostatic hypertrophy administration of androgens is of a great therapeutic value. But in cancer of prostate oestrogens are very useful probably by checking the growth of the epithelium and trying to keratinize it.

Prostate-specific antigen (*PSA*): Prostate produces and secretes into semen and blood stream PSA. It hydrolyses sperm motility inhibitor. It is widely used as screening test for prostate disease.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the mechanism of synthesis of androgens. Describe the functions of testosterone.
2. Describe the transport, metabolism and excretion of testosterone. Discuss the events involved in control of testicular activity.
3. Define spermatogenesis. Describe the various stages of spermatogenesis.
4. Describe the functions of the constituents of seminal fluids.

Short Notes

1. Functions of Leydig cells
2. Function of testis
3. Semen and its constituents
4. Impotency
5. Hypogonadism
6. Prostrate
7. Male sexual act
8. Prostatic hypertrophy
9. Fertilization of ovum

Chapter

81

Female Reproductive Organs

The female reproductive system consists the internal and external sex organs that are involved in process of human reproduction. The female reproductive system attains maturity at puberty and is capable to produce gametes. On fertilization and implantation of blastocyst with the uterine musculature, the placenta nourishes the foetus up to full term and thus female reproductive system is vitally important in producing the progeny.

Hippocrates believed that both males and females contribute their seed to conception; otherwise, children would not resemble either or both of their parents. It was nearly four-hundred after Hippocrates view when Galen discovered the source of 'female semen' as the ovaries in female reproductive organs.

Caspar Friedrich Wolff was a German physiologist and one of the founders of embryology and the Wolffian duct is named after him.

Reference: William A Locy. Biology and its Makers. Holt and Company, New York, 1908.

1733–1794

INTRODUCTION

Anatomy (Fig. 81.1)

The important female reproductive organs consist of:

1. Two ovaries; one on each side
2. Two connecting fallopian (uterine) tubes; uterus and vagina.

The fallopian tube is a muscular one, having an inner mucous membrane. From attachment at the uterus, the two fallopian tubes extend laterally, one on either side to the wall of the pelvis, and then turn downwards and terminate near the ovaries. Each tube enlarges forming ampulla and infundibulum, and at last bends downwards to end in a fimbriated margin. One of the fimbriae is attached to the ovary (ovarian fimbria).

Histology

Fallopian tube: The infundibulum is formed by a number of fimbriae and is funnel-shaped. The thin-walled ampulla is the largest segment of the tube and its terminal short segment extends to the isthmus which is thicker walled and shorter in diameter than that of the ampulla. The wall of the fallopian tube is composed of mucous membrane, and serous membrane. The epithelial lining of the mucous membrane consists of a layer of simple columnar cells some of which are ciliated but other is not. The cilia blow towards the uterus and have a mechanical function. The non-ciliated cells are secretory in nature.

Uterus: The uterus is a thick-walled, pear-shaped muscular organ, the inside of which is hollow. It has a body and its lower part is cervix, which is continuous with the body above by the internal os with the vagina below by the externales. The muscular wall of the uterus (myometrium) made up of smooth muscle fibres is arranged in three layers, an inner longitudinal layer, a thick oblique middle layer and a thin outer longitudinal layer. It responds to the posterior pituitary hormone, oxytocin. The inner mucous layer endometrium is lined by epithelial cells and contains many tubular coiled glands penetrating deeply into the underlying loose connective tissue (tunica propria). The uterine endometrium undergoes cyclic changes during different phases of menstrual cycle.

OVARY

1. More or less 7 million oocytes in the ovary of 30 weeks female foetus are enclosed by granulose cells by about 40 weeks, forming functional units the follicles, containing ova already in the prophase of meiotic division.

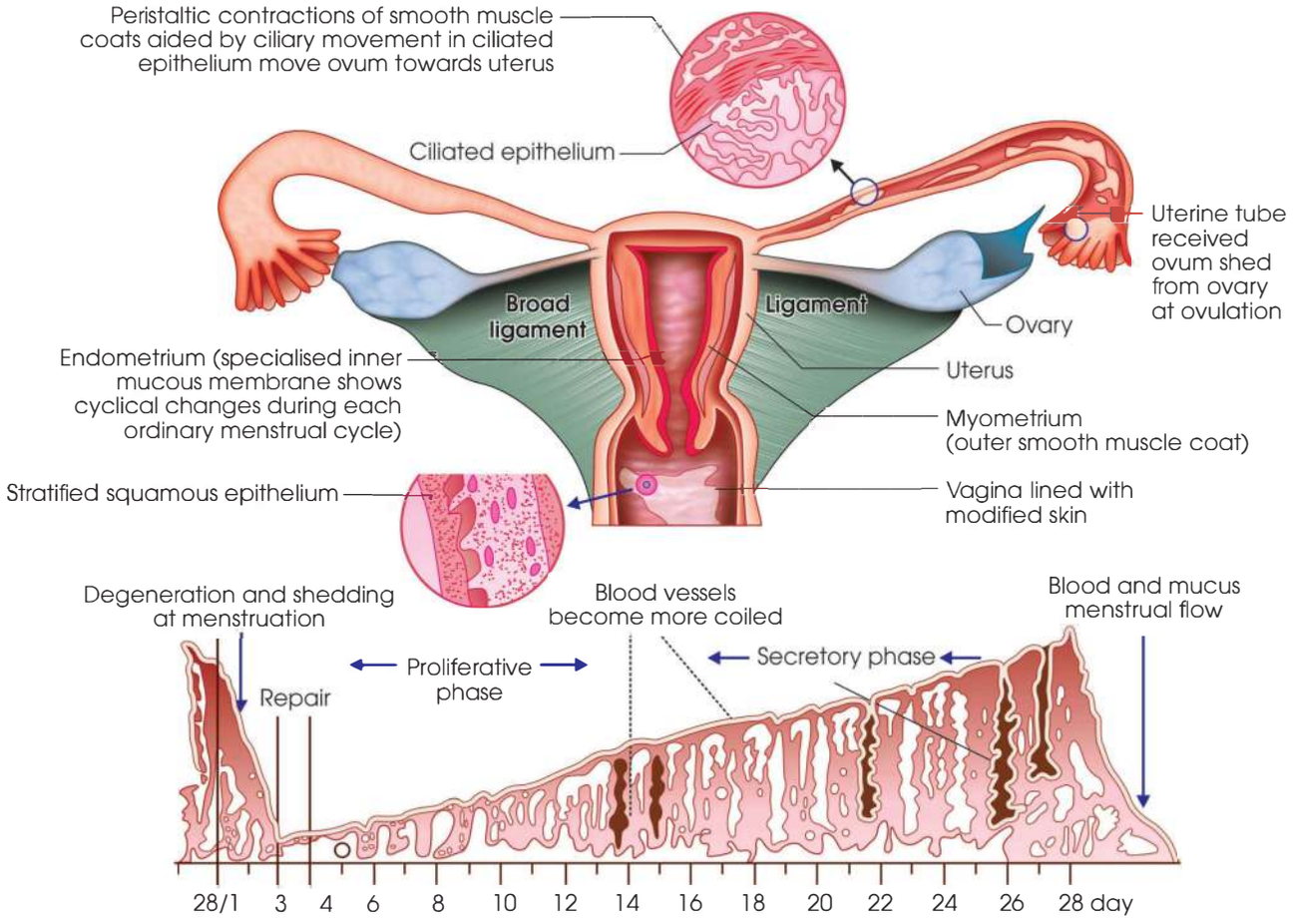


Fig. 81.1: Diagram showing the vagina, uterus, uterine tubes

2. These follicles undergo successive stages of development during foetal life and childhood, the number of primordial follicles declining from about 2 million just before birth to about 3, 00,000 in the adult.
3. The accumulation of atretic follicles forms most of the ovarian cortical stroma.
4. Either ovulation or corpus luteum formation does not occur before puberty.
5. Cyclic secretion of gonadotrophins takes place at puberty, leading to the full development of an adult ovary.

Structural Anatomy

Two somewhat bean-shaped bodies (4 × 2.5 × 1.5 cm), one on each side, near the free end of the fallopian tube, hanging from the broad ligament by a fold of peritoneum, called the mesovarium. They are richly supplied with blood vessels and nerves (vasomotor).

Histology (Fig. 81.2)

There is no organ in the female body which shows so much histological variations at different phases of life. In childhood, puberty, pregnancy and menopause, the ovarian structure shows characteristic variation. The following is a brief description of a normal ovary. Ovary consists of the following six elements.

Germinal epithelium: It is the outermost covering by a single layer of cuboidal cells, continuous with the peritoneum, derived from the coelomic epithelium. It is the parent tissue from which the primitive graafian follicles develop.

Tunica albuginea: Thin layer of eosinophilic collagenous connective tissue of low cellularity under germinal epithelium.

Stroma: It is a connective tissue network continuous with the tunica albuginea and containing spindle-shaped cells with a few involuntary muscle fibres. It supports the essential ovarian tissues and carries blood vessels, lymphatics and nerves.

Vesicular follicles or graafian follicles: Small islands of cells in various stages of development and scattered mostly at the peripheral part of the ovary. The immature one are called the primordial follicles. The central cell is the ovum. The remaining cells surround the ovum in a single layer forming a sort of capsule.

Function: It forms the female gamete (ovum) and secretes oestradiol.

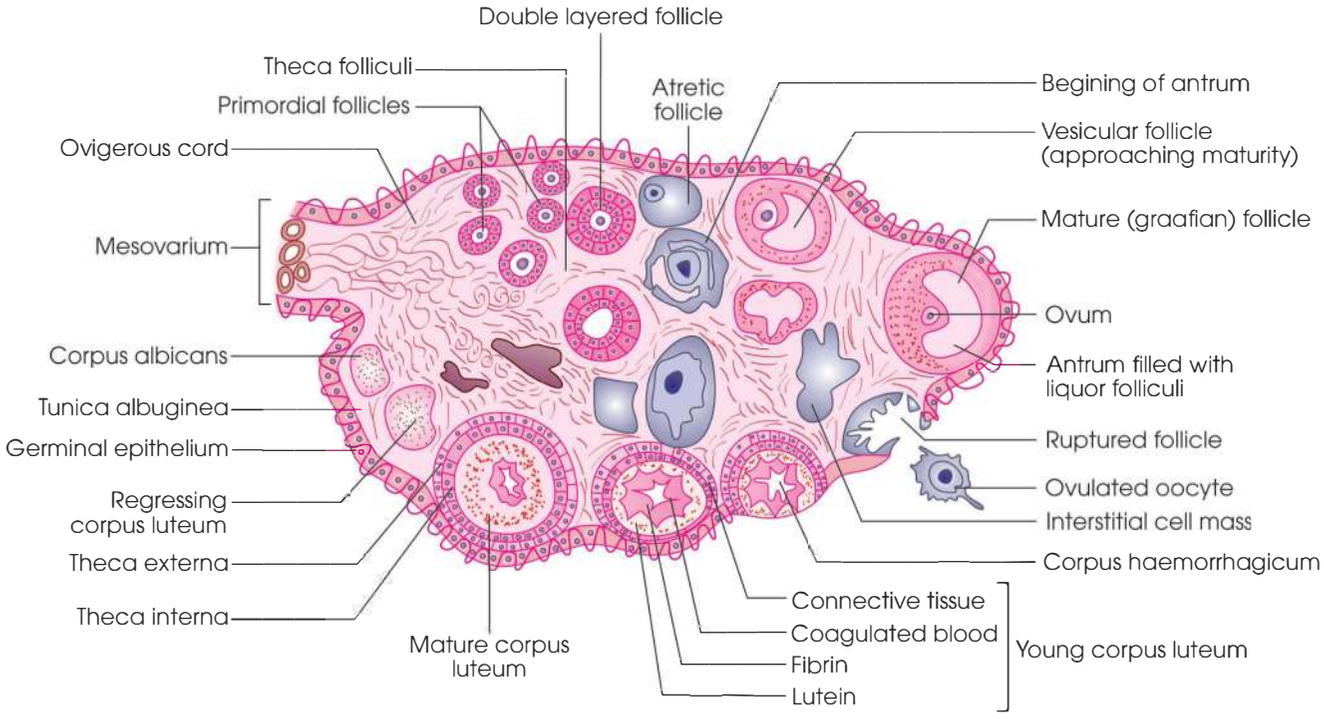


Fig. 81.2: Composite diagram of ovary showing development of follicle, formation of corpus luteum, atretic follicle, mature follicle, etc.

Corpus luteum: When the graafian follicle ruptures, corpus luteum develops on the remnants of the ruptured follicle.

Function: It is a temporary gland secreting progesterone.

Interstitial cells: Groups of polyhedral cells containing lipid granules representing stored active principle. This develops from the stroma cells or from the cells of the unruptured follicles. They secrete oestrogens.

In infancy, the ovaries are made up of spindle-shaped stroma cells. There is a cubical—celled germinal epithelium and a large number of primordial follicles. The follicles do not mature; there is no ovulation and no corpus luteum.

At puberty, the germinal epithelium contains flattened cells, a large number of maturing follicles ruptured or unruptured and corpora lutea of small size.

During pregnancy, the characteristic additional feature is the presence of a large corpus luteum.

At menopause, the ovaries atrophy, become smaller in size, the follicles disappear and are replaced by fibrous scars. The interstitial cells degenerate and very little oestrogen is formed.

Functions of Ovary

The two main functions of ovary are exocrine and endocrine function:

A. **Exocrine function:** It aids in oogenesis in fetal life and also in formation of mature ova. Ovulation is influenced by ovarian hormone and gonadotrophin hormones.

B. **Endocrine functions**—It secretes four hormones:
   1. Oestrogen—secreted by the graafian follicles (membrana granulosa or theca interna).
   2. Progesterone—secreted by the corpus luteum.
   3. Androgen.
   4. Relaxin

C. With the help of these four hormones, the ovary controls the whole reproductive life of the female. For instance, it is responsible for:
   1. All the puberty changes, such as:
      a. Growth and development of uterus, fallopian tube, vagina
      b. Menstrual changes
      c. Appearance of secondary sexual characters.
   2. Pregnancy and the changes associated with it, such as, embedding of ovum, development of placenta, further growth of mammary glands, etc.
   3. Relaxin helps in parturition.

LIFE HISTORY OF VESICULAR OF GRAAFIAN FOLLICLES

Development and Histology

1. The surface layer of the ovary—the germinal epithelium sends down finger-like processes called the genital cords (egg tubes of Pflüger). The cords become cutoff from the surface and are broken up

into small islands of cells of which one cell becomes enlarged and differentiated from its neighbouring cells into primary oocytes.

2. The rest cells surround the oocytes forming the primordial follicles. The primary oocytes are thus lined by a homogeneous membrane, called the zona pellucida. These are small spherical structures, about 0.5 mm in diameter, having a single cell at the centre representing the immature ovum. All the other cells remain surrounding the ovum in a single layer forming a sort of capsule (follicular epithelium). The number of immature primordial follicles varies with age. In the newborn, the number varies 2,50,000 to 5,00,000; at puberty—1,00,000 to 2,00,000; at menopause—nil. Of these, only about 400–500 follicles undergo maturation and ovulation during the whole sex life of the female (others degenerate).
3. Maturation of the vesicular follicles or graafian follicles (Fig. 81.3): In childhood the follicles do not mature. After childhood maturation begins but fails to be complete. The stages of the maturing process are briefly as follows: Under the influence of follicle-stimulating hormones (FSH) the primordial follicular epithelium multiplies forming several layers of cell surrounding the ovum. The ovum and the follicle gradually enlarges. Droplets of fluid appear between the cells, gradually run together and form a cavity (antrum formation) containing liquor folliculi. At this stage only the primordial follicle can be said as graafian follicle.

Although there are numerous graafian follicles, yet, at each ovarian cycle, only one follicle matures and undergoes ovulation. In other words, at each cycle, only one mature ovum is presented for fertilization (occasionally, two ova may be discharged producing binovular twins.)

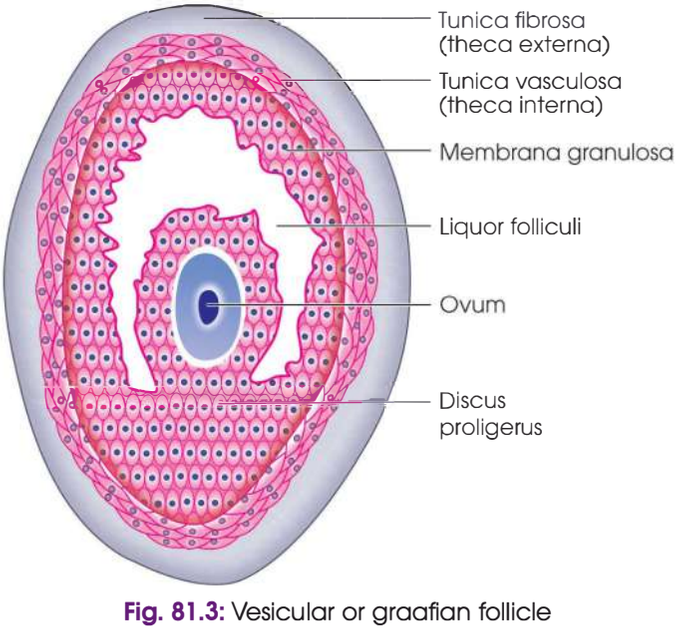


Fig. 81.3: Vesicular or graafian follicle

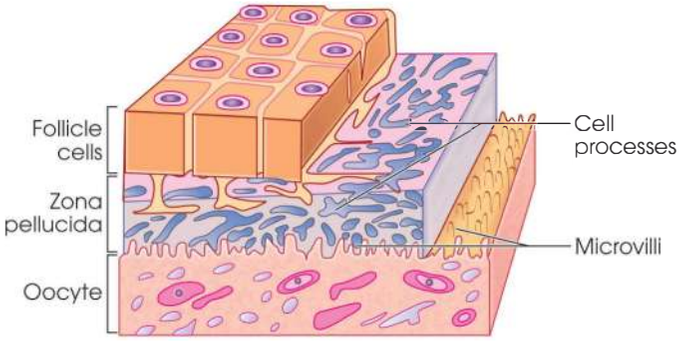


Fig. 81.4: Schematized representation of zona pellucida and structural relationship between follicle cells and oocyte. Cytoplasmic extensions of follicle cells permeate and penetrate zona pellucida, but do not establish contact (or syncytical continuation) with the ovum

4. The cavity thus formed, separates the surrounding cells into two layers: (a) The peripheral layer called the membrana granulosa (multi-layered follicular granulosa), and (b) the central layer discuses proligerus or cumulus oophorus (ovaricus). The innermost cumulus cells are disposed about the ovum in radial fashion, forming corona radiata.
5. The zona pellucida is conspicuously thickened and crossed by processes from the cells of corona radiate (Fig. 81.4). Microvilli from the ovum extend into the substance of zona pellucida. The thecal layers keep pace with the growing follicle and come to form quite a thick outer layer. The cumulus oophorus surrounds the ovum which remains attached eccentrically to the outer pole of the follicle.
6. In the mean time, the stroma cells surrounding the follicle become differentiated into two layers. The inner vascular layer called tunica vasculosa (theca interna) and outer fibrous layer known as tunica fibrosa (theca externa) (Fig. 81.3). At this stage the graafian follicle is not fully matured. It is matured only when the primary oocytes undergo meiotic division to lose one polar body and becomes secondary oocytes.

MATURATION OF THE OVUM

1. Before ovulation, the ovum must undergo the process of maturation. The oocytes increases in size, fat globules appear in the cytoplasm and a thin transparent structure develops between the follicular cells and the oocytes, known as the zona pellucida.
2. The primary oocyte of the graafian follicle undergoes first meiotic division (heterotypical) giving rise to secondary oocytes and one polar body. This is the full maturation of the graafian follicle and the ovum is discharged from the graafian follicle (ovulation) as a secondary oocytes.
3. The secondary oocytes contain half the number of standard chromosome (22X). Further differentiation

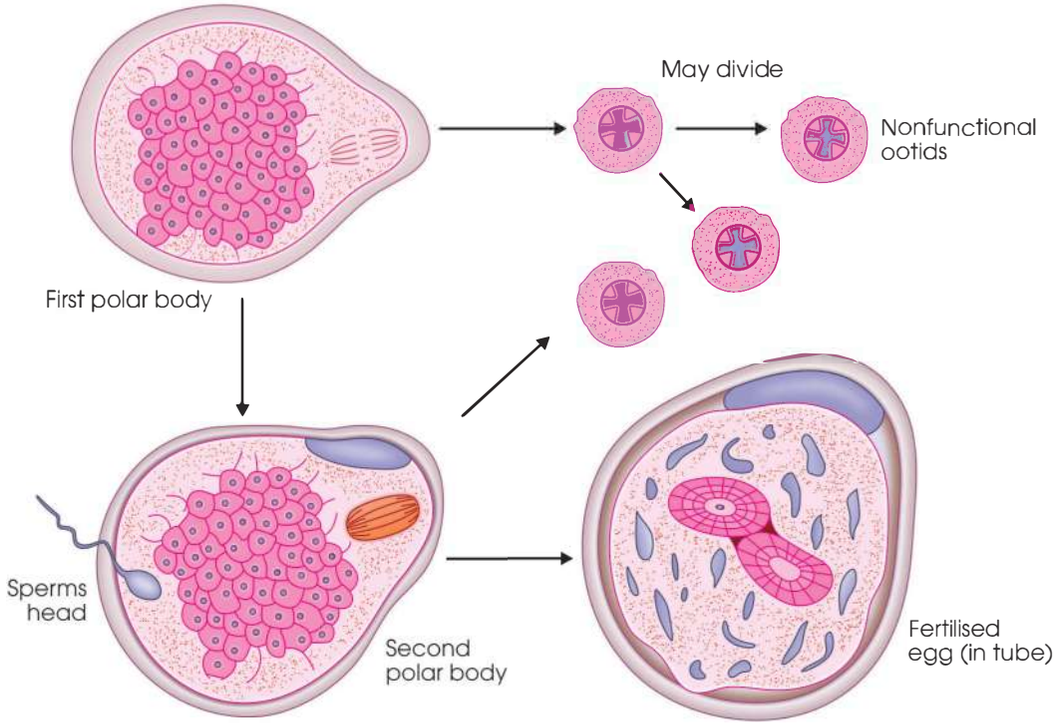


Fig. 81.5: Diagram showing the liberation of the polar bodies from the maturing ovum. Note that although it may divide again, as suggested in the diagram, the first polar body ordinarily degenerates without so doing. The presence of a sperm within the ovum is indicative of the fact that sperm penetration is ordinarily necessary before the second polar body is formed

of the secondary oocytes is not possible until it is fertilized by the sperm in the fallopian tube.

4. Second meiotic division (homotypical) of the secondary oocytes takes place only after penetration of the sperm in the zona pellucida (Fig. 81.5). With this second meiotic division matured ovum (22X) is formed by losing another polar body (Fig. 81.6).

Covering of the Ovum

The ovum is covered by the vitelline membrane which is again covered by the zona pellucida. In between the vitelline membrane and the zona pellucida there is a narrow space which is known as perivitelline space.

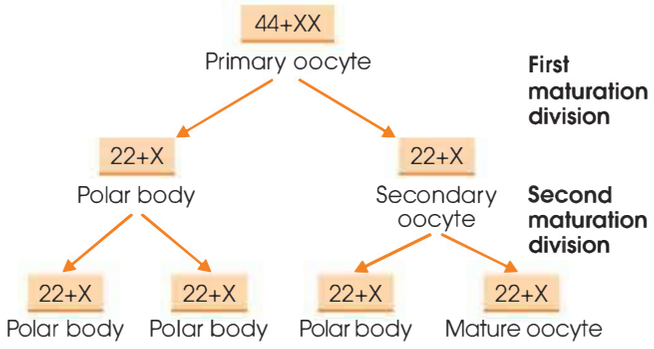


Fig. 81.6: Scheme shows two maturation divisions in the female germ cells where single ovum is formed from one primary oocyte

During the discharge of ovum (secondary oocytes) from the graafian follicle, several layers of epithelial cells from the cumulus oophorus (cumulus ovaricus adhere to the ovum. These epithelial cells are arranged radially over the zona pellucida and are collectively known as corona radiata (Fig. 81.7).

Control of Maturation of Ovum

Early maturation is chiefly controlled by FSH, but for full maturation both FSH and LH are necessary.

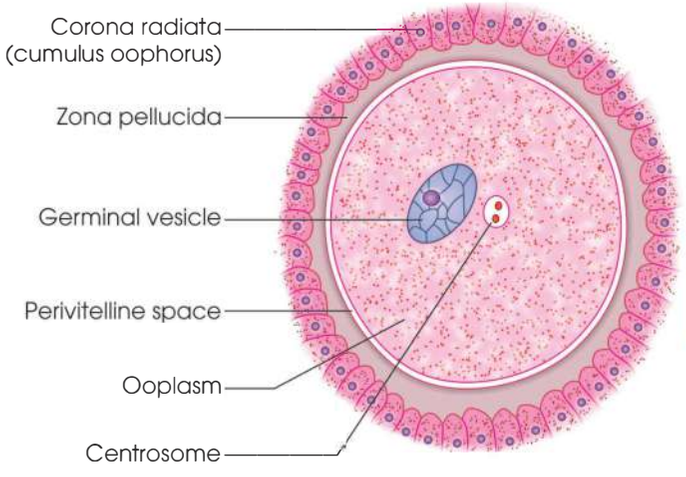


Fig. 81.7: Ovum surrounded by discus cells

OVULATION

Key Points

1. During the menstrual cycle, which is conventionally dated from the first day of bleeding, there is a gradual thickening of the lining of the uterus and the proliferation of straight glands; then in the postovulatory half of the cycle the glands become complicated and tortuous, the submucosal layer of tissue becomes very vascular and oedematous and the leucocytes infiltrates this layer.
2. The formation of this progestational or secretory type of endometrium is important for reception, nourishment and encouragement of the fertilized ovum.
3. Ovulation occurs at midcycle and there is wide variation from one individual to another.
4. At about the time of ovulation other changes are:
   a. An increase in urinary gonadotrophins,
   b. An increase in the number of large acidophilic squamous cells with small nuclei in vaginal smear,
   c. A peak in oestrogen output just before ovulation, 3–4 days after ovulation a rise in pregnanediol excretion. In anovulatory cycle none of these events occurs.
5. If fertilization does not occur, the endometrial degeneration and sloughing take place. At the period of sloughing, marked vasoconstriction of arterioles, a slowing of circulation with extravasations and pooling of blood in the stroma layer occur submucosal blood pools coalesce, and superficial layers of the endometrium, leucocytes and mucus are shed and menstrual discharge (Fig. 81.8). The discharged blood does not normally clot and may vary in amount from 20–200 ml in volume for a single period. This flow lasts 4–6 days in 95% of women. Premenstrual endometrium loses about half its thickness in about 3–4 days and reparative processes begin to be apparent.
6. ***Hormonal effect on ovulation***
   a. The ovarian interstitial cells and the thecal cells of the developing follicle can make oestrogen. Oestrogens have essential local effects in the ovary and may indeed prepare the ovary for stimulation by gonadotrophins.
   b. At the earliest stage of the cycle, certain follicles can be seen to be undergoing differentiation and growth, but when the hypophyseal gonadotrophic stimulation begins with FSH, a single follicle is selected for maturation and ovulation (of rarely 2) and other follicles undergo regression or atresia.
   c. The early preovulatory phase is characterized by a FSH. The FSH stimulates the ovary to produce more and more oestrogen, information in ovaries is feedback to the hypothalamic centre which regulates composition of gonadotrophin recipe. At this stage there is a fall in the release of FSH and facilitation in the release of LH.
   d. Both FSH and LH are required for the production of oestrogen by graafian follicle. The ovum is extruded from the ruptured follicle to the site of fertilization in the human—the fallopian tube (Fig. 81.11).
   e. Under the strong stimulus of LH, (LH surge) for ovulation the ruptured follicle cells change their characteristics to typical lutein cells and their enzymes profile at the same time. They produce progesterone, for pregnanediol is excreted within 3–4 days after ovulation. Growth of corpus luteum depends upon adequate blood supply. Vascular endothelial growth factor may be involved.

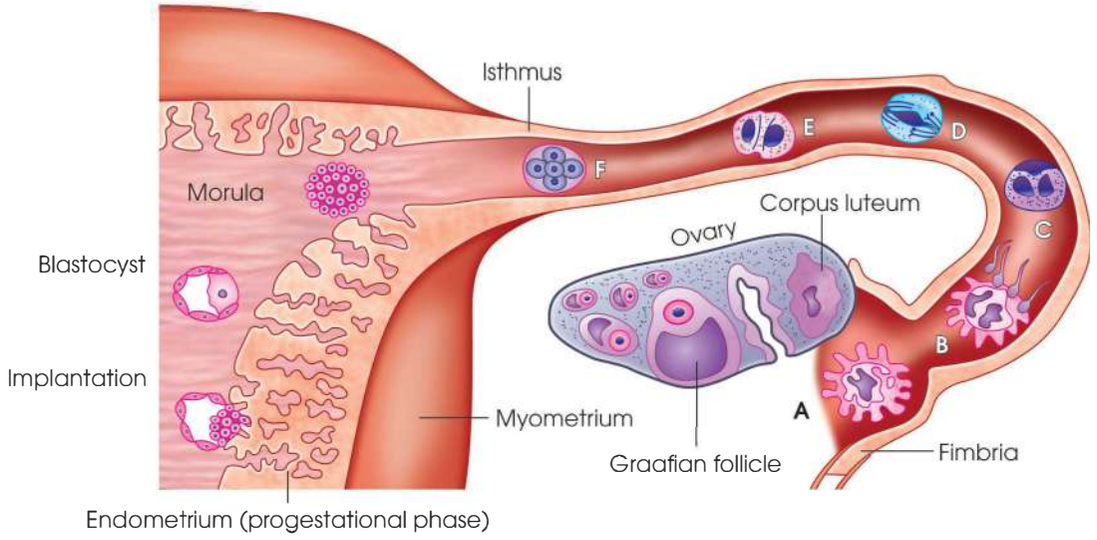


Fig. 81.8: Diagrammatic representation of the female genital tract showing the probable site of fertilization in the ampulla and the stages through which an embryo goes before fertilization and the site where the embryo is implanted A—oocyte immediately after ovulation, B—fertilization about 12–24 hours after ovulation, C—stage of male and female pronuclei, D—spindle of Ist mitotic division during which diploid number of chromosomes is restored, E—two-cell stage (about 48–50 hours old), F—Morula containing blastomeres

f. But corpus luteum also produces oestrogen and a secondary oestrogen excretion peak can be often detected during the second half of the postovulatory phase.
g. If fertilization does not take place, large amounts of oestrogen and progesterone instruct the pituitary through the hypothalamus to cut down the production and release of gonadotrophin.
h. Being deprived of the gonadotrophic stimulus the corpus luteum withers and dies, and there is abrupt withdrawal of progesterone and then of oestrogen. In its turn, the endometrium, which has grown with lavish amounts of oestrogen and progesterone, abruptly finds itself with an insufficient hormonal stimulus to sustain it, and the endometrium promptly deteriorates. Sloughing and bleeding begin and the cycle resumes 3–4 days later.
i. If fertilization takes place, CG (or HCG) that appears urgently prevents the degeneration of the corpora lutea and sustains it until the placenta can assume the burden of producing large amounts of steroids required during pregnancy. The relationship of the hypophyseal ovarian system is summarised below (Fig. 81.8).
j. It is commonly seen that small doses of oestrogen stimulate the output of FSH, large doses of estrogen inhibit FSH output and in moderate doses oestrogen stimulates the release of LH (Fig. 81.12).

FSH stimulates ovary → ovary secretes oestrogen → oestrogen stimulates the release of FSH → LH → ovary secretes large amounts of oestrogen → rising level of oestrogen stimulates the release of FSH → LH → occurrence of ovulation—development of corpora lutea begins and corpus luteum secretes progesterone and oestrogen (LTH is elicited in some species).

FERTILIZATION

If spermatozoa are recently deposited in the genital tract then fertilization of ovum occurs usually at the ampullary-isthmic junction of the fallopian tube. The penetration of the ovum by the sperm is brought about by the lysosomal enzymes present in the acrosome of the sperm. Only one sperm is allowed to penetrate the ovum. Once the ovum is fertilized, it causes a barrier for other sperms. After fertilization blastocyst, the developing embryo is formed and moves down the uterine tube into the uterus for implantation (Fig. 81.8).

IMPLANTATION

1. Implantation or uterine attachment of the blastocyst presumably occurs between 7th and 9th days after ovulation. It is believed that the penetration and erosion of epithelial cells of the uterine mucosa necessary for implantation result from combined effects of proteolytic enzymes which are produced by the trophoblast and by vascular changes in the endometrium (Fig. 81.9).
2. Progesterone increases the concentration of carbonic anhydrase in endometrium, particularly in the area surrounding the capillary. This tends in the transfer of bicarbonate from the blastocysts to the maternal circulation, causing alkalinity by conversion of bicarbonate to carbonate.
3. This alkalinity favors adhesion to and dissociation of the uterine epithelium so as to permit penetration by the blastocyst.
4. Once the blastocyst comes in contact with the endometrium, it becomes surrounded by an outer layer of syncytiotrophoblast, and by an inner layer of cytotrophoblast. The blastocyst then makes it space within the endometrium through the process of erosion by the syncytiotrophoblast and a placenta is gradually developed.

Adolf Friedrich Johann Butenandt was a German biochemist and Nobel laureate who was awarded the Nobel Prize in Chemistry for his research of sex hormones. He discovered the hormone estrone from the secretions from ovaries responsible for the sexual development of females. He was also the first to isolate the male hormone androsterone. The Nobel Prize in Chemistry of 1939 was divided equally between Adolf Friedrich Johann Butenandt and Leopold Ruzicka for their similar work on sex hormones.

Adolf Friedrich Johann Butenandt
1903–1995

Leopold Ruzicka
1887–1976

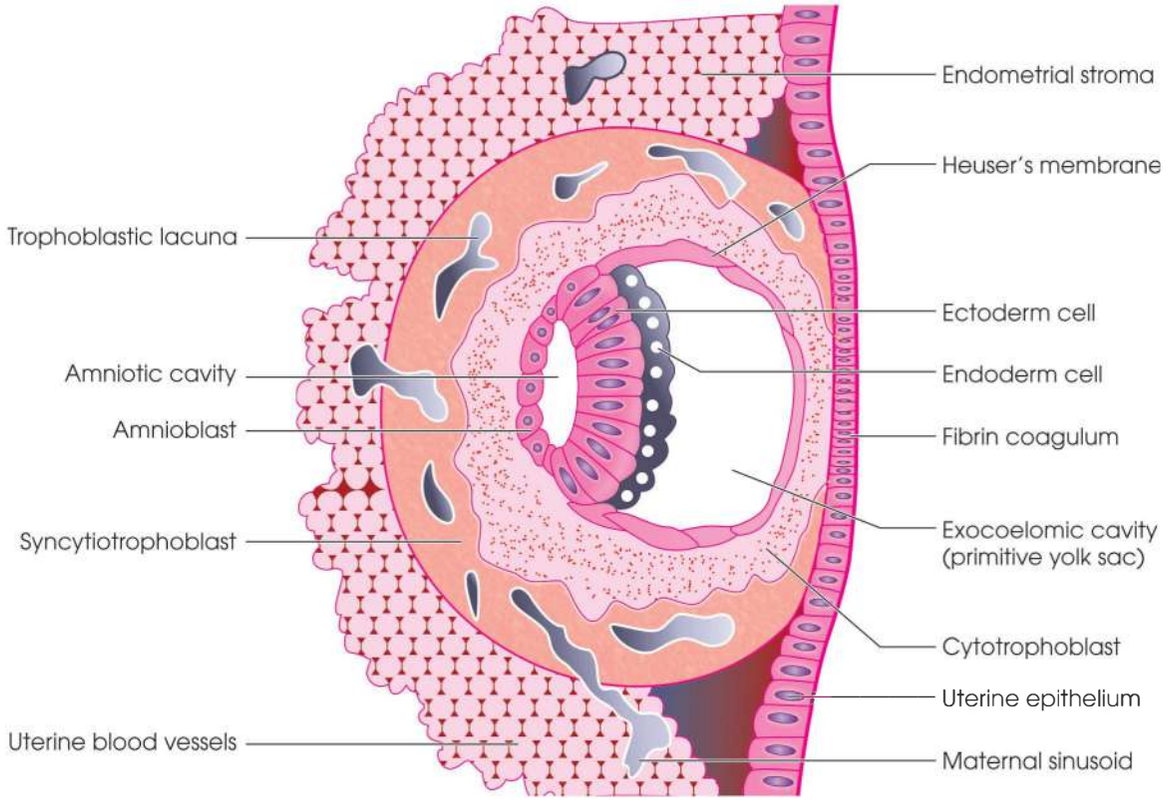


Fig. 81.9: Diagrammatic representation of a 9- to 12-day blastocyst after implantation to show developing ectoderm, entoderm, layers of the trophoblast, beginning of the uteroplacental circulation, etc. Note flat mesothelial cells which have delaminated from the inner surface of the cytotrophoblast to form Heuser's membrane. Amniotic cavity is well delineated and original uterine surface defect is closed by a fibrin coagulum

Applied physiology: Abnormal implantation: When the blastocyst implants abnormally in close proximity to the cervical internal as, this condition is known as placenta previa which causes severe bleeding in the latter part of pregnancy and during delivery. When implantation occurs in uterine tube, this condition is known as tubal pregnancy, which is dangerous because it causes severe internal haemorrhage, rupture of the tube and death of the embryo during the 2nd or 3rd month of pregnancy. However, implantations outside the uterus are known as ectopic or extrauterine pregnancies.

Ovarian Cycle: Brief Summary

1. The ovarian cycle, in brief, is that at puberty, under the influence of the pituitary gonadotrophins, the follicles start to grow regularly, release ova and form corpora lutea.
2. The first ovum is probably shed at about the time of the first menstrual period, but regular ovulation is not commonly established until the age of 16 or 17 years.
3. The adult ovary goes through a recurrent cyclical process which results in ovulation and menstruation and occupies about 28 days.
4. The cycle starts on the first day of the menstruation, and consists of two phases: the follicular phage during which ovum ripens and discharges; this lasts about 14 days and is followed by (2) the luteal phase.
5. Ovulation takes place normally between 13th and 17th days of the cycle and separates the two phases (Fig. 81.10).
6. The regularity of the cycle is usually controlled by the time of ovulation. Menstrual bleeding occurs 14 days after this event unless fertilization takes place.

Ovulation: Applied Comparative Physiology

Certain species have one or two oestrous cycles per year, at which time ovulation and receptivity to the male coincide with the male's sexual interest in the female. In rabbits, ferrets and cats, ovulation is the result of a compound neuroendocrine reflex which is initiated by the intravaginal tactile stimulation and involves the secretion of pituitary LH. Only primate's posse's menstrual periods, others have oestrous cycles. In some species, viz. baboon, the sexual skin provides an interesting and colorful exterior indication of waning and waxing of the sex cycle. The central stimulus to ovulation is affected to only a minor degree by environmental stimuli, being primarily regulated by an internal hormone cycle mediated by a hypothalamic clock of characteristic frequency 4–6 days in rat and mouse, 14 days in guinea-pig, 16 days in sheep, 20 days in cow, 21 days in sow, 27 days in macacus monkey, 28 days in women, 36 days in chimpanzee, 2 cycles a year in bitch, and 1 cycle per year in bat and marmot.

Applied Clinical Physiology: Drugs inhibiting Ovulation

Ovulation can be inhibited by both progesterone and testosterone, but synthetic compounds, e.g. norethindrone (Norlutin) and norethinodrel (Enovid) are extremely effective

and produce fewer undesirable side effects. Gemzell has used gonadotrophin mixtures in the management of infertility due to ovulation failure. Clomiphene has also proved to be effective in inducing ovulation in women with a history of infertility and works by cancelling out inhibitory influences which acts upon the GRF (gonadotrophin-releasing factor) complex in the hypothalamus.

FATE OF GRAAFIAN FOLLICLES

The follicles have four fates:

1. Before puberty—maturation is incomplete. The ovum dies and is phagocytosed by the granulosa cells. The follicles thus become transformed into fibrous scars. Even during active sex life large numbers of follicles undergo this fate.
2. Between puberty and menopause—about 400–500 follicles undergo complete maturation and ovulation.
3. After ovulation—corpus luteum grows on the ruins of the ruptured follicles.
4. After menopause—all the remaining follicles degenerate.

Functioning of Graafian or Vesicular Follicle

Forms mature ova.

1. Secretes oestrogen (oestradiol).
2. Provides a medium for the growth of corpus luteum.

Atretic Follicles

If the graafian follicle instead of going on to ovulation degenerates, there is death to the ovum being replaced by a ring of hypertrophied thecal cells. Such follicles are called atretic follicles.

Life History of Corpus Luteum

Formation and Histology

1. Corpus luteum grows on the remains of the ruptured follicles.
2. When ovulation occurs, there is sudden release of tension which causes rupture of blood vessels in the tunica vasculosa, leading to haemorrhage in the cavity of the follicle.
3. A blood clot forms at the site of the ruptured follicle; forming what is known as corpus haemorrhagica.
4. Granulosa cells and the stroma cells from the tunica vasculosa rapidly multiply and fill up the cavity, forming the corpus luteum. The cells enlarge and the fully formed corpus luteum is found to consist of columns of large conical cells with distinct nucleus and yellowish pigment granules—the lutein (Fig. 81.10). These granules represent the internal secretion of gland.
5. The corpus luteum attains its maximum size on the 19th day of menstrual cycle. In absence of pregnancy,

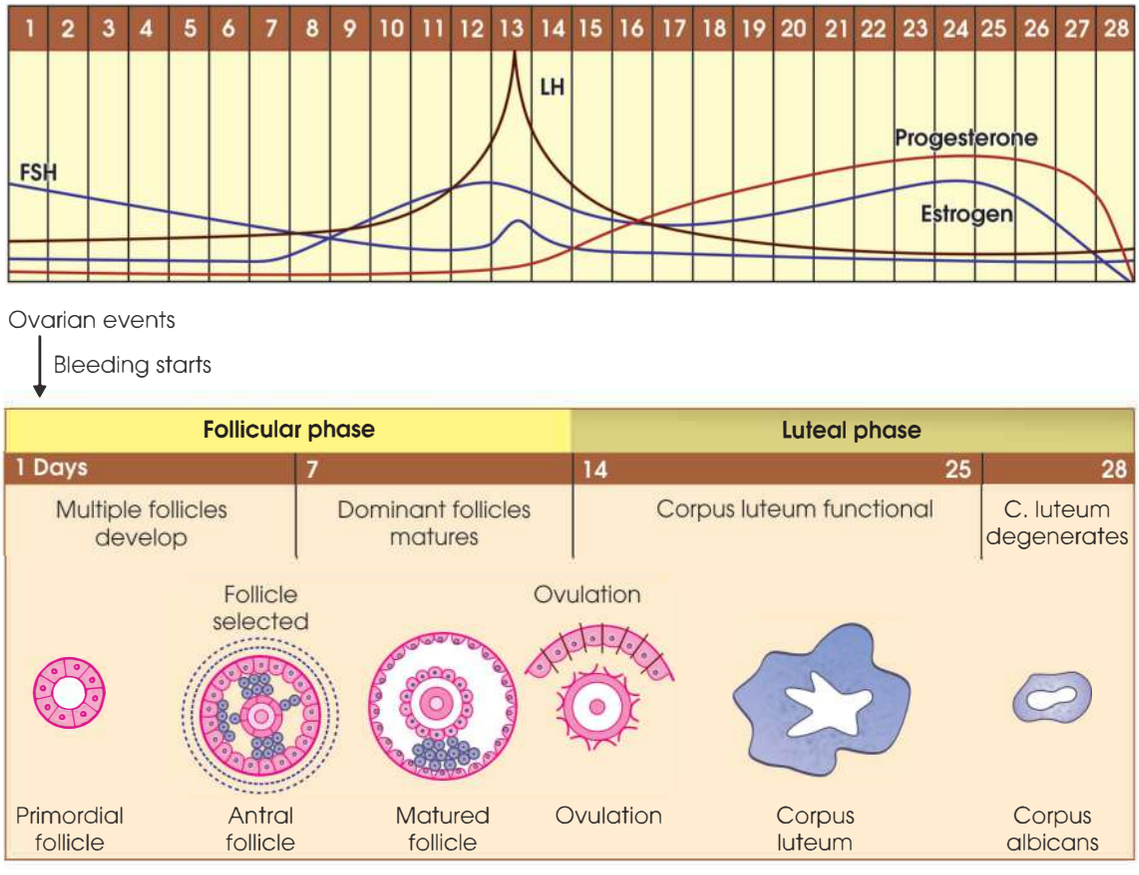


Fig. 81.10: Diagrammatic representation of ovarian cycle and associated hormonal secretion

it begins to degenerates 4 days before next cycle (that is 24 days of cycle), when menstruation begins. This corpus luteum is called the corpus luteum of menstruation or the false corpus luteum.

6. The degeneration takes place rapidly due to fatty infiltration and many of the cells are removed producing an appearance of a white fibrous structure, which is aptly termed corpus albicans. This structure atrophies, and after several months sinks deep within the stroma of the ovary as a tiny scar, called the corpus fibrosum.
7. If pregnancy takes place, the corpus luteum continues to grow attaining its largest size about the 3rd or 4th month. It degenerates in the latter months forming a fibrous scar (Fig. 81.12). This is called the corpus luteum of pregnancy or the true corpus luteum.

Maintenance of Corpus Luteum (Fig. 81.11)

The growth and secretion of corpus luteum is controlled by (i) LH of anterior pituitary and (ii) placental gonadotrophins. This is an additional but essential stimulus for continued growth of corpus luteum during pregnancy.

Key Points

1. The corpus luteum is essential for the maintenance of pregnancy, at least during the first trimester (about 90 days) of human gestation. An important factor in the functional persistence of the corpus luteum in human pregnancy is the production and secretion of chorionic gonadotrophin by the chorion cells of the placenta.
2. The corpus luteum at the earliest stage of human pregnancy provides oestrogen for the growth of the uterus and progesterone. Progesterone probably possesses a relaxing effect upon the uterus, which suppresses contraction. After the first trimester, the production of oestrogen and progesterone is taken over by the placenta itself.
3. For implantation to occur, migration of the blastocyst down the fallopian tube should be integrated with the development of the uterine endometrium and the activity of the myometrium. Tubal migration of

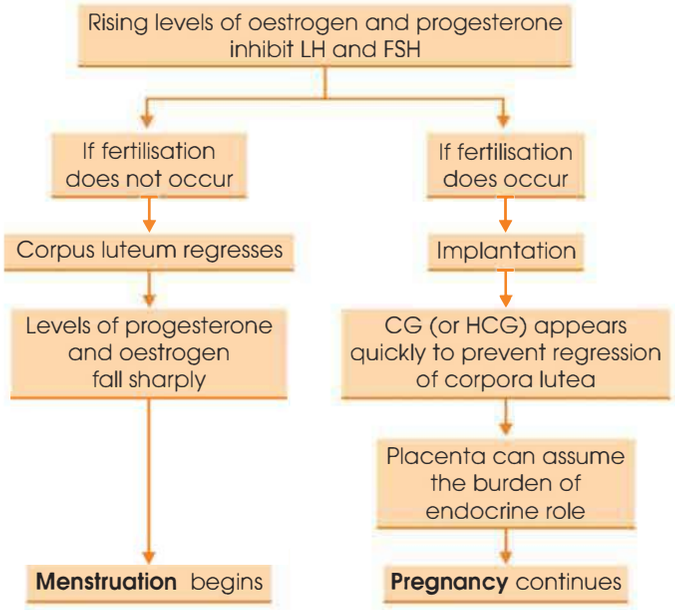


Fig. 81.12: Summarised representation of hormonal control of ovulation, menstruation and pregnancy

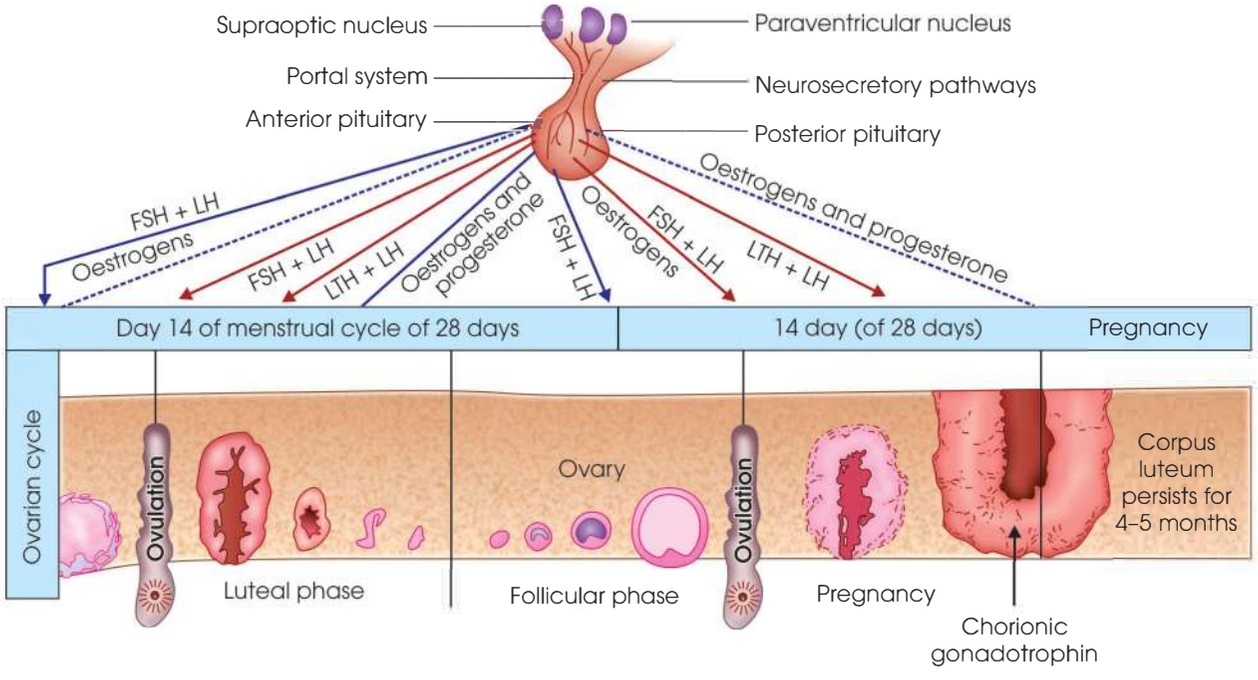


Fig. 81.11: Diagram shows female reproductive cycle

blastocyst is influenced by oestrogens and both oestrogens and progesterone are necessary for the development of secretory endometrium.

4. After implantation, continued secretion of progesterone is necessary for maintenance of the established pregnancy. Progesterone secretion originating at first from the corpus luteum has a functional life of 8–10 weeks during early pregnancy. Progesterone secretion shows an initial rise and a transient fall with the decline of function of the corpus luteum after the first few weeks of pregnancy and then rises again as the placental secretion of progesterone becomes established.

Applied Comparative Physiology: Lysis of the corpus luteum by a luteolytic factor

In some animal species, a specific internal secretion from the uterine mucosa is responsible for shortening the life of the corpus luteum in absence of implantation of a fertilized ovum of ova. When the uterus is under progesterone stimulus, the uterus may produce a luteolytic substance which causes luteal regression in absence of an embryo. Oestrogen may depress the luteolytic stimulus. It has been observed that granulosa cells from some ovaries at the preoestrous stage possess the existence of such, a uterine luteolytic factor.

Hypophyseal and Other Factors in Luteolysis

Luteolysis is considered to be functional and structural processes. Functional luteolysis decreases the secretion of progesterone in blood, coinciding with an increase in the 20α-steroid dehydrogenase. This enzyme makes a substantial decrease in the activity of progesterone by converting 20-keto group to 20α-hydroxyl. When progesterone level falls, pituitary LH is released, 20α-hydroxy derivative of progesterone increases and there is occurrence of luteolysis.

Structural luteolysis is morphologic regression of the corpus luteum. In the laboratory rat, hypophysectomy leads to functional luteolysis, but retards structural luteolysis.

Functions: Corpus luteum secrets oestrogen and progesterone which are essential for gestation and many other changes associated with pregnancy.

OESTROGENS

Definition

Oestrogens are compounds which can produce oestrus in ovariectomised animals.

Types

They are of two types: Synthetic and natural.

Synthetic Oestrogens

Several have been synthesised (Fig. 81.13). They are benzanthracene compounds and are not sterols. They are effective by mouth (not destroyed by liver). Important members known in this group are diethy stilboestrol and hexoestrol. Ethinyl oestradiol is another, synthetic oestrogen which is a modified form of oestradiol.

Natural Oestrogens

Chemistry

They are all sterol derivatives. They are less effective by mouth. Their structures (Fig. 81.14) are as follows:

Varieties

1. **Oestradiol** (with –OH at the 17C position): It is the hormone secreted by the ovary.
2. **Oestrone** (with –O at the 17C position): It is the possible circulating hormone.
3. **Oestriol** (with –OH at the 17C position and additional OH at the 16C position): It is found in adult female urine and increased during pregnancy, is also liberated from placenta. They are believed to be

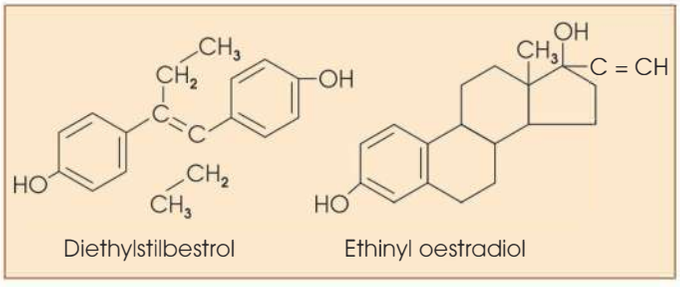


Fig. 81.13: Chemical structures of synthetic oestrogens

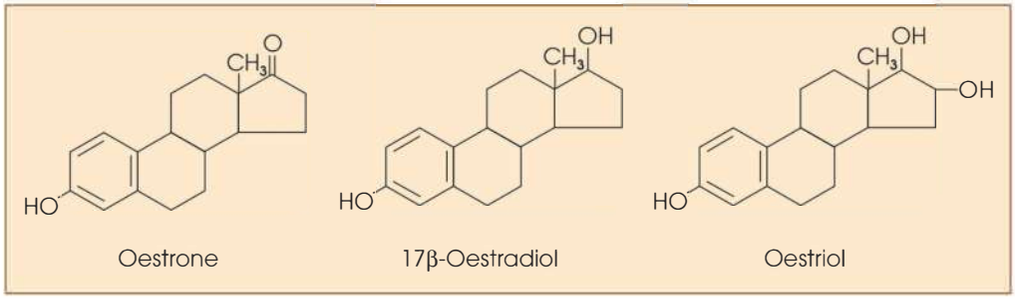


Fig. 81.14: Structural formulae of naturally occurring oestrogens

derivatives of oestradiol and are excreted in the urine as glucuronates. Increased excretion or oestriol occurs after administration of oestradiol or oestrone. There is close relationship between oestradiol, oestrone and oestriol in the body such as oestradiol → oestrone → oestriol.

Sources

1. **Ovary is the chief source**
   a. *From the graafian follicles:* The liquor folliculi and the follicular epithelium are rich in oestrogens. Histological and histochemical evidence supports the view that the primary source is the theca interna of the follicle. As the follicle matures oestrogen secretion increases maximum being at the time of ovulation.
   b. *From the ovarian interstitial cell:* These cells also seem to secrete oestrogen. Though the follicles may be destroyed by deep X-ray or radium, yet the ovaries secrete oestrogens and the animals get normal oestrus.
   c. The oestrogen secreted during the luteal phase of the cycle is formed by the theca-lutein cells of the corpus luteum.
2. **Adrenal cortex:** Oestrogen also secreted from adrenal cortex.
3. **Testes:** Small amounts of oestrogens have been extracted from testes, being locally synthesised.

Applied Comparative Physiology

Ovary and hormone secretion

Placenta: In cow and many other mammalian species it is the principal source of oestrogens during pregnancy.

Plants: Oestrogenic activity has been noted in about 50 species of plants. In some the amount is sufficient to cause reproductive abnormality in grazing animals.

Distribution

In addition to the above sources, oestrogens are widely distributed in animal tissues. They are found in the blood, muscles, urine of both pregnant and non-pregnant females and in the urine of adult males. The urine of stallions has very high oestrogen content and is one of the richest known sources. Small amounts have also been obtained from spermatozoa.

International unit

International unit for oestrone is defined as the activity of 0.1 µl of standard oestrone preparation; for oestradiol, as the activity of 0.1 µl of standard oestradiol preparation.

Synthesis of Oestrogens

1. The naturally occurring oestrogens are secreted by the theca interna cells of the ovarian follicles, by the corpus luteum, by the placenta, and in less amounts by the testis and adrenal cortex.
2. The ovarian stromal tissue also has the potential to make androgens and oestrogens, but they do so in negligible amounts in normal premenopausal women.
3. The first half of the menstrual cycle, or the follicular phase, is concerned primarily with secretion of oestrogens.
4. The rise in the progesterone occurs in the second, or luteal, phase due mostly to the formation of a corpus luteum. These patterns of steroidogenesis agree with the concept that oestrogens are largely secretory products of the theca-internal cells, and progesterone is secreted largely from granulosa cells of late follicle phase, about midcycle, and from cells of the corpus luteum derived from granulosa cells.
5. The principal reactions that occur in the transformation of 5-pregnenolone to progesterone and other progestational compounds, and, via androgens, to oestrogens are represented in Fig. 81.15.
   a. In the theca cells oestrogen production is for the most part through pregnenolone. The granulosa cells of the follicle first prior to ovulation and the corpus luteum after ovulation have an active series of enzymes for the conversion of 5-pregnenolone to progesterone, and thus progesterone is a chief secretory product. 17α-hydroxy progesterone is secreted to a lesser extent. A more limited conversion of progestin's to oestrogens occurs in these cells.
   b. Formation of progesterone from 5-pregnenolone involves hydrogen removal from 3-hydroxyl group of 5-pregnenolone by 3β-hydroxysteroid dehydrogenase, which utilizes NAD as a hydrogen acceptor. NADH is reoxidised by mitochondria and also probably by extra-mitochondrial lactic dehydrogenase in which pyruvate is reduced to lactate.
   c. The oxidation process of 3-hydroxyl by 3β-hydroxysteroid dehydrogenase is followed by shifting double bond from 5 position to 4 position catalyzed by an enzyme complex (δ5–4 isomerase). 5-pregnenolone and progesterone can be hydroxylated in the 17α-position forming the corresponding 17α-hydroxysteroid.
   d. A desmolase enzyme is able to cleave 17α-side chain of pregnenolone of progesterone to give either DHEA or 4-androstenedione respectively. Androstenedione is converted to oestrone by aromatization.
   e. Before DHEA is aromatized to oestrogen, DHEA is converted to its 5-androstene-3, 17-dione (3-keto derivative) by enzyme δ5, 3β-hydroxysteroid dehydrogenate (3β-hydroxysteroid dehydrogenase). However there is a separate enzyme δ5, 3-ketosteroid isomerase for the conversion of 5-androstenedione –3, 17 to 4-androstenedione.

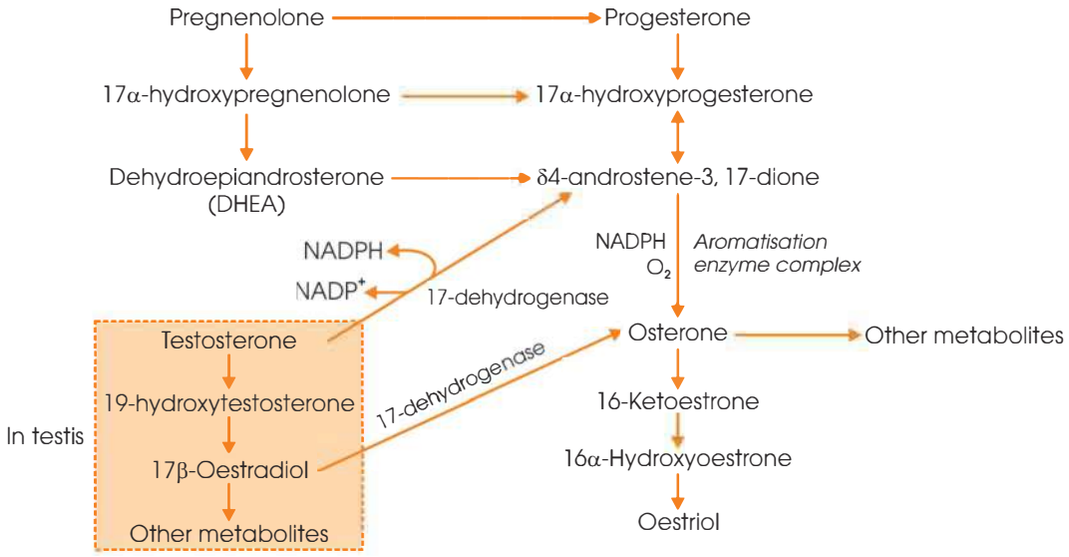


Fig. 81.15: Schematic representation of biosynthesis and metabolism of oestrogens

f. Aromatisation of androgens to oestrogens occurs greatly in the microsomes of the cell and also requires NADPH and molecular O_2. A 17-dehydrogenase enzyme can lead to an inter conversion of androstenedione and testosterone and the inter conversion of oestrone and oestradiol.

Metabolism and Excretion

1. The major secreted oestrogen, 17α-oestradiol, is in equilibrium in circulation with oestrone. Oestrone is again metabolized to oestriol probably in large amounts in the liver.
2. Oestradiol is the most potent oestrogen of the three and oestriol the least. About 60–70% of the circulating oestrogens are protein-bound. The rate of secretion ranges from 200 to 500 µg/day in women at the time of ovulation (in males, oestrogen-secretion rate is about 50 µg/day.)
3. Oestrogens are secreted throughout the menstrual cycle, but there are two peak times, one at the time of ovulation and the other during midluteal phase.
4. These are then destroyed in the liver being transformed into other products or are inactivated by conjugation with sulphates and glucuronates, in which form they are found in the urine. Traces may be found in un-combined form. Appreciable amounts are secreted in the bile and reabsorbed into the blood stream (enterohepatic circulation)
5. During menstrual cycle—oestrogen excretion starts rising from the resting phase and becomes maximum at the time of ovulation (14th day) and then falls (Fig. 81.11).
6. During pregnancy—excretion starts rising from the first week and reaches the maximum just before the onset of parturition. After delivery it falls but traces may still be found in the free uncombined form.

Mechanism of Action of Oestrogens

Oestrogen is bound to specific nuclear receptor proteins in the cells. These proteins act to increase RNA synthesis there. The two types of oestrogen receptors are present ERα on uterus and ERβ is present on ovaries. Most of the action are via mRNA and some actions are also mediated via second messenger mechanism which are mostly G protein-coupled receptors.

Actions of Oestrogen

In general, oestrogen stimulates the development and maintains morphological and functional state of the female reproductive system and secondary sexual characteristics. Oestrogen also contributes to the regulation of nitrogen and electrolyte metabolism, capillary reactivity, water balance, bone metabolism, etc. In the following discussion the general term oestrogen is used.

1. *On Ovary*

Physiological levels of oestrogen promote the pituitary release of LH. As a new crop of follicles begins to grow during and just after menstruation, the theca interna either spontaneously or in response to a constant low level of LH begins to secrete small amounts of oestrogen. The oestrogen can then act to increase LH release which in turn further increases oestrogen secretion in the first half of the menstrual cycle. Cyclic re-enforcing mechanism acts to promote oestrogen secretion and LH release. The increasing oestrogen will, by increasing LH release, progressively establish LH. Oestrogen has a direct stimulatory effect on follicle growth.

2. *On Fallopian Tube*

Oestrogen stimulates the epithelium and musculature of the fallopian tubes. Oestrogen promotes the motility

of the uterine tube, an activity which may play an important role in sperm transport.

3. *On Uterus*

In the absence of ovary, the uterus of the preadolescent remains infantile and that of the adult undergoes atrophy; an administration of oestrogen restores and maintains the adult morphology and functional activity. Oestrogen produces effects on the endometrium—increase in size and weight, increase in cell number, changes from the cuboidal to columnar type of epithelium, growth stimulation of uterine glands marked increase in water content, increase in vascularity, increase in protein content, and increase in alkaline phosphatase. Oestrogen has physiologic effects on the myometrium.

Oestrogen also stimulates the activity of uterine muscle—an increase in motility. Thus, in the human menstrual cycle one can correlate the stages of increased uterine motility with oestrogen titers. Oestrogen increases the sensitivity of the myometrium to oxytocin. Uterine threshold to oxytocin is lower in the follicular phase than the luteal stage of the cycle. Human uterus shows a progressive increase in response to oxytocin from mid gestation on to term.

4. *On Cervix*

Under the influence of increasing oestrogen levels during proliferative stage the mucus which is secreted by the cervical glands becomes more acidophilic and thinner, and approaches its lowest viscosity at ovulation. These changes may promote sperm survival and transport.

5. *On Vagina*

Oestrogen is responsible for vaginal enlargement to adult size which begins during adolescence. It is observed with oestrogen administration or with elevated endogenous oestrogen titers during follicular stage there occur proliferation (increased mitoses) and stratification (increased number of layers) of the vaginal epithelium, with subsequent cornification. This is a reliable index of oestrogenic function. Oestrogen stimulates glycogen and mucopolysaccharide deposition in squamous epithelial cells. The eventual conversion of this glycogen to lactic acid accounts for the pH—lowering effects of oestrogen on the vagina (pH = 4.5).

6. *On Mammary Glands*

Oestrogen hypertrophies the mammary glands at puberty including areolar development and pigmentation. Oestrogen primarily stimulates duct growth and has little effect on lobular alveolar system in the human female. Normal mammary growth requires the action of both oestrogen and progesterone. High doses of oestrogen inhibit pituitary prolactin secretion and oestrogen is used to prevent lactation and to dry her breast in recent parturient if breastfeeding is contraindicated, or not desired.

7. *On Secondary Sexual Characteristics*

Oestrogen is responsible for the development of the female secondary sexual characteristics that distinguish females from males.

8. *On Electrolyte and Water Metabolism*

Salt and water retention correlates with great rise of oestrogen titre at midcycle and with the luteal rise in oestrogen. It is observed in dogs and in human beings that an administration of oestrogen results in sodium and chloride retention, decreased urinary volume, increased extracellular fluid and blood volume, decreased RBC with Hb, and increased body weight. Effect of oestrogen on fluid and electrolyte balance is complicated by some oestrogen–adrenocorticosteroid interrelationships. In the humans, oestrogen has no influence on aldosterone secretion, but it retards metabolic degradation, increase plasma-protein blinding and decreases secretion of cortisol.

9. *Other Effects*

Oestrogen promotes protein metabolism and affects morphogenesis of the skeleton. Oophorectomy (loss of oestrogen) abolishes mating response and other sexual behavior patterns. Oestrogen may elevate the mitotic index of a number of tissues.

10. *Carcinogenesis*

Along with pronounced growth effects on accessory sex tissues, oestrogen has growth effects on other tissues also. This effect is due to stimulated cell division. This is correlated with the hypothesis that high rate of cell division predisposes a tissue to become cancerous. It has also been noted that some synthetic carcinogens are similar to oestrogen in chemical nature and can also cause typical oestrous changes in experimental animals.

On the basis of above actions on different biological processes, the physiological functions of oestrogens are described as follows:

Responsible for all the puberty changes; Such as (a) growth of uterus, vagina, stratification of vaginal epithelium; (b) increased contractility, secretion and ciliary movement of the fallopian tube; (c) development of breasts chiefly by proliferation of ducts; (d) menstrual changes (vide below); (e) appearance of secondary sex characters.

Functions of Oestrogen

1. **It is responsible for the proliferative stage of menstruation.**

2. **It causes growth of uterus during pregnancy:** The enormous growth of uterus is believed to be due to oestrogens aided by the mechanical stimulus of the growing embryo.
3. **Exerts synergistic action with oxytocin (causes onset of parturition):** It has been shown that oestrogens increase the sensitiveness of the uterine musculature to the action of oxytocin while progesterone depresses it. At full term, progesterone level falls. But oestrogen level still remains high. This enhances oxytocin effect and thus parturition starts.
4. **Oestrogen and progesterone often act synergistically,** viz.
   i. Menstrual changes: Progesterone can cause the premenstrual changes in the endometrium only after the proliferative changers has been already done by oestrogen. Progesterone alone will have no effect.
   ii. Breast formation: Glandular (lobulo-alveolar) development of breasts, as seen during pregnancy, only occurs by their combined action.
   iii. They may antagonists: In large doses, oestrogen antagonizes the actions of progesterone and prevents the progestational changes in the uterine mucosa.
5. Oestrogen is also necessary for the **maintenance of** pregnancy.
6. **Inhibits the secretion of anterior pituitary:** Particularly the FSH. In this way, anterior pituitary and ovaries maintain a reciprocal relationship. Due to this inhibitory action, administration of large doses of oestrogens may cause atrophy of the ovaries, arrest menstruation and produce sterility. Oestrogens have no direct action on the gonads. They work by inhibiting the follicle-stimulating hormone (FSH) of anterior pituitary.
7. **Inhibits thymus:** Oestrogens depress thymus and causes its involution at puberty.
8. **Exerts synergistic action with androgen:** In males oestrogen in physiological dosage acts synergistically with androgen and helps in the development of secondary sexual characters.
9. **Stimulates oestrus** in female animals.
10. **Stimulates the secretion of ACTH from anterior pituitary** and causes hypertrophy of adrenal cortex.
11. **May help water balance:** Administration of oestrogens causes water sodium and chloride retention, increase of blood volume and of the water content of muscles. Oophorectomy, on the other hand, causes loss of water and diminishes blood volume. They are all restored to normal by administration of oestrogens.
12. **Effect on protein synthesis:** Oestrogens increase total body protein as indicated by positive nitrogen balance. The effect is however much less than that of testosterone.
13. **Effect on bone growth:** Oestrogen induces positive calcium balance and thus increases skeletal growth. However, oestrogen (like androgen) hastens closure of epiphysis and thus stops growth.
14. **Effect on fat deposition:** Oestrogens cause increased deposition of fat in subcutaneous tissue and also in other particular regions to make a typical feminine body.
15. **Effect on cholesterol metabolism:** Possibly by its action on lipoproteins, oestrogens lower plasma cholesterol level.
16. **Secondary sexual characteristics:** The oestrogens are responsible for the development of the female secondary sexual characteristics that distinguish the female from the male, e.g. formation of narrow shoulders, broad hips thighs that converge, etc. the larynx retains its prepuberal proportions and voice stays high-pitched; there is less body hair and more scalp hair, etc. High levels of testosterone-oestrogen-binding globulin (TEBG) in the blood stream, as occurs naturally in women, are associated with scant body hair. TEBG inactivates the hormones responsible for stimulating hair follicles. Large doses of oestrogens slow sexual hair growth in many hairy women; can now, be viewed as the result of a concomitant increase in TEBG.

Applied Clinical Physiology

1. **Acne:** Oestrogens are said to move sebaceous gland secretions more fluid and thus inhibit formation of comedones (black heads) and acne. It is observed that oestrogens appear to aggravate the conditions of acne, excessive oiliness of the skin, and to modify the rate of sexual hair growth (hirsutism). Prolonged administration of large doses of oestrogns in women increases in plasma-testosterone concentration. It is believed that oestrogens may cause alternations in the peripheral metabolism by decreasing the metabolic clearance rates of testosterone.
2. **Carcinoma of breast:** For several decades, many investigators contended that oestrogens induced breast cancer. But lately the cause was attributed to Prolactin. Oestrogns stimulate prolactin secretion and mammary development only in the presence of the pituitary gland. Injections of prolactin contributed in the rate of tumor growth in rats with breast cancer. On the other hand, oestrogens failed to maintain tumor growth after Hypophysectomy. On this basis the temporary regression observed in human breast malignancies after hypophysectomy may be explained as resulting from

lack of prolactin. Large doses of oestrogens produce comparable benefits in controlling breast cancer is attributed to interference with tumor—stimulating potential of prolactin at level of target tissues.

PROGESTERONE

Progesterone is the active principle of corpus luteum.

Sources

1. Corpus luteum,
2. Placenta, adrenal cortex.

Varieties and Chemistry

1. Natural
2. Synthetic

Natural: Called progesterone—it is a sterol derivative with a side chain at the 17C position. Its structure is shown in Fig. 81.16. It is found in two crystalline forms, e.g., α and β.

Synthetic: Progesterone is comparatively ineffective by mouth. Synthetic, i.e. progestational agents (Fig. 81.17) who are effective orally have been formulated. Important members of these are ethisterone, 19-norprogesterone, A-norprogesterone, 6α-methyl-17α-acetoxyprogesterone. These compounds, as they inhibit ovulation are also used as oral antifertility agents.

International unit for progesterone is equal to one mg of the standard preparation.

Synthesis of Progesterone

1. Progesterone is secreted by the corpus luteum and the placenta. Secreted progesterone is possibly bound to protein. The de novo synthesis of progesterone from cholesterol by the placenta is important to the maintenance of human pregnancy after first trimester when ovarian function declines.
2. The placenta has enzymes for the synthesis of cholesterol from acetate and for the production of 5-pregnenolone from cholesterol. The formation of 5-pregnenolone may occur largely in the mitochondria and involves hydroxylation's at 20 and 22 positions of cholesterol side chain, followed by a cleavage of the side chin between 20 and 22 positions by a desmolase enzyme.
3. The formation of progesterone from 5-pregnenolone involves, the removal of hydrogen from 3-hydroxyl by 3α-hydroxysteroid dehydrogenase utilizing NAD as hydrogen acceptor and a shift of double bond from 5 to 4 position by 5,4-isomerase enzyme.
4. 17α-hydroxyprogesterone is obviously secreted along with oestrogen from ovarian follicles.
5. In the corpus luteum, 20α- and 20α-hydroxyl derivatives of progesterone are formed. Progesterone is an essential intermediate in the steroid biosynthesis in

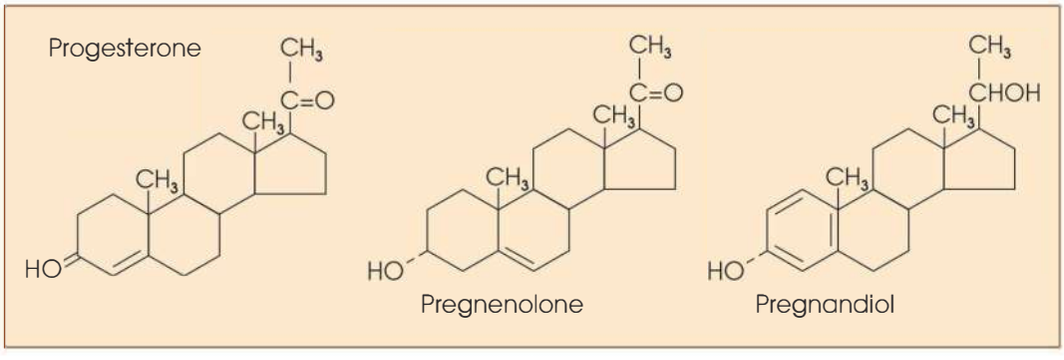


Fig. 81.16: Chemical formulae of naturally occurring progesterone

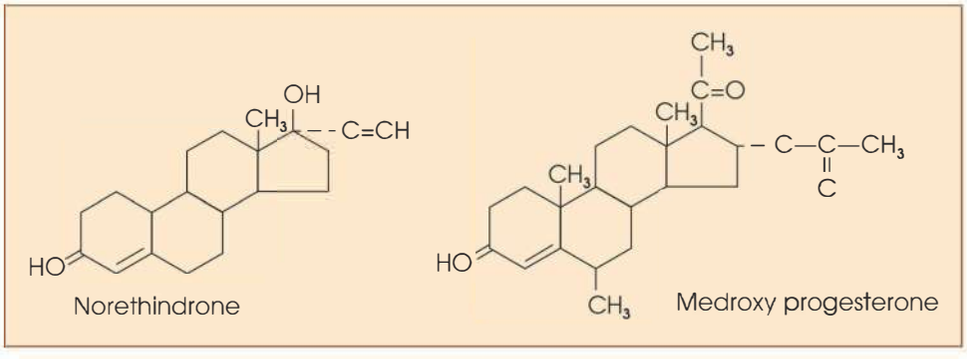


Fig. 81.17: Chemical formulae of some orally active synthetic progestin (21C position)

those tissues which secrete steroids and small quantities leak into the general circulation from the testis and adrenal cortex.

Metabolism and Excretion

1. Small quantities of progesterone are found in blood and urine.
2. During the metabolic processes progesterone gets reduced into an inactive derivative known as pregnanediol.
3. It is conjugated with glucuronic acid and sodium in the liver and appears in the urine as sodium-pregnanediol-20-glucuronide (Fig. 81.18).
4. It appears in the urine in the luteal phase of menstruation but not in the follicular phase. The excretion starts one or two days after ovulation (i.e. when corpus luteum has formed) becomes maximum about a week before the onset of menstruation and ceases 2–3 days before the period comes.
5. During pregnancy much larger quantities are excreted, the amount being maximum (about eight fold) during the eighth and ninth months.
6. It falls before parturition. Its presence in the urine is regarded as an index of progesterone secretion.

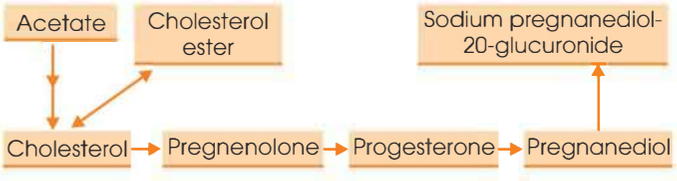


Fig. 81.18: Scheme showing biosynthetic and major metabolic pathways of progesterone

Mechanism of Action

Progesterone act on the nuclear receptor and increased gene transcription brings which influences the physiological functioning.

Action of Progesterone

Actions of progesterone are normally effective only when the uterus has been under the acting influence of oestrogens.

1. *On Uterus*

a. Following oestrogen-primed uterus, progesterone stimulates development, growth and activity of the endometrial secretory glands causing a thickening of the mucosa and continued water accumulation. Glands become highly developed and active, and a marked increase in glycogen deposition occurs. Glycogen droplets may be found in glandular cells. Higher secretory mucosa provides nutrients necessary for implanted blastocyst. Spiral arteries become slightly enlarged and tightly coiled. The endometrium becomes highly convoluted. If fertilization and implantation (nidation) occur, the corpus luteum, under the stimulation of CG, continues to secrete progesterone and oestrogen to maintain the gravid type of endometrium.

b. Progesterone diminishes spontaneous myometrial activity. The progesterone-dominated uterus will not conduct an excitation wave and so such a uterus could not participate in the organized contractions necessary for expulsion of the fetus.

c. Progesterone lowers and may block the sensitivity of the uterus to oxytocin. Progesterone in appropriate amounts inhibits oestrogen-induced sensitization to oxytocin.

2. *On Ovary*

The effect of progesterone on the ovary is indirect through alteration in pituitary gonadotrophin release. It is known that oestrogen and progesterone in combination can block gonadotrophin release.

3. *On Fallopian Tube*

Progesterone may be responsible for diminished muscular activity during luteal stage.

4. *On Cervix*

The cervical mucus is reduced in amount and becomes more viscous during luteal phase under the influence of progesterone.

5. *On Vagina*

Progesterone induces cellular proliferation and increased mucous secretion of the vaginal epithelium. Cornified cells are reduced in number. Vaginal smear shows a few cornified cells, various leucocytes and clumped epithelial cells having folded edges.

6. *On Mammary Glands*

Progesterone stimulates mainly lobuloalveolar growth following oestrogen action.

7. *On Kidneys*

Large dosages of progesterone produce natriuresis, presumably by blocking action of aldosterone on the kidney.

8. *On DNA*

Progesterone does not possess a significant anabolic effect. At least, some of its effects are owing to an action on DNA to make synthesis of new mRNA.

Progesterone is responsible for a rise of 0.5 to 1.0°C in the basal (waking) temperature of the body after ovulation and through the luteal phase of the cycle. On the basis of above actions, the physiological functions of progesterone are described as follows.

Functions of Progesterone

1. Progesterone is essential for the *maintenance of pregnancy* and various other changes associated with it. It also takes part in menstruation. Its functions are briefly summarised below.
2. *Responsible for premenstrual changes of uterine mucosa and takes an essential part in pregnancy, for instance:* Embedding of ovum.
3. Progesterone desensitizes the *uterine muscle* to the action of oxytocin.

   This is important for the following:

   a. During menstruation corpus luteum degenerates, progesterone is absent, oxytocin works unopposed and uterine muscle powerfully contracts. This helps to expel the menstrual discharge.

   b. During pregnancy progesterone secreted by the corpus luteum and placenta neutralizes oxytocin action, uterine contraction absolutely ceases and the growth of uterus is facilitated.

   c. At full term corpus luteum dies and placenta also degenerates to some extent. Hence, progesterone secretion falls. Oxytocin acts unopposed and parturition starts.
4. *Development of breasts:* Breasts develop further during pregnancy-chiefly due to the proliferation of the glandular elements. During pregnancy, both progesterone and oestrogens hormones are present in the body and are responsible for the breast changes.
5. *Inhibits oestrous or menstrual cycle and ovulation:* During pregnancy, maturation of follicles, ovulation, oestrous or menstrual cycle are inhibited also. The production of pituitary luteinizing hormone (LH) is inhibited by large doses of progesterone. Experimentally, injected progesterone prevents ovulation. Its purpose is to prevent formation of further embryos (superfoetation) during pregnancy. Probably it acts by inhibiting FSH.
6. *Causes enlargement of birth canal:* At full term birth canal enlarges due to growth of vagina and relaxation of pelvic ligaments. The same effect can be experimentally produced by giving progesterone along with oestrogens, but not with former alone.
7. *Relation with oestrogens:* It helps, completes and antagonizes oestrogen action.
8. *Protein catabolic activity:* Progesterone has slight protein catabolic activity.
9. *Water and salt metabolism:* In animals progesterone causes mild salt and water retention, but administered to men or women it causes salt loss. On the other hand, the synthetic progesterone has a mild sodium-retaining effect.
10. Progesterone stimulates respiration and this is confirmed by the fact that in women during the luteal phase of menstrual cycle, the alveolar pCO_2 is lower than in males.

Relaxin

Relaxin is a water-soluble polypeptide hormone present in pregnant mammalian ovary, placenta and uterus. Relaxin level of blood reaches maximum at the terminal stages of pregnancy. Bioassy: (1) *In vitro* inhibition of motility of mouse uterus; (2) Measurement of the length of interpubic ligament with a transilluminating device and ocular micrometer.

Androgens

In the biosynthetic pathway of oestrogens, testosterone is an intermediate. A large amount of androgens present in pathological ovaries is possibly due to enzymatic defects. There is no definite evidence that normal mammalian ovary produces significant amounts of androgenic steroids. The small amounts of testosterone in the plasma of women are formed peripherally, mainly from precursors, such as androstenedione.

Control of Ovarian Functions

1. **Anterior pituitary** (vide pituitary gland).

   FSH, having half-life about 170 minutes, controls (a) maturation of the graafian follicles, and (b) secretion of oestrogens.

   LH, having half-life about one hour, controls (a) full maturation of graafian follicles; ovulation; formation, growth and maintenance of corpus luteum; and (b) secretion of progesterone. The stimulating effect of LH on progesterone secretion by the corpus luteum is accompanied by an increased formation of cycle AMP. The increased cyclic AMP initiates a reaction involving protein synthesis and leads to steroid secretion. Lactogenic hormone or prolactin or luteotrophic hormone (LTH) has got influence on the secretion of progesterone from corpus luteum and so it is known as luteotrophic hormone. There is reciprocal relation between ovarian hormones and pituitary gonadotrophins. Oestrogen and progesterone inhibit the secretion of gonadotrophins—FSH and LH from the anterior pituitary respectively (Fig. 81.19).
2. **Ovary:** In addition to its effects through the anterior lobe of the hypophysis, oestrogens directly affect the ovary. Oestrogen given to immature hypophysectomised rats; increases ovarian weights. Thus, target organ for a hormone might be the same one that produces it.

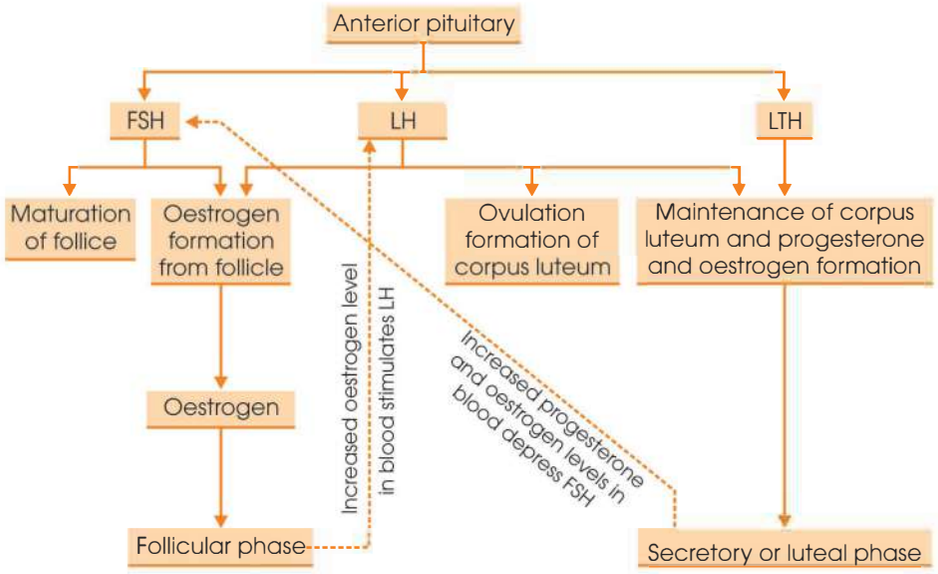


Fig. 81.19: Schematic representation of hormonal effects upon the ovary and the uterus

3. **Uterus:** Progesterone released from corpus luteum is essential for the implantation of blastocysts, and is necessary during the early part of gestation. There is clear evidence that stimuli from uterus influence ovarian function. It is possible that uterine endometrium synthesizes a specific luteolytic factor named as luteolysin, which acting on the ovary causes involution of corpus luteum. Removal of uterus (hysterectomy) maintains corpus luteum as during pregnancy. This uterine effect is not mediated through pituitary, it is a direct one. Prostaglandin present in the uterus is responsible for the luteolytic activity.
4. **Pineal gland:** It is postulated that melatonin or some other active principle present in the pineal gland has antigonadal activity. The action may either be a direct one or through anterior pituitary and central nervous system. Pinealectomy causes an increase in ovarian weight. On the other hand, administration of pineal extract decreases ovarian weight and reduces the incidence of oestrus.
5. **Adrenal cortex:** Adrenal cortex secretes sex hormones, but to a lesser extent than do the gonads. Oestrogen is secreted mainly by the ovaries and in smaller amounts by the adrenal glands and by testes in male.
6. **Thyroid:** Thyroid hormones have various effects on the female reproductive system. Hypothyroidism, can cause ovulatory dysfunction and is one of the major cause of impaired female fertility
7. **Thymus:** Oestrogen inhibits thymus. At puberty it involutes.
8. **Feedback effects:** It is probably that secretion of FSH and LH is inhibited by circulating levels of oestrogen and progesterone during the luteal phase of menstrual cycle. The site is apparently the hypothalamus.
9. **Diet** should have enough caloric value. Starvation depresses ovarian functions.
10. **Vitamins E,** A, ascorbic acid and some members of B complex are essential.
11. **Temperature:** The optimum temperature for the ovaries is a bit higher than that of testes. While undescended testis is sterile—the ovaries can only work when inside the abdomen at a higher temperature. One curious finding is that—if the ovaries of rats be grafted at a cooler place, say, the pinna not only ovulation stops but it manufactures male hormone instead of oestrogens.

Applied Experimental Comparative Physiology

Hypothalamus: In some mammals such as cat and rabbit, ovulation takes place only during coitus. Experimentally, it has been shown that sensory impulses arising from the female genitalia reach the hypothalamus and reflexly stimulate the secretion of gonadotrophins by the anterior pituitary. After stimulation of the hypothalamus, ovulation occurs, and this is due to the release of a releasing factor (LRF, vide pituitary) from the hypothalamus, which circulates in the blood stream and stimulates the secretion of gonadotrophic hormone (LH or ICSH) of the anterior pituitary. In other mammalian species such as rat and human, the median eminence and the tuberohypophyseal neurons of the hypothalamus release FSH-RF and LRF into the hypophyseal portal vessels which in turn control the secretion of FSH and LH from pituitary. Lesion of the hypothalamus causes abolition of gonadotrophic hormone secretion and atrophy of the ovary along with changes in the reproductive organs and stoppage of sexual cycle. The presence of another hypothalamic centre affecting gonadotrophin secretion in rats is indicated by the observation that lesions below the paraventricular nuclei are associated with development of multiple follicular ovarian cysts and constant vaginal cornification.

MENSTRUATION

Definition

Cyclical discharge of blood, mucus and certain other substances from the uterus in the reproductive life of the females, at an average interval of 28 days (24–32 days) is called menstruation.

It occurs every month from puberty to menopause. It is absent:

1. Before puberty,
2. During pregnancy, and
3. After menopause (45–55 years).

Duration: The flow lasts for 4–6 days without any appreciable pain.

Composition: It is made up of:

1. Blood (30–40 ml),
2. Stripped of endometrium,
3. Mucus,
4. Leucocytes, and
5. An unfertilized ovum

Changes and Influence of Hormone in Menstrual Cycle

The menstrual blood which comes out from the uterus clots promptly due to rapid formation of fibrin. If the blood remains in the uterus for some time fibrin is deposited on the endometrium and as a result there is partial clotting. Intrauterine clots if retained for a longer period dissolves due to the action of plasmin.

During each cycle the uterine mucosa (Fig. 81.20) gradually hypertrophies. The whole purpose is to prepare suitable bed for the reception and implantation of the fertilized ovum. If pregnancy takes place, the proliferated mucosa becomes converted into placenta. If pregnancy does not take place, the hypertrophied mucosa breaks down and is discharged as menstruation. Menstruation, therefore, may be described as the funeral of the unfertilized ovum or as the weeping of the uterus for the lost ovum.

The endometrial changes during the whole menstrual cycle have been divided into four stages: (i) the resting or postmenstrual phase, (ii) the proliferative of reparative or oestrogenic phase, (iii) the secretory or progestational or luteal or premenstrual or progravid phase, and (iv) the menstrual phase. The phases of menstruation and pregnancy are shown in Fig. 81.20.

1. The 1st and 2nd phases may be called follicular phase. They are due to the action of gradually increasing amounts of oestrogen.
2. In the beginning of the cycle theca interna of the vesicular or graafian follicle secretes oestrogen and mediated through the secretion of follicular fluid by the granulose, sensitize the follicle to FSH secreted by the anterior pituitary.
3. FSH initiates the maturation of only one follicle (very seldom, two), which has been primed by oestrogen.
4. The secretion of oestrogen reaches maximum at the time of ovulation, and such high level of the hormone inhibits the secretion of FSH but stimulates the secretion of LH.

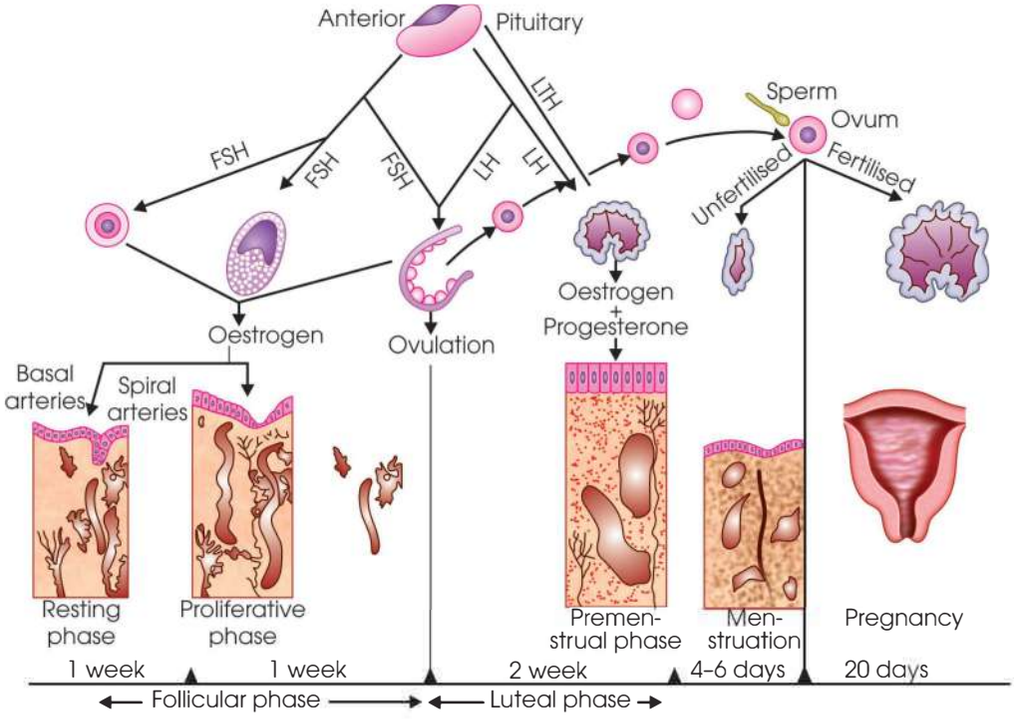


Fig. 81.20: Diagrammatic representation of the hormonal control during the menstrual cycle

5. Anterior pituitary begins to secrete LH and LTH probably in increasing amounts at the stage.
6. LH acting on sensitized follicle causes ovulation and then together with LTH helps in the development of corpus luteum.
7. Progesterone secretion starts—causing the premenstrual changes—luteal phase. If pregnancy occurs, placental gonadotrophins stimulate further growth of corpus luteum. More progesterone is secreted and the endometrium develops into a full-fledged placenta. But if fertilization does not take place, the high level of progesterone inhibits the secretion of LH and LTH. This causes involution of corpus luteum, fall in progesterone secretion and dissolution of uterine endometrium. Above sequence of events in the ovary and uterus has been presented schematically in Fig. 81.21. The hypertrophied endometrium breaks down and discharged as menstruation.

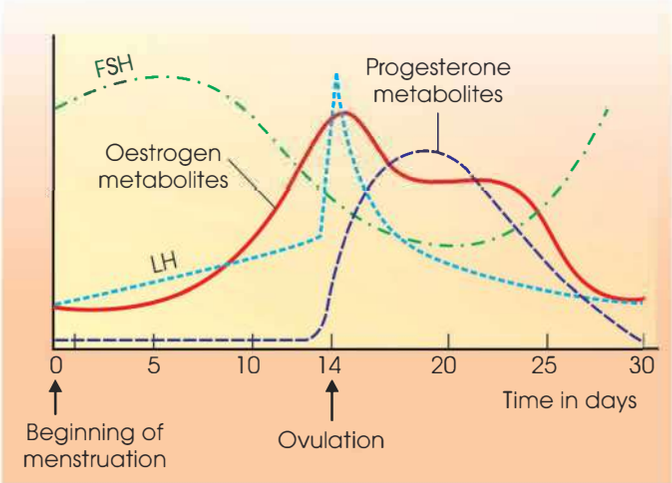


Fig. 81.22: It shows probable changes in blood levels of FSH and LH, and urinary outputs of oestrogen and progesterone metabolites during the menstrual cycle

These phases are briefly summarized below:

The nature of outputs of LH, FSH, oestradiol and progesterone is summarized in Fig. 81.22.

1. Oestrogen output is at a minimum during menstruation, and then rises slowly during the follicular phase, the rate of rise being increased just before ovulation. After ovulation it falls to a plateau while the corpus luteum is active and then falls to menstrual levels as the corpus luteum degenerates.
2. Progesterone output appears to be at a very low level during the follicular phase. It begins to rise quickly just before ovulation occurs and reaches a peak soon afterwards, thereafter declining until next menstrual bleed. FSH stimulates follicular growth. In a normal oestrous or menstrual cycle

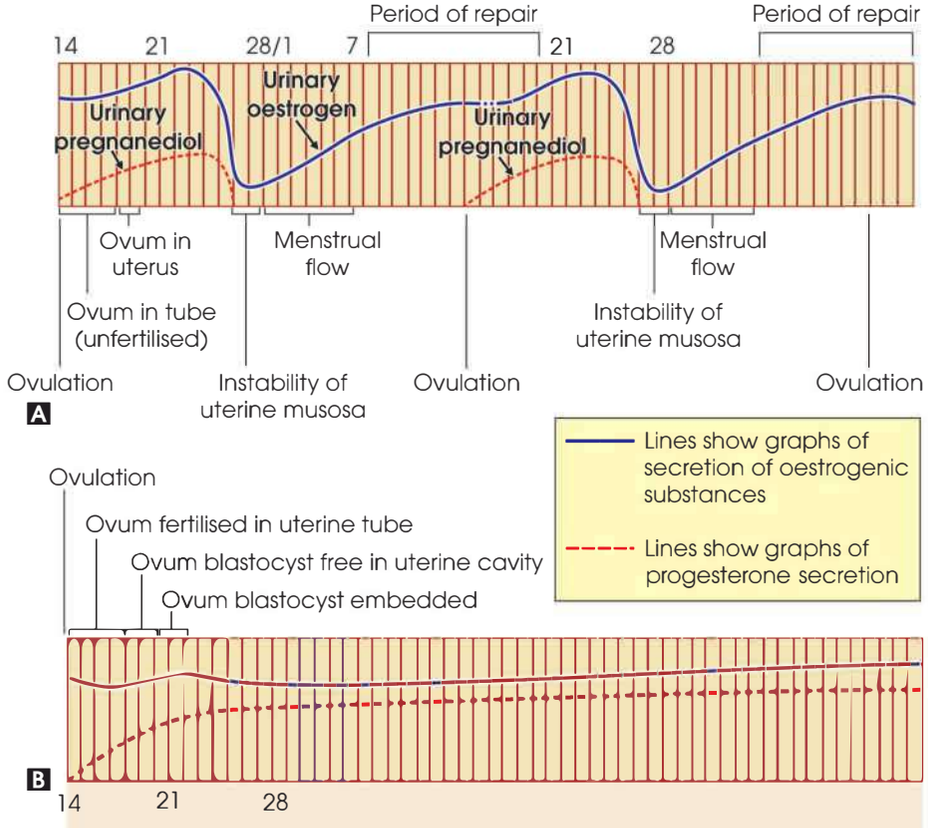


Fig. 81.21: (A) Diagram shows graphical representation of menstrual cycle in absence of fertilization. (B) Diagram shows graphical representation following fertilization cleavage and blastocyst

there is a burst of LH release about the time of ovulation.

3. **Gravid cycle:** After ovulation, it takes about a week for the ovum to reach the uterus. If fertilization has been taken place, the zygote will be undergoing rapid embryonic development and by the early part of second week of the luteal phase it will have become embedded in the uterine mucosa (nidation, implantation). By this time, the peripheral elements of the blastocyst (so-called chorion) begin to secrete a hormone (human chorionic gonadotrophin hCG). This hormone helps in sustaining the life and function of the corpus luteum beyond the usual limits of a menstrual cycle. The cycle is not therefore interrupted by a menstrual flow and this circumstance may be denoted as the first skipped period. A progestational or secretory endometrium becomes a gestational endometrium simply by the fact of pregnancy. It undergoes further progestational development during early weeks of pregnancy.

Applied Clinical Physiology: Anovulatory Cycle, Vaginal Cycle and Amenorrhea

1. *Anovulatory cycle:* Anovulatory menstrual cycle is sometimes found in young girls and towards the end of menopause. In some animals, e.g. rhesus monkey, anovulatory cycle is the usual feature. In anovulatory menstrual cycle no ovulation occurs and so no corpus luteum is formed. The endometrium changes up to proliferative phase and similar vascular changes as in ovulatory cycle also occur. When there is bleeding its duration may be same as that of ovulatory cycle.
2. *Vaginal cycle:* Under the influence of oestrogens, the vaginal epithelium becomes cornfield which can be identified in the vaginal smear, while under the influence of progesterone, thick mucus is secreted and the epithelium proliferates becoming infiltrated with leucocytes. Clinically it is often of importance to determine the time of ovulation. Biopsy of the endometrium indicates the functional level. A convenient indication is to determine the basal body temperature. At the time of ovulation there is a change, usually a rise. The cause of the change is not known.
3. *Abnormalities of ovarian function:* If menstrual periods are absent, the condition is known as amenorrhea. Primary amenorhoea is the condition when menstrual bleeding has never occurred. Cessation of the cycle in women with previously normal periods is known as secondary amenorrhea. If during regular periods, the flow is scanty, it is called oligomenorrhoea and if profuse, it is known as dysmenorrhea.

Menopause or Female Climacteric

In women with advancing age (45–55 years) certain irregularities in sex life occur due to gradual irresponsiveness of the ovaries to the pituitary gonadotrophin (FSH). Under this condition the senility comes in the ovary, mostly in the corpus luteum, and oestrogen level in the blood stream decreases greatly through the pituitary gonadotrophin level in the blood stream is high. With these irregularities in gonadal functions, particularly in gametogenesis, the cyclic changes in endometrium are not observed. Finally the menstruation fails to occur and the women cannot bear children any more. It is usually marked by atrophy of breasts, uterus, uterine tubes and ovaries. This condition is known as menopause. Therefore, menopause is the physiological cessation of menstrual flow in women.

Summary of changes and influence of Hormones during the Menstrual Cycle

1. During the period of menstrual flow; FSH is secreted from the anterior pituitary. This causes growth and development of follicles in the ovary. At the end of about 2 weeks, the maturity of one follicle occurs. Under the influence of FSH, the theca interna begins to secrete gradually increasing amounts of oestrogens. This may be called proliferative or oestrogenic phase of the menstrual cycle. It lasts normally about 2 weeks.
2. Oestrogens now help to repair and proliferation of the uterine endometrium. They make an increased thickening, keratinisation and glycogen storage of vaginal epithelium. They may also aid libido. The rising oestrogen-level in blood stimulates LH secretion towards the end of two weeks. LH somehow aids in the ovulation or rupture of mature follicle and release of ovum (about 13 to 15 days) before the beginning of next menstrual flow. LTH is now released from the anterior pituitary.
3. Together with this LTH, LH causes the remains of ruptured follicles to be transferred into the corpus luteum which secretes increasingly large quantities of progesterone and small amounts of oestrogens during the secretory or progestational phase of the menstrual cycle.
4. Progesterone possesses a secretory effect on the endometrium of the uterus. This effect makes increased secretion and nutrient storage within the mucosa of the uterus in preparation for the reception and nourishment of a fertilized ovum. Progesterone also effects quietly upon the uterine musculature which favors implantation of the embryo. When the progesterone level in blood increases towards the end of the menstrual cycle there appears a feedback effect upon the anterior pituitary by causing it to secrete less and less LH and LTH. As the productions of LH and LTH are thus inhibited, there are involution of the corpus luteum and cessation of progesterone secretion.
5. Menstruation may be a cause of the resulting low levels of progesterone and oestrogens in blood. Due to lack of appropriate amounts of oestrogens there may be an effect of vasospasm of the spiral arteries to the endometrium. This results in inadequate nutrition of superficial layers of the endometrium. Decreased progesterone level in blood is no longer enough to inhibit the pituitary FSH production, so FSH is again secreted and the menstrual cycle resumes (Fig. 81.22).
6. If there are occurrence of fertilization and implantation, the corpus luteum persists and secretes continuously large quantities of oestrogen and progesterone under the stimulating influence of CG (chorionic gonadotrophin) which is produced by the developing placenta and whose action is similar to that of LH and LTH.

Certain complains are generally, encountered by the menopausal women. These complaints are flushing of the skin, feeling of warmth and also a marked increase in sweating especially about the head and the neck. In association with the above complaints they may experience certain emotional disturbances and arthralgias (associated with arthritis). Other menopausal problems may include obesity, believed to result from decreasing caloric expenditure as a result of oestrogen deficiency, osteoporosis due to decreasing protein anabolism, causing a loss of protein matrix particularly to the vertebral column. Osteoporosis causes decalcification and softening of bones which may result in compression fractures of bones.

Excess gonadotrophin secretion during menopause is not the cause of these syndromes as may be supposed but oestrogen therapy has got some satisfactory effects in ameliorating the certain symptoms.

ROLE OF THE CENTRAL NERVOUS SYSTEM (CNS): IN HYPOPHYSEAL-OVARIAN AXIS

Many observations suggest that the central nervous system bears a link in the communications between the adenohyophysis and the ovary (Fig. 81.23). It is seen that destructive lesions of the CNS, especially at the base of the brain, cause either ovarian hypofunction or hyperfunction. It is said that emotional disturbances can cause profound irregularities of the menstrual cycle and can impair fertility in women.

If the pituitary gland is grafted in a hypophysectomised animal at a site remote from the anterior chamber of the eye or beneath the renal capsule, in its newer site the tissue becomes revascularised and recovers a certain amount of its original capacity to secrete trophic hormones, but gonadotrophins are not secreted in appropriate amounts to maintain normal gonadal function for some weeks postoperatively. If such a transplanted gland is retransplanted back to the sella turcica, normal gonadal function may be resumed.

The hypophyseal-portal system of blood vessels represents a pathway of information transfer from the hypothalamus to the adenohyophysis. Gonadotrophin output is controlled by messages which reach it from the brain and the locus of the feedback action of oestrogen may be in the CNS. The brain is involved in the feedback inhibition of gonadotrophin secretion by oestrogens and androgens. Lesions in the hypothalamic paraventricular nuclei prevent gonadal atrophy which occurs due to administration of the steroid hormones. Therefore sex steroid hormones may alter the threshold of response to stimulation of brain centres which regulate gonadotrophin secretion.

HORMONES AND SEXUAL BEHAVIOUR

1. Patterns of sexual behaviour in animals are commonly regulated by the effects of gonadal steroid hormones secreted in response to hypothalamic-hypophyseal rhythms and related to seasonal factors or characteristic ovarian cycles.
2. In humans, steroid hormones are equally necessary as a background for sexual behaviour but they are relatively small effective on the

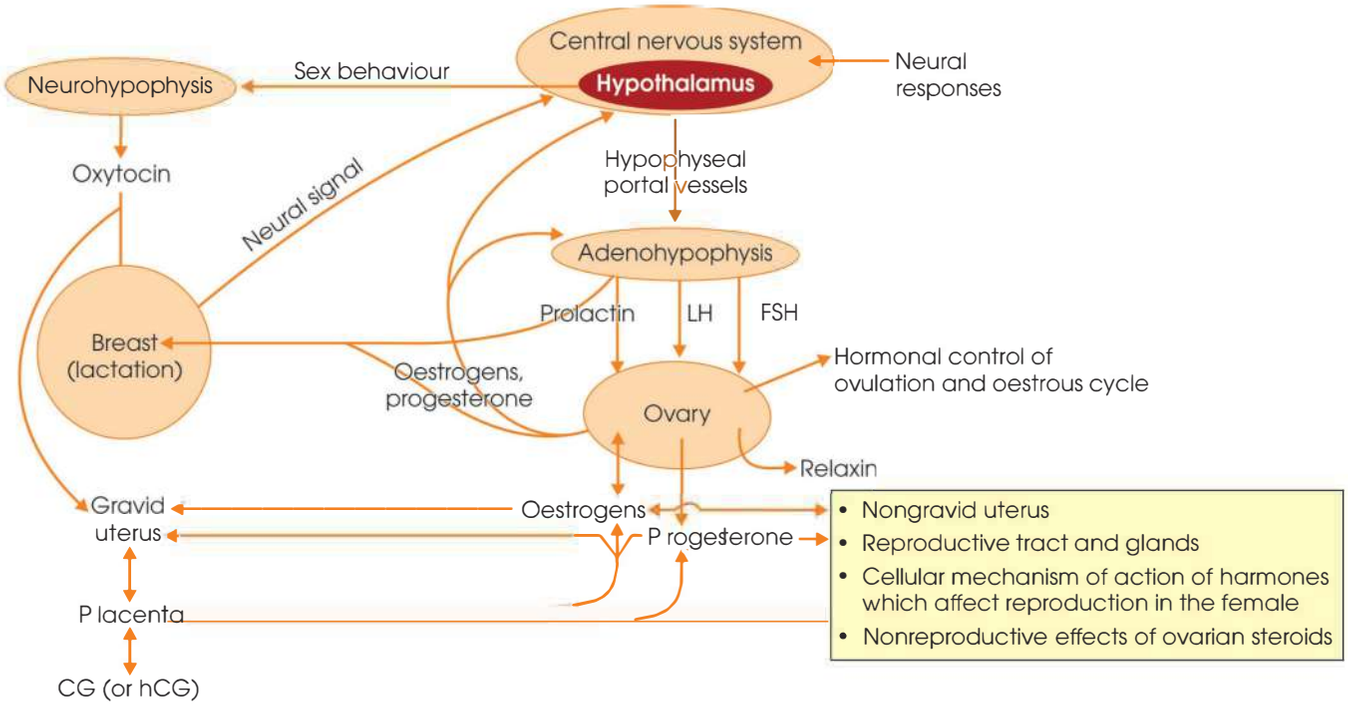


Fig. 81.23: Schematic outline of the neuroendocrine control of reproduction in the female

frequency and timing of sexual activity except at the extremes of concentration (e.g. decline in potency and libido following failure of pituitary or testicular function, and enhanced libido accompanying androgen excess).

3. In the male, testosterone is essential for the development and maintenance of libido and potency. Once established; libido may be retained despite the development of moderate androgen deficiency, though there is generally some decline in potency when androgen secretion is impaired. The decline in sexual potency which occurs with ageing in males is not due to lack of androgen, because testosterone secretion remains almost constant with advancing ages. In human with true androgen deficiency, testosterone treatment causes marked improvement in libido, but in psychogenic impotence the secretion of testosterone is generally normal and androgen administration has little effect. In humans, oestrogen treatment causes a striking decline in libido and potency due to inhibition of pituitary LH secretion and reduced secretion of testosterone.
4. In the female, gonadal steroid hormones have less clear-cut effects on sexual activity, whereas androgen secretion by the adrenal gland may be a major factor in promoting libido. Activity of the pituitary or adrenal failure is followed by loss of libido, whereas ovarian failure is relatively less effective on sexual function. When a woman is treated with testosterone analogues, excess androgen is sometimes accompanied by enhanced libido, while oestrogen and progesterone are relatively little effective on the intensity of libido. However in the female, secretion of oestrogen maintains normal genital function and to this extent it is an important contributing factor to sexual activity. Although high rates of oestrogen secretion are associated with sexual receptivity and oestrous behaviour in most other vertebrates, there is little evidence in the women for oestrogen-programmed sexual activity.
5. Normally psychic factors are important in the patterns of human sexual behaviour. On the other hand, steroid hormones maintain necessary genital development and libido which provide background for sexual function.
6. Effects of castration on sexual behaviour may vary from species to species. In the male, prepuberal castration abolishes sexual behaviour, but postpuberal orchiectomy may only diminish sexual pattern. In the female, oophorectomy does not eliminate sexual activity and interest, while adrenalectomy does eliminate sexual activity and interest.
7. Androgen treatment can restore full sexual activity to the prepuberal castrate male animal. On the other hand, full sexual activity and interest can be restored by oestrogen treatment to those female animals whose sexual activity is abolished by oestrogen deprivation.
8. Androgen treatment may increase sexual drive doing no alteration of its direction in the homosexual human male, who often shows no overt evidence of androgen deficiency, while in the heterosexually adjusted women, androgen administration may increase libido and responsiveness to sexual stimulation. Specific regions of the hypothalamus are involved in the central integration of sexual behaviour.
9. The gonadal hormones in the adult activate previously established pattern of sexual behavior. In the morphologically and psychosexually undifferentiated mammals a different function of the male hormone (androgen) has been demonstrated.
10. During this early developmental period, prenatal or postnatal depending upon the species, the male hormone organizes the tissues, probably neural, that mediate the display of sexual behaviour in the adult. Fundamental in establishing the form and extent of sexual behaviour displayed by the individual are the actions of genes and chromosomes. The pattern of sexual behaviour displayed, including the presence or absence of specific components of sexual behaviour of the vigour of display, has been shown to be heritable.
11. Morphological abnormalities of the reproductive system in man are associated with chromosomal abnormalities, but disorders of sexual behaviour are not. The type of sexual behaviour associated with abnormal sex chromosomes depends more on functional characteristics of the developing gonad than on the chromosomal factors.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the morphological and physiological changes in reproductive organ during ovarian cycle.
2. Describe the morphological and physiological changes reproductive organ during menstrual cycle.
3. Discuss the hormonal changes during menstrual cycle.
4. Describe the mechanism of actions and functions of oestrogen.
5. Describe the mechanism of actions and functions of progesterone.

Short Notes

1. Functions of ovary
2. Functions of oestrogen
3. Function of progesterone
4. Ovulation
5. Implantation
6. Fertilization
7. Hormones and sex behaviour
8. Relaxin
9. Androgens in females

Chapter

82

Pregnancy

INTRODUCTION

Pregnancy induces physiological changes in body functions to nurture the growth and development in the foetus as to have normal full term baby delivery. These physiological adaptations during pregnancy favour and ensure that there is no intrauterine growth retardation; and foetus develops normally fully up to term.

If the ovum be fertilized pregnancy begins. Normally, it lasts for 280 days (viz. ten menstrual cycles), at the end of which parturition takes place.

Physiological Changes during Pregnancy

Main changes are:

1. **Uterus and birth canal:** Uterus enlarges mainly due to hypertrophy but partly to hyperplasia of uterine muscle fibres. The individual muscle fibre becomes wider by 6 or 7 times and longer by 10 or 11 times than non-pregnant uterus. Connective tissue in between the muscle fibres also increases. The weight of the uterus increases. The weight of the uterus increases up to 1000 g at full term. Cause:
   a. Progesterone inhibits movement and facilitates growth.
   b. Oestrogen stimulates growth directly.
   c. Mechanical tension and irritation caused by the growing foetus also act as an important stimulus.
   d. Development of placenta.
   e. Enlargement of the birth canal and relaxation of the pelvic ligaments.

Vincent du Vigneaud was an American Biochemist who received the Nobel Prize in Chemistry for his research into sulfur compounds and the first synthesis of the polypeptide hormone, oxytocin in 1955.

Reference: Ragnarsson ULF. The Nobel trail of Vincent du Vigneaud. Journal of Peptide Science. 2007;13(7):431–433.

1901–1978

2. **Breast:** Mammary glands proliferate and development of breasts is completed. Lactation begins after parturition. Pigmentation of the areola and nipple occurs. The pigmentation may be due to ACTH or MSH (melanocytes-stimulating hormone).
3. **Ovaries**
   a. Formation and growth of corpus luteum in the early months and its degeneration in the later months.
   b. Cessation of ovulation.
4. **Blood**
   a. Blood volume and blood cholesterol are increased.
   b. Plasma fibrinogen level also increases. There is an increase of plasma α- and β-globulins and there is a decrease of plasma albumin. Plasma iron level falls. There is an increased erythrocyte sedimentation rate.
5. **Circulatory system:** Cardiac output is increased. Heart may be enlarged. It may be due to enlarged uterus pressing the diaphragm and causing the change of position of the heart. There is slight fall of systolic blood pressure and greater fall of diastolic blood pressure. Blood flow in the forearm and hand is increased.
6. **Respiration:** Vital capacity is increased. Tidal volume and pulmonary ventilation are increased.
7. **Digestive system:** Nausea and vomiting occur in the early months of pregnancy. Hypochlorhydria and hypotonicity of the colon are often found.
8. **Excretory system:** There is an increased glomerular blood flow and glomerular filtration. Sometimes glycosuria is found. Excretion of the following sex hormones occurs in the urine:
   a. Oestrogen,
   b. Pregnanediol, and
   c. Placental gonadotrophins.
9. **Endocrine system**
   a. Thyroid gland is enlarged and increased thyroid hormones secretion occurs.

b. Adrenal cortex is enlarged especially the zona fasciculata. Secretion of cortisol is increased.
c. Parathyroids are enlarged. Secretion of parathormone is increased.

10. **Metabolism**
    a. *Carbohydrate:* Renal threshold may be lowered and as a result glycosuria may occur during pregnancy.
    b. *Protein*: There is positive nitrogen balance and more nitrogen is retained in the body provided there is intake of balanced diet.
    c. *Lipid:* Lipaemia often occurs.
    d. *Water:* Increased water retention usually occurs in later months of pregnancy. Water is retained in the amniotic fluid, placenta, foetus, breast, uterus, blood and other tissues. There is increased blood volume. The retention of Na and H_2O is probably due to effects of female sex hormones.

Other Changes

a. High outputs of protein and steroid hormones from the placenta produce a variety of maternal changes during pregnancy. Most of these effects occur owing to high levels of plasma-oestrogen, which stimulate the synthesis of a group of hormone-transport proteins by the liver.
b. SHBG (sex hormone-binding globulin) or GBT (gonadal hormone-binding globulin) or TEBG (testosterone-binding globulin) which binds androgens and oestrogens is rapidly increased. It probably helps to minimize the circulating level of free oestrogen. CBG (cortisol-binding globulin) and TBG (thyroxine-binding globulin) are also increased, resulting in high levels of cortisol and thyroxine in blood. Because of increased binding of these hormones, their physiologically effective free levels are not markedly raised and forms of hormone excess do not unfold.
c. Formation of renin substrate by the liver is also increased by oestrogen causing an elevation of plasma-renin activity during pregnancy and a high level in plasma-angiotensin II.
d. As pregnancy advances, there is an accompanying rise in aldosterone secretion and excretion. This rise in aldosterone secretion may be due to elevation of plasma-angiotensin on the one hand, and due to inhibitory effect of high concentration of progesterone and its hydroxylated derivatives on Na retention by the renal tubules on the other hand. High concentration of rennin appears in the pregnant uterus and amniotic fluid, but does not contribute to the maternal plasma-renin level and do not possess any local action upon the uterus and its contents.

Pregnancy Tests

These tests are performed when confirmation of pregnancy is needed. Most of the tests are carried out with the patient's urine and are based on the fact that the placenta produces human chorionic gonadotropin (hCG), which is excreted in urine. If urine contains hCG and it is injected into immature female test animals, the ovaries will undergo maturation. The first satisfactory test was done by Aschheim and Zondek in 1927–28. Most of the other biological tests are modifications of the original.

Immunologic pregnancy tests were introduced in 1960. This was improvement is pregnancy testing leading to at home testing.

Biological Tests

Aschheim-Zondek test or mouse test—0.4–0.5 ml of the morning urine from a woman thought to be pregnant is injected subcutaneously twice daily for 3 days into 3 or 4 immature mice (3–4 weeks old). On the 4th or 5th day, the mice are sacrificed and the ovaries are examined. The test is positive if blood-filled follicles (ovulated) or corpora lutea are found in the ovaries. The method is 99% accurate. Disadvantages are the cost of animal maintenance and the 4 to 5 days required to perform the test.

Friedman test or rabbit test—uses mature female rabbits that have been isolated from males for at least 6 weeks. The rabbits, normally two, are injected intravenously with 10–15 ml of test urine. One rabbit is examined 24 hours later, the second one in two days. A positive test is identified when the fresh corpora lutea appear in ovaries. The test is 99% accurate, but it is used infrequently because of the greater cost of test animals.

Hogben test—injection of 20–30 ml urine into the dorsal lymph sacs of South African female clawed toad (*Xenopus laevis*) will cause appearance of a large number of ova within 6–12 hours.

Sperm-shedding test or Galli-Mainini test—5 ml urine injected into dorsal lymph sacs of the male toad (*Bufo arenarum*) or male frog (*Rana pipiens*). One to two hours later the toad's or frog's urine is aspirated from the cloaca with a pipette and examined under the microscope for spermatozoa. The presence of sperm cells indicates a positive test.

Immunological tests: Antibodies to human chorionic gonadotrophin (hCG) can easily be produced in rabbits and the antiserum so produced can be used to detect the presence of hCG in urine. The principle of the haemagglutination test is; sheep red cells coated with hCG will agglutinate in hCG antiserum from rabbits. But if urine containing hCG reacts with the antiserum first, the antibodies are used up and so are not available to cause agglutination of the sensitized sheep cells. Thus, agglutination means a negative result (i.e. no pregnancy), and failure of agglutination means a positive result. The test gives an answer in 2 hours.

A comparable test using antigen-coated latex particles instead of haemagglutination has also been developed. In 1970, the discovery of monoclonal antibodies led to the developed of the relatively simple and cheap home pregnancy tests.

In addition to these, several physical signs associated with the generative organs are of diagnostic importance. During pregnancy (1) the vagina shows (a) vascularity, (b) softening, and (c) increased secretion. The increased vascularity changes the colour of the vaginal wall from its usual pink mucosa to a bluish or cyanotic colour. This is known as **Chadwick's sign**. (2) Another physical sign that is most reliable is **Hegar's sign**. This is found as a softening of the isthmus or junction between the cervix and body of the uterus, which results in a greater mobility between two areas. This may be felt by the physician on bimanual pelvic examination.

PLACENTA

A functional connection between the embryo and the uterus is necessary in which development of the foetus occurs within the uterus, and in which nutrients for the foetus come directly from the uterus rather than from the yolk stored in the ovum. This connecting structure, the placenta allows for nutritional, respiratory, and excretory interchange of material by diffusion between the embryonic and the material circulatory systems, and consists of both embryonic and uterian tissues. The placenta also functions as a barrier that excludes from the embryonic circulation bacteria and many large molecules.

Formation and development: The fertilized ovum enters the uterus and eats it way into the hypertrophied endometrium. The gap closes over the ovum and it becomes embedded. This process is known as implantation or nidation (Fig. 82.1). The site of implantation is commonly on the dorsal wall of the uterus. The portion of the decidua that covers the projecting ovum is called decidua reflex and that portion of the mucous membrane which intervenes between the ovum and the muscular layer of the uterus, is the decidua basalis, in which there is a great dilatation of the maternal blood vessels and extensive proliferation forming the so-called placenta. The stimulus for the growth of the placenta comes from (1) Increased secretion of progesterone, at first from the corpus luteum and then from the placenta itself. (2) Irritation—mechanical and probably chemical—exerted by the growing embryo.

Histology

Placenta consists of two parts: (1) Maternal, and (2) foetal. The maternal part (Fig. 82.2) consists of large blood sinuses, incompletely partitioned by fibrous septa. Maternal blood circulates through these

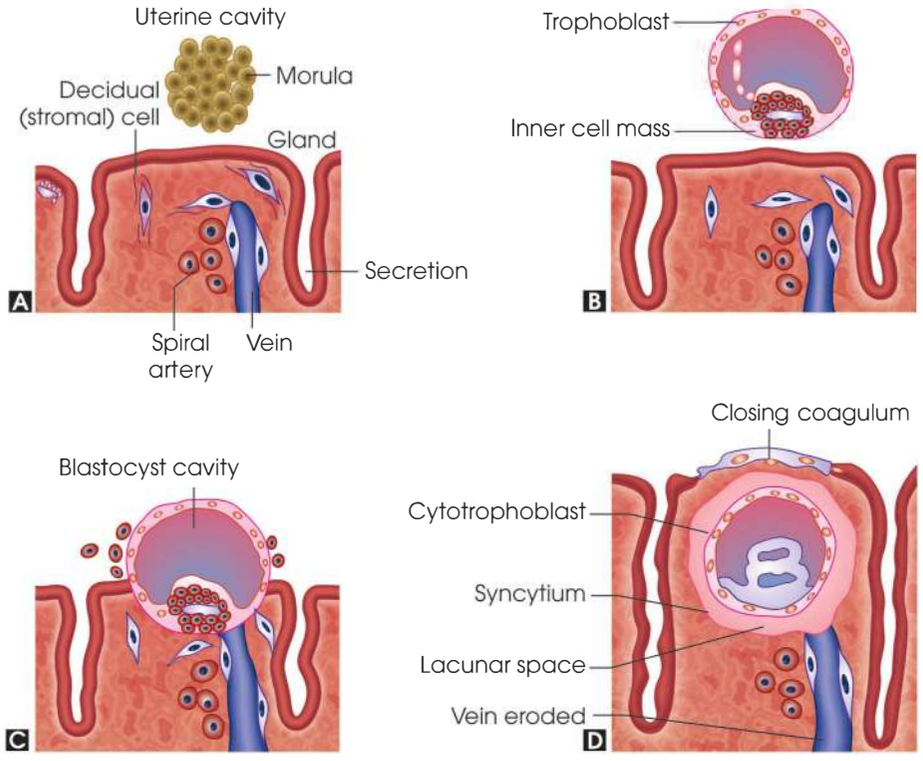


Fig. 82.1A to D: Implantation of the fertilized ovum in the uterine cavity. (A) Cell division has led to the formation of the compact morula; (B) Reveals the cavity of blastocyst and inner cell mass of a slightly later ovum; (C) Process of implantation; (D) Sealed coagulum shows the implanted ovum within the uterine wall

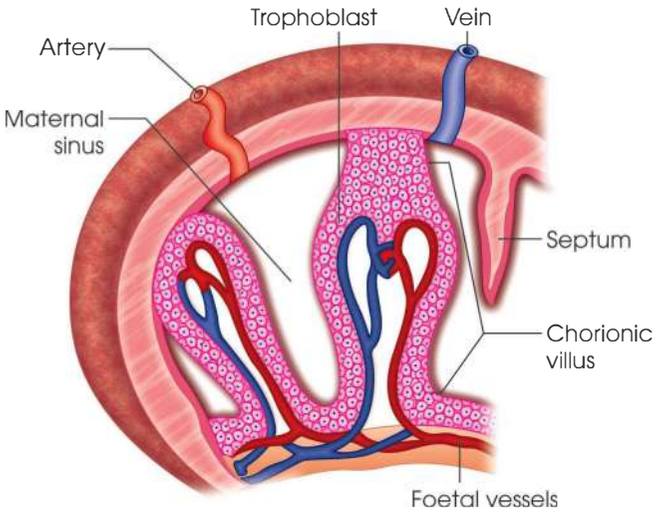


Fig. 82.2: Diagrammatic representation of the histological structure of placenta showing the circulation of maternal and foetal blood

sinuses—arterial blood entering through the uterine arteries and venous blood passing out through the uterine veins. The foetal part (Fig. 82.3) consists of numerous finger-like processes—the chorionic villi—projecting into the maternal sinuses and being bathed all round by the material blood. These villi contain foetal capillaries through which foetal blood circulates. They remain covered by a layer of syncytium, the trophoblast. Some villi float freely, others remain attached to the material decidua by thin prolongations of the trophoblast (Fig. 82.4).

With the growing of the embryo the structure of the trophoblast becomes differentiated into two distinct cell layers—the cytotrophoblastic layer (cellular trophoblast) and syncytium trophoblast which secrete chorionic gonadotropin. The cytotrophoblastic layer is inner, well-defined and discrete layer. The cells of this layer are generally known as Langhans cells (Fig. 82.5). The cells generally elaborate chorionic growth hormone-prolactin (CGP). This layer persists up to first half phase of the pregnancy and then disappears gradually. At term it is nearly absent. The outer trophoblast layer or syncytial trophoblast is outermost layer over the cytotrophoblast and is bathed into the maternal sinus. This layer persists all throughout the pregnancy. The cells of this layer elaborate oestrogen and progesterone mainly and also chorionic growth hormone-prolactin.

Thus, maternal blood is separated from the foetal blood by two layers—the cytotrophoblastic layer and the outer trophoblast layer (syncytial layer). Exchange of gases, nutrient and metabolites take place through these membranes (Fig. 82.4).

Functions of the Placenta

In the foetus, the respiratory system and the digestive system are not functioning. The kidneys and liver are also just having their functions gradually. The functions of these systems and organs, as well as certain other important functions are carried out by placenta. The functions are summarised below:

1. **Nutritive:** All the nutritive elements from the maternal blood pass into the foetus through the placenta. It is generally assumed that substances of low molecular weight a dialyzable pass simply through diffusion. Placenta is permeable to glucose in both the direction. Placenta can store considerable amount of glycogen and lipid which are essential in case of emergency of the foetus. Besides these, placental tissue can form

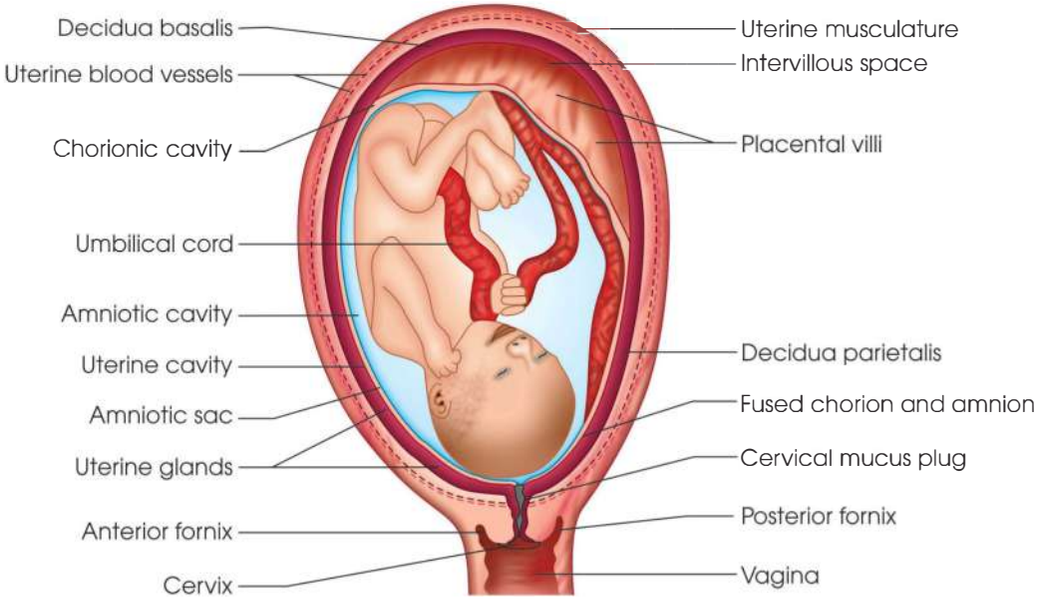


Fig. 82.3: Diagram represents the position of growing embryo within uterus and connecting link of the embryo with maternal parts through umbilical cord

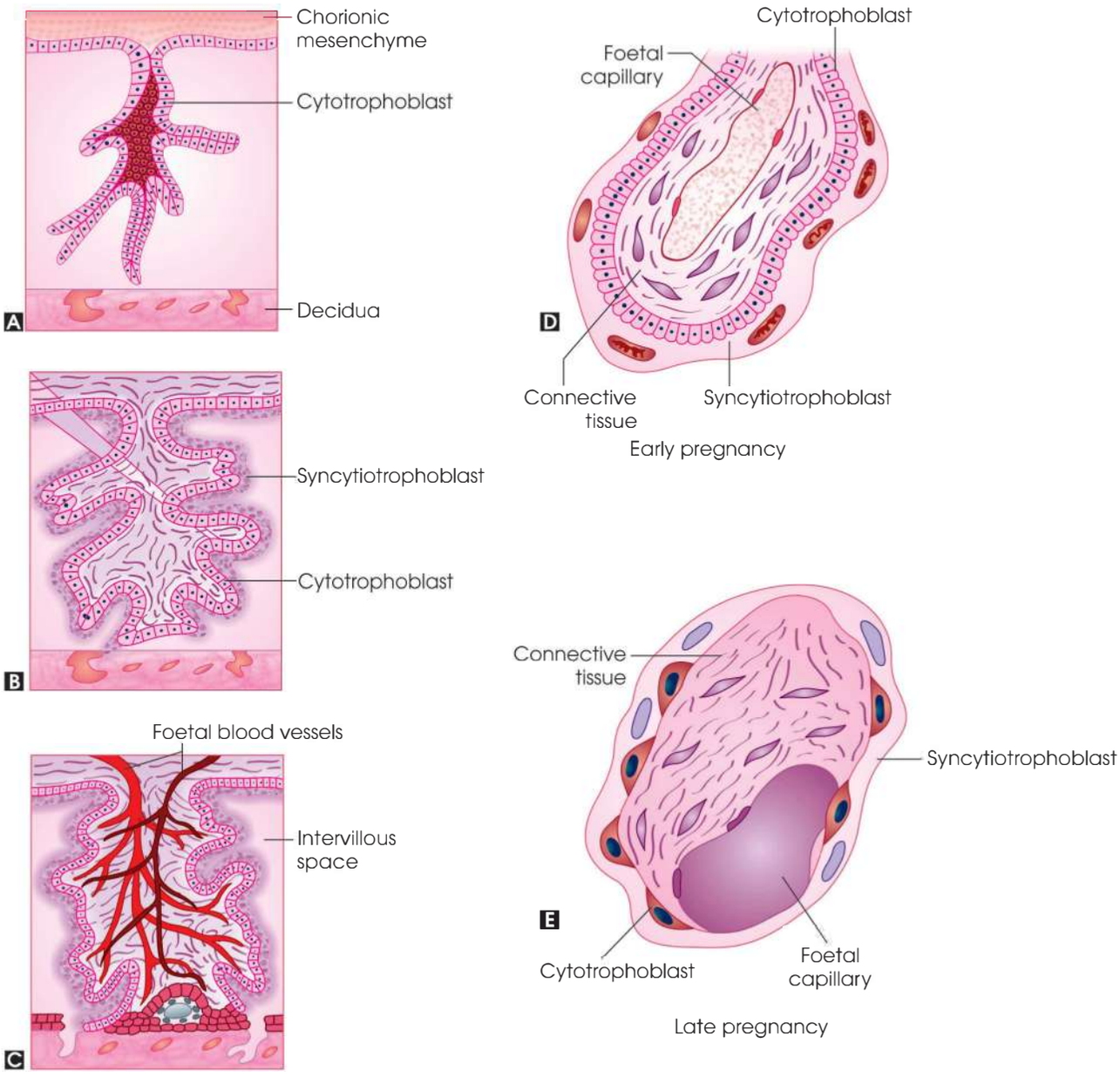


Fig. 82.4A to E: (A) Primary trophoblastic villus with a central core of cuboidal cells; (B) Well-defined cuboidal cells covered by a second layer devoid of intercellular boundaries; (C) Extended loose connective tissue into the villus from the foetus. Microscopic structure of chorionic villi in early pregnancy (D) and in late pre-pregnancy (E)

fructose from glucose. Fructose can pass from the mother to the foetus but not from the foetus to the mother.

2. **Excretory:** The foetal metabolites partly diffuse into maternal blood through placenta and are excreted by the mother.
3. **Respiratory:** The placenta contains numerous blood sinuses and the chorionic villi remain in these sinuses. Oxygen passes from the maternal to the foetal blood, while CO_2 passes in the reverse direction (Fig. 82.6). The chorionic villi have got thicker and less permeable cellular layers and hence, rapid gaseous interchange is difficult. Moreover, the maternal blood in the placenta has a relatively low O_2 pressure. This also makes oxygenation of foetal blood more difficult. But in spite of it, adequate oxygenation takes place, as the foetal haemoglobin has the property of taking up oxygen at relatively low oxygen pressure and its oxygen dissociation curve shows a marked deviation to the left. It is 70% saturated at 20 mm and 90% saturated at 40 mm O_2 pressure.

Transfer of CO_2 is also carried out adequately due to two reasons:

1. The pressure difference is enough.
2. CO_2 being several times more soluble and diffusible than O_2 can pass out more quickly than the latter.
3. Storage: Glycogen, fat, inorganic ion, etc.

The full-term placenta showing the maternal and foetal portions

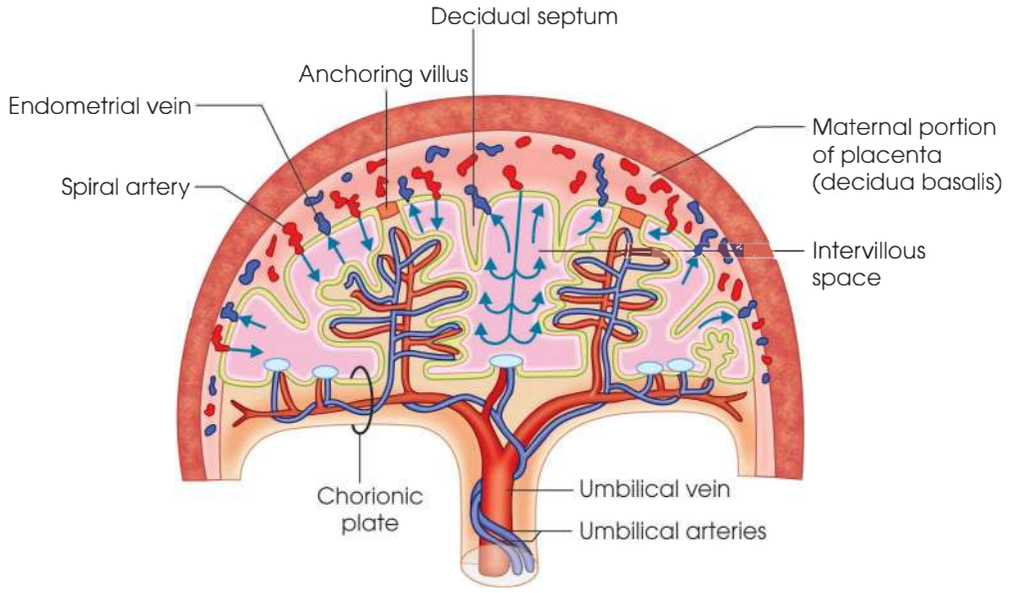


Fig. 82.5: Diagrammatic representation of human placental barrier near term

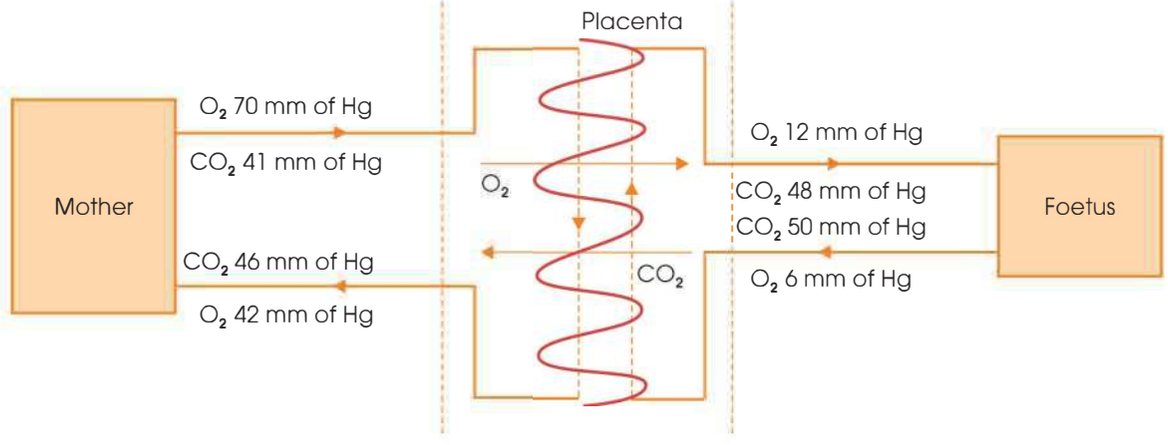


Fig. 82.6: Diagrammatic representation of gaseous interchanges in the placenta

4. Endocrine functions: Placenta secretes the following hormones:
   i. Chorionic gonadotrophin (CG) or placental gonadotrophin or human chorionic gonadotrophin (hCG)

This non-pituitary gonadotrophin has also been named pregnancy urine extract (PUE), chorionic luteotrophin, anterior pituitary-like hormone (APL). But the last term is misleading since its action differs from that of the pituitary gonadotrophins. CG is found in the plasma and urine of the pregnant human female and also in that of individuals with certain gonadal tumors (chorion epithelioma, hydatidiform mole, and teratoma). Gonadotrophin from gonadal tumour may not be similar with CG.

a. **Human chorionic gonadotrophin:** The hCG is a glycoprotein with a high content of sialic acid and other carbohydrate residues. Its molecular weight is about 30,000 (according to some, 100,000). Soon after implantation of trophoblast, the growth of chorion cells leads to the secretion of protein hormone chorionic gonadotrophin. The placental gonadotrophin in human is called human chorionic gonadotrophin. This hormone stimulates the ovary and, along with pituitary hormones and other factors, maintains oestrogens and progesterone secretion and aids in the maintenance of the corpus luteum of pregnancy. Actions of the hCG are primarily luteinizing and luteotrophic, but it has a little FSH activity. By about the end of first trimester the placenta provides necessary oestrogens and progesterone for the maintenance of pregnancy. The presence of CG in plasma and urine can be detected by radio-immunoassay as early as 8–10th days of the first

missed period, i.e. 22–24th days of pregnancy. The role of hCG in pregnancy seems to be confined to its transient stimulating effect on the corpus luteum. Ovariectomy before the 3rd month leads to abortion or miscarriage but after the third mouth has no effect on the pregnancy. The international unit of CG is defined as the activity contained in 0.1 mg of standard preparation. CG again falls towards the end of pregnancy and almost disappears a few days before the onset of parturition.

The hCG disappears after placenta is expelled: If the foetus dies excretion ceases showing that secreted by the foetal chorion. Certain pregnancy tests depend on the presence of this hormone in the urine of pregnant women. Function differs according to the species. In women, its function is to help further growth brought about by nitrogen, potassium and calcium retention, and persistence of corpus luteum just like LH.

In certain other pathological conditions, viz. chorion epitheliomas and hydatidiform mole in the females, this gonadotrophin is excreted in the urine.

b. **Chorionic 'growth hormone prolactin' (CGP) or human chorionic-somatomammotrophin (HCS) or human placental lactogen (HPL):** The placenta also secretes human placental lactogen.

c. **Oestrogens:** This steroidal hormone is secreted from the syncytial trophoblastic layer of the chorionic villi.

d. **Progesterone:** Placenta also secretes progesterone. It is also secreted from the syncytial trophoblastic layer of the chorionic villi.

e. **Chorionic thyrotropin:** Placenta secretes thyroid-stimulating factor which accounts for the increased thyroid-stimulating activity of the sera of pregnant women and of patients with tumours of chorionic tissue. Its structure and physiological role are uncertain.

f. **Relaxin or uterine-relaxing factor (URF):** This hormone helps in relaxation of the ligament of the symphysis pubis and is secreted from the placenta, uteri and also from ovaries.

g. **Growth hormone**, ACTH and MSH have also been detected in the placenta. It is not know if they are produced or stored in the organ.

h. The placenta may also secrete renin.

Thus, with the help of its hormones, placenta:

- Stimulates the growth of mammary glands
- Inhibits lactation
- Stimulates the growth and persistence of corpus luteum
- Inhibits ovulation
- Controls anterior pituitary
- Stimulates thyroid and adrenal cortex (via anterior pituitary)
- Stimulates growth of uterus and placenta itself, etc. In other words, all the important changes during pregnancy are carried out with the help of placenta.

In addition to this, placenta in some unknown way inhibits lactation. It is claimed that high titres of oestrogen and progesterone during pregnancy inhibit the secretion of milk; because milk secretion is increased after parturition when the titres of oestrogen and progesterone become low.

HORMONAL REGULATION IN PREGNANCY

Key Points

1. All of the uterine changes of the postovulatory phase of the menstrual cycle can be regarded as preparation for the participation of hormones in pregnancy before fertilization and the implantation of the fertilized ovum. If fertilization does not occur and there is a decrease in the production of oestrogens and progesterone by the corpus luteum, the appearance of endometrial shedding and menstrual bleeding occurs. If fertilization and endometrial implantation of the fertilized ovum occurs there is no drop in production of sex steroid hormones by the corpus luteum and both progesterone and oestrogen continue to exert their effects on the gravid uterus.
2. In some species, including the human, the corpus luteum provides oestrogen and progesterone during early pregnancy but later the placenta takes over the function of producing them.
3. The persistence of functioning corpus luteum in the earliest pregnancy occurs because the chorionic tissue beings to produce CG at least as early as two weeks after ovulation. Thus, the corpus luteum is sustained although pituitary trophic influences are removed.
4. When the growth and differentiation of the placenta take place, the placenta begins to make more and more oestrogen and progesterone and when the output of oestrogen and progesterone mounts, the output of CG diminishes. Both oestrogen and progesterone take part in the continuing structural growth of the uterus and mammary glands in pregnancy.
5. Oestrogen, which acts as a specific growth hormone for uterine smooth muscle cells, stimulates the growth of the uterine muscle mass and thus contributes to the contractile force that will ultimately be needed to drive out the foetus at the time of delivery.
6. Progesterone which exerts its inhibiting effect on the uterine smooth muscle prevents the establishment of effective, co-ordinated contraction of the uterine muscle and insures the persistence of feeble,

ineffectual, fibrillatory contraction until appropriate information for the expulsion of the foetus is given. Progesterone in association with oestrogen assists to prepare mammary glands for lactation by stimulating the formation of new glandular elements.

7. Placenta produces adrenal cortical steroid hormones apart from CG, oestrogen (oestriol in the human) and smaller amounts of progesterone. From the placental tissue of the human, trace amounts of ACTH, growth hormone, lactogenic hormone, androgens, vasopressin, and relaxin have been extracted. Of course, androgens could simply be metabolic intermediates in the synthesis of oestrogens, and others are all protein or peptide in nature or at least some of them might be artifacts of preparation. There is also the possibility that traces of hormones found in the placenta could simply represent elements present in maternal blood. However, the presence in the same tissue of a trophic hormone (CG) and steroid hormones suggests that trophic hormone acts locally to stimulate the production of steroids.
8. Just before the beginning of labor both progesterone and oestrogen levels fall, the progesterone fall occurring before that of oestrogen. There is an ageing process which occurs in the placenta and its impaired vascularisation is the cause of its diminished steroid hormone output at term. The decrease in availability of progesterone may be:
   a. The withdrawal of an inhibitory effect of progesterone on the oestrogen-primed uterine muscle causes development of coordinated squeezing movements of the uterus by oxytocin in aiding the expulsion of the foetus and placenta.
   b. The withdrawal of the depressing effect of progesterone on prolactin release by the pituitary is essential for the initiation of the process of lactation in the mammary glands which have already been repaired for this event by the compensatory actions of progesterone and oestrogen.
   c. During pregnancy, thyroxine and cortisol are produced in larger amounts than normal, and their concentration in blood gradually increases up to the period of parturition.
   d. They may simply be sequelae of some modifications that occur in the rate of globulin production by the liver which is inundated with great amounts of oestrogen and progesterone or disposal in one way or another.

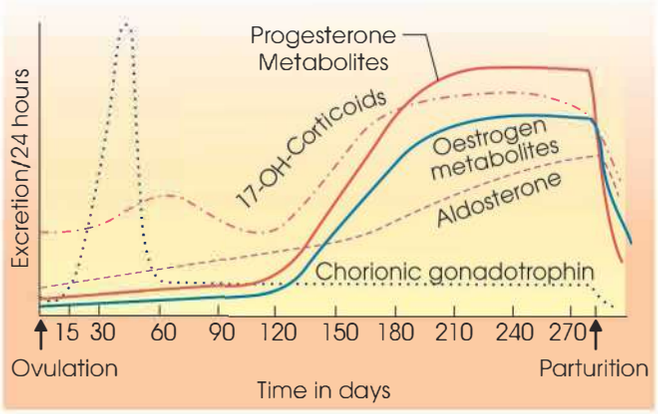


Fig. 82.7: Graphical representation shows urinary outputs of hormones during pregnancy

   e. In the latter part of pregnancy, aldosterone excretion in the urine is significantly elevated. It is not impossible that the intra-abdominal pressure and the consequent inferior vena caval compression may set up a volume receptor call for aldosterone. A summary of exception patterns of the hormones in pregnancy is given in Fig. 82.7.

Summary

1. Changes in the uterus are controlled by oestrogens and progesterone.
2. Activity of the corpus luteum is controlled by chorionic gonadotrophin and hence oestrogens (and uterine contents later in pregnancy).
3. Activity of the ovary is controlled by the anterior pituitary. In pregnancy ovulation is inhibited.
4. Activity of the anterior pituitary affects uterine contents by an unknown mechanism.
5. The pituitary gonadotropin secretion increase until just before parturition.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the physiological changes during pregnancy.
2. Describe the hormonal changes during pregnancy.

Short Notes

1. Functions of placenta
2. Placental hormones
3. Pregnancy diagnostic test
4. Human chorionic gonadotrophin

Chapter

83

Parturition

INTRODUCTION

Parturition is achieved by the effects of uterine muscle, associated in the later stages by all the skeletal muscles which may be used to raise the intra-abdominal pressure.

PROPERTIES OF UTERINE MUSCLE

This muscle contains both actin and myosin and although slower and less strong, the basic mechanism of contraction is almost same as in the skeletal muscle. During pregnancy, actomyosin content of the upper region of the uterus becomes double. This is hormonally stimulated since in animals with bicornuate nuclei with a pregnancy in only one horn, change, are the same in both horn. In an ovariectomised animal, oestrogens increase the actomyosin content of uterine muscle but progesterone has no effect. If an ovariectomised animal is treated with oestrogens alone, an electrically-stimulated excised strip behaves as follows:

1. A series of shocks give progressively increasing responses until a plateau is reached (positive staircase)
2. Increasing the frequency raises the plateau
3. Oxytocin causes a chain of action potentials and contraction
4. The resting membrane potential is 40.50 mV
5. Local electrical stimulation leads to contraction of the whole strip.

If an ovariectomised animal is treated with both oestrogen and progesterone behaves as follows:

1. A series of stimuli gives progressively diminishing responses until a plateau is reached
2. Increasing the frequency lowers the plateau
3. Local electrical stimulation leads to a contraction confined to the part stimulated
4. Oxytocin fails to cause a contraction
5. The resting membrane potential is 50–60 mV.

The cause of these differences is not certain but possibly has an ionic basis. Calcium and potassium-free solutions have a little effect on progesterone-dominated uterus, but convert an oestrogen-dominated uterus into one of the progesterone types

Towards the end of pregnancy, the following factors aid expulsion of the foetus:

1. Oestrogen raises the content of uterine actomyosin.
2. An increasing stretch tends to make the uterus contract like all smooth muscle. Oxytocin trends to cause contraction of the uterus.
3. Relaxin softens birth canal and relaxes the ligament. Either stretch or oxytocin is not important for uterine contraction. In bicornuate uteri, contraction occurs even in the empty horn. Contraction may also occur in hypophysectomised animals and humans.
4. Progesterone may be the only factor which opposes uterine contraction.

Process of Parturition

Overall processes of parturition is summarised below.

Parturition takes place, normally, at about 280 days from the beginning of the last menstrual period and results in childbirth. It is brought about by the periodic contraction of smooth muscles of uterine wall, aided by contractions of skeletal muscles of abdominal wall. Various investigations into the causes of the onset of parturition at the end of ninth month and into the process of labour have been carried out. At present, however, the mechanisms involved in the process of labour are complex and not yet fully clear. It is not the phenomena of a single factor but of multiple factors are expected to play synchronously for smooth delivery of the baby. During gestation the placenta remains in a quiescent state but as the labour approaches, the uterine myometrium becomes irritable and excitable. It is claimed that at the end of gestation, the contractile protein (the actin and myosin) concentrations of the uterine muscles are increased greatly and help in forceful contraction during labour.

Hormonal factors which play as key roles in determining the onset of labour are the hormones elaborated from the ovaries and placenta. It is claimed

that levels of progesterone and oestrogen in the blood as well as in the uterine muscles actually determine the onset of labour. Oestrogen stimulates the uterine contraction whereas progesterone inhibits it; and pregnancy is maintained by the dominant action of progesterone. It is due to progesterone block which maintains pregnancy and as soon as progesterone level is decreased during the end of gestation, labour starts. It has been further reported that during pregnancy the placenta secretes progesterone directly into the uterine tissue rather than to the general circulation. This effect tends to increase the progesterone concentration in the uterine myometrium so as to inhibit contraction.

During the onset of labour oestrogen level in the blood is increased and progesterone level is decreased. Oxytocin secreted from the posterior pituitary then brings about vigorous contraction of the uterus. Oestrogen level in the blood and uterine tissue potentiates the oxytocin effect. Relaxin secreted from the ovaries and placenta enlarges the birth canal by relaxing the pubic ligaments. The foetus is moved towards the cervix by the vigorous contraction of uterus, and stimuli from the cervix reflexly secrete oxytocin (Ferguson reflex). Distention of the cervix and vagina stimulates the hypothalamus for the liberation of oxytocin from the posterior pituitary. So, with the proper hormonal balance and timing, the smooth parturition takes place. Factors involving in the process of parturition have been presented schematically in Fig. 83.1.

Corticosteroid levels and local formation of angiotensin by the action of uterine renin may initiate the onset of labour, although there is no convincing evidence for either of these hypotheses, and the level of angiotensin II in amniotic fluid remains unchanged during the onset of labour. Plasma level of certain prostaglandins rises during labour and may have some possible role in parturition.

Duration of labour is variable. However, the average length of time is about 12–18 hours. During first stage or stage of dilatation the cervix of uterus is dilated and as a rule the amnion is ruptured and the amniotic fluid is expelled. During second stage or stage of descent the child descends through the vagina and is expelled. During third stage or placental stage, the membranes of the foetus are expelled.

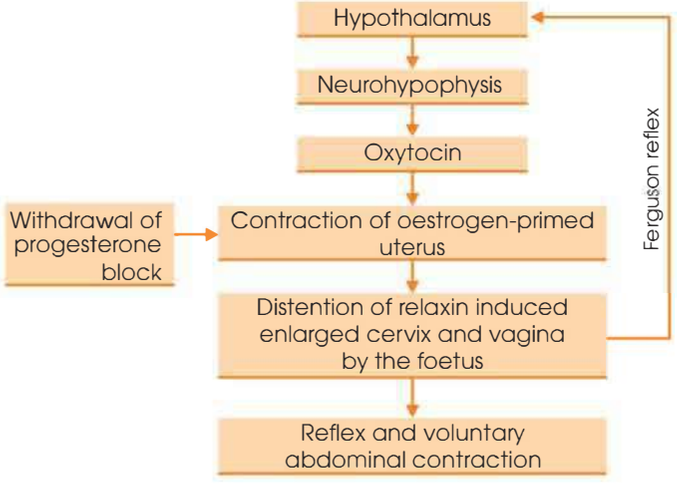


Fig. 83.1: Hypothetic scheme describing the factors involved in parturition

Involution

It is the process of rapid decrease in the size of the uterus. It is brought about by a gradual autolysis of self-digestion of the uterine wall and requires from 6–8 weeks. During this period, the uterus again resumes its original position in the pelvic cavity and approximately its original size.

TWINS AND MULTIPLE BIRTHS

According to the nature of origin, twins may be divided into two distinctly separate classes or groups which as follows: (1) Monozygotic or uniovular (identical) and (2) dizygotic or biovular (fraternal).

Monozygotic twins: They occur from a single ovum and are fertilized by a single sperm. At the early stages of the development of the daughter cell following fertilization up to the establishment of the axis and primitive streak, the zygotic material may be divided into two complete halves which give rise to two separate embryos. The chorionic and amniotic sacs may be either separate or common for both the embryos. In this case the twins are always of the same sex, i.e. either two male babies or two female babies having same blood group and tissues of same antigenic potencies. So, they are named as identical twins. Conjoined twins or double monsters are originated from incomplete division of the unizygote.

Dizygotic twins: These types of twins are developed from discharge of two ova at a time and fertilized by separate sperms. The embryo develops in separate chorionic sac in most cases. They may be of either same or opposite sexes having separate antigenic constitution. They have got no more similarity (or resemblance) to each other than do other children of the family. The type of twining may be hereditary.

Twining takes place once in about seventy-five births and about two-thirds of them are of dizygotic origin.

Multiple births, more than twins, e.g. triplets, quadruplets or quintuplets, may occur from any of the above origins or from a combination of both of them.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the process of parturition.

Short Notes

1. Twins and multiple births
2. Properties of uterine muscle.

Chapter

84

Foetal Circulation

INTRODUCTION

Peculiarities in Foetal Circulation

1. In foetal life, the two ventricles, right and left, have got common function in circulating blood to the periphery. With the functional differentiation following birth, structural differentiation in relation to functions becomes inevitable. Such changes are observed not only in heart but also in other essential organs of the body. In foetal life, the thickness of the right and left ventricular wall is almost same but following birth as the pulmonary and systemic circulations are gradually separated by the fusion of the ductus arteriosus, the thickness of the left ventricular wall is gradually increased with the increased workload. All throughout the adult life the left ventricle has to maintain the systemic circulation (high resistant circuit) whereas the right ventricle has to maintain the pulmonary circulation (low resistant circuit).
2. In foetal life, the respiratory function of the lungs is absent and the lungs remain as solid organ. For this reason major part of the blood, coming from the right ventricle, is shunted through patent ductus arteriosus to the descending aorta, and small amount of blood to the lung only for its nutrition. But following birth, as the respiratory function is gradually resumed, the circulatory status is changed. Ductus arteriosus is fused and anatomical dissociation in between the pulmonary and systemic circulation thus occurs. So, in foetal life, right and left hearts work in parallel but in adult life they work in series.
3. Placenta takes the important part in maintaining the respiration, excretion and nutrition of the foetus. The exchanges of nutrient materials, gases and also of the waste products occur in placenta. The blood after being loaded with O_2 and nutrient materials from the placenta returns to the foetus through the umbilical vein. Unlike in adult life, the O_2 saturation in the arterial blood in foetal life is different from region to region and this is mostly related with the functional importance of the particular organs in comparison to the others. The vital organs, like brain and heart, get blood supply with higher saturation of O_2 (62%), whereas the periphery gets lower saturation of O_2 (58%).
4. Foetal haemoglobin has the higher holding capacity of O_2 than the adult haemoglobin. For this reason the O_2 dissociation curve of foetal haemoglobin is shifted more towards the left.
5. Through foramen ovale connection between the inferior vena cava and left auricle is present in foetal heart only to avoid mixing with deoxygenated blood in the right auricle and also to supply well-oxygenated blood to the brain and heart. With the onset of respiration in the newborn baby, the circulatory pattern is abruptly changed and the foramen ovale is gradually fused against the interatrial septum.

In foetal heart capillary–fibre ratio is 1:5, whereas in adult heart it is 1:1.

Pulmonary veins carry deoxygenated blood, as the foetal lung behaves like a solid mass, gaseous exchange is out of question.

Course of Circulation

It has been discussed earlier that the placenta is of paramount importance in foetus in maintaining different essential functions like respiration, excretion and nutrient exchange of the growing embryo.

1. Left and right umbilical arteries supply foetal blood to the placenta and blood is returned from the placenta by two umbilical veins at early embryonic life and later it is returned only by the persistent left umbilical vein as the right one is fused afterwards. Umbilical impression (umbilicus) in adults is the position of the fused umbilical cord which makes blood-vascular link with the placenta in foetal life (Fig. 84.1).

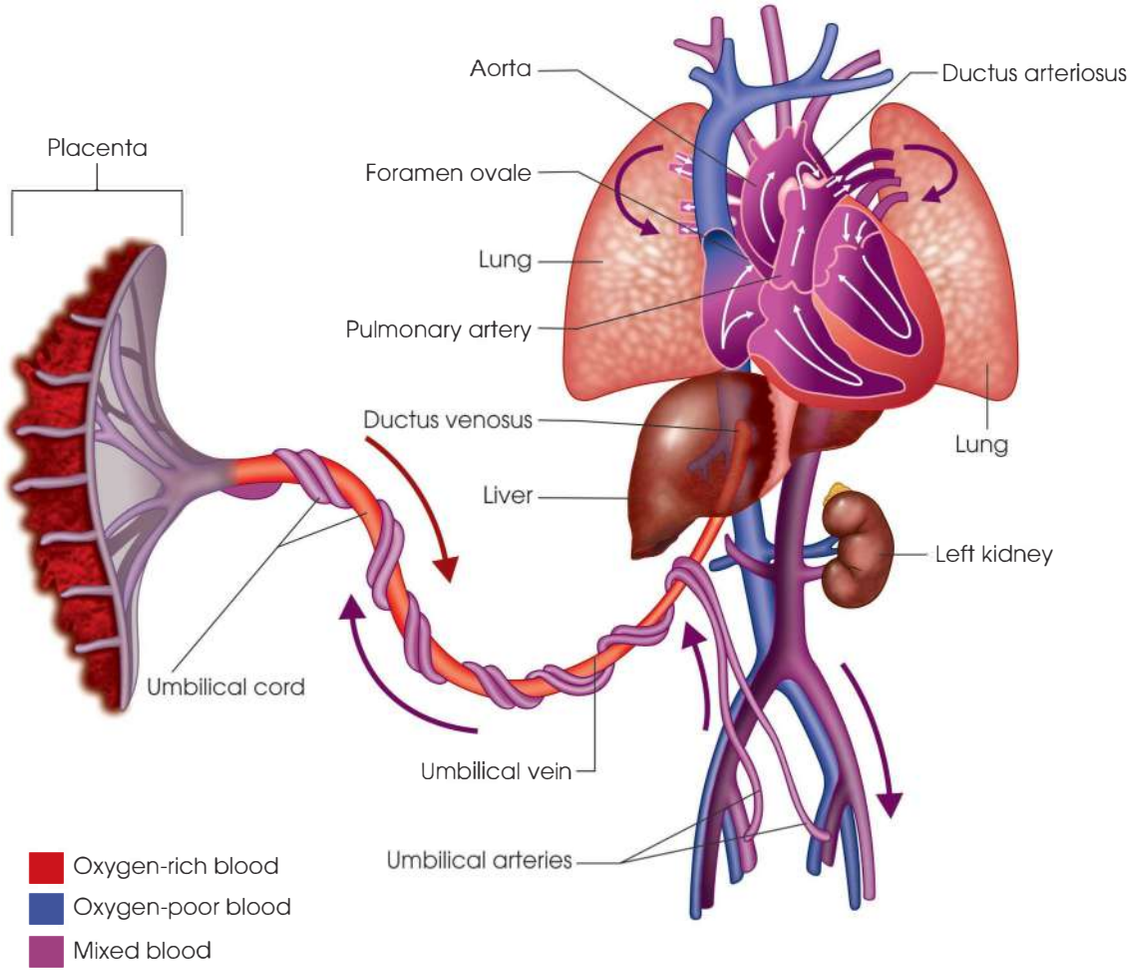


Fig. 84.1: Diagrammatic representation of the anatomical organization of the foetal circulation including placenta (microscopic) showing blood vessels to run from and to the placenta

2. Thus, the blood loaded with O_2 and nutrient material leaves placenta by persistent left umbilical vein and ends in the liver.
3. The umbilical vein carries blood, saturated with 80% O_2. Here, part of the blood is directly shunted to the inferior vena cava by ductus venosus and the rest is mixed with the portal blood.
4. Inferior vena cava thus carries blood from the lower portion of the body, from the hepatic vein and also from ductus venosus. Here in the inferior vena cava, O_2 saturation of blood becomes 67% and major part of the blood is poured directly into the left atrium through foramen ovale, and smaller part to right atrium.
5. By the edge of the inter-atrial septum—the crista divides, the inferior vena caval blood splits into two streams, of which one goes to the left atrium through foramen ovale (for avoiding further mixing with deoxygenated blood in right atrium) and other goes to the right atrium (Figs 84.2 to 84.4).
6. In the left atrium the blood losses its O_2 saturation further as it mixes with the venous blood from the lung which contains deoxygenated blood. From the left atrium blood enters the left ventricle and thence to the aorta.

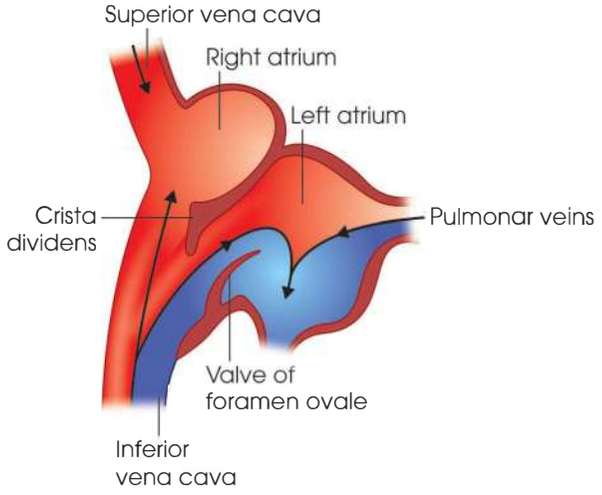


Fig. 84.2: Diagrammatic representation of the great veins in the foetus indicating the splitting of blood flow of inferior vena cava into two streams by the crista dividens with one passing through the foramen ovale and other going into the right atrium (modified by Dawes)

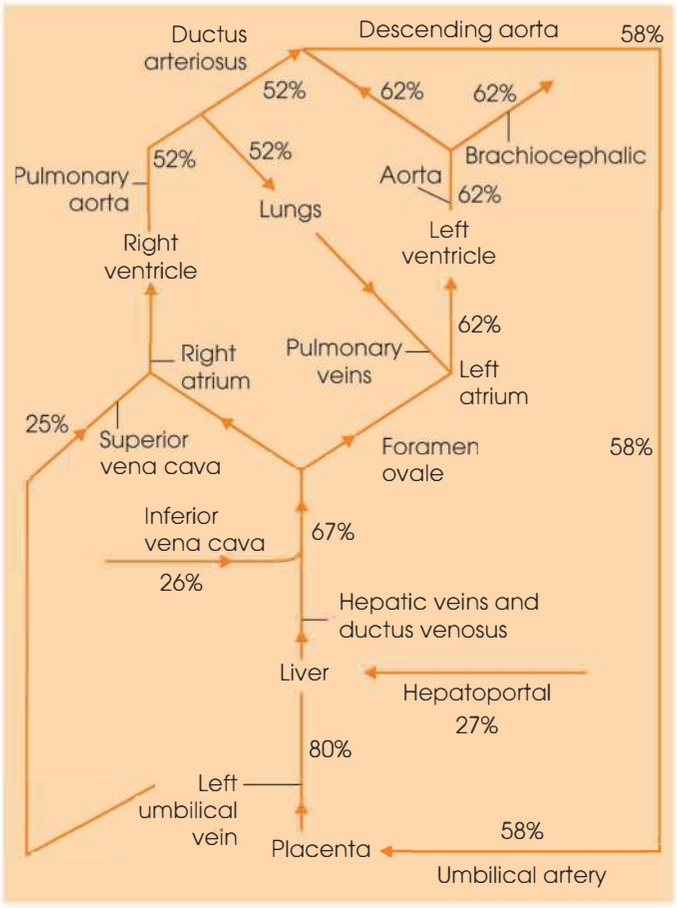


Fig. 84.3: Schematic representation of the mean percentage of oxygen saturation and distributing pattern of blood through the heart and blood vessels of the foetus (modified by Dawes)

7. The ascending aorta actually carries blood, saturated with 62% O_2 and passes through brachiocepahlic trunk and descending aorta. Thus, brain and heart get blood, 62% saturated with O_2. But blood while passing through the descending aorta receives blood from the ductus arteriosus which carries deoxygenated blood (52% O_2) from the right ventricle.
8. Right atrium receives blood from the lower part of the body and also from the upper part of the body. O_2 saturation of the blood in the right atrium becomes 52%. From here it is poured in the right ventricle and thence to the pulmonary arch of the aorta. Here, major portion (78%) of blood is shunted through ductus arteriosus to the descending aorta and lesser part (22%) is directed to lung for its nutrition. Thus, after mixing in the descending aorta, the O_2 saturation of the blood comes to 58%. This blood while following the course through the abdominal aorta gives off branches to the neighbouring organs and returns to the placenta through two umbilical arteries.

In the placenta, the branches of the umbilical artery project like villi within the maternal sinus and gaseous exchange is taken place in between the foetal and maternal blood. O_2 is taken up by the foetal blood and CO_2 is discharged into the maternal sinus across the walls of the villi. Nutritive materials for the foetus are also taken from the placenta and excretory products are discharged into the maternal sinus. Of the total cardiac output of the two hearts, 57% is supplied to the placenta and foetal membranes, 10% to the lungs, 15% to the forepart and 18% to the hindparts. Blood flow through foramen ovale and ductus arteriosus is also high and is 46% and 35% of the total cardiac output of both ventricles respectively.

CHALLENGES OF NEW EXISTENCE

The foetus in the uterus lives at a temperature of 33°C—the temperature of the amniotic fluid. His lungs are solid. The pressure in the pulmonary artery is higher than the pressure in the aorta. In addition to this, the foetus arrives at a new world with myriads of sensory stimuli conveyed to its eyes, ears and skin. Adaptation to this new world requires a set of completely new physiological adjustments. The process of physiological adjustment from the newborn infants to full-grown child is gradual and consists of changes especially in

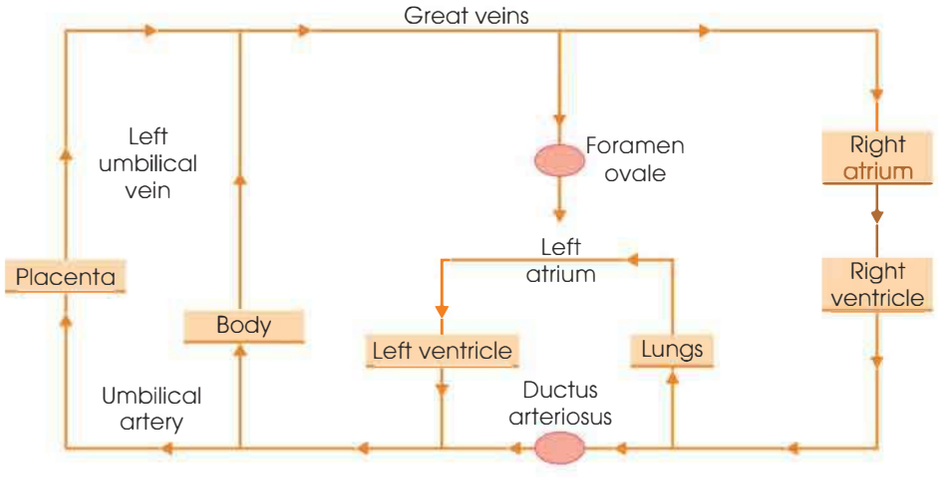


Fig. 84.4: Schematic representation of the foetal circulation (modified by Dawes)

the mechanism of circulation, respiration, temperature regulation, functions of the kidney, intestine and liver.

Changes in Circulation after Birth

Closure of the Foramen Ovale

With tying of the umbilical cord, the inferior vena caval pressure falls and the systemic arterial pressure rises. Accordingly, the left atrial pressure exceeds the vena caval pressure because venous return for the pulmonary bed to the left auricle is increased tremendously within this period. Besides this, venous return through the inferior vena cava is curtailed greatly following tying. The valves of the foramen ovale are fused against the wall of the interatrial septum (Fig. 84.5).

Closure of the Patent Ductus Arteriosus

Within an hour or two, O_2 saturation of the blood is restored up to 90%. Duties arteriosus is then gradually constricted with the increase of O_2 saturation of the blood and finally it is obliterated. Certain amines also have got relation with prompt obliteration of the ductus arteriosus (Fig. 84.5).

Closure of the Ductus Venosus

With the cessation of blood flow though the umbilical cord after birth, the ductus venosus is closed within an hour or three, because the pressure drop is such that cannot keep the vessel open. So, functional closure is observed very sharply (Fig. 84.5). In some cases where the portal venous pressure is raised, this vessel may remain open.

Changes in the Cardiac Muscle and its Blood Vessel

In foetal life, thickness of the wall of the right and left ventricle is more or less same and even the total mass of the right ventricle exceeds that of the left by 25% at term (Hort, 1966). The number of fibres in the two ventricles is approximately same and is not changed with ages though the major changes are observed in length and thickness of the fibres. Just after birth, functional statuses of the two ventricles are changed abruptly. The workload in the left ventricle is increased whereas the same is decreased in the right ventricle. To cope with the increased workload, the left ventricular wall grows rapidly and this growth is related with the rapid growth of the infant and the increase in peripheral resistance. The growth of the right ventricle is decreased gradually. RNA concentration in the left ventricle is increased from first day of birth and there is a little change in right ventricle. Blood flows in the two ventricles are obviously changed. The left ventricular flow is increased greatly with simultaneous decrease in right ventricular blood flow. Capillary–fibre ratio in both ventricles is also altered. It becomes 1:1 in adult life.

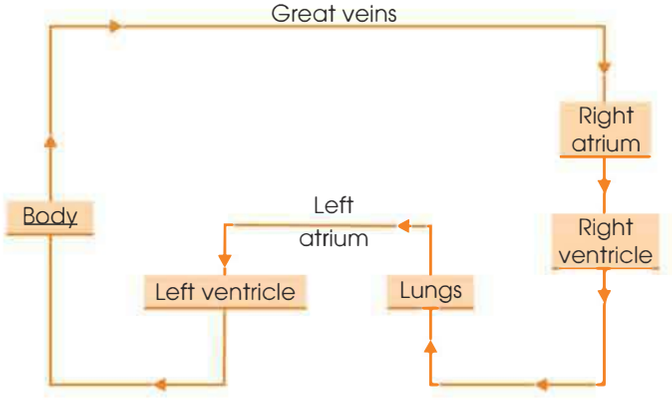


Fig. 84.5: Schematic representation of neonatal circulation after closure of foramen ovale and of still functioning ductus arteriosus. This occurs within a few minutes after birth (modified by Dawes)

Circulation

Circulatory changes are observed following occlusion of the umbilical cord and the cessation of umbilical blood flow. When the umbilical cord is tied the peripheral vascular resistance of the foetal blood vessels is tremendously increased. Not only that, blood pressure is also increased. As the placenta is cut off from the foetus, the newborn baby begins to suffer from O_2 lack. CO_2 is accumulated in the blood and when the condition becomes severe, the baby begins to have first respiratory effort (Fig. 84.5).

Changes in the Lungs and Respiration

With the onset of respiration, pulmonary vascular resistance is greatly decreased with associated increase in pulmonary blood flow. These changes occur within a minute or two. With the fall of pulmonary resistance and along with the increase of resistance in the abdominal aorta direction of blood flow through the ductus arteriosus is changed. Blood begins to flow from the aorta towards the lungs through the patent ductus arteriosus (Fig. 84.5).

APPLIED CLINICAL PHYSIOLOGY: INBORN ERRORS OF METABOLISM IN THE NEWBORN

Galactosaemia and phenylketonuria are the two examples which appear shortly after birth. These conditions are rare but when present their early detection is of great clinical importance.

Galactosaemia

In this condition there is a failure of utilization of galactose. Lactose is the principal sugar in the milk. Lactose is converted into galactose by the enzyme lactate in the small intestine. The galactose is converted into glucose in the liver. The glucose is metabolized with the production of heat and energy. In galactosaemia

galactose cannot be converted into glucose. Galactose accumulates in the blood producing diarrhoea and vomiting. Galactose appears in the urine and reduces Benedict's reagent. If the child survives there will be liver damage, cataract and mental retardation. Galactose-free diet is essential for these babies. Milk should be excluded from the diet of the baby.

Phenylketonuria

In this condition phenylalanine cannot be converted to tyrosine (then to thyroxine), epinephrine and norepinephrine. Phenylalanine and phenylpyruvic acid accumulate in the blood producing toxic changers in the brain and causing mental deficiency. The phenylketone is found in the urine and gives a bluish-green colour with ferric chloride. In such cases, the diet of the baby must have a low and controlled level of phenylalanine.

EXAM-ORIENTED QUESTIONS

Essay

1. Discuss the peculiarities in foetal circulation.
2. Describe the changes in circulation after birth.
3. Describe foetal circulation.

Short Notes

1. Closure of foramen ovale
2. Phenylketonuria
3. Galactosaemia

Chapter

85

Development of Breast and Lactation

INTRODUCTION

Breast is a cutaneous structure. It develops as an invagination of the surface epithelium into the underlying connective tissue as solid columns of cells. Later on, the cell columns become hollowed out into ducts. These ducts branch out into terminal tubules which end in alveoli that secrete milk. Around the ducts and to a lesser extent the alveoli remain modified muscle fibres, called myoepithelium. They are elongated and longitudinally striated cells. Their contraction helps to press out milk. The mammary gland on each side consists of 15–20 lobes separated by connective tissue septa. In the actively secreting gland the number and size of alveoli increase and the secreting cells remain filled up with minute fat droplets. The secretion is discharged by rupture of the free ends of the cells, leaving the nucleus and basal cytoplasm intact. Regeneration of these cells quickly takes place. In the resting non-lactating gland, these features are not seen. At menopause, the breasts involutes, the alveoli shrink, and the gland atrophies.

CONTROL OF BREAST DEVELOPMENT AND LACTATION

Development of Mammary Glands

1. In women, the mammary development requires direct concerted actions of oestrogens, progesterone pituitary hormones, and the presence of basal levels of thyroxine, cortisol and insulin. Oestrogen causes the development of mammary ducts and progesterone stimulates the formation of lobules and alveoli.
2. Optimum mammary growth in animals also requires the presence of growth hormone and prolactin. In women, normal development is initiated by oestrogen, progesterone and growth hormone (Fig. 85.1).
3. With the onset of puberty, the growth of the mammary glands occurs due to liberation of oestrogen. This development is only due to proliferation of the duct. It has been observed that only oestrogen cannot initiate ductus proliferation and GH and adrenal corticoids are also required. As seen in hypophysectomised animals if only oestrogen is administered then appreciable ductus growth does not occur.
4. During pregnancy breasts develop further chiefly due to the development of lobules and alveoli. This is caused by the simultaneous action of oestrogens, progesterone, GH, adrenal corticoids and prolactin (anterior pituitary).

Lactogenesis: Secretion of Milk

Active lactation starts only after delivery and removal of placenta. This shows that placenta inhibits the action of prolactin. In all species other than the human female prolactin is well-defined protein of the anterior pituitary and is normally kept under inhibitory control by the hypothalamus. Normally prolactin levels are higher in females than in males and are stimulated by oestrogen. But after delivery prolactin levels rise considerably and initiate lactation. It is possibly due to the action of large amounts of oestrogens and progesterone which have been experimentally found to inhibit milk secretion of lactating glands. When placenta is removed, prolactin acts unopposed due to withdrawal of oestrogen and progesterone and free lactation starts. Free flow of milk occurs after the birth of the child. There is diminution of oestrogen level in blood which in turn promotes the secretion of lactogenic hormone or prolactin from anterior pituitary. Adrenal cortex has a definite role in the initiation of lactation.

Galactopoiesis (Maintenance of Lactation)

For the maintenance of lactation following parturition, continued secretions of prolactin along with ACTH, GH and TSH from the anterior pituitary are required.

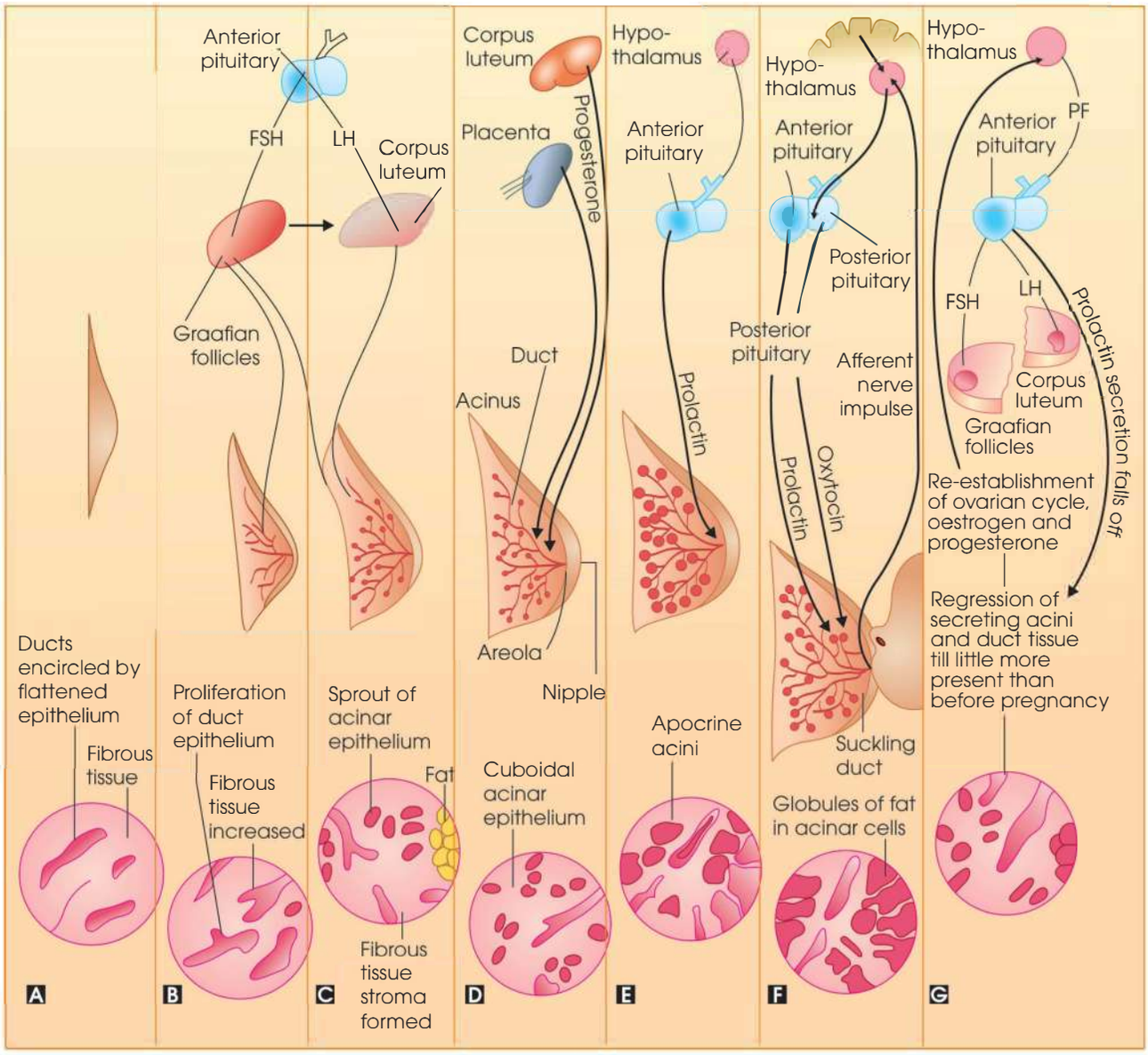


Fig. 85.1A to G: Mammary glands at different phases of life. (A) Small and undeveloped glands in childhood, (B) In girls at puberty; (C) In maturity when ovarian hormonal cycle established and ova being shed regularly; (D) Breast in pregnancy; (E) Breast gland after child-birth; (F) Lactating breast; (G) Post-lactation breast gland

Besides these, suckling is required for the maintenance of lactation, because by this process both prolactin and oxytocin are secreted. Prolactin helps in the process of lactation and oxytocin is required for milk ejection. If the titres are removed from the mother then mammary glands involutes quickly and lactation thus ceases. Prolactin and gonadotrophin seem to have a reciprocal relationship. Ovulation tends to be depressed during the initial phases of lactation and when ovulation recurs, lactation often lessens.

Ejection of Milk

The milk that collects in the subareolar milk sinuses can be withdrawn by suckling. But the ejection of milk from the mammary acini into the duct system—a process commonly known as the letting down, in which both the mother's subjective response and the mechanical stimulation of suckling play a part. Suckling produces nerve impulses that are carried by way of the lateral funiculus of the spinal cord to the hypothalamus.

Effects of Suckling

Suckling stimulates lactation as well as ejection of milk in two ways:

1. *Mechanical:* It drains away the accumulated milk and makes room for fresh secretion.
2. *Reflex:* Suckling reflexly stimulates anterior pituitary, which secretes more prolactin. The release of prolactin appears to be an intrinsic property of the anterior pituitary. The hypothalamus forms

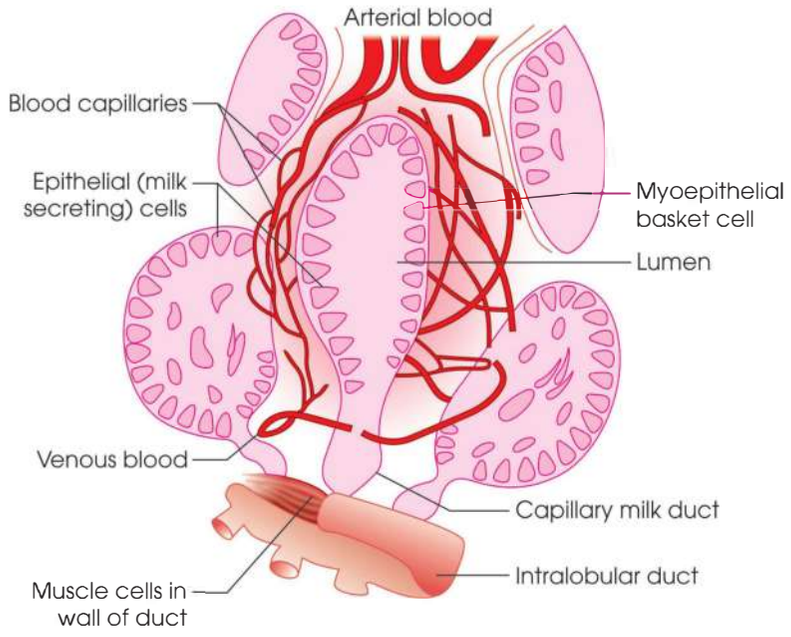


Fig. 85.2: Blood vessels and myoepithelial basket cells surrounding the alveoli of the mammary gland

prolactin-inhibitory factor (PIF) that prevents secretion of prolactin. Oestrogen and chlorpromazine that stimulate lactation lower the concentration of PIF in hypothalamus and probably permit, thereby prolactin secretion. During suckling the afferent impulses from the nipple reach the hypothalamus and then through the hypothalamohypophyseal tract, neurohypophysis discharges oxytocin and a little vasopressin in the blood. The oxytocin circulates into the bloodstream and causes contraction of the myoepithelial basket cells surrounding the alveoli of the gland and thus ejection of the accumulated milk (Fig. 85.2). So, suckling produces both secretion and ejection of milk.

Inhibition

Emotional excitement like worry, fear, sadness, etc., during lactation may inhibit milk flow. Administration of epinephrine has similar effect. Emotional stress might inhibit the release of oxytocin, acting through neurohypophysis. Effect of epinephrine, on the other hand, might be due to constriction of mammary blood vessels. Disturbances in milk ejection cause engorgement of mammary glands and cessation of lactation.

Colostrum

Secretion of mammary gland at the end of pregnancy and at the beginning of lactation is known as colostrum. Unlike milk, it is yellow in colour and is secreted from the breast only for a few days after the birth of the child. Colostrum contains a little fat but numerous cell fragments, free-fat droplets, lymphocytes, monocytes, histiocytes, desquamated epithelial cells and colostrum corpuscles. It also contains a large amount of γ-globulins in most mammals and is formed due to imbalance between secretion and removal from the gland.

APPLIED CLINICAL PHYSIOLOGY

Hormone and Cancer

Carcinoma is the malignant growth of the tissue due to abnormal multiplications of cells at any part of the body. This abnormal multiplication is possibly due to absence of feedback controls that normally limit the cellular growth and differentiation. The etiology of cancer is not yet known though investigations on various aspects have been undertaken all over the world. Considering the incidence of cancer in different tissues of the body in respect of male and female hormones have been indicated to be some of the causes of such disease. There is evidence that prolonged stimulation to cell division acts as one of the factors causing the tissue to become carcinomas. The oestrogen is not only stimulating the growth and differentiation of the accessory sex organs but also of other tissues of the body. The incidence of breast carcinoma in women of childbearing ages is mostly oestrogen-dependent. This type of carcinoma is dependent upon the amount of oestrogen presents in circulation. So, this growth is highly stimulated during pregnancy and for any such conditions when the oestrogen level of blood is heightened. This growth of the carcinoma can be inhibited for some time (months or years) but cannot be curtailed by bilateral ovariectomy. Because oestrogen

secreted from the adrenal gland of this patient may maintain the growth of carcinoma. Bilateral adrenalectomy or administration of glucocorticoids which inhibit the ACTH secretion from anterior pituitary may produce another temporary remission of the carcinoma recurring after castration. When the disease recurs for the second time after adrenalectomy, it may be inhibited by hypophysectomy. There is also evidence that GH stimulates in breast carcinoma. There are some carcinomas of prostate which are androgen-dependent and regress temporarily after castration or hypophysectomy.

An understanding of lymphatic drainage of the breasts has great importance in relation to malignant condition of breasts. Malignant cells may readily spread from the affected breast to other areas of the body though the lymphatic vessels and nodes that drain adjacent areas.

Recent studies reveal that prolactin can induce breast cancer, not oestrogen.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the physiological changes during process of breast development and lactation.

Short Notes

1. Lactogenesis
2. Colostrum
3. Galactopoiesis
4. Ejection of milk

Chapter

86

Controlled Reproduction and Family Planning

INTRODUCTION

World population as on April 2018 is 7.6 billion predicted to reach 8.6 billion in 2030 and to reach 9.8 billion in 2050 and 11.2 billion in 2100. Food production can be increased to some extent but not to that extent. The only answer to this problem lies in the controlled reproduction and planned family.

In order to check the population explosion, various sociomedical measures have been taken. Contraceptive measures to prevent pregnancy are widely employed for the controlled reproduction and a planned family all over the world. Mass education is necessary for proper use of the contraceptive measures in developing countries like India.

Population can be controlled by controlling the sexual intercourse according to physiological principles, e.g. rhythm method and withdrawal method.

Physiological Methods

1. *Withdrawal technique or coitus inerruptus:* Withdrawal of penis just before orgasm (climax) is not at all dependable. Failure rate of this method is 17%.
2. *Rhythm method:* In women with regular menstrual cycles ovulation occurs between the 9th and 19th days after the beginning of the menstrual bleed.

For birth-controlled purposes it is sufficient to know only the earliest possible and last possible dates on which the next period starts. It is also important to remember that only one ovum normally is expelled per cycle and this ovum remains alive for only 24 hours. Spermatozoa after entering the uterus remain alive only for 48 hours. Thus, there is a minimum period of 3 days in each cycle during which intercourse should not be allowed to avoid pregnancy. At the same time it is important to note that it is extremely difficult to precisely determine the exact day of ovulation.

To calculate the infertile days during the preovulatory phase, 18 is subtracted from the shortest recorded cycles. Correspondingly in the luteal phase the infertile days are determined by subtracting 11 from the longest cycle. Thus, in the case of women whose cycles extend from 25 to 32 days, the 'safe period' extend up to day 7 (25–18 = 7) and from day 21 (32–11 = 21) onwards.

Use of Some Barriers to the Entry of Sperms into the Cervix at the time of Coitus

Male condoms: There made up of rubber sheaths (condoms) and are worn over the penis during intercourse. Similarly, female condoms (Fig. 86.1) are the rubber diaphragm placed in the cervix. Cervical diaphragms are coated with spermicidal jelly or foam and applied just before the intercourse and must be left in place for 6 to 8 hours after intercourse.

Use of Chemical Spermicidal Agents before or after Intercourse

1. Films, jellies, foams, suppositories, etc. are used before coitus.

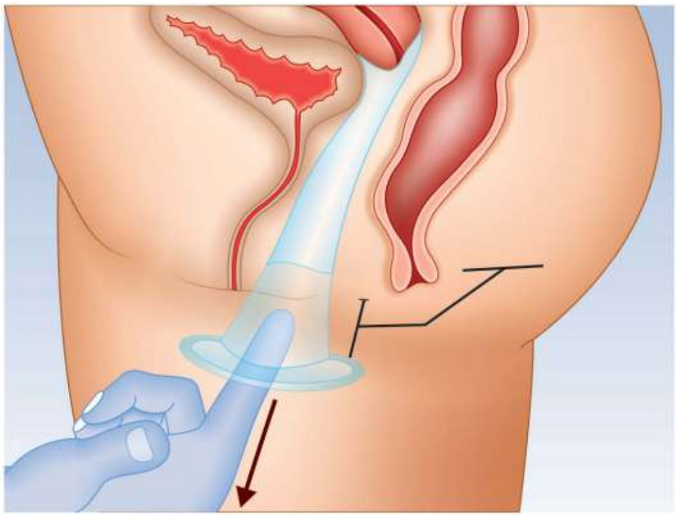


Fig. 86.1: Female condom being placed

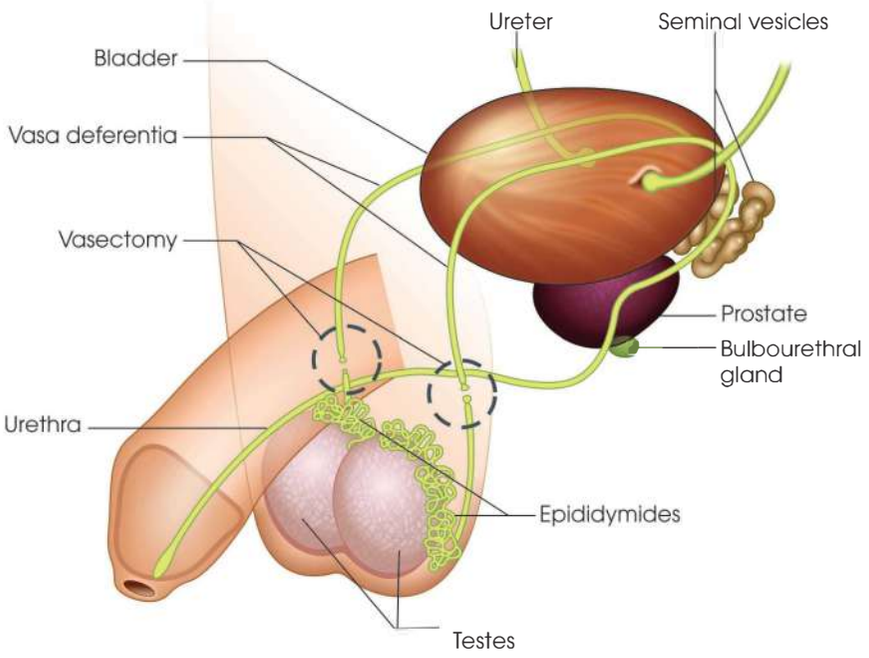


Fig. 86.2: Vasectomy

2. Vaginal douche are used for irrigating the vagina to wash out the sperms after intercourse.

Interruption of normal paths of the sperms or ovum: Sterilization operations are being advocated more and more as a method of permanent contraceptive measure in developing countries like India.

Males: Vasectomy (Fig. 86.2) in males and ligation of the fallopian tubes (tubectomy) in females. Often these measures are permanent and are particularly useful for those who lack in strong motivation, intelligence and fore thought before sexual intercourse.

Following male sterilization operation (vasectomy); the spermatogenesis and hormone production continues normally.

Females: Ligation and division of the fallopian tubes are not associated with any known change in the female physiology. Ovulation and regular menstruation continue. The unfertilized ovum is lost in the peritoneal cavity (Fig. 86.3).

IUCD (Fig. 86.4)

If a foreign body is placed within the uterus the implantation of fertilized ovum in the uterus becomes difficult. This knowledge has been utilized in the use of loop as an intra-uterine contraceptive device (IUCD). Intra-uterine contraceptive device (IUCD) as a method for contraception has been widely tried in India. It is suggested that the presence of an IUCD makes the uterine environment hostile to the nidation of the fertilized ovum, or its presence interferes with the chain of events which leads to the attachment of the blastocyst to the uterine wall. Excessive bleeding uterine cramp (pain), expulsion of the IUCD, infection and uterine perforation are some of the complications of IUCD. Failure rate of IUCD is about 5%.

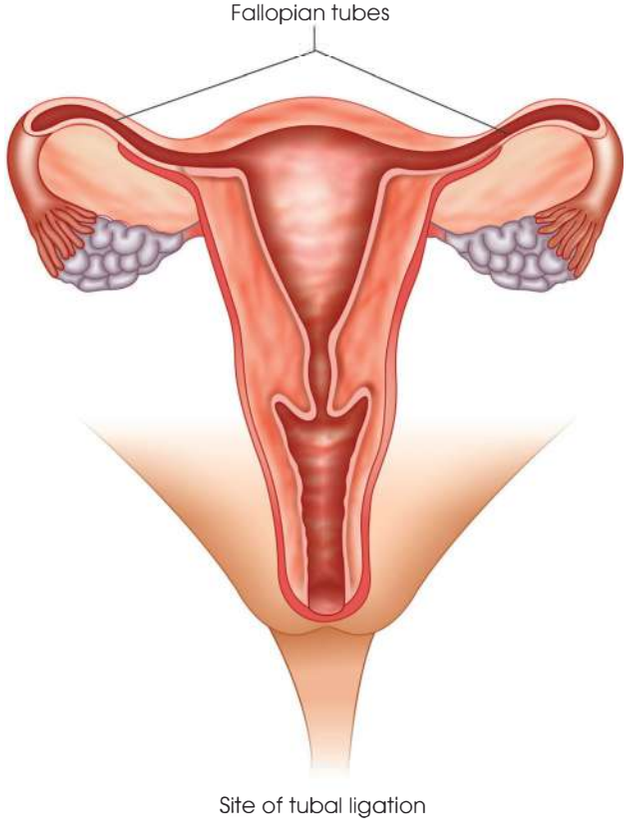


Fig. 86.3: Tubectomy

CONTRACEPTIVE PILLS

The use of hormone or combination of hormones prevent conception, e.g. oral contraceptive pills. Oral contraceptives:

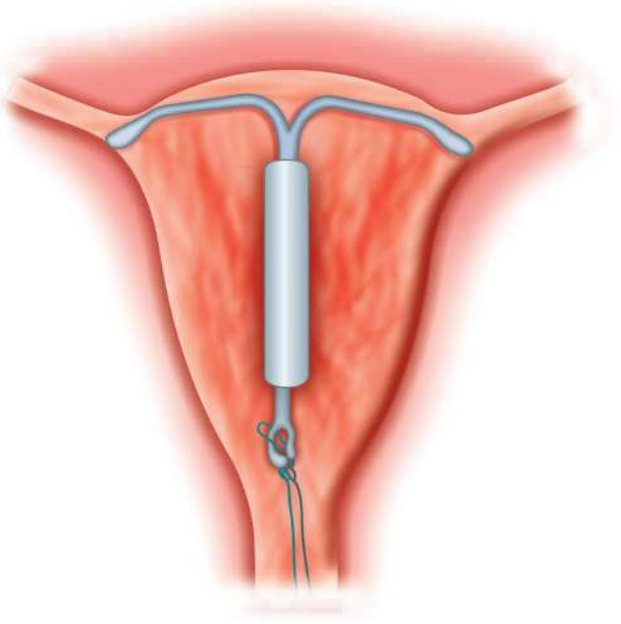


Fig. 86.4: IUCD (intra-uterine contraceptive device)

Of all the contraceptive measures, oral contraceptive pills are most effective. If properly taken, they are nearly 100% successful in preventing pregnancy.

Oral contraceptive regimes are generally of three types: (i) Classical pills regime, (ii) sequential pills regime, and (iii) luteal supplementation pills regime.

A 'classical pill' is a combination of an orally active progesterone-like substance (gestagen or progestational agent) and a small dose of oestrogen. In 'sequential pill regime' patient receives a high dose of oestrogen for part of the cycle followed by a mixture of oestrogen and gestagen. In 'luteal supplementation pill regime' the patient takes progestational agents in low dosage throughout the whole menstrual cycle. Exact modes of action of various contraceptive pills are not definitely known. However, the classical pills inhibit ovulation by (i) suppressing of the midcycle peak in LH output which is brought about probably by modifying secretion of luteinizing hormone release factor (LRF) by hypothalamus; (ii) modifying tubal transport of ovum; (iii) inducing endometrial changes which make nidation of the fertilized ovum unlikely; (iv) render the cervical mucus thicker and hostile to sperm penetration. The sequential pills inhibit ovulation due to its action on hypothalamus which in turn inhibits secretion of mainly follicle-stimulating hormone release factor (GnRH). Sequential pills cause less alteration of the cervical mucus and endometrial changes. Luteal supplementation pills unlike other two preparations do not inhibit ovulation but there occur endometrial changes, changes of the cervical mucus and increases in the motility of the fallopian tubes. The hormonal checkmate produced by the pills leaves the ovary in a quiescent stage. The activity and size of the ovary are consequently reduced.

Different Varieties of Pills

1. Birth control pills: These contain both estrogen and progestin, or only progestin.
2. Implants: Small rods are implanted beneath the skin and they release a continuous dose of hormone to prevent ovulation.
3. Progestin injections are given into the muscles of the upper arm or buttocks once every 3 months as contraceptive measure.
4. Skin patch technique is very preferably used nowadays. It is placed on shoulder, buttocks, or other part on the body. It releases a continuous dose of hormones containing both estrogen and progestin.
5. Vaginal ring is a flexible ring about 2 inches wide. It is placed into the vagina. It releases the hormones containing both progestin and estrogen.

Side Effects of the 'Pills'

Use of oral contraceptive pills does not cause any major alteration of normal physiology. However, usages of oral contraceptives for a long time, have been shown to induce hypertension in susceptible women by causing increased production of angiotensionogen and via renin angiotensin system stimulating aldosterone secretion. The chances of venous thromboembolism, cerebral thrombosis and jaundice are marginally increased after prolonged use of 'pills'.

OTHER METHODS

Progestin implant: Progestin capsules are implanted in the body and its action lasts for months or years. When pregnancy is desired the capsule may be taken out. Progestin in slowly released from the implant and prevents pregnancy by acting on ovulation. It does not stop normal cycles.

Abortion: Abortion is method of contraception when conception has already taken place. Adaptation of this method for controlling population explosion is perhaps the last resort.

EXAM-ORIENTED QUESTIONS

Essay

1. Discuss methods of contraception in males and females.

Short Notes

1. Condom
2. IUCD
3. Oral contraceptive
4. Sterilization methods
5. Tubectomy
6. Vasectomy

CLINICAL CASE SCENARIO

Reproduction

Q1. A 10-year-old girl was diagnosed as a case of precocious puberty. Explain this clinical condition and the cause for the same.

Ans. In precocious puberty there is early onset of puberty. The cause of precocious puberty becomes difficult to ascertain and it can be normal early occurrence or due to damage to the inhibitory system of the brain (infections or trauma), hypothalamic hamartoma, germ cell tumours, congenital adrenal hyperplasia, gonadal tumours, etc.

Q2. A 24-year-old male diagnoses as a case of male infertility. What are the various causes for male infertility?

Ans. The causes for male infertility are testicular tumour and viral orchitis. The congenital cause of male infertility includes cryptorchidism, Klinefelter's syndrome and Kallmann syndrome (gonadotrophin deficiency).

Q3. An 18-year-old married female reported of missed period which surpassed 15 days back. She wanted to confirm the pregnancy. What test will be performed to confirm the pregnancy?

Ans. The immunological test for detection of early pregnancy can be carried out in the patient. Human chorionic gonadotrophins are present in urine of the pregnant woman. In the immunologic test 1 drop of antiserum containing antibody to human chorionic gonadotrophin (hCG) is placed on glass slide. One drop of urine is added and mixed with antiserum by gently rotating the slide for 30 seconds. Two drops of latex antigens are to be added and slide gently rotated for 2 minutes. The pregnancy test is diagnosed to be positive if agglutination is absent.

Q4. A 22-year-old married male with undescended testis was diagnosed as a case of sterility. Diagnose the condition. What is the cause for sterility?

Ans. The clinical condition of undefended testis is known as cryptorchidism. The high temperature in the abdomen prevents the complete development of seminiferous tubules due to which the spermatogenesis does not occur leading to sterility.

Q5. A 19-year-old married female reported to the hospital with complaints of unprotected intercourse last night and fear of getting pregnant. How will you counsel the patient?

Ans. The female may be advice to take the classical pill (progestin with oestrogens), the two of this tablet may be taken immediately and another two after twelve hours. This regime is recommended within two days of unprotected intercourse to prevent pregnancy.

Q6. Describe the congenital abnormalities: Androgen insensitivity syndrome and intersexuality.

Ans. Androgen insensitivity syndrome is a genetic disorder in which genetically male develop sexually as a female due to failure in utilization of androgens. Intersexuality: A person who has gentalia and or sexual traits which are not clearly male or female.

Q7. A 32-year-old male was diagnosed as case of impotency. What are the likely causes of impotency?

Ans. The likely cause of impotency is disease such as diabetes mellitus, multiple sclerosis, cavernosa disorders, neurogenic disorders, patient on antidepressant therapy, smoking and in patient suffering from anxiety disorders.

IN VITRO FERTILIZATION: 2010 NOBEL PRIZE FOR PHYSIOLOGY AND MEDICINE

86

Sir Robert Geoffrey Edwards was an English Physiologist and Pioneer in reproductive medicine was awarded 2010 Nobel Prize for Physiology and Medicine for the development of *in vitro* fertilization.

1925–2013

Willard Myron Allen (1904–1993) an American Gynaecologist conducted research with his anatomy professor, George W. Corner in 1927 monitoring changes in the corpus luteum of rabbits. The corpus luteum produces progesterone, which is required for the maintenance of pregnancy. This hormone was unknown until Allen and Corner's discovery of it in their experiments. For this research, Allen earned a master's in science in 1929. He is well known for his description of the "Allen-Masters" syndrome which is the laceration of ligaments causing abnormal mobility of the cervix.

The first 'test tube baby' Louise Brown in 1978 was born in Manchester, UK, by the ingenious work of Patrick Steptoe and Robert Edwards. Sir Robert Geoffrey Edwards, was an English Physiologist and Pioneer in reproductive medicine, and *in vitro* fertilization (IVF).

Charles Brenton Huggins (1901–1997) was awarded the Nobel Prize for Physiology or Medicine in the 1966 for discovering that hormones could be used to control the spread of some cancers. He specialized in prostate cancer research. **Charles Brenton Huggins.**

Edgar Allen (1892–1943) was an American Anatomist and Physiologist who discovered oestrogen and also studied the hormonal mechanisms that control the female reproductive cycle.

Elwood Vernon Jensen (1920–2012) received the Albert Lasker Award for Basic Medical Research in 2004 for his research on estrogen receptors. Elwood Jensen in 1961was first to identify that the hormone action is mediated via nuclear receptors as he tracked radioactively labelled oestradiol-17β in female sexual tissues formed a complex in the nucleus with a protein receptor. ►

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Section

X

Nervous System

Chapter

87

Introduction to Nervous System

INTRODUCTION

The nervous system is the most important organisation which controls and integrates the different bodily functions and likewise maintains a stability or constancy of the internal environment despite extreme changes in the external environment. The activity of the nervous system depends upon a complex interplay of numerous dynamic interactions or regulatory reactions. This system is absolutely necessary for the reception, storage and release of different sensory and motor information for regulating or initiating a particular behaviour of the individual ranging from the cellular to the gross animal being. The unique feature of nervous system is that unlike any other systems, the nervous system can inhibit or modify any sensory signal so any unimportant sensory impulse can be ignored without responding to it. It is a very complicated system; structures and organs are specialised for different specific purposes.

The whole nervous system can be divided into two main systems:

1. Central nervous system.
2. Peripheral nervous system.

> The central nervous system consists of brain and spinal cord, whereas the peripheral nervous system consists of: (i) Craniospinal nerves having 12 pairs of cranial nerves and 31 pairs of spinal nerves (Fig. 87.1A), (ii) visceral nervous system comprising sympathetic nervous system and parasympathetic nervous system. The above subdivisions have been presented schematically.

Although functionally and structurally the surface epithelium and the nerve cells have departed a long way from each other, yet the fact stands that they are the offspring of the same parent—the ectoderm.

CENTRAL OR SOMATIC NERVOUS SYSTEM

The central or somatic nervous system (Figs 87.2 to 87.4) is symmetrically arranged into two lateral halves—one-half being the mirror image of the other. It consists broadly of:

1. Spinal cord—inside the vertebral column
2. Brain—inside the cranial cavity—skull. The foramen magnum is the limiting line.

SPINAL CORD

1. Spinal cord being surrounded by its covering lies loosely within the vertebral column and is extended from the foramen magnum as far down as the interspace between the 12th thoracic segment and the lower border of the 1st lumbar vertebra.
2. During early development (Fig. 87.3), the spinal cord is extended up to the lower end of the sacrum, but with the further development and mostly at fourth month of development, the vertebral column is elongated more rapidly than the spinal cord. Due to in proportionate development of the cord and the vertebral column, the spinal cord, being anchored to the medulla oblongata, is pulled upward in the spinal canal and causing its caudal end to reach the lower border of the first lumbar spines in individual to individual and it is slightly lower in women.
3. The spinal cord is mostly cylindrical in shape and is flattened anteroposteriorly. It has got two swelling, one in cervical-6 and other in lumbar-3 of the spinal cord (Fig. 87.1B).
4. Physiologically, the spinal cord is regarded as made up of a series of superimposed segments, from each of which a pair of nerve roots arise.
5. Intrinsically the spinal cord is a continuous and unsegmented structure with 31 pairs of nerves emerging from it.
6. Each segment of the spinal cord gives rise to dorsal and ventral root filaments.
7. Dorsal and ventral roots together form a single pair of nerves. 31 segments of the spinal cord

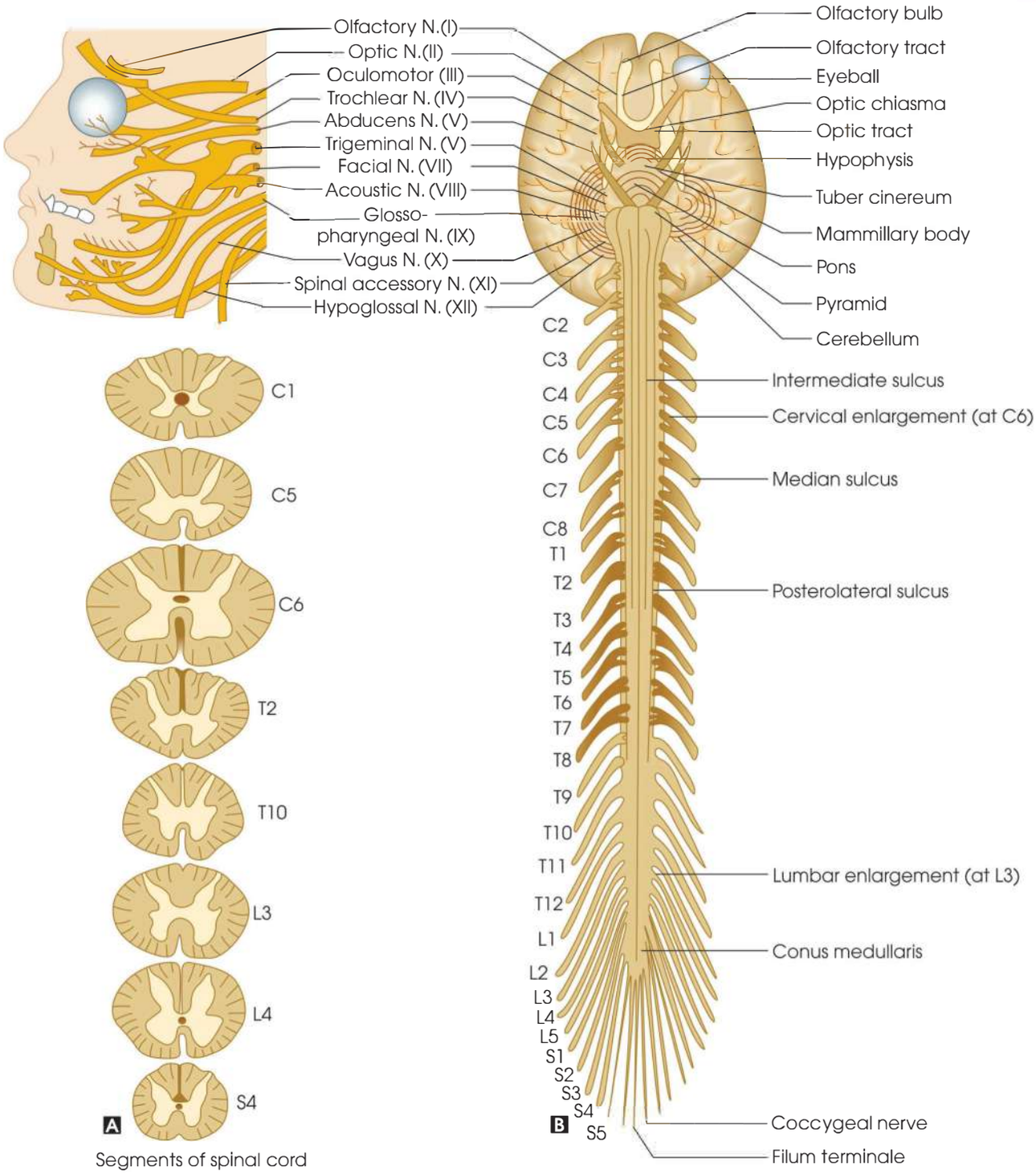
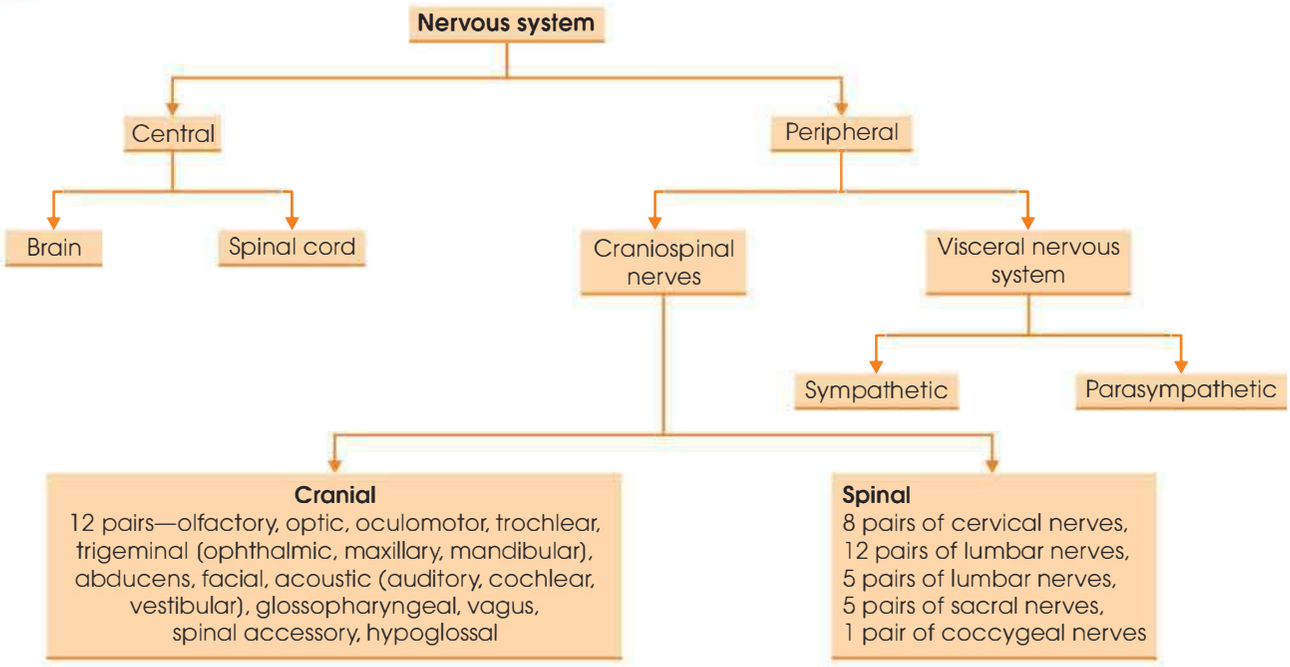


Fig. 87.1A and B: Diagrammatic representation of the brainstem with 12 pairs of attached cranial nerves; spinal cord with 8 pairs of cervical nerves, 12 pairs of thoracic nerves, 5 pairs of lumbar nerves, 5 pairs of sacral nerves and 1 pair of coccygeal nerves in A. Some spinal cord segments at different levels varying in shape, size and topography of grey and white matter with letters and numbers of the corresponding segments in B

correspond to 8 pairs of cervical and 12 pairs of thoracic, 5 pairs of lumbar and 5 pairs of sacral and 1 pair of coccygeal nerves.

8. As the cord ends at the level of lower border of the 1st lumbar vertebra, spinal segments evidently do not correspond numerically with the vertebrae overlying them. Thus, during early development, each segment of the spinal cord corresponds closely with the respective embryonic vertebrae.
9. The spinal nerves also pass at laterally to their intervertebral foramina. But later as the vertebral column develops more rapidly than the spinal



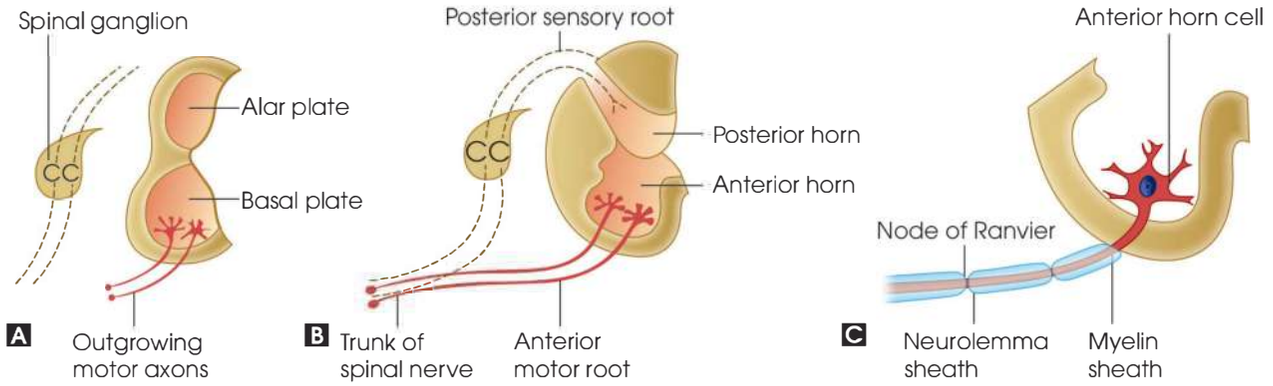


Fig. 87.2A to C: A shows outgoing motor axons of cells in the basal plate and the centrally and peripherally growing fibres of the nerve cells in spinal ganglion. In B, nerve fibres of the ventral motor and dorsal sensory roots join to form the trunk of the spinal nerve. In C, diagram shows an anterior horn cell and its axon surrounded by neurolemma and myelin sheath

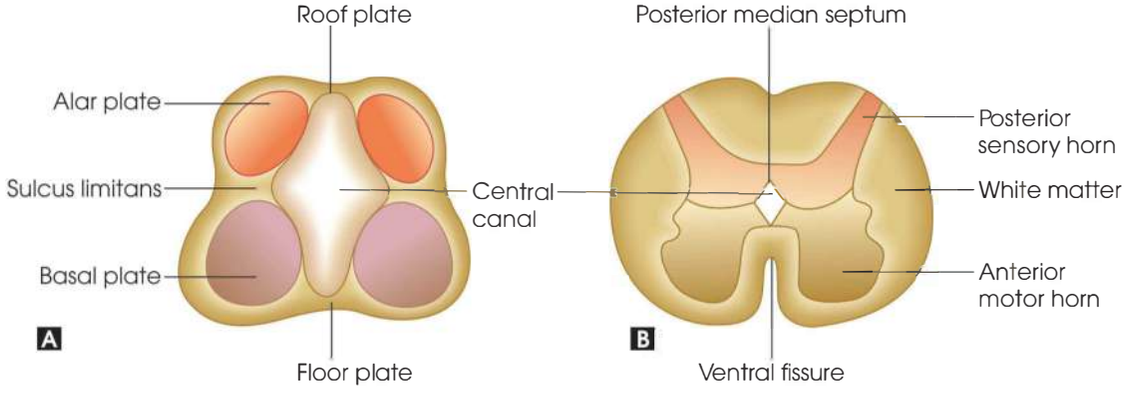


Fig. 87.3A and B: Diagrammatic representation of two successive stages in the development of the spinal cord showing the formation of anterior and posterior horns, etc.

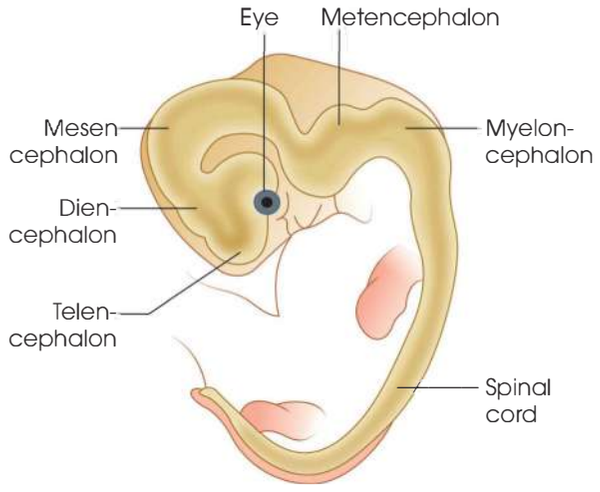


Fig. 87.4: Diagrammatic representation of development of the nervous system, showing the neural tube in stipple. Note the expansion at the cranial end and constrictions demarcating subdivisions of the brain

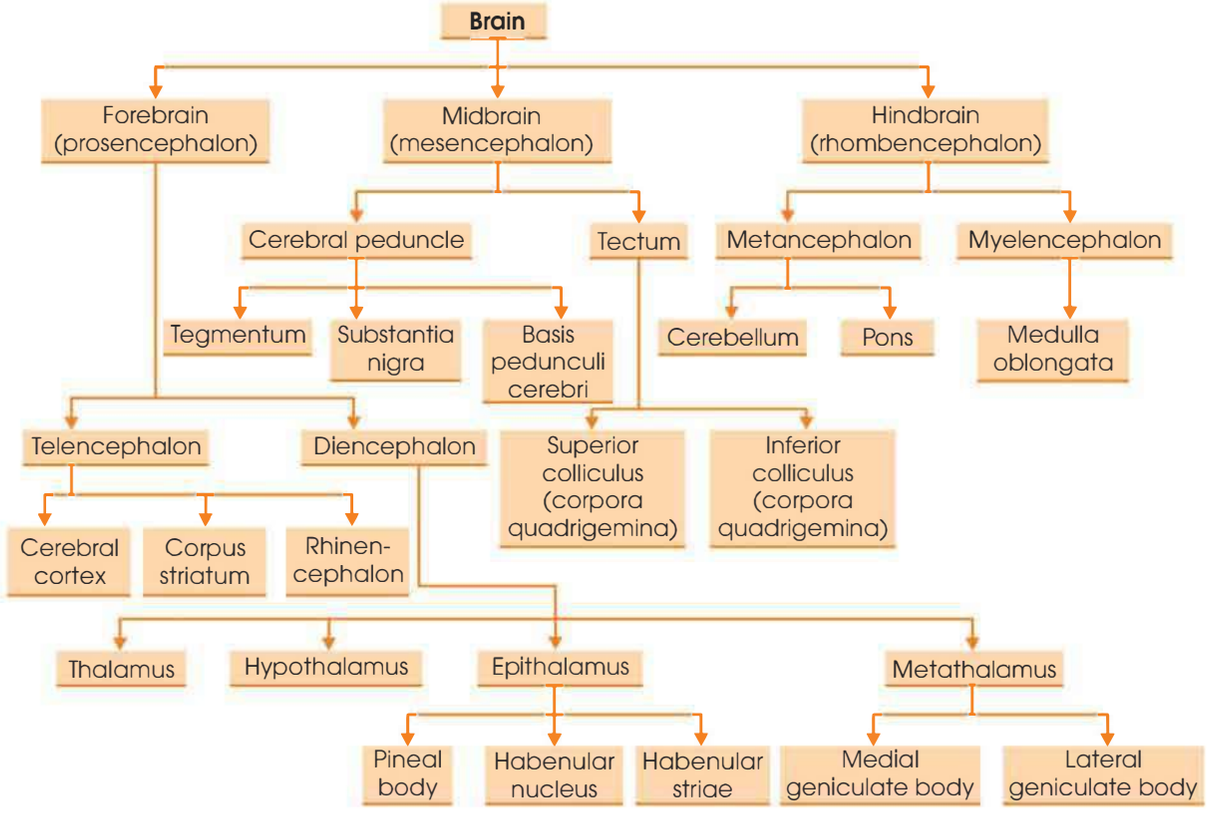
cord, the segments of the latter does not correspond the respective vertebra. For this reason the interval between the spinal origin of the nerve and its vertebral exit is different from segment to segment. Hence, the lumbar and sacral nerves have long roots (Fig. 87.5).

10. Spinal cord from its upper limit to the tip of the conus medullaris is about 45 cm in the male and 43 cm in the female. The weight of the spinal cord is about 35 gm.

BRAIN

Brain may be subdivided (Figs 87.6 and 87.7) as follows:

1. **Medulla:** It is situated in the posterior cranial fossa. It is the upward continuation of the cervical spinal cord extending from the foramen magnum to the caudal border of the pons. It is the centre for the autonomic reflex control of the circulation, heart and lungs. It is also the integrated autonomic reflex centre for swallowing, coughing, sneezing, gagging and vomiting.
2. **Pons:** It is situated in front and above the medulla, with various nuclei and tracts. It appears anteriorly as a bulging mass of transverse fibres and is separated from the cerebellum posteriorly by the IV ventricle. Furthermore, the external feature of the pons is the broadband of predominantly transverse fibres. It is demarcated from the cerebral peduncles of the midbrain by the superior pontine sulcus and from anterior surface of the medulla by the inferior pontine sulcus.
   The pons takes part in regulation of respiration and also other important vital regulations.
3. **Cerebellum:** Above and behind the medulla and attached to the central nervous system by three peduncles: Superior, middle and inferior. The cerebellum is concerned with the co-ordination and adjustment of smooth movement. It is thus related with posture. Degree and extent of movement (volitional) is determined by cerebellar feedback control.



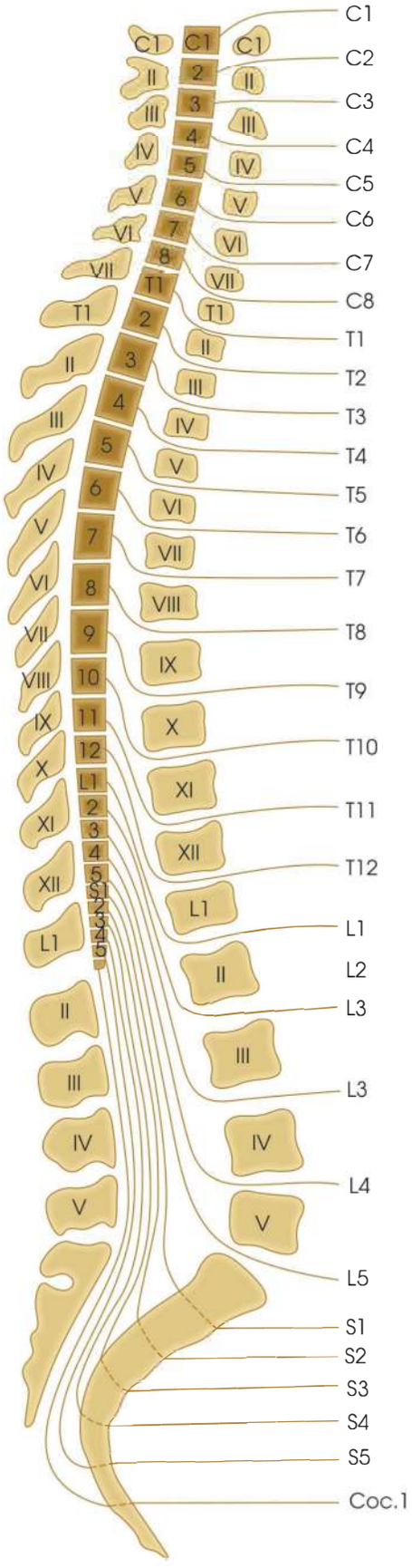


Fig. 87.5: Diagrammatic representation of the segments of the spinal cord with reference to the bodies and spinous processes of the vertebrae (Haymaker and Woodhall)

4. **Midbrain:** It is the upward continuation of the brainstem. Through it passes the aqueduct of Sylvius. Dorsally to the aqueduct (tectum) are present certain collections of the nerve cells, viz. superior colliculus, inferior colliculus. Laterally and below the aqueduct lay the red nucleus and the third nerve nucleus. The part ventral to the aqueduct is called the cerebral peduncle. The peduncle is divided by a dark line of nerve cells containing melanin called the substantia nigra into two areas: Ventral and dorsal. The ventral area is called the crusta or pes. The cortical fibres descend through it. The dorsal area is called tegmentum. Through it pass, the entire ascending and some descending fibres, such as the medial fillet, the lateral fillet, the ventral, dorsal and longitudinal bundles, the rubrospinal and tectospinal tracts, etc.
5. Geniculate bodies—medial and lateral.
6. Cerebrum
7. Thalamus
8. Basal ganglia: Hypothalamus.

Meninges, Ventricles and Cerebrospinal Fluid

The brain and spinal cord remain covered by three membranes (meninges), which from outside inwards are known as dura mater, arachnoid mater and pia mater (Figs 87.9 and 87.10); under the arachnoid there is subarachnoid space, containing cerebrospinal fluid. The interior of the nervous system is hollowed out by four cavities (ventricles) and two canals, all filled up with cerebrospinal fluid. One cavity is present in each cerebral hemisphere, called the lateral ventricle.

They open into a common central cavity—the third ventricle, through an opening on each side—the foramen of Monro (interventriclular foramen). The third ventricle is continued down through the midbrain as the aqueduct of Sylvius (cerebral aqueduct) (Figs 87.7 to 87.9). The aqueduct opens into another dilatation in the medulla—the fourth ventricle, which again is continued downwards as the central canal of the spinal cord.

The roof of the fourth ventricle has three perforations—the central one is called the foramen of Magendie ending directly to the cisterna magna, and the two lateral ones—the foramina of Luschka ending into the cisterna pontis on the basal aspect of the brainstem. Through these foramina, the cerebrospinal fluid enters the subarachnoid space (Fig. 87.11). Thus, the cerebrospinal fluid surrounds the whole central nervous system being both inside and outside it. The ventricles and canals are lined by a ciliated cubical epithelium, called the ependyma. The movements of the cilia help the circulation of the cerebrospinal fluid.

Blood Supply

Very rich—the average blood flow of normal subjects in resting condition is 54 ml per 100 gm of brain tissue

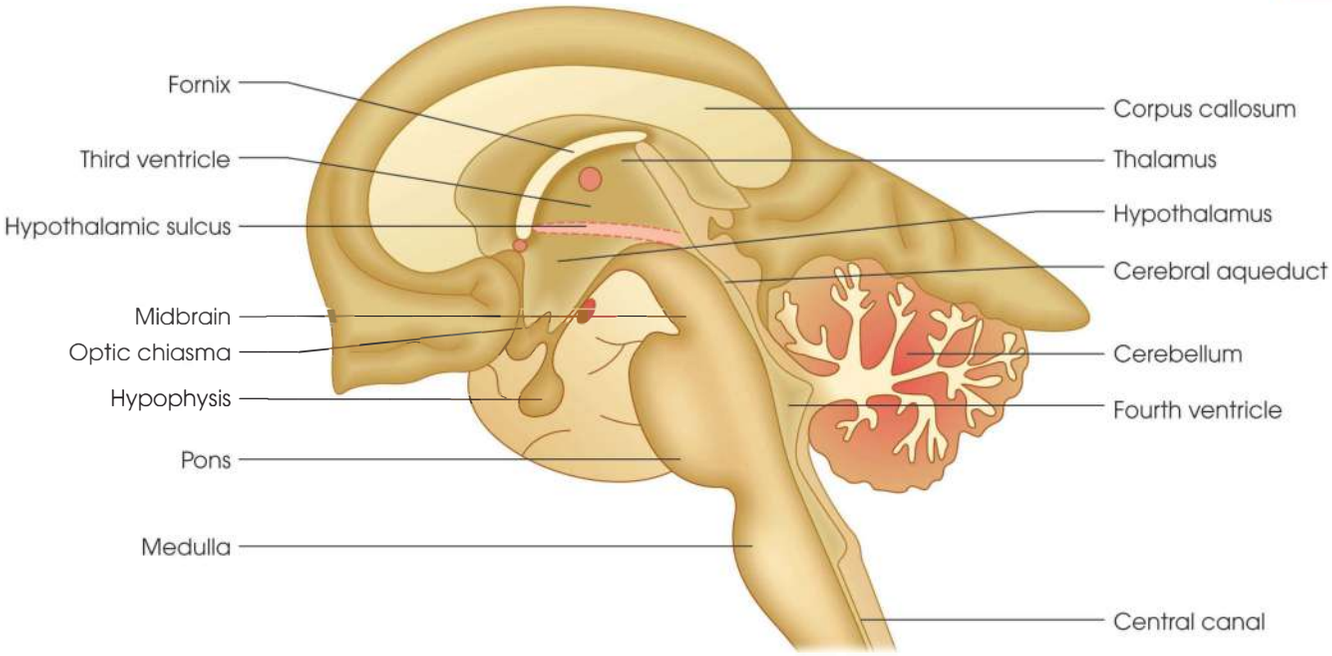


Fig. 87.6: Diagrammatic representation of median sagittal section of the brainstem

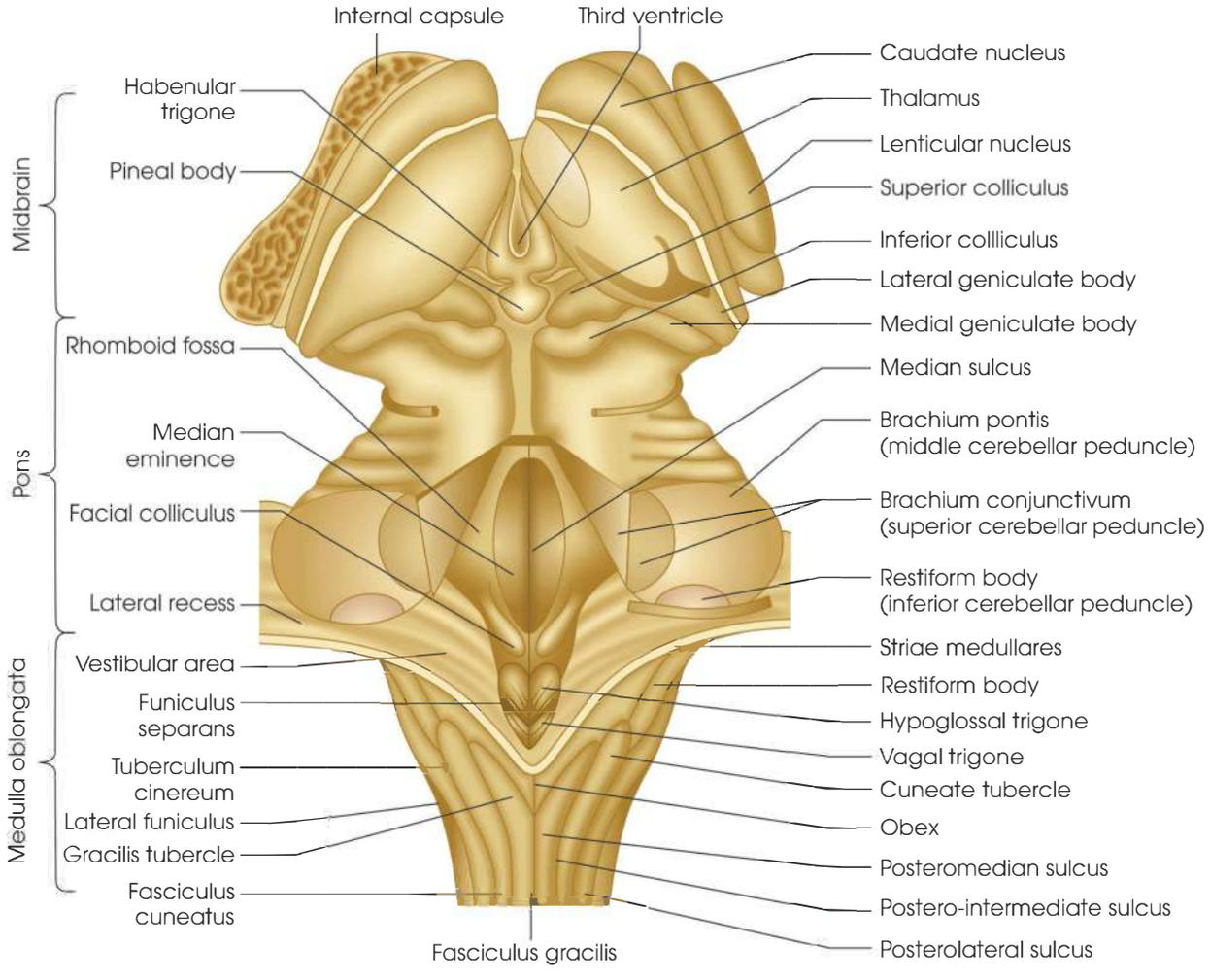


Fig. 87.7: Diagrammatic representation of the ventricles of the brainstem showing the lateral view at the left side and the dorsal view at the right side

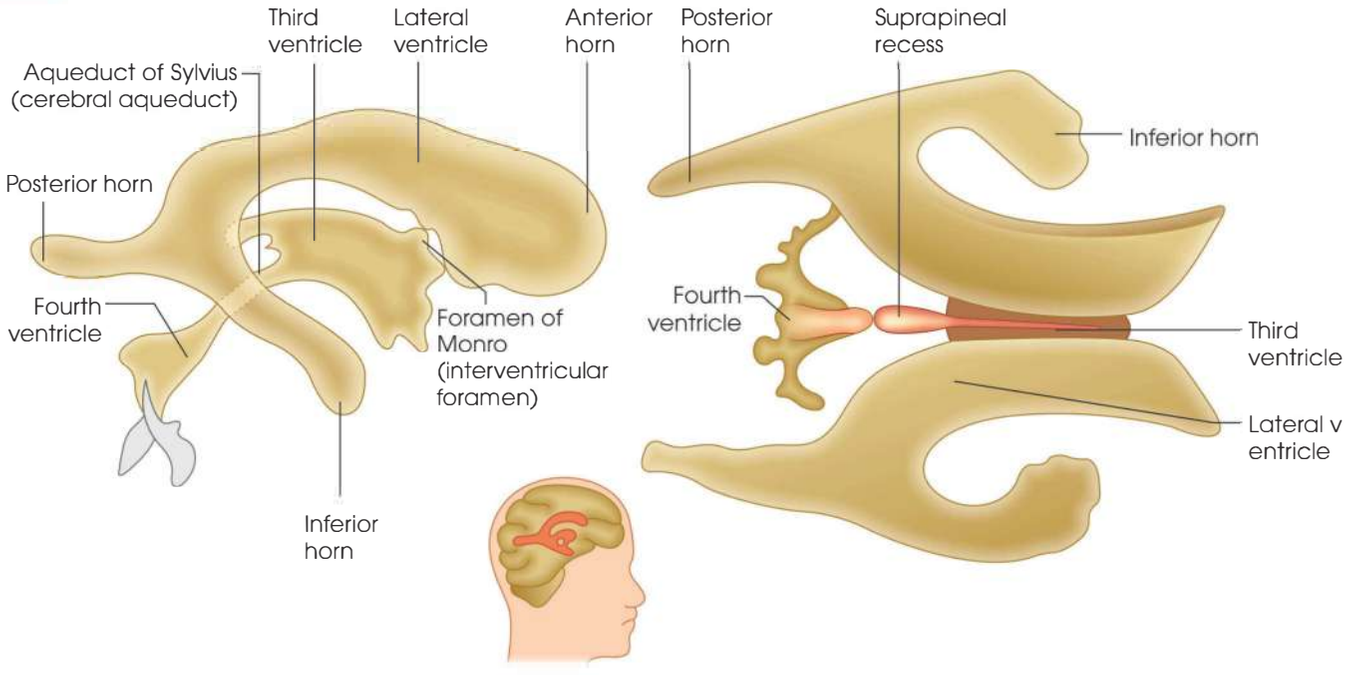


Fig. 87.8: Diagram showing the posterior view of the human brain stem

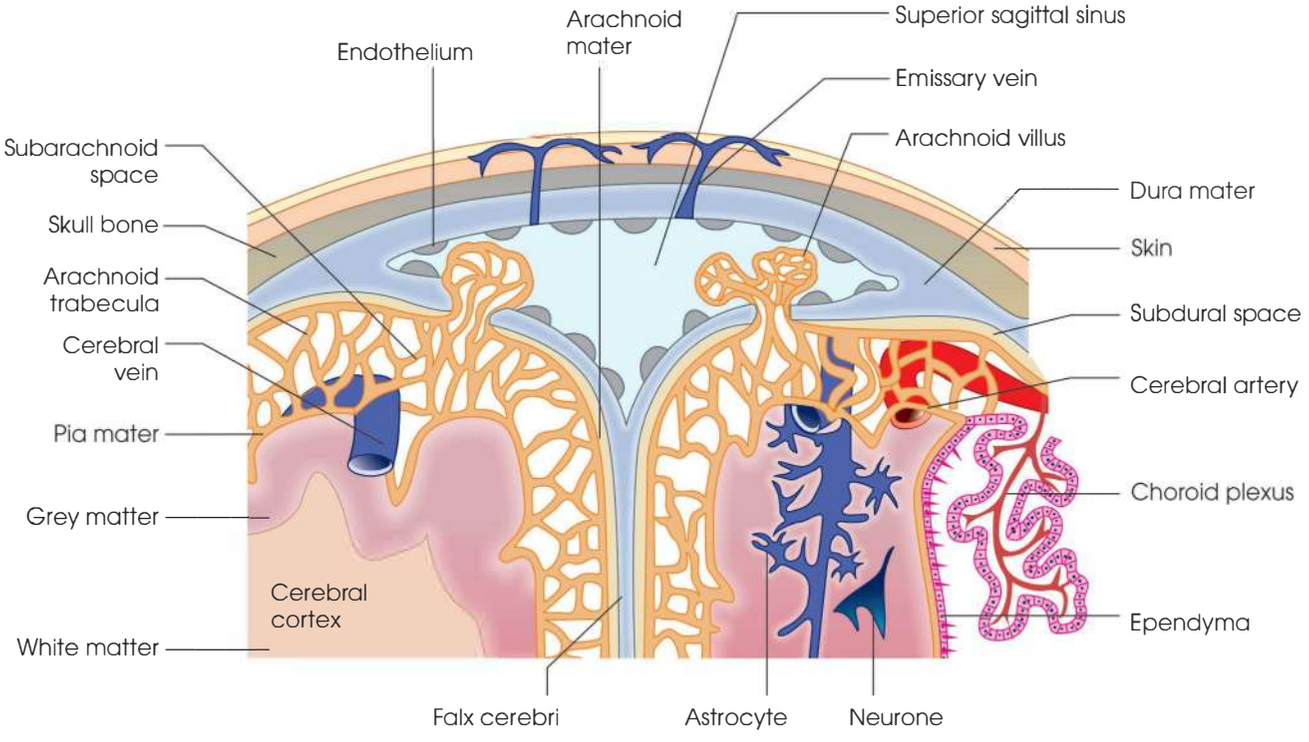


Fig. 87.9: Diagrammatic representation of the coronal section through the vertex of the cranium showing the cerebral meninges, superior sagittal sinus and arachnoid villus in relation to the brain and skull bone

per minute. Taking the weight of brain as 1400 gm, the total cerebral blood flow is 750 ml or above per minute.

Metabolism

- O_2 consumption of nervous system is 3.5 ml per 100 gm per minute
- Respiratory quotient of nervous system is 0.99 per 100 gm per minute.
- Glucose consumption of nervous system is 5.5 mg per 100 gm per minute. Very little store of food or O_2.
- Hence, it is easily affected by anoxic, toxic or metabolic derangements.

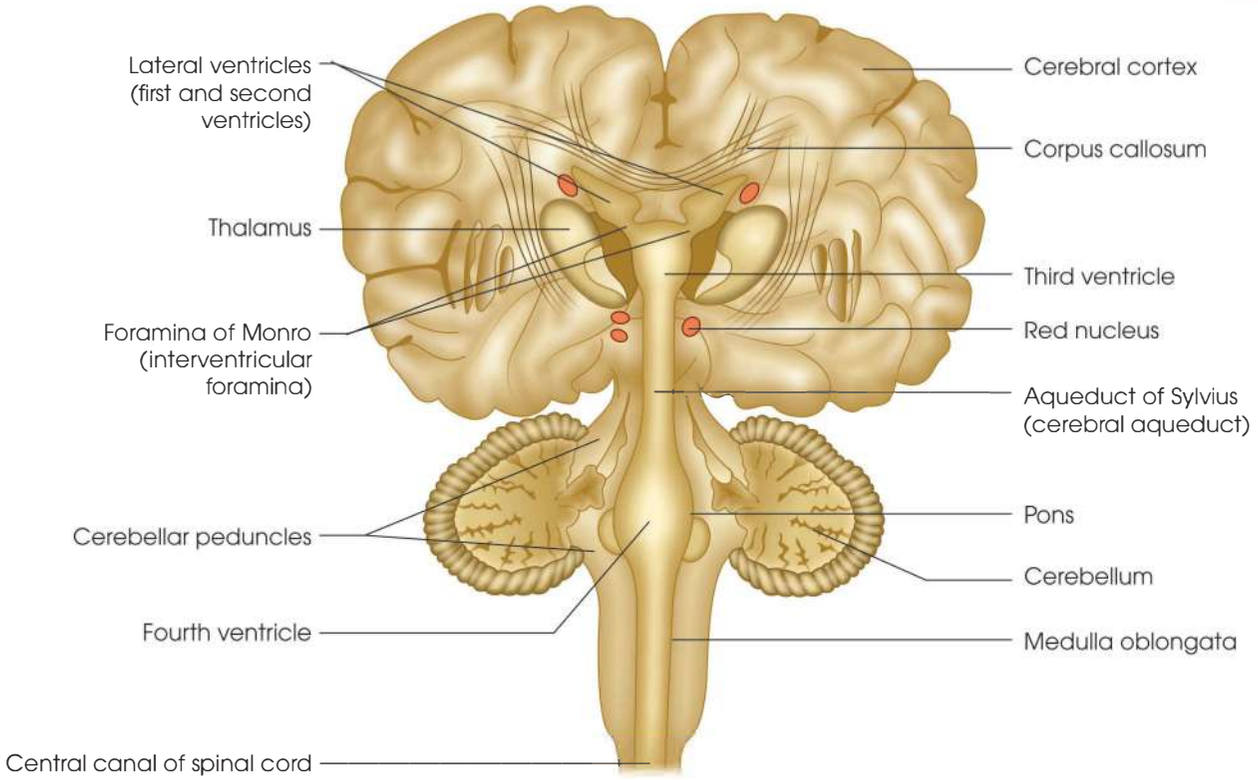


Fig. 87.10: Diagrammatic representation of the coronal section through cerebral hemispheres, brainstem and spinal cord showing approximate relationship of the important parts

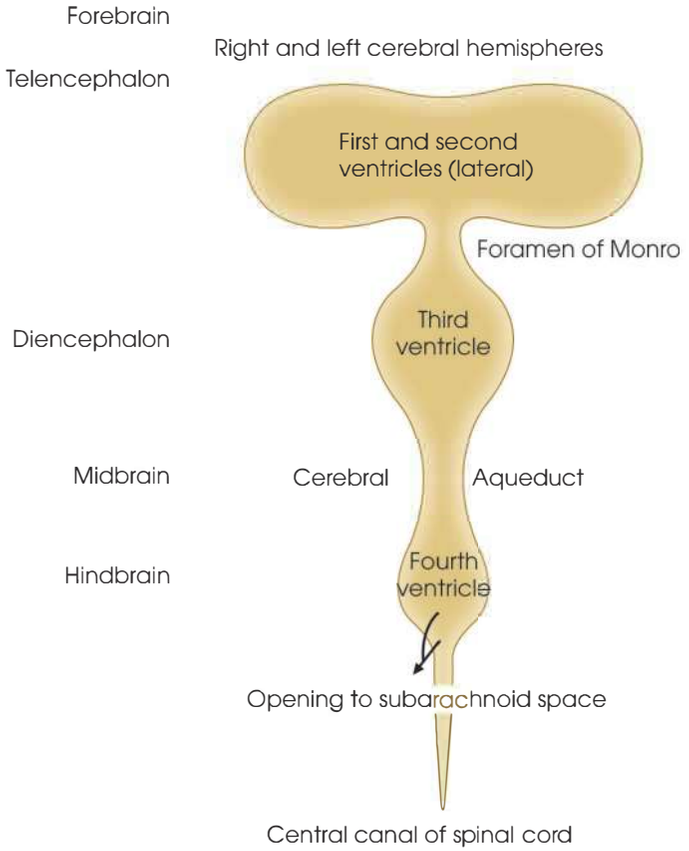


Fig. 87.11: Schematic representation of the four ventricles in the brainstem corresponding to early formation of the forebrain (with specialised developing formation of the telencephalon—forming right and left cerebral hemispheres and the diencephalon), to the midbrain and the hindbrain

David Hunter Hubel
1926–2013

Torsten Wiesel
1924–

David Hunter Hubel, a Canadian neurophysiologist and Torsten Wiesel received the Nobel Prize in Physiology or Medicine (shared with Roger W. Sperry), for their discoveries concerning information processing in the visual system in 1981.

Roger Wolcott Sperry was a neuropsychologist and neurobiologist who was awarded the Nobel Prize in Physiology or Medicine in 1981 along with David Hunter Hubel and Torsten Nils Wiesel for his work with split-brain research.

Roger W. Sperry
1913–1994

EXAM-ORIENTED QUESTION

Short Notes

1. Brain
2. Spinal cord
3. Cerebrum
4. Cerebellum
5. Meninges
6. Midbrain

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Chapter

88 General Principles of the Nervous System

The following broad facts about the arrangement and working processes of the nervous system will be very helpful for further study.

1. **Divisions of nervous system:** Nervous system has two parts:
   a. *Central or somatic nervous system* (cerebrospinal or voluntary)
   b. *Autonomic nervous system* (vegetative of involuntary).

   The later is generally unconscious and is not under the control of 'will'. It reflexly regulates the activities of the viscera. The former is responsible for consciousness and voluntary control.
2. **Symmetrical arrangement:** The nervous system is arranged symmetrically into two lateral halves. Consequently, except a few, all the centres, tracts, nerves, etc. are bilateral.
3. **Neuron doctrine:** The neurons are the structural and functional units. They communicate with each other directly or indirectly through synapses. A synapse is a relay station which transmits the impulse from one neuron to the other.
4. **Principle of peripheral control:** Control of the spinal cord and cerebellum is same-sided (homolateral or ipsilateral), i.e. one lateral half of these structures controls the same half of the body. But the control of cerebrum, thalamus and corpus striatum is mostly opposite-sided (contralateral), i.e. the structures on one side control the opposite half of the body.
5. **Three-neuron arrangements:** From the periphery to the centre there are generally three neurons and two synapses.
6. **Principle of decussation:** Nerve tracts destined for thalamus and cerebral cortex will cross and their control is contralateral. Crossing takes place always in the second neuron. But spinal and cerebellar connections do not cross as their control is homolateral.
7. **Principle of exit and entrance (Bell-Magendie law):** Nerve fibres entering the spinal cord go through the posterior root and nerve fibres emerging from the spinal cord come out through the anterior root.
8. **Seat of consciousness:** Consciousness depends upon the coordinated activities of interneurons of the brain.
9. **Varieties of nerve impulses:** Two types of nerve impulses are described.

Afferent and Efferent

Afferent: These are sensory, centripetal or incoming impulses. They may be either conscious or unconscious. They are subdivided into three groups.

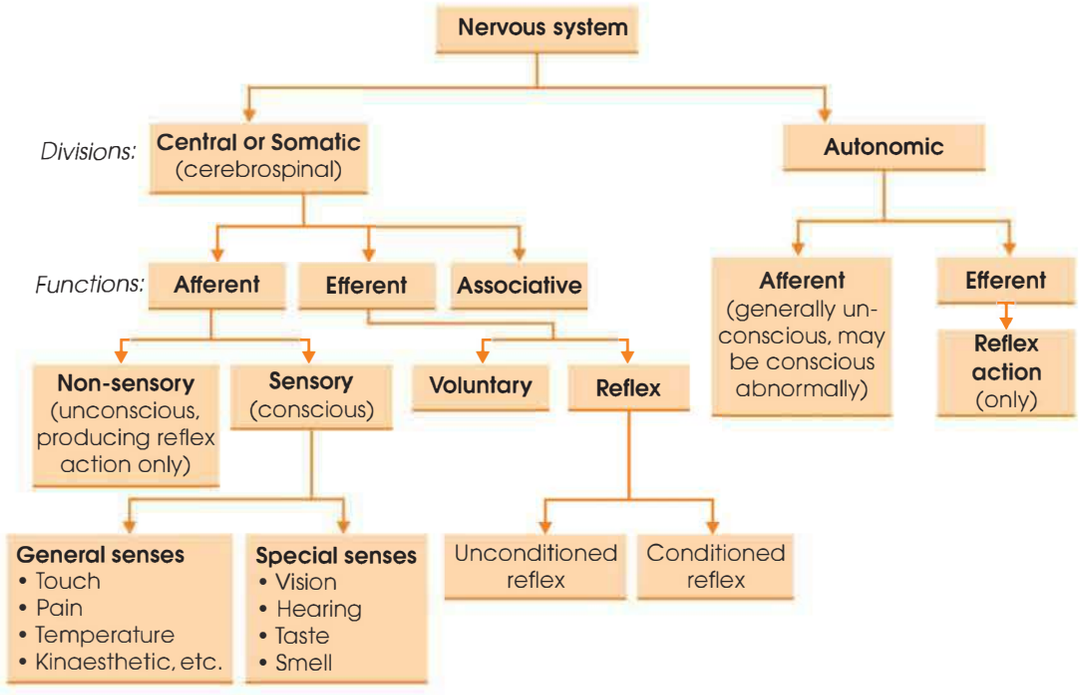
a. *Exteroceptive:* Impulses set up by stimuli coming from outside, viz. (a) cutaneous senses like touch, pain, temperature, etc. and (b) special senses like vision, hearing, taste and smell.
b. *Proprioceptive:* Kinesthetic impulses, i.e. those coming from the muscles, tendons, ligaments, joints, etc. The labyrinthine impulses (vestibular) belong to this group. Proprioceptive impulses give information regarding the position of the head and other parts of the body.
c. *Enteroceptive:* These are impulses arising from the viscera. They mostly belong to the autonomic system.

Efferent: These are outgoing, centrifugal or motor. These again may be of two types:

a. Reflex (involuntary)
b. Voluntary (motor unit).

General functions of the nervous system: Depending on the type of nerve impulse and its interpretation, functions of the nervous system may be of the following three types:

1. *Sensory functions:* These may be either conscious or unconscious. When conscious they are called sensations. In the involuntary nervous system they are usually unconscious.
2. *Motor functions:* These may be of two types:
   a. Reflex or involuntary.



b. Voluntary: In the autonomic nervous system, all motor effects are reflex. In the central or somatic system motor functions are involuntary (reflex) or voluntary.

3. *Associative functions:* For instance, idea, memory, intelligence, etc. These are carried out mainly by the cerebrum.

A brief summary of the functional divisions of the nervous system is given in the following scheme:

Note

Neuron, structure, classification of nerve fibres, properties of nerves and neuronal transmission has been explained in Section of Nerve Muscle Physiology.

Classification of Neurotransmitters

The neurotransmitters are synthesized in the neuron; they become localized in presynaptic terminal; they bind to receptor site on postsynaptic membrane and are removed by enzymatic action from its specific site of action.

They are classified as small molecule transmitters and large molecule transmitters.

Small molecule transmitters

1. Acetyl choline
2. Amines: Dopamine, epinephrine, norepinephrine and serotonin.
3. Amino acids: Excitatory: Aspartate and glutamate
4. Amino acids: Inhibitory: Glycine and GABA
5. ATP

Large molecule transmitters are

1. Opioid peptides: Enkephalin, endorphin, vasopressin and substance P
2. Gases: Nitric oxides
3. Others: Purine, pyrimidines, cannaboids (anandamide)

NATURE OF TRANSMISSION IN THE CNS: SMALL MOLECULE TRANSMITTERS

A. Acetylcholine: Cholinergic Transmission (Figs 88.1 and 88.2)

1. It is the excitatory neurotransmitter and acts on postganglionic sympathetic junction, neuromuscular junction, postganglionic parasympathetic nerve ending, preganglionic nerves in CNS, motor nerves, along projection of basal forebrain complex to hippocampus and neocortex and postmesencephalic complex. Acetyl CoA combines with choline in presence of choline acetyltransferase to form acetylcholine.
2. It is degraded by acetylcholine esterase (AChE) .
3. They act via nicotinic and muscarinic receptors. The muscarinic receptors are of five types M1 (located on autonomic ganglia), M3 on glands and smooth muscles, M2 on heart and M1, M4 and M5 in CNS.
4. Damage to the cholinergic nerve ending in the brain is associated with the memory deficits associated with Alzheimer's disease. It promotes REM sleep causes parkinsonism-like state, has been shown to alter the metabolism of dopamine.

The stimulatory action of acetylcholine on smooth muscles and gland is mediated via muscarinic receptor while stimulatory action on sympathetic ganglia and skeletal muscle is mediated by nicotinic receptors.

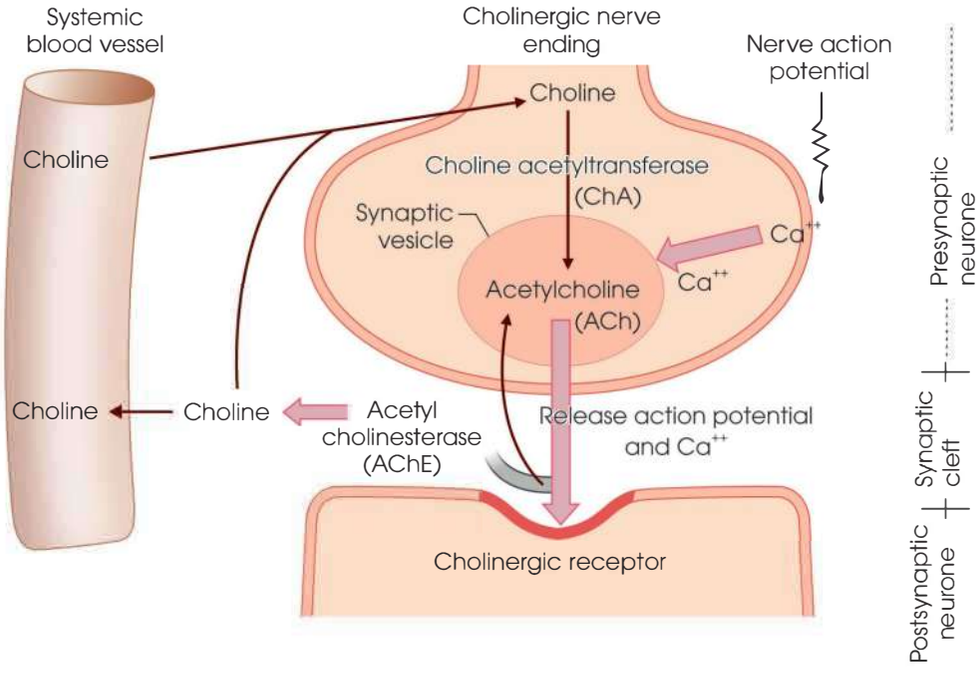


Fig. 88.1: Processes involved in synthesis, release and deposit of ACh at cholinergic nerve terminals and receptor site during transmission of nerve impulse

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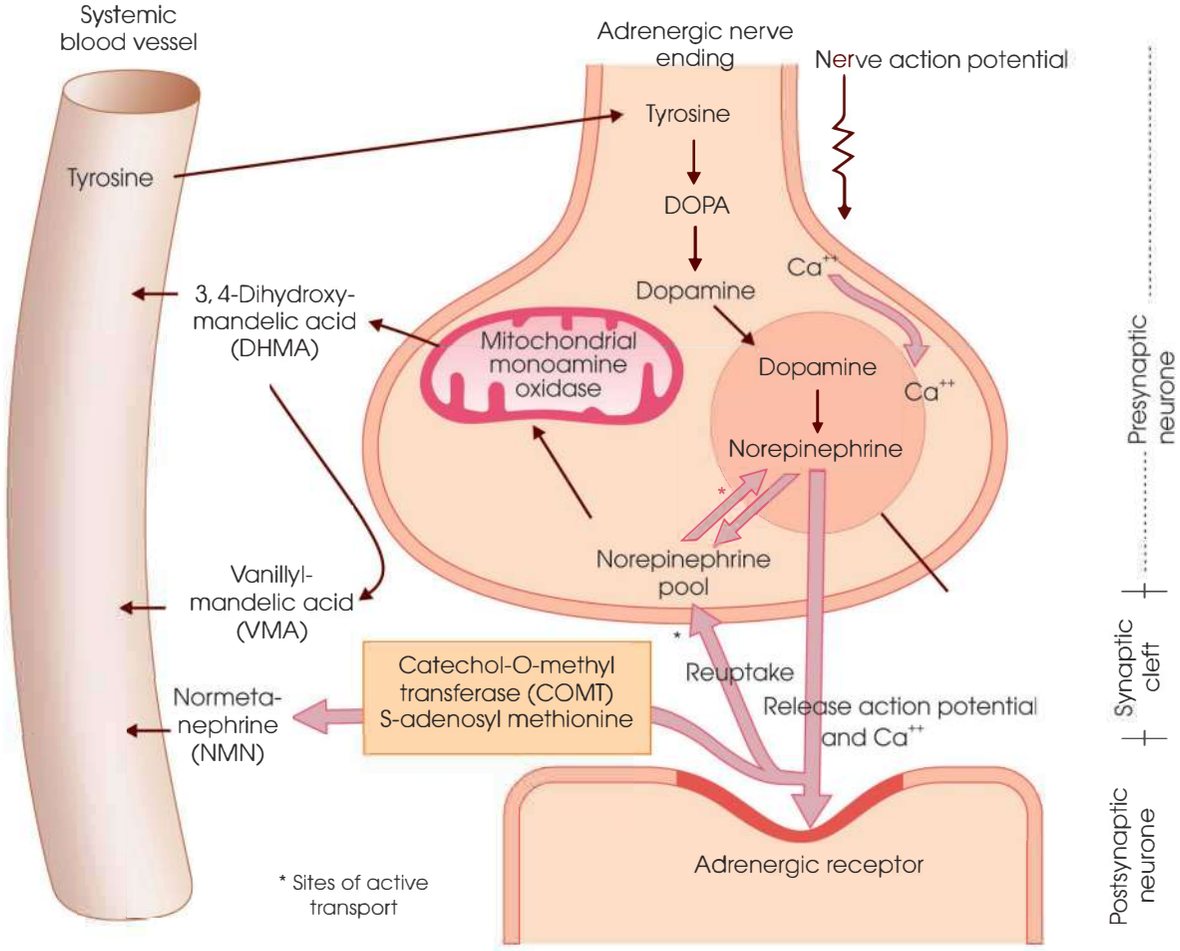


Fig. 88.2: Processes involved in synthesis, release and deposit of norepinephrine at the adrenergic nerve terminal and receptor site during transmission of nerve impulse
*Sites of active transport

B. Central Adrenergic Transmission

Epinephrine and norepinephrine are the major transmitter agent in the postganglionic sympathetic neurons. Norepinephrine is produced in brain in the locus coeruleus, which are located in the pons. Epinephrine and norepinephrine are secreted from adrenal medulla.

Key Points

1. Epinephrine and norepinephrine are produced by hydroxylation and decarboxylation of tyrosine. They by catabolism form normetanephrine, metanephrine and vanillylmandelic acid.
2. Midbrain, pons, medulla; cerebral cortex, hippocampus, cerebellum and spinal cord contains catecholamines in lower concentration. In the hypothalamus, olfactory bulb, retina, median eminence, limbic system, large amounts of amines are present. There action is mediated via α and β receptors. Epinephrine action is pronounced on β while norepinephrine is having more affinity for α receptors. Norepinephrine acts via α_1, β_{1-2} (postsynaptic, excitatory) and action via α_2 receptor is inhibitory. The α_1 receptors are located in smooth muscle, α_2 in CNS, nerve terminals and islet cells of pancreas, β_1 on heart, β_2 on bronchial smooth muscles, JG cells of kidney and skeletal muscle blood vessels.
3. It acts as neuromodulator, modifies behaviour, arousal, degree of alertness, ECG activity and sleep. It plays an important role in mood, memory and hormone regulation and homeostasis.

C. Dopamine

It is formed from tyrosine. It is usually inhibitory. It is present in neurons of substantia nigra along the Nigrostriatal dopaminergic pathway projects to putamen and caudate nucleus. It is catabolized to inactive product through COMT and MAO in liver, reuptake into adrenergic nerve endings and also diffused away from nerve endings to body fluid. It acts via D1–D5 metabotropic receptors. The loss of inhibitory influences is associated with Parkinson's disease. Increased dopamine concentration causes schizophrenia.

D. Other Transmitters

1. **Serotonin:** It is a monoamine neurotransmitter. It is distributed in regional manner and is present in higher concentration in the intestine and remaining is in hypothalamus, brainstem and the spinal cord. Enzymes required for synthesis and breakdown are present in the brain. It enhances stimulation of myenteric neurons and modulates gastrointestinal motility. Its role in CNS is in regulation mood, behaviour and sleep.
2. **Histamine:** This amine is also present in the highest concentration in the hypothalamus. It participates in local immune responses, regulates physiological function in the gut and acts as a neurotransmitter in brain, spinal cord. In stomach, it stimulates parietal cell to secrete HCl. It acts via four histamine receptors H1 through H4. It is responsible for wakefulness and it prevents sleep.
3. **Glutamate:** It is an excitatory neurotransmitter of CNS (responsible for nearly 75% of excitatory transmission in the brain). The site of its synthesis is brain, spinal cord and hippocampus. Their action is mediated via three types of ionotropic receptors, e.g. NMDA, AMPA and kianate receptors. It gets cleared from the brain ECF by Na^+ dependent uptake system in neurons and neuroglia. It is involved in long-term potentiation involved in memory and learning by causing Ca^{++} influx.
4. **Gamma-aminobutyric acid (GABA)** has got some inhibitory effects. It is the inhibitory neurotransmitter of CNS and is also found in retina. It is formed by decarboxylation of glutamate. There are three types of GABA receptors, e.g. GABA—A, B and C. It is present in highest concentration in colliculi, diencephalon, and occipital lobes but in lower concentration in the pons, medulla, and most of the cerebral cortex. It acts by stabilising membrane potentials at their resting value. It decreases the excitatory activity.
5. **Glycine** also acts as a mediator responsible for direct inhibition in the spinal cord, brainstem and retina. Glycine receptor makes postsynaptic membrane more permeable to Cl^- ion. It is deactivated in the synapse by reabsorption which occurs by active transport back into the presynaptic membrane.
6. **ATP:** It is neurotransmitter present in noradrenergic postganglionic sympathetic neurons. ATP acts as a neuromodulator of both the release and action of ACh. ATP is also a substrate of adenylate cyclase, especially participating in transduction pathways of G protein-coupled receptor signal and this is important in brain function.
7. **Peptides:** Role of substance P (SP) in the CNS is reported over 36 years ago. It is a basic polypeptide and has got a molecular weight of about 1600 daltons. It is an undecapeptide and composed of a chain of 11 amino acid residues. It is present in highest concentration in the hypothalamus, dorsal root of the spinal nerves and also comparatively in large amount in substantia nigra. This substance is associated with transmission in the sensory pathways in the spinal cord. It is a neurotransmitter and neuromodulator.
8. **Aspartate:** It is a acidic amine and excitatory neurotransmitter in spinal cord. Aspartate and glycine form an excitatory/inhibitory pair in the ventral spinal cord.

Role of other Neuroactive Peptides: Large Molecule Transmitters

1. **Opioid peptides:** They include: Endorphins, enkephalins and dynorphins. β-endorphin is made from pro-opiomelanocortin (POMC). It is produced in pituitary gland, hypothalamus, brainstem. Enkephalin is made from proenkephalin (PENK). It is produced throughout brain and spinal cord. Dynorphin is made from prodynorphin (PDYN). It is produced throughout brain and spinal cord. They are present in pain pathways, limbic circuits and in reticular formation (enkephalins). Mu (μ), kappa (κ), and delta (δ) opioid receptors are the main classified receptor subtypes. Opioids act at all opioid receptors, but with different affinities.
2. **Hormones:** ADH also known as vasopressin conserves body water by reducing the loss of water in urine. Oxytocin aids in parturition and lactation.
3. **Peptides:** Somatostatin: It acts as growth hormone inhibiting hormone in hypothalamus and inhibits insulin secretion in pancreas. It is mediating synergistic action in cognition and locomotion.
4. The other polypeptides present as cholecystokinin, gastrin, bradykinin, neurotensin, endothelin, gastrin related peptide, VIP and neuropeptide Y and nitric oxide. The nitric oxide is the endothelium derived relaxing factor which produces vasodilatation.

EXAM-ORIENTED QUESTIONS

Essay

1. Discuss the nature of transmission in CNS.
2. Discuss the arrangement and working processes of the nervous system.

Short Notes

1. Acetylcholine
2. Peptides
3. Amino acids
4. Serotonin
5. Central adrenergic transmission
6. Cholinergic transmission

Chapter

89 Synapse

INTRODUCTION

Syapse is the junctional region where one neuron ends and the other begins. The terminal branches of the axon (presynaptic terminals) of other neurons (presynaptic cell) come in contact with the cell body (soma) or the dendrites of another (postsynaptic cell). Many presynaptic neurons may converge on any single postsynaptic neurons and the axon of any presynaptic neuron may divide into multiple branches and may diverge to end on multiple postsynaptic neurons.

CLASSIFICATION

According to the nature of connections, the synapses can be classified as such:

1. Axosomatic synapse (Figs 89.1 and 89.2B)
2. Axodendritic synapse (Fig. 89.3)
3. Axo-axonic synapse.

In axosomatic synapses, the presynaptic terminal of the axon ends in the cell body (soma) of the neuron. In the cerebellum synaptic connections in between the basket cell and the Purkinje cells are of axosomatic type. The axons of basket cell make synapses with the soma of the Purkinje cells. This type of synapse is also present in cerebral cortex where basket cell makes synapse with the soma of the pyramidal cells (Fig. 89.2B).

In axodendritic synapse, the presynaptic fibres of any axon end in the dendrites of the postsynaptic cell. This type of synapse is also present in cerebellum where climbing fibres form axodendritic connections with the dendrite of the Purkinje cell (Fig. 89.2A).

Axo-axonic synapse is also claimed to be present and in such synapse, presynaptic fibres of any axon ends in the axon of the postsynaptic cells.

ANATOMY OF THE SYNAPSE

1. Microscopic anatomy of a motor neuron of the anterior horn cells of the spinal cord shows the main body of the neuron-soma, dendrites, axon and multiple presynaptic terminals (synaptic knobs)

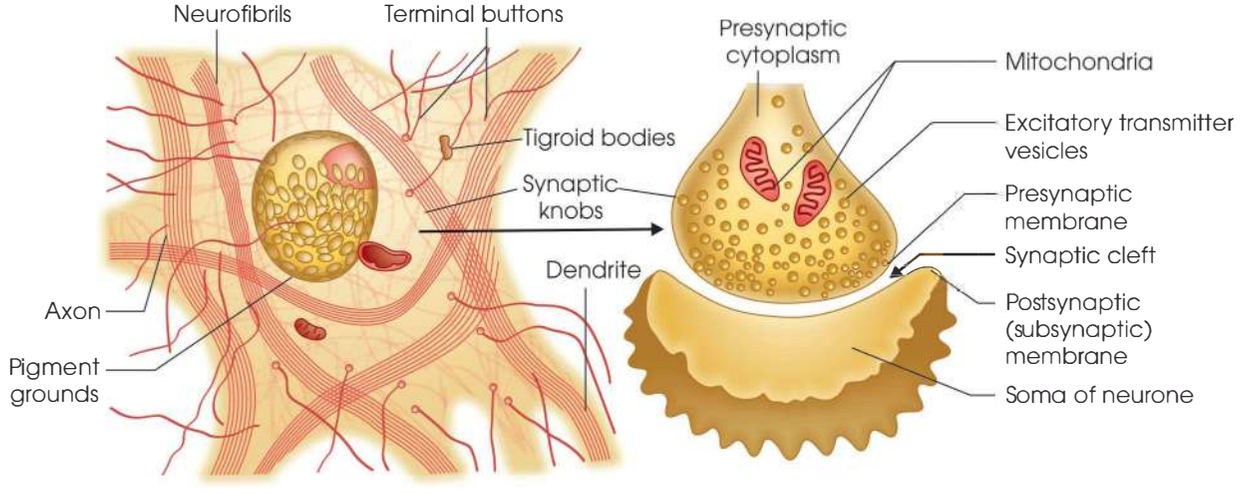


Fig. 89.1: Schematic structure of a neuron. Synaptic terminations link neurons. They do not adhere to the cell surface but are separated by the inter-synaptic space. Within the cytoplasms of the neuron are found typical neurofibrils, mitochondria, pigment granules, and tigroid bodies (left side). On the right side an electron microscopic structure of an axosomatic synapses

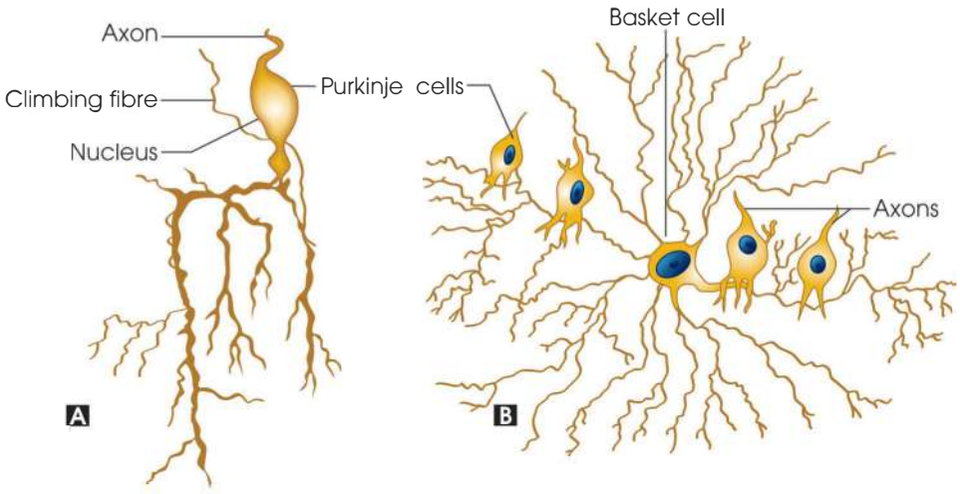


Fig. 89.2A and B: Diagrammatic representation of almost parallel axodendritic system upon the dendrites of a Purkinje cell of the cerebellum showing climbing fibres (left side) and axosomatic synapses of the axon of a basket cell upon the Purkinje cells of the cerebellum (right side)

ending in the soma and dendrites. These presynaptic terminals are the ends of the neurofibrils of other neurons (Fig. 89.2).

2. Electron microscopic structure shows that there are two types of presynaptic terminals. In one type the ends of the presynaptic terminals are enlarged to form a knob or button which is known as synaptic knob (Fig. 89.3).
3. The synaptic knob has an intact membrane. The membrane of the synaptic knob is known as presynaptic membrane and that of the soma, the postsynaptic (subsynaptic) membrane. The synaptic knob has got intimate contact with a portion of the membrane of the postsynaptic cell. The synaptic knobs are separated from the soma of the postsynaptic cell by a synaptic cleft having an average width of approximately 200 Angstroms (1Å = mμ) (Fig. 89.4).
4. The synaptic cleft actually represents the real discontinuity of cell cytoplasm in the synaptic junction. The synapse of brain cortex (central synapse) has parallel intersynaptic filaments (canaliculi) of about 50 Angstroms crossing the synaptic cleft. These filaments are fixed at both ends with the presynaptic and subsynaptic (postsynaptic) membranes. At present the functions of these filaments are not clear.
5. Besides these there is a web of filaments which is implanted on the subsynaptic membrane and extended at a varying and considerable distance in the postsynaptic cytoplasm. This web of filaments (canaliculi) is known as subsynaptic web (SSW). This subsynaptic web has been observed in the central synaptic knob contains mitochondria and a large number of synaptic vesicles.
6. The synaptic vesicles are more concentrated towards the sites fronting the synaptic clefts. The tubular (vesicular) neuroprotofibrils and the vesicles of the endoplasmic reticulum are present but less

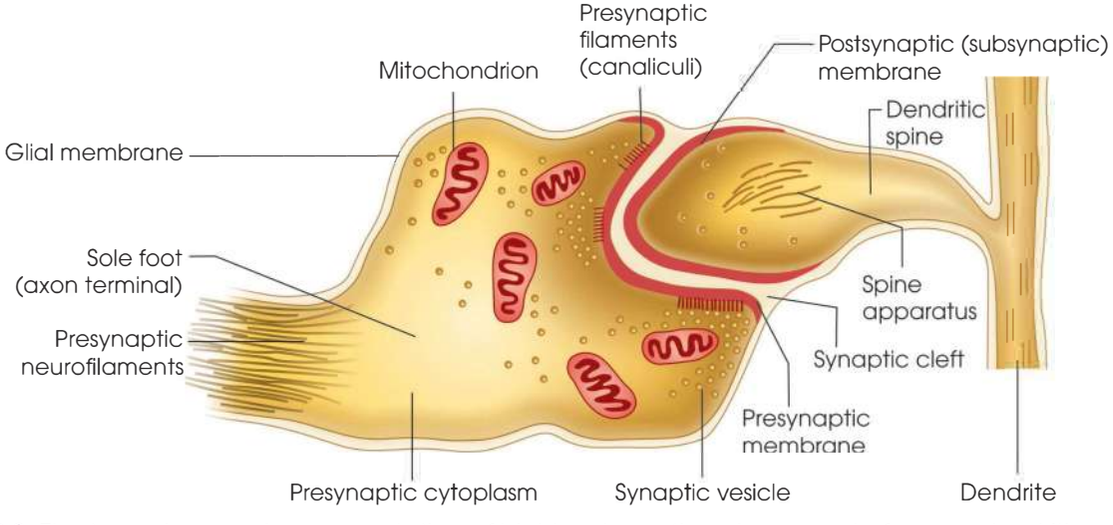


Fig. 89.3: Electron microscopic representation of highly schematic enlargement of an axodendritic synapse

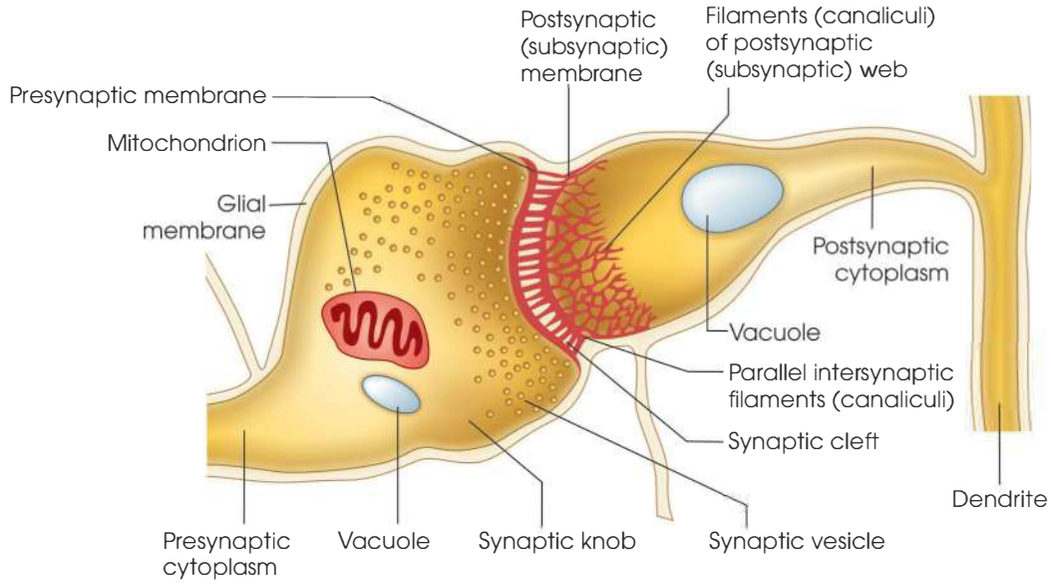


Fig. 89.4: Electron microscopic representation of highly schematic enlargement of the synapse of the brain cortex (central synapse)

conspicuous. The synaptic vesicles contain the excitatory transmitter materials that mediate transmission of impulses from the presynaptic neurons to the postsynaptic neurons (Figs 89.4 and 89.5).

MECHANISM OF SYNAPTIC TRANSMISSION

Key Points

1. The *transfer of information across a synaptic junction* is called synaptic transmission and these transmissions are brought about either by chemical or by electrical or by both processes.
2. Nerve action potential (NAP) arriving at the axonal terminals, initiates a series of events, causing either a transmission of an excitatory or inhibitory in nature across the synapse or neuro-effector junctions. The neurotransmitter substances are probably synthesized in the region of the axonal terminals and stored there in the synaptic vesicles.
3. At rest these transmitter substances are also slowly liberated from these vesicles at a very slow amount which is incapable producing any propagated impulse. However, when the NAP reaches axon terminals, there is synchronous release of several quanta of transmitter substance.
4. Transmitter substances thus released diffuse across a distance of 100–500 Å of the synaptic cleft and combines with the hypothetical receptor substance of the postsynaptic membrane causing increase permeability of membranes.
5. There are two types of permeability changes in the postsynaptic membrane. One is the generalised increased permeability of all types of ions causing a localised depolarisation of the membrane and

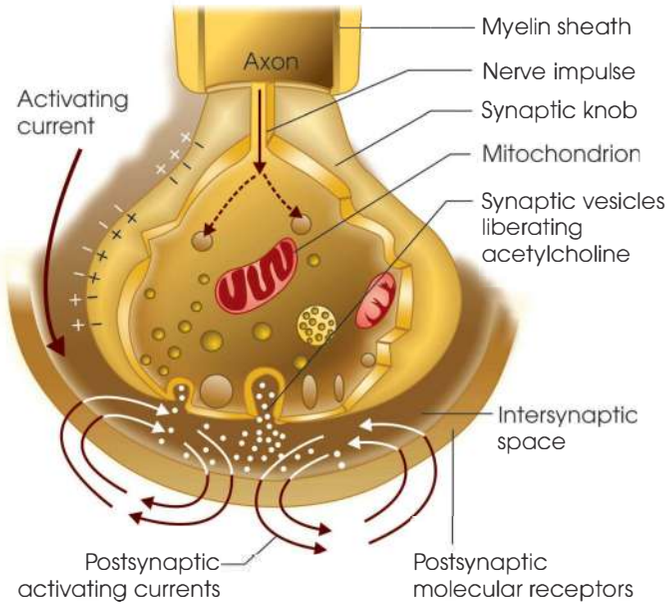


Fig. 89.5: Schematic representation of synaptic excitation. The transmission of nerve impulse is linked to a specific electrochemical process. Activating current first travels along neuronal process afterwards radiates over the synapse and cause the liberation of acetylcholine contained in the synaptic vesicles. Acetylcholine traverses the intersynaptic space and becomes attached to molecular receptors which are situated on the postsynaptic membrane (the neuronal cytoplasm to be activated) and this causes a postsynaptic current of action in this membrane. Free acetylcholine liberated is hurriedly destroyed by the acetylcholinesterase. The mitochondrion transmits energy necessary for these processes.

excitatory postsynaptic potential. Other mechanism is the selective increase in permeability of the membrane to only the smaller ions like K^+ and

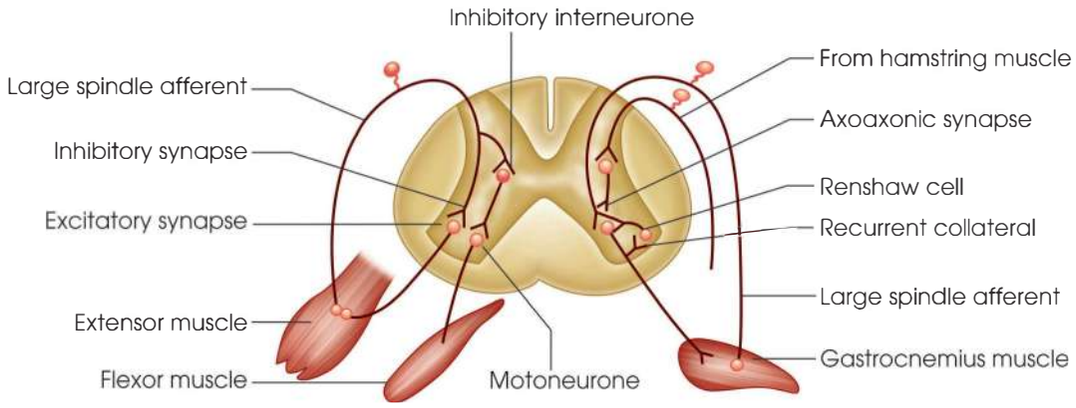


Fig. 89.6: Diagrammatic representation of the excitatory and inhibitory pathways in the spinal cord

chloride ions, causing hyperpolarisation of the membrane, and that constitutes the inhibitory postsynaptic potential (IPSP).

6. If the EPSP exceeds threshold value, then it initiates the propagated NAP in the postsynaptic neuron or muscle action potential (MAP) in most skeletal and cardiac muscles. During the development of the EPSP, simultaneously IPSP may be developed at the same site by the incoming NAP from the other sources. The propagation of nerve impulse by the EPSP is dependent upon the intensity of this postsynaptic potential.
7. In the CNS and also at other sites, inhibition can also result from the depolarizing action of a transmitter on presynaptic sites. As soon as the impulse is transmitted, the transmitter substance is immediately destroyed by the specific enzymes present in the rim of the synaptic gutter. To cite an example: AChE (acetylcholinesterase) in the cholinergic junction (Fig. 89.6).

NATURE OF TRANSMITTER SUBSTANCES

1. Acetylcholine is the transmitter substance of the cholinergic effector organ and released at post-ganglionic autonomic nerve endings and pre-ganglionic sympathetic nerve endings at some sites of the CNS.
2. **Glycine** acts as a mediator responsible for direct inhibition in the spinal cord.
3. **Glutamic acid** has got some powerful excitatory effect on some central neuron.
4. GABA (**γ-aminobutyric)**: It is the fast inhibitory synapses perhaps of every part of the brain.
5. **Dopamine** regulates motor behaviour, pleasures related to motivation and also emotional arousal. Dopamine concentration decreases in parkinsonism and increases in schizophrenia.
6. **Serotonin** in central nervous system neurons regulates sleep, mood, behaviour, temperature, memory and appetite.
7. **Epinephrine and norepinephrine** are involved in alertness response, fight, flight reaction, etc.
8. **Histamine** is released from mast cells and tuberomammillary nucleus of hypothalamus thus influencing its function.

Neuromuscular Junction

Explained in details in Section of Nerve Muscle Physiology.

EXCITATORY AND INHIBITORY POSTSYNAPTIC POTENTIALS

89

Excitatory Postsynaptic Potential (EPSP)

When an excitatory volley of impulses excites a motor neuron, depolarisation of the cell membrane occurs. This is known as excitatory postsynaptic potential (EPSP). It is of brief duration. When the stimulus is stronger, excitatory postsynaptic potential (EPSP) reaches the threshold level and the nerve impulse is set up. The ionic events underlying the development of excitatory postsynaptic potential is presumably due to increased Na^+ permeability to postsynaptic membrane, if more excitatory synaptic knobs become active by propagated action potential then the liberation of excitatory transmitter material from synaptic vesicles is maximum. This state enhances the Na^+ permeability to postsynaptic membrane, producing excitatory postsynaptic potential.

Inhibitory Postsynaptic Potential (IPSP)

When a motor neuron receives an inhibitory volley of impulses, hyperpolarisation of the cell membrane occurs. This is called inhibitory postsynaptic potential (IPSP). It has a longer latency. The hyperpolarisation exerts an inhibitory effect on excitatory postsynaptic potential (EPSP) and depolarisation of the cell membrane at the axon hillock and causes inhibition in setting up the nerve impulse. Ionic basis of inhibitory postsynaptic potential (IPSP) is due to increased

permeability of postsynaptic membrane to K^+ and Cl^- but not of Na^+. Under such state K^+ from the postsynaptic cell begins to come out (efflux) and Cl^- begins to enter producing negativity within the postsynaptic cell. This negativity is hyperpolarisation of the membrane and membrane potential becomes 90 mV. The decreased excitability of the nerve cell during IPSP is due to hyperpolarisation which hinders the membrane potential to reach its firing level.

PROPERTIES OF SYNAPSE

1. Synaptic Response

At the synaptic junction, impulses are received and discharged. But there is no relationship between the receipt and discharge of impulses. Sometimes many impulses are received from different sources but the neuron discharges its own. So, it may be said that the synapse not only acts as a relay station but it may also act as an integrator. The integrating mechanism of the synapse is found in the cerebral cortex.

2. Law of Forward Conduction (Sherrington)

An impulse is allowed to pass through a synapse in one direction only, viz. from the axon of one neuron to the dendrite of the next. But some synapses can transmit impulses in both directions. They are bidirectional and usually electrical in nature, where presynaptic and postsynaptic membranes are in close apposition and often fused at several points.

3. Synaptic Delay

The impulse while passing through a synapse takes a certain length of time. The time between the arrival of the impulse and causing initial depolarisation is called synaptic latency. The depolarisation gradually rises to a spike height. So, the synaptic delay is the sum of the synaptic latency and the time taken for depolarisation leading to a spike height in the neuron. Synaptic delay in chemical synapses is less than 0.5 millisecond whereas in electrical junctions they are extremely short as there is no release of chemicals.

4. Seat of Fatigue

The physiological seat of fatigue is in the central nervous system, probably at the synapses. The mechanism underlying the synaptic fatigue is presumably due to exhaustion of transmitter material from the synaptic vesicles following repeated presynaptic stimulation at a faster rate.

5. Synaptic Inhibitions

Inhibition may be defined as an active process which either prevents the onset of activity in a structure or stops the activity already present. It may be either postsynaptic or presynaptic and direct or indirect. Inhibitory impulse causes hyperpolarisation or the cell membrane beneath the synapse. This is known as inhibitory postsynaptic potential (IPSP). This is due to increased permeability of the cell membrane to K^+ and Cl^- caused by the liberation of an inhibitory chemical transmitter. Na^+ permeability is decreased; and efflux of K^+ and influx of Cl^- from postsynaptic terminals hyperpolarise the postsynaptic membrane. The net effect is increased negativity in the cell with increased membrane potential (–90 mV). Thus, the inhibitory postsynaptic potential is developed. The inhibitory postsynaptic potential (IPSP) opposes the excitatory postsynaptic potential (EPSP).

Motor neurons while traversing the spinal cord to the anterior nerve root give off collaterals which make excitatory synaptic connections with a special group of cells called the Renshaw cells situated at the anterior horn (Fig. 89.6). But the Renshaw cells in turn send inhibitory impulses to these motor neurons. Due to the 'feedback' mechanism the discharge of impulses from the motor neurons is inhibited. It is probable that collateral endings of the motor neuron liberate acetylcholine which stimulates the Renshaw cells.

Postsynaptic Inhibition

Inhibition can be defined as an active process that either prevents the onset of activity in a structure or stops activity already present. It may be postsynaptic or presynaptic. The postsynaptic inhibition is produced across a synapse having axosomatic connection and is due to release of an inhibitory transmitter. This inhibitory transmitter then acts on the postsynaptic membrane of the junction and inhibits it (Fig. 89.7).

There are two chemically transmitting synapses on a nerve cell of which one is excitatory having axodendritic connection and other one is inhibitory having axosomatic connection (Figs 89.7 and 89.8). The excitatory synapses when stimulated by the incoming afferent volley liberate transmitter substances which open up the sodium and potassium ionic gates in the subsynaptic membrane. Depolarisation occurs causing the development of EPSP and when the EPSP attains a critical level the impulse is propagated through the axon. But when inhibitory synapses are stimulated by an incoming afferent volley, there is release of transmitter substance which opens up chloride and/or K^+ gate causing hyperpolarisation of the postsynaptic membrane and thus the IPSP develops. So, if the inhibitory synapse is stimulated sometimes earlier than the excitatory one or if these two synapses are stimulated simultaneously then there is possibility of inhibition as the inhibitory synapse by hyperpolarisation may antagonise the depolarising action of the excitatory synapse.

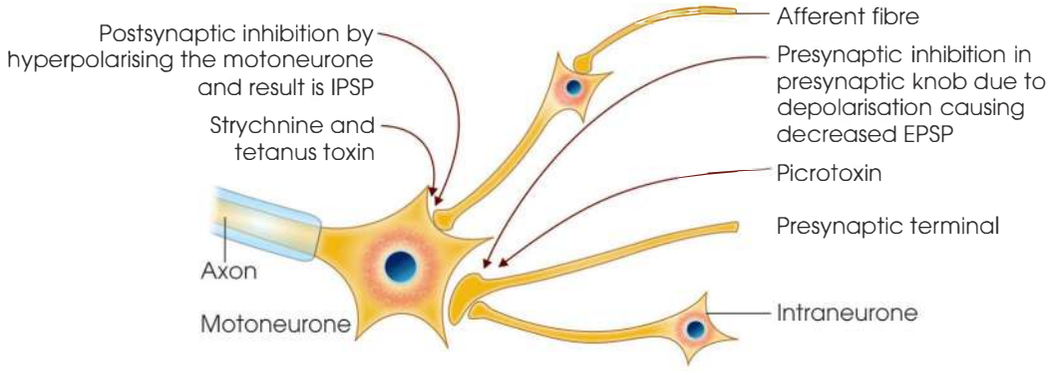


Fig. 89.7: Arrangements of central neurons that cause presynaptic and postsynaptic inhibitions

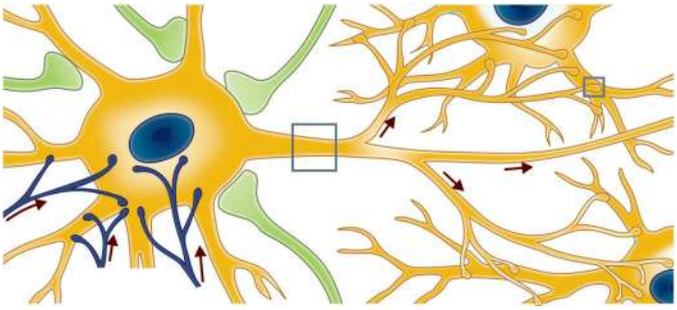


Fig. 89.8: Nature of synaptic connection in the CNS in relation to its inhibitory and excitatory states

So, the hyperpolarising effect of inhibitory synapse will prevent the generation of impulse by the excitatory synapse. Thus, the excitatory postsynaptic potential developed by stimulation of an appropriate afferent nerve is depressed.

In summary, the postsynaptic inhibition is due to release of inhibitory transmitter which is capable of changing the permeability of the postsynaptic membrane to either potassium or chloride or both. This change of permeability of the membrane will cause hyperpolarisation of the postsynaptic membrane and consequently, the action potential elicited by the excitatory stimulus will fail to occur.

Presynaptic Inhibition (Fig. 89.7)

Primary afferent fibres and possibly the axons of several other types of neurons may be subjected to a prolonged depolarisation, exerted at or near the terminals of the axon. The presynaptic depolarisation blocks or decreases the action potential that is propagating towards the axon terminals and consequently, a reduced amount of transmitter substance is released by presynaptic action potential. This inhibitory phenomenon has been termed as presynaptic inhibition.

This type of inhibition was originally described by Frank and Fuortes (1957). They described that muscle afferent volleys produce an inhibition of the EPSP and reflex discharges of motor neurons, elicited by a testing volley, without any other remarkable effect upon those motor neurons and also without eliciting IPSP.

The presynaptic inhibition is always associated with a depolarisation of the presynaptic fibres (primary afferent depolarisation, PADP). The presynaptic depolarisation is responsible for the depression of EPSP because it reduced the size of the presynaptic impulse and hence decreased the liberation of the excitatory transmitter.

Example: The presynaptic inhibition exerts a powerful action on all of large afferent fibres entering the spinal cord. Presynaptic inhibition is exerted both onto those Ia terminals making monosynaptic excitatory contacts on motor neurons and onto those conveying excitation to neurons of ascending tracts.

Presynaptic inhibition can be demonstrated by eliciting a monosynaptic EPSP of either extensor or flexor motor neuron and if it is preceded by volleys from any dorsal root. Ipsilateral flexor components of Group Ib and Ia fibres are more effective in causing the inhibition. This inhibition may endure as long as 200–300 msec and is extremely resistant to strychnine. Strychnine and tetanus toxin depress the postsynaptic inhibition. Picrotoxin, another convulsive drug, depresses the presynaptic inhibition.

6. Convergence and Divergence of Nerve Impulses

Since the axons of many neurons can form a common synapse with the next neuron, a number of nerve impulses from various sources may converge onto a single nerve cell and may be transmitted through it. Convergence of impulses occurs into the final common path, e.g. convergence of afferent impulses to the anterior horn cells. Similarly, there is also some divergence of impulses (on the afferent side), e.g. divergence of visual impulses from the retina to the occipital cortex (Fig. 89.9A and B).

7. Synaptic Block

The inhibitory transmitter may be blocked at the synaptic junction. Strychnine blocks the inhibitory activity and causes reduction or abolition of inhibitory

postsynaptic potential (IPSP) in most of the synaptic junctions. Tetanus toxin also has got similar effects. Strychnine and tetanus toxin produce convulsion by blocking the inhibitory transmitter mechanism.

8. Summation

If the stimulus be subminimal and applied to an afferent nerve there will be liberation of a chemical transmitter which will cause excitatory postsynaptic potential (EPSP), but this EPSP will not be sufficient to produce discharge of impulses from the motor neurons. But if a number of subminimal stimuli be applied, their effects will be summated together and the EPSP will be sufficient to induce the motor neurons to discharge impulses and produce the reflex response. This is called summation. Two types of summation are found.

Spatial Summation (Fig. 89.10)

Two afferent fibres having synaptic connection with same motor neuron when stimulated simultaneously, there will be summation of EPSP producing a spike discharge. This effect is known as spatial summation. When these afferent fibres are stimulated individually no effect will be seen.

Temporal Summation (Fig. 89.11)

When one of the afferent nerve fibres is stimulated before the decay of first stimulation (none of two can produce spike in the motor neuron); and each of it on stimulation produces some EPSP and their effects gets summated to generate a spike discharge. Such type of effect is known as temporal summation.

9. Occlusion

When a reflex contraction is produced by simultaneous stimulation of two afferent nerves, the amount of tension (T) in the muscle is less than the sumtotal of the tensions ($t_1 + t_2$) set up in the same muscle when the two afferent nerves are separately stimulated (i.e. $T < (t_1 + t_2)$. This is explained on the assumption that some nerve cells remain common to both the reflex paths.

10. Ephaptic Transmission

'Ephapse' means false synapse. Ephaptic transmission is the process of transmission of an electrical impulse from one axon to another without having any synaptic connection (i.e. false synapse). If one nerve fibre falls on the other fibre then threshold stimulation of the one fibre will cause excitation of the other by the propagation of impulse through the ephapse (false synapse) (Fig. 89.12). This was first observed by Hering (1882). Experimental studies in modelled pyramidal neurons revealed that the extracellular electric fields are found throughout the living brain and they affect the neural coding and information processing via ephaptic transmission, independent of synapses.

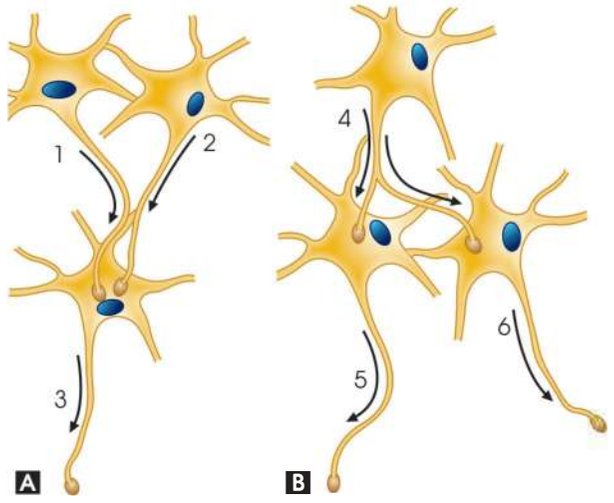


Fig. 89.9A and B: (A) Convergence; (B) Divergence. 1–3 is pathway for convergence and 4–6 is pathway for divergence

11. Synaptic Plasticity

The ability of synapses to weaken or strengthen over time, in response to increases or decreases in the synaptic activity is known as synaptic plasticity. It plays a vital role in formulation and storage of learning and memory. As receptors across the synaptic cleft are activated by neurotransmitters, the connection between the two neurons is strengthened when both neurons are functionally active during the receptor's signalling mechanisms. This process of synaptic strengthening is called as long-term potentiation.

The plasticity of synapses in the presynaptic cell can be controlled by altering the release of neurotransmitters. The postsynaptic cell effects can be modulated by regulating and altering the function and number of its receptors. Short-term synaptic plasticity action occurs on a timescale of tens of milliseconds to a few

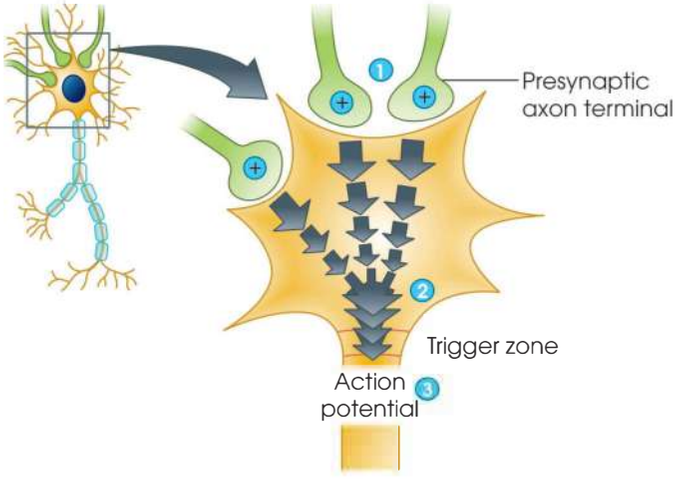


Fig. 89.10: Spatial summation

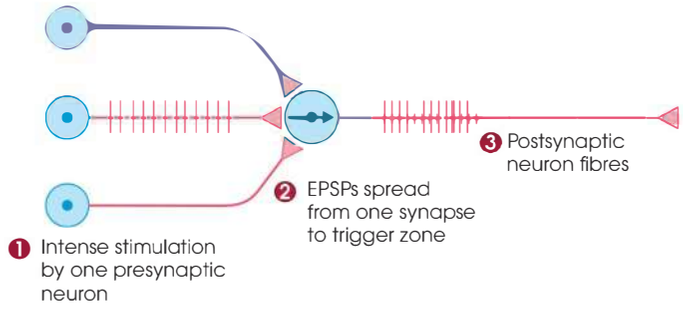


Fig. 89.11: Temporal summation

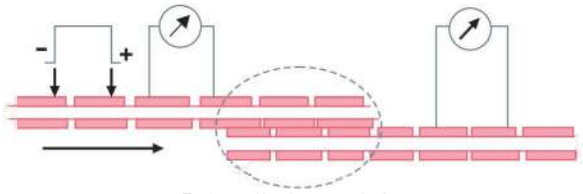


Fig. 89.12: Showing ephaptic transmission. Arrow represents direction of propagation

minutes and long-term plasticity, lasts from minutes to hours. Short-term plasticity may also strengthen or weaken a synapse.

The two forms of long-term plasticity are: Long-term depression (LTD) and long-term potentiation (LTP). NMDA-dependent LTD and LTP require the binding of glutamate, and glycine or D-serine for activation of NMDA receptors. LTP involves interactions between the specific presynaptic inputs and postsynaptic neurons and they form a synaptic association, and this is specific to the involved stimulated pathway of synaptic transmission. The increase in the intracellular calcium concentration and minimum level of post-synaptic depolarization at the postsynaptic neuron induces LTD. Thus, long-term stabilization of synaptic changes is ascertained by a parallel increase of pre- and postsynaptic structures such as axonal button, postsynaptic density and dendritic process.

Applied Physiology: Synaptopathy

The dysfunction of synapse leading to a disease of the spinal cord, peripheral nervous system and brain is called synaptopathy. Mutation in a gene encoding a synaptic protein such as a neurotransmitter receptor, ion channel, or a protein related to neurotransmitter release is mainly responsible for synaptopathy. Synaptic channelopathies for example episodic ataxia are type of synaptopathies caused by ion channel mutations.

Sir Bernard Katz, a German Biophysicist research uncovered fundamental properties of synapses, the junctions across which nerve cells signal to each other and to other types of cells. He shared the Nobel Prize in Physiology or Medicine in 1970 with Julius Axelrod and Ulf von Euler for their work on synapses.

Bernard Kartz
1911–2003

Sir Charles Scott Sherrington was an English Neurophysiologist, Histologist, Bacteriologist, and a Pathologist who was awarded the Nobel Prize in Physiology or Medicine with Edgar Adrian, in 1932 for their work on the functions of neurons.

Sir Charles Scott Sherrington
1857–1952

Sherrington struggled to identify a proper term that emphasized a union between two separate elements, and the actual term "synapse" was suggested by the classical scholar Arthur Woollgar Verrall.

Arthur Woollgar Verrall
1851–1912

EXAM-ORIENTED QUESTIONS

Essay

1. Define synapse. Classify synapses. Describe excitatory and inhibitory synaptic transmission.
2. Define synapse. Discuss the functions of synapse.

Short Notes

1. Synaptic inhibition
2. Synaptic delay
3. Synaptic plasticity
4. Convergence and divergence in synapse
5. Excitatory synaptic transmission
6. Inhibitory synaptic transmission

SYNAPSES

1. The term synapse was introduced by the English Neurophysiologist Charles Sherrington in Michael Foster's Textbook of Physiology in 1897.
2. The British classics scholar Arthur Woollgar Verrall coined the word synapse.

REFERENCE

Hill, AV (1975). "Jewels in My Acquaintance with CS Sherrington, FRS". Notes and Records of the Royal Society. 30 (1): 65–68.

Chapter

90

Nerve Endings and Receptors

DEFINITION

Nerve endings are the terminal bodies where the nerve fibres end in the periphery.

Histology (Fig. 90.1)

Histologically, there are two fundamental types of endings:

1. *Free terminals:* In this type of nerve ending the nerve fibres end as naked twigs of axis cylinder, without any special covering.
2. *Connective tissue body:* In this type of nerve ending the nerve fibre ends inside a special connective tissue body. All such bodies are built up on the same histological plan.

The characteristic features of nerve endings are:

1. The capsule is made up of layers of connective tissues.
2. Inside the capsule, there is a core of soft cellular material.
3. Inside the core ends the naked axis cylinder, and it is either as a single process or by various forms of arborisations.
4. While terminating, the myelin sheath becomes completely blended with the lamellated connective tissue body and lastly the axis cylinder ends in the core as a naked process (same as it began). All the end organs having a connective tissue of body have got this common plan. They differ from one another by the complexity of the capsule and the mode of termination of the axis cylinder.

Functions

Functionally, the nerve endings may be:

1. Motor
2. Sensory

The motor endings transmit the motor impulses to the muscles. Acetylcholine, is liberated at the endings and sets in the chemical changes which is preceded by contraction of muscles. The sensory endings receives the afferent sensation, hence are also called the sensory receptors.

RECEPTORS

Sensory receptors are a specialised structure that can be stimulated by environmental changes as well as by

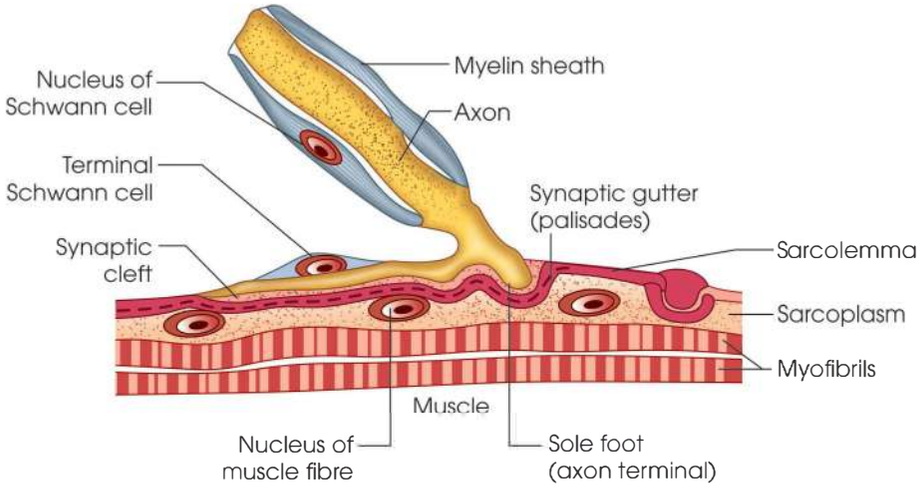


Fig. 90.1: Diagrammatic representation of the relationship of nerve ending to the muscle fibres (neuromuscular junction)

changes within the body. It can be defined as the terminal afferent endings that undergo depolarisation in response to specific type of physical stimuli. These receptors are capable of transforming different types of energy into nerve impulses that travel through sensory nerve fibres toward the central nervous system. Their functions are generally specific, one type carrying one kind of sensory impulse, such as of touch, heat, cold, etc. For this reason they are also known as the peripheral analysers. Sensation occurs only when the impulses, carried through the sensory nerves are decoded and analysed. They are of various types—differing in structure and functions.

The receptors may be classified in three ways:

1. In terms of their morphological entity.
2. In terms of the properties of the external stimuli to which they respond.
3. And in terms of functions which they subserve.

There are different types of receptors in the body and as there is no conventional method, it has been classified in different ways. For the sake of convenience, the sensory receptors have been classified broadly into two:

1. **General sensory receptors** subserving cutaneous, deep and visceral sensations.
2. **Special sensory receptors** subserving different special functions like carrying sensations for hearing, vision, taste, smell, etc. These have been presented systematically under classification of nerve endings.

Receptor as a Biological Transducer

Transducer is structure which transforms one kind of energy into another. Receptors behave like transducer and transmit any type of physical energy into an electrical energy, the intensity being coded by amplitude modulation. The receptor is capable of transforming local, graded and non-propagated electrical energy into non-graded, all-or-none and propagated electrical response.

Initiation of Impulse in Sensory Receptors

Concepts of generator potential and action potential: If a receptor is stimulated, then electrical activity originating at the nerve endings can be recorded. The initial electrical activity which is stationary, non-propagated but graded is called generator potential or receptor potential (Fig. 90.2). The generator potential is localised in this region without being propagated actively over the rest of the sensory nerve fibre. It has got no refractory period and is not affected by local anaesthetics, like procaine, which usually blocks the conduction along the nerve fibre.

Generator potential is not the synonym of action potential: Action potential follows all-or-none law, is propagating and non-graded. Action potential is

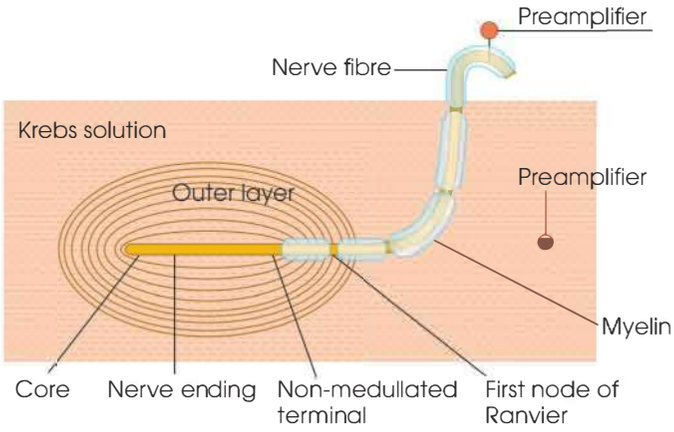


Fig. 90.2: Demonstrates the method of recording generator potential and action potential from isolated pacinian corpuscle which is bathed in Krebs solution. Recording is carried out by placing one electrode on the axon and the other electrode is placed on the surrounding fluid—the Krebs solution. Active stimulus is mechanical pressure (Mountcastle)

developed only when the generator potential attains a threshold level due to graded activity (Fig. 90.3). When the magnitude of the generator potential is about 10 mV, an action potential is generated in the sensory nerve. If the intensity of stimulus in the receptor is further increased then the generator potential is increased further and the frequency of discharge of action potential is increased. Frequency of discharge of action potential is proportional to the magnitude of the applied stimuli.

Source of Generator Potential

This has been studied very successfully in the eye of horseshoe crab and in some vertebral mechano-receptors—the frog's spindle and the pacinian corpuscle of the cat. Pacinian corpuscle has been studied in detail as because the receptor is relatively large and can be isolated, studied with microelectrodes and subjected to micro-dissection.

Key Points

1. These corpuscles are surrounded by concentric lamellae of connective tissues and consist of straight, unmyelinated ending of sensory nerve fibre of 2 μm in diameter. The myelin of the sensory nerve begins inside the corpuscle.
2. It has been shown by micro-dissection techniques that after removal of the connective tissue lamellae, there is still initiation of generator potential, along with propagated action potential.
3. If bits of inner core of the corpuscle are removed, still there is no defect in the initiation of generator potential and subsequently the action potential is initiated.

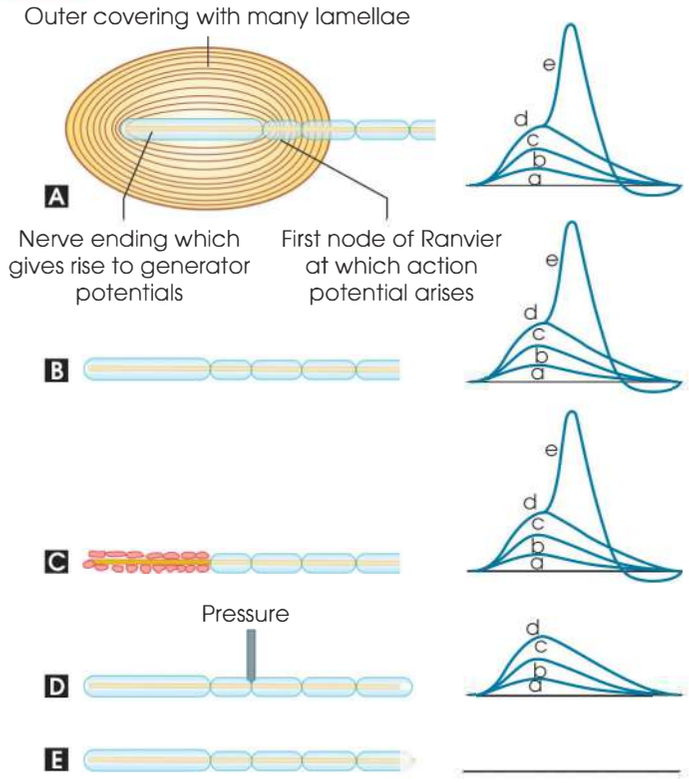


Fig. 90.3A to E: This demonstrates the site of origin of generator potential and also demonstrates the mechanism of development of action potential. Recording method as: (A) It shows development of generator potential in graded pattern (a, b, c, d) as the stimulus strength is gradually increased with the development of propagated action potential (e) in a lamellated pacinian corpuscle. (B) It shows development of same generator potential (a, b, c, d) as well as action potential (e) though the concentric lamellae of the corpuscle are removed. (C) Development of same generator potential (a, b, c, d) and action potential (e) though the inner core is partially removed in an unlamellated corpuscle. (D) Generator potentials (a, b, c, d) as usual are developed, but action potential (e) is not developed after blocking the first node of Ranvier by pressure. (E) Demonstrates failure of development of generator or action potential after degeneration of axon (after Loewenstein).

4. If the unmyelinated nerve terminal is allowed to degenerate following section of the sensory nerve several days earlier, then no generator potential is developed. *From all these experiments it is clear that generator potential is developed in the unmyelinated nerve terminal and not in the elements of corpuscle as because majority of the latter can be removed without affecting the development of generator potential.*
5. The generator potential is local to the nerve terminal and results from a process taking place there while the conducted action potential to which it normally leads is set up in the membrane of the first node of Ranvier. *Thus a generator potential is, in short, a depolarisation of the sensory nerve endings, which, if attains a certain magnitude, then may stimulate the sensory nerve fibre itself. There is a definite relationship in between the magnitude of generator potential and the frequency of discharge of the action potential.*

Mechanism of Initiation of Generator Potential

Biophysical principle underlying the process of initiation of generator potential is not clear. It is known that due to stimulation of the receptor, there are increase of Na^+ conductance, inward rush of Na^+ through the membrane of the unmyelinated terminal. The resultant influx of Na^+ causes the development of generator potential. The magnitude of the permeability change is proportional to the intensity of the stimulus (Fig. 90.4). Na^+ depletion diminishes the generator potential in pacinian corpuscles. Perfusion with Na^+ free solution but made isotonic with choline chloride or sucrose does not abolish the generator potential but only reduces it to about 10% of the control value. *It thus indicates that generator potential is initiated by permeability to Na^+ and also to other ions as well.*

Thus, the sequences of events that take place in the initiation of generator potential and subsequently the action potential in a receptor are as follows.

Stimulus induces local change in permeability of Na^+ ions and probably other ions produce local depolarisation; there is initiation of local, non-propagated and graded potential which progresses into a generator potential after attaining the threshold level and producing action potential (all-or-none and propagated).

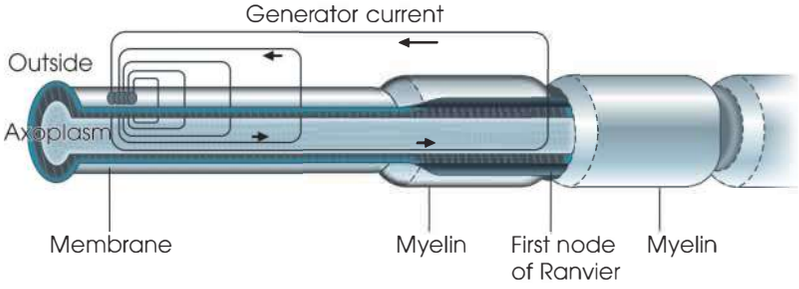


Fig. 90.4: Showing the local change in membrane permeability and resulting flow of generator current reaching the first node of Ranvier (Loewenstein)

Properties of Receptors

1. **Differential sensitivity:** Each receptor is sensitive to a specific stimulus. The receptor is designed for this stimulus and does not respond to other types of stimuli in normal strength. This specific stimulus is called as the adequate stimulus for that receptor organ.
2. **Relation with strength of stimulus:** As strength increases, the frequency of discharge rises and sensation becomes more intense.
3. **Muller's law of specific nerve energies:** Each receptor organ with its afferent nerve transmits only one modality of sensation. Generally action potentials in all nerve fibres are similar, yet action potential developed from a pressure receptor, causes a sensation of pressure not of warmth or cold. This is under the purview of the doctrine of specific nerve energies. The sensation perceived due to impulses generated in a receptor depends upon the specific part of the brain they ultimately activate. The sensory pathways from sense organs to the cortex run as a discrete fibres. As for example, it a sensory (fibre for pressure receptor is stimulated then the sensation evoked is one of the pressure).
4. **Projection:** When any part of the sensory pathway is stimulated, conscious sensation is referred to the location of the receptor and is called the law of projection. As for example, if a cortical area for impulses from the left hand is stimulated, the subject reports pains in his left hand but not in the head.
5. **Intensity discrimination:** The intensity of stimuli is transmitted to the brain by variation of the frequency of action potentials generated by the particular receptor and by variation in the number of receptors achieved. The magnitude of the sensation perceived is proportional to the log of the intensity of the stimulus and this is called Weber-Fechner law and expressed mathematically: S = K log I/Io where S is the intensity of sensation felt, I is the intensity of stimulus for evoking the sensation, Io is the threshold stimulus-intensity and K is constant. It has been modified further that the magnitude of a sensation is the power function of the intensity of stimulus. The rhythmic discharges from a particular group of receptors constitute the sensory code for transmission.
6. **Recruitment:** According to the strength of stimuli the numbers of sense organs are activated but when the strength is increased a large number of receptors are recruited.
7. **Adaptation:** If a sensory organ is stimulated for some time then the frequency of discharge from that organ is gradually declined though the constant stimulation is continued. This phenomenon is known as adaptation. There are slowly adapting receptors and rapidly adapting receptors. In slowly adapting receptors like the muscle spindles, with the onset of stimulation the frequency of discharge is increased initially but declines slowly (Fig. 90.5). On the other hand, in rapidly adapting receptors like the hair receptors of the skin or of the pacinian corpuscle, the frequency of discharge is increased initially but declines abruptly and becomes silence although the stimulation is applied constantly (Fig. 90.6).
8. **Inhibition:** Sometimes efferent inhibitory axons may impringe on the dendrites of receptors. If such inhibitory axons are stimulated then these axons inhibit the discharges of receptors they innervate. This process is known as inhibition. These inhibitory axons terminate in close apposition to the stretch sensitive dendrite of the receptor. On excitation of the inhibitory axons, firing of receptors due to constant stretch ceases (Fig. 90.7).

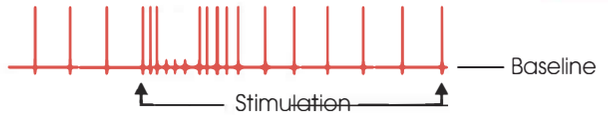


Fig. 90.5: Showing the nature of discharge in slowly adapting receptors. Such receptors, with the starting of stimulation, adapt very slowly showing gradual decrease of rate of discharge

Fig. 90.6: Showing the nature of discharge in rapidly adapting receptors. Such receptors adapt very rapidly as evidenced from rapid abolition of discharge though the stimulus is continued

Classification and Varieties of Nerve Endings

According to structure and function, the nerve endings may be of various types (Figs 90.7 and 90.8). The following is a brief list of both somatic and autonomic nerve endings.

Receptor organs are also classified according to form of energy, they respond to:

1. Mechanoreceptors, e.g. touch, pressure
2. Chemoreceptors—taste, smell
3. Thermal receptors—warmth, cold
4. Osmoreceptors
5. Electromagnetic receptors—rods and cones
6. Nociceptors—pain nerve endings.

General Senses

1. **Cutaneous endings**—carrying superficial sensation.
2. **Free nerve ending**
   a. For pain—probably always free nerve terminals.
   b. For touch—free terminals around hair roots help touch sensation.
   Free nerve endings mediate deep sensation of pain. These are present in between the muscle fibres in tendons and joints.

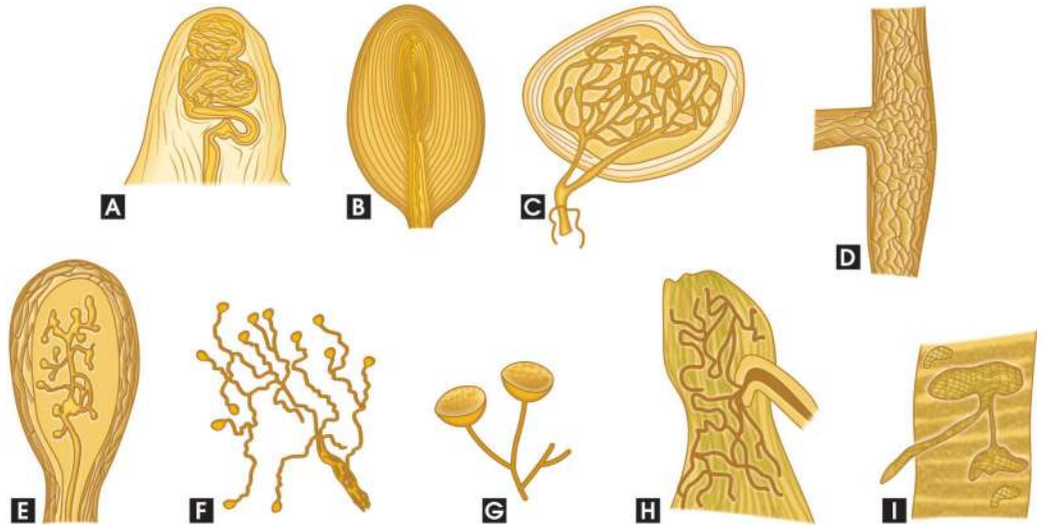
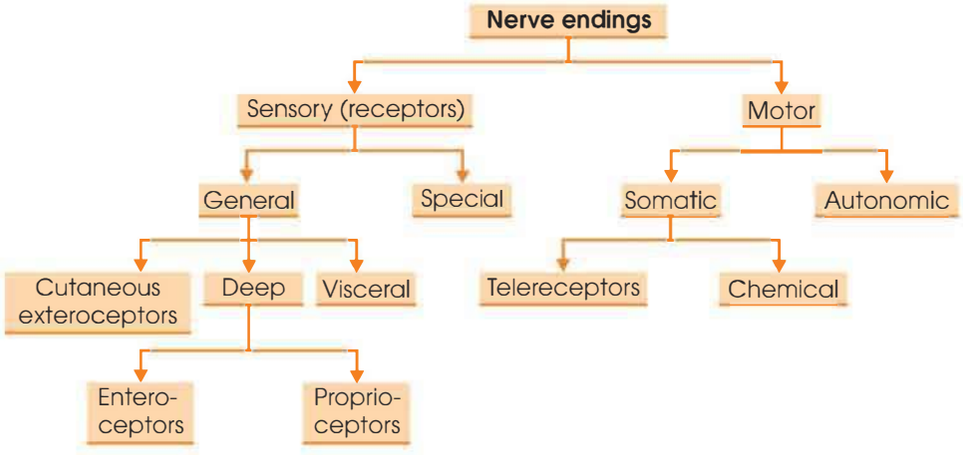


Fig. 90.7A to I: Nerve endings. (A) Meissner's corpuscle (touch); (B) Pacinian corpuscle (deep pressure); (C) End bulb of Krause (cold); (D) End organ of Ruffin (warmth); (E) Organ of Golgi-Mazzoni (heat); (F) Free nerve terminals (pain and touch); (G) Merkel's disc (touch); (H) Golgi bodies or organ of Golgi; (I) End plates



Receptors having a special connective tissue body are:

a. For touch (simple contact)—tactile corpuscles (Meissner's corpuscles), Merkel's discs. The Merkel's disc and Meissner's corpuscles are located along fingertips, lips, base of hair orifices and nipples, are sensory nerve endings of Aβ fibres.
b. For deep pressure (distortion): Pacinian corpuscles. The pacinian corpuscles are located in skin, subcutaneous tissue, mesentery, tendons and joints. They detect pressure and sustained touch sensation. Their sensory nerve endings are Aβ fibres.
c. For heat—end organs of Golgi-Mazzoni and of Ruffini. They are located in dermis. They detect warmth, pressure and touch sensation. They carry impulses via Aδ or C group of fibres.
d. For cold—end bulb of Krause. These are mechanoreceptors. They are located along conjunctiva, lips, tongue, genitalia, and nerve sheaths. Their sensory nerve endings are Aδ fibres.
e. Free nerve terminals (without any special body). They are mechanoreceptors and carry pain and temperature sensation via Aδ and C group of fibres.

3. Proprioceptors of muscles, tendons and joints: For kinaesthetic impulses, i.e. stretch, tension, etc.
   All possess special connective tissue bodies:
   a. Muscle receptors
   b. Pacinian corpuscles
   c. Uncapsulated nerve endings.
   There are two types of muscle receptors such as:
   a. Muscle spindle
   b. Golgi tendon organ

Muscle spindle (Fig. 90.9) is a special type of receptor presents within the muscle. The muscle consists of a bundle of two to ten slender striated muscle fibres enclosed within a thin connective tissue capsule. The capsule is tapered at both ends. The modified muscle fibres within the capsule are known as intrafusal fibres. The capsule is attached at either tapering end to the endomysium of the extrafusal muscle fibres or to the tendon or to the extrafusal muscle fibres. Thus, the capsule of the

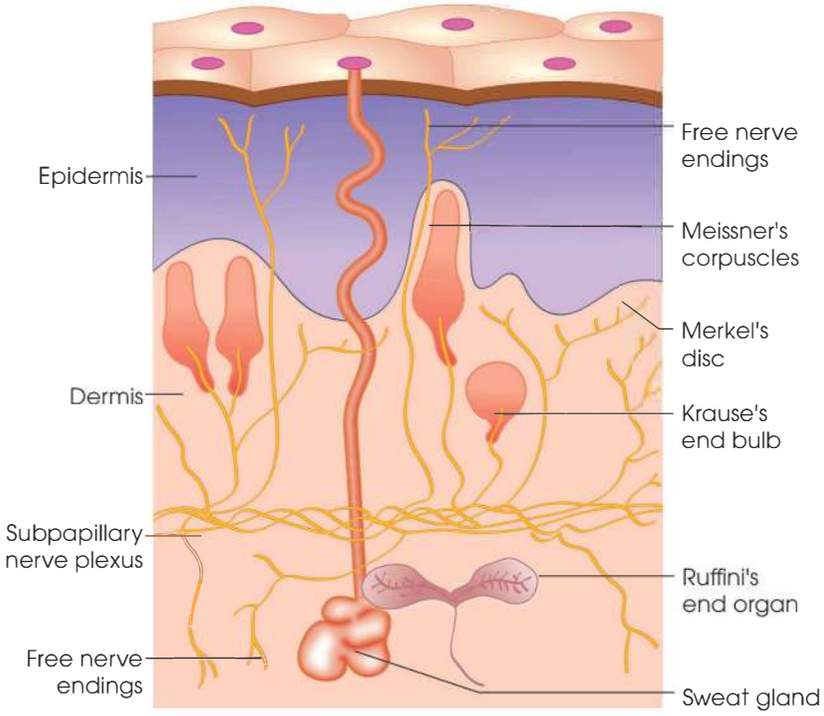


Fig. 90.8: Diagrammatic representation of nerve endings found in dermis and epidermis of human fingertip showing two papillary ridges

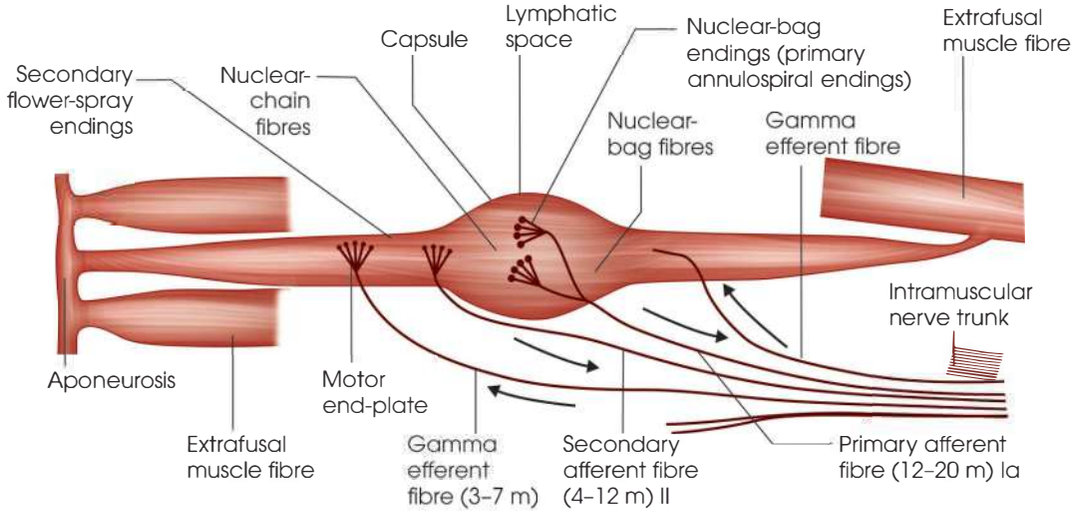


Fig. 90.9: Diagrammatic representation of a muscle spindle

intrafusal muscle fibres is arranged in parallel with the extrafusal fibres. Boyd (1962) from histological studies has classified the intrafusal fibres into two groups:

1. **Nuclear-bag fibres** displaying an aggregation of nuclei in the equatorial part.
2. **Nuclear-chain fibres** with only a single row of nuclei lying in a chain (Fig. 90.10). The both intrafusal fibres at its terminal ends (polar ends) are striated and contractile, whereas the central end of each fibre is unstriated, probably non-contractile. This portion is known as nuclear-bag region. This is separated from the connective tissue capsule by a lymph space filled with tissue fluid and traversed by nerve fibres and connective tissue fibres. At either side of the nuclear-bag region (primary annulospiral region) lie the nuclear-chain regions where the nuclei are arranged in central core.

Note

Viscous neuclear-bag fibres are innervated by the γ1 motor nerve fibres. These gamma efferent fibres terminate in discrete polar end-plates. On the other hand, the finer γ2 motor fibres end in γ trails on the nuclear-chain fibres and form a diffuse terminal reticulum along much of polar regions of the chain fibres.

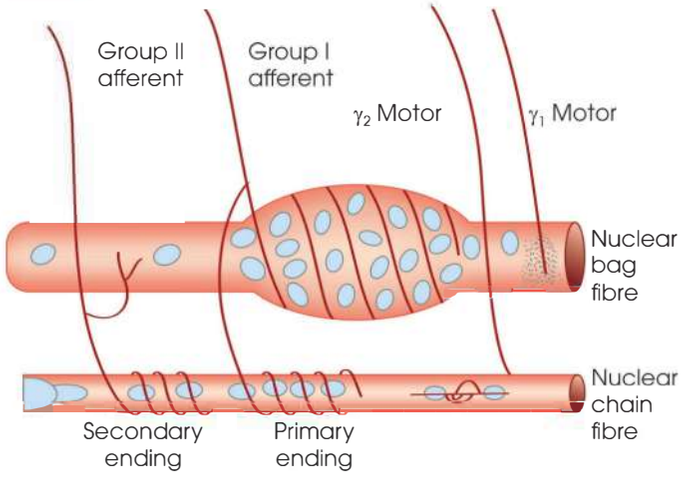


Fig. 90.10: Diagram shows a simplified representation of the central region of the muscle spindle (*Boyd*)

Three types of nerve fibres supply this special type of muscle.

1. The large afferent nerve fibres are 12–20 μm in diameter and have conduction velocity of 70–120 msec. These are known as primary afferent fibres-Ia, and they end in the nuclear-bag region. Before ending in the intrafusal fibres the myelin sheath finally winds round the muscle fibres forming a spiral ending.
2. The second groups of nerve fibres (Group II), known as secondary afferent fibres of 4–12 μm in diameter and having conduction velocity of 30–70 msec, enter the spindle to form a small ring which coils or sprays like varicosities on either side of the nuclear-bag region. These types of endings are known as secondary flower-spray endings.
3. Third sets of nerve fibres are fusimotor fibres or gamma efferent fibres of 3–7 μm in diameter, enter each spindle and end at the motor end-plates of tapering polar regions (contractile and striated ends) of the intrafusal fibres. The extrafusal fibres are supplied by alpha motor fibres. Afferent fibres from the muscle spindle enter the spinal cord and synapse in the alpha motor neuron (Fig. 90.11) form which the alpha efferent fibres arise, and then a monosynaptic path is established and acts as stretch or myotactic reflex.

Golgi tendon organ lies in the tendon and in tendinous band and aponeurosis within the muscle, and is a simple receptor and receives myelinated Group Ib fibres having diameter of 12–20 μm and conduction velocity of 70–120 msec. Both the muscle receptors are stimulated by stretch but the threshold for stimulus is higher for Golgi tendon organs than that of the muscle spindle. The muscle spindle is stimulated following a little stretch or contraction of the localised poles of the intrafusal fibres due to gamma motor (fusimotor) activity. As the intrafusal fibres are arranged in parallel with the extrafusal fibres, the contraction of the latter reduces the tension in the muscle spindle. Afferent discharges from the muscle spindle afferents (Ia) thus decrease during muscle (extrafusal) contraction (Fig. 90.12).

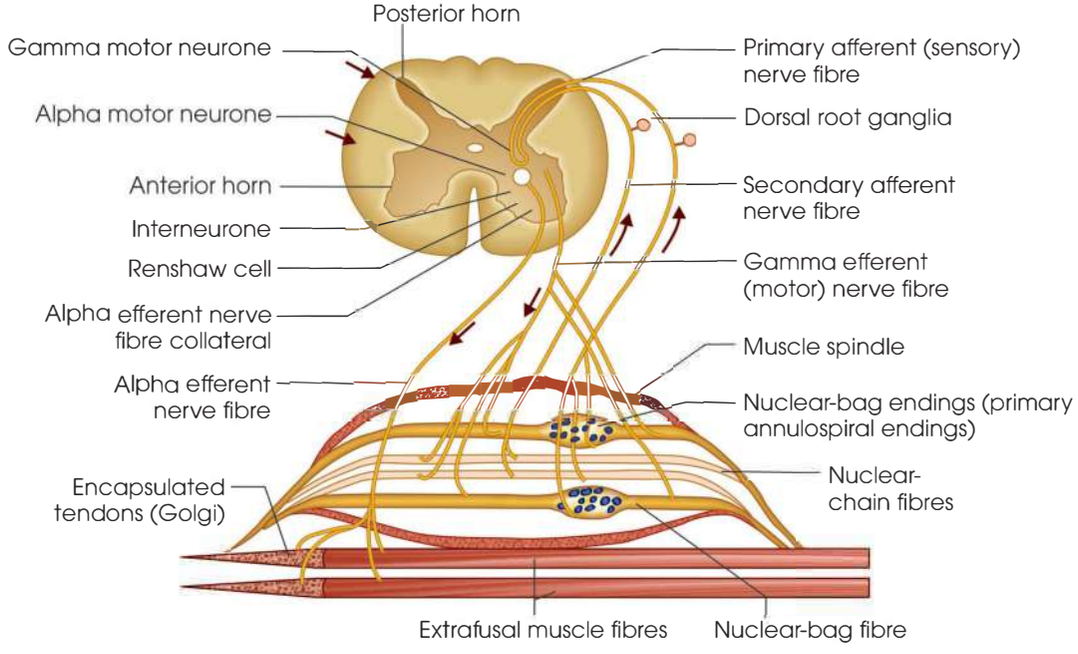


Fig. 90.11: Diagrammatic representation of the afferent and efferent connections of the extrafusal fibres (ordinary muscle) and intrafusal fibres of muscle spindle with the spinal cord motor neurons. Secondary and primary afferent fibres carrying impulses from the muscle spindle end in the alpha motor neuron of the spinal cord through dorsal root ganglion. Gamma efferent fibres from the spinal cord end in the end-plate of the extrafusal fibres. A subsidiary Renshaw interneuron conducting system is also shown to stabilise the activity of the alpha motor neuron

Golgi tendon organs are not stimulated by fusimotor activity and stimulated during excessive stretch as in case of clasp knife reflex. Clasp knife reflex is a disynaptic reflex.

Myotactic or stretch reflex is a monosynaptic reflex and mediated by the muscle spindle afferents (Ia). Muscle tendon organs discharge profoundly during muscular contraction (contraction of the extrafusal fibres) causing excessive stretch of the muscle tendon (Fig. 90.13) but remain practically silent during rest of the muscle.

Mechanism of Stretch Reflex

1. The neuronal mechanism of the stretch reflex at the spinal level may have at least three types of afferent nerve fibres: (a) Primary spindle afferent (Group Ia), (b) Secondary spindle afferent (Group II) transmitting its impulses to the spinal cord along smaller diameter and therefore more slowly conducting fibres, (c) Golgi afferent (Group Ib) producing autogenetic inhibition at high tension.
2. The central connections between incoming afferents and parent motor neuron pool may be direct (monosynaptic excitatory) or via interneurons. The descending impulses may modify the excitatory activity of these interneurons. The motor output is in two parts: (a) The γ-outflow(s) to the intrafusal muscle fibres by means of which the sensitivity of spindle afferents to stretch may be modified, and (b) the α-motor neuron output (the final common path) by which contraction of extrafusal muscle fibres is ultimately achieved.
3. In addition to the afferents from muscle, other reflex pathways may converge on the large (α) motor neurons and modify stretch reflex. Cutaneous sensations and especially pain are suitable examples.

SUMMARY

Receptors

1. **Pacinian corpuscles** are oval bodies and composed of concentric laminae. The afferent fibre penetrates to the centre of the corpuscle and pressure is the adequate stimulus. These receptor organs are present in baroreceptors, tendons, joints and periosteum, beneath the tendinous insertion and in subcutaneous tissues. These are also present in the abdominal mesentery. Micro-dissection demonstrates that a series of layers are separated by small amounts of fluid. In the centre there are blood vessels and a single nerve ending. The final portion of the nerve is unmyelinated, but there is one complete length of myelin and one node of Ranvier within the corpuscle.
2. **Labyrinthine impulses**—saccule, utricle, etc. (for details refer to 'Vestibular Apparatus': Otolith Organs). They maintain posture and equilibrium.
3. **Visceral** (autonomic): Either free terminals or special cells.
   a. *For pain:* Non-medullated free terminals.
   b. *For stretch and tension* (hollow organs, capsules, serous membranes, etc.): Free terminals—as in carotid sinus and aortic arch. (Pacinian corpuscles are also found in the viscera and

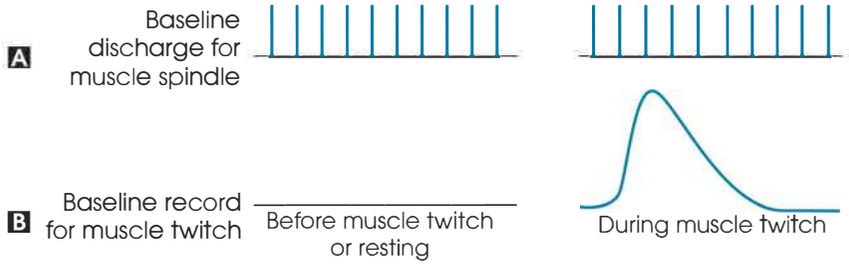


Fig. 90.12A and B: Demonstrates the nature of spindle discharge from spindle afferent fibres during contraction of extrafusal muscle fibres. (A) Shows baseline discharge from muscle spindle afferents during rest and activity of the extrafusal fibres. (B) Shows records of muscle twitch during rest and activity

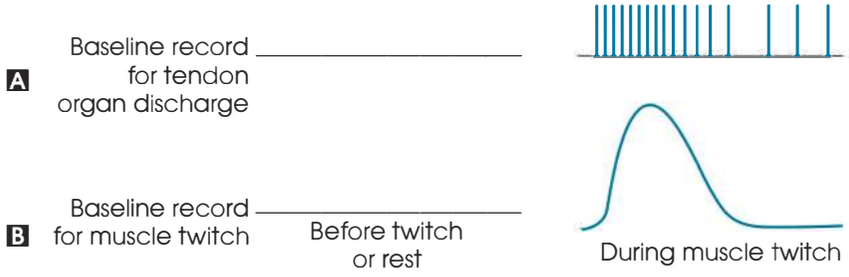


Fig. 90.13A and B: Demonstrates the nature of activity of tendon organ afferents during rest and activity. (A) Shows the records of pattern of discharge during rest and activity; (B) Shows records of muscle twitch during rest and activity

Table 90.1

Variety	*Histology*	*Distribution*	*Function*
Sensory			
A. Cutaneous			
1. Tactile corpuscles (Meissner's corpuscles)	Ellipsoidal lamellated connective tissue body, soft central core where axis cylinder ends in a complex manner	Papillae of the skin just under epidermis, specially hands and feet. Only one per 35 sq mm	Subserves *touch* (their number, being few, there must by other touch endings, viz. free terminals around hair follicles, etc.)
2. Pacinian corpuscles	Large oval body, lamellated like *onion,* naked axis cylinder ends in the core by arborisation.	In the dermis specially of hands and feet. Also in deeper structures like joints, tendons, etc. Also in the viscera, viz. peritoneum.	Carry *pressure, stretch* and *kinaesthetic* impulses. Gross deformity of shape is the adequate stimulus.
3. End bulb of Krause	Spheroidal connective tissue body, axis cylinder ends in a basket-like network. In animals, oblong or cylindrical. In the duck's bill axis cylinder ends in one or two expansions between 2–3 large core cells.	Conjunctiva, papillae of skin, lips, tongue, genital organs (*genital corpuscles*), in the structures near joints (*articular corpuscles*), epineurium of nerve trunks, etc.	Supposed to carry *cold* sensations.
4. End organ of Ruffini	Long cylindrical body, axis cylinder ends in flat expansions.	Skin and subcutaneous tissue of the fingers.	Carry sensation of *heat.*
5. Organ of Golgi-Mazzoni	Spheroidal or oval body, axis cylinder ends in flat expansions.	Skin and subcutaneous tissue of the fingers. Also in tendons and fascial sheaths of muscles.	Carry sensation of *heat*.
6. Free nerve terminals	The nerves at first form a *deep primary plexus,* then a *superficial secondary plexus,* from which terminal filaments pass to the surface, ramify among and inside the cells. End-points have knob-like expansions.	Widely distributed throughout the body. Dermis, cornea, etc. Also found between the muscle fibres, in tendons, fascia joints, serous membrane, etc.	1. Carry *pain* sensation for which there is no organized nerve endings. 2. Carry *touch.* Free terminals in skin and around hair roots are believed to carry touch impulses.
7. Glogi tendon organ	Flat bodies, between bundles of tendon fibres. Naked axon terminates in varicose arborisations.	Fond in the tendons near the junction with the muscle.	Carry, *kinaesthetic* impulses, i.e. stretch, tension, pressure, etc.
Motor			
1. End-plates	Naked axon is expanded into an end foot (sole foot) which ends into a specialized structure of the muscle membrane (motor end-plate). Sole foot contains mitochondria and vesicles filled with acetylcholine. Muscle membrane (sarcolemma) has got multiple folds which are collectively called synaptic gutter. The sole foot is bathed within the synaptic gutter. The sole foot is separated from the sarcolemma by the synaptic cleft **(palisades)** filled with extracellular fluid. Choline esterase is present in the rim of the synaptic gutter.	In all the voluntary muscles.	Transmits *motor impulses*. *Acetylcholine* is secreted at these endings, which initiates, chemical changes underlying muscular contraction.
2. Free nerve terminals (autonomic only)	The nerves from a *plexus,* from which terminal filaments pass to the surface, remify among and inside the cells. End-points have knob-like expansions.	Involuntary and cardiac muscles, glands, etc.	Transmits *motor impulses*. *Acetylcholine* is secreted at the preganglionic and postganglionic parasympathetic nerve endings and norepinephrine is secreted at the postganglionic sympathetic nerve endings. Preganglionic sympathetic nerve endings also secrete acetylcholine.

peritoneum—probably subserving stretch and tension.)

c. *Chemoreceptors*—sensitive to chemical changes of blood. These are special types of cells as found in carotid and aortic bodies.

4. **Special senses**

Telereceptors (distance receptors)

a. For vision: Rods and cones (retina)

b. For hearing—organ of Corti (internal ear)

Chemical receptors

a. For taste—taste buds

b. For smell—olfactory cells

Motor Endings

a. **With special connective tissue body** (somatic)—motor end-plates—in the voluntary muscles.

b. **Free nerve terminals** (autonomic)—supplying plain and cardiac muscles, blood vessels, glands, etc.

Some important nerve endings are described as follows:

Golgi apparatus, the Golgi tendon organ and the Golgi tendon reflex

Camillo Golgi was an Italian physician, biologist, pathologist, scientist, and Nobel laureate. Several structures and phenomena in anatomy and physiology are named for him, the Golgi apparatus, the Golgi tendon organ and the Golgi tendon reflex.

1843–1926

Reference: Cimino G. Reticular theory versus neuron theory in the work of Camilo Golgi. Physis RIV Int Stor Science 1999;36(2):431–472.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the property of receptors.

Short Notes

1. Classify nerve endings
2. Pacinian corpuscles
3. Muscle spindle
4. Classification of receptors
5. Golgi tendon organ

Chapter

91

Reflex Action

DEFINITION

Reflex action is an involuntary (automatic) effector response due to a sensory stimulus. It is the basic physiological unit of integration in the neural activity.

Varieties of Reflexes

There are mainly two types of reflexes:

a. **Unconditioned reflexes or inborn reflexes:** These are inherent, fixed and cannot be altered normally.
b. **Conditioned reflexes:** All are acquired. Can be established and abolished (*vide* under Conditioned Reflexes).

REFLEX ARC

Complete pathway (Fig. 91.1) for reflex action, three parts:

Afferent limb: It consists of:

1. Receptor
2. Afferent or sensory nerve fibre.

Centre: It consists of nerve cells where the sensory stimulus is converted into a motor impulse.

Efferent limb: It consists of:

1. Efferent or motor nerve fibre and its endings
2. Effector organ—muscle.

VARIETIES OF REFLEX ARCS

Synapse: It is a communicating link of two neurons.

Simple or two-neuron reflex arc or monosynaptic reflex arc: Has two neurons only, e.g. stretch reflex (*see* Fig. 91.14).

Three-neuron reflex arc or disynaptic reflex arc: Extension and crossed extension reflexes are the examples of this arc. There is a connecting neuron in between the afferent fibre and the motor neuron.

Polysynaptic or multisynaptic reflex arc: Several neurons. One or more internuncial (intercalated) neurons are also involved. Withdrawal reflex is a typical

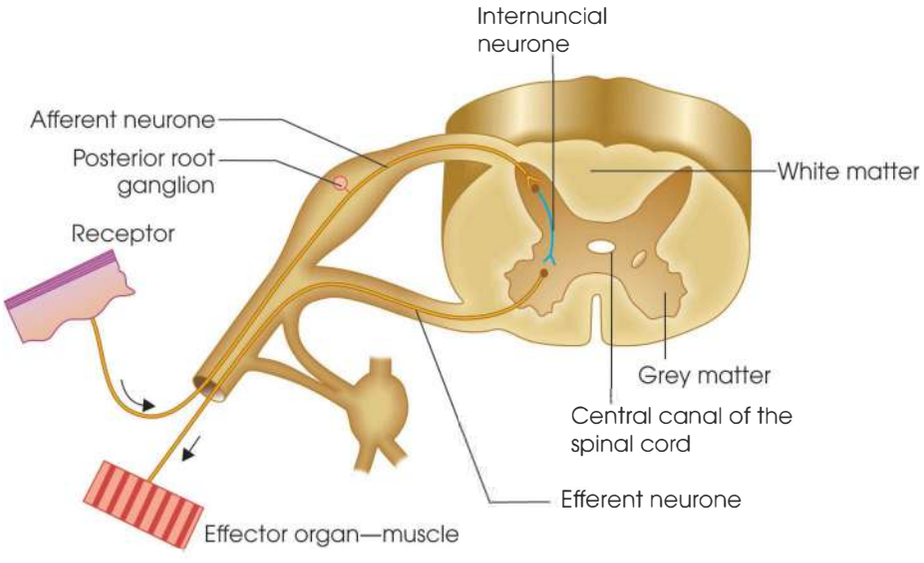


Fig. 91.1: Reflex arc

polysynaptic reflex and occurs in response to a noxious and usually painful stimulation of the muscles, skin and subcutaneous tissues (*see* Fig. 91.15).

Complex reflex arc: The axon of sensory neuron, while passing upwards, gives off collaterals at different levels, each of which may form separate reflex arcs. Thus, the same fibre will carry conscious sensations to cortex and also form multiple reflex arcs.

Asynaptic reflex arc: This reflex arc is not concerned with the synapse or nerve cell and also known as axon reflex arc. This is not a true reflex arc, and afferent and efferent limbs of this reflex arc are constituted by the branching of a single nerve fibre; because the reflex is obtainable even after section of the posterior root peripheral to their ganglia as long as the cut nerves are not degenerated.

GENERAL CHARACTERISTICS OF REFLEX ACTION

1. Irradiation

If the sensory stimulus be too strong, the impulse would spread onto many neighbouring neurons in the centre and produce a wider response. For instance, a weak pinprick on the finger will produce a reflex movement of that finger only. But if the prick be too hard, the whole hand will jerk up. If this process continues.

There will be recruitment of more and more motor neurons. Irradiation is due to transmission of the impulse through a large number of collaterals of the afferent fibres and their interneurons. A strong stimulus will cause reflex contraction of the extensor muscles of the opposite limb.

2. Delay

There is a short interval between the application of stimulus and the onset of reflex response. This period is called total reflex delay. If from this, the time taken by the nerve impulse to traverse the motor and sensory limbs of the reflex arc, be subtracted, the remainder will be the central delay (reduced reflex time). This time is lost in crossing the number of synapses in the central nervous system.

3. Summation

If the stimulus be subminimal and applied to an afferent nerve there will be liberation of a chemical transmitter which will cause excitatory postsynaptic potential (EPSP), but this EPSP will not be sufficient to produce discharge of impulses from the motor neurons. But if a number of subminimal stimuli be applied, their effects will be summated together and the EPSP will be sufficient to induce the motor neurons to discharge impulses and produce the reflex response. This is called summation. Two types of summation are found.

A. *Spatial Summation*

Spatial summation is the mechanism of eliciting an action potential in a neuron with input from multiple presynaptic cells. Excitatory postsynaptic potential summation generates an action potential, and summation of inhibitory postsynaptic potentials can prevent generation of action potential. The EPSP will be sufficient to induce the motor neurons to discharge impulses and produce the reflex response.

B. *Temporal Summation*

Here a series of subminimal stimuli are applied on the same spot, one after the other. The first shock causes a change in excitability somewhere on the pathway of flexion reflex which persists for several to summate with the effect of the second shock. Sherrington called this persisting change central excitatory state. It seems that alterations of the central excitatory state during the flexor reflex took place in the motor neurons of the flexor muscle, in the motor neuron pool as it was termed. Electrical recording with fine electrodes inside the spinal cord has now shown that afferent nerve fibres which elicit the flexion reflex, end on the interneurons in the posterior horn of grey matter and do not themselves run through to the motor neurons in the anterior horn.

When the afferent nerves are stimulated simultaneously there is liberation of chemical transmitter substance which causes excitatory postsynaptic potential (EPSP). When excitatory postsynaptic potential is adequate the reflex response occurs.

Scratch reflex: On repetitive stimulation of the skin behind the ears, neck, shoulder and in a dog after spinal section in the cervical region produces scratching movement of the corresponding hindlimb due to alternate contraction of flexor and extensor muscles. The scratch reflex cannot be elicited by electrical excitations of cutaneous nerve trunks or of posterior roots; apparently such volleys are not recognised as objects to be scratched at; but small shocks applied through a fine pin (electric flea) pushed just into the epidermis are successful. Scratch reflex is an example of temporal summation.

4. Occlusion (Fig. 91.2)

When a reflex contraction is produced by simultaneous stimulation of two afferent nerves, the amount of tension (T) in the muscle is less than the sumtotal of the tensions ($t_1 + t_2$) set up in the same muscle when the two afferent nerves are separately stimulated (i.e. $T < (t_1 + t_2)$. This is explained on the assumption that some nerve cells remain common to both the reflex paths.

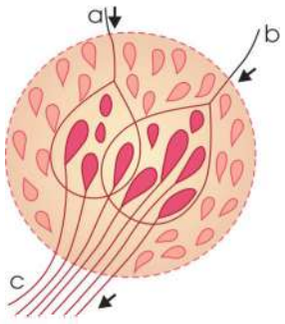


Fig. 91.2: Phenomenon of occlusion. a and b are separate afferent paths each including several neurons. c is the common motor path. Note that one neurone is common to both the reflex paths

5. Subliminal Fringe

This is exactly the reverse of occlusion. Here the total tension due to separate stimulations ($t_1 + t_2$) is less than the amount of contraction (T) obtained with simultaneous stimulation of the two spots ($T>(t_1+ t_2)$. It is explained on the following lines. During separate stimulation, the impulse becomes adequate for some synapses but inadequate (subliminal) for others (high-resistance synapses). But during simultaneous stimulation of two spots, such subminimal stimuli coming from two sources, will be summated together and be able to pass through the high-resistance synapses; so that the effect with simultaneous

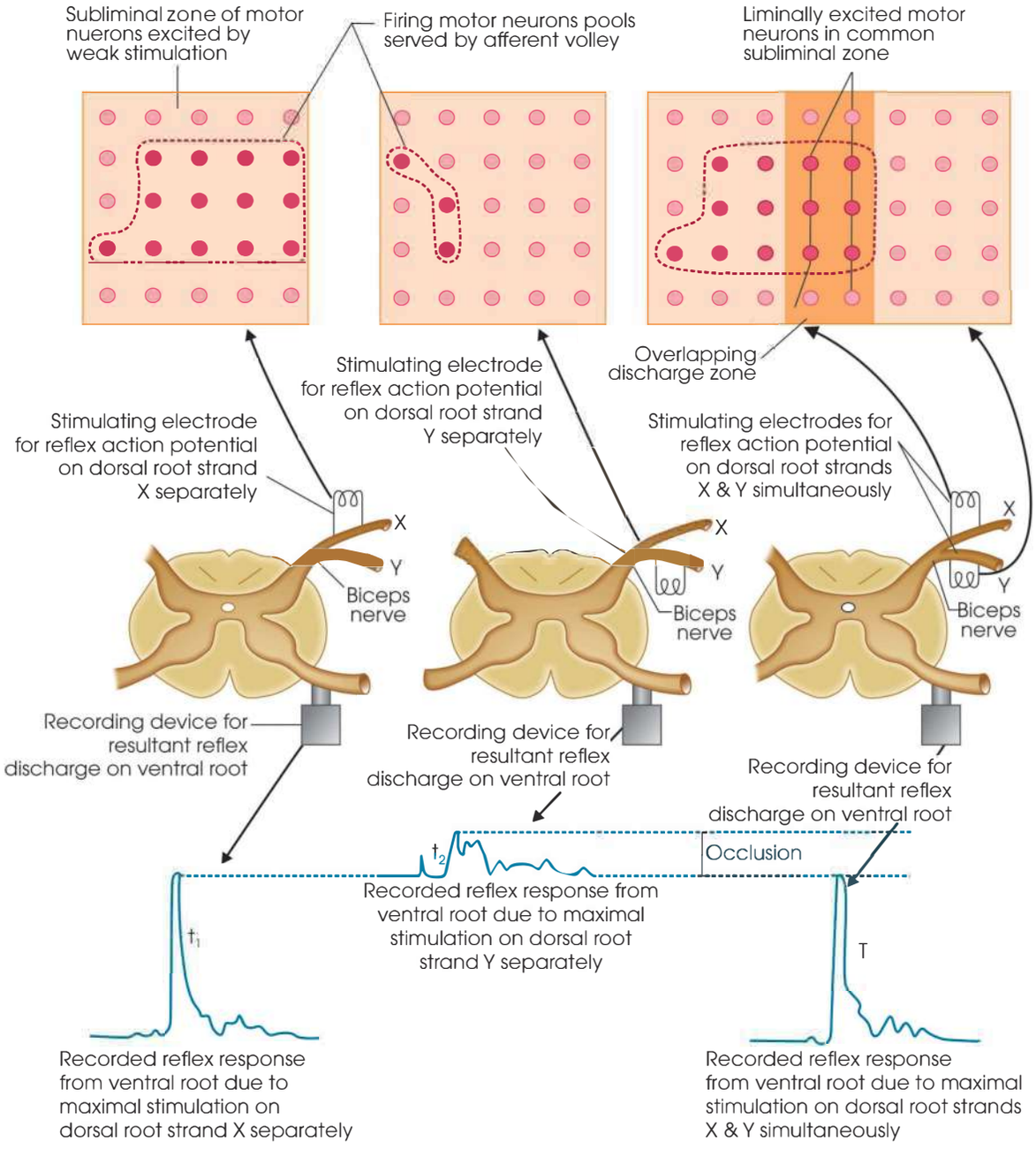


Fig. 91.3: Diagrammatic representation of the experimental demonstration and of mechanism of occlusion

stimulation will be stronger than the sumtotal of effects produced by separate stimulations (a, b and c) (Fig. 91.4).

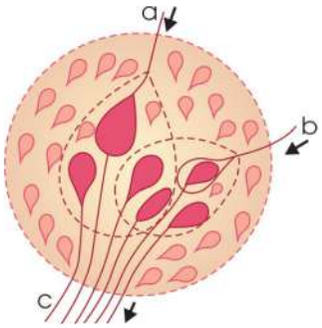


Fig. 91.4: Phenomenon of subliminal fringe. When stimulated alone, only the black cell is excited. When stimulated together, the two high-resistance synapses (shaded) which remain common to both the dotted fields, these neurons are excited and the effect becomes greater

6. Facilitation

If a reflex be elicited repeatedly at proper intervals, the response becomes progressively higher for the first few occasions. Each subsequent stimulus seems to exert a better effect than the previous one and makes the passage of the next impulse easier.

In other words, the passage of a reflex impulse facilitates the transmission of the next impulse (beneficial effect by reducing synaptic resistance). The change of state by which the second subliminal impulse is rendered liminal is spoken of as facilitation (Fig. 91.5).

7. Inhibition

In this phenomenon a stimulus diminishes or inhibits the effects of another stimulus. Impulses through the sensory fibres from protagonist muscles lead to a reflex response of those muscles but at the same time inhibit the action of the antagonist muscles. Sherrington

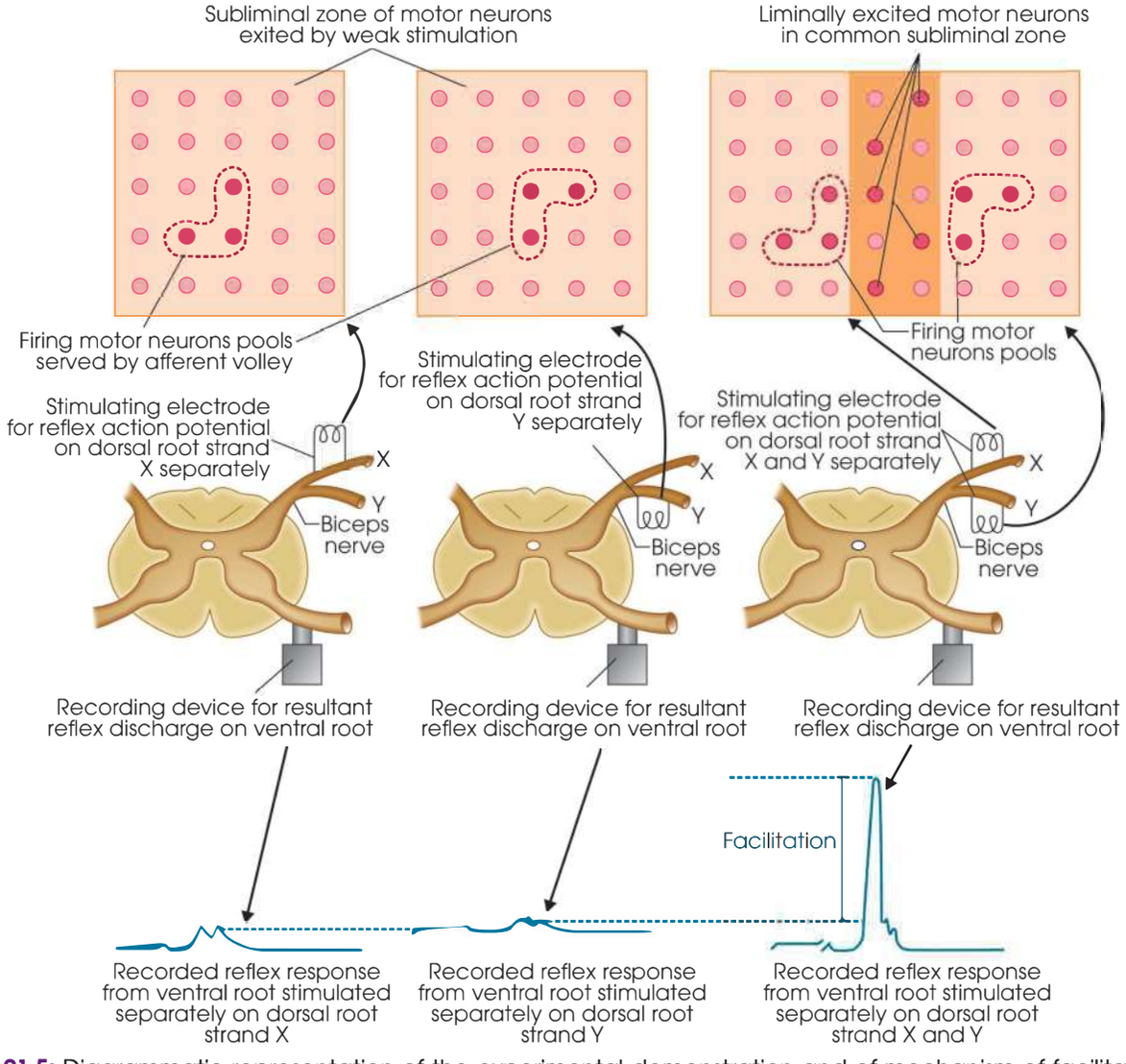


Fig. 91.5: Diagrammatic representation of the experimental demonstration and of mechanism of facilitation

demonstrated that when the flexor muscles of a joint are stimulated and the extensor muscles are inhibited. Such reciprocal effects are due to the inhibitory activity exerted by the interneurons.

8. Recruitment

When muscle fibres are stimulated directly through their motor nerve, the tension very quickly rises to the maximum. But if they are stimulated reflexly through a sensory nerve, the tension in the muscle develops gradually to the peak. After repeated stimulation of the afferent nerves more internuncial neurons are activated and lead to excitation of more number of the motor neurons. If the stimulation is continued, effective summation occurs. All these effects may be said as due to the recruitment of more and more motor neurons. But there is always a limit of recruitment.

9. After-discharge

After reflex contraction (by tetanising current) if the stimulation is discontinued, the muscle does not completely relax at once. It relaxes gradually. Certain amount of contraction lingers in the muscle for some time. This is due to the fact that the centres go on discharging motor impulses for a brief period, even after the sensory stimuli are stopped. It is due to stimulation of the motor neurons through the internuncial paths. The impulses which travel in the internuncial paths (long or delay paths) take longer time to reach the motor neurons. So, even after cessation of afferent stimulation these impulses travel for certain periods and stimulate the motor neurons.

10. Fatigue

If a particular reflex be repeatedly elicited at frequent intervals, the response becomes progressively feebler and finally disappears altogether. This phenomenon is called fatigue. The seat of fatigue is in the central nervous system, probably at the synapses; because a muscle, under reflex fatigue, will contract when the motor nerve or the muscle itself is directly stimulated. Fatigue comes first at the synapses, then in the motor endings and lastly in the muscle.

11. Fractionation

When a stimulus is applied directly on the motor nerve of a muscle, the amount of contraction becomes much higher than, when the same muscle is made to contract reflexly (i.e. by stimulating the appropriate sensory nerve). This indicates that one fraction of the sensory impulse is lost in the central nervous system apparently to overcome the synaptic resistance (strength of the impulse is reduced while crossing a synapse). A portion of the motor neuron pool supplying the muscle is only stimulated. There is also graded response in flexor reflex and crossed extensor reflex with simultaneous increase in the strength of stimulus.

12. Reciprocal Innervations

In a reflex action when one group of muscles contract, the antagonistic group relaxes to the same degree. Both the processes of contraction of the flexors and relaxation of the extensors occur simultaneously. The changes are recorded by connecting the muscles with the levers. The afferent impulses pass by dorsal root into the spinal cord, stimulate the motor neurons supplying the flexors and inhibit the motor neurons supplying the extensors (Fig. 91.6) (Sherrington).

Reciprocal relations of monosynaptic and polysynaptic reflex arcs have been shown in Figs 91.7A and B.

If Group II, III and IV afferent fibres are stimulated, then they influence diffusely, motor neurons supplying muscles acting at several joints. If the Group I afferent is stimulated then it influences the motor neuron supplying muscles acting at a single joint.

13. Rebound Phenomenon

Just as a muscle can be reflexly excited, so also it can be reflexly inhibited (tone reduced and muscle elongated due to relaxation—reflex inhibition). After such reflex inhibition with a tetanising current, if the stimuli be stopped, the muscle instead of going back to its former length becomes shorter. In other words, the muscle tone increases above the normal resting value. This is called rebound phenomenon.

Final Common Path

All neural influences affecting muscular contraction pass through final common paths which receive numerous converging input signals at a particular spinal segment from various spinal and supraspinal inhibitory and excitatory pathways.

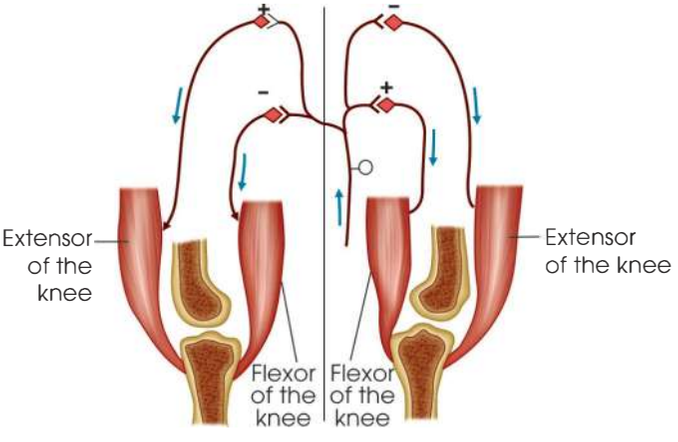


Fig. 91.6: Reciprocal innervations (modified after Sherrington)

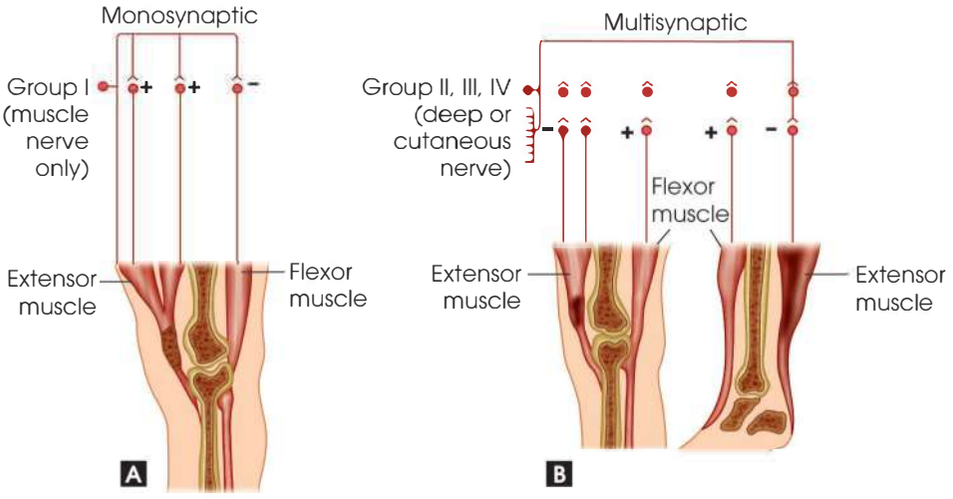


Fig. 91.7A and B: (A) Monosynaptic reflex; (B) Polysynaptic reflex

Central Excitatory and Inhibitory States

The spinal cord at a particular level shows prolonged changes in excitability resulting from the activities of reverberating circuits of the segmental and suprasegmental pathways and the particular prolonged state of activity is called excitatory or inhibitory state.

UNCONDITIONED REFLEXES

As mentioned before, unconditioned reflexes are inborn. The nerve paths are fixed from the very birth. Any alteration is considered as disease. Hence, examination of reflexes is a great help in the diagnosis of various diseases.

Classification of Reflexes

Physiological

1. *Segmental:* The reflex arc passes through only one segment of the spinal cord, e.g. tendon jerk.
2. *Intersegmental:* The arc involves tracts of spinal cord in different segments, e.g. crossed extensor.
3. *Suprasegmental:* The arc involves nuclei above the cord and the segments of cord itself, e.g. attitudinal postural reflexes.

Clinical

1. Superficial—elicited from skin or mucous membrane, e.g. corneal, plantar, etc.
2. Deep—elicited from tendons, e.g. tendon jerk.
3. Visceral—elicited from organs, e.g. digestive, micturition reflex, etc.
4. Pathological—presents only in abnormal condition, e.g. Babinski's sign.

Superficial Reflexes

Stimulation of certain areas of skin or mucous membrane causes contraction of corresponding muscles, due to their surface origin they are called superficial reflex. The examples are plantar reflex, abdominal reflexes, cremasteric reflex, conjunctival reflex, corneal reflex, etc.

Brief details about some important superficial reflexes are given Table 91.1 .

The reflex arcs for superficial reflex are not definitely known. They seem to be long and complex, including a number of intercalated neurons. The impulse appears to be carried up by fibres in the posterior column tracts and spinothalamic tracts and ends somewhere in the midbrain, thalamus or even the forebrain. From the region, it is then carried down by the pyramidal, or more probably the extrapyramidal tract (being more primitive) and is passed onto the corresponding anterior horn cells. The nerve path for deep reflexes, on the other hand, is simple and short ending quickly in the cord itself. This explains why in the case of upper motor lesions, the superficial reflexes are lost (reflexes are damaged), but the deep reflexes are exaggerated (release phenomenon).

DEEP REFLEXES OR TENDON REFLEXES

Brief details about some important deep reflexes are given Table 91.2.

Tendon reflexes are deep proprioceptive (kinaesthetic) reflexes and should be regarded as fractionated stretch reflexes. A sharp tap on the slightly stretched tendon, will elicit an equally sharp contraction of the corresponding muscles. These reflexes show characteristic variations in many diseases and are of great diagnostic value. Knee jerk (Fig. 91.8B), ankle jerk (Fig. 91.11), biceps jerk (Fig. 91.8A), triceps jerk (Fig. 91.8C), etc. are the examples. Knee jerk is briefly described as follows.

Table 91.1: Superficial reflex: Elicitation and response

Superficial reflexes	*Method of eliciting*	*Response*	*Centre*
Plantar	Scratching the skin of the sole.	Normally plantar flexion of the great toe (Fig. 91.8D). But in case of infants (before walking) and also in pyramidal lesions (corticospinal at any level above the 1st sacral segments, the normal response is chaned into dorsiflexion of the great toe an often associated with fanning of the outer toes)	Lumbar 5 to sacral 2. Most probably the sacral 1.
Bulbocavernous	Stimulation of glans penis.	Contraction of the bulbocavernosus muscle.	Sacral 3 and 4.
Anal	Scratching of the neighbouring skin of the anal sphincter.	Contraction of external anal sphincter.	Sacral 4 and 5 and Coccygeal segments.
Gluteal	Scratching the skin of the buttock.	Contraction of the gluteal muscles.	Lumbar 4 and 5 and upper sacral segments.
Upper abdominal (epigastric)	Scratching below costal margin.	Retraction of hypochondrium of the same side.	Thoracic 6 and 7
Lower abdominal	Stroking above the inguinal ligament.	Contraction of the lower abdominal wall on the same side.	Thoracic 10 and 12
Cremasteric	Stroking skin of inner thigh.	Drawing up of testicle.	Thoracic 12 to lumbar 2
Conjunctival and corneal	Touching conjunctiva of cornea.	Winking	Thoracic 12 to lumbar 2. Nuclei of Vth and the cranial nerves.

Table 91.2: Deep reflex: Elicitation and response

Deep reflexes	*Method of eliciting*	*Response*	*Centre*
Knee jerk or patellar tendon reflex	Tapping patellar tendon	Jerking forward of leg	Lumbar 2 to 4
Ankle jerk or achilles tendon reflex	Tapping tendo-Achillis.	Plantar flexion of foot	Lumbar 5 to sacral 2
Jaw jerk	Tapping the chin with the mouth partly open	Jerk the jaw	Pons
Biceps jerk	Tapping biceps tendon	Flexion of forearm	Cervical 5 and 6
Triceps jerk	Tapping triceps tendon	Extension of forearm	Cervical 6 and 8
Supinator jerk	A blow upon the styloid process of the radius	Contraction of supinator and flexion of the elbow	Cervical 5 and 6

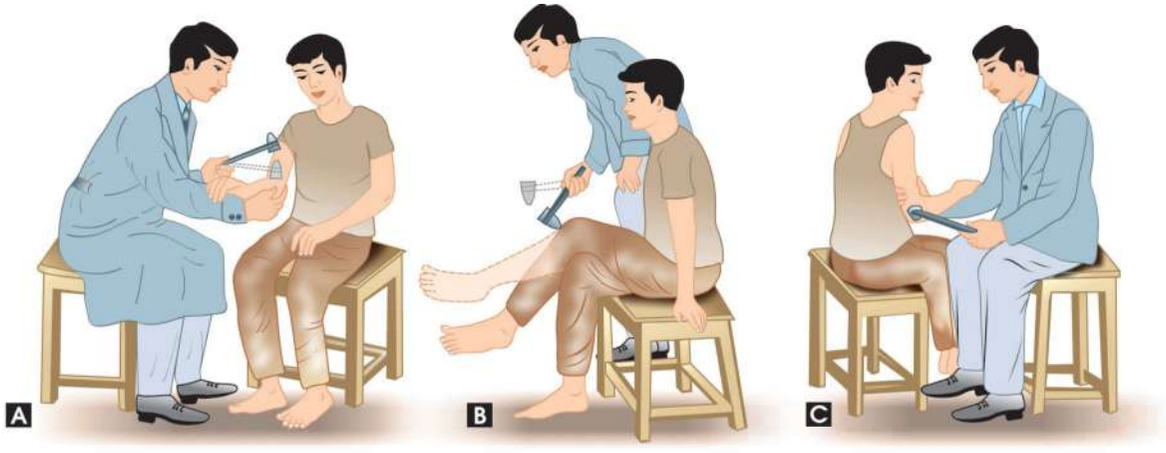


Fig. 91.8A to C: Diagrammatic representation of reflexes. (A) Biceps tendon reflex (flexion of forearm on percussion of biceps tendon); (B) Patellar tendon reflex or knee jerk (extension of leg on percussion of patellar ligament); (C) Triceps tendon reflex (extension of forearm on percussion triceps tendon)

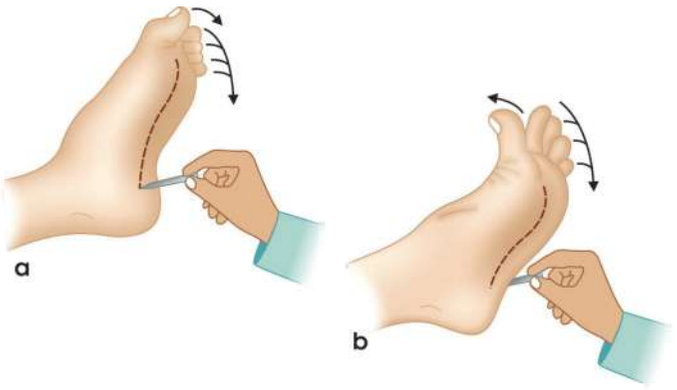


Fig. 91.8D: Diagrammatic representation of plantar reflexes. (a) Normal plantar reflex, (b) Babinski's plantar reflex

PATELLAR TENDON REFLEX OR KNEE JERK

Reflex Path

1. The sharp tapering on the patellar tendon causes stretch on the muscle spindle of the extensor muscle and afferent impulses pass through the primary afferent fibres to the spinal motor neuron via dorsal root ganglion.
2. This afferent fibre synapses with the alpha motor neuron of the spinal cord (Fig. 91.10). The impulse thus reaching the spinal cord stimulates the alpha motor neuron and the contraction of extensor extrafusal muscle fibres occurs. With this a short jerky forward movement of the leg occurs.
3. It is a monosynaptic reflex. For this jerky movement the flexor muscles relax, simultaneously with the contraction of the extensor (Fig. 91.9), due to inhibitory motor influences exerted on the antagonistic muscle group during reflex.
4. Renshaw cells of the spinal cord are stimulated during the alpha motor neuron activity and inhibit in turn the alpha motor neuron discharge.

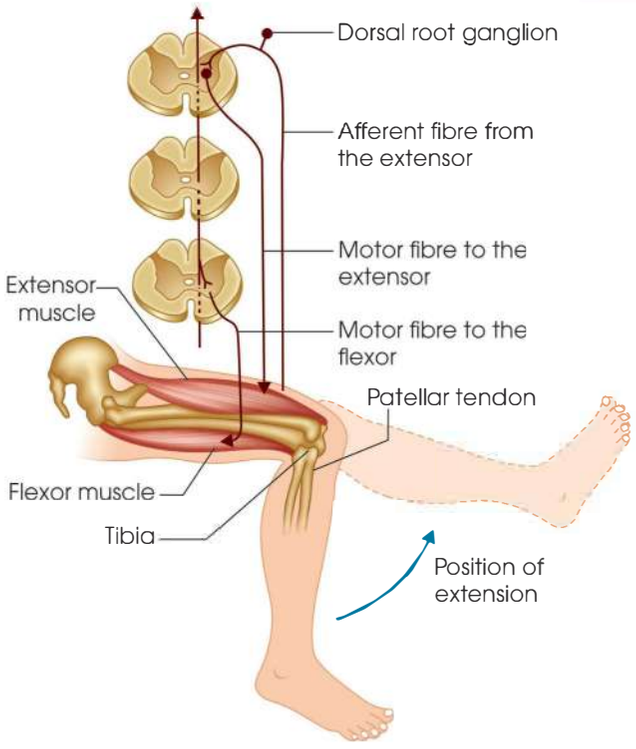


Fig. 91.9: Diagrammatic representation of knee jerk (patellar tendon reflex); along with patellar tendon of extensor muscle attached to the tibia below the knee

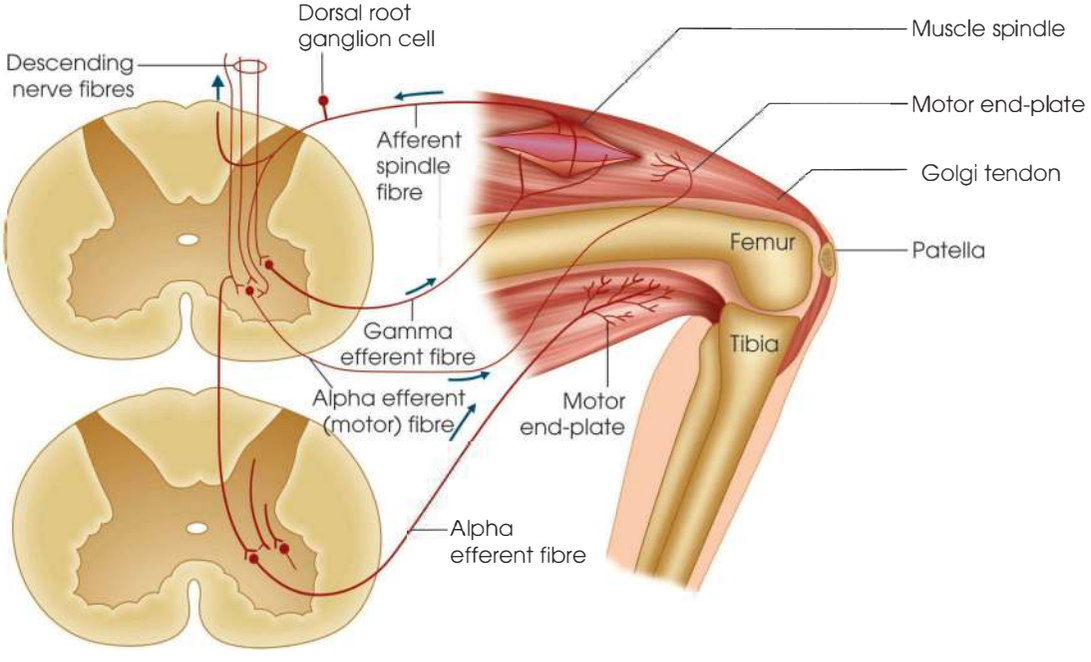


Fig. 91.10: Diagram showing mediation of myotatic reflex pathway of afferent and efferent fibres and principal receptors of muscle spindles. It also shows the gamma motor loop system comprising the afferent and efferent connections in between the muscle spindle and the spinal cord motor neuron

5. Reinforcement: Knee jerk may be reinforced by a strong simultaneous voluntary act, viz. clenching the jaw, squeezing the hands, etc. Reinforcement is due to overflow (irradiation). When the voluntary act precedes the reflex by a long interval (0.5 second), the jerk is inhibited. This is called negative reinforcement.

   Knee jerk is abolished in lower motor neuron lesions, exaggerated in upper motor neuron lesions, and becomes pendular in certain cerebellar diseases.
6. Knee clonus or patellar clonus: This is found when knee jerk is highly exaggerated and is a dependable sign of the upper motor neuron lesion. When the patella is sharply pressed down, the quadriceps shows a series of clonic contractions as long as the stretch is maintained. Clonus is nothing but 'repeated jerk'. As soon as the muscle relaxes the maintained patellar pressure stretches the muscle again, so that the muscle again contracts. This alternate contraction and relaxation will go on rhythmically, as long as the pressure is continued.

Ankle Jerk

1. The jerk represented in Fig. 91.11 is an ankle jerk.
2. The reflex is elicited by striking the tendon of ankle extensors (soleus and gastrocnemius muscles) with a specific hammer. It consists of a twitch contraction of these muscles.
3. To record the contraction, the foot rests on a board. Contraction of ankle extensors causes an increase in the downward pressure, exerted by the front of the foot on the board, which is recorded on a CRO.
4. The action potential of ankle extensors is led off by surface electrodes on the calf muscle. Oscilloscope time base is triggered by contact of the hammer with the skin over the tendon.
5. The blow itself causes a short rise in tension which appears as a small hump before the beginning of muscle twitch.
6. If the latency of the reflex be measured from the contact of the hammer with the skin to the start of the action potential, it would be about 45 msec. On the other hand, nerve conduction time is about 35 msec, together with a brief central delay, from the muscle to the spinal cord and back again.
7. An optimal motor twitch in the extensor muscle, elicited by an electrical stimulus to the motor nerves, is shown in Fig. 91.11. The time base is triggered by stimulus.
8. The action potential and twitch tension are larger and the latency is much shorter. But the duration of the action potential and the twitch are much the same as in the reflex jerk, showing the reflex discharge with a highly synchronous volley of nerve impulses.
9. Ankle clonus.

In pyramidal lesions, sudden dorsiflexion of the foot will cause rhythmic contractions of the calf muscles—producing ankle clonus. It will continue as long as the flexion is maintained. This is seen in upper motor neurone lesions only. The explanation and significance are same as patellar clonus.

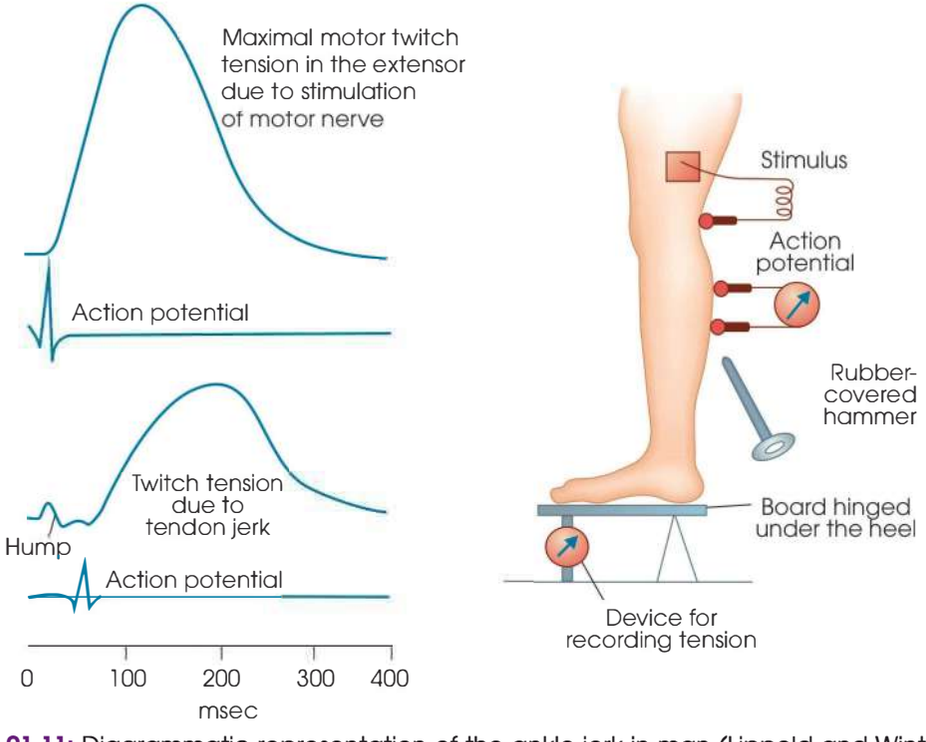


Fig. 91.11: Diagrammatic representation of the ankle jerk in man (Lippold and Winton)

STRETCH REFLEX (MYOTATIC REFLEX)

When the tendon of a denervated muscle is pulled upon, the muscle passively elongates. But if the same pull is applied to a muscle (extensor) with intact nerve supply, the muscle instead of elongating, actively contracts against the pull. The contraction is proportional to the degree of stretch and is maintained as long as the stretch is kept up. This is called stretch reflex. That it is a reflex action is further proved by the fact that, section of corresponding posterior roots abolishes it. The postural reflexes belong to this class.

IMPORTANCE OF STRETCH REFLEX

This is the chief mechanism for the production of muscle tone and maintenance of posture. In erect posture, gravity tends to flex the hip, knee and ankle. This slight initial flexion stretches the antagonistic extensors, causing their contraction. Due to this contraction the subject remains standing.

The salient features of stretch reflexes are:

1. Stretch reflexes are seen in the antigravity extensor muscles only and not in the flexors.
2. The stimulus arises by the stretch of the muscle and is received by the kinaesthetic stretch receptors in it.
3. The stretch receptors generate and send off series of impulses continually along the afferent fibres when the muscles are stretched. As the degree of stretch increases, more receptors are affected, the frequency of afferent impulses rises and, hence, more and more motor units are recruited into action. Consequently, more contraction is generated in the muscle. In this way, the degree of stretch and contraction become proportional.
4. Stretch receptors do not undergo rapid adaptation and consequently generate impulses so long as the stretch is kept up. This is in great contrast with other types of receptors.
5. The rate of discharge of motor neurons is slow, about 9 per second. This explains absence of fatigue in posturing muscles.
6. Stretch reflexes are mediated by simple reflex arcs (monosynaptic). Hence, their latent periods are short (0.5 msec) and there is very little after-discharge (because of very few synapses).
7. It only takes place in the affected muscles and does not spread to any other (i.e. no irradiation). They can be inhibited by evoking an antagonistic reflex.

ELECTROPHYSIOLOGY OF SPINAL REFLEXES

1. The electrical responses that are recorded from the ventral root following stimulation of the dorsal root are considered as reflex responses (Fig. 91.12).
2. The ventral root responses elicited by dorsal root stimulation may occur through the activation of more than one synapse.
3. If the response occurs through the involvement of one synapse then it is called monosynaptic (Fig. 91.13).
4. If it occurs through the involvement of more than one synapse is called multisynaptic or polysynaptic (Fig. 91.14).

Monosynaptic Reflex

Monosynaptic reflexes are elicited by stimulation of large afferent fibres Ia originating from the muscle spindle of extensor and flexor muscles and having conduction velocity of about 70–120 msec and diameter of 12–20 μm. If the latency of the reflex is measured then it will be observed that the shortest latency is being around 0.5 msec which is a delay corresponding to the time necessary to traverse only one synapse (Fig. 91.13). Monosynaptic discharges occupy the efferent fibres of the muscle nerve in which the afferent discharge originates. Furthermore, monosynaptic discharge returns to the muscle from which the afferent volley originates.

Polysynaptic Reflex

Polysynaptic reflexes are involved with more than one synapse and hence the name. The reflex pathways may go through 2, 3, 4 or more synapses (Fig. 91.14). Many interneurons are involved in these reflexes. The motor neuron is not stimulated directly but indirectly through the different interneurons. The afferent nerves involved in polysynaptic reflex arc are the Group of II, III and IV fibres.

Withdrawal Reflexes

1. Withdrawal reflex in the human can be elicited from the leg of a healthy subject by a painful stimulus applied to the skin. Kugelberg, Eklund and Grimby (1960) have shown that with the stimulus applied to the underside of the great toe, the response obtained would be flexion at all joints (Fig. 91.15A).
2. There are upward movement of the toes, flexion of the ankle, knee and hip and forward flexion of the trunk (Fig. 91.15B).
3. When the stimulus would be moved further back on to the sole of the foot the toes moved downwards instead of upwards, the other joints flexing as before.
4. The similar response is observed by firmly stroking the sole of the foot. When the electrical stimulus is applied under the heel the toes again moved downwards but now the ankle is extended too, other joints again flexing. Again when the stimulus is applied on the buttock, the trunk, hip and ankle are extended, the knee partly flexed, and the toes moved downwards (Fig. 91.15A).

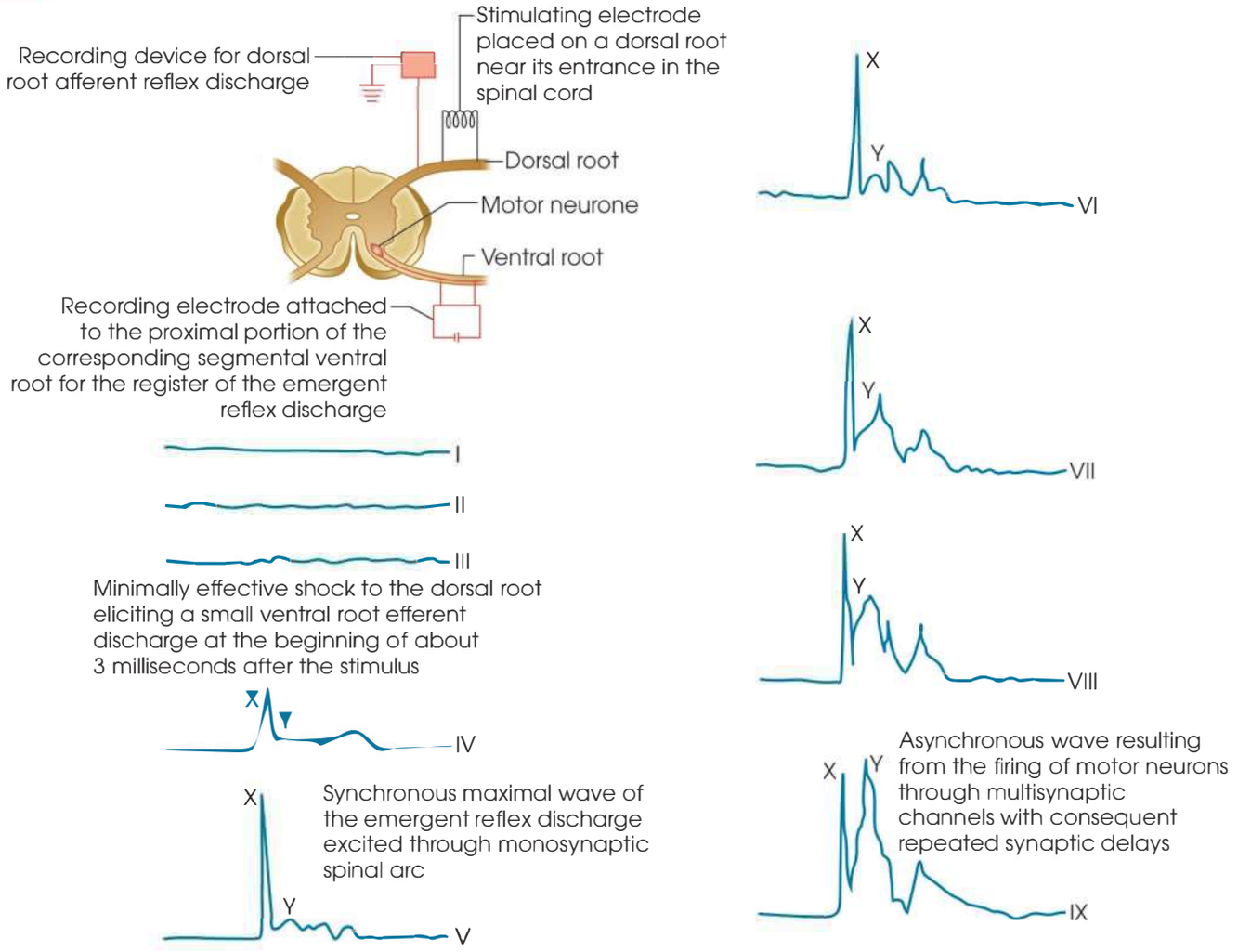


Fig. 91.12: Diagrammatic representation of spinal reflex discharges due to stimulation of dorsal spinal root at varying current strength. With the increase in shock strength, the amplitude of synchronous (monosynaptic) discharge 'X' rises maximally in 'V' in comparison with 'IV', but there is a little change in 'X' with further increase of shock strength. On the other hand, the amplitude in asynchronous (multisynaptic) discharges rises slowly with the increase of stimulus strength when the synchronous (monosynaptic) discharge has attained its maximal peak (V–IX)

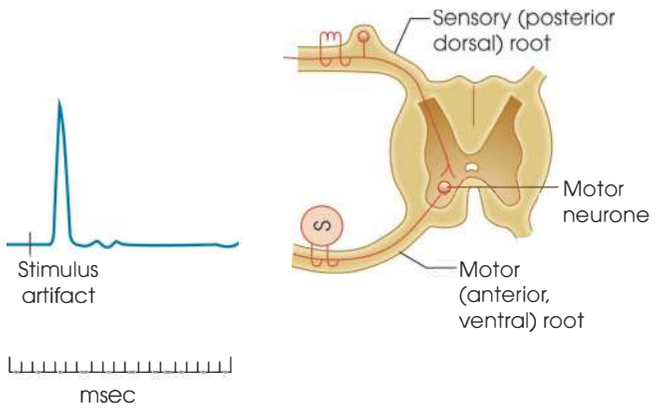


Fig. 91.13: Showing the monosynaptic reflex arc (right) and also monosynaptic reflex response (left). Monosynaptic reflex response is observed after stimulation of the Group Ia afferent fibres of the gastrocnemius nerve

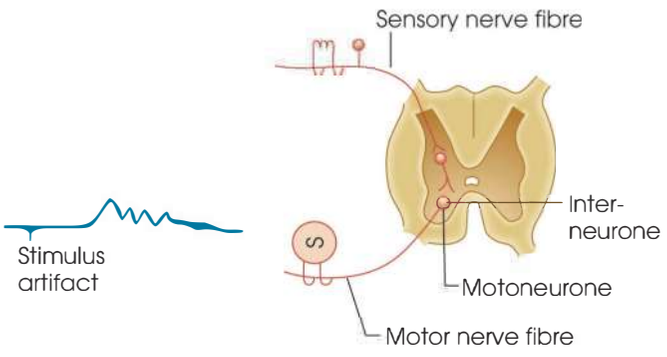


Fig. 91.14: It represents the polysynaptic reflex arc (right) and reflex response (left). Polysynaptic reflex response observed after stimulation of the cutaneous nerve (only two neurons are shown)

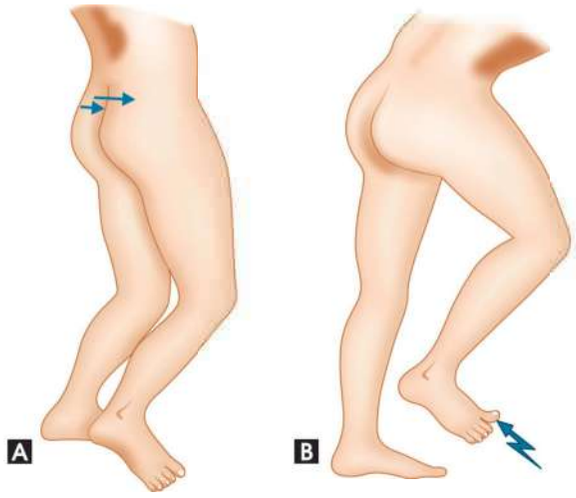


Fig. 91.15A and B: Diagrammatic representation of the withdrawal response to painful stimuli applied to the buttock in A and to the underside of the great toe in B. Shaded areas depict the contractile trunk muscle

5. Each effect of these movements is to withdraw the stimulated point from the stimulus; but in addition, they contain components that are certainly not a part of the withdrawal, extension of several joints and downward movement of the toes. This is due to the irradiation of flex or response.
6. In a standing subject, the reflex effect of these components might be to press the toes downwards and assist to maintain standing. If the stimulus be inconsistent with effective withdrawal, this only does not take place when the stimulus is applied to a toe. Therefore, it is believed that the reflex response of the human leg to the painful stimulus has dual functioning of defence with the maintenance of posture.
7. If the corticospinal motor tracts from the brain, without which the human cannot stand, be damaged, components of the withdrawal response which appear to assist standing disappear. Electrical stimulus to the sole of foot in such cases has produced exactly the similar response, viz. upgoing movement of the toes and flexion at all other joints, as stimulation of the underside of the toe in a healthy subject. Firm stroking of the sole in such patients also produces an upward movement of the toes. In infants, before they begin to stand up and before the corticospinal tracts receive their myelin sheath, has got the same response.
8. An upgoing great toe belongs to part of the general flexion reflex of the limb, but, although morphologically a movement of flexion, but anatomically it is extension. Hence, neurologists describe an upgoing movement of the great toe as an extensor plantar response. A healthy plantar response is termed as flexor.

Applied Physiology

In a spinal man if an upward movement of the great toe be accompanied by the flexion of the leg, this will be one of the first reflexes to appear during recovery from the spinal shock. The response of the great toe to a firm-stroke on the sole with a blunt point (the so-called plantar response) has great importance in clinical diagnosis, as an upward movement of the big toe is usually the first unequivocal evidence of disease of the motor pathways. This sign was first described by Babinski in 1896.

MOTOR UNIT AND ELECTROMYOGRAM (EMG)

One motor neuron and its axon supply not only muscle fibre but a quite number of muscle fibres. The muscle fibre supplied by one motor neuron through its single axon together with branches is called motor unit (Fig. 91.16A). The number of muscle fibres in a motor unit varies. In cat's leg muscle it has been observed 120–165 fibres in one motor unit.

EMG

1. Figure 91.16A shows the anatomical organisation of a motor unit showing one motor neuron and its axon to innervate certain muscle fibres.
2. Motor unit activity can be recorded by inserting coaxial deep needle electrode (Fig. 91.16B) into the muscles which is to be studied. The electrodes then connected to the electromyograph and record that is obtained during muscular activity is known as electromyogram (Fig. 91.17C).
3. Coaxial electrode can be made from a hypodermic needle by introducing an insulated inner wire within it (Fig. 91.16B). Potential differences are recorded from a small volume of muscle in the immediate neighbourhood of the needle tip. Thus, most of the electrical activity is from the active fibres near the

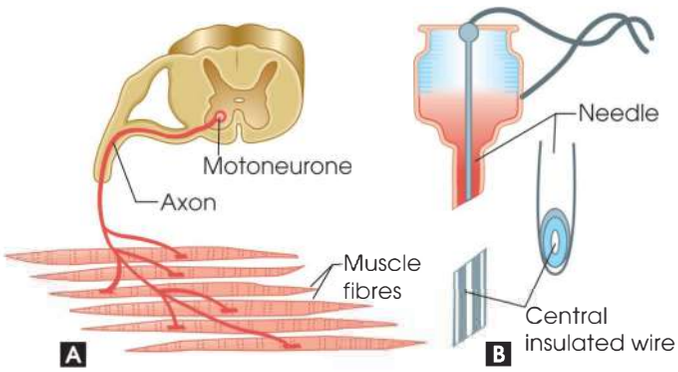


Fig. 91.16A and B: (A) The anatomical organisation of a motor unit showing one motor neuron and its axon to innervate certain muscle fibres. (B) The coaxial deep needle electrode

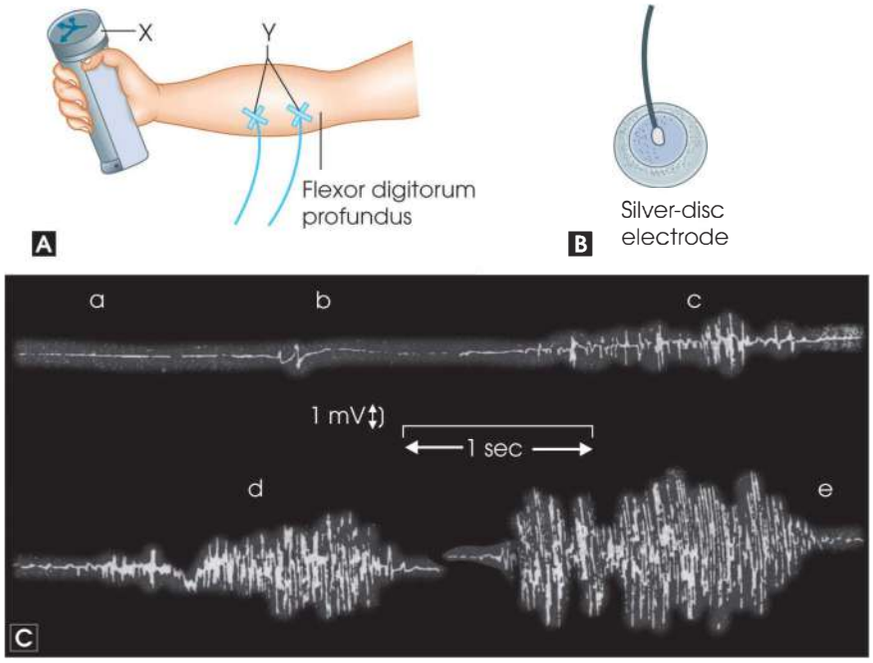


Fig. 91.17A to C: (A) Showing the recording of EMG from flexor digitorum profundus with the help of surface electrodes (Y). The muscle was activated by a dynamometer (x). (B) Silver-disc (surface) electrode. (C) Electromyograms recorded from flexor digitorum profundus through surface electrode at different workloads given by dynamometer; a = rest, b = at 10 kg, c = 20 kg, d = 30 kg, e = 38 kg (maximum capacity of the individual). *Courtesy* by Dr. (Mrs.) J. Koley, Department of Physiology, Calcutta University

electrode. Sometimes surface electrodes are used instead of coaxial deep muscle electrode.

4. The two surface electrodes are placed over the skin at a reasonable distance over the muscle to be studied (Fig. 91.17A). Figure 91.17B shows the silver-disc electrode used for recording.
5. During rest of the muscle there is no action potential recorded (Fig. 91.17C—a), but as soon as the muscle becomes active, potentials are recorded (Fig. 91.17C—b to e). The potential recorded during activity is the resultant of the asynchronous discharge of motor units in the vicinity of electrodes. With minimal voluntary activity, a few number of motor units discharge and with increasing voluntary effort more and more units are brought into action. This is known as recruitment of motor unit. Gradation of muscular activity is a part of function of a number of motor units activated.
6. Electromyographic studies have got clinical importance in diagnosis of motor unit disorders including peripheral nerve injuries, neuro-muscular disorders such as the myotonia, myasthenia gravis, etc.

Applied Physiology: Startle Reflex

Nineteenth century saw lumberjacks who were known as Jumping Frenchmen of Maine. They suffered from a rare disease of unknown origin. The clinical manifestation of this disorder is exaggerated startle reflex. These patients exhibit sudden movements in all parts of the body or they may jump, yell or even may violently hit anyone. These patients cannot resist repeating vocalizations made by another individual or repeating movements similar to those made by others. One school of thought attributed disease to genetic cause while others opined that it could be a formed habit or culture-bound syndrome.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the general characteristics of reflex action.
2. Describe the superficial and deep reflexes.

Short Notes

1. Reflex arc
2. Classification of reflexes
3. Monosynaptic reflex
4. Polysynaptic reflex
5. Withdrawl reflex
6. EMG
7. Stretch reflex
8. Ankle clonus

Chapter

92

Sensory Systems

INTRODUCTION

1. **Sensations** are feelings aroused by change of environment. If the organism has to fight for its existence, it must be kept informed about the various events in and around it. The different ways by which the organism may be aware of its surrounding are called sensations.
2. **Sensory units:** The area supplied by one sensory fibre is called a sensory unit.
3. **Dermatome** (Fig. 92.1): The area of skin supplied by single spinal root fibre forms the dermatome. It is supplied by sensory neurons that arise from a spinal root ganglion.

Dermatome maps are commonly used in clinical neurology. These maps are valuable for the localization of varied sensory phenomena in patients with neurological disorders. Dermatomes for all sensory roots have been mapped out in Fig. 92.1.

4. **Anaesthetic zone:** It is done by cutting a posterior root and noting the corresponding anaesthetic zone on the skin. It is not a perfect interpretation as adjoining nerves overlap (Fig. 92.2).
5. **Residual sensation:** It is identified by cutting posterior roots above and below, and noting the residual sensory area. Vasodilatation: The stimulation of the peripheral end of the cut posterior root causes cutaneous vasodilatation of the corresponding area.

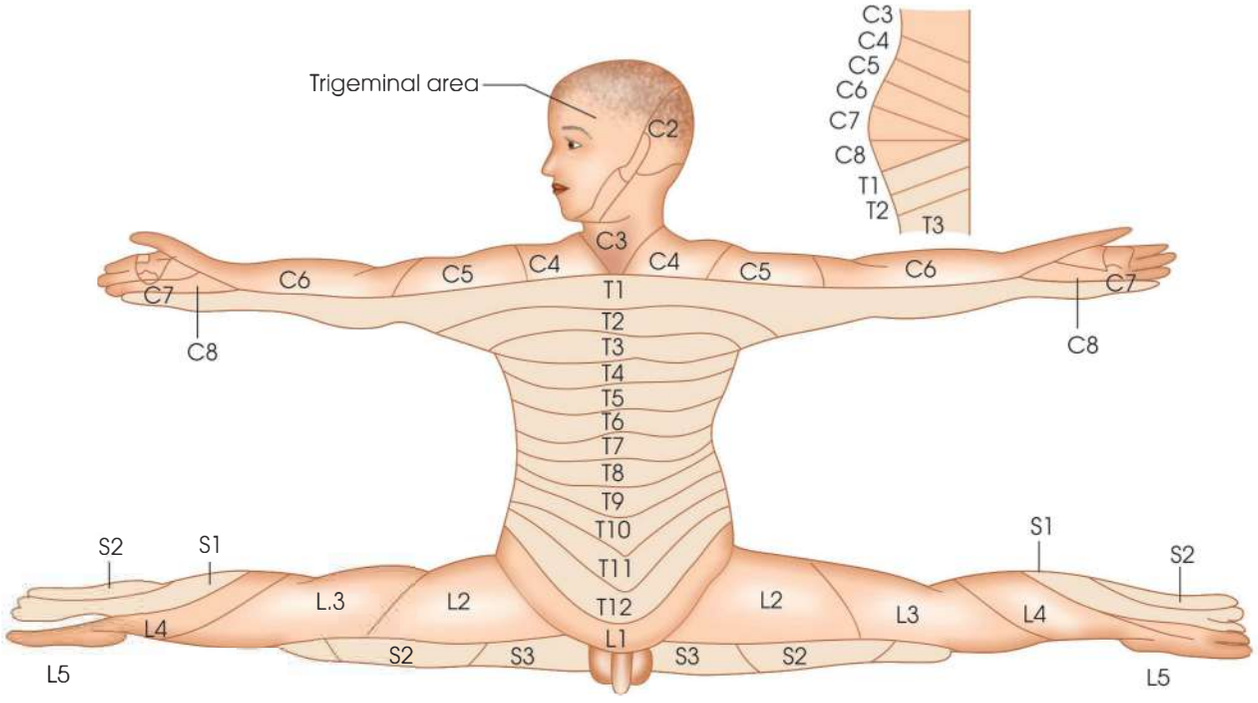


Fig. 92.1: Segmental arrangements of dermatomes. The inset shows the scheme of migration of metameres during development C = cervical, T = thoracic, L = lumbar, S = sacral (from Strong and Elwyn, Luciani)

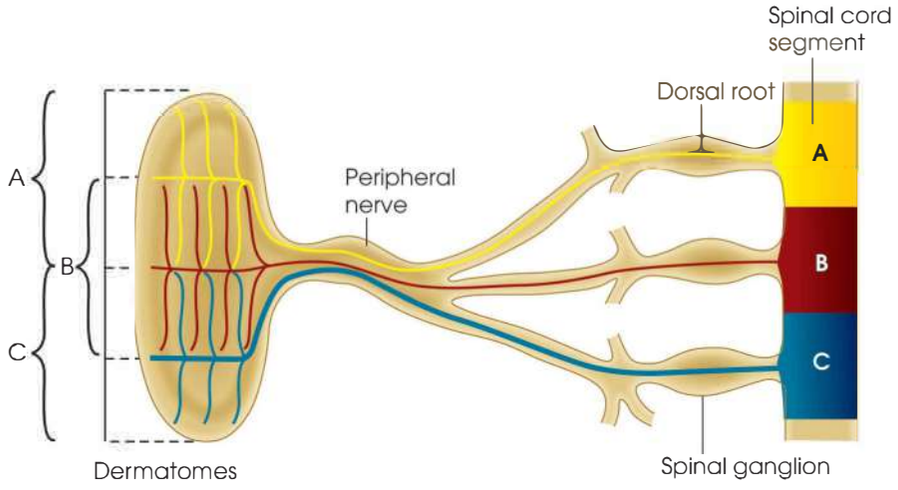


Fig. 92.2: Diagrammatic representation radicular and peripheral innervation of cutaneous areas showing overlapping of nerve fibres in the dermatomes

SENSORY MECHANISM

For each sensation the following mechanism is involved:

1. An exposure to appropriate stimulus.
2. Sensitization of a specific nerve ending which is selectively sensitive to that stimulus.
3. The sensory pathway which carries the impulse to the central nervous system.
4. The nerve centre where the impulse is finally interpreted as a particular sensation. Psychical centre—where the 'meaning' of the sensation is analysed and understood.

PROPERTIES OF SENSATIONS

Sensations differ from one another in various respects—modality, quality, intensity, adaptation, duration, and localisation or projection.

1. Modality

a. The ability to distinguish the characteristic of a sensation from all other sensations is known as its modality. Sensations aroused by stimulation of sense organs, viz. the eye or ear, bear no resemblance to each other; to most people it is inconceivable that the stimulation of the eyes could evoke the sensation of taste or hearing.

b. The modality of a sensation aroused by the stimulation of a given sense organ is fixed—Müller's law or law of specific nerve energies.

2. Quality

Quality means the nature of sensation. Sensation of the same modality may vary in quality. Thus, we speak of a warm or cold breeze and of a red or green light. Quality depends on the nature of receptor stimulated (peripheral analyser or surface detector) and the interpretation by the central nervous system. For instance, some individuals cannot distinguish between red and green (colour blindness) and there is also tone deafness.

3. Intensity

a. It denotes the degree of sensation.

b. It depends on the frequency of afferent impulses passing up the sensory nerve. Stronger the stimulus, higher will be frequency and more intense will be the sensation. Two sensations of the same quality may differ in intensity. A warm the object delivers little energy and a hot object delivers much energy to the receptors.

c. Although the intensity of a sensation cannot be measured, the strength of stimulus evoking the sensation can generally be stated quantitatively. Weber discovered the relationship between the ability to detect and increase or decrease in the intensity of a sensation and an increase or decrease in the strength of a stimulus.

d. Weber's law states that the least perceptible increase in the intensity of a stimulus is a constant fraction of the original stimulus.

e. But Weber's law does not apply to weak or very strong stimulus.

f. The smallest variation in the strength of the stimulus which is just sufficient to produce an appreciable variation of sensations always bears a constant ratio to the total strength of the stimulus.

For instance, if difference can be appreciated between 20 gm and 21 gm (i.e. 1/20), then a weight of at least 10 gm has to be added upon 200 gm to make any appreciable difference. The ratio varies with the type of sensations, viz. for light 1/100; for cutaneous pressure 1/30–1/10; for weight 1/70–1/40.

4. Adaptation

It will be recalled that the structures of muscles and nerves adapt to a constant stimulus. The frequency of impulses gradually decreases due to adaptation. It has been stated that the speed with which adaptation sets in differs in various receptors. For instance, a slight bending of a hair causes a distinct sensation, but, if the hair is kept in this new position the sensation quickly disappears. This is true for touch in general. The adaptation to pain sensation is exceedingly slow or absent.

5. Extent

It indicates the area from which the sensation arises. It depends upon the number of receptors simultaneously stimulated.

6. Duration

It is self-evident that a sensation occupies a certain length of time. However, a sensation is not necessarily coexistent with the stimulus. The duration of a sensation may be shorter than that of stimulation because of adaptation. On the other hand, sensations may outlast the period of stimulation and thereby give rise to after-sensation.

7. Localisation or Projection

It is the ability to locate the exact spot from which the sensation arises. Sensations are concerned more intimately with the brain than with any other part of the body. Yet when a sensation is experienced we are never conscious of our brain. Sensations are invariably projected or referred either to some part of our own body or to some part of the environment.

Most of our sensations, particularly those that are sometimes designated as special sensations, would be no value to us unless proper projection accompanied them.

Localisation shows a number of curious phenomena:

a. *Accuracy:* It is most accurate with cutaneous sensations; less with deep sensations (somatic) and least with the visceral sensations (autonomic).
b. *Sensory irradiation:* With a strong stimulus the sensation will irradiate to a wider area beyond the stimulated spot.
c. *Referred sensation:* Here the sensation is localised at a spot far away from its origin.

Stereognosis: Although it has a large cortical component, it can be regarded as the attribute of perceiving and understanding the form and nature of objects by means of intact touch and pressure sensation without looking at them.

CLASSIFICATION OF SENSATIONS

I. General sensations:
   Three divisions:
   1. Superficial
   2. Deep
   3. Visceral.

II. Special senses

These are taste, smell, vision, hearing (*vide* under the chapter of 'Special Senses').

General Sensations

Superficial Sensations

Characters

1. Arises from the skin
2. Localisation is accurate
3. Adaptation is quick.

Distribution: Two forms:

1. Punctiform—well localized; viz. touch spots, heat spots, cold spots, etc.
2. Diffuse—sensation spread diffusely in between the spots.

Parts: Two parts: Epicritic (discriminative), protopathic (crude).

Epicritic and Protopathic Sensations

The protopathic sensations are the crude parts of the various cutaneous sensations.

Epicritic sensations represent the finer discriminative aspects of cutaneous sensations.

Varieties

1. Touch
2. Temperature—including heat and cold
3. Pain

1. *Touch*

a. Adequate stimulus: It is the light contact.
b. End organs: Meissner's corpuscles, Merkel's discs and free nerve terminals (especially rich around the hair roots)
c. Fibres concerned: Touch sensation is carried by thicker myelinated fibres.
d. Action potentials—larger
e. Localisation—accurate
f. Adaptation—quick
g. Perception parts—two parts:
   1. Epicritic
   2. Protopathic

A. ***Epicritic touch includes***

a. Light touch—tested with cotton wool, von Frey's hair, etc.

b. Tactile localisation—the ability to tell more or less accurately which part of the skin is touched. It is tested with aesthesiometer.
c. Tactile discrimination: The ability to recognise touch at two points.

Tested with Weber's compass: There is minimum distance in between the two compass points and on testing the person recognizes the two points touched. The distance varies according to the site and motility of the part. Greater the motility, lesser is the distance. Such as, tip of tongue 1.1 mm, fingertip 2.3 mm, palm 11.3 mm, back, upper arm, thigh 67.1 mm, etc.

Aristotle's experiment: In our brain there is a field corresponding to the field of the periphery of our body exposed to the environment. Normally if two widely separated areas of the skin are simultaneously stimulated by two discrete objects, two sensations are experienced. When these two areas are brought into close proximity to each other so that they can be simultaneously stimulated by one object, two distinct objects are felt. This is done in Aristotle's experiment (Fig. 92.3) where the middle finger is crossed over the index finger and the point of a blunt pencil is moved along the crotch.

B. ***Protopathic touch includes***
Crude touch or pressure (deformity)—tested with different weights.

2. Temperature Sensations

a. There are two varieties: Cold and heat
b. These are two distinct sensations received by two different kinds of end organs. Cold spots are more numerous than heat spots (Fig. 92.4). In the conjunctiva there are cold spots only.
Three-basin test: One hand is placed in hot water and the other hand into cold water for a short time. The hand should be dipped in the water for about 2 minutes. Then both the hands are dipped in tepid water. Note the difference in temperature sensation, between the two hands.
c. Parts: Adoptation of thermal sensation is fairly quick.
Two parts: Epicritic and protopathic.
1. Epicritic thermal sense includes the ability to recognise small variations of temperature between 24° and 38°C. A subject, whose epicritic thermal sense is lost, will not be able to recognise any difference of temperature within this range.
2. Protopathic thermal sense: The subject will feel cold below 24°C and warm above 38°C. In between, no difference can be felt.

Fig. 92.3: Aristotle's experiment

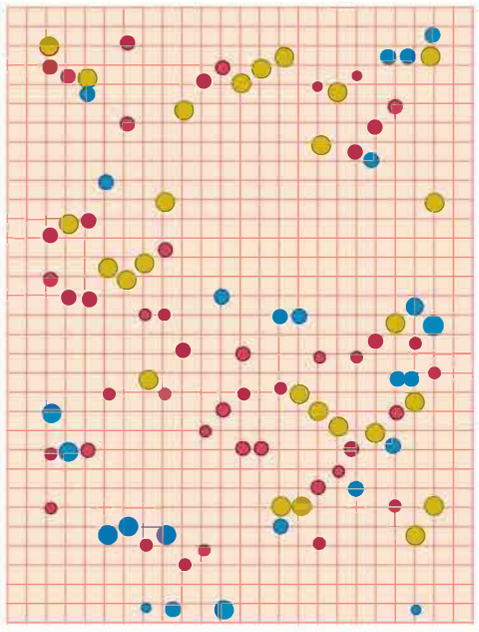


Fig. 92.4: Distribution of cold and heat spots. Dark dots—cold spots; circles—heat spots. To be noted that, cold spots are more numerous than heat spots (Halliburton)

Ernst Heinrich Weber was a German physician and one of the founders of experimental psychology. His studies on sensation and touch, along with his emphasis on good experimental techniques gave a new insight to future psychologists, physiologists, and anatomists.

1795–1878

3. Pain Sensations

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. It is discussed below.

Deep Sensations

Origin: Arise from deeper structures, supplied by somatic nerves.

Localisation: Inaccurate and often referred.

Adaptation: Much delayed.

Varieties

1. Kinaesthetic
2. Vibration sense

3. Visceral sensation
4. Deep pain
5. Labyrinthine.

1. **Kinaesthetic** (proprioceptive): It is the ability to recognise the degree of movement and position of the muscles and limbs.
   a. *Origin*: It originates from muscles, tendons, joints, bones, ligaments, etc.
   b. *End organs:* Muscle spindles, Golgi tendon organ, pacinian corpuscles, etc.
   c. *Stimulus:* Gross structural deformity and stretch. These sensations are very important for posture, muscle tone and equilibrium.
2. **Vibration sense:** Tested by placing the handle of a vibrating tuning fork on the part. (It is probably same as 'kinaesthetic sensation'.) Point to be noted is that the vibration sense persists even after section of the cutaneous nerves but not after the posterior roots.
3. **Visceral sensations:** The activities of the viscera, supplied with autonomics are generally unconscious. Under abnormal conditions, only the following sensations may arise:
   a. Visceral pain
   b. Extremes of heat and cold, viz. in oesophagus, stomach and rectum.
   c. A feeling of distension and tightness—stomach, bladder, etc. Other sensations are absent in the viscera.
4. **Deep pain:** The deep somatic pain is initiated by stimulation of nociceptors in ligaments, tendons, bones, blood vessels, fasciae and muscles, and is dull aching.
5. **Labyrinthine sensation:** A sensation of rotation or movement of one's self (subjective vertigo) or of one's surroundings (objective vertigo) in any plane. The term is sometimes used erroneously as a synonym for dizziness.

Pain

1. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.
2. Pain is probably the most fundamental and primitive sensation. Pain may be observed more or less all over the body.
3. It is protective in nature and always indicates some serious trouble in the locality, such as a structural damage or some sort of serious functional or metabolic derangement.
4. Naked nerve endings are presumably the sense organs for pain and are distributed all over the body.
5. Pain sensations are transmitted by two types of fibres—slow fibres and fast fibres.

The slow fibres are unmyelinated: These are dorsal root C (d.r.C) fibres having slow rate of conduction (0.5–2 msec) and diameter of 0.4–1.2 µm. Due to its slow conduction velocity, the C types of fibres are generally called slow fibres. The fast fibres are the small myelinated: These are A-δ fibres having diameter of 2–5 µm, conduction velocity at the rate of 12–30 msec. Having higher conduction velocity than that of the d.r.C types of fibres, these fibres are generally called fast fibres. According to the presence of separate types of pain fibres and also of different conduction velocity pain has been classified in two—slow and fast. Slow pain is carried by the d.r.C fibres whereas the fast pain is carried by the A-δ fibres.

Classification of Pain

A. International association for the study of pain (IASP) in the year 1944 classified pain according to specific characteristics:
   1. Region of the body involved (e.g. abdomen, lower limbs)
   2. System whose dysfunction may be causing the pain (e.g. nervous, gastrointestinal)
   3. Duration and pattern of occurrence
   4. Intensity and time since onset
   5. Cause

B. Clifford J. Woolf and other researchers criticised the above classification citing that it is inadequate for guiding research and treatment.

   Woolf suggests three classes of pain
   1. Nociceptive pain
   2. Tissue damage and the infiltration of immune cells produces pain due to inflammation.
   3. Any disease due to damage to the nervous system or as result of its abnormal function (e.g. fibromyalgia, irritable bowel syndrome, tension type headache, etc.) produces pathological pain.

C. As per physiological classification of pain: They are of three types:
   1. *Superficial pain:* Superficial pain is initiated by activation of nociceptors in the skin or other superficial tissue, and is sharp, well-defined, and clearly located.
   2. *Deep pain:* The stimulation of nociceptors in bones, blood vessels, fasciae, tendon and ligaments produce dull aching, poorly localized deep somatic pain.
   3. *Visceral pain:* It is diffuse and difficult to locate.

The following varieties of pain are briefly described below.

Superficial Pain

a. *Effective stimulus:* Structural damage.
b. *Nerve endings:* Free terminals.
c. *Distribution:* Both punctiform and diffuse. These nerve endings are more uniformly distributed than other sensations.

d. *Localisation:* Fairly accurate but often irradiates (nocisensor system).
e. *Two varieties:* Epicritic and protopathic

A. Epicritic pain has the following characters:
   a. The stimulus is lighter (low threshold).
   b. Localisation accurate, so that finer discriminations possible.
   c. Distribution: It is uniformly diffuse.

B. Protopathic pain has the following peculiarities:
   a. The threshold is high. A stronger stimulus is required to arouse pain sensation.
   b. Reaction is excessive. The same stimulus will cause greater pain here, than on a normal spot.
   c. Localisation inaccurate.
   d. Distribution punctiform, i.e. not uniform. In certain areas, only protopathic pain is present, such as glans penis.

Deep Pain

a. It arises from deep somatic structures, such as muscles, tendons, ligaments, joints, bones, etc.
b. Effective stimulus: It is ischaemia, injury, etc.
c. *Localisation:* It is fairly accurate (accompanied) by increased tone of the muscle, hyperaesthesia and vasodilatation of the overlying skin). Nearer the surface the greater is the accuracy of localisation. Quality of deep pain varies according to the site. Lewis recognises several varieties, viz. muscle pain, tendon pain, etc.

Visceral Pain

a. This is the chief sensation present in the viscera. It is poorly localised, unpleasant, associated with nausea and autonomic symptoms. These pain sensations are radiated to other areas. Generally, the afferent impulses from viscera (Fig. 92.5) are unconscious. But under abnormal conditions pain sensation may be felt. Visceral pain has the following peculiarities:
b. Effective stimulus—may be of different types, such as increased tension, strong irregular contractions, sudden ischaemia, etc. Cutting, burning, crushing, piercing, etc. produce no pain.
c. Quality of pain also varies, such as gripping, shooting, aching, etc.
d. Localisation is faulty and is often referred. If the neighbouring somatic structures are involved, localisation may be fairly accurate.
e. Pathway—visceral pain afferents from structures above the thoracic pain line and those below the pelvic line.

Theories of Pain

a. **Specificity theory:** Von Frey (1895) argued that the body has a separate sensory system for perceiving pain—just as it does for hearing and vision and this

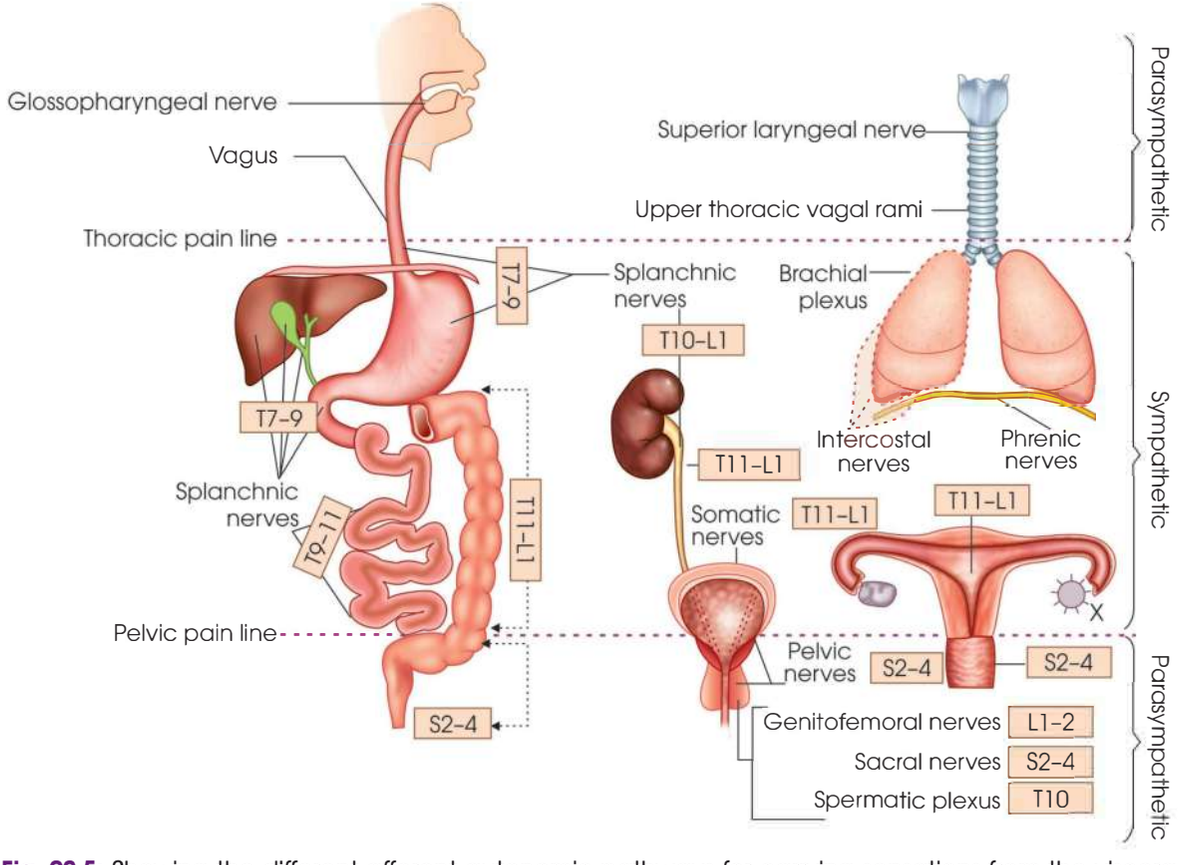


Fig. 92.5: Showing the different afferent autonomic pathways for carrying sensations from the viscera

system contains its own special receptors for detecting pain stimuli, its own peripheral nerves and pathway to the brain, and its own area of the brain for processing pain signals. But this structure is not correct.

b. **Pattern theory:** Goldschneider (1920) proposed that the receptors for pain are shared with other senses, such as of touch and there is no separate system for perceiving pain. According to him individual feels pain when certain patterns of neural activity occur, and these appropriate types of activity reach excessively high levels in the brain. Such patterns of activities can only occur on intense stimulation as strong and mild stimuli of the same sense modality produce different patterns of neural activity, being hit hard feels painful, but being caressed does not. This theory was not widely accepted.

c. **Dermatomal theory of pain**

Referred pain: Pain arising from the viscera is often referred to that region of body surface which is supplied by the posterior root of the same spinal segment.

Influence of dermatomal rule: As a rule pain is generally referred to an area of some embryonic segment or dermatome from which this pain area has been developed embryonically. As for example, heart and arm have same segmental origin. So, if pain occurs in the heart, then it will be referred to the arm. Similarly, testicle has migrated from the primitive urogenital ridge from which kidney and ureter also developed. Distension of ureter will cause pain the testicle.

Theorises of convergence and facilitation: This theory holds that somatic and visceral afferents converges on the same spinothalamic neurons (Fig. 92.6). Thus, if irritation occurs in the viscera, the visceral afferents are stimulated, then signal reaches the brain and pain is projected to this somatic area equally.

Theory of facilitation (Fig. 92.7): This theory holds that owing to the effects of subliminal fringe, the incoming impulses from viscera lowers the threshold of spinothalamic neurons receiving afferents from somatic area so that minor activity in the pain pathways from somatic areas (activity which would commonly die out in the spinal cord) passes onto the brain.

But neither the convergence nor the facilitation theory alone is responsible for referred pain. Possibly both are responsible for such pain.

d. **Gate control theory**

Gating of pain: Simultaneous stimuli coming from large sensory fibres such as tactile fibres reduce the transmission of pain signals. This is because dorsal horns of spinal cord act as "gates" which control the entry of pain signals in presence of excessive tactile signals.

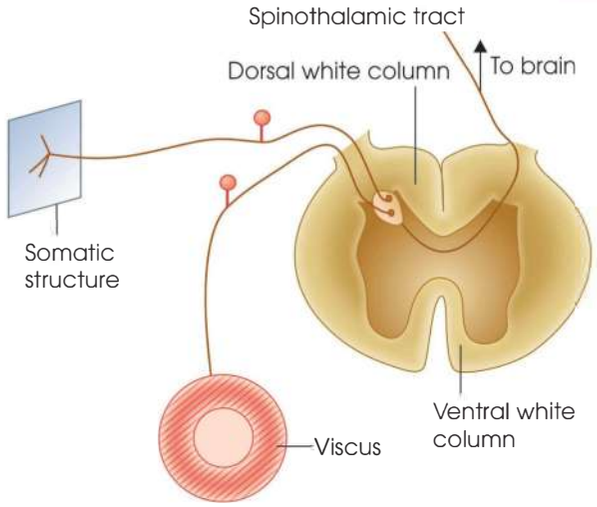


Fig. 92.6: Showing the convergence of visceral and somatic afferents on the spinothalamic neurons in the spinal cord

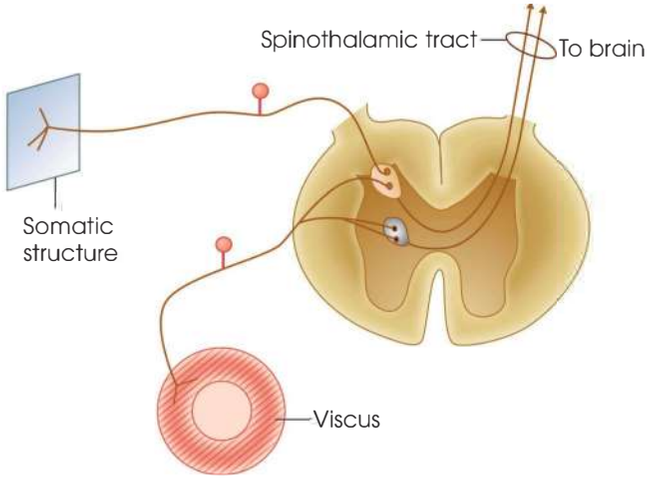


Fig. 92.7: Showing the process of facilitation in the spinothalamic neurons

There the 'opening and closing' of the gate is mainly influenced by three factors:

1. The amount of activity in the pain fibres tends to open the gate. Stronger the noxious stimulation more active will be the pain fibres and eventually gates open.
2. The information about harmless stimuli or mild irritation, such as touch in or light scratching the skin is carried by the A-β fibres which tend to close the gate, and the perception of pain is inhibited even though noxious stimulation exists. This is the reason why gently massaging near associated area decreases the pain.
3. Messages from neurons in the brainstem and cortex have efferent pathways to the spinal cord, and the impulses they send tend to influence the opening or closing of the gate. As brain impulses influence the gating mechanism the individual who are hypnotized or distracted by other environmental stimuli may not perceive the pain of an injury.

Pain Pathway (Fig. 92.8)

Transmission of Pain Sensation

The transmission of pain sensation occurs in three stages. The pain impulse is transmitted to the sensory cortex from affected area as detailed below:

A. **Impulses are transmitted from the site of transduction along the nociceptor fibres to the dorsal horn in the spinal cord:** The A-δ fibres and C fibres terminate in the dorsal horn of the spinal cord. There is a synaptic cleft between the nociceptive dorsal horn neurons and terminal ends of the A-δ fibres and C fibres. The excitatory neurotransmitters (nitric oxide; adenosine triphosphate; substance P; glutamate; calcitonin gene-related peptide and bradykinin) are released, bind to specific receptors in the nociceptive dorsal horn neurons thereby transmitting the pain impulse across the synaptic cleft.

B. **Impulses from the spinal cord are relayed to the brainstem:** The pain impulse is then transmitted from the spinal cord to the brain stem and thalamus via two main nociceptive ascending pathways. These are the spinothalamic pathway and the spinoparabrachial pathway.

C. **Impulses are carried and relayed through connections between the thalamus, cortex and higher levels of the brain:** The brain does not have a discrete pain centre, so when impulses arrive in the thalamus they are directed to multiple areas in the brain where they are processed.

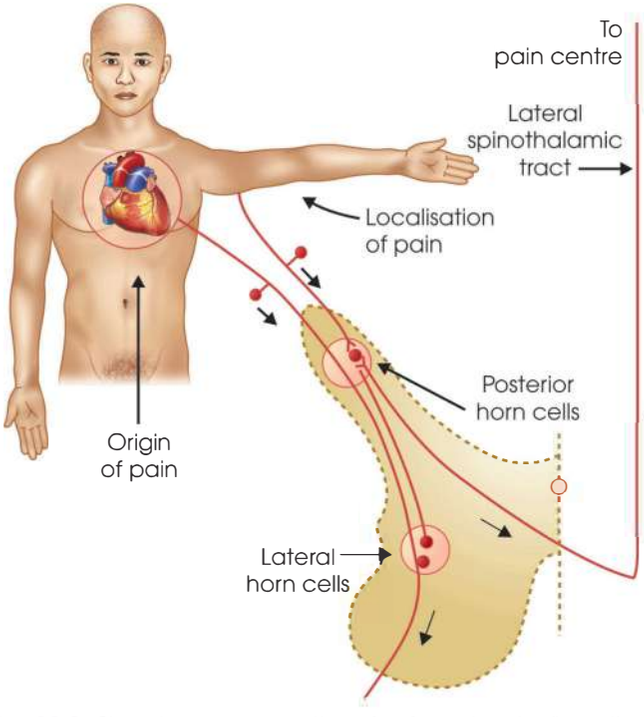


Fig. 92.8: Showing nerve paths of referred pain (heart). A lateral horn cell transmits the impulse to posterior horn cells

Tracts Conveying Pain Sensation

a. There are two pathway; fast and slow pain pathways.
b. A-δ: Transmission through the larger, myelinated A- δ fibres occurs faster. The conduction velocity is 5–15 ms.
c. *C fibres:* The slow pain is carried by C fibres. The small unmyelinated C neurons are responsible for the transmission of diffuse or dull aching sensations. The conduction velocity of C fibres is 0.5–2 ms.
d. The pain pathway by A-δ fibre is called neospinothalamic pathway (it carries information to the midbrain, thalamus and post-central gyrus where pain is perceived) while pathway of C fibre is called paleospinothalamic pathway [it carries information to the reticular formation, pons, limbic system, and midbrain (arousal in response to nociception)].
e. Neospinothalamic pathway carry impulses via spinothalamic tract while paleospinothalamic pathway carry impulses via spinoreticular tract. The other tracts involved with pain sensation are: Spinomesencephalic tract (concerned with pain modulation), spinotectal tract (initiates eye movement to painful stimuli and spinohypothalamic tract and spinoparabrachial pathways (concerned with autonomic and reflex responses to nociception). Investigative studies in rat's revealed role of spinoparabrachial pathways in emotion mediated modulation of pain. The spinoparabrachial projections along with NTS projections are transmitted to limbic and cognitive higher centres such as the amygdala, hypothalamus and periaqueductal grey (PAG).

Lateral (Dorsal) Spinothalamic Tract (Fig. 92.9)

Origin, distribution and termination: The dorsal spinothalamic tract (lateral spinothalamic tract) is an ascending one which occupies the lateral column of the white matter in the spinal cord. Some posterior root fibres (axons of the first-order neuron) of all segments after entering the spinal cord end round the cells of the substantia gelatinosa of Rolando. These unmyelinated fibres of the posterior root are known as tract of Lissauer (fasciculus posterolateralis). The second-order neuron starts from these cells. Most of the axons of second-order neuron cross in the anterior white commissure, obliquely to the opposite side of the same segment and ascend in the lateral column of the cord. Some fibres of the second-order neuron, before crossing, may ascend up one segment and then cross in the anterior white commissure to reach the lateral column of the opposite side of the cord.

This tract together with ventral (anterior) spinothalamic tract constitutes the spinal lemniscus in the medulla oblongata. The spinal lemniscus then ascends up to join the medial lemniscus in the upper part of the

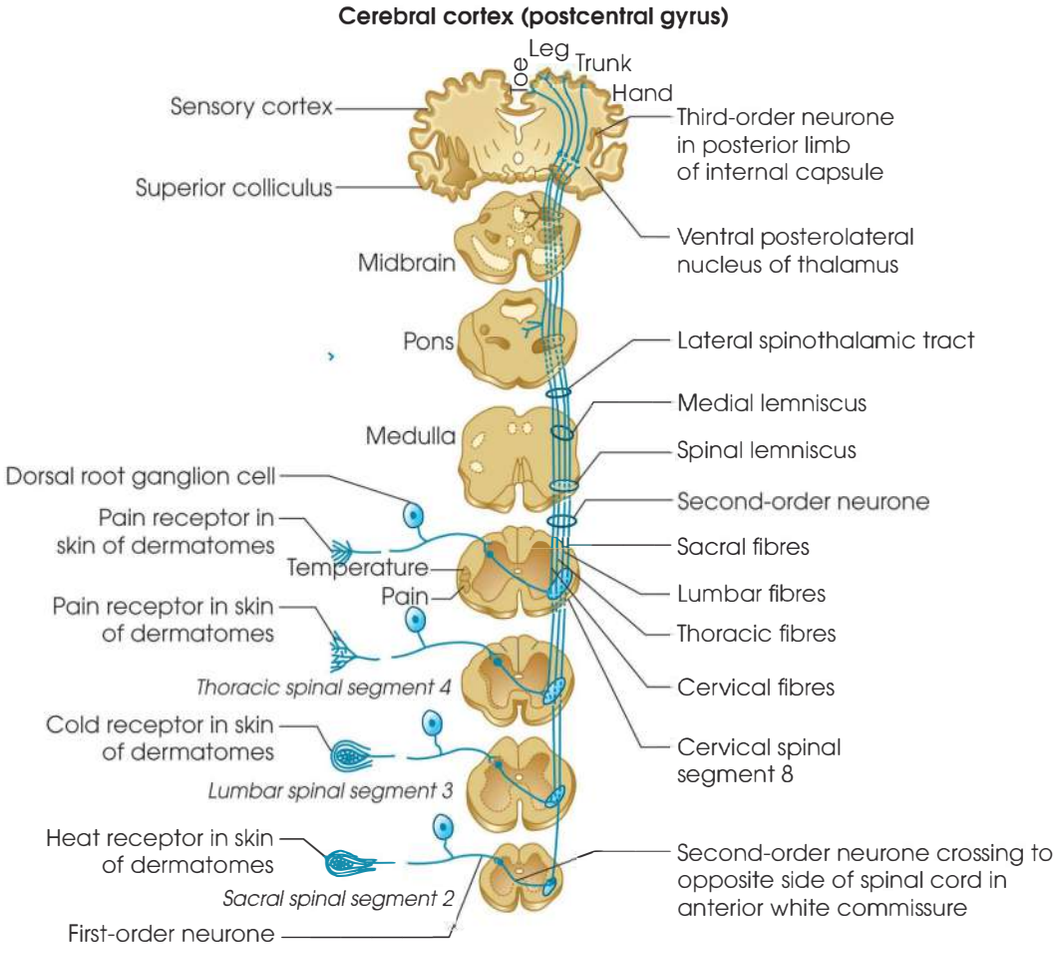


Fig. 92.9: Diagrammatic representation of dorsal (lateral) spinothalamic tract

medulla oblongata and finally terminates in the ventral posterolateral nucleus of the thalamus. The lateral spinothalamic tract at higher brain stem level sends several collaterals into the reticular formation and tegmentum before ending in the thalamus. Here third-order neuron starts and axons of this neuron terminate in the postcentral gyrus of the cerebral cortex through the posterior limb of internal capsule.

Spinoreticular Tract (Fig. 92.10)

Cell stations of these fibres are lying in the posterior horn cells at all levels of the spinal cord. These fibres ascend in the anterolateral funiculus and terminate chiefly in the nucleus reticularis gigantocellularis and partly in the lateral reticular nucleus in the medulla. In the pons, certain fibres terminate in the nucleus reticularis pontis caudalis. A small number of fibres also terminate in the mescencephalic reticular formation. This tract also gives collaterals to the thalamus and hypothalamus.

Pain sensations in face and head region are carried by trigeminal nerve

A. 1st order neuron carried by trigeminal nerve (cell body in trigeminal/gasserian ganglion) enter pons, descend to medulla forming the spinal trigeminal tract and synapse in brainstem nuclei.
B. The 2nd order neurons arise and cross midline and ascend as trigeminothalamic tract and relay at venteroposterior medial nucleus of thalamus.
C. The 3rd order neurons from venteroposterior medial nucleus of thalamus relay sensation to sensory cortex.

Perception of Pain

Perception of pain is the end result of the neuronal activity of pain transmission and where pain becomes a conscious multidimensional experience. The multidimensional experience of pain has affective—motivational, sensory-discriminative, emotional and behavioural components.

When the painful stimuli are transmitted to the brain stem and thalamus, multiple cortical areas are activated and responses are elicited.

These areas are:

a. *The reticular system:* This is responsible for the autonomic and motor response to pain.
b. *Somatosensory cortex:* This is involved with the perception and interpretation of sensations. It

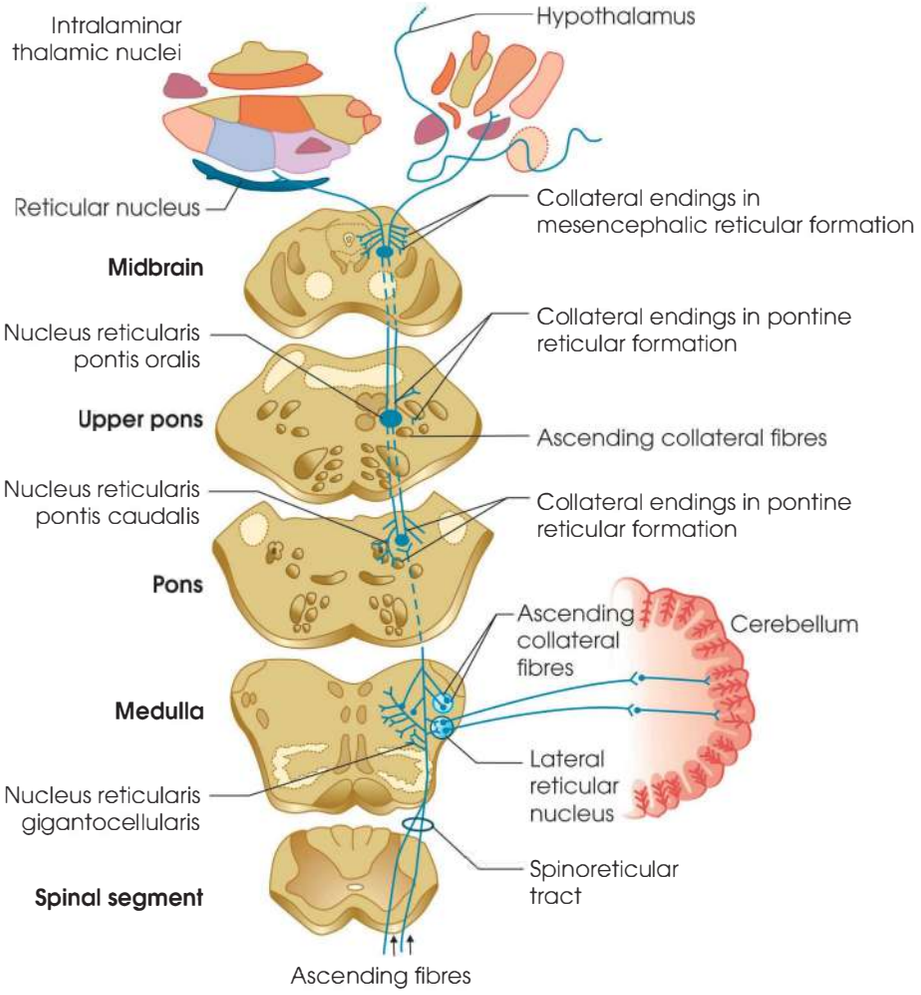


Fig. 92.10: Diagrammatic representation of spinoreticular and collateral reticular projections at different brain stem levels

identifies the intensity, type and location of the pain sensation and relates the sensation to past experiences, memory and cognitive activities. It identifies the nature of the stimulus before it triggers a response, e.g. where the pain is, how strong it is and what it feels like.

c. *Limbic system:* This is responsible for the emotional and behavioural responses to pain, e.g. attention, mood, and motivation, and also with processing pain and past experiences of pain.

Modulation of Pain

Descending pain inhibitory pathway: Pain is modulated via descending modulatory pain pathways (DMPP). They inhibit afferent pain signal.

Mechanisms

1. Pain afferents stimulates the neurons in peri-aqueductal gray (PAG)—gray matter surrounding the cerebral aqueduct in the midbrain. This results in activation of efferent (descendent) anti-nociceptive pathways.
2. Impulses are transmitted from cerebral aqueduct in the midbrain to the spinal cord to the dorsal horn.
3. These inhibit or block transmission of nociceptive signals at the level of dorsal horn.

The descending inhibition involves the release of inhibitory neurotransmitters that block or partially block the transmission of pain impulses by acting on the opiate receptor located on the dorsal horn cells and prevent the release of substance P and therefore produce analgesia. Inhibitory neurotransmitters involved with the modulation of pain include: Endogenous opioids (enkephalins and endorphins); serotonin (5-HT); norepinephrine (noradrenaline); gamma-aminobutyric acid (GABA); neurotensin; acetylcholine; and oxytocin.

ITCH AND TICKLE

Relative low-frequency stimulation of C fibres presumably produces itching sensation. Whereas tickling sensation is generally produced by very mild frequency stimulation moved across the skin. It is suggested that the C fibre system which is responsible for itching is not the same as that responsible for pain. An itching sensation is commonly regarded as

annoying and a tickling usually as pleasurable, whereas pain sensation is unpleasant.

Applied Physiology

1. Causalgia or **heat pain** is a condition of persistent burning sensation following nerve injuries. This burning sensation is intensified due to reduction in its threshold value. But pricking sensation is not heightened. Causalgia is often associated with sweating and vasomotor changes. Causalgia may be happened due to presence of uninsulated C fibres in the surrounding tissues and forming false synapse (ephapse) with postganglionic sympathetic fibres. Continuous discharges that pass through the sympathetic efferent fibres then set up afferent impulses in adjacent pain fibres (C nerve fibres) through ephaptic transmission.
2. **Thalamic pain**
   The occlusion in the thalamogeniculate artery (a branch of the posterior cerebral artery), which supplies blood to the lateroposterior half of the thalamus, causes a thalamic lesion. The symptoms include excruating intracranial pain in the contralateral side of the thalamic lesion and sensory loss.
   Similarly, lesions in the spinothalamic tract may lead to thalamic pain syndrome or Dejerive-Roussy syndrome. These patients experience spontaneous aching and burning pain in body regions where sensory stimuli in general do not lead to pain.
3. **Myofascial pain syndromes:** This is one of the most common causes of chronic pain. These conditions include: Myalgia, myositis, fibrositis, muscle strain, injury to the muscle and fascia. The pain is a result of muscle spasm, tenderness and stiffness.

Pain Management

Physical medicine and rehabilitation: Medicines such as analgesics, physiotherapy if the conditions warrant, behavioural therapy, electrotherapy and therapeutic exercises have proven to be beneficial. Transcutaneous electrical nerve stimulation (TENS): It is indicated for any chronic musculoskeletal condition under the gate control theory of pain. Similarly, acupuncture which involves the insertion and manipulation of needles into specific points on the various body locations to relieve pain is also helpful in releiving pain in chronic conditions. Various clinical research studies opine that acupuncture reduces joint pain and so this therapy can be effective in reducing pain caused by knee osteoarthritis. The process of needling in acupuncture affects the concentrations of the naturally occurring opiate substances: Dynorphin, endorphin, and enkephalin of the cerebrospinal fluid (CSF). These endorphins and enkephalins modulate and block the pain arising from the musculoskeletal system.

Patric David Wall
1925–2001
Patrick David "Pat" Wall was a Neuroscientist the gate control theory of pain. He was known globally as expert in pain research.

EXAM-ORIENTED QUESTIONS

Essay

1. Define sensation. Describe the mechanism involved in perception of sensation. Describe the properties of sensation.
2. Define pain. Classify pain. Describe the theories of pain.
3. Define pain. Describe the pathways involved in perception and modulation of pain.

Short Notes

1. Classification of sensation
2. Superficial and deep sensation
3. Vibration sense
4. Visceral pain
5. Modulation of pain
6. Causalgia
7. Thalamic pain
8. Pain management
9. Pain modulation

Chapter

93

Arrangement of Grey and White Matter in the Spinal Cord

INTRODUCTION

The spinal cord is a primary centre of reflex action for the trunk and limbs, and consists of the main conducting paths to and from higher centres in the spinal cord and brain. The cord may be considered as consisting of more or less autonomous segments. Each segment is related by afferent and efferent nerve fibres to its own specific segmental area of the body, as well as to the segments above and below. It is obvious from the large amount of spinal cord space devoted to ascending and descending tracts that the brain exerts an important controlling influence over the segments.

Spinal cord is symmetrically divided into two lateral halves, dorsally by a septum known as posterior median septum and ventrally by a fissure (cleft) known as anterior median fissure (Fig. 93.1).

CENTRAL CANAL

It is lined by the cubical ciliated epithelium—the ependyma. Cerebrospinal fluid (CSF) circulates through this canal. The central canal actually pierces through the isthmus (commissure) of the two symmetrical lateral halves of the grey matter. Parts of the grey matter in front of the central canal is known as anterior (ventral) grey commissure and the same on behind the central canal is known as posterior (dorsal) grey commissure.

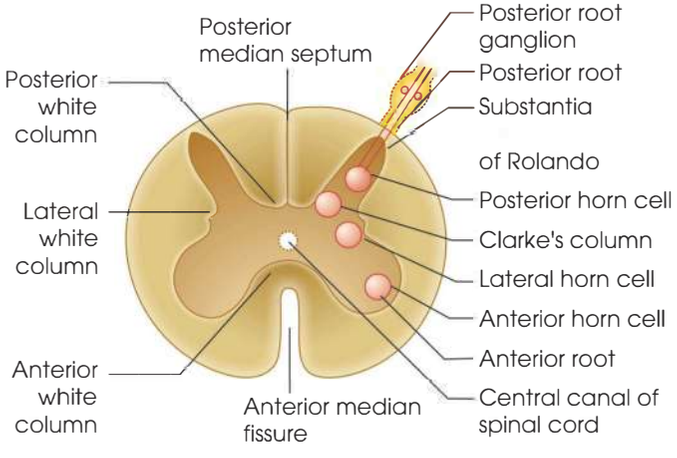


Fig. 93.1: Transverse section of the spinal cord showing arrangement of grey and white matter

GREY MATTER

It is in the form of a rough crescent one on each side. Each crescent has three parts: Anterior horn, lateral horn and posterior horn. Grey matter is chiefly composed of three elements:

1. Nerve cells
2. Neuroglia

Nerve fibres, dendrites or axons which are mostly of unmyelinated fibres supported by a group of neuroglial cells.

Nerve cells: There are three important collections of nerve cells:

Anterior horn cells (motor): The cells are multipolar and are arranged in different groups. α- and γ-motor neurons are present. α-motor neurons innervate the extrafusal fibres and γ-motor neurons innervate the intrafusal fibres of the muscle spindle. Renshaw cells, a group of interneurons, are present in the antero-medial part of the anterior horn cells. These cells send antidromic inhibitory impulses to the motor neurons. The anterior nerve root takes origin from these cells.

Posterior horn cells (sensory): Relay station for posterior nerve root. At the base of the posterior horn there are specialised cells known as Clarke's column or dorsal nucleus. Found only in the lower cervical, thoracic and upper lumbar regions (C7–L3). They are the relay stations for spinocerebellar fibres. At the tip of the posterior horn there are closely packed cells called substantia gelatinosa of Rolando. At the medial part of the posterior horn there are large round or oval nerve cells.

Lateral horn cells (autonomic): Relay station for autonomic. Found only in the thoracic and upper lumbar regions (T1–L2). The cells are smaller than those of anterior horn cells. They are also known as intermediolateral cell groups. They give preganglionic sympathetic fibres and then emerge out through the anterior spinal root.

Neuroglia

There are two important collections, viz.

1. Substantia gelatinosa centralis—around the central canal.
2. Substantia gelatinosa of Rolando—at the tip of the posterior horn.

WHITE MATTER

White matters of the spinal cord surround the grey matter and consist of myelinated and unmyelinated fibres. Myelinated fibres are predominating. It has been described that the white matter is incompletely divided into symmetrical two lateral halves. The lateral half of white matter on each side is divided into three compartments, anterior white column (funiculus), lateral white column (funiculus) and posterior white column (funiculus) by the fibres of the ventral and dorsal spinal roots. White matter in front of the grey commissure is known as anterior (ventral) white commissure and the same in behind the grey commissure is known as posterior (dorsal) white commissure. Ascending and descending tracts and transverse fibres are passing through the white matter to occupy their respective positions.

THE SPINAL NERVE

There are 31 pairs of spinal nerves. The first cervical nerve originates from the medulla oblongata and leaves the spinal canal between the occipital bone and atlas. Other cervical spinal nerves arise from the spinal cord, and each leaves the spinal canal through an intervertebral foramen above the vertebra whose number it bears. The eighth spinal nerve emerges from the vertebral column below the seventh cervical vertebra. All the other spinal nerves emerge from the spinal cord below the vertebra whose number it bears. The coccygeal nerves pass from the lower extremity of the spinal canal.

Mixed Nerves

Spinal nerves consist primarily of medullated nerve fibres and are named mixed nerves due to contents of motor and sensory fibres. Each spinal nerve is formed by the union of anterior and posterior roots.

Anterior Spinal Root

These are composed entirely of motor fibres. They are:

1. The axons of anterior horn cells (somatic)
2. Axons of the lateral horn cells (autonomic)—in the thoracic and upper lumbar regions only.
3. The autonomic fibres represent the preganglionic fibres of sympathetic (pupil dilator, pilomotor, vasomotor, cardiac accelerator, etc.).

Posterior Spinal Root

It consists of afferent fibres only: Recent studies show that some vasodilator fibres are also present. The posterior root is composed of the axons of posterior root ganglion, and contains both somatic and autonomic fibres, as described below:

1. The somatic afferents come from the skin and deep somatic structures.
2. Autonomic afferents come from the viscera. All have their cell station in the posterior root ganglia. The nerve fibres of posterior root are 40% non-medullated and 60% medullated.

Never fibres have been broadly classified into three: A, B and C. The A fibres (thickest) come from the touch and kinaesthetic endings. The B fibres (medium) carry thermal sensations and probably localised pain. The C fibres (thinnest) carry diffuse skin pain, ischaemic muscle pain, etc. (The motor fibres in the posterior root are believed to be vasodilator fibres of the C Group.)

DISTRIBUTION OF THE TERMINAL BRANCHES OF SPINAL NERVES

After leaving the spinal column, each spinal nerve mainly divides into:

1. The recurrent branch which is distributed to the meninges (hence meningeal).
2. The ventral branch which supplies the extremities and parts of the body wall in front of the spine.
3. The dorsal branch which supplies the muscles and skin of the back of the head, neck and trunk.
4. Another one is the visceral branch which is supplied by the nerves from T1 to L3.

All these connect with the sympathetic ganglia by means of the white and grey rami fibres (Fig. 93.2) which pass from the nerve to the ganglia and vice versa. From the sympathetic ganglia to their final distribution, the autonomic nerves are formed. These nerves form cardiac, coeliac, hypogastric, pelvic and enteric plexuses (*vide* autonomic distribution). A quite number of nerve fibres from the sympathetic ganglia return to and are distributed with the spinal nerve to innervate sweat glands, arrector pili muscles, smooth muscles of all blood vessels. After emerging from the cord, spinal nerves form the cervical, brachial, lumbar and sacral plexuses from which the peripheral nerves are formed. In the thoracic region there is no plexus, but the fibres pass as intercostal nerves out into the intercostal spaces to innervate intercostal muscles, upper abdominal muscles and the skin of the abdomen and chest.

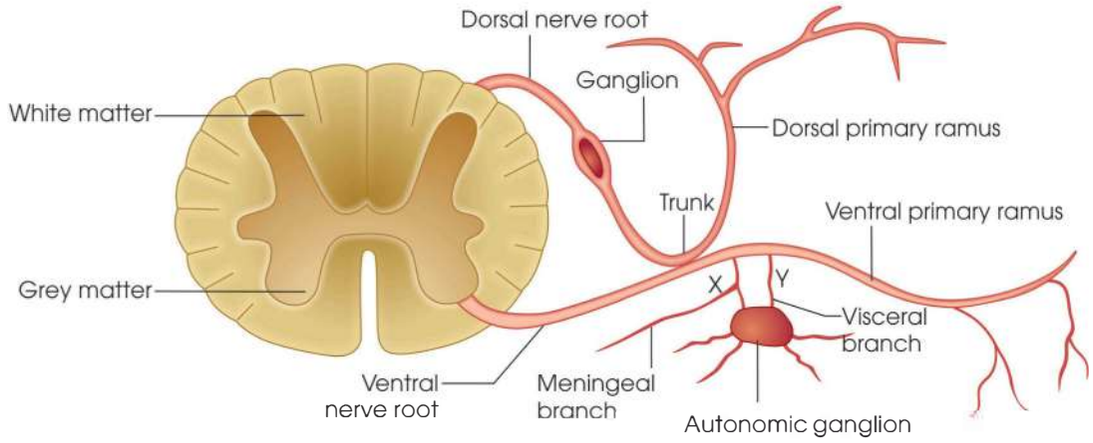


Fig. 93.2: Showing branches of a typical thoracic spinal nerve (diagrammatic). X = white ramus, Y = grey ramus

Applied Physiology

Sampaio-Baptista et al conducted 'Diffusion Tensor Imaging' and found that white matter changes with motor learning along with increases in myelination.

EXAM-ORIENTED QUESTION

Short Notes

1. Nerve cells
2. Neuroglia
3. Spinal nerves
4. Mixed nerves
5. Distribution of terminal branches of spinal nerve.

REFERENCE

Sampaio-Baptista, C.; Khrapitchev, A. A.; Foxley, S.; Schlagheck, T.; Scholz, J.; Jbabdi, S.; Deluca, G. C.; Miller, K. L.; Taylor, A.; Thomas, N.; Kleim, J.; Sibson, N. R.; Bannerman, D.; Johansen-Berg, H. "Motor Skill Learning Induces Changes in White Matter Microstructure and Myelination". Journal of Neuroscience. 2013, 33 (50): 19499–19503.

Chapter

94

The Ascending and Descending Tracts

INTRODUCTION

Fibres carrying different sensations enter the spinal cord through the posterior roots. Inside the cord, a rearrangement takes place. Fibres carrying one kind of impulse tend to collect into a bundle. Such bundles are called sensory tracts. Motor tracts are also formed on similar lines.

DEFINITION: TRACTS

A tract may be defined as a bundle of fibres carrying one or a group of motor or sensory impulses in the central nervous system.

Functionally nerve tracts (fasciculi) may be grouped in each column (funiculus) into ascending (sensory), descending (motor) and intersegmental fibres (Fig. 94.1).

Ascending Tracts (Sensory Tracts)

1. Tract of Goll (fasciculus gracilis).
2. Tract of Burdach (fasciculus cuneatus).
3. Comma tract of Schultze (tractus interfascicularis).
4. Dorsal spinothalamic tract (lateral spinothalamic tract).
5. Spinotectal tract.

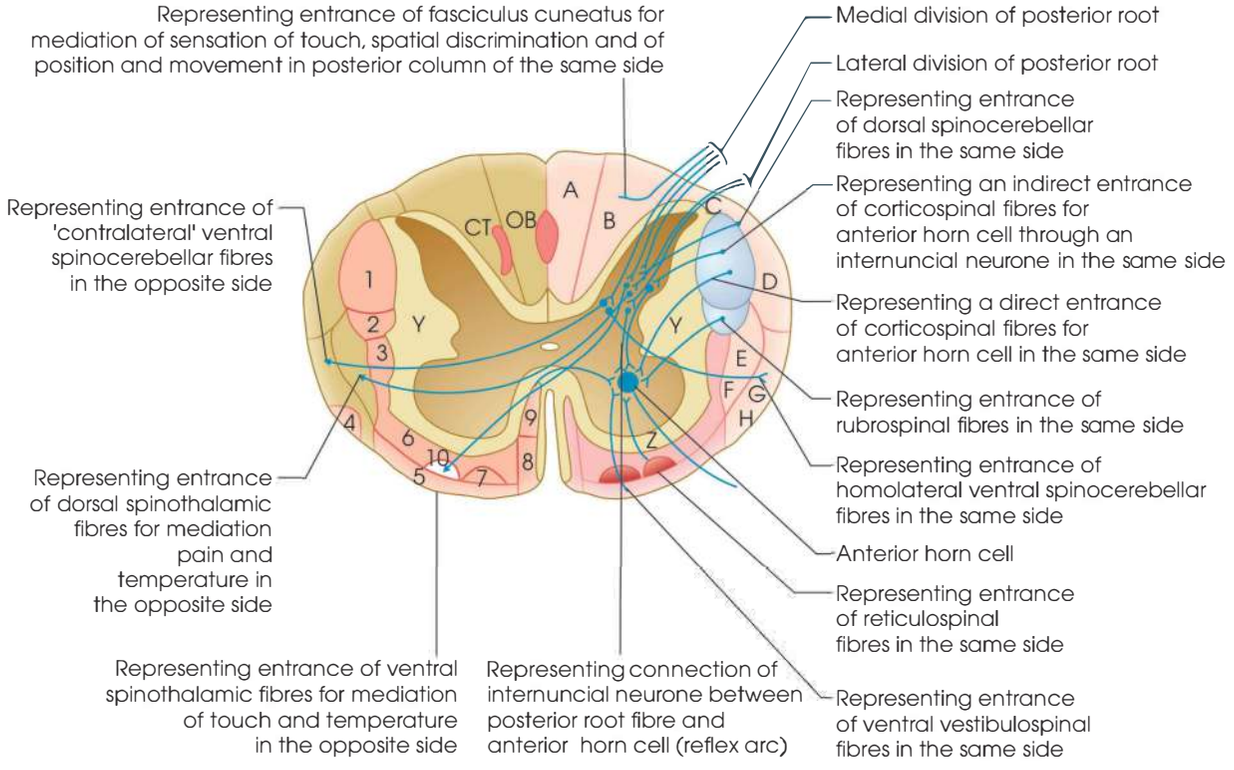


Fig. 94.1: Diagrammatic representation of cross-section of a spinal cord showing the centrally placed grey matter composed of nerve cell bodies and nerve fibres (dendrites and axons) including intersegmental fibres. Principal descending (motor) and ascending (sensory) tracts passing through the white matter of the spinal cord have also been shown

6. Dorsal spinocerebellar tract (Flechsig's tract).
7. Ventral spinocerebellar tract (Gower's tract).
8. Spino-olivary tract.
9. Spinoreticular tract.
10. Spinovestibular tract.
11. Spinopontine tract.
12. Spinocortical tract.
13. Ventral (anterior) spinothalamic tract.

Descending tracts (Motor tracts)

Pyramidal Tracts

a. Crossed pyramidal tract (large lateral corticospinal tract).
b. Direct pyramidal tract (uncrossed anterior corticospinal tract).
c. Uncrossed small lateral pyramidal (corticospinal) tract. Corticobulbar tract.

A. Extrapyramidal Tracts

1. Rubrospinal tract.
2. Tectospinal tract and tectobulbar tract
3. Reticulospinal tract.
4. Dorsal vestibulospinal tract.
5. Ventral vestibulospinal tract.
6. Olivospinal tract (bulbospinal tract).
7. Descending medial longitudinal fasciculus.

Intersegmental fibres (both ascending and descending):

1. Ground bundle of anterior column or funiculus (anterior intersegmental or sulcomarginal fasciculus).
2. Ground bundle of lateral column or funiculus (lateral intersegmental fasciculus).

Posterior column or funiculus consists of:

1. Posterior intersegmental fasciculus (posterior ground bundle).
2. Septomarginal fasciculus:
   a. Posterior septomarginal fibres (in cervical and upper thoracic segments)
   b. Dorsal peripheral strand (in lower thoracic segments)
   c. Oval bundle of Flechsig (in lumbar segments)
   d. Triangular area of Philippe-Gombault (in sacral segments)

ASCENDING TRACTS (AFFERENT TRACTS)

Note

From periphery to the centre, there are three neurons and two relays. For cerebral tracts, crossing takes place in the second neuron. For cerebellar tracts there is no crossing. Complete description of a tract should include the following headings: Origin, situation, course, and extent, number of neurons, crossing, termination and function.

Afferent Tracts in the Posterior Column (Funiculus)

1. Fasciculus gracilis (tract of Goll).
2. Fasciculus cuneatus (tract of Burdach).
3. Comma tract of Schultze (tractus interfascicularis).

Afferent Tracts in the Lateral Column (Funiculus)

1. Dorsal spinothalamic tract (lateral spinothalamic tract).
2. Spinotectal tract.
3. Flechsig's tract [direct or dorsal (posterior) spinocerebellar tract].
4. Gower's tract [indirect or ventral (anterior) spinocerebellar tract].
5. Spino-olivary tract.
6. Spinoreticular tract.
7. Spinovestibular tract.
8. Spinopontine tract.
9. Spinocortical tract.

Afferent Tracts in the Posterior Column (Funiculus)

Afferent (sensory) tracts in the posterior column—fasciculus gracilis (tract of Goll) (Figs 94.2 and 94.3)

Origin: It is made up of axons of the bipolar cells of the posterior root ganglia receiving afferents from the lower half of the body.

Situation and extent: After entering the spinal cord the fibres run in the posterior column and extend throughout the cord. Below the midthoracic region it occupies the whole breadth of the posterior column; but above this level its fibres are pushed medially by the tract of Burdach.

Neuron, crossing and termination: Since the fibres belong to the first-order neuron, they do not cross and remain on the same side.

These fibres end in four ways:

1. Some fibres make reflex connections at different segments.
2. Some fibres end round the posterior horn cells and then cross and join the ventral spinothalamic tract of the opposite side.
3. Some fibres give descending branches which makeup the comma tract of Schultze (tractus interfasciularis),
4. Majority of the fibres end in the medulla in the nucleus gracilis (Fig. 94.4). Here, first relay takes place and second-order neuron arises.

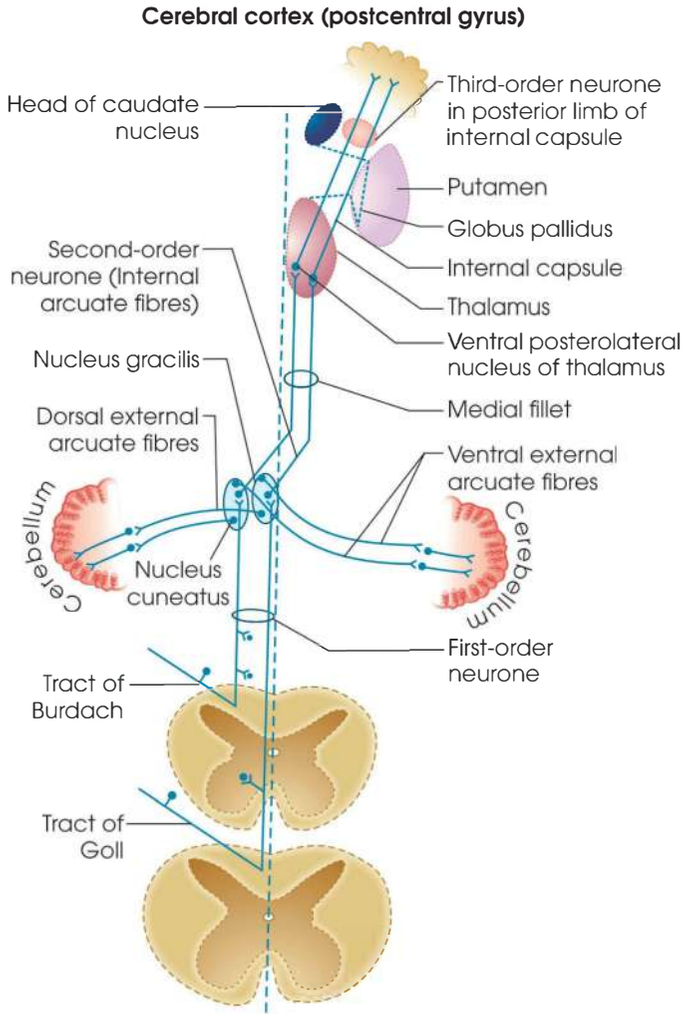


Fig. 94.2: Diagrammatic representation of tracts of Goll and Burdach (simplified)

5. The axons of this neuron are divided into two groups: External and internal arcuate fibres.
   a. The external arcuate fibres are further subdivided into two groups: Dorsal and ventral external arcuate fibres. The dorsal external group passes through the inferior cerebellar peduncle of the same side and ends in the cerebellum. The ventral external group crosses to the opposite side, passes through the inferior cerebellar peduncle and ends in the cerebellum on the opposite side.
   b. The internal arcuate fibres, being axons of the second-order neuron, cross to the opposite side, enter the medial fillet or lemniscus, pass through the midbrain and end in the ventral posterolateral nucleus of the thalamus. Here, the second relay takes place and the third-order neuron arises. The axons of this neuron pass through the posterior limb of the internal capsule and end in the postcentral gyrus (sensory cortex).

Functions: This tract carries the following impulses from the lower half of the body:

1. Fine touch, tactile localisation and tactile discrimination.
2. Kinaesthetic sensations.
3. Sense of vibrations.
4. Some unconscious impulses (probably kinaesthetic) passing to the cerebellum through the external arcuate fibres.

It may constitute the sensory pathway for some superficial reflexes.

Fasciculus Cuneatus (Tract of Burdach) (Figs 94.2 and 94.3)

The general description, viz. course, relays, termination and functions, etc. of this tract is same as that of Goll.

The following are the differences:

1. It is made up of posterior root fibres from the upper half of the body.
2. It is situated laterally in the posterior column of the upper thoracic and cervical regions only.
3. Ends in the medulla in the nucleus cuneatus (lateral to nucleus gracilis).
4. It carries the same sensory impulses but from the upper half of the body.

Comma Tract of Schultze (Tractus Interfascicularis) (Fig. 94.4)

It is made up of short descending branches derived from the tracts of Goll and of Burdach. It is situated in the posterior column between these two tracts and looks like a 'comma' in transverse section. Its functions are:

1. It establish intersegmental communication.
2. It forms short reflex arcs. Some workers hold that it contains motor fibres also. The peculiarity of this tract is that although sensory in function, it is descending in course.

Afferent (Sensory) Tracts in the Lateral Column

Dorsal Spinothalamic Tract (Fig. 94.5)

Origin, distribution and termination: The dorsal spinothalamic tract (lateral spinothalamic tract) is an ascending one which occupies the lateral column of the white matter in the spinal cord. Some posterior root fibres (axons of the first-order neuron) of all segments after entering the spinal cord end round the cells of the substantia gelatinosa of Rolando. These unmyelinated fibres of the posterior root are known as tract of Lissauer (fasciculus posterolateralis). The second-order neuron starts from these cells. Most of the axons of second-order neuron cross in the anterior white commissure, obliquely to the opposite side of the same segment and ascend in the lateral column of the cord. Some fibres of the second-order neuron, before crossing, may ascend up one segment and then cross in the anterior white commissure to reach the lateral column of the opposite side of the cord.

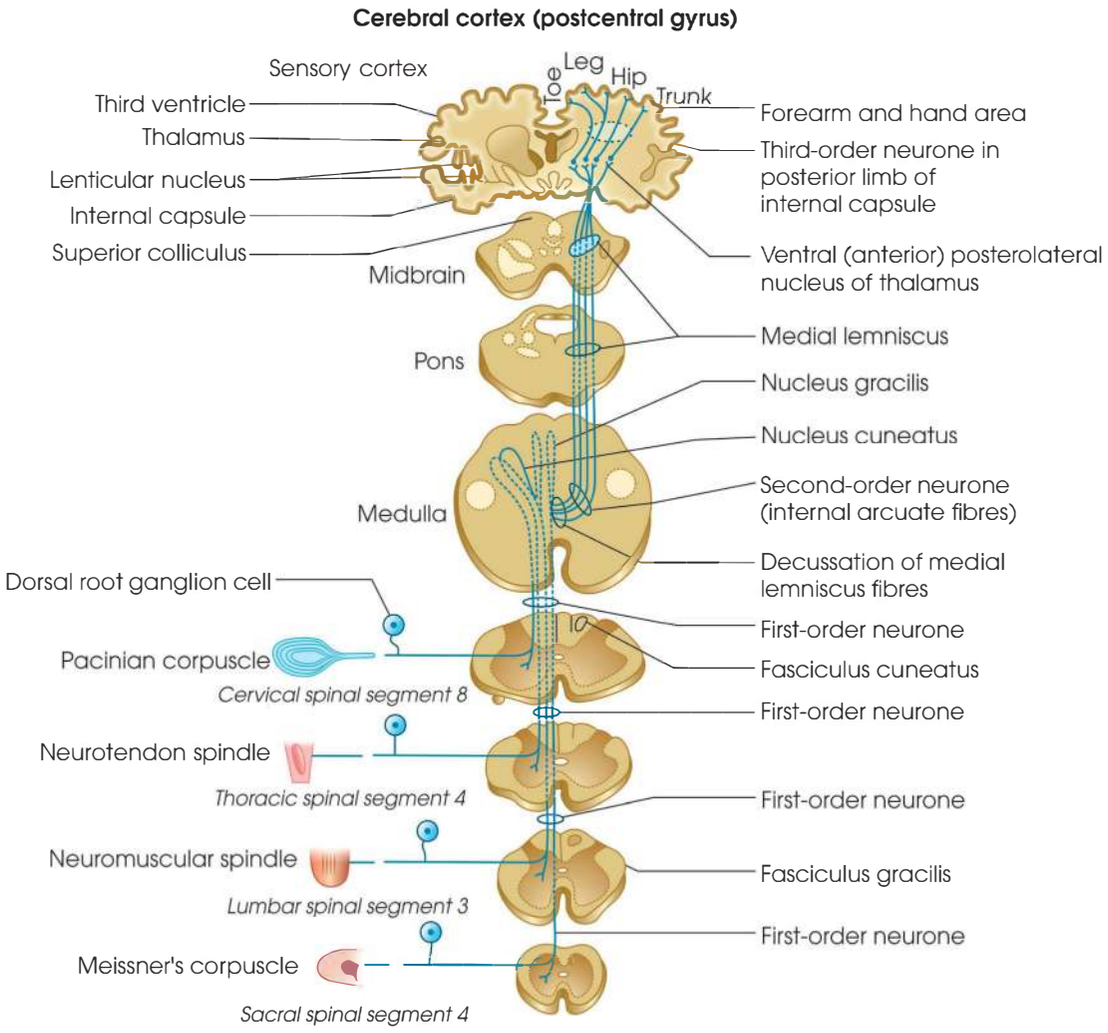


Fig. 94.3: Diagrammatic representation of internal arcuate fibres showing its origin and termination through medial lemniscus into the thalamus and thence into the cortex

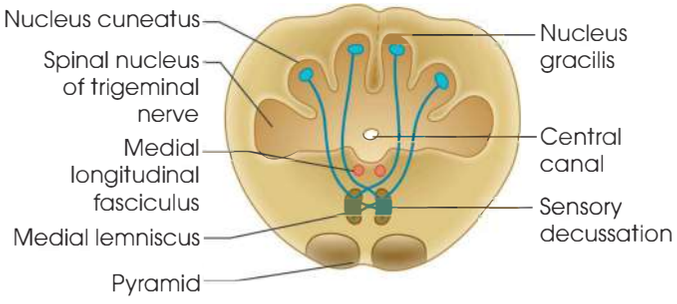


Fig. 94.4: Diagrammatic representation of the transverse section of the caudal (lower) part of the medulla at the level of afferent (sensory) decussation of pyramids

This tract together with ventral (anterior) spinothalamic tract constitutes the spinal lemniscus in the medulla oblongata. The spinal lemniscus then ascends up to join the medial lemniscus in the upper part of the medulla oblongata and finally terminates in the ventral posterolateral nucleus of the thalamus. The lateral spinothalamic tract at higher brain stem level sends several collaterals into the reticular formation and tegmentum before ending in the thalamus. Here third-order neuron starts and axons of this neuron terminate in the postcentral gyrus of the cerebral cortex through the posterior limb of internal capsule.

Functions

1. The lateral spinothalamic tract carries
2. Fibres of all pain impulses
3. All temperature impulses—both heat and cold
4. Unilateral section of this tract causes a complete loss of pain and temperature on the opposite side of the body and owing to the oblique crossing of axons of the second-order neuron, the contralateral sensory loss extends to a level one segment below that of the lesion.

Spinotectal Tract (Fig. 94.6)

Fibres arise from the posterior horn cells of the opposite side. It is situated in this lateral column, ventral to the

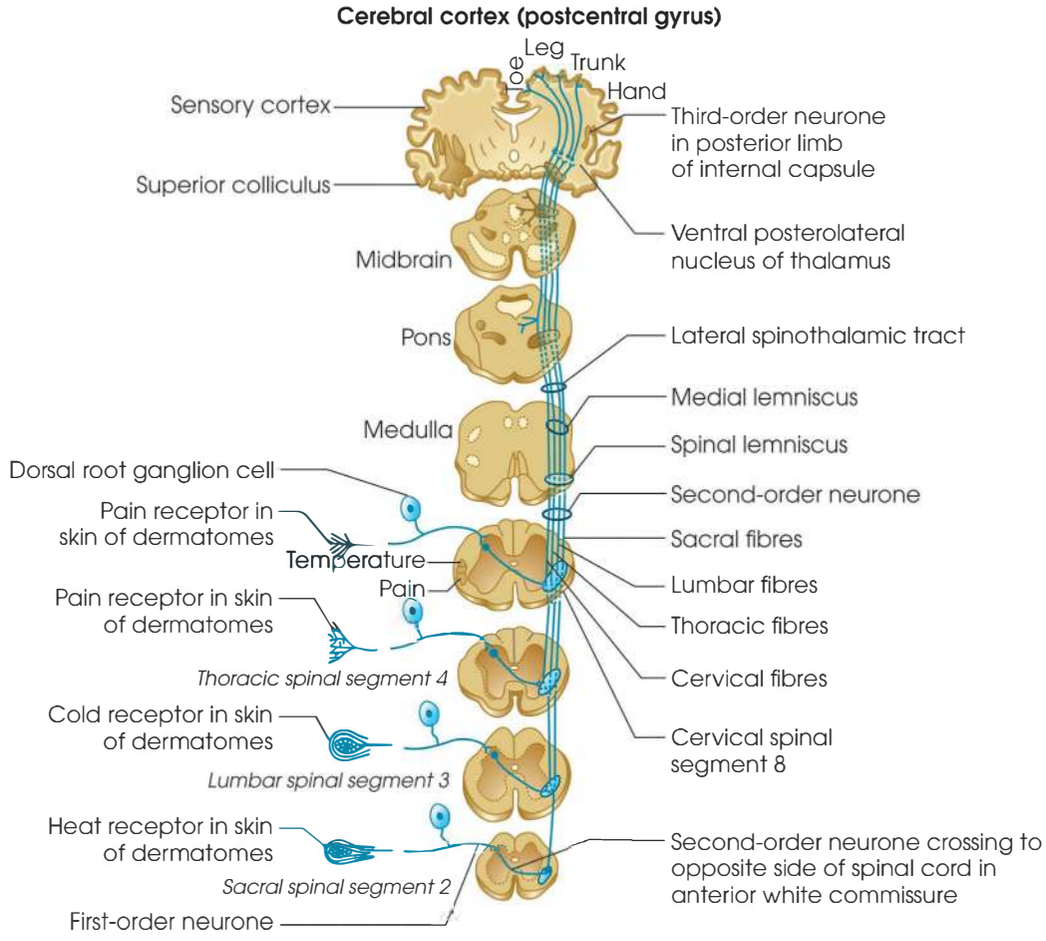


Fig. 94.5: Diagrammatic representation of dorsal (lateral) spinothalamic tract

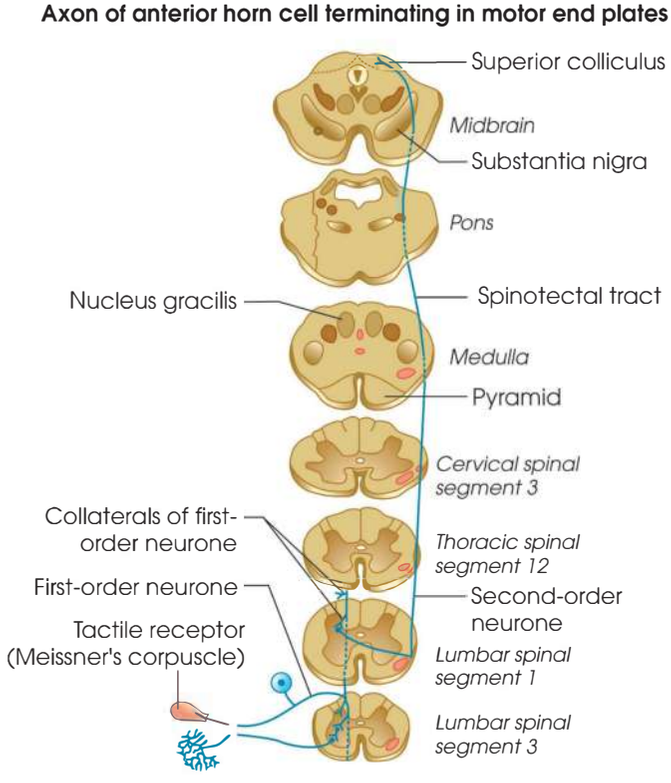


Fig. 94.6: Diagrammatic representation of spinotectal tract

lateral spinothalamic tract, being most prominent in the cervical region pass through the medial or mesial fillet or lemniscus and end in the superior colliculus (midbrain).

Function: It subserves spinovisual reflexes.

Flechsig's Tract (Direct or Dorsal (Posterior) Spinocerebellar Tract) (Fig. 94.7)

Some fibres of the posterior root end round Clarke's column of cells on the same side. Here the second-order neuron arises and constitutes this tract. Although the second-order neuron, yet the fibres will not cross; because they are destined for the cerebellum. The fibres bend laterally, enter the lateral white column, and occupy the most peripheral part lateral to the spinothalamic tract and dorsal to Gower's tract. It extends through the upper lumbar, thoracic and cervical regions. In the medulla it enters the inferior cerebellar peduncle of the same side and ends in the vermis. Here the third-order neurone arises and passes to the cerebellar cortex.

Function: It carries unconscious kinaesthetic impulses to the cerebellum (essential for posture).

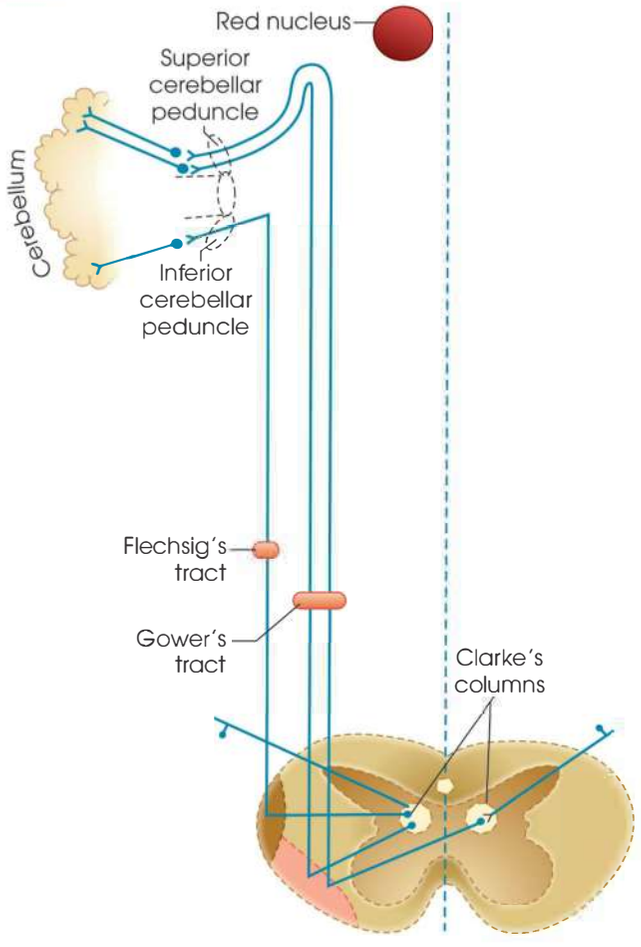


Fig. 94.7: Diagrammatic representation of Flechsig's tract and Gower's tract

Gower's Tract (Indirect or Ventral (Anterior) Spinocerebellar Tract) (Fig. 94.7)

Like the above it also carries unconscious kinaesthetic impulses to the cerebellum. But it has the following differences with Flechsig's tract: Composition and origin—it is made up of fibres arising from Clarke's columns of both sides. It is composed mostly of crossed and partly or uncrossed fibres. The presence of crossed fibres is an apparent violation of ipsilateral cerebellar control.

Situation: The tract makes its appearance first in the third lumbar region of the spinal cord and remains in the lateral white column, just ventral to Flechsig's tract.

Course, extent and termination: It passes through the cord and medulla, enters the midbrain and goes up to the level of the red nucleus (without termination). Here, the fibres turn sharply backwards and downwards, and enter the superior cerebellar peduncle of the same side and end in the vermis. Smith (1961) has described that this tract initially crosses at the spinal level and at least some fibres recross in the cerebellar region. From here the third-order neuron arises and goes to the cerebellar cortex.

Function: It carries unconscious kinaesthetic sensation.

Spino-olivary Tract (Fig. 94.8)

This tract is originated from the cells of the dorsal horn of grey matter of all levels of the spinal cord, runs in parallel with the olivospinal tract and ends mostly in the inferior olivary nucleus of the opposite side. More than half of the fibres cross in the medulla oblongata.

Function: The spino-olivary tract transmits proprioceptive impulses to the cerebellum via the inferior olivary nucleus. It is claimed that this tract constitutes a component of the spinocerebellar tract.

Spinoreticular Tract (Fig. 94.9)

Cell stations of these fibres are lying in the posterior horn cells at all levels of the spinal cord. These fibres ascend in the anterolateral funiculus and terminate chiefly in the nucleus reticularis gigantocellularis and partly in the lateral reticular nucleus in the medulla. In the pons, certain fibres terminate in the nucleus reticularis pontis caudalis. A small number of fibres also terminate in the mescencephalic reticular formation. This tract also gives collaterals to the thalamus and hypothalamus.

Function: This tract plays an important role in the maintenance role in the maintenance of consciousness and awareness.

Spinovestibular Tract

This tract is originated from the spinal fibres projecting largely upon the dorsal part of the lateral vestibular nucleus. It ascends in the ipsilateral column of the spinal cord from the level as far as lumbar segments.

Function: This tract is concerned with postural reflexes.

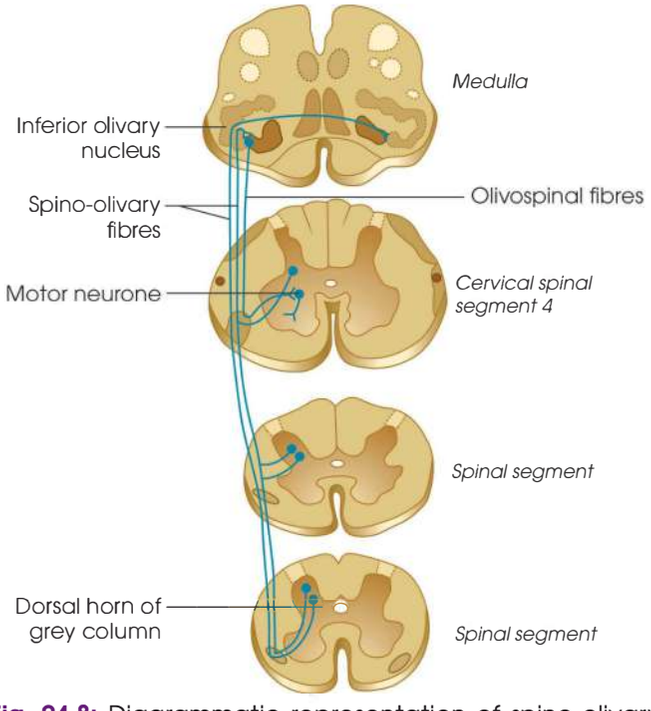


Fig. 94.8: Diagrammatic representation of spino-olivary tract and of olivospinal tract

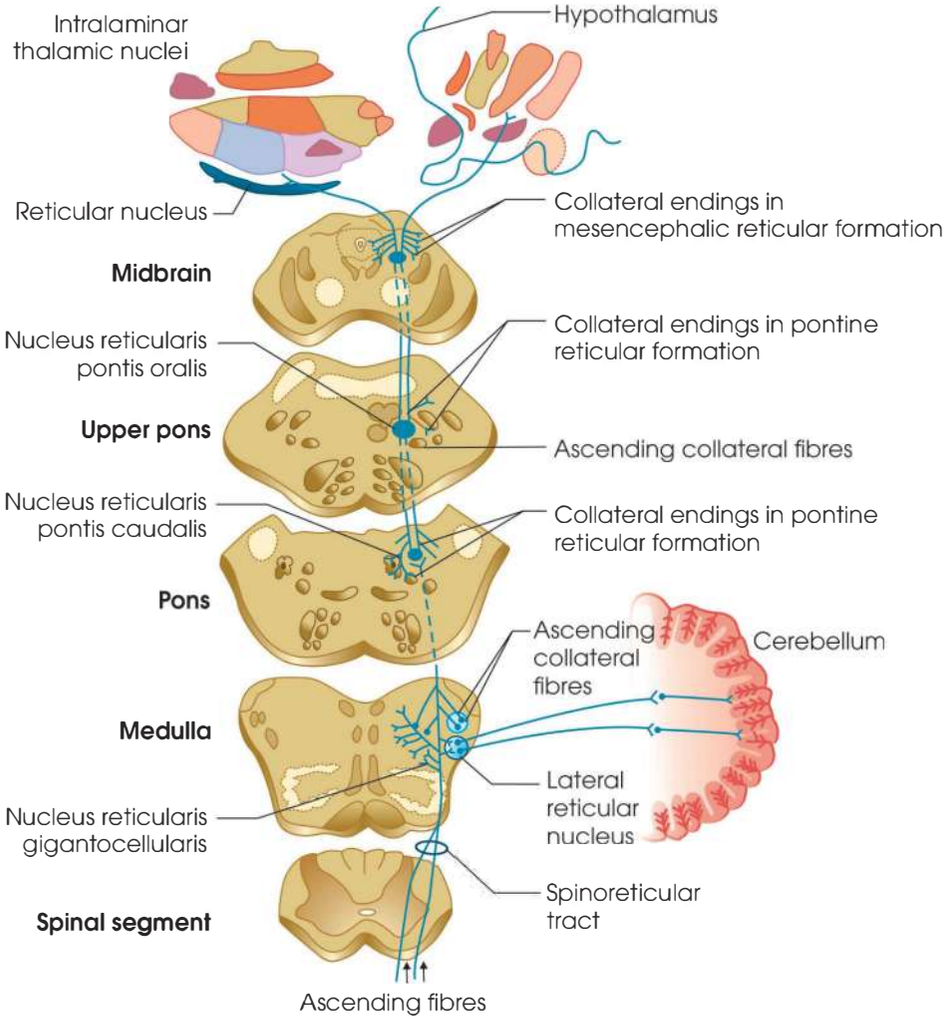


Fig. 94.9: Diagrammatic representation of spinoreticular and collateral reticular projections at different brain stem levels

Spinopontine Tract

These fibres are largely collateral fibres and ascend along with the spinocortical fibres and lastly terminate in the pontine nucleus.

Function: It is suggested that these fibres are concerned with the certain exteroceptive impulses to the cerebellum.

Spinocortical Tract

The presence of these fibres has been described recently. This tract ascends in parallel with the corticospinal tract. These fibres arise from all parts of the spinal cord and largely from the cervical region. The functions of these fibres are not clear.

Afferent (Sensory) Tracts in the Anterior Column

Ventral (Anterior) Spinothalamic Tract (Fig. 94.10)

Origin, distribution and termination: This tract originates from the large cells of the nucleus centrodorsalis of the posterior horn and second-order neuron starts from here. Axons of the second-order neuron ascend in the posterior column for two or three spinal segments and then cross obliquely in the anterior white commissure and thus ascend in the anterior or anterolateral column of the opposite side as ventral (anterior) spinothalamic tract.

Most of the fibres are crossed and a small number of fibres are uncrossed and may ascend homolaterally as anterior spinothalamic tract. While ascending upward the ventral (anterior) spinothalamic tract runs in parallel with the lateral spinothalamic tract in the spinal lemniscus.

As the tracts ascend towards the brain stem, a certain number of fibres are reduced gradually. The tracts give certain collaterals to the dorsolateral part of the brain stem reticular formation and also to the lateral reticular formation. At the upper border of the pons and midbrain, this tract along with dorsal spinothalamic tract (lateral spinothalamic tract) and internal acruate fibres runs in the medial lemniscus and terminates in the ventral posterolateral nucleus of the thalamus. The

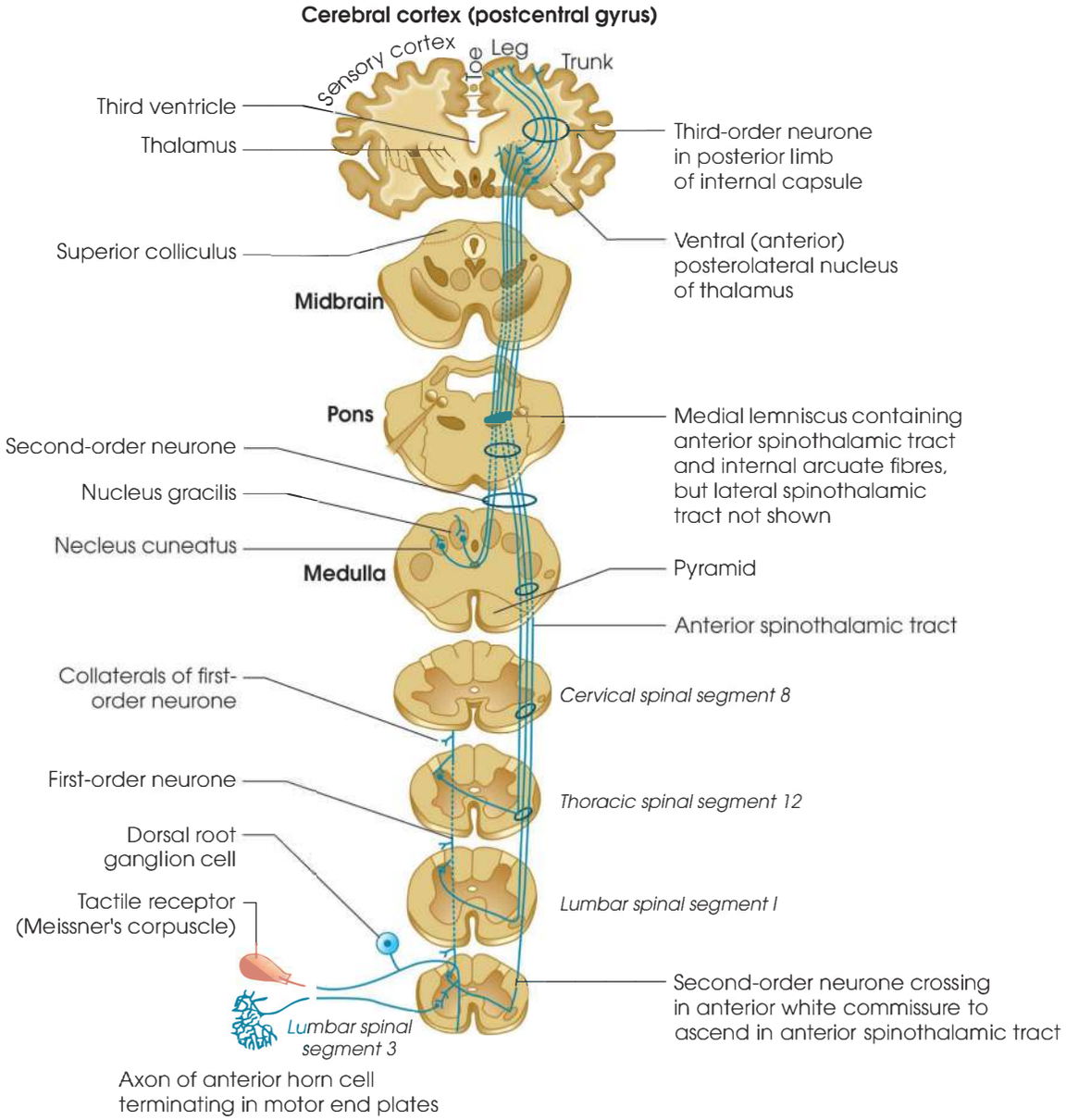


Fig. 94.10: Diagrammatic representation of ventral (anterior) spinothalamic tract

thalamus is known as subcortical centre for the spinothalamic tract. Here second relay starts and axons of the third-order neuron in posterior limb of the internal capsule terminate in the postcentral gyrus.

Function: This tract is for pain, temperature and crude touch.

Summary of the Pathways of Various Sensations

Path of Touch

Tactile corpuscles thicker medullated fibres in the sensory nerves posterior root spinal cord. Here, the touch fibres become divided into two parts:

1. Epicritic part passes through the tracts of Goll and Burdach.
2. Protopathic part passes through the ventral (anterior) spinothalamic tract.

Path of Pain and Temperature

Nerve endings for pain are the free nerve terminals, for cold end organs of Krause; for heat, organs of Ruffini and the Golgi-Mazzoni bodies. Pain is carried by fine non-medullated fibres, whereas thermal senses by medium-sized medullated fibres. All pass through the sensory nerves to the posterior root and enter the spinal cord. Fibres carrying pain and temperature sensations constitute Lissauer's tract and end in the posterior horn cells. From the posterior horn cells the second-order neuron arises and forms the dorsal spinothalamic tract (lateral spinothalamic tract). The crude part (protopathic) of temperature sensation and pain end in the thalamus, whereas the fine part (epicritic) of temperature sensation is relayed to the sensory cortex (Fig. 94.11).

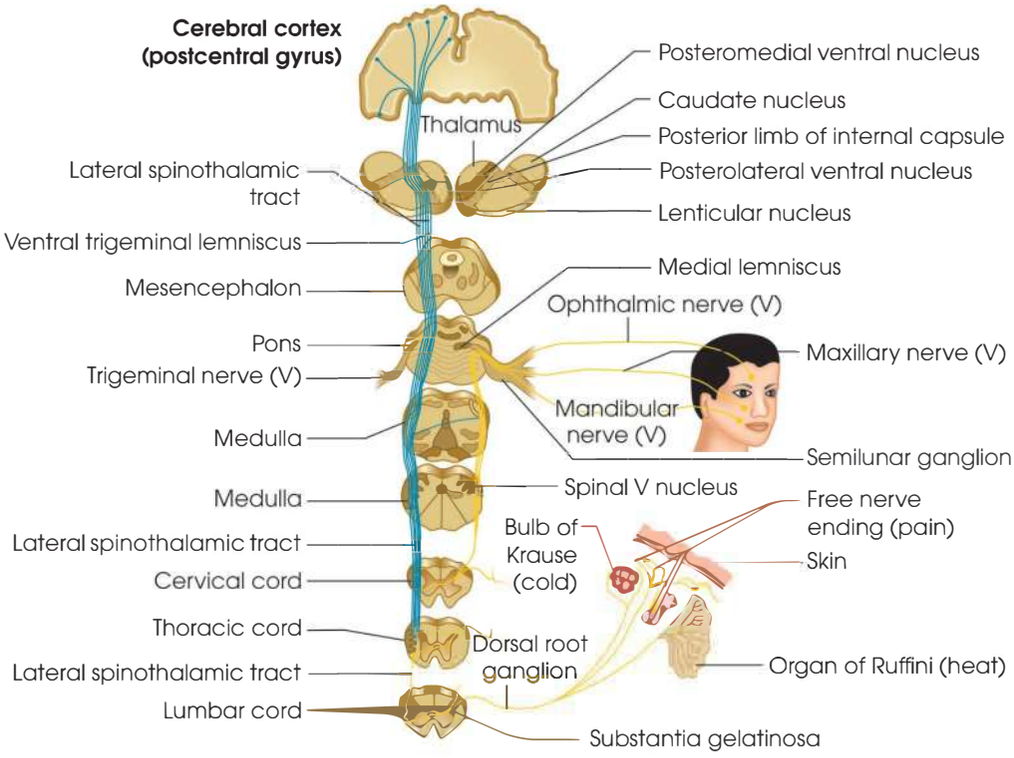


Fig. 94.11: Diagrammatic representation of the conscious pathway for pain and temperature including the types of receptors

Path of Kinaesthetic Impulses (also Vibration Sense)

End organs—muscle spindles, Golgi bodies, pacinian corpuscles, etc. (Fig. 94.12). Impulses pass along the sensory nerve posterior root spinal cord. Here, two divisions—conscious kinaesthetic impulses pass through the tracts of Goll and Burdach and unconscious kinaesthetic impulses pass through Flechsig's and Gower's tracts.

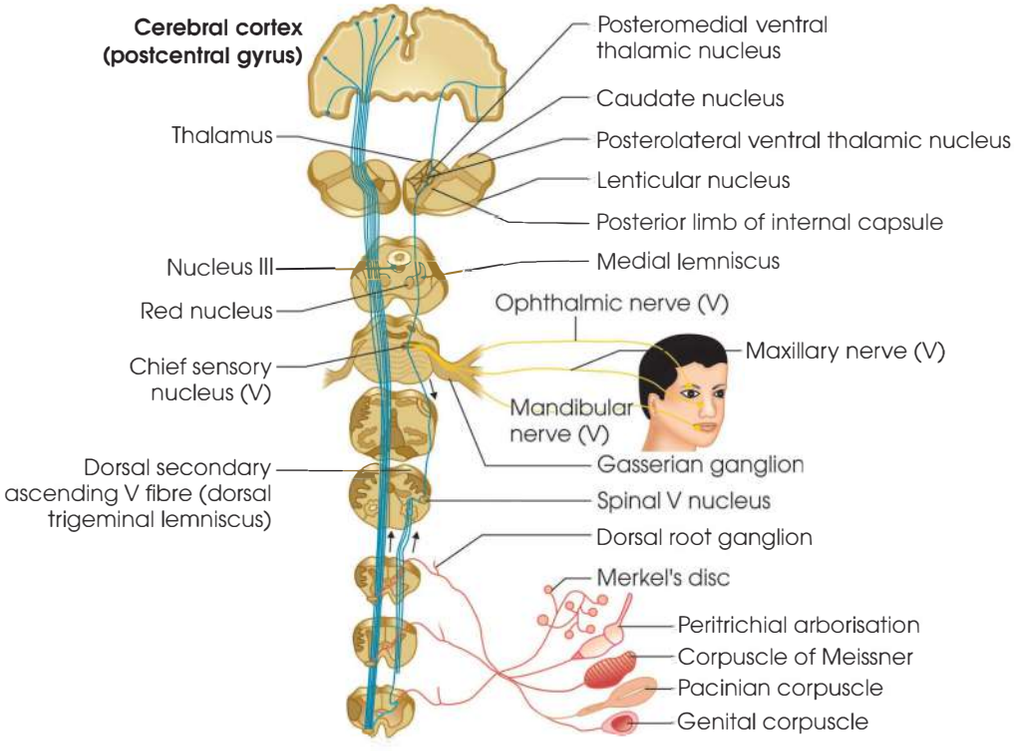


Fig. 94.12: Showing the conscious pathway for light (crude) touch

Path of Non-sensory Afferent Impulses

These afferent impulses do not rise to the level of consciousness. Hence, the tracts carrying them will end somewhere below the thalamus. They are mentioned below.

Spinocerebellar tract: Flechsing's and Gower's tracts. They carry non-sensory kinaesthetic impulses to cerebellum. It is very important for tone, posture and equilibrium.

Those fibres of Goll and of Burdach which are relayed to the cerebellum through the external arcuate fibres probably carry unconscious kinaesthetic impulses.

Spinotectal tract ending in the superior colliculus and responsible for spinovisual reflexes.

Small intersegmental tracts (*comma tract of Schultze, Septomarginal tract, etc.*): It is necessary for coordination and reflex.

Spino-olivary fibres: From spinal cord to inferior olive, probably for reflex.

How Posterior Spinal Root Ends?

The posterior root is composed of:

1. Autonomic fibres
2. Somatic fibres.

The autonomic fibres all end in the lateral horn cells. The somatic fibres terminate as follows:

a. Fibres carrying pain, temperature and crude touch end round the posterior horn cells on the same side. From here, the second-order neuron arises and passes out as to spinothalamic tract. Before ending in the posterior horn the pain and temperature fibres constitute the so-called tract of Lissauer.

b. Fibres carrying unconscious kinaesthetic impulses end in Clarke's column of the same side. From here the second-order neuron arises and carries the impulses to the cerebellum through the two spinocerebellar tracts.

c. Some fibres pass directly to the anterior horn cells and establish various reflex arcs, viz. knee jerk, etc.

d. Fibres carrying conscious kinaesthetic impulses and fine touch enter the posterior white column of the same side; constitute the tracts of Goll and of Burdach and end in the nucleus gracilis and the nucleus cuneatus respectively in the medulla. Collaterals of these tracts also end at:

- Round the posterior horn cells
- Form short intersegmental tracts, such as comma tract of Schultze
- May form reflex arcs.

DESCENDING TRACTS

Motor Tracts or Efferent Tracts

Pyramidal tracts

1. Crossed pyramidal tract (large lateral corticospinal tract).
2. Direct pyramidal tract (uncrossed anterior corticospinal tract).
3. Uncrossed small lateral pyramidal (corticospinal) tract: Corticobulbar tract.

Extrapyramidal tracts

1. Rubrospinal tract.
2. Tectospinal tract and tectobulbar tract.
3. Reticulospinal tract.
4. Vestibulospinal tracts.
5. Olivospinal tract (bulbospinal tract).
6. Descending medial longitudinal fasciculus.

Pyramidal or Corticospinal Tracts

(Figs 94.13 and 94.19)

Composition

This is the longest tract starting from the motor cortex and reaching up to the last segment of the cord. These tracts are constituted by the fibres originating from the cells of the cortex, pass through medullary pyramid and enter the spinal cord. Due to incomplete decussation

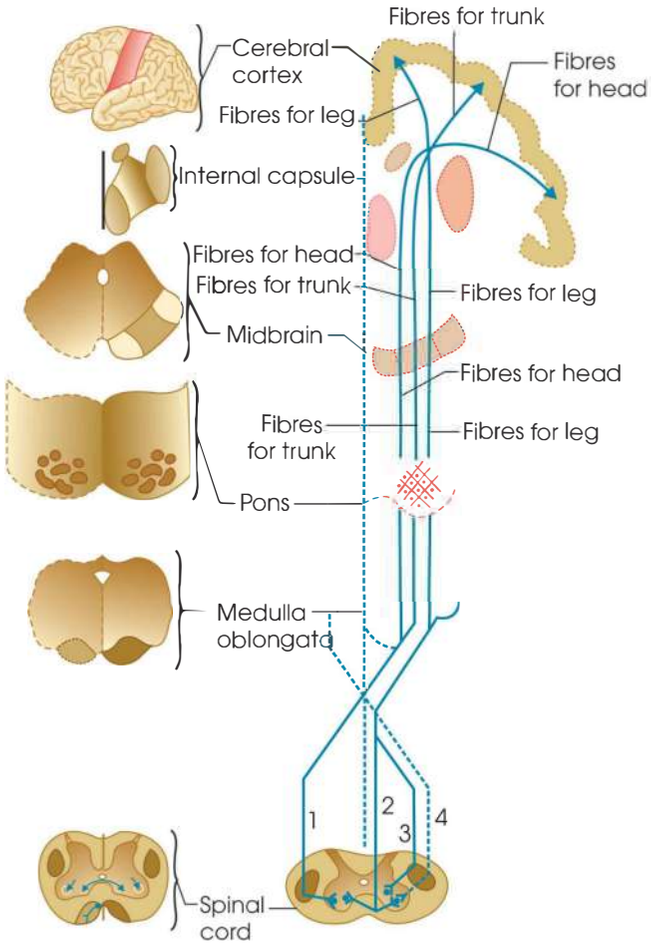


Fig. 94.13: Composite diagrammatic representation of pyramidal tracts (simplified). 1 = Crossed pyramidal tract. 2 = Direct pyramidal tract. 3 = Uncrossed small pyramidal tract. 4 = Crossed pyramidal tract from the other side

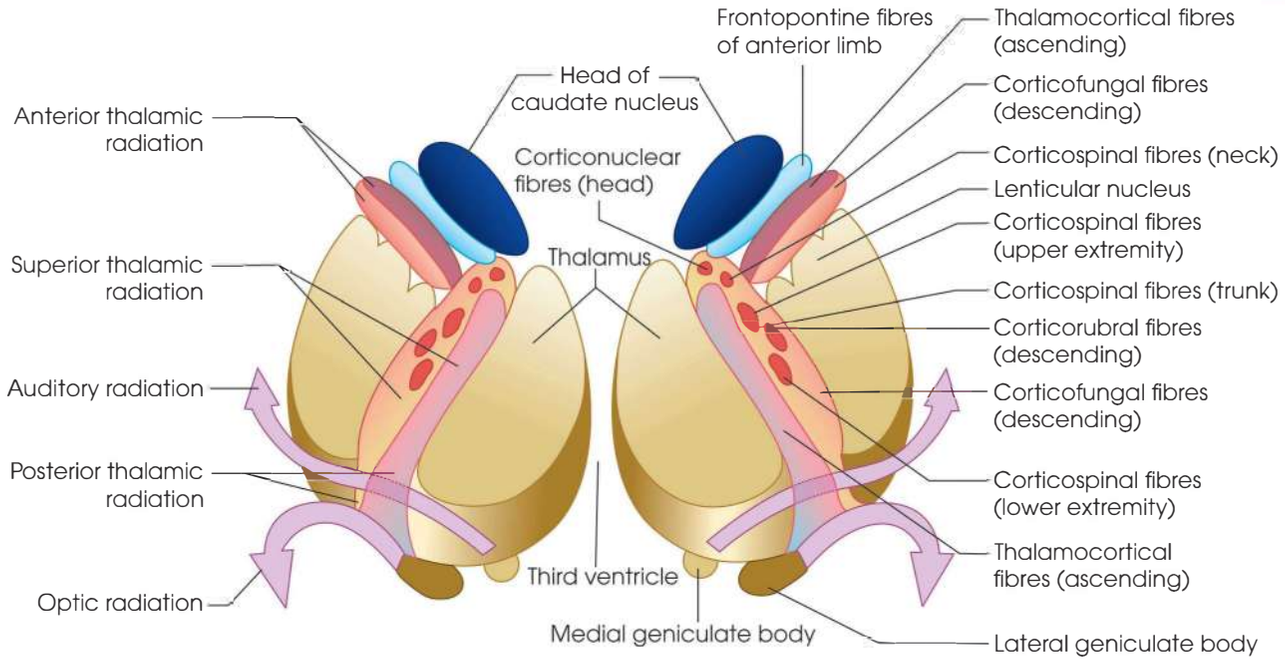


Fig. 94.14: Diagrammatic representation of different components of the internal capsule showing thalamic, auditory and optic radiations

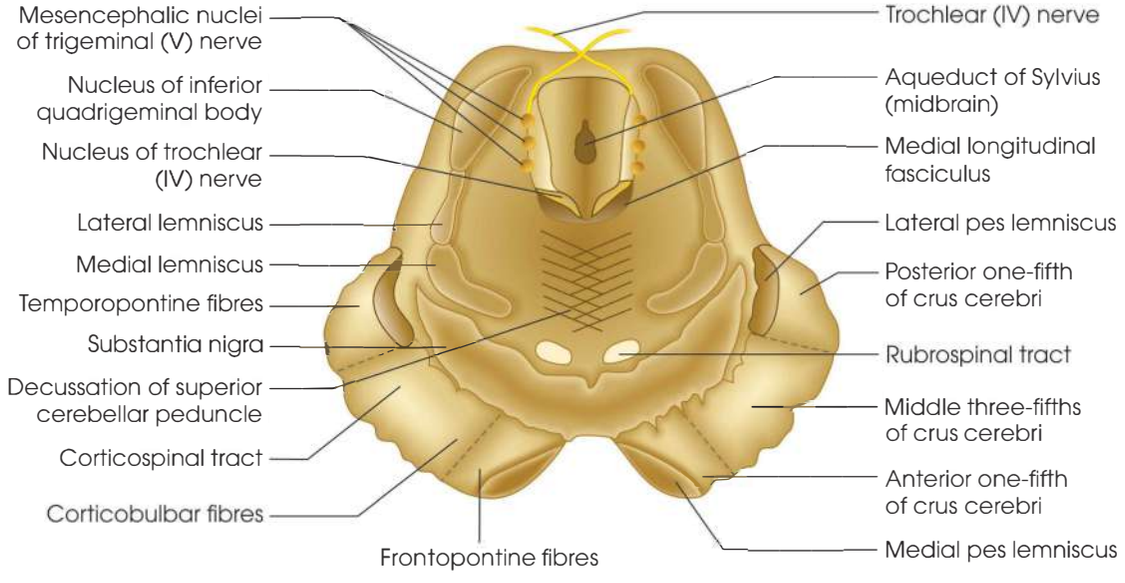


Fig. 94.15: Diagrammatic sectional representation of the midbrain showing the space of reticular formation surrounded by medial lemnisci at the level of inferior quadrigeminal body

at the junctions of the medulla and spinal cord, there originate the three tracts:

1. The crossed pyramidal tract (large lateral corticospinal tract).
2. The direct pyramidal tract.

It is present only in the higher animals and man where cerebrum has developed. It is composed of about one million nerve fibres of which 60% are myelinated and 40% are unmyelinated. Of the myelinated fibres over 80% are of 1–3 µm size, only 4% are over 11 µm and 2% are 12–20 µm. Since majority of fibres are of small diameter, the tract must be a slowly conducting pathway.

Origin

It is generally believed that the fires arise from the giant (large) pyramidal cells (Betz cells) of area 4 in the precentral gyrus.

But two observations are against this conclusion:

1. There are only about 35,000 Betz cells, which can account for only 6% of the fibres of this tract. After

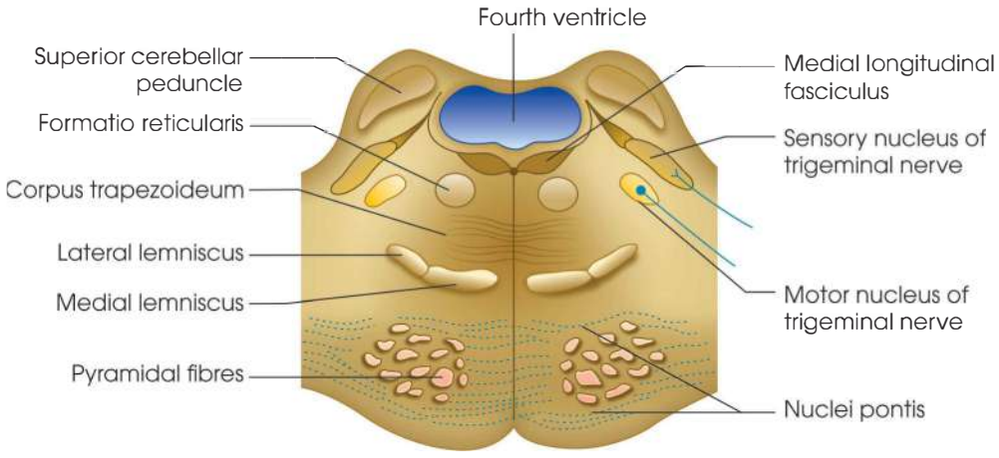


Fig. 94.16: Diagrammatic sectional representation through the upper pons

ablation of area 4, only 25% of the fibres degenerate and 75% survive.

2. The origin of this tract is not only from areas 4 and 6 but also from frontal and parietal lobes as after ablation of areas 4 and 6. All the pyramidal fibres do not degenerate. Ablation of areas 1, 2, 3, 5 and 7 leads to degeneration of the remaining fibres.

Course and Termination of Pyramidal Tracts

The course of pyramidal tracts is described below region by region.

In the cortex: As mentioned above, fibres arise from the whole of the precentral gyrus. The fibres are arranged upside down like the motor centres (*vide* motor area). Those for the toes are at the top, those for the trunk in the middle and those for the head, below. The fibres descend in the same plane (coronal) as occupied by the central sulcus.

Corona radiata: The cerebral hemisphere is connected with the brain stem and spinal cord by projection fibres. These projecting fibres of the cerebral cortex converge towards the brain stem as a radiating mass of fibres which is known as corona radiata. The fibres then converge and pass through the internal capsule.

In the internal capsule: The cortical fibres then pass through the internal capsule, occupying the genu (bent of the internal capsule) and the anterior two-thirds of the posterior limb. The cortical descending fibres which pass through the genu of the internal capsule constitute the corticobulbar or corticonuclear tract. The cortical descending fibres which pass through the anterior two-thirds of the internal capsule are known as corticospinal or pyramidal tracts. Here the plane of the fibres rotates through one right angle and the relative position of the fibres changes. The 'head' (upper extremity) fibres now occupy the most anterior part, the 'leg' (lower extremity) fibres, the most posterior part and the 'trunk' fibres remain in the middle.

Here, the tract gives fibres to the following: Corticobulbar (corticonuclear) fibres pass down the midbrain and end round the motor nuclei of V, VII, IX, X, XI, XII cranial nerves of the same and opposite side through the intercalated neurons of the reticular formation. Just behind the pyramidal tract remain the thalamic radiation, optic radiation, auditory radiation and temporopontine fibres (Fig. 94.14).

Following fibres pass through the anterior limb of the internal capsule:

1. Thalamofrontal
2. Frontothalamic
3. Frontopontine
4. Corticostriate (for details *vide* internal capsule).

In the midbrain: The corticospinal and corticobulbar fibres occupy the middle three-fifths of the crus cerebri. The anterior one-fifth is occupied by the frontopontine and the posterior one-fifth by the temporopontine fibres (Fig. 94.15). Here, the plane of the pyramidal tract turns through another right angle and the fibres undergo a second rearrangement. The 'head' fibres remain medially, 'leg' fibres laterally and the 'trunk' fibres in the middle.

In the pons: The pyramidal fibres occupy the most ventral aspect of pons in front of the trapezium. While passing through the nuclei points and the crossing fibres of the middle cerebellar peduncle, the tract is broken up into scattered bundles and the previous arrangement of fibres is probably lost (Fig. 94.16).

In the medulla: While coming out of pons the scatted fibres are reunited and enter the medulla as a thick bundle. It occupies the most anterior part of the medulla producing a distinct bulge—the pyramid. In the lower part of medulla the majority of fibres cross, while the rest pass down on the same side (Figs 94.17 and 94.18).

In the spinal cord: Pyramidal fibres end in the spinal cord mostly at the interneurons in the following manner (Figs 94.13, 94.19 and 94.20).

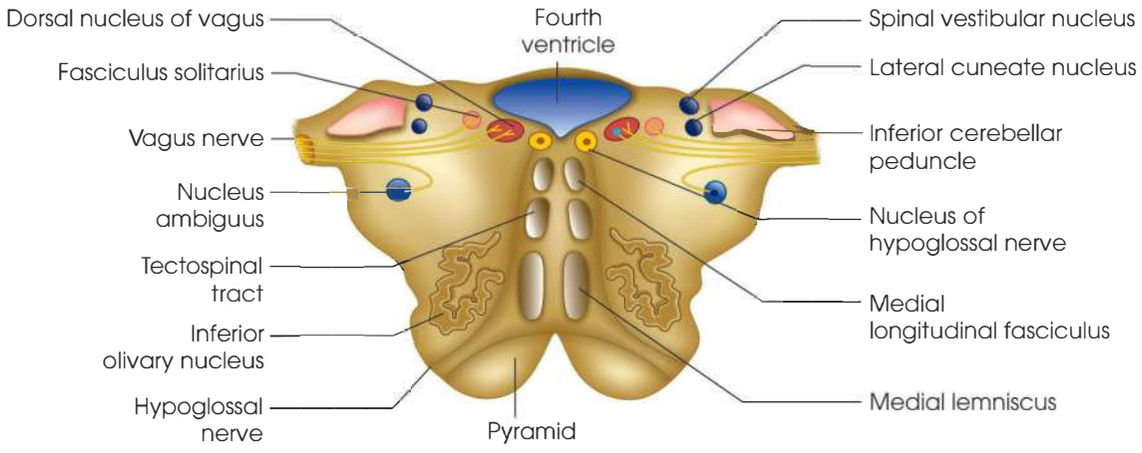


Fig. 94.17: Diagrammatic sectional representation through the upper medulla showing the space of the reticular formation between the pyramids and the central grey matter on the floor of the fourth ventricle

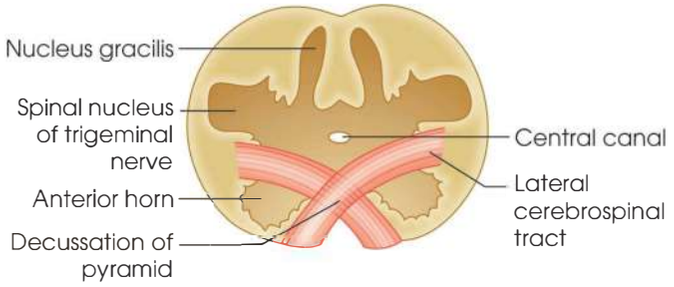


Fig. 94.18: Diagrammatic representation of the dorsal aspect of the medulla at the level of efferent decussation of pyramids (cerebrospinal fibres)

Crossed pyramidal tract (large lateral corticospinal tract): The fibres which cross in the medulla constitute this tract. While crossing, the fibres bend a little backwards, enter the lateral white column and remain just behind the rubrospinal tract. It extends throughout the whole cord and at each segment some fibres leave the tract, turn inwards and end round the anterior horn cells either directly or through interneurons.

Direct pyramidal tract (Uncrossed anterior corticospinal tract): It is made up of those fibres which do not cross in the medulla. The tract enters the anterior white column near the median fissure (cleft). Some of its fibres cross to the opposite side through the anterior white commissure and end round the anterior horn cells of the opposite side (Fig. 94.13). The rest of the fibres remain on the same side and end round the anterior horn cells of the same side. It is generally held that this tract does not reach beyond the thoracic region, but others have traced it up to the sacral region. One should note that although the fibres do not cross in the medulla, some of them cross in the spinal cord near their termination.

Uncrossed small lateral pyramidal tract: Lately Fulton and Sheehan have described the presence of another tract of a few uncrossed lateral pyramidal fibres (anterolateral pyramidal tract of Barnes) descending through the lateral white column and terminating on the same side. The presence of these and the second group of fibres of the direct pyramidal tract indicates that certain muscles in the body must have bilateral control from both cerebral hemispheres.

In pyramidal lesions of one side they will escape paralysis. The respiratory muscles are the typical examples.

Regarding the termination of the pyramidal fibres there are two views:

1. The general belief is that they end directly round the anterior horn cells.
2. Schäfer holds that they first end somewhere near the posterior horn and are then relayed to the anterior horn cells by an internuncial neuron.

Of all the pyramidal fibres 55% end in the cervical, 20% in the thoracic and 25% in the lumbosacral region.

Pyramidal cells and their axons are known as upper motor neuron and spinal cord motor neurons with their axons are known as lower motor neuron.

The paralysis of the upper motor neuron shows loss of the volitional movement, loss of superficial reflexes, increased deep reflexes, spasticity and the sign of Babinski. The paralysis of the lower motor neuron shows loss of all voluntary and reflex movements. Loss of muscle tone along with muscular dystrophy is observed.

Functions of the Pyramidal Tracts

1. The pyramidal tracts convey motor impulses to the spinal cord for controlling the voluntary movement especially the movement of fingers and hand subserving skill work.
2. They also form a part of the pathways for superficial reflexes like the cremasteric, abdominal and plantar reflexes.

Table 94.1: Effects of spinal transection

Complete transection	*Incomplete transection*
Smooth muscles—function returns first. Hence, • Retention of urine due to sphincter action • Blood vessels regain tone • Blood pressure rises. **Voluntary muscles**—tone of the flexor muscles returns after 2–3 weeks causing *paraplegia* in flexion. Hip and knee flexed; ankle and toes dorsiflexed. **Reflex movements** • **Spontaneous flexion** movements—early and frequent. • **Flexor reflexes—return first.** A painful stimulus on the sole will elicit it—hip and knee flexed, ankle and big toe dorsiflexed. Other toes abducted and may be dorsiflexed. [Sometimes plantar flexed.] This movement is obviously a protective *withdrawal reflex,* away from the cause of injury. In spinal animals the flexor reflex spreads to the extensor muscles of the opposite side causing *crossed extensor reflex,* but in man it remains either limited to the limb concerned or produces flexion of the opposite limb. • **Extensor reflexes** (deep reflexes)—return much later. Difficult to clicit. *Extensor reflex never obtained* knee jerk returns 1–5 weeks after the flexor reflex (relaxation *sudden and complete due to absence of* quadriceps tone). Ankle jerk returns still later. • **Mass reflex**—sometimes a widespread reflex may be elicited by scratching any area below the section, such as flexor spasm of the lower limbs and contraction of the abdominal wall, evacuation of the bladder, profuse sweating, etc.	**Smooth muscles**—function returns first. Hence, • Retention of urine due to sphincter action • Blood vessels regain tone • Blood pressure rises. **Voluntary muscles**—tone of the extensor muscles returns causing *paraplegia* in extension. Hip and knee extended; ankle and toes plantar flexed. **Reflex movements** • **Spontaneous extension** movements—early but infrequent. • **Flexor reflexes—return later.** Can be weakly elicited by similar painful stimuli, usually accompanied by extension of the opposite limb **(crossed extensor reflex).** Gentle flexion of the limb causes extension of the opposite limb **(Phillipson's reflex).** Then the flexed limb becomes extended and the other one flexed. In this way, the movement alternates in the limbs producing a *stepping movement.* This shows that in incomplete transection the *range of reflex activity is greater* and movements of locomotion can be carried out to some extent reflexly and unconsciously by the lower parts of the central nervous system. • **Extensor reflexes return much early** and easy to elicit. Knee jerk sows prolonged period of relaxation due to higher quardriceps tone. *Extensor thrust reflex is constantly present and is diagnostic* (with the legs flexed, if foot is pressed, contraction of quardriceps and posterior calf muscles). • **Mass reflex**—usually not much because the controlling effect of the brain stem persists.

Effects of Section of the Pyramidal Tracts

After the section of pyramidal tracts in rhesus monkeys at the lower level of the medulla oblongata or in the lateral column of the spinal cord following effects are observed:

Voluntary movement: Disturbance of voluntary movements especially of the opposite arm and leg. The discrete movements of the fingers, walking, grasping, scratching, etc. cannot be properly performed.

Muscle tone: Diminution of muscle tone especially of the limbs is encountered. Increased muscle tone and exaggerated reflexes occur after section of both pyramidal and extrapyramidal tracts.

Reflexes: Abolition of superficial reflexes, namely abdominal, cremasteric, etc. and slowing of the deep reflexes.

In human beings the acute lesion of pyramidal tracts involving also the extrapyramical fibres (which remain intermingled) at the level of the internal capsule gives rise to paralysis of the opposite side of the body.

This is called hemiplegia. The muscles remain flaccid and reflexes cannot be elicited. Voluntary movements of the upper and lower limbs cannot be performed. This is the stage of shock. The shock stage usually passes away and the tone of the muscles of the paralysed limbs increases and the muscles become spastic. Superficial reflexes, viz. abdominal, cremasteric, etc. are lost on the affected side and plantar reflexes become extensor, i.e. Babinski response. The deep reflexes, viz. knee jerk, ankle jerk, etc. are exaggerated. Ankle clonus may be present.

Corticobulbar (Corticonuclear) Tracts (Fig. 94.20)

These tracts originated from the cells in the inferior portion of the precentral gyrus and the caudal part of the inferior frontal gyri pass through genu of the internal capsule (Fig. 94.14) and are largely distributed bilaterally to the intercalated neurons in the reticular formation. These intercalated neurons then in turn project abundantly into the motor cranial nerve nuclei. Golgi studies of the intrinsic organisation of the reticular formation have indicated the presence of such connection between the intercalated neurons and the cranial nerve nuclei. Kypers (1958) has indicated that in man some corticofugal fibres pass directly to the motor trigeminal, facial, and hypoglossal and also supraspinal nuclei.

Functions

1. The corticobulbar tracts are essentially meant for volitional control of the muscles of the larynx, palate, upper and lower face, jaw, eye, etc.

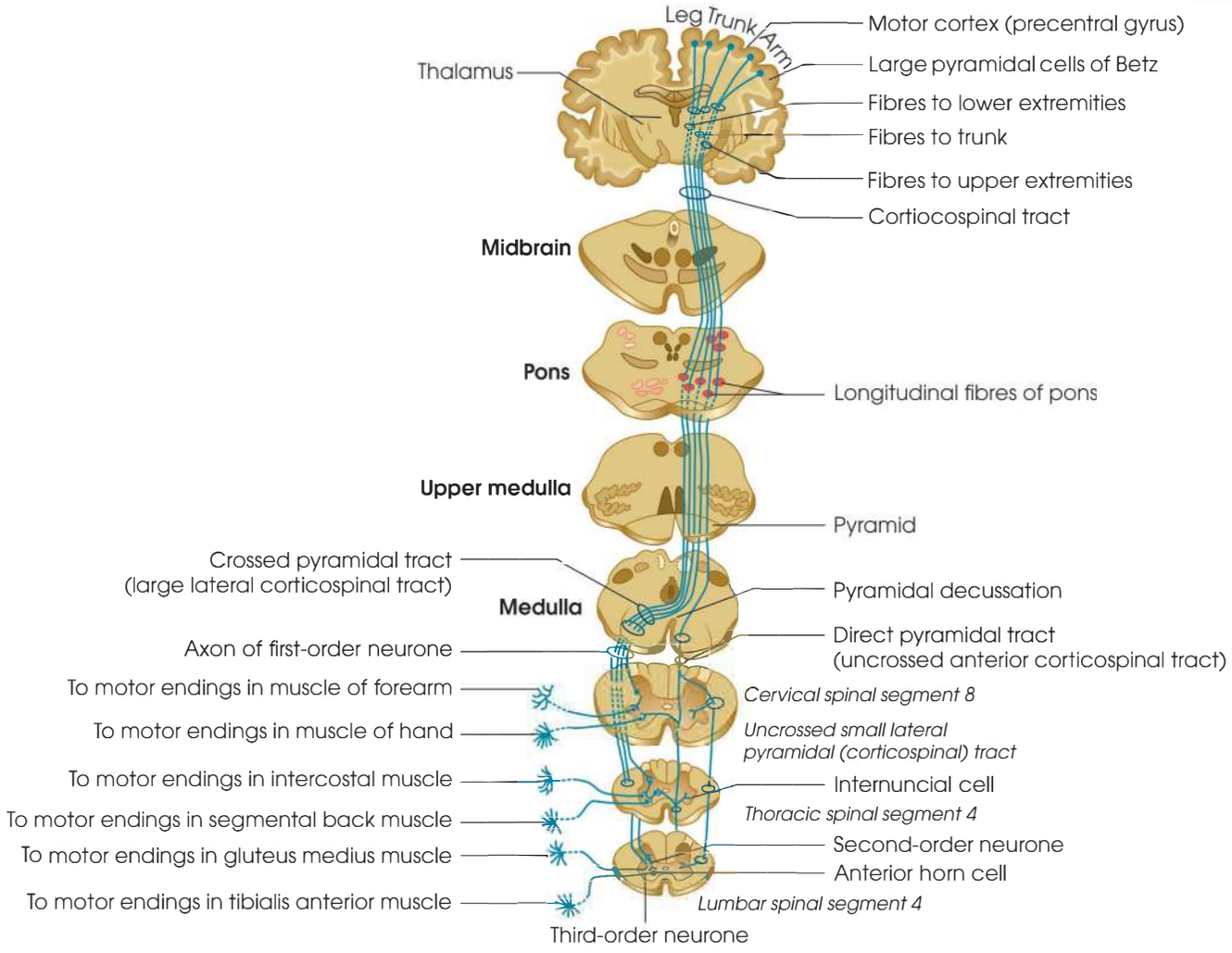


Fig. 94.19: Diagrammatic representation of crossed pyramidal tract (large lateral corticospinal tract), direct pyramidal tract (uncrossed anterior corticospinal tract) uncrossed small lateral pyramidal (corticospinal) tract, but crossed pyramidal tract of the opposite side is not shown

2. Pseudobulbar palsy is a condition, resulting paralysis or weakness of the muscles which control swallowing, talking and movements of the tongue and lips due to bilateral lesions of the corticobulbar tracts.

Extrapyramidal Tracts

Extrapyramidal tracts are those motor pathways which may act as the alternative route for volitional impulses and which form the platform on which the pyramidal system works skillfully.

With this conception of the extrapyramidal system, it is expected that all tracts belonging to this system must be connected, directly or indirectly, with the corpus striatum or cerebrum or both. It is integrated at various levels all the ways from the cerebral cortex to the spinal cord. When the neural pathway is interrupted, the integrated activities below the section are disturbed or released from the control of higher brain centres. The cortical regions controlling these tracts are the areas 8 and 6 specially the latter (extrapyramidal area). Since these areas exchange fibres with area 4 (pyramidal area), they seem to work in perfect co-ordination. The following tracts are believed to satisfy this condition and, therefore, belong to this system (Fig. 94.21).

Rubrospinal Tract (Monakow's Bundle, Prepyramidal Tract)

It is a relatively small bundle of fibres arising from the nucleus magnocellularis of the red nucleus crosses immediately to the opposite side (Forel's decussation) ventral to the sylvian aqueduct. While descending down through the brain stem, some fibres of this tract end in the cerebellum and a moderate number also project to the lateral reticular nuclei of the medulla. This tract is not extended below the thoracic segment of the spinal cord in man. Cervical cord receives maximum number of fibres. It lies dorsally in pons, ventrally in medulla, enters the lateral white column of the spinal

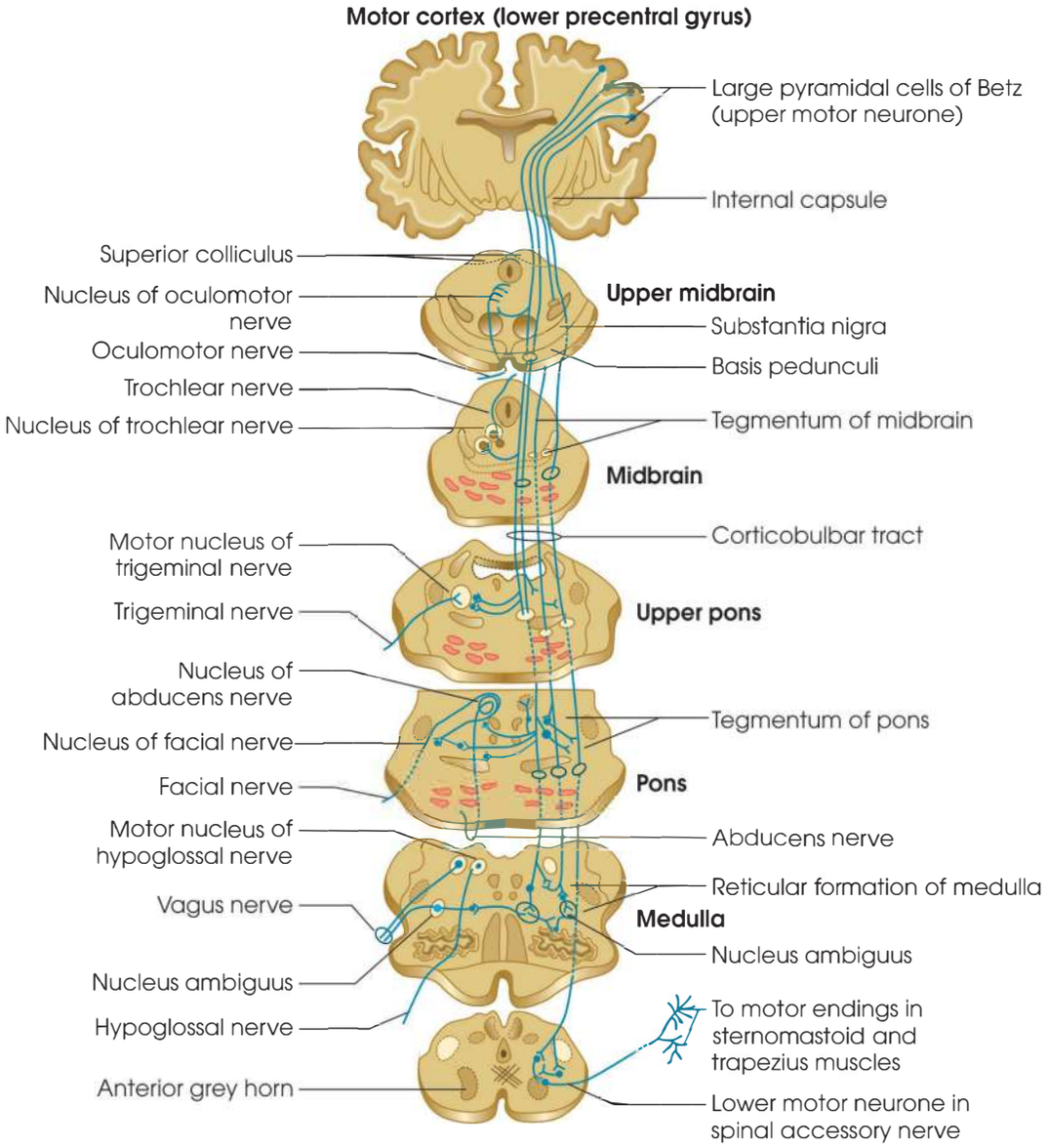


Fig. 94.20: Diagrammatic representation of corticobulbar tract showing the connection with the different motor nuclei of cranial nerves through intercalated neurones in the reticular formation

cord in front of the crossed pyramidal tract and ends largely upon internuncial neurons in the intermediate zone at the base of the anterior horn cells (Fig. 94.23).

Functions

The red nucleus and rubrospinal tracts have got facilitatory influence over flexor muscle tone.

Tectospinal Tract and Tectobulbar Tract

These two tracts are originated from the deeper layers of the superior colliculus and cross at once (decussation of Meynert) ventral to central aqueduct. At the medullary level the fibres of the tectospinal tract descend in the medial longitudinal fasciculus as far as lower cervical segments and terminate upon the internuncial and anterior horn cells (Fig. 94.24).

Functions

The tectospinal tract conveys impulses subserving reflex postural movements in response to visual and auditory stimuli. The tectobulbar tract is distributed to the mesencephalic reticular formation bilaterally and to the contralateral pontine and medullary reticular formation.

Reticulospinal Tracts

These tracts are originated from the neurons of the pontine and medullary reticular formation and descend in the anterior and anterolateral portions of the spinal cord. Fibres from the pontine reticular formation, mainly crossed, are originated from the nuclei of reticularis pontis oralis and of reticularis pontis caudalis, and descend chiefly in the medial part of the

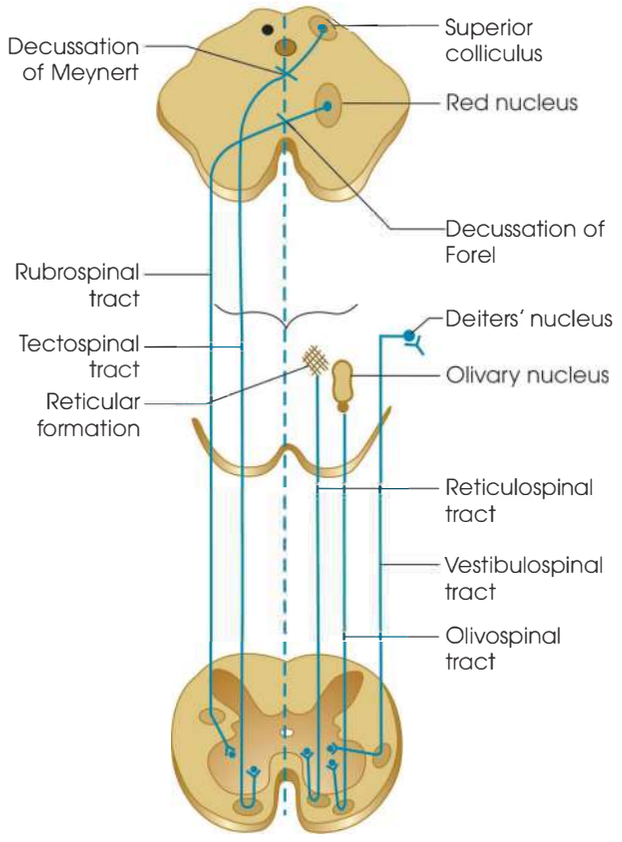


Fig. 94.21: Composite diagrammatic representation of extrapyramidal tracts (simplified)

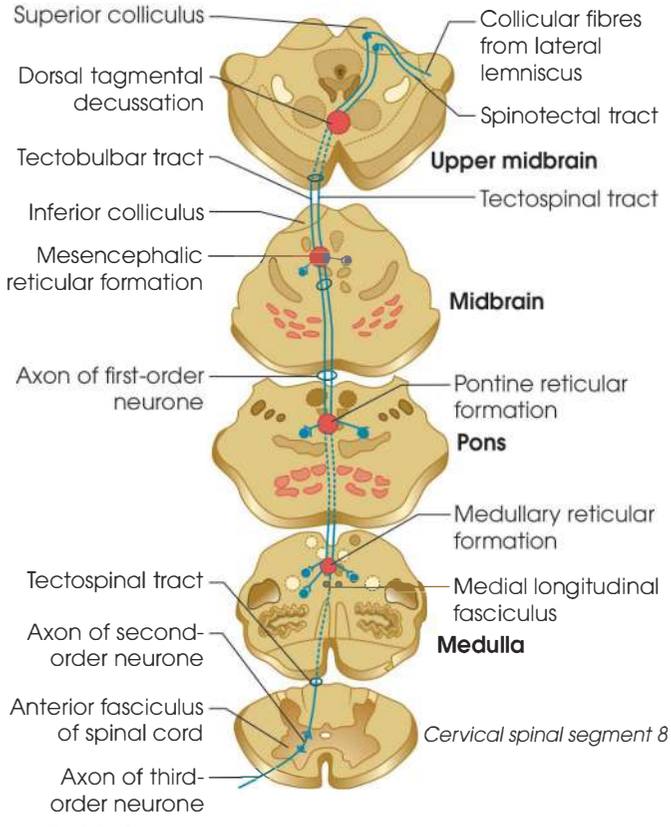


Fig. 94.22: Diagrammatic representation of rubrospinal tract and rubroreticular fibres

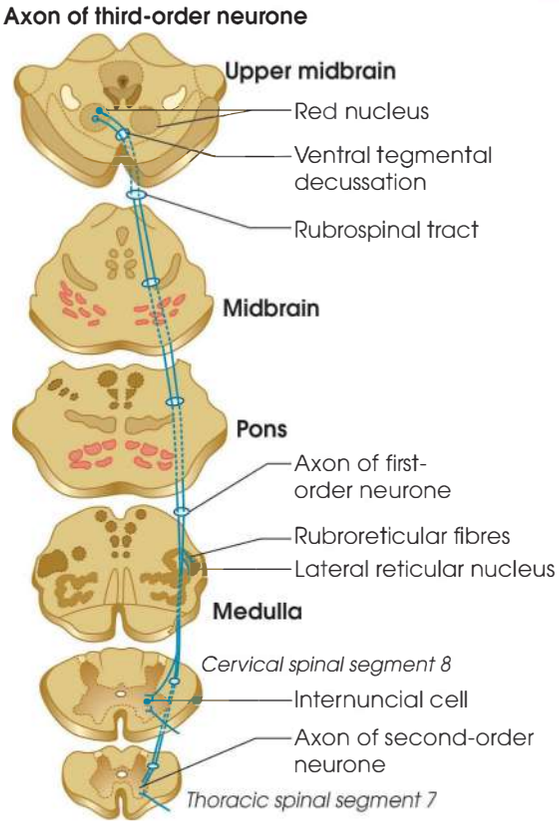


Fig. 94.23: Diagrammatic representation of tectobulbar tract and tectospinal tract showing separate locations of reticular formation

anterior funiculus of the spinal cord and for this reason these fibres are also known as medial reticulospinal fibres (Fig. 94.24).

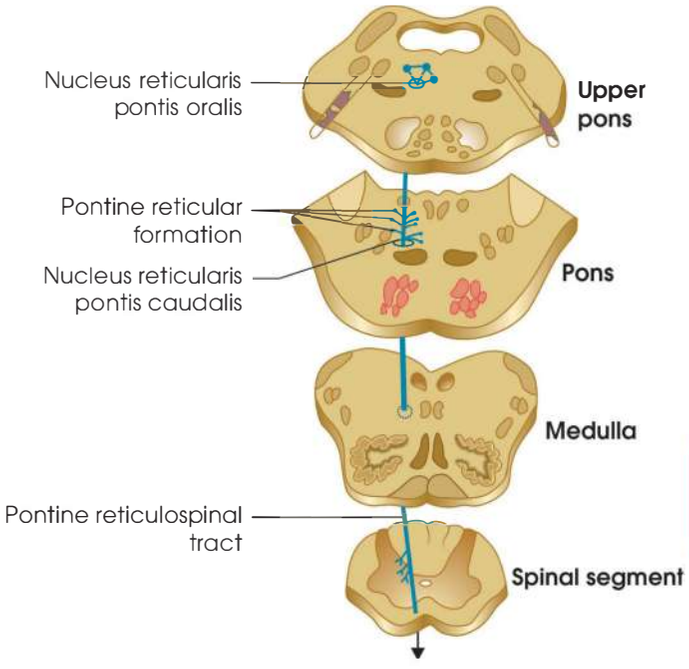


Fig. 94.24: Diagrammatic representation of pontine reticulospinal tract (medial reticulospinal fibres)

Medullary reticular fibres, mostly uncrossed, are originated from the nucleus reticularis gigantocellularis and descend primarily in the anterior part of the lateral funiculus. Most of the axons of these tracts terminate upon the internuncial neurons (internuncial neurons travel between segments, sending projections up to the brain stem and cerebellum) of the anterior horn of the spinal cord and hence these fibres are also known as lateral reticulospinal fibres (Fig. 94.25).

Functions

Stimulation of the brain stem reticular formation can facilitate or inhibit voluntary movement.

1. Alter muscle tone.
2. Respiration is modified.
3. Blood pressure is altered.
4. Central transmission of sensory impulses is altered.

It has been observed that nucleus reticularis gigantocellularis (with the exception of its most rostral part) constituting the medullary reticular fibres is related to inhibition. Stimulation of the nucleus reticularis gigantocellularis produces inhibition of exaggerated extensor muscle tone in decerebrate animals. On the other hand, the nucleus of medullary reticular fibres has got exaggerated effect on the extensor muscle tone in the decerebrate animals as the suppressor area (4S) of the cerebral cortex fails to inhibit the motor activities of this nucleus. Recent studies have claimed that medullary reticulospinal tract influences the spinal cord—motor neuron whose axons terminate in the motor end-plate of the intrafusal fibres of the muscle spindle.

Normally the area 4S (suppressor area) inhibits the motor activities of the nucleus of the medullary reticulospinal tract. Other effects of stimulation of these neclei produce deep inspiration and depression of blood pressure.

The nucleus reticularis pontis caudalis and nucleus reticularis pontis oralis constituting the pontine reticulospinal tract and also the dorsal nucleus of the reticularis gigantocellularis of the medulla are concerned with facilitation. The stimulation of these nuclei facilitates voluntary movement, expiration and also increases pressor (vasomotor) effects.

Vestibulospinal Tracts

The lateral vestibulospinal tract is originated from the lateral vestibular nucleus (Deiters' nucleus) of the medulla of both sides. This nucleus also receives fibres from the vestibular division of the eighth cranial nerve and also from the cerebellum. This tract descends the entire length of the spinal cord and ends in the medial part of the anterior horn cells of the grey matter (Fig. 94.26). This tract does not descend in the medial longitudinal fasciculus.

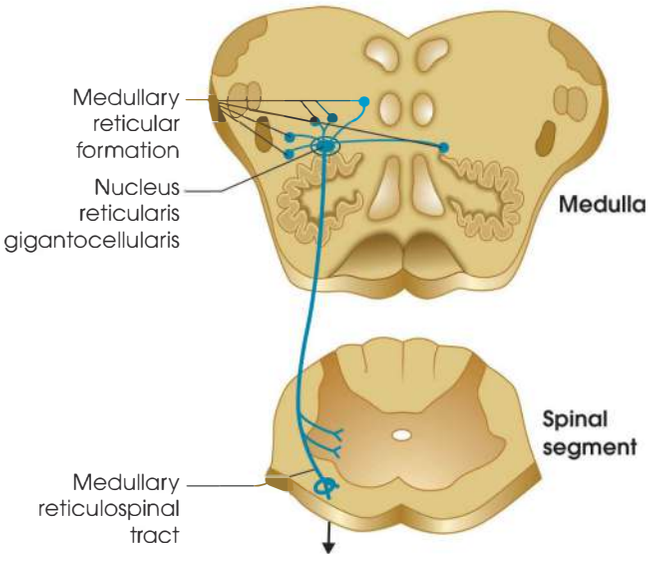


Fig. 94.25: Diagrammatic representation of medullary reticulospinal tract (lateral reticulospinal fibres)

The medial vestibulospinal tract: A small number of fibres, crossed and uncrossed, originated from the medial and probably from the inferior vestibular nucleus also, descend in the medial longitudinal fasiculus up to upper thoracic spinal segment and enter the sulcomarginal area of the anterior funiculus (Fig. 94.27). The superior olivary nucleus does not give any fibres to the spinal cord. It is claimed that this descending tract may project some fibres to the lower brain stem reticular formation. Besides these, this tract may give fibres to the visceral motor nuclei, such as dorsal motor nucleus of vagus, autonomic cell groups and secretory nuclei.

Functions

Lateral vestibular tract exerts facilitatory influences on reflex spinal activities and also spinal mechanism underlying the muscle tone. Electrical stimulation of the lateral vestibular nucleus produces increased extensor muscle tone of the forelimbs or hindlimbs. Cerebellar influence on muscle tone and posture is exerted through the mediation of the vestibulospinal tract.

Medial vestibulospinal tract is concerned with different, reflex phenomena such as nausea, vomiting, vasomotor reactions, palpitation, perspiration, facial pallor, etc. It also appears to be concerned with conjugate horizontal eye movements and integration of eye and neck movements.

Olivospinal Tract (Bulbospinal Tract or Tract of Helweg)

It possibly arises from the inferior olivary nucleus, enters the anterior part of the lateral white column and ends round the anterior horn cells. The existence of this tract is doubtful. It is found in the cervical region only.

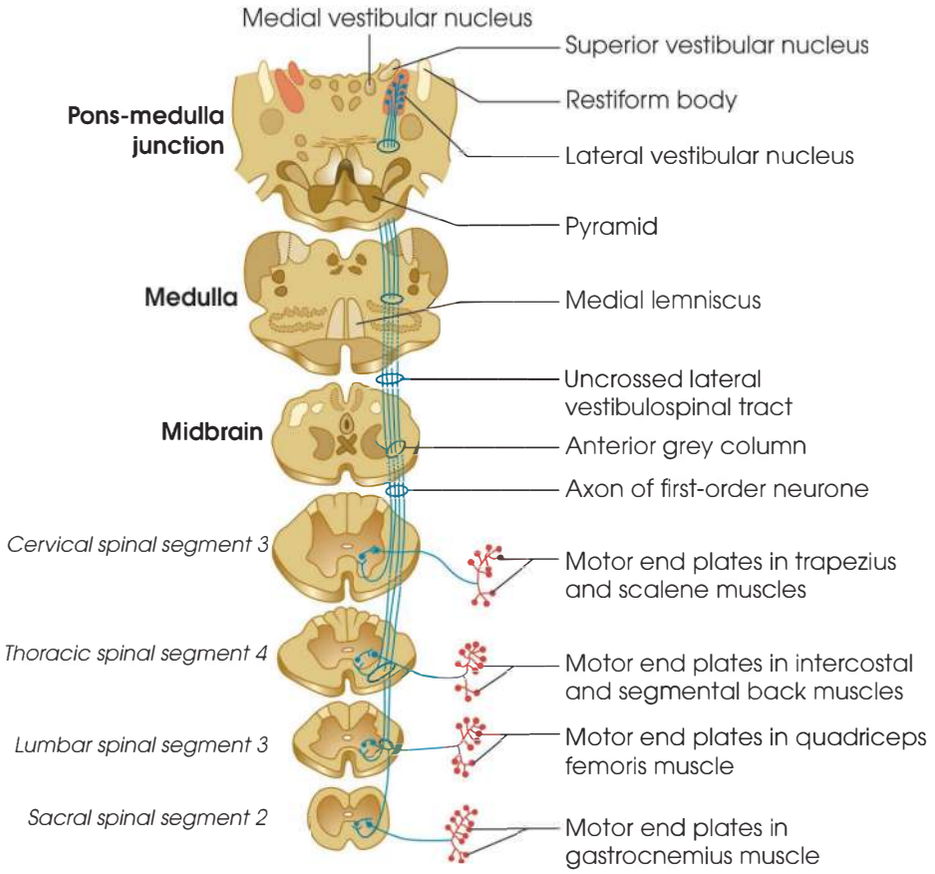


Fig. 94.26: Diagrammatic representation of uncrossed (direct) lateral vestibulospinal tract

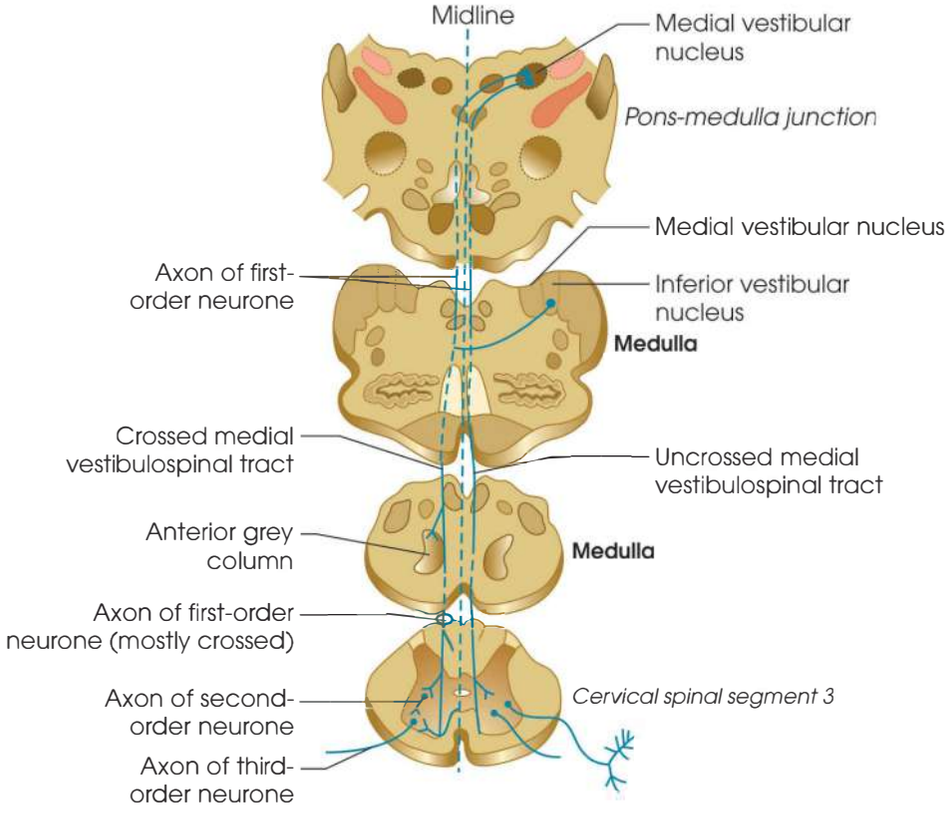


Fig. 94.27: Diagrammatic representation of crossed (indirect) and uncrossed (direct) medial vestibulospinal tracts

Function

The function of this tract is unknown. Since cortex communicates with the thalamus and the latter with olivary nucleus, this tract possibly constitutes an important pathway through which impulses from cortex and thalamus may reach the spinal cord.

Descending Medial Longitudinal Fasciculus

The medial longitudinal fasciculus is originated from the medial vestibular nucleus, reticular formation, superior colliculus and the interstitial nucleus of Cajal. This bundle descends in the posterior part of the anterior funiculus of the spinal cord. This bundle is well defined only in the upper cervical segments of the spinal cord. Below these levels, this bundle is not so well defined but a few fibres have also been traced to lumbar level.

Functions

Main functions of medial longitudinal fasciculus are the co-ordination of reflex ocular movements and integration of eye and neck movements.

Functions of Extrapyramidal Tracts

1. Corticonuclear (corticobulbar) fibres control the movements of the eyeballs.
2. All the other tracts are collectively responsible for tone, posture and equilibrium. (Rubrospinal tract-mainly tone and posture; Tectospinal—visuospinal reflexes; Vestibulospinal—equilibrium.)
3. They control complex movements of the body and limbs (automatic associated acts), such as co-ordinated movements of arms and legs during walking.
4. The cortex exerts tonic inhibitory control over the lower centres through these tracts. Damage to these tracts or ablation of area 6 causes increased rigidity of the muscles (release phenomenon).
5. When pyramidal tracts are damaged, the extra-pyramidal tracts may carry the volitional impulses to some extent.

INTERSEGMENTAL FIBRES (BOTH ASCENDING AND DESCENDING FIBRES)

These fibres are present for making connecting links among spinal segments at different levels. These fibres arising from the nerve cells of the grey matter of one segment descend or ascend at different levels and ultimately end around the cells of the same or of the opposite side. Such intersegmental fibres are:

1. Ground bundle of anterior column or funiculus (anterior intersegmental or sulcomarginal fasciculus).
2. Ground bundle of lateral column or funiculus (lateral intersegmental fasciculus).
3. Posterior column or funiculus consists of:
   - Posterior intersegmental fasciculus (posterior ground bundle).
   - Septomarginal fasciculus:
     a. Posterior septomarginal fibres
     b. Dorsal peripheral strand
     c. Oval bundle of Flechsig
     d. Triangular area of Philippe-Gombault.
4. Ground bundle of anterior funiculus (anterior intersegmental or sulcomarginal fasciculus). This ground bundle connects the anterior horn cells of one side with those of the opposite side or of the same side at different levels of the spinal cord.
5. Ground bundle of lateral funiculus (lateral intersegmental fasciculus). These fibres originating from the lateral horn cells ascend upwards into the medial longitudinal fasciculus.
6. Posterior column or funiculus is:

   Posterior intersegmental fasciculus (posterior ground bundle): These fibres originating from the posterior horn cells connect different segments of the spinal cord.

   Septomarginal fasciculus: This fasciculus includes:

   1. The intersegmental fibres originating from the posterior horn cells connect with the corresponding.
   2. posterior horn cells at lower levels.
   3. The descending fibres of the medial division of posterior nerve roots.
   4. The septomarginal fibres present in the cervical and upper thoracic regions are commonly described as posterior septomarginal fibres or comma tract of Schultze.
   5. The septomarginal fibres at lower thoracic regions are known as dorsal peripheral strand.
   6. The fibres of the septomarginal fasciculus at lumbar segments are known as oval bundle of Flechsig (fasciculus septomarginalis).
   7. The fibres of the septomarginal fasciculus in sacral segments lying against the posterior region of the median septum are called triangular area of Philippe-Gombault.

EFFECTS OF SECTION OF THE ANTERIOR ROOT

Degenerative Changes

a. Degeneration of peripheral portion.
b. Degeneration of white rami communicantes up to the sympathetic ganglion.
c. Chromatolysis of the anterior and lateral horn cells.

Functional Changes

a. Flaccid paralysis (lower motor neuron type) of the affected muscles
b. Loss of reflexes
c. Muscular wasting
d. Reaction of degeneration—present
e. Sympathetic paralysis.

EFFECTS OF SECTION OF THE POSTERIOR ROOT

Degenerative Changes

If distal to the ganglion
a. Degeneration of the peripheral fibres up to the receptor organs.
b. Degeneration of the fibres of recurrent sensibility.
c. Degeneration of the antidromic vasodilator fibres.
d. Chromatolysis of the ganglion cells.

If proximal to the ganglion:
1. Degeneration of the tracts of Goll, Burdach and Lissauer. Comma (descending) tract up to the next neurone.
2. Chromatolysis of the ganglion cells.

Functional Changes

1. Loss of all sensations
2. Incoordinated movements of the muscles due to loss of kinaesthetic sensations
3. Loss of muscle tone and reflexes
4. Trophic ulcers (due to loss of sensations)
5. Vasomotor disturbances due to degeneration of the antidromic vasodilator fibres.

EFFECTS OF SECTION OF THE MIXED SPINAL NERVE

Degenerative Changes

1. Degeneration of the peripheral fibres (somatic and autonomic)
2. Chromatolysis of the ganglion cells, anterior horn cells, and lateral horn cells.

Functional Changes

1. Loss of all sensations
2. Complete paralysis of the lower motoneurone type
3. Trophic ulcers
4. Reaction of degeneration—present
5. Sympathetic paralysis and vasodilatation due to section of white rami communicantes of the sympathetic ganglion
6. Paralysis of sweat glands and pilomotor nerves
7. Vasodilatation followed by vasoconstriction
8. Loss of reflexes

Hemisection of the Spinal Cord

The term 'hemisection' is technically used to indicate a lesion involving one lateral half of the spinal cord. If it is due to an injury, a stage of spinal shock first appears, during which the subject may become unconscious, the muscles are all flaccid and reflexes abolished. In case the patient survives, this stage gradually passes off and typical features of the lesion gradually develop. These features are very helpful in locating the site of injury. The typical features of spinal hemisection (Fig. 94.28) are as follows:

- Red—crossed and direct pyramidal tracts.
- Black—tracts of Goll and Burdach, and spinothalamic tract.

Degenerative Changes

1. The peripheral parts of the cut fibres degenerate up to the next neuron.
2. The central parts of the fibres and the related nerve cells may degenerate to a variable extent.
3. There may be transneuronal degeneration.

Functional Changes below to Level of Section

Same side

Sensory Changes

1. Fine touch, tactile localisation, tactile discrimination and kinaesthetic senses are lost. It is caused by damage to the tracts of Goll and Burdach.

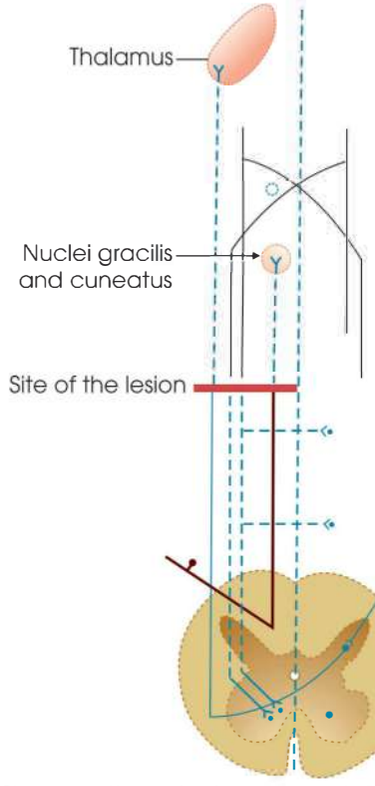


Fig. 94.28: Showing the principal nerve tracts affected in hemisection

2. Pain, temperature and crude touch remain unaffected. Because spinothalamic fibres cross to the opposite side below the level of section and, are therefore, not affected.

Motor Changes

Extensive paralysis of the upper motor neuron type, caused by damage to the crossed pyramidal tracts. Since some fibres of the direct pyramidal tract of the opposite side (which end in the same side) may escape, some muscles on the side of the lesion may not be paralysed.

Upper motor neuron paralysis has the following features:

a. Paralysed muscles are rigid due to increased tone.
b. Deep reflexes—exaggerated.
c. Superficial reflexes—lost.
d. Babinski's sign—positive (Fig. 94.29).
e. Muscles not much wasted.
f. Reaction of degeneration (RD)—absent.

Vasomotor: Temporary loss of vasomotor tone due to damage to the fibres coming down to the lateral horn cells from the vasomotor centre in the medulla. The blood vessels are dilated and the skin may be congested. But later on the intact lateral horn cells will start acting as subsidiary vasomotor centres and the tone returns.

Opposite side

Sensory Changes

a. Complete loss of pain, temperature and crude touch. Caused by injury to the spinothalamic fibres which come from the opposite side and are caught up in the lesion.
b. Kinaesthetic sensations, fine touch, etc. will persist. Because the posterior column tracts of the opposite side are not injured.

Motor Changes

a. Either no paralysis or paralysis of a few muscles only. The latter is due to the possible involvement of some fibres of the direct pyramidal tract of the same side and these fibres cross ultimately to the opposite side. The paralysis will be of upper motor neuron type.
b. Analysing the above findings it will be seen that below the level of section there is extensive sensory loss, but a little motor loss on the opposite side. White on the same side there will be extensive motor loss but a little sensory loss. This phenomenon is known as Brown-Séquard syndrome.

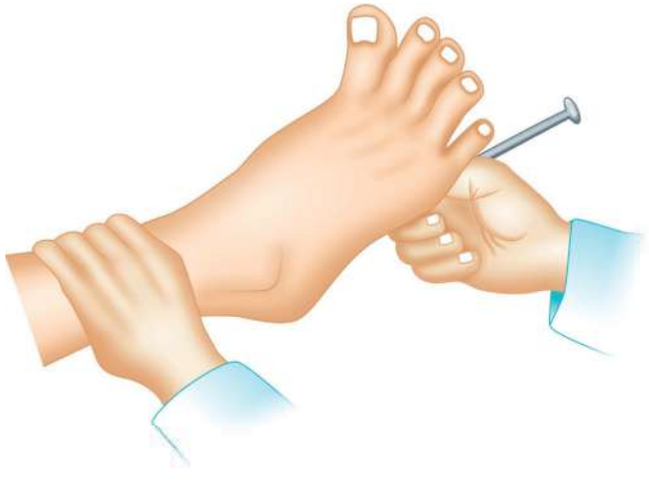


Fig. 94.29: Babinski's sign

Functional Change

At the Level of Section

Same side

Sensory Changes

Complete anaesthesia, because the posterior nerve root, the posterior horn cells and the spinothalamic fibres—crossing to the opposite side—are all lost.

Motor Changes

Complete paralysis of the lower motor neuron type caused by damage to the anterior horn cells.

Lower motor neuron paralysis has the following features:

a. Paralysed muscles are flaccid—due to loss of tone.
b. All reflexes—superficial and deep—are lost.
c. Muscles degenerate and undergo wasting.
d. Reaction of degeneration—present (ACC > CCC).

Vasomotor: Complete and permanent vasomotor paralysis caused by injury to the lateral horn cells.

Opposite side

Sensory Changes

There may be some loss of pain sensation, because the pain fibres of the spinothalamic tract cross horizontally in the same segment and may be caught up in the lesion.

Motor Changes

Nil or very slight: Due to damage to some direct pyramidal fibres of the same side.

Above the Level of Section

Same side: There will be a band of hyperaesthesia, possibly due to irritation of the upper cut ends of the damaged fibres.

Opposite side: Hyperaesthesia may be referred.

Regional Peculiarities of Hemisection of the Spinal Cord at Different Levels

The above description holds good for every case of hemisection, but certain characteristic features will be present according to the particular region involved.

In the Cervical Region

There will be the following three additional features:

a. Constriction of pupil on the same side. Because the pupil-dilating fibres, which come from medulla and pass out through the first, second and third thoracic anterior roots, are involved (same change will take place if the upper three thoracic segments are involved).
b. If the fourth, fifth and sixth cervical spinal roots are involved, there will be loss of biceps, triceps, supinator and pronator jerks.
c. Paralysis of the same side of the diaphragm, due to involvement of the phrenic nerve (4, 5, 6 cervical).

In the Lumbar Region

If it involves the third and fourth lumbar, the additional features will be:

a. Loss of knee jerk.
b. Some disturbance of micturition.

In the Lumbosacral Region

The additional feature will be loss of the sphincter control.

Applied Considerations on Spinal Transections

The motor and sensory changes described above indicate the broad principles of physiological changes that take place in different types of 'transection' of spinal cord. The term incomplete transection is used to indicate a partial lesion involving both sides of the spinal cord. In such cases, some of the extrapyramidal tracts (especially vestibulospinal) escape and thus the brain stem still exert its control over the anterior horn cells. Whatever the type of spinal transection may be, the subject may have the following three stages:

1. Stage of spinal shock
2. Stage of reflex activity
3. Stage of reflex failure.

The first and the third stages are more or less same in both incomplete and complete transections, but remarkable differences are found in the second stage between incomplete and complete transections (Table 94.1). The clinical manifestations of complete transection and its difference with incomplete transection are as follows.

COMPLETE TRANSECTION OF THE SPINAL CORD

Stage of Spinal Shock (Stage of Flaccidity)

A period comes when all spinal reflex responses are depressed in association with or without consciousness depending upon the extensiveness of the damage. Gradually the reflex responses return and become relatively hyperactive. Below the level of section:

1. Muscles are paralysed and flaccid.
2. All reflexes lost.
3. Sphincters are at first paralysed but quickly regain tone causing retention of urine. If above second lumbar, fall of blood pressure due to vasomotor damage.
4. Absence of movements and vascular tone in the paralysed parts reduces circulation causing stagnation. Hence, slight pressure may cause oedema, and nutrition of the limb suffers.
5. Skin becomes cold, blue and liable to bedsores.

Higher the animal, more profound and lasting will be the effect of spinal shock, viz. in cats—a few minutes, in monkey—a few days, and in man—about three weeks; because, in higher animals the spinal cord is more under the influence of higher centres. The phenomenon of spinal shock points out that the whole nervous system works as a single unit. Changes in one part affect the activities of distant regions (diaschisis).

The cause of spinal shock is not known, perhaps related with the cessation of tonic neuronal discharges from the upper brain stem or supraspinal pathways.

Stage of Reflex Activity (Stage of Recovery)

It is associated with reflex excitability. The first reflex response reappeared in man is slight contraction of flexor and adduction to noxious stimuli. The knee jerk often comes back first.

Stage of Reflex Failure

a. The isolated cord has less power of resistance. In case any toxaemia or infection develops, reflex functions gradually fail, viz.
b. The reflexes become more difficult to elicit.
c. The stimulus threshold raised.
d. Mass reflexes abolished.
e. Muscles become flaccid and undergo wasting.
f. Bedsores develop.
g. Cystitis and paralysis of urinary sphincters.
h. Hypercalcaemia leading to hypercalcinuria (hypercalciuria) which predisposes to urinary infection. The termination of such cases takes place through septicaemia, uraemia, inanition, etc.

Incomplete Transection of the Spinal Cord

As mentioned above the manifestations of the first and third stages are same as those of complete transection. But in the second stage (stage of reflex activity) incomplete transection shows certain characteristic features, quite distinct from those of complete transection.

In incomplete transection, some extrapyramidal tracts escape, so that the influence of brain stem on the cord is maintained. But in complete transection the cord below the level of lesion is cut off from the higher centres.

The chief distinctive features of the two types, as seen in the stage of reflex activity (second stage), are noted below.

As commonly seen in civil practice, a slow inflammatory disease of the spine (tubercular) or a tumour will exert gradually increasing compression on the spinal cord producing at first hemisection, then incomplete transection and lastly, complete transection. Hence, the features of one will gradually merge into those of other.

Spinal Animal (Animal with Transection of the Spinal Cord)

The animal will have the same three stages as in man: Stage of spinal shock is less in intensity and duration. A monkey with thoracic cord cut will go on catching flies. In the second stage there will be paraplegia in flexion, and crossed extensor reflex. Extensor thrust reflex will be regularly obtained because the cord has control on the extensor arcs (in man only found in incomplete transection). Spinal animal also shows presence of scratch reflex and mark-time (locomotion) reflex.

EFFECTS OF LESIONS AT VARIOUS LEVELS OF THE CENTRAL NERVOUS SYSTEM (Fig. 94.30)

Massive lesion of cerebral cortex may cause hemiplegia, monoplegia depending upon the extent of damage. If the internal capsule is lesioned then contralateral hemihypoesthesia, and even homonymous hemianopia as well as hemiplegia may occur. Unilateral lesion of midbrain involving the oculomotor (III cranial) nerve may cause, besides contralateral spastic hemiplegia, ptosis of upper eyelid, paralysis of ocular muscle, dilatation of the pupil along with loss of pupillary light reflex. Lesion in pons involving facial (VII cranial) nerve and also the descending motor fibres will cause crossed hemiplegia along with homolateral facial paralysis. Lesion in the medulla oblongata destroying the descending motor tracts and hypoglossal (XII cranial) nerve cause crossed hemiplegia and homolateral paralysis of lingual muscles. Complete transaction of the spinal cord involving all the descending and ascending tracts causes paraplegia.

LEMNISCUS OR FILLET

Definition

Any prominent nerve tract formed by crossed sensory fibres in the central nervous system.

Varieties

There are four fillets:

1. Spinal lemniscus or spinal fillet—same as the spinothalamic tract.
2. Trigeminal lemniscus or trigeminal fillet—formed by the crossed fibres arising from the sensory nuclei of the trigeminal nerve. Carries general senses from head, neck, face, mouth, eyeballs and ears.
3. Lateral lemniscus or lateral fillet—formed by the second neurons in the auditory pathways (*vide* path of hearing).

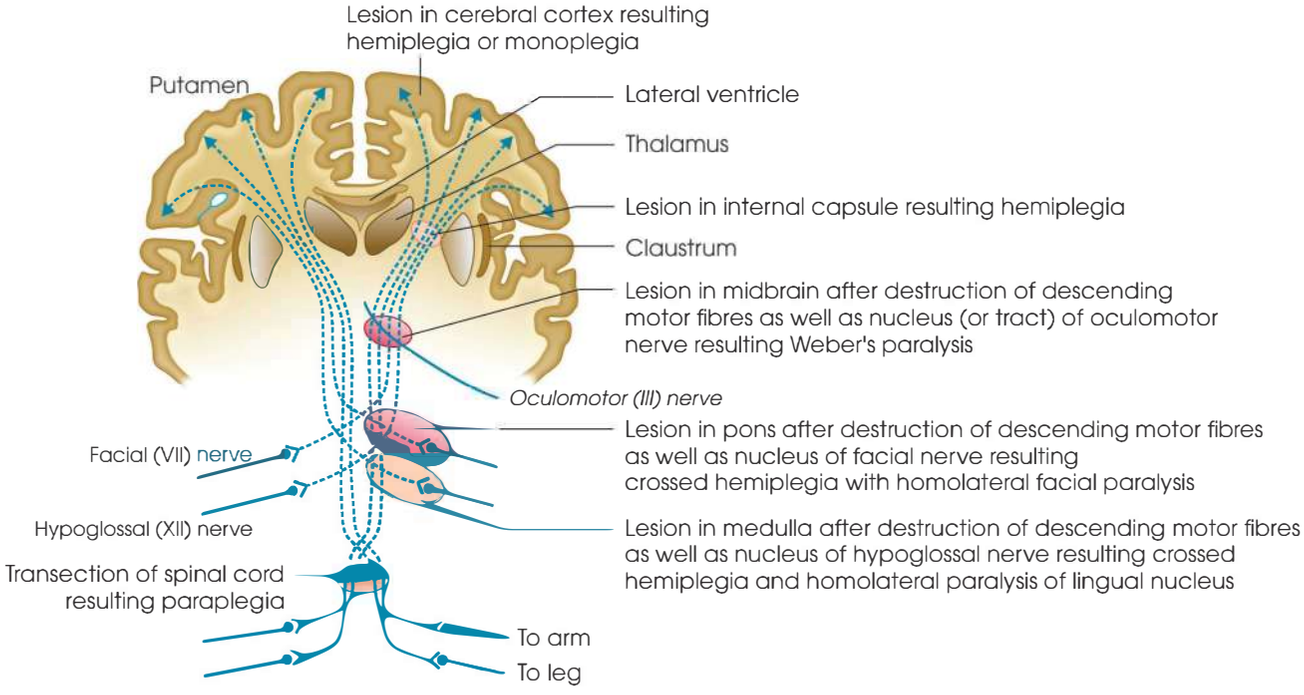


Fig. 94.30: Diagram represents the effects of lesions at various levels of central nervous system

4. Mesial lemniscus or mesial (medial) fillet—formed by:
   a. Spinal lemniscus or spinal fillet
   b. Internal arcuate fibres
   c. Trigeminal lemniscus or trigeminal fillet
   d. Fibres from the sensory nuclei of other cranial nerves, especially seventh (taste), ninth, tenth (respiratory passages) and vestibular impulses. It passes through the midbrain in the tegmentum and ends in the lateral nucleus of the thalamus. Carries general sensations from the whole body, also taste and vestibular impulses. Hence, in the upper part of brain stem, there are only two lemnisci or fillets—lateral and medial. Except the lateral lemniscus of fillet, almost all other sensory fibres merge in the medial lemniscus or fillet.

EXAM-ORIENTED QUESTIONS

Essay

1. Enlist the ascending tract. Discuss the course and functions of dorsal and ventral spinothalamic tract.
2. Enlist the acending tract. Discuss the course and functions of dorsal and ventral spinocerebellar tract.
3. Enlist the descending tracts. Enlist the ascending tract. Discuss the course and functions of pyramidal tracts.
4. Enlist the descending tracts. Enlist the ascending tract. Discuss the course and functions of extrapyramidal tracts.
5. Describe the motor and sensory changes along the site of lesion and below in lesion in hemisection of spinal cord.
6. Describe the motor and sensory changes along the site of lesion and below in lesion in complete section of spinal cord.

Short Notes

1. Tract of Goll (fasciculus gracilis).
2. Tract of Burdach (fasciculus cuneatus).
3. Comma tract of Schultze (tractus interfascicularis).
4. Dorsal spinothalamic tract (lateral spinothalamic tract).
5. Spinotectal tract.
6. Dorsal spinocerebellar tract (Flechsig's tract).
7. Ventral spinocerebelar tract (Gower's tract).
8. Spino-olivary tract.
9. Spinoreticular tract.
10. Spinovestibular tract.
11. Spinopontine tract.
12. Spinocortical tract.
13. Ventral (anterior) spinothalamic tract.
14. Rubrospinal tract.
15. Tectospinal tract and tectobulbar tract
16. Reticulospinal tract.
17. Dorsal vestibulospinal tract.
18. Ventral vestibulospinal tract.
19. Olivospinal tract (bulbospinal tract).
20. Descending medial longitudinal fasciculus.
21. Lemniscus.
22. Crossed pyramidal tract (large lateral corticospinal tract).
23. Direct pyramidal tract (uncrossed anterior corticospinal tract).
24. Uncrossed small lateral pyramidal (corticospinal) tract.
25. Rubrospinal tract.
26. Tectospinal tract and tectobulbar tract.
27. Reticulospinal tract.
28. Vestibulospinal tracts.
29. Olivospinal tract (bulbospinal tract).
30. Descending medial longitudinal fasciculus.

Chapter

95

Brain Stem

INTRODUCTION

The brain stem (Fig. 95.1) frequently includes the midbrain containing the cerebral and cerebellar peduncles, corpora quadrigemina, red nucleus, etc. the medulla oblongata (spinal bulb), and pons varolii.

MIDBRAIN (MESENCEPHALON)

1. The midbrain connects the forebrain with the hindbrain.
2. Its dorsal part includes four rounded eminences, called the corpora quadrigemina (superior and inferior colliculi) which contain important correlation

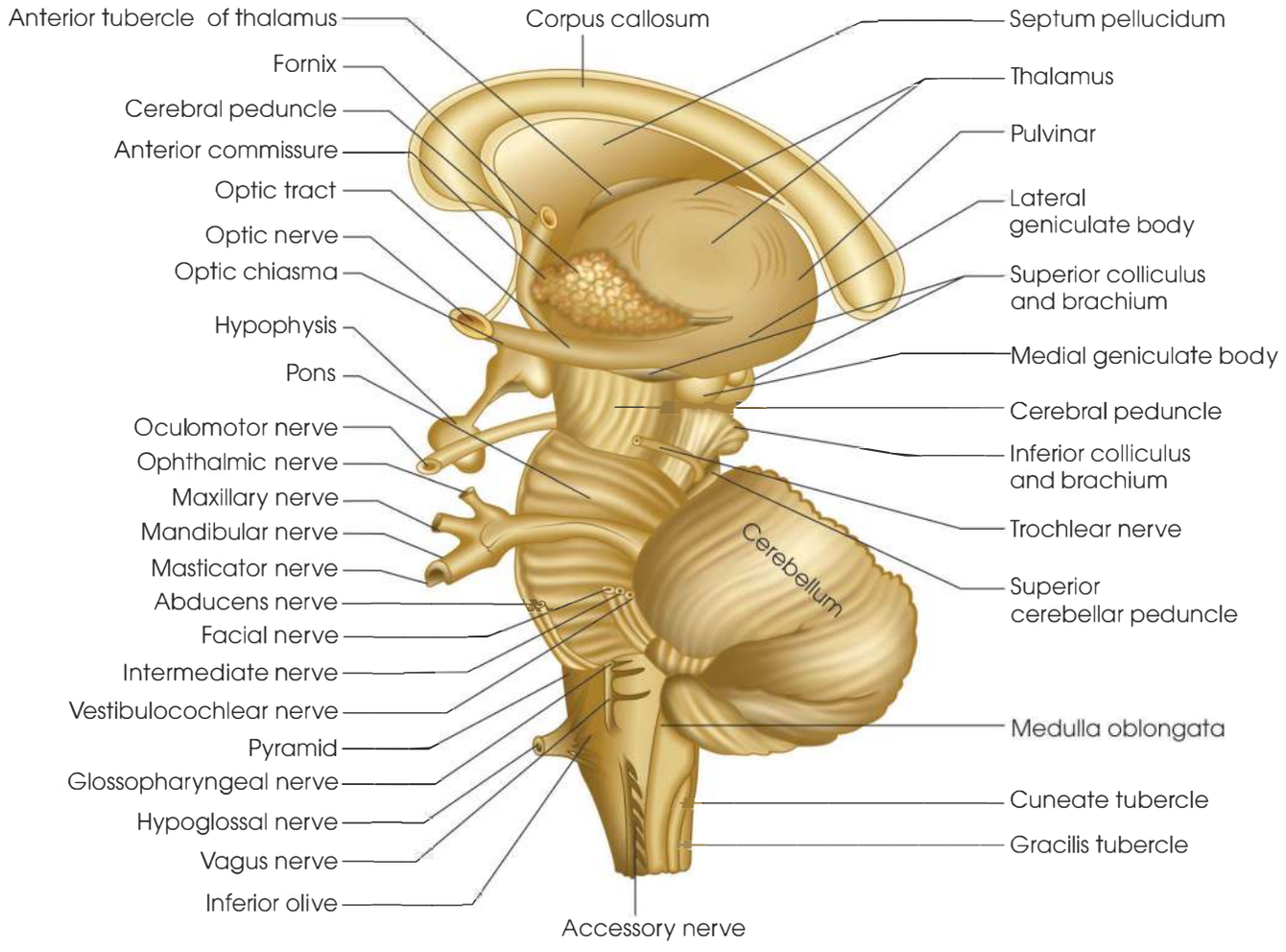


Fig. 95.1: Diagrammatic representation of the lateral view of the brain stem and relationship of attached cranial nerves

centres and also nuclei concerned with motor co-ordination.

3. Its ventral part consists of a pair of cylindrical bodies, called the cerebral peduncles, which are great masses, commonly of white matter, uniting the pons with the thalamic region of the cerebrum.
4. In between the ventral and the dorsal part there is the cerebral aqueduct (aqueduct of Sylvius) which is surrounded ventrally and laterally by the nuclei or origin of the oculomotor nerves (Figs 95.2, 95.3 and 95.5).

From before backwards, the cerebral peduncles consist of the following parts:

Basis pedunculi: They are made up largely of the descending and ascending fibres tracts from the cerebrum above, and the cerebellum medulla and spinal cord below (Fig. 95.4). The pyramidal tracts occupy the middle three-fifths of the basis pedunculi, the frontopontine and corticonuclear fibres occupy the medial one-fifth and the lateral one-fifth is occupied by temporopontine tract.

Substantia nigra: This is the most voluminous mass of deeply pigmented cells, extending the whole length of the midbrain and projecting into the caudal diencephalon. Substantia nigra is regarded as an important extrapyramidal or non-pyramidal nucleus, largely because it is one of the structures of this system that is consistently affected in paralysis agitans. The rigidity and akinesia of the parkinsonian syndrome are caused by lesions involving the substantia nigra. Degenerative changes in this nucleus may impair semiautomatic associative movements which normally accompany voluntary movements, such as swinging of the arms during walking.

Tegmentum: The narrow aqueduct, somewhat triangular in section, is surrounded by a broad layer of central grey matter that is poor in myelinated fibres,

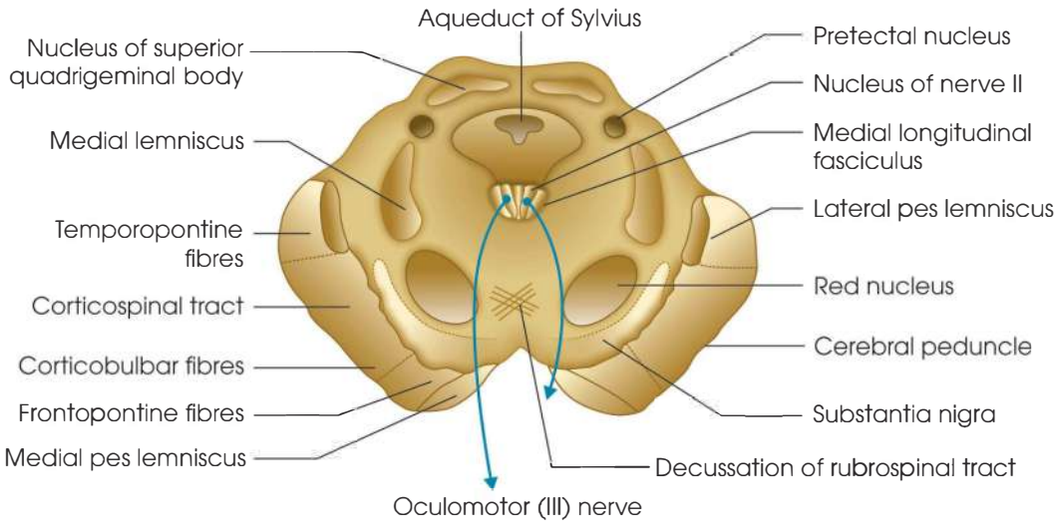


Fig. 95.2: Schematic transverse section through upper part of the midbrain. The pretectal nucleus is actually rostral to the plane of the section. The reticular formation occupies the space between the substantia nigra and central grey matter

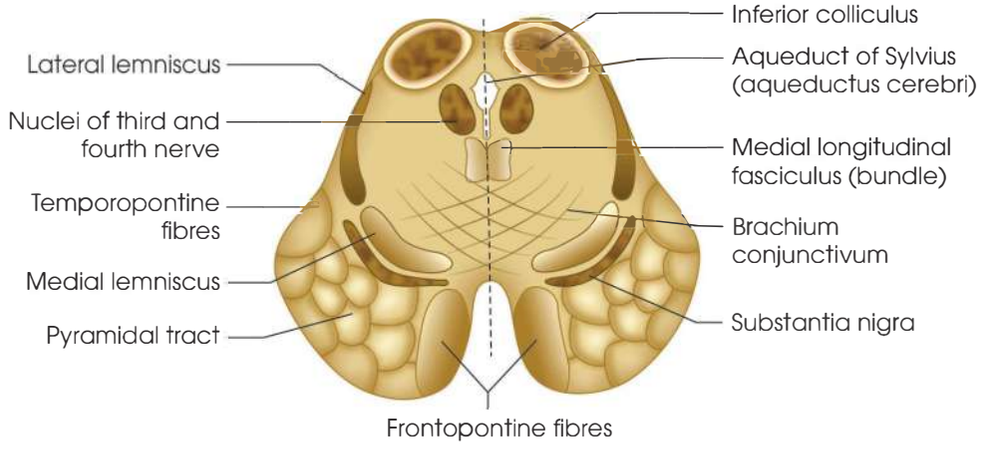


Fig. 95.3: Showing a section through the midbrain at the level of inferior colliculus

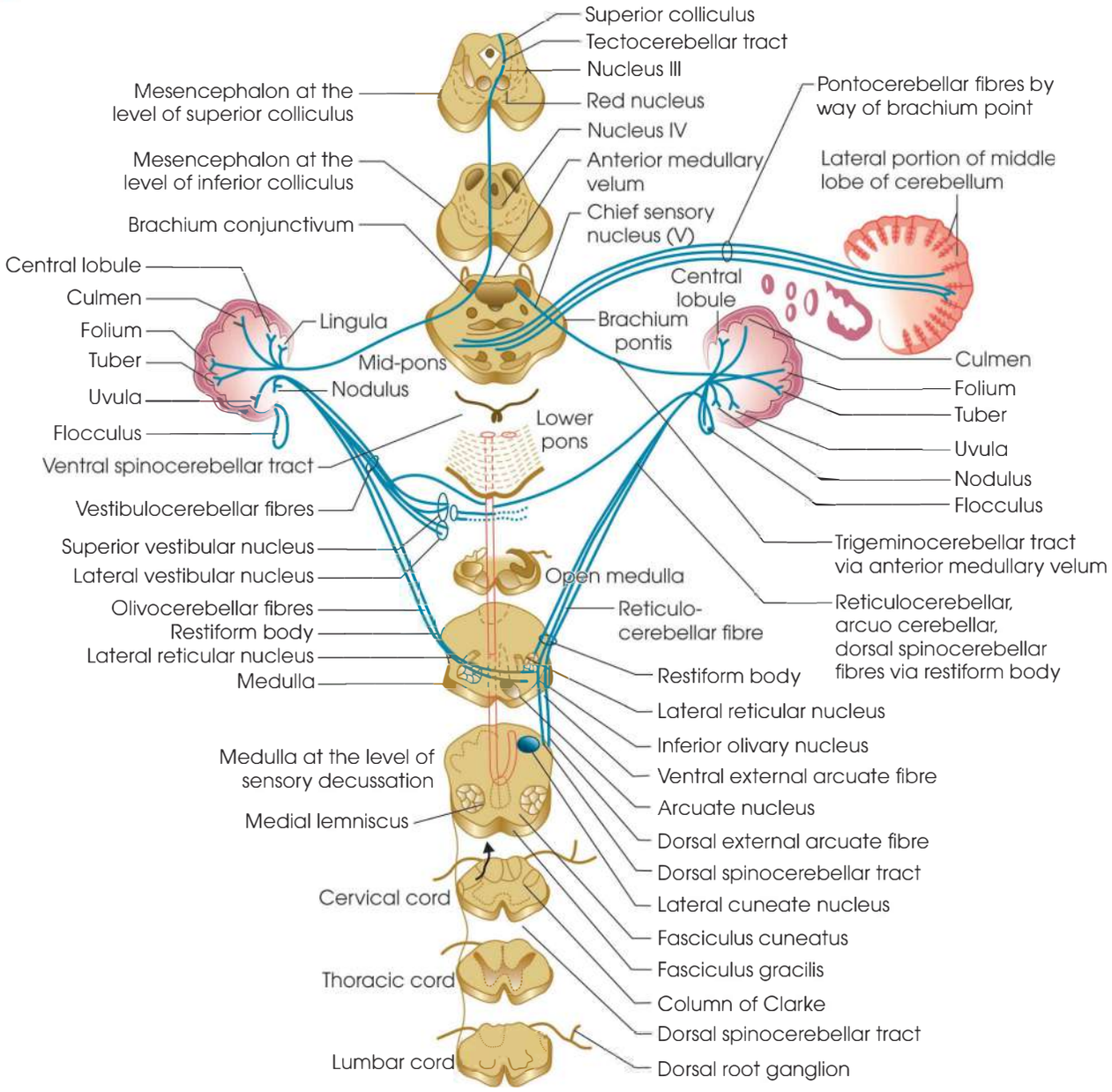


Fig. 95.4: Diagrammatic representation of afferent fibres of the cerebellum from the midbrain, pons, medulla and spinal cord

and contains numerous diffusely grouped cells. From below upwards, three decussations take place within it which have dentatothalamic fibres, the rubroreticulospinal tracts and the tectospinal tracts.

RED NUCLEUS

It is a large oval mass of grey matter in the tegmentum of midbrain lying below the thalamus. The colour of the red nucleus is due to the presence of a reddish-brown lipochrome. Phylogenetically, it consists of an old part with large cells (nucleus magnocellularis) and a new part with small cells (nucleus parvocellularis). From the old part, the motor fibres arise; while the new part receives all the afferent fibres.

Connections (Fig. 95.5)

Efferent

1. To globus pallidus: Rubrostriatal.
2. To lateral nucleus of thalamus: Rubrothalamic.
3. To inferior olivary nucleus: Rubro-olivary (not shown).
4. To formatio reticularis of pons and medulla.
5. To motor nuclei of cranial nerves: Rubrobulbar.
6. To spinal cord: Rubrospinal tract.

Afferent

1. From motor cortex (areas 4 and 6): Corticorubral.
2. From globus pallidus of the same side: Pallidorubral tract.

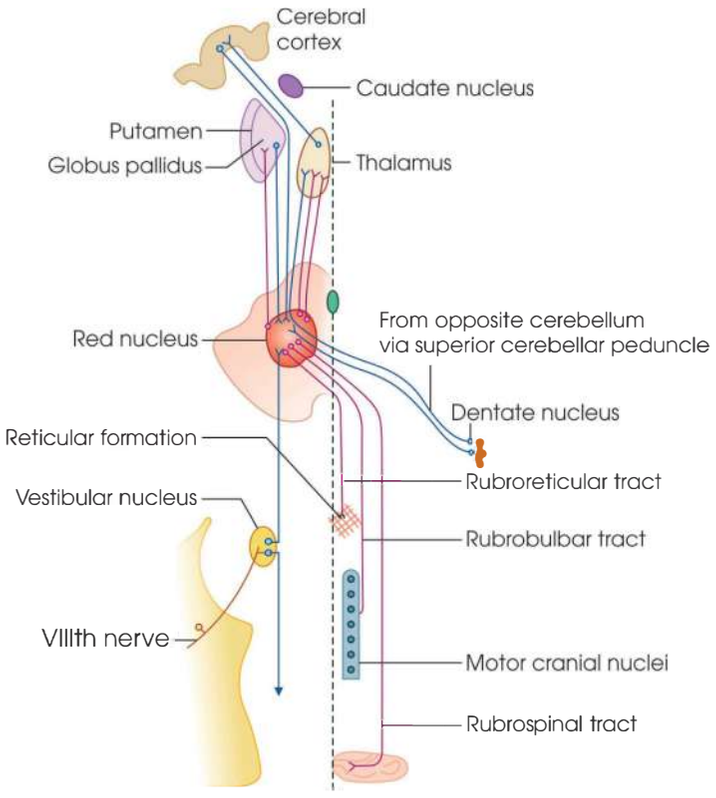


Fig. 95.5: Connections of corpus striatum. Red—efferent; Black—afferent; Red (dotted)—intrastriatal

3. From vestibular nucleus of the same side—through posterior longitudinal bundle.
4. From cerebellum of opposite side—arise from dentate nucleus of opposite cerebellar hemisphere, pass through superior cerebellar peduncle and enter the red nucleus. Some fibres actually end in it (dentatorubral tract). Others pass through it to the thalamus without having any synaptic connection in the red nucleus (dentato-rubrothalamic tract). Probably the kinaesthetic impulses from spinal cord carried through Flechsig's and Gowers' tracts are relayed to the red nucleus through these fibres.

Characteristic Features of Red Nucleus

1. The nucleus ruber or red nucleus consists of two groups of cells: Nucleus magnocellularis and nucleus parvocellularis. The former group comprises the caudal one-third of the whole nucleus and is made up of large nerve cells which give rise to the rubrospinal tract.
2. The latter group consists of small nerve cells and comprises the cranial two-thirds of the red nucleus.
3. The red nucleus extends from the hypothalamus to the caudal border of the superior colliculi (Fig. 95.5). In the human being, the large cells are few and the rubrospinal tract is small.
4. A rubroreticular tract arises from most of the cells of the nucleus and ends in the reticular grey matter in the brain stem.
5. From here the impulses are transmitted to the spinal cord through reticulospinal fibres.

Functions of Red Nucleus

a. In small mammals, the red nucleus plays an important role in helping to maintain normal body posture and normal muscle tone by means of its afferents from cerebellum, vestibule and muscle, and from its efferent rubrospinal and rubroreticular fibres. This nucleus is 0.5 cm in diameter and a centre for righting reflex (example cat righting reflex).
b. Red nucleus has sparse control over hands, as the rubrospinal tract is more associated with large muscle movement such as that for arms (but not associated with lower limb since the tract terminates in the superior thoracic region of the spinal cord). The red nucleus plays a role as part of the integrative process in the crawling motion of babies particularly at the developmental stage.
c. The majority of red nucleus axons (via its parvocellular part) relay information from the motor cortex to the cerebellum through the inferior olivary complex of the medulla.
d. It receives afferent fibres from various locations within the diencephalon; these are: Superior colliculi (tectorubral tract), dentate nucleus (dentatorubral tract), cerebral cortex (corticorubral tract) and inner pallidum (pallidorubral tract) and send its axon to spinal cord via corticospinal tract and to olive via

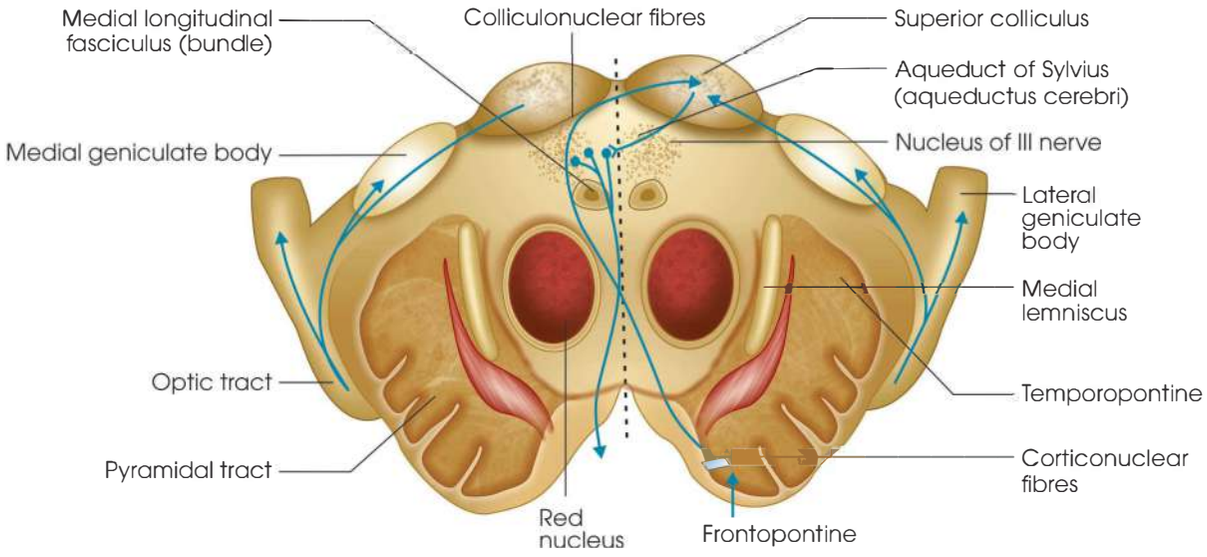


Fig. 95.6: Diagram represents a section through the midbrain at the level of superior colliculus

rubro-olivary fibres and are involved in the coordination of muscle tone, body position and gait.

Superior colliculi: The superior colliculi are responsible for visual reflexes and reflexly alter the position of the trunk, head eyes and limbs in response to retinal impulses by means of the tectospinal tract. This tract connects the superior colliculi with the pupil-dilator centre in the thoracic cord (T1 and T2). Passing to the oculomotor nuclei, colliculonuclear tract produces constriction of the pupil during light reflex.

The oculomotor nerve (III) arises from a nucleus in the floor of the cerebral aqueduct. The fibres of the motor root of the trigeminal arise from two nuclei, a superior, located in the cerebral aqueduct, and an inferior, located in the upper part of the pons. It is debatable whether the fibres from the superior nucleus are afferent or efferent.

PONS VAROLII

Anatomy

1. It is a thickening located above the medulla oblongata. It appears anteriorly as a bulging mass of transverse fibres and is separated from the cerebellum posteriorly by the IV ventricles.
2. The prominent internal feature of the pons is the presence of transversely crossing bundles of the brachium pontis (middle cerebellar peduncle). These bundles run from the pons to the opposite cerebellar hemisphere and vice versa, and break up the pyramidal tract into scattered groups of fibres where the nucleus pontis lies with small masses of grey substance.
3. The medial lemniscus is connected by central fibres from the sensory nuclei of V, VII, IX and X nerves (Figs 95.7 and 95.8) to pons.
4. In transverse section, two main portions in pons are visualised. The posterior or tegmental portion represents the cranial continuation of the reticular formation of the medulla. Within this tegmental portion the motor and sensory nuclei of cranial nerves (V, VI, VII and VIII) are present.
5. The larger anterior or basilar portion of the pons is the transverse pontine fibres, pontine nuclei, and descending fibre bundle of the corticobulbar and corticospinal tracts. The corticospinal tract forms a compact bundle on each side at the lower end of the pons and forms the pyramid of the medulla.

Function

Pons is primarily concerned with the maintenance of normal rhythm of respiration. Different experimental studies have led to the conclusion that pons has got two separate respiratory centres—the pneumotaxic centre and apneustic centre.

The pneumotaxic centre is situated in the upper pons and is the dominant part. It controls the exaggerated activity of the apneustic centre and thereby produces a rhythmical respiratory activity characteristic of normal respiration. The apneustic centre is under the inhibitory control of both the vagus nerves and the pneumotaxic centre.

MEDULLA OBLONGATA (SPINAL BULB)

Anatomy

1. Medulla is a conically expanded continuation of the cervical spinal cord and is extended from the foramen magnum to the caudal border of the pons. It is approximately 28 mm in length.
2. Its transverse diameter of the foramen magnum is 9–12 mm and near the pons is about 24 mm. Sulci

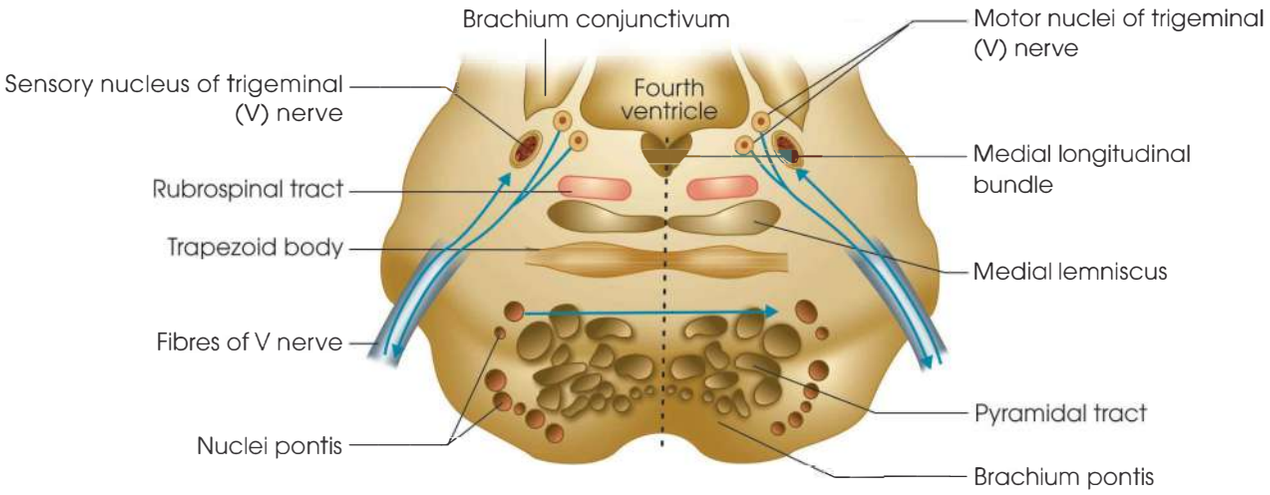


Fig. 95.7: Diagrammatic representation of a section through the upper part of pons varolii

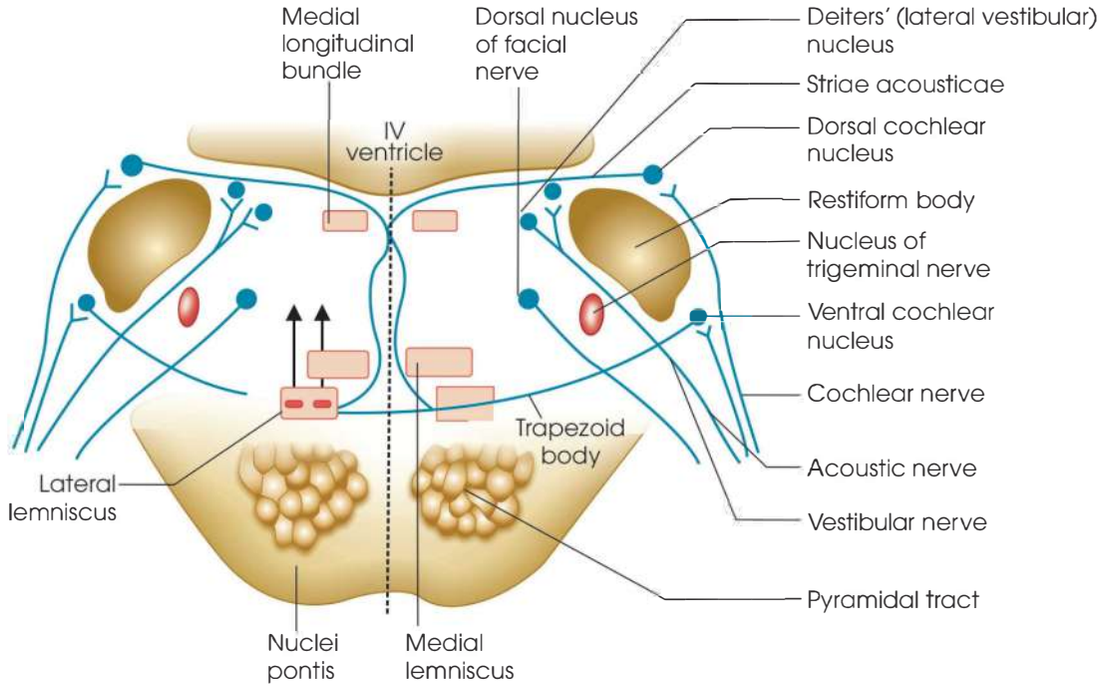


Fig. 95.8: Showing a section through the lower part of pons

which are present on the surface of the spinal cord are also continued upward into the medulla.

3. A section at the level of the lower third of the medulla oblongata shows a decussation of the pyramidal tracts which pass from the ventral part of the medulla through the base of the ventral horn of grey matter. Then the tracts come to lie in the lateral columns where they descend into the spinal cord.
4. The wider dorsal columns push the dorsal horns of grey matter apart from the pons to upper cervical region. On either side of the ventrolateral region there are rubrospinal tract, the spinothalamic tract and the dorsal and ventral spinocerebellar tracts (Fig. 95.9).
5. A section through the olive shows that the central canal approaches the dorsal surface of the medulla oblongata and appears approximately at the calamus scriptorius into the IV ventricle.
6. The funiculus gracilis ending in the nucleus gracilis and the funiculus cuneatus ending in the nucleus coneatus replace the dorsal columns. A new relay station arises from the nuclear cells of the gracilis and cuneatus. Most of the fibres cross internal arcuate fibres to lie dorsal to the pyramid; as medial lemniscus and a certain number of fibres pass the restiform body of both sides (Fig. 95.10).
7. Cardiac, vasomotor, vomiting, deglutition centres, etc. lie in the floor of the IVth ventricle at the level of

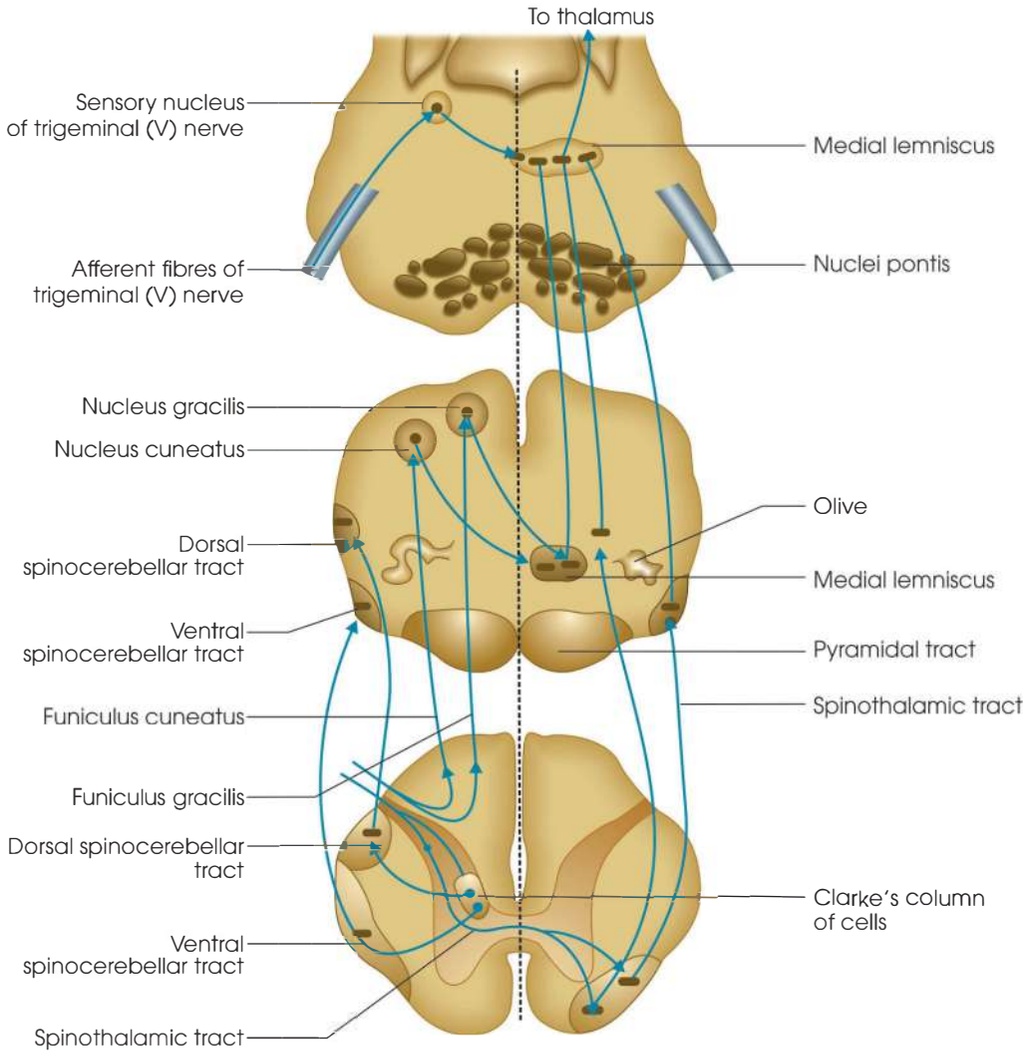


Fig. 95.9: Diagrammatic representation of the course of ascending tracts

the calamus scriptorius and near the dorsal nucleus of the vagus. In the medullary and pontine reticular formation the respiratory centres are situated. The olive contains a wavy layer of grey matter. Though the olivary function is not clear, the olive gives rise to the (descending) bulbospinal tract. The ventral spinothalamic fibres migrate medially lying dorsolaterally to the medial lemniscus and the lateral spinothalamic fibres remain lateral to the olive.

8. Nuclei of the VII IX, X, XI and XII cranial nerves (Figs 95.11 to 95.13) and medulla oblongata.
   a. The motor somatic fibres of the hypoglossal (XII) nerves lie near the midline of the medulla.
   b. The ascending afferent fibres of facial (VII), glossopharyngeal (IX) and vague (X) nerves are situated lateral to the nucleus of XII.
   c. The descending afferent fibres of VII, IX and X nerves, which end in grey matter, lie in (XI) nerves arise from a column of cells which extend from the lower border of pons to C5 and lie lateral and ventral to the column of dorsal nuclei.
   d. Autonomic efferent fibres of VII, IX and X arise in the column of the dorsal nuclei.
   e. The vestibular division of the VIII nerve ends in the vestibular nuclei (Fig. 95.11).

Function of Medulla Oblongata

1. *Control of Cardiovascular Function*

The integrity of medullary structures is essential for the maintenance of normal cardiovascular tone. Medulla is responsible for maintaining the vasoconstrictor tone.

A depressor area is localised to the medial reticular formation and extends chiefly into the caudal end of the bulb. Pressor area exhibits continuous accelerator tonic discharge in the inferior cardiac nerves. Similarly, the depressor area also exhibits a continuous inhibitory influence of the spinal cardiovascular neuron (Fig. 95.14). The functional integrity of the medullary vasomotor area subserving the pressor and depressor reflexes is mostly dependent upon the relative

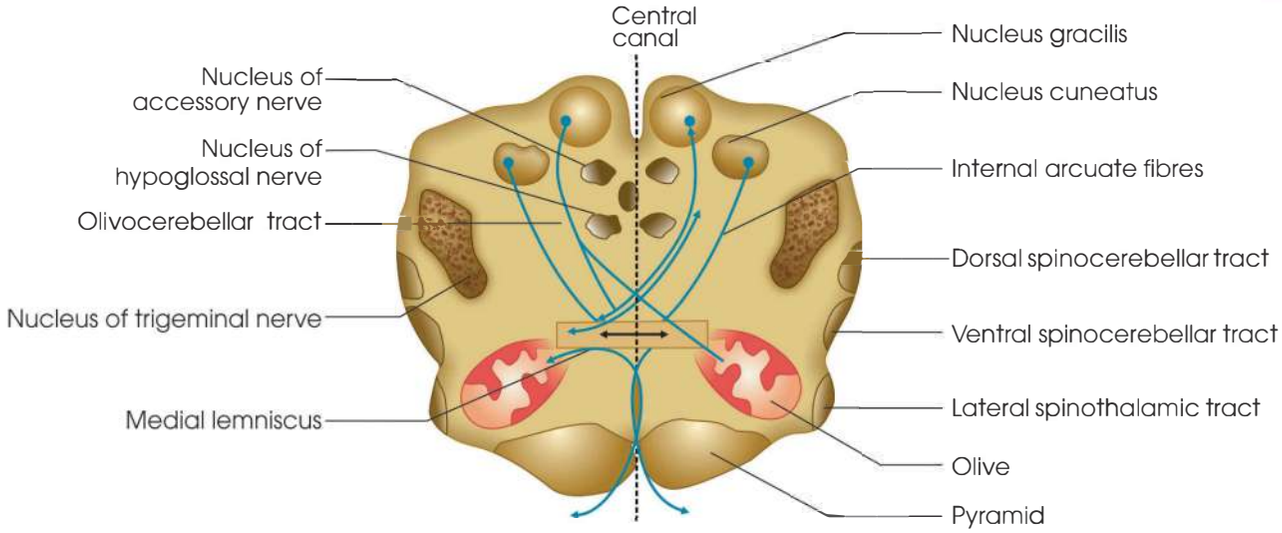


Fig. 95.10: Diagram shows a section through the medulla at the level of olivary nucleus

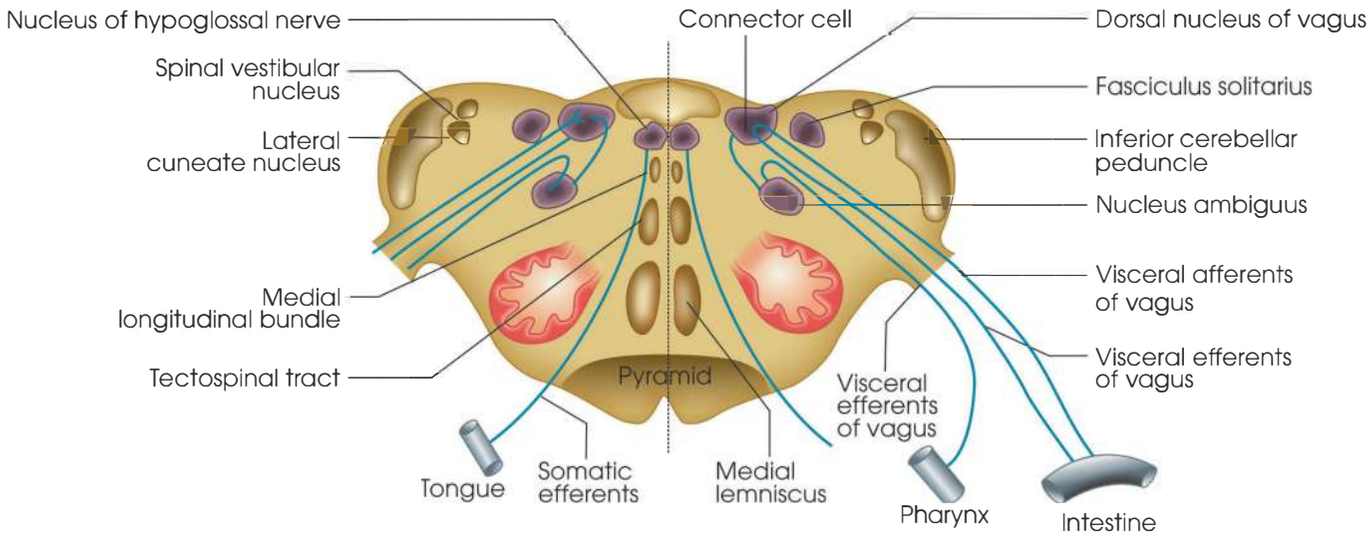


Fig. 95.11: A section through the upper region of the medulla oblongata showing origin of the vagus (X) and hypoglossal (XII) nerves (diagrammatic)

functional activities of the specific systemic baro- and chemoreceptors. Pressor and depressor reflexes are also elicited by stimulation of various afferent somatic nerves and these reflexes are partly mediated through the medulla oblongata like pressor and depressor areas.

The heart rate has been considered to be under the control of two centres—the medullary accelerator centre and medullary inhibitor centre. The accelerator centre is believed to be located within the reticular structures of the pressor centre but the exact position is still unknown. The inhibitor centre is possibly located in areas which are in communication with the vagal nucleus and amygdaloid nucleus.

Thus, medulla oblongata maintains the cardiovascular tone and vasoconstrictor tone.

Control of Respiration

The medullary respiratory centre has been found to have two parts located bilaterally. One is for inspiration and other for expiration (Fig. 95.15). The inspiratory centre is stimulated with the increase in CO_2 concentration of body fluid; frequency and depth of respiration are increased. Expiratory centre also acts in part by inhibiting the inspiratory centre. Regulation of the rhythmic respiration is dependent upon the alternating activity of the two portions of the respiratory centre.

Besides these controlling functions of the medulla on respiratory and cardiovascular activity, the medulla has got other functions too. The medulla is responsible

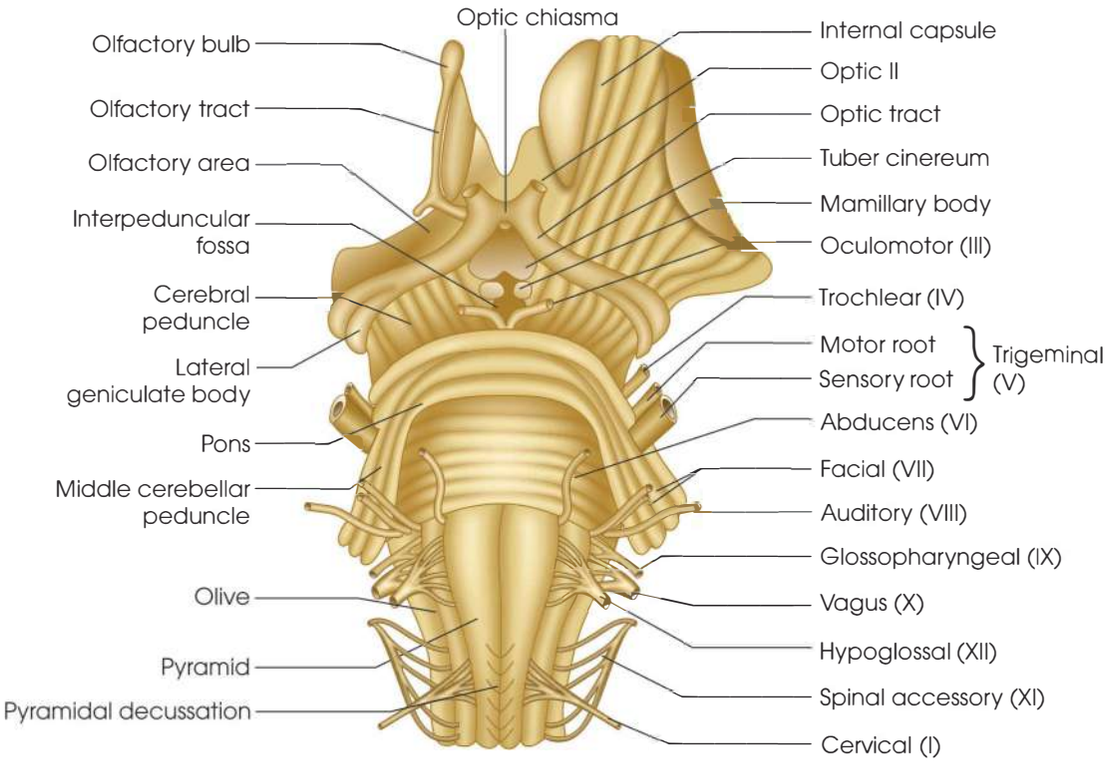


Fig. 95.12: Diagrammatic representations of the anterior view of the brain stem and attached cranial nerves

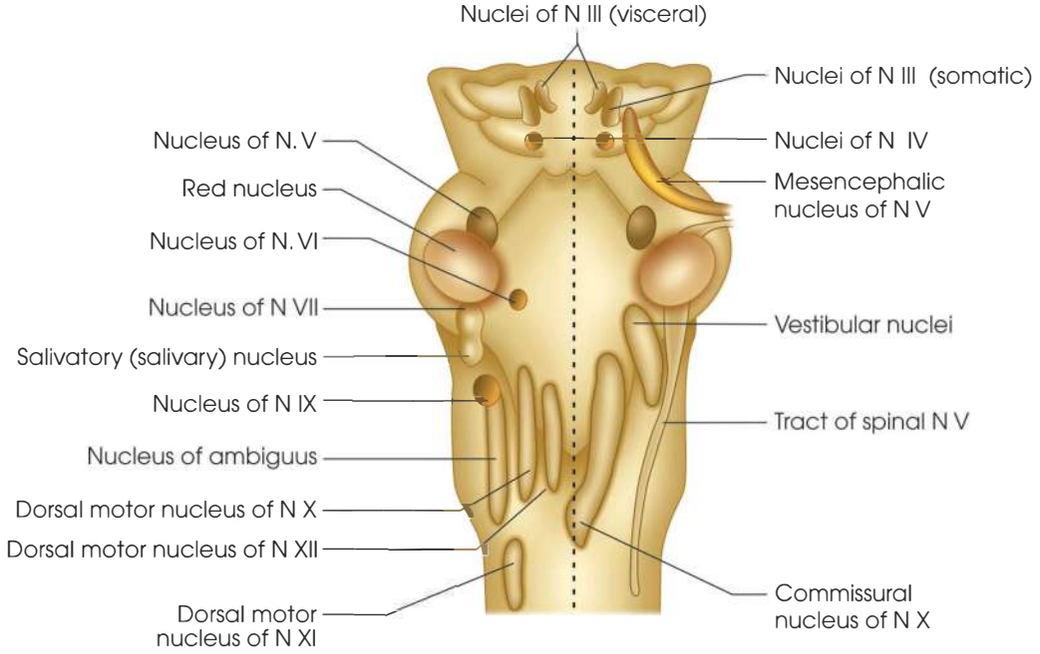


Fig. 95.13: Diagrammatic representation of nuclei of origin of cranial nerves on the posterior surface of the brain stem

for different visceral afferent and efferent mechanisms subserving various other reflexes. These are:

1. Coughing reflex
2. Sneezing reflex
3. Swallowing reflex
4. Reflex hyperglycaemic effect
5. Salivary reflex
6. Sucking reflex
7. Vomiting reflex

The medulla oblongata is a vitally important part of the central nervous system. Disturbances in the medulla oblongata may lead to death from respiratory and cardiac arrest.

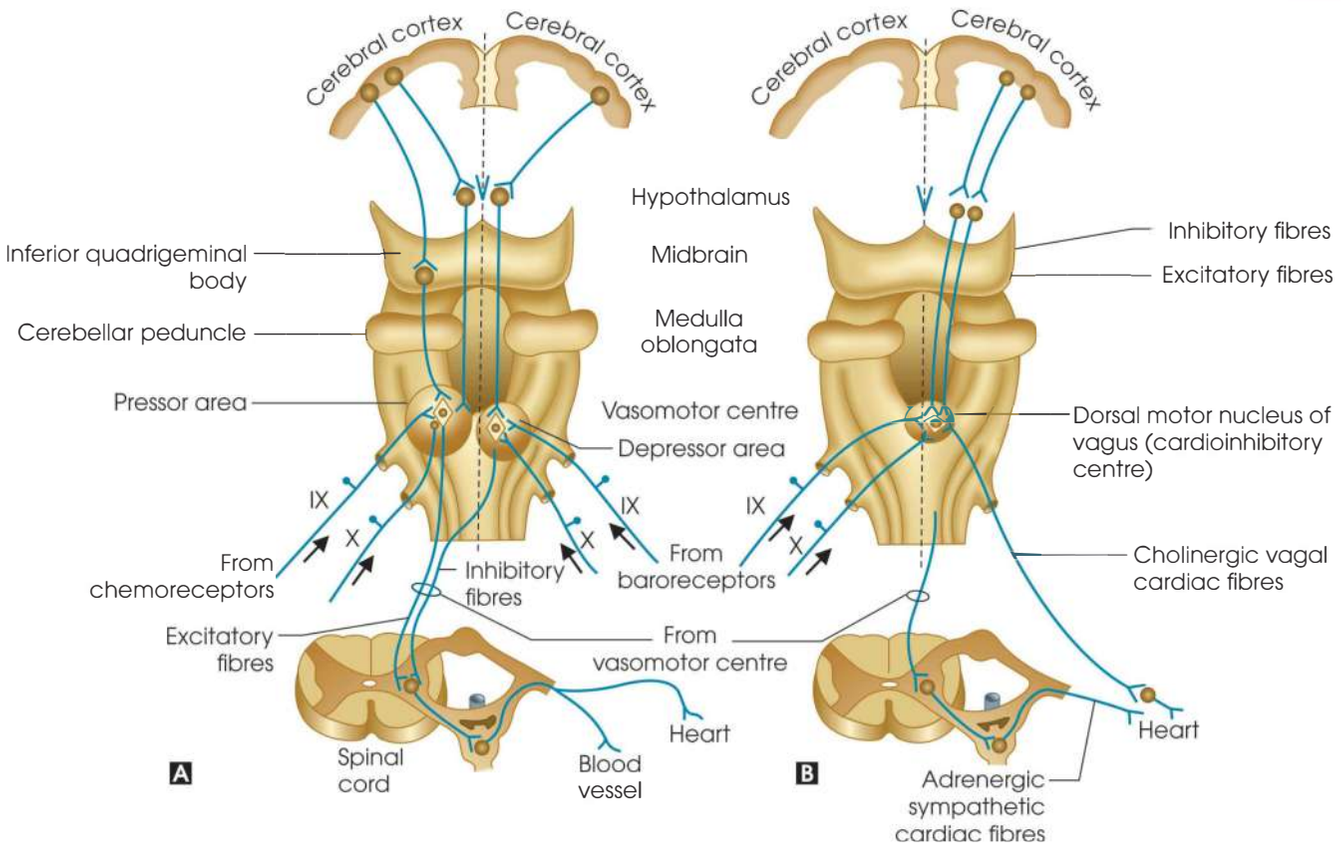


Fig. 95.14A and B: Simplified diagram showing the cardiovascular regulating mechanism by the medulla with the help of autonomic innervations. 'A' represents blood pressure vasomotor controlling mechanism. 'B' represents cardiac controlling mechanism

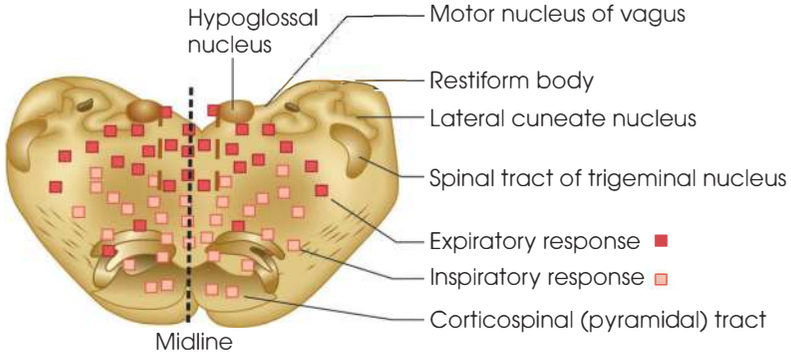


Fig. 95.15: Diagrammatic representation of a section through the medulla oblongata at the level of brachium conjunctivum (superior peduncle) with the distribution of inspiratory and expiratory centres

Posture and Movement

Besides this the medullary reticular formation is also related with the posture and movement.

Reflex Centre

The reflex centre of vomiting, coughing, sneezing, and swallowing are located in medulla oblongata. These reflexes which include the pharyngeal reflex, the swallowing reflex and the masseter reflex are known to be bulbar reflexes which are under the influence of medulla oblongata.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the afferent and efferent connections of red nucleus. Discuss the functions of red nucleus.
2. Describe the structural details and functions of medulla oblongata.
3. Describe the structural details and functions of pons.

Short Notes

1. Anatomical structure of midbrain.
2. Functions of medulla oblongata.
3. Functions of pons.

Chapter

96 Cerebellum

ANATOMY

Cerebellum is the largest part of the hindbrain and lies behind the pons and medulla oblongata. The median portion of the cerebellum is separated from the pons and medulla by the cavity of the IV ventricle (Fig. 96.1). Average weight of the cerebellum in the adult is approximately 150 gm and proportion between the cerebrum and the cerebellum is about 8 to 1, in the infant about 20 to 1.

Anatomical Classification

Cerebellum consists of the two cerebellar hemispheres divided by a medial vermis. The each hemisphere of cerebellum is divided into anterior lobe, posterior lobe (middle lobe) and flocculonodular lobe.

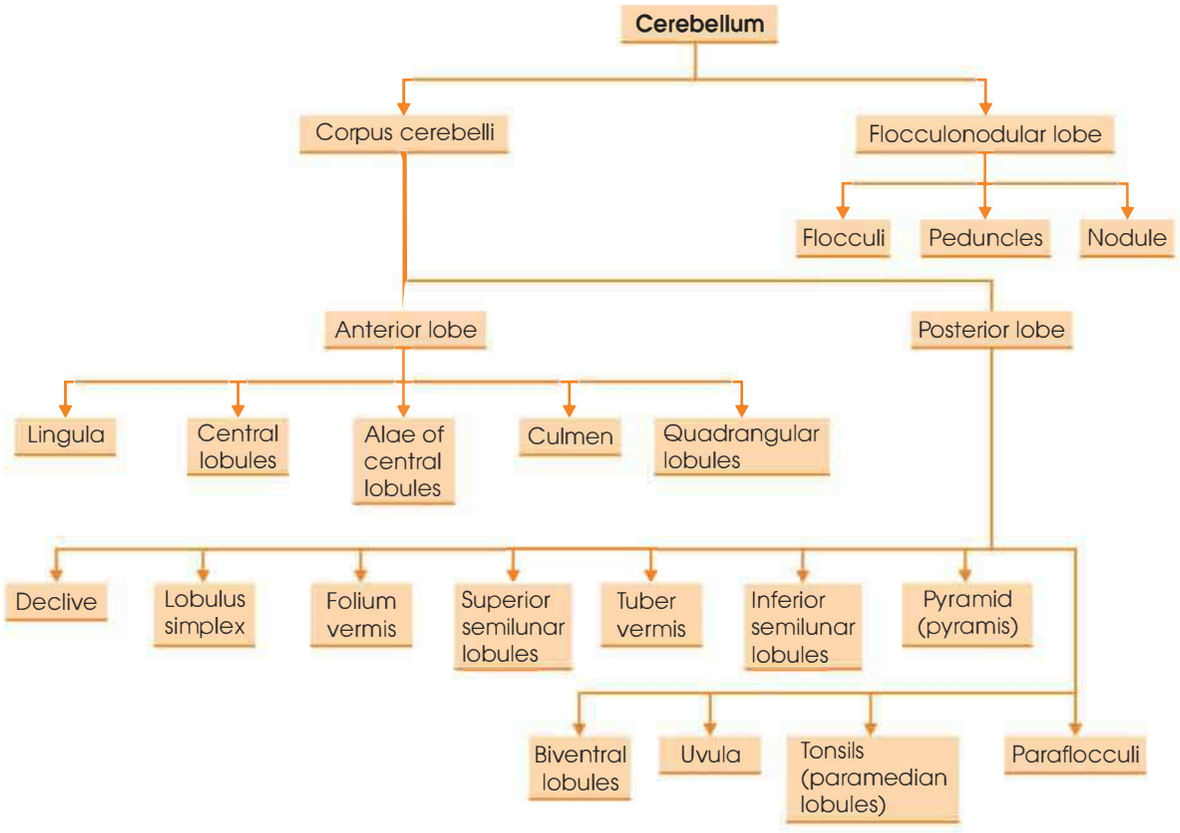
Functional and Morphological Subdivision of Cerebellum

For details *see* flowchart below.

PHYLOGENETIC SUBDIVISIONS

Phylogenetically, the cerebellum has been divided into three parts:

1. Archicerebellum
2. Palaeocerebellum
3. Neocerebellum (Figs 96.3 and 96.4).



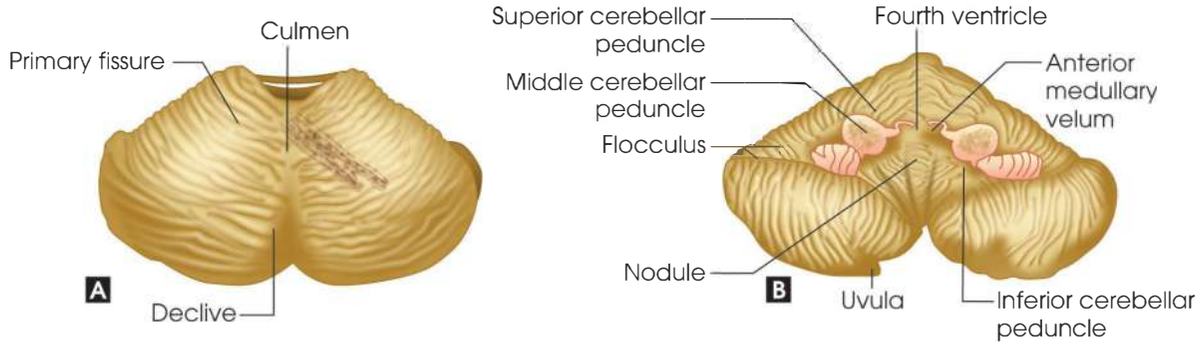


Fig. 96.1A and B: Diagrammatic representation showing superior surface (A) and inferior surface (B) of the human cerebellum

Archicerebellum

Archicerebellum consists of flocculonodular lobe together with lingual, i.e. nodule, both flocculi with their peduncles, and lingula. The flocculonodular lobe is exclusively vestibular in its connections, but together with lingula there are also spinocerebellar connections in addition to vestibular connections.

Palaeocerebellum

It is longer than the archicerebellum but smaller than the neocerebellum. It is constituted with the anterior lobe excepting lingula, but together with pyramid and uvula. So, it consists of central lobule, alae of central lobule, culmen, quadrangular lobule, uvula and the pyramid on the ventral aspect. It is mainly spinocerebellar in its connections.

Neocerebellum

It is the largest and includes the whole of the posterior lobe with the exception of the pyramid and the uvula. It is predominantly corticopontocerebellar in its connections.

Functional Subdivisions

In general form the cerebellum consists of right and left cerebellar hemispheres joined by a narrow median strip of the vermis.

From functional point of view, the cerebellum has been subdivided by Larsell and also by others into two fundamental parts:

1. Flocculonodular lobe.
2. Corpus cerebelli (Fig. 96.4).

These subdivisions not only have got functional significance but of morphological and embryological significance. The flocculonodular lobe is separated from the corpus cerebelli by the posterolateral fissure.

The flocculonodular lobe consists of two parts:

a. *Anterior lobe* includes lingual, lobus centralis and culmen.

b. *Posterior lobe* includes parafloccule, pyramid, uvula, lobus simplex, declive and tuber.

The corpus cerebelli comprises the rest of the cerebellum and is further subdivided by primary fissure into anterior lobe and middle lobe or the posterior lobe (Figs 96.2 to 96.4A and B).

Recent Concept of Functional Classification

Based on connections of cerebellum with other parts of motor control system, it is divided into three parts:

1. *Vestibulocerebellum:* The nodulus in the vermis and flanking flocculus in the hemisphere on each side from the vestibulocerebellum. It has connections between vestibular apparatus and flocculonodular lobe. It controls body posture and equilibrium and also aid in visual fixation during movements via vestibulo-ocular reflex.
2. *Spinocerebellum:* The rest of the vermis and adjucent medial portions of the hemisphere form spinocerebellum. It receives proprioceptive input from the body as well as copy of the motor plan from the cerebral motor cortex. By comparing plan with performance it smooths and coordinates movements. The vermis projects to the brain stem areas concerned with control of axial and proximal limb muscles called medial pathways. Whereas the hemispheres project to the brain stem areas concerned with control of distal limb muscles (lateral brain stem pathways) (Fig. 96.4B). Spinal cord relays information to entire anterior lobe and part of posterior lobe.
3. *Neocerebellum:* The lateral protions of the cerebeller hemispheres are called cerebrocerebellum. They are the phylogenetic newest reaching greatest development in humans. They interact with motor cortex in planning and programming of movements. This part of cerebellum receives information from pons and cereberal cortex and controls skilled voluntary movements.

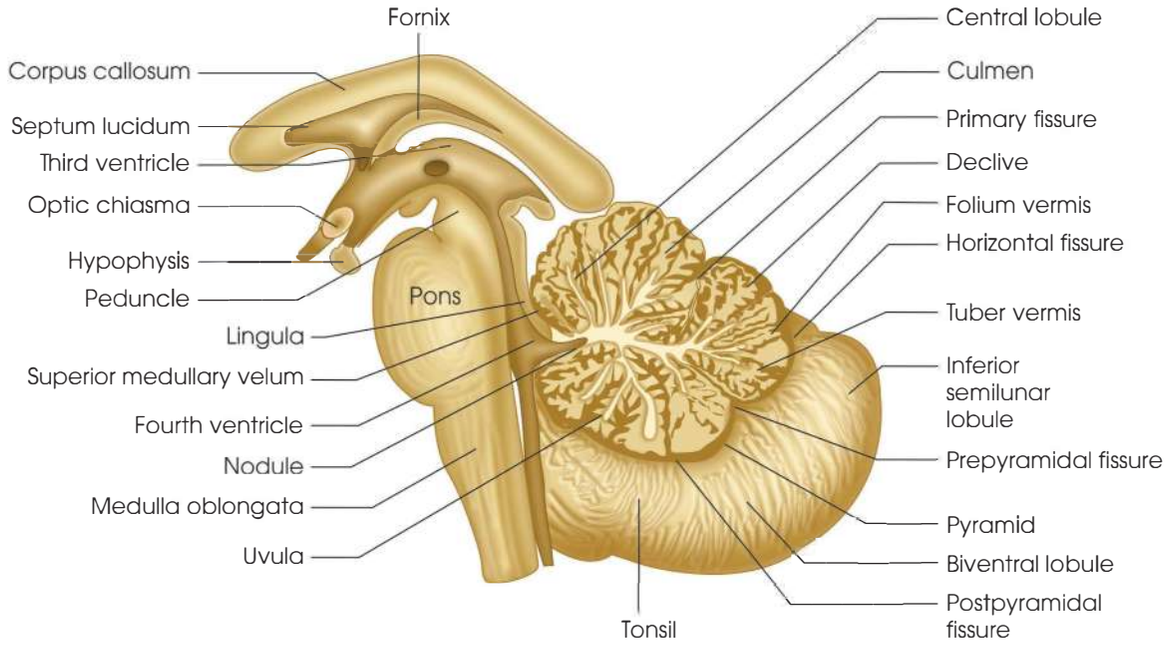


Fig. 96.2: Diagrammatic representation of the median sagittal section of the cerebellum showing principal lobules by name and showing also brain stem

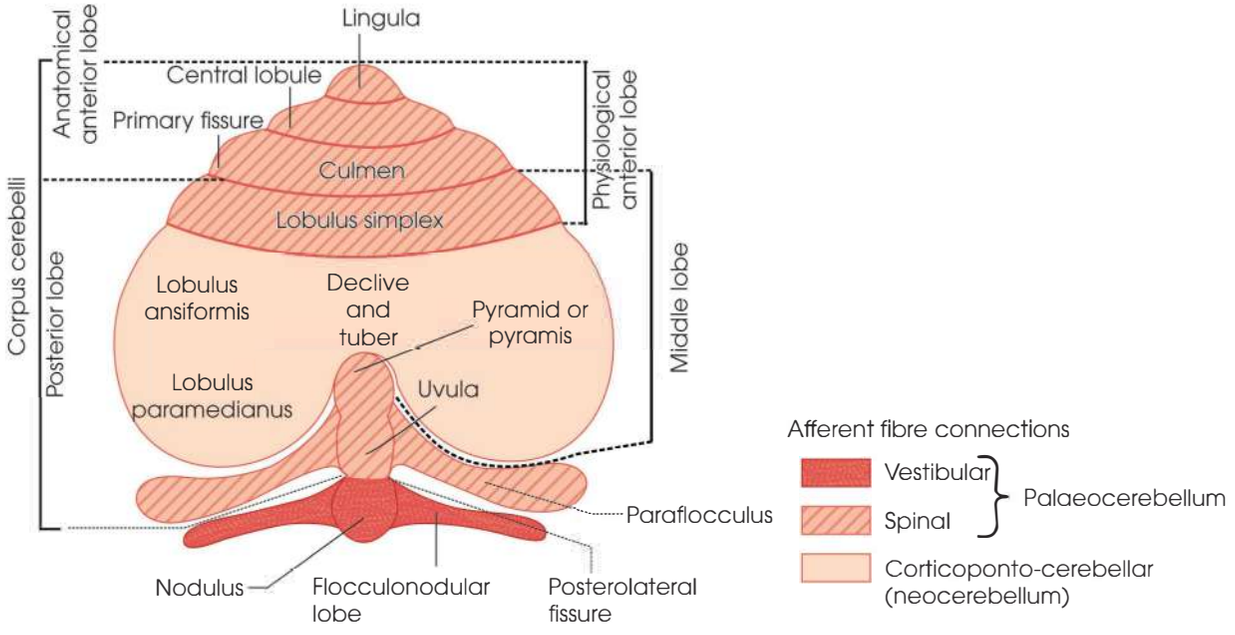


Fig. 96.3: Schematic representation of principal divisions of the cerebellum of the Macaque showing afferent connections (modified Best and Taylor)

CEREBELLAR NUCLEI

There are four pairs of nuclei—nucleus fastigii, nucleus globosus, nucleus emboliformis, and nucleus dentatus (Fig. 96.5). The medial portion of the spinocerebellum projects to the fastigial nuclei and from there to brainstem areas. The adjacent hemispheral portion of spinocerebellum project to emboliform and globose nuclei from there to brainstem areas. The cerebrocerebullum projects to dentate nuclei from there directly or indirectly to ventrolateral nuclei of thalmus.

Histology (Fig. 96.6)

The grey matter of the cerebellar cortex is thrown into folds and shows the following three distinct layers from inside outwards.

1. Granular layer (inner layer).

It contains

1. Small granular cells.
2. Golgi cells (type II).

The granular cells have multiple short dendrites and one long axon. The latter ascends to the molecular

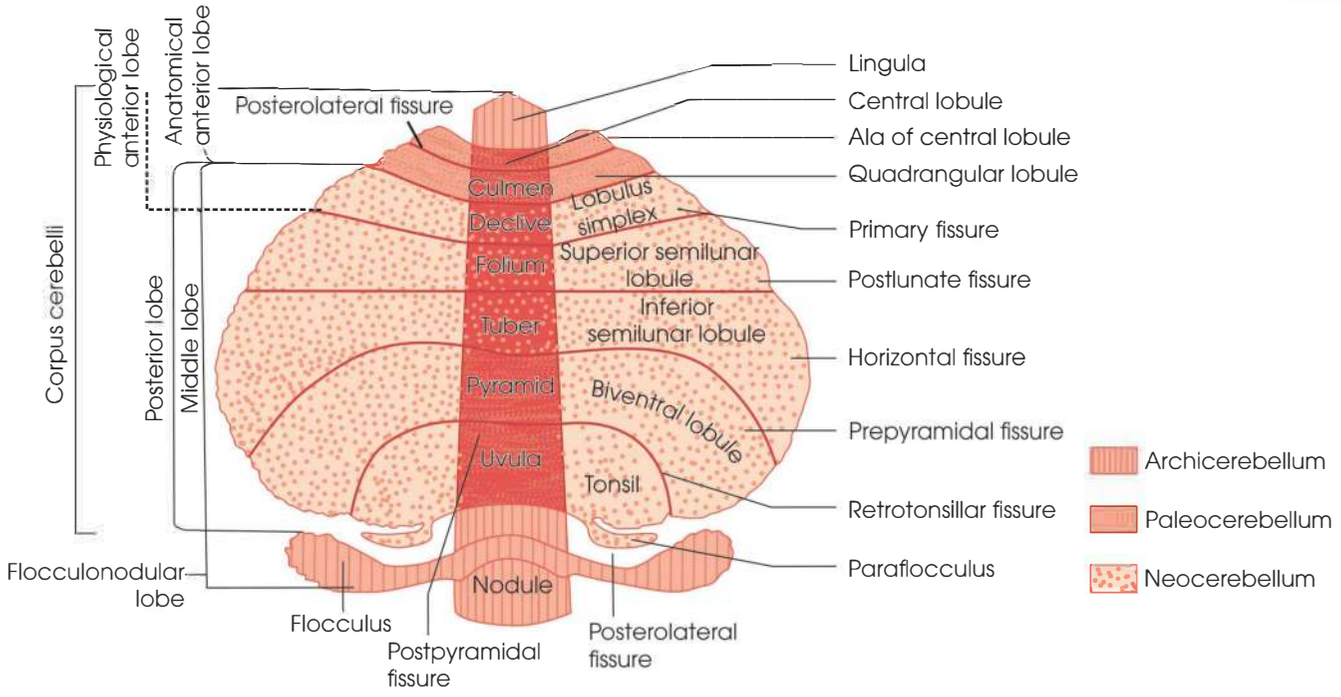


Fig. 96.4A: Diagrammatic representation of the morphological and functional subdivisions of the cerebellum as seen from the superior surface

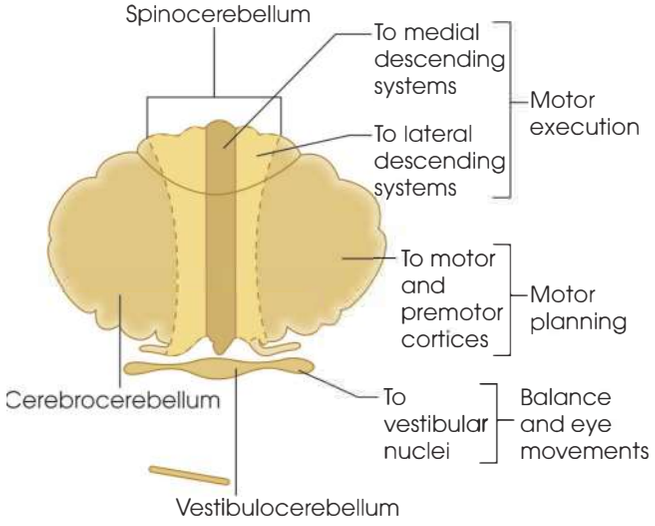


Fig. 96.4B: Functional division of cerebellum

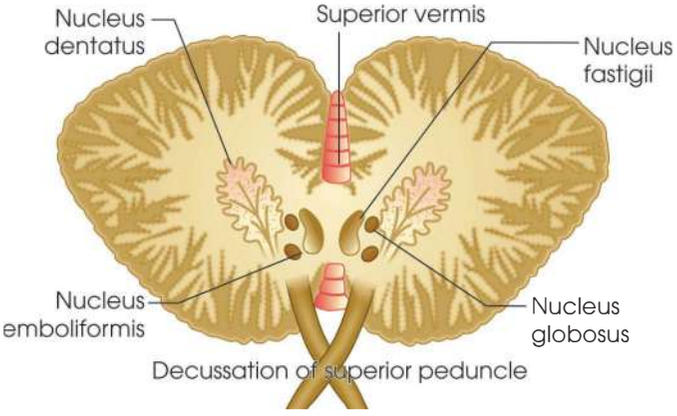


Fig. 96.5: Diagrammatic representation of the horizontal section through the cerebellum showing the cerebellar nuclei (modified after Best and Taylor)

layer, bifurcates into the transverse branches parallel to the surface and communicates with many cells.

2. Intermediate layer of Purkinje cells (middle layer). These cells are characteristic feature of cerebellum. They have large flask-shaped bodies with freely branching dendrites extending into the molecular layer and one axon passing down to the cerebellar nuclei.
3. Molecular (plexiform) layer (outer layer) consists of (a) small stellate cells, and (b) basket cells. The latter send transverse fibres ending round the bodies of many Purkinje cells and receive impulses from granular cells.

The afferent fibres entering the cerebellum go mostly straight to the cortex and are of two types:

1. Climbing fibres go up and communicate with the dendrites and bodies of the Purkinje cells. Derive proprioceptive input from the inferior olive that comes from all over the body. Inferior olive receives input from the vestibular system, spinal cord and the cerebral cortex through a number of pathways. Afferent fibres carry kinaesthetic, vestibular and cortical impulses (via pontine nuclei).

   All the other cerebellar afferent pathways terminate in the mossy fibres in the cerebellar cortex.
2. Mossy fibres provide direct proprioceptive input from all parts of the body and input from cerebral

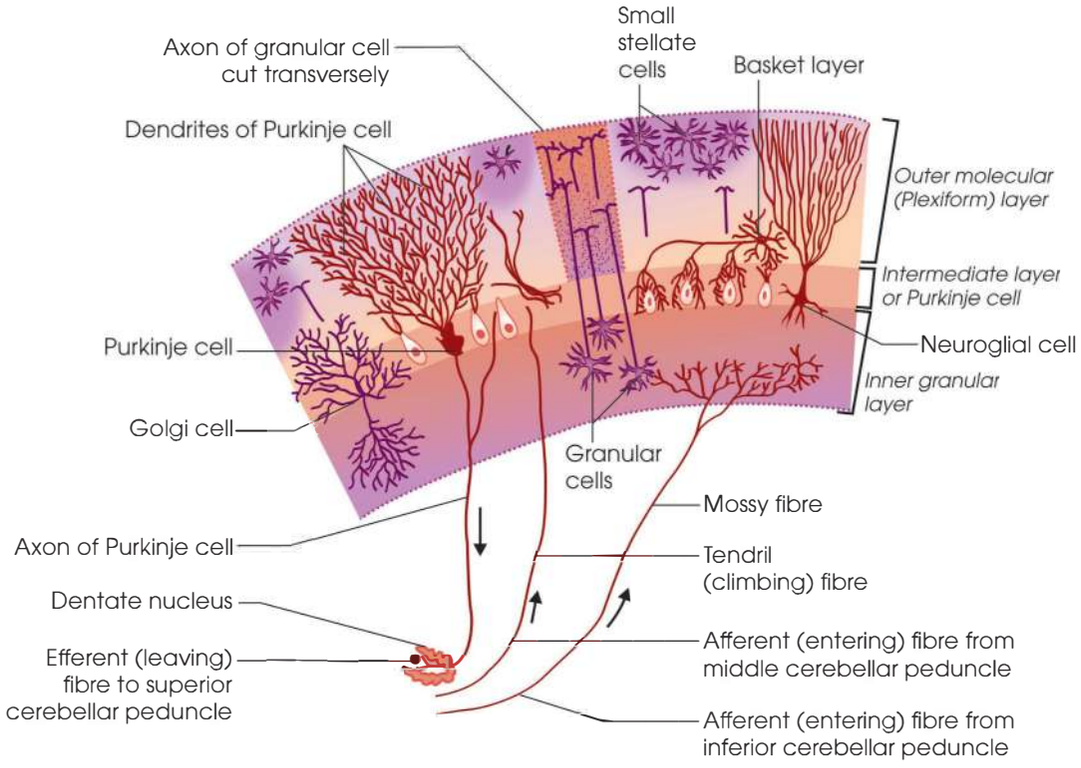


Fig. 96.6: Diagrammatic representation of cross-section of a folium of the cerebellum showing cellular connections. The Purkinje cells form a single stratum of large, flask-shaped cells at the junction of the molecular layer with the granular layer. Granular cells synapse with dendritic processes of the Purkinje cells of which axons enter the white matter and end in the cerebellar nuclei. The Golgi cells lie at the junction of the molecular and granular layers, and their dendrites pass into the molecular layers, and their form axodendritic synapses with the axons of granular cells. The tendril fibres wrap around the dendrites of the Purkinje cells. The basket cells receive impulses from the granular cells

cortex and pontine nuclei. Spinocerebellar fibres pass through inferior cerebellar penducle end in the granular layer.

Efferent Fibres Leave Cerebellum in Two Stages

1. From the cortex to the deep nuclei;
2. From the deep nuclei to extracerebellar regions.

Efferent fibres communicate with the motor centres at all levels of the central nervous system.

The white matter of the cerebellum lies deep in the grey matter and forms a white cove. It is composed of three sets of fibres such as:

1. Projection fibres passing through the peduncles (superior, middle and inferior) make connections with the extracerebellar region (Fig. 96.3).
2. Association fibres connect different regions of the same hemisphere.
3. Commissural fibres connect cortical areas of the cerebellar hemisphere with the other.

CONNECTIONS

The afferent (entering) and efferent (leaving) fibres connecting cerebellum with the extracerebellar regions run through three large bundles which are known as superior, middle and inferior cerebellar peduncles (Figs 96.7 to 96.10).

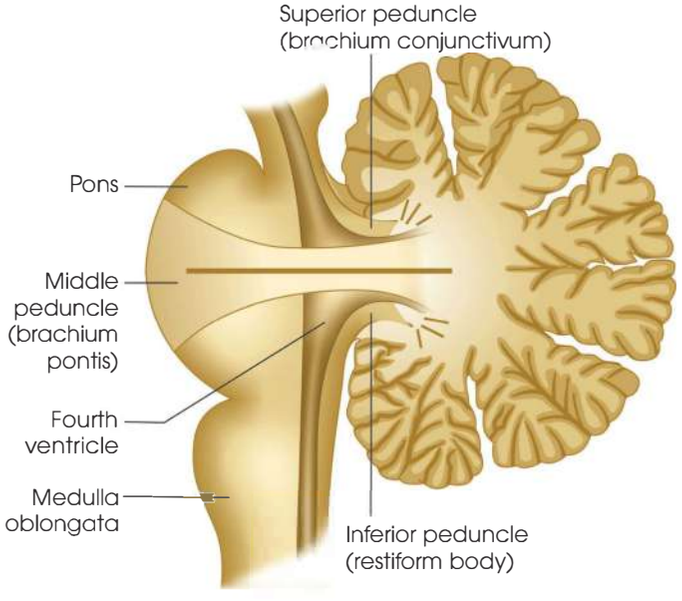


Fig. 96.7: Diagrammatic representation of the cerebellar peduncles (Best and Taylor)

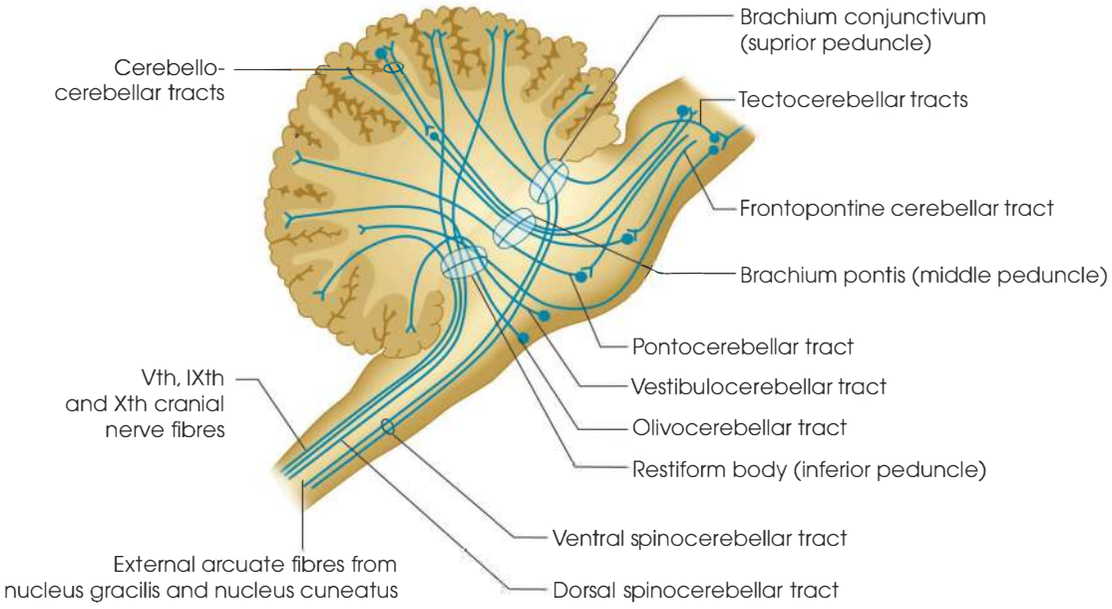


Fig. 96.8: Schematic representation of main afferent tracts to the cerebellum

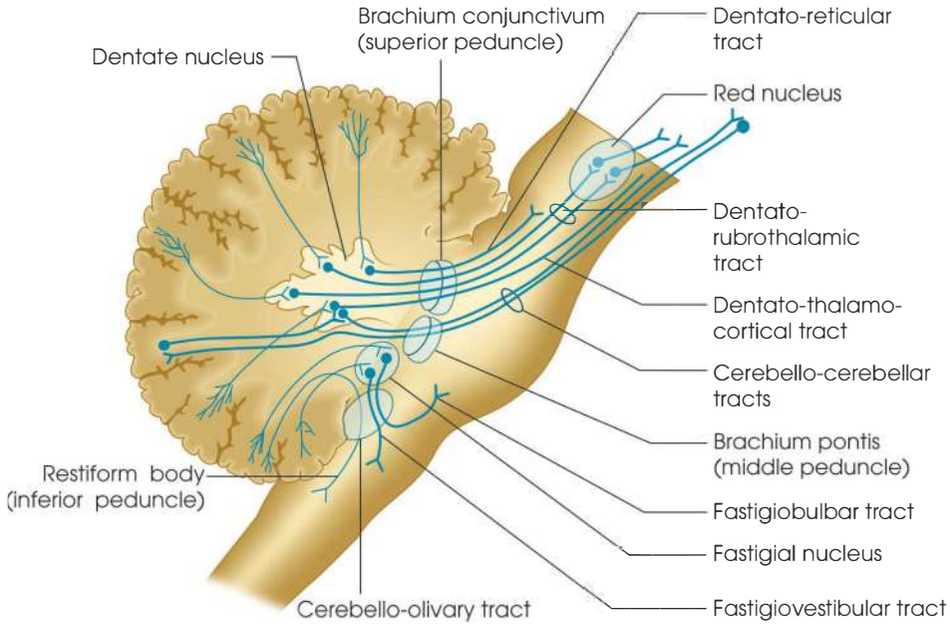


Fig. 96.9: Schematic representation of main efferent tracts from the cerebellum

Inferior Cerebellar Peduncle (Restiform Body)

Fibres passing through this peduncle are predominantly afferent and carry sensory impulses from labyrinth, joints, voluntary muscles, skin, etc. and efferent fibres to the vestibular nuclei.

Afferents

Dorsal spinocerebellar tract: The fibres of the tract from Clarke's column end in the anterior lobe, middle lobe of both sides, but mainly of the same side. The fibres also end in the nodule.

External arcuate fibres: Originating from the nucleus gracilis and nucleus cuneatus of the same of the side (dorsal) and also from opposite end in the paramedian lobule of the middle lobe and lobules simplex of the anterior lobe.

Vestibulocerebellar tract: Originating from the vestibular nucleus of the same side and also directly from the vestibular nerve, it passes to the three cerebellar nuclei: Nucleus globosus, nucleus emboliformis and mainly to nucleus fastigii and is relayed to the cortex of the flocculondular lobe and of the uvula.

Olivocerebellar tract: Originating from the olivary nucleus of the same side as well as from opposite side it ends in the cortex of the middle lobe.

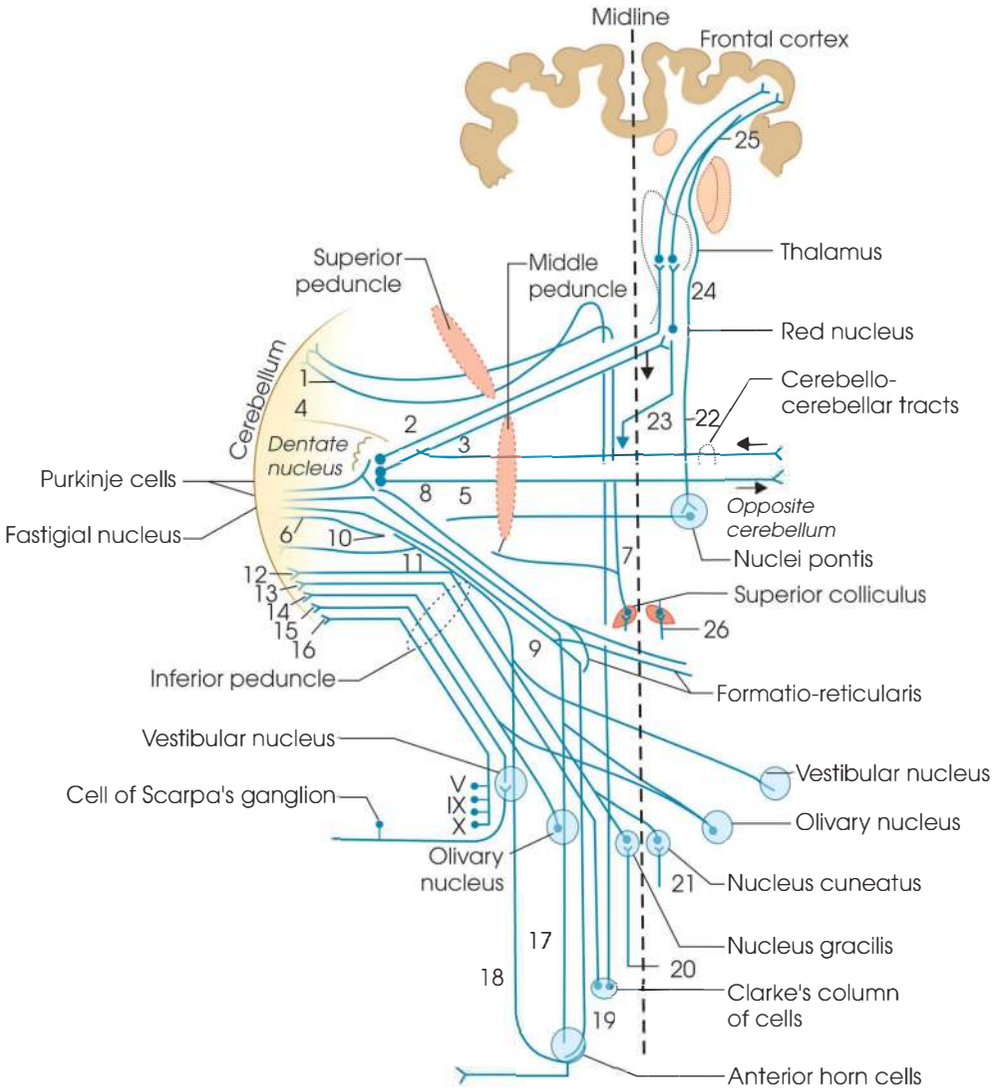


Fig. 96.10: Schematic representation of principal connections of the cerebellum. Red—efferent; Black—afferent. 1 = Ventral spinocerebellar tract (Gowers' tract). 2 = Dentatothalamic tract through red nucleus to thalamus. 3 = Dentatorubral tract—one branch passing down to end in various nuclei. 4 and 5 = Cerebellocerebellar tracts (4 = from opposite cerebellum and 5 = to opposite cerebellum). 6 = Pontocerebellar tract from nuclei pontis of opposite side. 7 = Tectocerebellar tract from superior colliculus. 8 = Dentatoreticular tract of both sides. 9 = Cerebello-olivary tract to olivary nucleus of both sides. 10 = Fastigiobulbar tract to formatio reticularis of both sides. 11 = Fastigiovestibular tract to vestibular nucleus of both sides. 12 = External arcuate fibres from nucleus gracilis and nucleus cuneatus. 13 = Dorsal spinocerebellar tract (Flechsig's tract) from Clarke's column of cells. 14 = Olivocerebellar tract from olivary nucleus of both sides. 15 = Vestibulocerebellar tract from vestibular nucleus of same side. 16 = Fibres from V, IX and X cranial nerves. 17 = Olivospinal tract. 18 = Vestibulospinal tract. 19 = Reticulospinal tract. 20 = Tract of Goll. 21 = Tract of Burdach. 22 = Frontopontine tract. 23 = Rubrospinal tract. 24 = Rubrothalamic tract. 25 = Thalamocortical tracts. 26 = Spinotectal tracts

Fibres of the fifth cranial nerve and also of ninth and tenth cranial nerves: They end in the pyramid, uvula and paraflocculus.

Tectocerebellar tract: It originates in the midbrain colliculi and ends in the cerebellum. Its course is not clearly known.

Efferents

Fastigiovestibular tract and fastigiobulbar tract: Originating from the flocculonodular lobe and roof nucleus (nucleus fastigii), they end in the vestibular nuclei and medullary reticular formation. The fibres from the medullary reticular formation descend in the spinal cord as vestibulospinal tract or reticulospinal tract.

Cerebello-olivary tract: Originating from the cerebellum it ends in the olivary nuclei of both sides.

MIDDLE CEREBELLAR PEDUNCLE (BRACHIUM PONTIS)

Afferents

1. **Pontocerebellar tract.** Arising from the pontine nucleus, it ends in the middle lobe of the opposite side and a few fibres end in the homolateral

hemispheres and vermis. This tract also constitutes the secondary neurons of the frontopontocerebellar tract.

2. **Fibres from cerebellum to cerebellum.** Fibres from the dentate nucleus of one side end in the cerebellar hemisphere of the opposite side.

SUPERIOR CEREBELLAR PEDUNCLE (BRACHIUM CONJUNCTIVUM)

Efferents

Fibres arising from the dentate nucleus and a few from the other nuclei decussate in the midbrain with the fibres of the opposite side and run as descending and ascending fibres. The ascending fibres comprise the:

1. Dentatothalamocortical tract
2. Dentatorubrothalamic tract.

Dentato-thalamo-cortical tract: This tract ends directly into the lateral nucleus of the thalamus and is relayed to the cerebral cortex at areas 4 and 6.

Dentato-rubrothalamic tract: Originating from the dentate nucleus this tract crosses in the region of the midbrain and ends in the nucleus parvocellularis or nucleus magnocellularis of the red nucleus. Impulses from the parvocellularis of the red nucleus reach the cerebral cortex (areas 4 and 6) via rubrothalamic tract.

Descending tract comprises the fibres which end in the reticular formation of the pons, medulla oblongata and cervical spinal cord.

Afferents

1. **Ventral spinocerebellar tract:** Originating from Clarke's column this ascends through the spinal cord, medulla oblongata and pons, and ultimately ends in the cerebellum.
2. **Tectocerebellar tract:** Originating from the superior colliculus it ends in the cerebellum.

Considering the above connections with the extra-cerebellar nuclei, it may be argued that the cerebellum has got cerebro-cerebello-cerebral connections. Because the cerebellum makes connection with the cerebral cortex (areas 4 and 6) as described and the cerebral cortex (areas 4 and 6) in turn makes connection with the cerebellum through the frontopontocerebellar tract.

Steady voluntary movement initiated by the pre-central motor cortex is maintained by this pathway.

FUNCTIONS OF CEREBELLUM

Role of Archicerebellum (Via Vestibulocerebellum and Spinocerebellum Connections) in Maintenance of Posture and Equilibrium

1. **Maintenance of posture and equilibrium:** The flocculonodular lobe being connected with the vestibular nuclei plays an important role in regulation of posture and equilibrium. Although the flocculonodular lobe is exclusively vestibular in its connections, but together with lingula it is spinocerebellar in addition to vestibular connections. Thus, by vestibulocerebellum component it not only controls body posture and equilibrium but also aid in visual fixation during movements via vestibulo-ocular reflex and by spinocerebellar component it control axial and limb muscle movement and postural reflexes. In human, it can adjust the tone of both protagonists and antagonists and thus exerts a perfect synergic control on antagonistic muscles.

Role of Palaeocerebellum (Via Spinocerebellar Connections) in Maintenance of Muscle Tone

Maintenance of muscle tone: It is spinocerebellar in its connections predominantly. The anterior lobe helps in the maintenance of muscle tone and synergic movements, necessary for the regulation of posture by inhibiting the gamma motor neuron discharges of muscle spindle and increased excitability of stretch reflex. Cerebellum is an important site of linkage for alpha gamma system which plays important role in maintenance of muscle tone. The palaeocerebellum acts as a receptive organ for tactile, proprioceptive, auditory and visual impulses. It helps in the maintenance of muscle tone and synergic movements which are necessary for regulation of posture.

Role of Neocerebellum in Control of Movements

Control of movements

Voluntary movements

a. It receives predominantly corticopontocerebellar fibres. Through these fibres it helps in the integration and co-ordination of muscular movements.
b. It receives fibres from the nuclei pontis. Each cerebellar hemisphere receives fibres from the opposite side.
c. The nuclei pontis receives fibres from the frontal and temporal lobes of the cerebral cortex.
d. Some fibres are also received from the pyramidal tract.
e. Through this path the cerebellum receives impulses from the cerebral cortex and is influenced by it.
f. Again, from the dentate nucleus of the cerebellum some fibres are projected to the red nucleus and some to the thalamus and then are relayed to the cerebral cortex dentato-rubrothalamo-cortical fibres.

   By its connections with cerebral cortex, it guides and controls all voluntary movements, so that they may be accurate in time, force, direction and extent. The neocerebellum also receives some tactile and proprioceptive impulses through the spinal cord.
g. The cerebellum controls the actions of motor cortex through a feedback mechanism. It is concerned with smooth pattern of movement and regulation of the

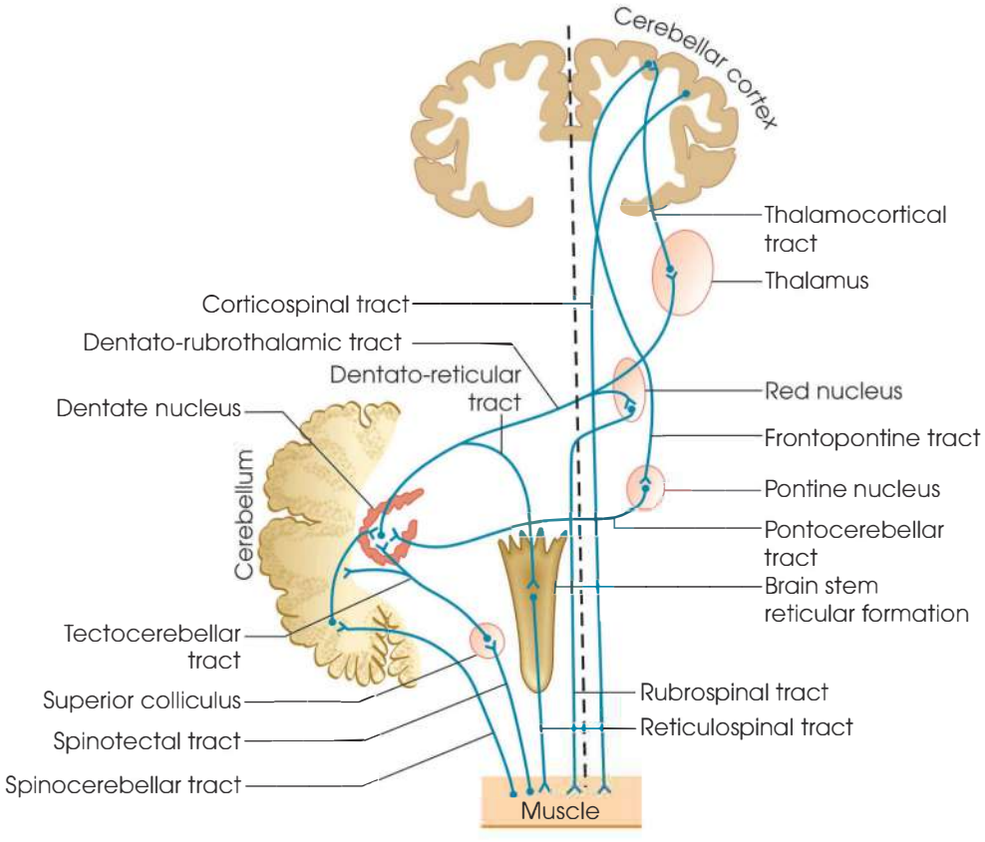


Fig. 96.11: Schematic representation of the cerebellar feedback system

precision of the movement. The diagram describes the pathways of feedback mechanism controlling the activity of the motor cortex (Fig. 96.11).

- During voluntary movements the motor cortex transmits motor impulses to the spinal cord motor neuron through the corticospinal tract.
- Collateral impulses are also transmitted to the cerebellum simultaneously through the fronto-pontocerebellar pathways. Thus, during motor movements, the spinal cord motor neuron as well as the cerebellum get the motor impulses simultaneously.
- The cerebellum also receives the afferent impulses from the muscle spindle, tendons, etc. through the spinocerebellar tract and then sends impulses to the dentate nucleus and thence to the cerebral cortex back through dentato-rubrothalamo-cortical pathways.
- The degrees and extent of the movement for performing a particular work is being determined by the feedback or error-controlling activity of the cerebellum. The cerebral motor cortex generally sends impulses for more than it is actually required for performing a work and the cerebellum then automatically inhibits the cerebral cortex after calculating the appropriate time and rate of movement required to reach the point of intention.

Comparator of a Servomechanism

Regulation of Motor Activity

a. The recent idea about cerebellar function is that it acts as a 'comparator of a servomechanism'.
b. It is an organ which receives proprioceptive, tactile, visual and auditory impulses and is also connected with the activities of the corticospinal neuron.
c. Through the cerebellocerebral pathway it exerts its controlling influence over the corticospinal neuron and regulates the motor activity. It controls the range, force and direction of movement.
d. In general, the cerebellum is not involved with sensation or consciousness, because its removal does not cause any impairment of them. But it plays a very important role in the reflex regulation, posture and modulation or co-ordination of reflexes involved in motor acts.
e. It acts as a feedback centre in between the cerebral cortex and peripheral motor movements and interruption of such feedback pathway may lead to oscillatory movement, i.e. what the cerebral cortex initiates, the cerebellum regulates them.

Control of Involuntary Movements

The afferent fibres for control of involuntary movements via olivocerebellar fibres carry proprioceptive, kinaesthetic and sensory information from all part of

body; and extra-pyramidal impulses from reticular formation, motor cortex and basal ganglia to deep cerebellar nuclei. The cerebellum integrates the information and sends efferent impulses to same area to correct error in the involuntary movements. The degrees and extent of the movement for performing a particular work is being determined by the feedback or error-controlling activity of the cerebellum.

Cerebellum and learing: Cerebellum is concerned with learned adjustments that make coordination of movements easier when a given task is perform over and over. As a motor task is learned activity in the brain shifts from prefrontal areas to the parietal and motor cortex and the cerebellum. The basis of learning in the cerebellum is probably the input via the olivary nuclei. The mossy fibre—granule cell—Purkinje cell pathway is highly divergent hence climing fibres may paticipate in motor learning by influencing the effectiveness of mossy fibres in exciting Purkinje cells.

Purkinje cell receives input from a single climbing fibre but it makes 2000–3000 synapses on it. Climbing fibre activation produces a large complex spike in the Purkinje cell and the spike produces long-term modification of the pattern of mossy fibre input to that particular Purkinje cell. Climbing fibre activity is increased when a new movement is being learned and selective lesions of olivary complex abolish the ability to produce long-term adjustments in certain motor responses.

Although the archicerebellum (vestibulocerebellum) the palaeocerebellum and the neocerebellum are functionally different, yet they work in close cooperation. The neocerebellum guides to organise accurate motor impulses for precise volitional movements, whereas at the same time, the palaeocerebellum and archicerebellum adjust the postural mechanism and thus create a suitable background against which all volitional movements take place.

CEREBELLAR LESIONS

Cerebellar lesions of one hemisphere or peduncles will cause dysfunction on the same side of the body.

Lesions of the vermis will affect both sides. The signs and symptoms of cerebellar disease are much more manifested following lesions in the cerebellum. The clinical manifestations of the disease can be described under two broad headings:

1. Defects of posture
2. Defects of voluntary movement.

Defects of Posture

1. *Hypotonia*—muscle tone is lost and becomes flabby.
2. *Defective attitude*—face turned towards the opposite side.
3. Post-pointing and vertigo—defective arm deviates to the side of lesion when raised straight in front with eyes closed (Barany's pointing test). *Vertigo* is the sensation when the surrounding environment is rotating. It is not due to cerebellar disease but of vestibular or labyrinthine disorders.
4. *Static tremor* may develop when head or limb is held steadily.
5. *Nystagmus and deviation of eyes jerky movement* of eyeball especially when looking at the side of lesion.
6. *Deep reflexes*—weak and sluggish and knee jerk becomes pendular.

Defects of Voluntary Movement

1. *Asthenia*—weakness of movement.
2. *Ataxia*—incoordinated movement.
3. *Decomposition of movements*—a complex movement is carried out in two parts.
   - *Asynergia*—inco-ordination between the protagonists and antagonists.
   - *Dysmetria*—wrong judgement about the force and extent of movement.
4. *Gait*—reeling, legs wide apart, deviates to the same side.
5. *Speech*—scanning.
6. *Intentional tremor*—tremor during voluntary movement.
7. *Adiadochokinesis* (after Babinski)—inability of the patients to execute probation and supination of the forearm rapidly, or extension and flexion of fingers.

The diseases related to cerebellar degeneration are characterized by unsteady, lurching wide-legged walking accompanied by a back and forth tremor in the trunk of the body. The patient may also present with unsteady and jerky movement of the arms or legs; slowed and slurred speech; and nystagmus.

The causes of cerebellar disorders are multiple sclerosis, acute and haemorrhagic shock, spinocerebellar ataxias, Friedreich ataxia, transmissible spongiform encephalopathies (such as 'Mad cow disease' and Creutzfeldt-Jakob disease), etc.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the afferent and efferent connections of cerebellum. Discuss the functions of cerebellum.
2. Describe the afferent and efferent connections of cerebellum. Describe the comparator servomechanism.

Short Notes

1. Role of neocerebellum in control of movements.
2. Cerebellar lesions.
3. Role of cerebellum in controlling involuntary movements.
4. Role of cerebellum in controlling voluntary movements.

Chapter

97 Thalamus

INTRODUCTION

This is a large collection of nerve cells at the top of the midbrain forming the medial boundary of internal capsule and lateral boundary of third ventricle. The following five main nuclear masses have been found in the thalamus:

1. Medial nuclear mass
2. Lateral nuclear mass
3. Midline nuclei
4. Intralaminar nuclei
5. Pulvinar nuclei.

The medial nuclear mass and lateral nuclear mass are separated from each other by a vertical septum-the internal medullary lamina. In the internal medullary lamina there are also clusters of nerve cells, which are known as intralaminar nuclei. In the adjacent side of the medial nuclear mass there is a discrete group of nerve cells which are known as midline nuclei. At the posterior portion of the nuclei of lateral mass there is a large nuclear mass which is called as pulvinar nuclei.

The medial nuclear mass consists of two distinct cell groups:

1. Anterior nucleus
2. Medial dorsal nucleus.

The lateral nuclear mass contains, like the medial nuclear mass, two distinct cell groups:

1. Dorsal group of the thalamus (lateral nuclei)
2. Ventral group of the thalamus.

The ventral groups of the thalamus are also composed of three portions

1. Ventral anterior nucleus
2. Ventral lateral nucleus
3. Ventral posterior nuclei.

The ventral posterior nuclei again contain two cell groups:

1. Ventral posterolateral nucleus
2. Ventral posteromedial nucleus.

The lateral nuclei of the thalamus which are also described as dorsal group of nuclei are composed of lateral dorsal nucleus and lateral posterior nucleus.

The anatomical divisions of the thalamic nuclei have been presented schematically:

The medial geniculate body and lateral geniculate body are also included as a part of the thalamus.

These two nuclei are known as metathalamus.

CONNECTIONS (Fig. 97.1)

Anterior nuclear group

I. ***Anterior nucleus***

1. *Afferent:* (i) Mamillary bodies—mamillothalamic tracts.
2. *Efferent:* (i) Paracentral lobules; (ii) Posterior part of cingular gyri.

Medial nuclear group

II. ***Medial dorsal nucleus***

1. *Afferent:* (i) Prefrontal areas of cerebral cortex; (ii) Hypothalamus.
2. *Efferent:* (i) Hypothalamus; (ii) Corpus striatum; (iii) Prefrontal cortex.

Ventral Nuclear Group

Ventral Anterior Nucleus

1. *Afferent:* Globus pallidus via lenticular and thalamic fasciculi.
2. *Efferent:* Different areas of corpus striatum, globus pallidus and also in part to anterior insular cortex (Angevine and Others, 1962).

Ventral Lateral Nucleus

1. *Afferent:* (i) Globus pallidus; (ii) Dentate nucleus of the cerebellum of the opposite side via dentatothalamic tract; (iii) Ipsilateral red nucleus (rubrothalamic tract).
2. *Efferent:* Precentral areas of the cerebral cortex (area 4).

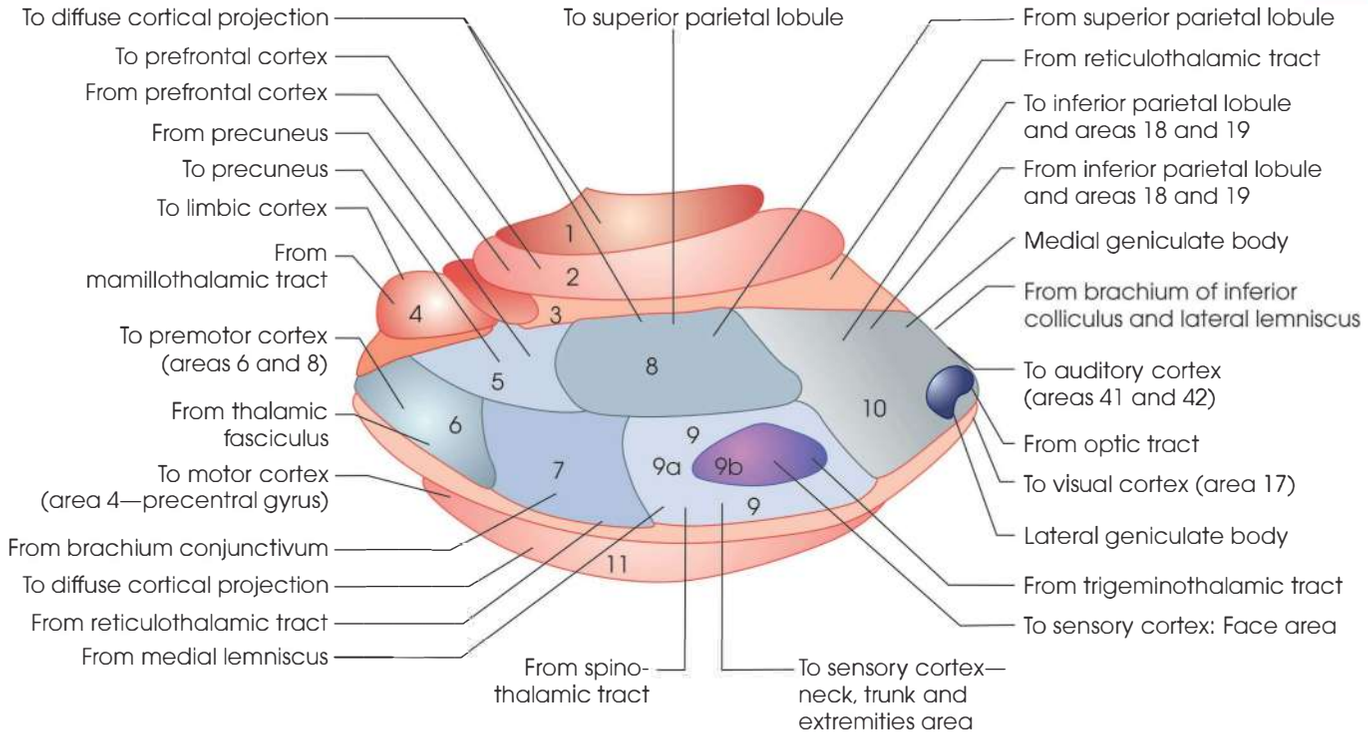


Fig. 97.1: Diagrammatic representation of principal thalamic nuclei, and also major effernet (black line) and afferent (red line) connections of thalamic nuclei. 1 = Midline nuclei. 2 = Medial dorsal nucleus. 3 = Intralaminar nuclei (internal medullary lamina). 4 = Anterior nucleus. 5 = Lateral dorsal nucleus. 6 = Ventral anterior nucleus. 7 = Ventral lateral nucleus. 8 = Lateral posterior nucleus. 9 = Ventral posterior nuclei (9a = Ventral posterolateral nucleus and 9b = Ventral posteromedial nucleus). 10 = Pulvinar nuclei. 11 = Reticular nucleus

Ventral Posterior Nuclei

Ventral Posteromedial Nucleus

1. *Afferent:* (i) Crossed fibres from the spinal and superior sensory trigeminal nuclei, ascending in association with the medial lemniscus; (ii) Uncrossed dorsal trigeminal tract.
2. *Efferent:* Post-central gyrus.

Ventral Posterolateral Nucleus

1. *Afferent:* Medial and spinal lemnisci.
2. *Efferent:* Post-central gyrus.

Lateral Nuclear Group

Lateral Dorsal Nucleus

1. *Afferent:* Pre-central cortex.
2. *Efferent:* Pre-cuneal cortex.

Lateral Posterior Nucleus

1. *Afferent:* Superior parietal lobule (areas 5 and 7).
2. *Efferent:* Superior parietal lobule and a few fibres to post-central and pre-central regions of the cortex.

Pulvinar Nuclei

It has got internuclear connections with medial and lateral geniculate bodies (metathalamus) and also medial dorsal nucleus. It receives and sends fibres to supramarginal, angular convolutions, superior parietal lobule, occipital and posterior temporal cortex.

Midline nuclei are found in the massa intermedia:

1. *Afferent:* (i) Corpus striatum and also from brain stem reticular formation.
2. *Efferent:* (i) Cerebral cortex; (ii) Red nucleus; (iii) Body of Luys (subthalamic nucleus); (iv) Midbrain nuclei; (v) Hypothalamus.

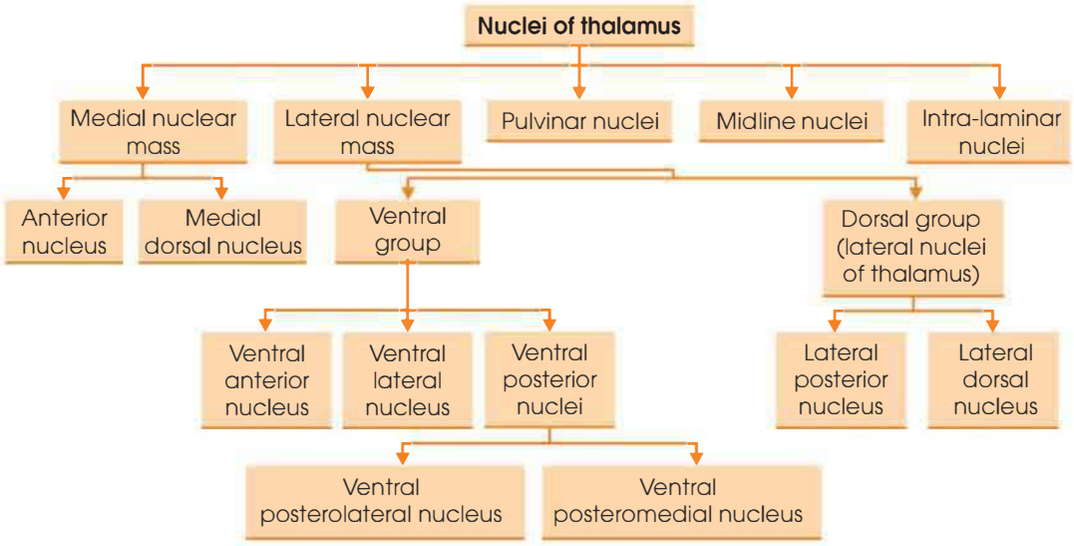
Intralaminar Nuclei Group

1. *Afferent:* (i) Medial and trigeminal lemnisci; (ii) Reticular formation of the brain stem—reticulothalamic tract.
2. *Efferent:* Globus pallidus and also with neighbouring thalamic nuclei.

Metathalamic Nuclei

Medial geniculate body

1. *Afferent:* Ascending auditory fibres originating from the trapezoid nuclei, superior olivary nuclei, lateral lemniscus and the inferior colliculus.
2. *Efferent:* Auditory cortex and also fibres to nucleus of lateral lemniscus, trapezoid body, superior olivary nucleus.



Lateral Geniculate Body

1. *Afferent:* Lateral geniculate body is the end station of the optic tract.
2. *Efferent:* Visual cortex and also send fibres to the calcarine cortex, superior colliculi and pretectal area.

Functions of the Thalamus

1. Relay station: It is the great relay station for pathways coming from cerebellum, cerebral cortex (post-central gyrus) and projection from the peripheral sensory systems.
   a. It is a relay station for auditory and visual stimuli. Auditory impulses are relayed in medial geniculate body while visual impulses are relayed in lateral geniculate body.
   b. Ventral lateral nucleus receives cerebellar impulses and relay them to areas 4 and 6 of frontal lobe. Through this path; cerebellum guides and controls functions of cerebrum.
   c. It receives somasthetic sensation from the opposite half of the body. It receives all sensations carried by the medial, spinal and trigeminal lemnisci. Ventral posterior nuclei receive the medial, spinal, and trigeminal lemnisci. Through these lemnisci, pain, temperature, touch and kinaesthetic sensations from the different parts of the body and from the face reach these nuclei. Except pain sensation all the impulses are relayed to the post-central gyri (areas 3, 1, 2) of the cerebral cortex. Vestibular impulses are relayed to temporal lobe and taste sensations are relayed to the inferior part of post-central gyri.
   d. It is connected with limbic lobe and hypothalamus via its anterior nucleus and plays role in autonomic, emotional and behavioural responses.
2. It plays an important role in sleep and wakefulness and is integrative centre for sleep.
3. The conscious and alertness response is maintained by thalamus. The ventral part of the thalamus includes the reticular nucleus and surrounds the dorsal thalamus. Afferent impulses from the reticular formation of the brain stem project to the intra-laminar nuclei. The reticular nucleus receives impulses from the intra-laminar nuclei. From the reticular nucleus efferent impulses are projected to the cerebral cortex. The reticular nucleus plays a great role in the arousal and alerting reactions.
4. It is responsible for subcortical perception of sensation.
5. The overall muscular movements are controlled by thalamus through its connection to cerebellum and basal ganglia.
6. It plays an important role in recapping memory. Thalamic connection to specific sites of the mesio-temporal lobe aids in differentiation of the functioning of recollective and familiarity memory.
7. *Emotional reactions:* Thalamus is an important reflex centre. The emotional reactions, such as that of rage are mediated through thalamus.
8. It helps in language and speech by integrating 10 cortical and subcortical inputs.

Applied Physiology: Thalamic Syndrome and Prion's Disease

Dejerine-Roussy syndrome also known as thalamic pain syndrome is a condition developed after a thalamic stroke. The ischaemic strokes and haemorrhagic strokes can cause lesion in the thalamus. The lesions in one of the hemisphere of the brain; produces an initial lack of sensation and tingling in the opposite side of the body. The numbness may progress after few weeks or months into a severe and chronic pain which is not proportional to an environmental stimulus, called dysaesthesia (unpleasant, abnormal sense of touch) or allodynia (central pain sensitization).

The following features are seen (thalamic syndrome): All epicritic sensibilities are lost but crude sensations remain, such as:

a. Light touch, tactile discrimination and localisation are lost, but crude touch, pressure, etc. can be felt.
b. Astereognosis and sensory ataxia due to the loss of cutaneous and kinaesthetic sensations.
c. Any difference of temperature between 24°C and 38°C cannot be perceived.
d. Movements of limbs can only be recognized when of considerable amplitude.
e. Emotional aspects of sensations (affective character) are heightened. Relatively weak stimulus will arouse excessive feeling, such as a slight painful stimulus will cause excessive pain. Paroxysmal spontaneous pain occurs.
f. Thalamic lesions produce abnormal involuntary movements. Intention tremor and choreoathetosis are features of thalamic lesions.

He was a Swiss Anatomist who invented the microtome. He was the first to assign that thalamus is the main product of the embryonic diencephalon in 1893. He investigated during period of years 1879 and 1886 regarding the development of the nervous system in a collection of 12 human embryos from 2 to 8.5 weeks development. He observed the progressive outgrowth of nerves into the fingers.

Wilhelm His Sr.
1831–1904

REFERENCE

Krogman, Wilton M., The Human Skeleton in Forensic Medicine, Springfield Illinois: Charles C. Thomas, 1962; 358–359.

Prion's Disease

Hereditary prion disease in which degeneration of the thalamus occurs lead to fatal familial insomnia. The degeneration of the thalamus causes the patient to gradually lose their ability to sleep and develops a state of total insomnia, eventually leading to death. The damage to the thalamus can also result in comatose state.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the afferent and efferent connections of thalamus. Discuss the functions of thalamus.

Short Notes

1. Thalamic syndrome
2. Prion's disease

Dejerine-Roussy Syndrome

Gustave Roussy
1874–1948

Joseph Jules Dejerine
1849–1917

Gustave Roussy a Swiss-French Neuropathologist, and **Joseph Jules Dejerine** a French Neurologist in 1906.

Described the central post-stroke pain (CPSP) in their research paper entitled: "Le syndrome thalamique". The name Dejerine-Roussy syndrome was coined after their deaths.

REFERENCE

Robert H. Wilkins; Irwin A. Brody. Neurological Classics. Thieme, 1997; 93.

Chapter

98

Mamillary Bodies and Internal Capsule

INTRODUCTION

The two small round nuclear masses lie below the floor of the III ventricle and behind the optic chiasma. These nuclear masses receive fibres from ascending pathways and the olfactory areas of the brain. They also send fibres to the thalamic and other brain nuclei. They constitute relay stations for olfactory fibres and are concerned with olfactory reflexes.

INTERNAL CAPSULE

It is a V-shaped band of fibres, bounded medially by thalamus and caudate nucleus and laterally by the lentiform nucleus. The apex of V looks inwards. Most of the ascending and descending cortical fibres pass through this area. Since a large number of fibres remain condensed in this small area, slight damage (haemorrhage, etc.) to this region causes extensive loss of function on the opposite side. It is divided into three segments:

1. Anterior limb—between caudate and lentiform nuclei.
2. Posterior limb—between thalamus and lentiform nucleus.
3. Genu—the bend.

The fibres passing through it are enumerated below, from before backwards (Fig. 98.1).

Lateral striate branch of the middle cerebral artery, recurrent branch of the anterior cerebral artery and anterior choroidal branch of the internal carotid artery supply the internal capsule.

Applied Physiology

One of the branches of the lateral striate artery or the lenticulostriate artery is frequently ruptured and it is known as Charcot's artery of cerebral haemorrhage. The rupture of this artery is due to the fact that the lenticulostriate artery remains under a very high pressure and it has no collateral branches. Haemorrhage due to the rupture of this artery causes 'apoplexy'. In apoplexy there is paralysis of the muscles of the opposite side of the body (hemiplegia), loss of consciousness, loss of control over the sphincters, etc.

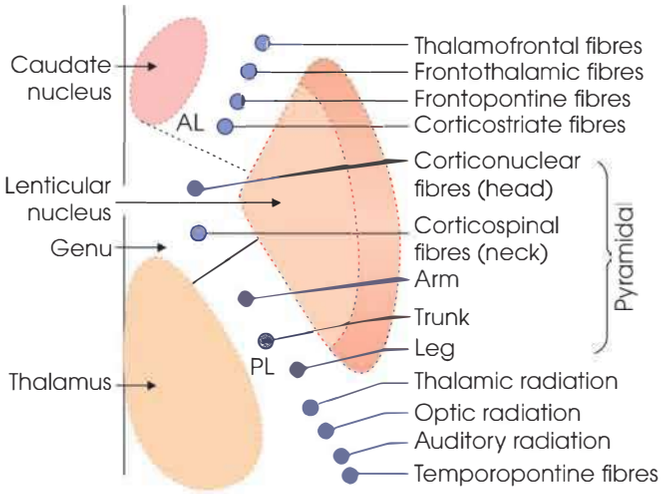


Fig. 98.1: Schematic representation of internal capsule showing the arrangement of ascending and descending fibres in it. AL: Anterior limb. PL: Posterior limb

EXAM-ORIENTED QUESTION

Short Notes

1. Mamillary bodies
2. Internal capsule

Chapter

99

The Basal Ganglia

INTRODUCTION

The basal ganglia are deep sub-cortical nuclei located at the upper part of brain stem and base of forebrain. It is also known as primitive motor cortex. The parts of basal ganglia are caudate nucleus, globus pallidus, putamen, subthalamic nucleus and substantia nigra (Figs 99.1 and 99.2). The red nucleus is functionally related to basal ganglia.

The caudate nucleus and putamen together form the neostriatum or corpus striatum. The putamen and globus pallidus together are known as lenticular nucleus.

The characteristic peculiarity of basal ganglia is that it receives inputs from cerebral cortex and send inputs to cerebral cortex via thalamus, it influences functions of extra-pyramidal system and mainly concerned with control of posture and equilibrium.

The basal ganglia play an important part in controlling the voluntary, reflex and automatic associated movements of the body. Diseases of the different nuclear inclusions of the basal ganglia produce disturbances in muscular activities (muscular rigidity, tremor, athetosis, chorea, etc.).

Basal ganglia have role in planning and programming of movements along with lateral cerebellum (Fig. 99.3).

INTERCONNECTIONS

1. The interconnections of basal nuclei (Fig. 99.4) are complex.
2. On each side:
   a. Projections of the caudate nucleus in part to the putamen.
   b. The putamen to the globus pallidus.
   c. The globus pallidus via the ansa lenticularis, to subthalamic nucleus, substantia nigra, thalamus and fibres to hypothalamus.
   d. Efferent pathway from the lenticular nucleus (putamen and globus pallidus) to the thalamus, subthalamic nucleus (also known as body of Luys), substantia nigra, red nuclei, etc.

Feedback circuit projects from the motor cortex to the caudate nucleus and from the caudate nucleus back to the cortex via the lenticular nucleus, ansa lenticularis and thalamic ventrolateral nucleus.

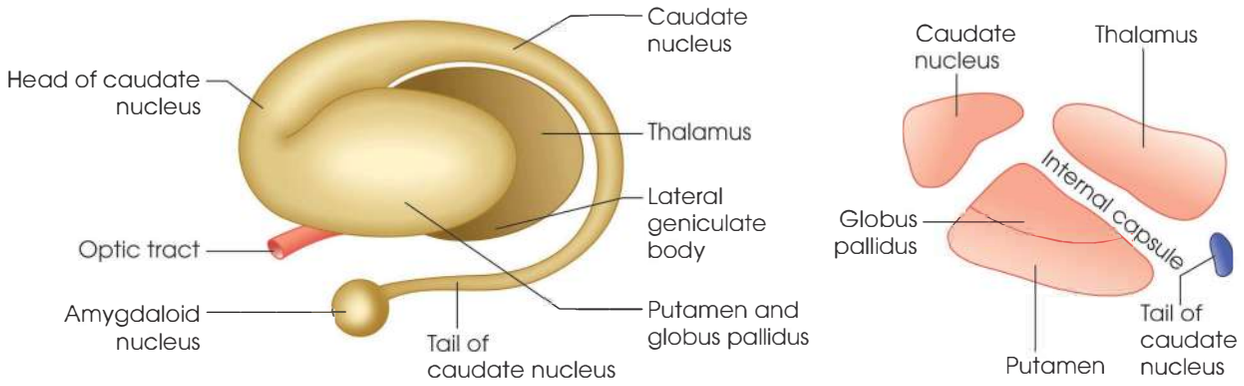


Fig. 99.1: Diagrammatic representation of the basal ganglia

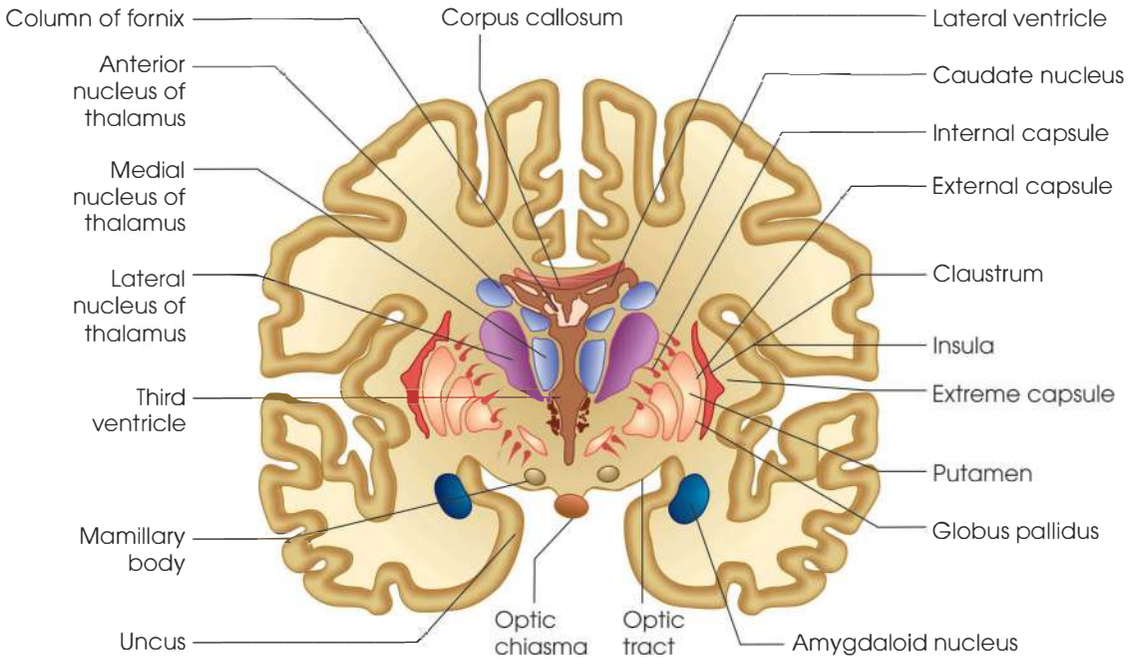


Fig. 99.2: Diagrammatic representation of frontal section through the basal ganglia

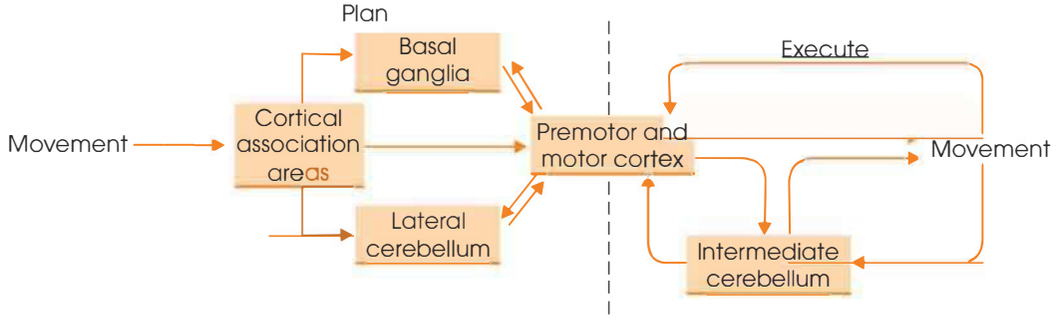


Fig. 99.3: Control of voluntary movement. Commands for voluntary movement originate in cortical association areas. The cortex, cerebellum and basal ganglia work cooperatively to plan movements. Movements are executed by the cortex and are relayed via the corticospinal tracts to motor neurons. The cerebellum provides feedback to adjust and smoothen movement.

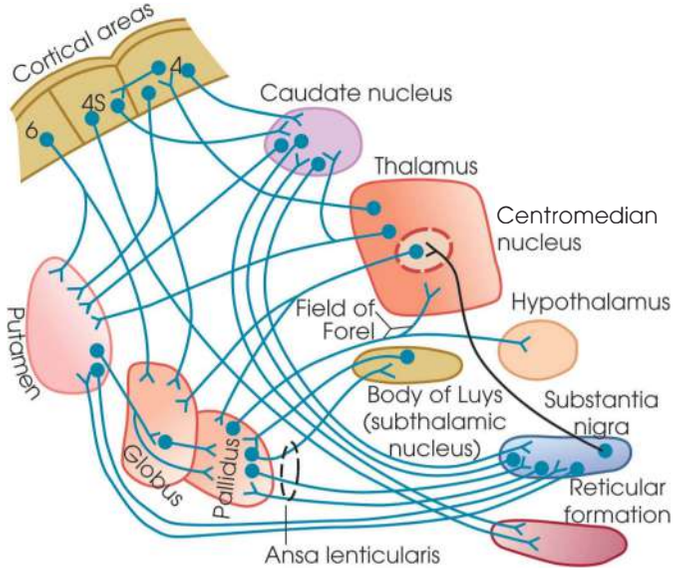


Fig. 99.4: Schematic diagram showing interconnections of basal ganglia, thalamus and cerebral cortex

BASAL GANGLIA CONNECTIONS OF PHYSIOLOGICAL IMPORTANCE

Summary of afferent, efferent and internuclear connections which are mainly involved in its physiological functioning are:

1. *Afferent:* The neostriatum (caudate nucleus and putamen) receive afferents from cerebral cortex and thalamus and the inputs are excitatory via glutamate.
2. *Efferent:* The inhibitory GABAergic relay is from globus pallidus and substantia nigra to thalamus.
3. *Internuclear connections:* From substantia nigra to neostriatum (inhibitory dopaminergic)

   From neostriatum to substantia nigra (inhibitory GABAergic)

   From neostriatum to globus pallidus (inhibitory GABAergic)

   From globus pallidus to subthalamic nucleus (inhibitory GABAergic)

From subthalamic nucleus to globus pallidus (excitatory glutaminergic)

Inorder to have ion depth knowledge of functional physiology of basal ganglia the individual connections needs to be understood in details.

CORPUS STRIATUM

Anatomy

Corpus striatum is a mass of grey matter—lateral and anterior to thalamus. The anterior limb of internal capsule divides it incompletely into two parts:

1. The smaller anterior part is called the caudate nucleus. It lies medial to the anterior limb of the internal capsule.
2. The larger posterior part is known as the lentiform (lenticular) nucleus, lying lateral to the internal capsule. The lentiform nucleus is subdivided into a larger outer part—the putamen and a smaller inner part, the globus pallidus (pallidum).

Connections of the Corpus Striatum (Fig. 99.5)

Intrastriatal (arising and ending within it):

1. From putamen to globus pallidus.
2. From caudate nucleus to putamen.
3. From lateral to the medial part of the globus pallidus.

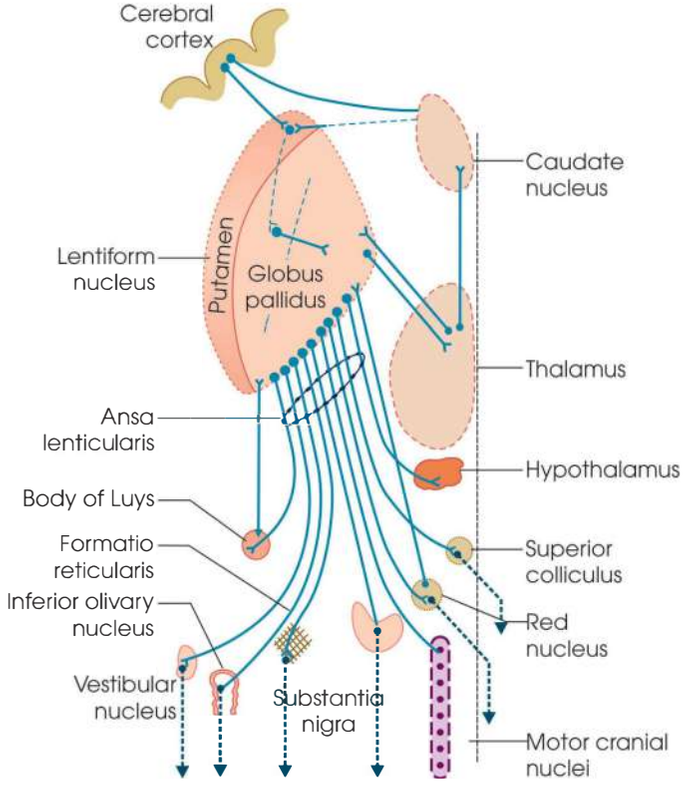


Fig. 99.5: Connections of corpus striatum. Red—efferent; Black—afferent; Red (dotted)—intrastriatal

Efferent (striofugal fibres). All arise from globus pallidus and end outside.

1. Striothalamic. From globus pallidus to lateral nucleus of thalamus.
2. Striosubthalamic or ansa lenticularis. From globus pallidus to red nucleus, and other motor nuclei of the midbrain and hindbrain.
3. Striocortical. A few fibres may go to cerebral cortex.

Afferent (striopetal fibres). Arise elsewhere but end in corpus striatum.

1. Thalamostriate. Thalamus to caudate nucleus and globus pallidus.
2. From body of Luys to globus pallidus.
3. From red nucleus to globus pallidus.
4. Putamen and caudate nucleus receive fibres from the cerebral cortex (areas 4, 4S, 6, 8S and 2S). These fibres are relayed to globus pallidus from where the fibres are further projected into the reticular formation.

Commissural fibres: From globus pallidus of one side to that of opposite side.

From the above it is clear that corpus striatum communicates directly or indirectly with: Cerebral cortex (areas 4, 4S, 6, 8S and 2S)

1. Thalamus
2. Hypothalamus cerebellum
3. Midbrain, pons and spinal cord (through extrapyramidal tracts).

In other words, it guides and controls the activities of almost all the important parts of nervous system, both somatic and autonomic. Caudate nucleus and putamen act as the receiving centre, whereas globus pallidus acts as the discharging centre of basal ganglia.

SUBSTANTIA NIGRA

It is a crescentic mass of nerve cells containing melanin (hence blackish). It lies between the crus cerebri and tegmentum of midbrain.

Connections of Substantia Nigra (Fig. 99.6)

Efferent

- To striatum
- To thalamus
- To red nucleus via globus pallidus

Afferent

- From cerebral cortex (precentral gyrus).
- From caudate nucleus and putamen.
- From subthalamic nucleus.

Body of Luys or Corpus Luysi (Subthalamic Nucleus)

It lies lateral and ventral to the red nucleus and dorsal to the substantia nigra. It is quite distinct from the

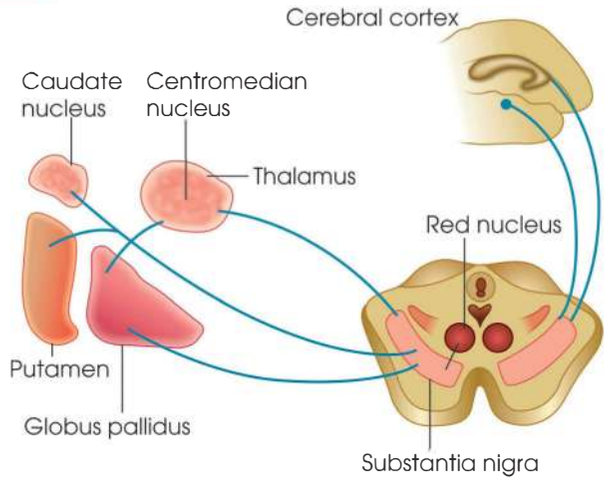


Fig. 99.6: Schematic representation of some connections of substantia nigra with other parts of basal ganglia (subthalamic nuclear connection not shown)

hypothalamic nuclei. It is connected with red nucleus, substantia nigra, globus pallidus (pallidum) and probably others. Functionally, it is believed to be a part of the extra-pyramidal system. The subthalamic nucleus sends excitatory gluatminergic relay to globus pallidus.

Functions of the Basal Ganglia

Functions of the basal ganglia are still not clear but from the various experimental studies following functions can be stipulated:

1. It is mainly involved in **planning and programming** of movements. It prevents after discharge and oscillations in motor systems and brings over smooth conduction of muscular movements.
2. It **controls automatic and associated movements:** These movements; normally are initiated by area 6 and are mediated through corpus striatum such as swinging of arms during walking.
3. **Checks abnormal involuntary movements:** In lesions of the corpus striatum, abnormal involuntary movements occur.
4. **Inhibits stretch reflex and controls reflex muscular activity:** Corpus striatum by exerting inhibitory effect on the spinal reflexes regulates the activity of the muscles which maintains posture. It inhibits the stretch reflex and thereby the muscle tone. Thus, diseases of the basal ganglia produce muscular rigidity which is the characteristic disease such as Parkinson's paralysis agitans. Lesions in the globus pallidus and substantia nigra are concerned with the tremor in parkinsonism.
5. The basal ganglia activities increase during **slow, damp, steady movements** and are unresponsive during rapid movements.
6. The appropriate muscle tone for **skilled movements** is provided by globus pallidus.
7. The caudate nucleus is responsible for **cognition** and cognitive responses during muscular movements.
8. The **co-ordination of impulses** for skilled movement is carried by substantia nigra.
9. **Controls the group movements for emotional expressions:** Subjects suffering from striatal diseases show lack of emotional expressions (mask-like appearance).
10. **Controls eye movement:** Basal ganglia control eye movements. The neural activity in the superior colliculus (deep layer) brings over the eye movement towards the corresponding point in space which is intended to be seen. The strong inhibitory projection from the substantia nigra pars reticulata of basal ganglia are directed towards superior colliculus. Substantia nigra pars reticulata neurons fire continuously at high rates, but they pause and stop firing at the onset of an eye movement thus releasing the superior colliculus from inhibition. Eye movements begin with caudate nucleus activation, which inhibits the substantia nigra pars reticulata via the direct GABAergic projections, and this in turn disinhibits the superior colliculus.
11. **Motivation:** Studies have revealed that basal ganglia also participate in process of motivation. The dopaminergic projection from the ventral tegmental area and nucleus accumbens plays a central role in the brain's reward system.
12. **It is the primitive motor cortex for voluntary muscular activity:** In lesion of pyramidal tracts and area 6 of percentral cortex, the basal ganglia and extra-pyramidal tracts help in the voluntary movements.

APPLIED PHYSIOLOGY

Clinical Manifestations Associated with the Diseases of the Basal Ganglia

Diseases of the basal ganglia show the following clinical features such as:

1. Muscular rigidity causing disturbances in postural reflexes.
2. Abnormality in reflex muscular activity.
3. Disturbances in automatic and associated movements.
4. Voluntary movements are impaired no doubt but no paralysis is observed in human beings.

The clinical syndromes of diseases of the basal ganglia are:

1. Parkinsonism: Paralysis agitans.
2. Progressive hepatolenticular degeneration of Wilson's disease.
3. Chorea.
4. Athetosis.
5. Torsion spasm.
6. Hemiballismus or hemichorea.

Parkinsonism: Paralysis Agitans

The main features in this syndrome are:

Coarse tremor in head and limbs: The tremor becomes more pronounced during emotional excitement and disappeared during sleeping. Section of the lateral corticospinal tract may cause disappearance of the tremor.

Muscular rigidity: Affecting all muscles, specially the flexors causing a general attitude of flexion. The man sits like a statue. The characteristic features of rigidity of the muscles are different from those in decerebrate rigidity. Here stretch reflexes are normal. Lead-pipe rigidity is the feature during passive motion of an extremity with a plastic, dead-feeling resistance. Occasionally there is cogwheel rigidity which is a series of 'catches' during passive motion.

Disturbances in movements: Control of smooth co-ordinating movements is absent. All movements are weak, slow, irregular, and easily fatigued. The patients move in haste with short quick steps and having tendency of falling on the ground. If the patient is asked to check his movement (propulsion and retropulsion) cannot do so quickly and move a little forward.

Absence of automatic and associated movements is the striking features of the parkinsonism. Swinging of the arms during walking is absent. The striking absence of associated movements is called poverty of movement.

All the features described above are not observed in each patient and are caused due to lesion of substantia nigra.

Progressive Hepatolenticular Degeneration or Wilson's Disease

This syndrome was first described by Wilson (1912) and accordingly it is known as Wilson's disease. This is caused by the cellular degeneration of the putamen and globus pallidus. The caudate nucleus is not practically affected. The main features of this syndrome are:

1. *Muscular rigidity* where both the flexor and extensor muscles are affected. The rigidity is very widely spread and affects the muscles of face, trunk and limbs. The rigidity of the facial muscles always gives blank expression as the mouth is kept widely open.
2. *Increased tremor*-like involuntary movements which are often exaggerated during excitement. *Cirrhosis of liver* is often encountered possibly due to disturbances in copper metabolism.
3. *Emotional disturbance* which involves involuntary laughing or crying.
4. Certain greenish-brown pigmentation is generally encountered in the cornea.
5. *All reflexes* generally remain unaffected.

Chorea

It is the disease caused by irregular and spasmodic movements beyond the patient's control and voluntary movements even become jerky.

It is mainly of two types of which one is the childhood disease caused by rheumatic fever and hence it is known as rheumatic chorea or St. Vitus's dance or Sydenham's chorea. Other one is adult type and is a rare familial disease and is transmitted as a dominant character to the off-spring. The main feature of this type of disease is the abnormal gesture and distortion of face during speaking. This disease is known as Huntington's chorea. It is due to disease of small cells of caudate nucleus and putamen.

Athetosis

It is the disease occurring often in the childhood associated with damage to the caudate nucleus and putamen during birth. It is a form of abnormal involuntary movements. In choreoathetosis there are quicker and jerky involuntary movements. These abnormal movements are absent during sleep and predominant during waking.

Torsion Spasm

It is a rare disease and consists of abnormal involuntary turning, twisting movements of trunk, neck and distortion of extremities of the body causing a bizarre caricature.

Hemiballismus or Hemichorea

It is the result of vascular lesions in subthalamic nucleus of Luys and often observed in older age groups having cerebral arteriosclerosis. Clinical features of this disease are flinging abnormal movements of the extremities on one side of the body. This abnormal movement can be abolished by dividing the corticospinal tract or by section of the anterior white column of the spinal cord.

James Parkinson is famous for his 1817 work, an essay on the shaking palsy in which described the clinical condition "paralysis agitans" for the first time, a condition that was renamed later as Parkinson's disease by Jean-Martin Charcot.

James Parkinson
1755–1824

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He was an American born—British Neurologist and first to describe about Wilson's disease.

Samuel Alexander Kinnier Wilson
1878–1937

Karl differentiated the caudate nucleus from the putamen. He identified the globus pallidus and its inner and outer segments.

Karl Friedrich Burdach
1775–1847

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the afferent and efferent connections of basal ganglia. Discuss the functions of basal ganglia.
2. Describe the afferent and efferent connections of basal ganglia. Add note on Parkinson's disease.

Short Notes

1. Hemiballismus
2. Chorea
3. Athetosis

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Chapter

100

The Reticular Formation

INTRODUCTION

Diffused ill-defined mass of nerve cells and fibres forming a meshwork or reticulum in the central portion of the brain stem is collectively known as reticular formation.

It is extended downwards into the spinal cord and upward in the thalamus and subthalamus. Brain stem reticular system consists of the bulbar reticular formation, pontomesencephalic tegmentum, hypothalamus, subthalamus, and certain thalamic nuclei including the thalamic reticular nuclei. These include all cells and their connections excepting the cranial nerve nuclei, relay nuclei of the cerebellar system and relay nuclei of the lemniscal system.

The brain stem reticular formations are concerned with arousal phenomena, alertness, and maintenance of attention and with sleep. It is also concerned with the muscle tone and posture, regulation of vegetative visceral and vasomotor responses, emotional expression, etc.

With the above physiological functions, the brain stem reticular formation comprises mainly two systems—ascending reticular activating system and descending reticular system.

THE ASCENDING RETICULAR ACTIVATING SYSTEM

Key Points

1. The parts of the reticular formation which play roles in wakefulness and in controlling the overall degree of activity of the brain are called the ascending reticular activating system.
2. The reticular activating system is a complex multineuronal and polysynaptic pathways; and collaterals from long ascending sensory tracts as well as from the trigeminal, auditory, visual and olfactory systems is projected into it.
3. The ascending reticular activating system begins in the lower brain stem and extends upward through the mesencephalon, thalamus and finally projected throughout the cerebral cortex (Fig. 100.1).
4. Ascending reticular activating system of the brain stem sends impulses to the cerebral cortex via two pathways. One pathway originating from the mesencephalic reticular formation runs upwards to the subthalamus and is projected diffusely to the cerebral cortex. Another pathway originating from the mesencephalon runs upwards through intralaminar and midline nuclei of the thalamus to the ventral anterior nuclei and reticular nuclei of the thalamus and ultimately projects in all parts of the cerebral cortex.
5. **Functions of the mesencephalic (midbrain) reticular activating system:** The stimulation of the midbrain reticular activating system produces wakefulness by generalised activation of the entire brain including cerebral cortex, thalamus, basal ganglia, brain stem and spinal cord. Wakefulness is generalised and enhanced activities of the different parts of the brain and sleep is the lack of adequate brain excitation. During sleep the reticular activating system is almost dormant.

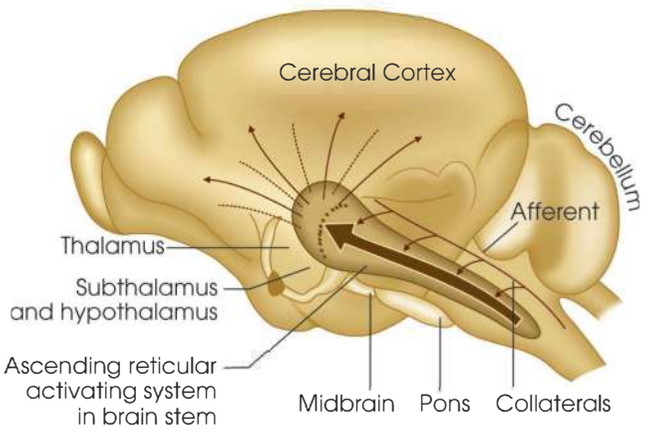

Fig. 100.1: Diagrammatic representation of ascending reticular activating system (Ganong)

6. **Functions of the thalamic portion of the reticular activating system:** This portion of the reticular activating system is different from that of the midbrain activating system. The projections from this nuclear mass ends to a specific area of the cerebral cortex. Besides this, it relays some of the mesencephalic (midbrain) facilitatory signals to the cerebrum in diffused manner so as to cause a generalised activation.
7. **Cerebral activation of the reticular activating system:** In turn cerebral cortex also activates the reticular activating system by sending fibres from sensory motor cortex of precentral and postcentral gyri, the frontal cortex, cingulate gyrus, hippocampus and other structures of the rhinencephalon (Fig. 100.2). This activating system of the cerebrum is important as the motor activity of the body is highly associated with the wakefulness.

Feedback Theory for the Maintenance of Activation of the Reticular Activating System (Fig.100.3)

Once the reticular activating system is activated, it is maintained in a reverberatory fashion for some time. The ascending reticular activating system greatly intensifies the degree of activities of cerebral cortex and in turn cerebral cortex stimulates the reticular activating system. This increased activity of the reticular activating system increases degree of muscle tone and also other peripheral activities. These peripheral activities may cause increased somatic impulses which are transmitted to central nervous system so as to produce the high degree of arousal activity.

This shows that the activity of the reticular activating system produces increased peripheral activities which stimulate in turn the reticular activating system to evoke increased excitation. Furthermore, with the excitation of the reticular activating system, sympathetic system

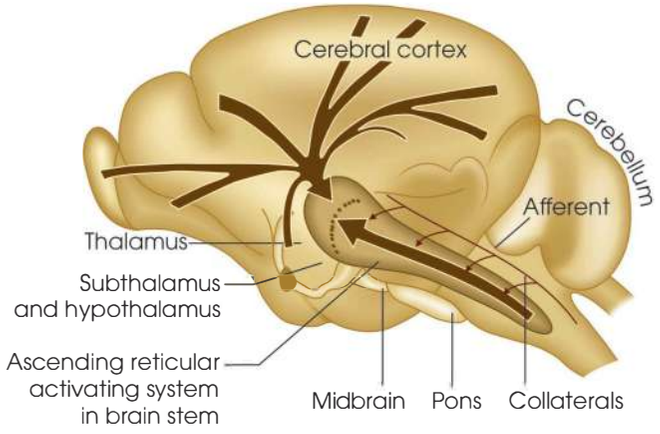

Fig. 100.2: Schematic representation of the convergence of pathways from the spinal afferent systems and from the cerebral cortex on the reticular activating system (modified Guyton)

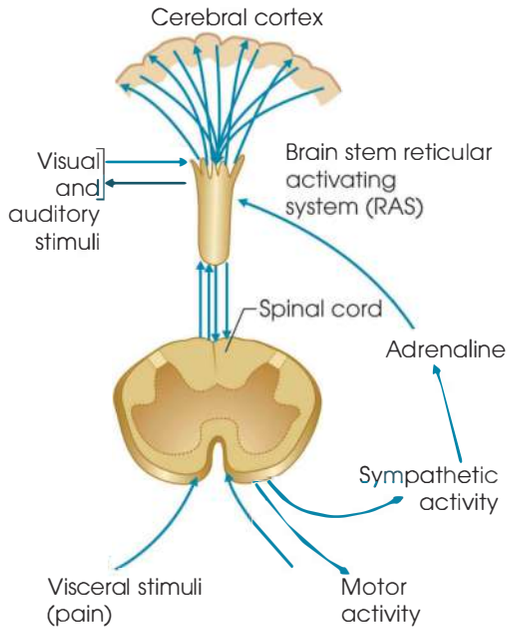

Fig. 100.3: Schematic representation of the feedback mechanism in the development of wakefulness and sleep

is stimulated with the liberation of epinephrine which stimulates in turn the mesencephalic portion of the reticular activating system. Sleep and wakefulness (Fig. 103.3) in an individual can be explained on the basis of the above feedback theories. Once the reticular activating system is excited it is maintained for some time by the feedback impulses originated from cerebral cortex and back, peripheral muscles and back and sympathetic activity and back through liberation of epinephrine. After a prolonged wakefulness, the neuronal cells of the reticular activating system becomes inexcitable and the feedback mechanism gradually fails to keep the reverberatory process active—causing further depressions of the reticular activating system and sleep ensures. After a period of sleep the neuronal cells of the reticular activating system get back its excitability and if further activated by any arousal signal then wakefulness occurs with the onset of feedback process.

Applied Physiology

Barbiturate anaesthesia depresses the reticular activating system by acting on the mesencephalic portion of the reticular activating system. Other anaesthetics probably have specific depressant effects on the mesencephalic reticular activating system.

THE DESCENDING RETICULAR SYSTEM

The descending reticular system comprises functionally two distinct descending reticular projections, such as:

1. Descending inhibitory reticular projection.
2. Descending facilitatory reticular projection.

These descending reticular pathways are organized as reticulospinal tracts which modify the activities of the spinal motor neuron.

Descending Inhibitory Reticular Projection (Fig. 100.4A)

If the ventromedial part of the medullary reticular formation, areas 4S, 2, 8, 19, 24 and caudate nucleus are stimulated then there is inhibition of movements induced reflexly or voluntarily or by stimulation of the motor cortex. The bulbar reticular inhibitory areas are under the inhibitory control of suppressor areas (4S, 2 8, 19, 24) and caudate nucleus. These inhibitory areas are also under inhibitory control of the inhibitory projection fibres from the cerebellum through nucleus fastigius. The corticostrionigral and corticopontocerebellar pathways project over the bulbar reticular inhibitory system which relays in turn the fibres as reticulospinal tract to end finally on the γ-motor neuron of the spinal cord. Stimulation of any part of the inhibitory pathways leads to inhibition of γ-motor as well as muscle spindle discharge, and knee jerk reflex.

Descending Facilitatory Reticular Projection

Stimulation of the facilitatory areas causes increased γ-motor neuron activity producing increased extensor muscle tone, increased discharge from the muscle spindle and also inhibition of flexor reflexes. Descending facilitatory reticular projections are reticulospinal and vestibulospinal tracts (Fig. 100.4B and C).

FUNCTIONS OF THE RETICULAR FORMATION

1. Smooth and purposeful movements, posture and muscle tone are maintained by the balanced activities of the facilitatory and inhibitory descending pathways of the brain stem reticular formation. Ascending reticular activating system maintains the alertness and wakefulness of the animal by any arousal reaction. Stimulation of reticular formation not only exerts wakefulness of the animal but it makes alert to the external environment that has been created during that period. It may be said that reticular formation is indispensable for initiation and maintenance of wakefulness.
2. Damage to the reticular activating system produces commatose state.
3. It is considered to be the higher centre for autonomic nervous system.
4. It is concerned with the regulation of different viscerovascular vegetative functions such as cardiac, vascular, respiratory, gastro-intestinal and metabolic.
5. It also plays in regulation of endocrine functions. Afferent connection from the reticular formation to

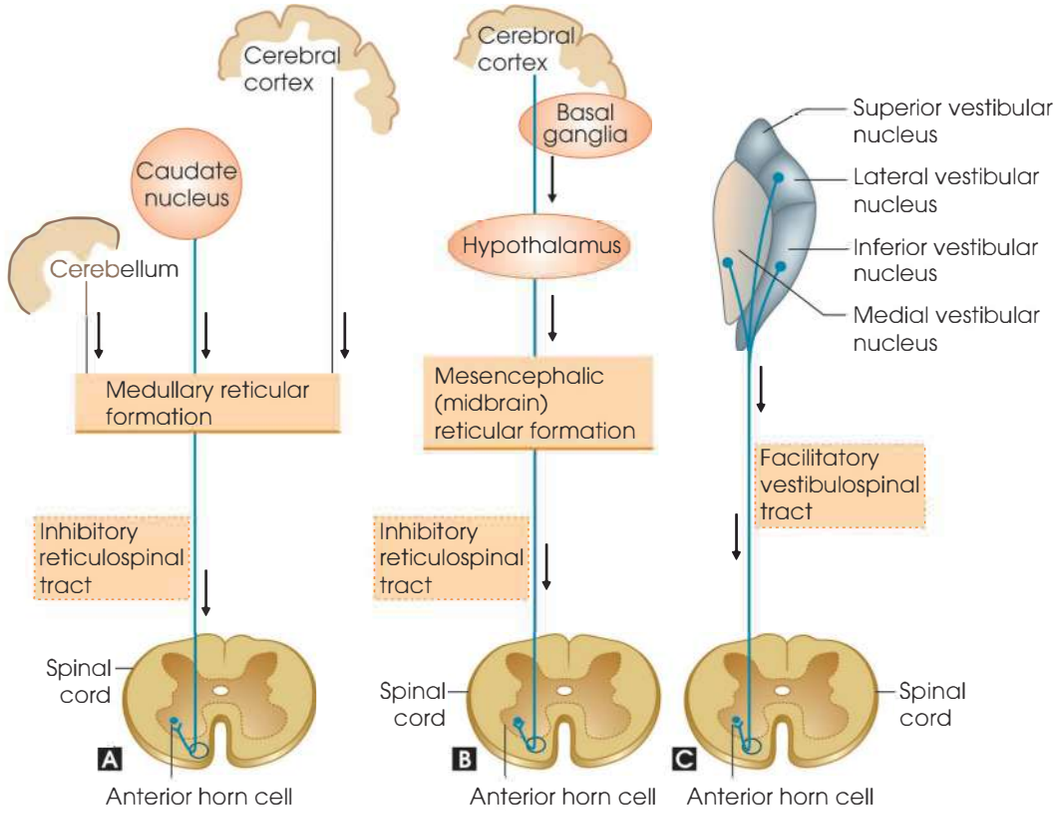

Fig. 100.4A to C: Diagrammatic representation of principal extra-pyramidal facilitatory and inhibitory pathways in the spinal cord

the hypothalamus alters the anterior pituitary function particularly in the secretion of ACTH.

6. It is also concerned with the emotional and sex behaviours of the individual. The limbic system and reticular formation are networks of neurons that function together thus influencing emotion. It has regulatory influence on the formation of conditioned reflexes and development of learning processes. It also takes part in the control of the body temperature.
7. It also comprises the important nuclear group responsible for feeding thirst and satiety.
8. Reticular formation also controls the sensitivity of tactile receptors and of certain other sensory receptors such as in the retina and cochlea. It is also capable of modifying the conduction along various sensory pathways in the thalamus and sensory cortex.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the feedback theory for the maintenance of activation of the reticular activating system. Describe the functions of reticular activating system.
2. Describe the ascending and descending reticular activating system. Discuss the functions of reticular formation.

Short Notes

1. Descending reticular activating system
2. Ascending reticular activating system.

Chapter

101

Muscle Tone and Posture

INTRODUCTION

The passive partial continuous contraction of the muscles is defined as muscle tone. The relaxed muscles exhibit a small degree of tension called resting muscle tonus or tone. Hence, tone is referred as a status of contraction of resting muscle. The maintenance of posture and progression of movement depend on controlled and monitored tone in the large postural muscles. Posture specifies the way in which body is positioned in sitting or standing position. The vestibular apparatus maintains the balance of body during movement and is termed as equilibrium.

MUSCLE TONE

1. Muscle tone is purely a reflex process. It is produced by continual asynchronous discharge of motor impulses from the anterior horn cells, reflexly generated by a sensory impulses arriving at them from the periphery through the posterior roots.
2. Thus, muscle tone is maintained by the impulse activity of afferent nerves whose endings lie in the muscle spindles.
3. This group Ia afferent discharge reflexly excites the α-motor neuron supplying the extrafusal skeletal muscle fibres (Fig. 101.1). This reflex arc is monosynaptic and both afferent (Group Ia) and efferent (α-motor fibre) limbs of the arcs contain large fibres having diameter of about 12–20 μm. γ-motor fibres contain small fibres having diameter of about 3–7 μm.
4. Destruction of either the afferent (for example by tabes) or the efferent (e.g. due to trauma or poliomyelitis) limbs of the arc causes abolition of tone. Thus, muscle tone is abolished due to (i) destruction of posterior root carrying afferent fibres (Group Ia), (ii) destruction of motor nucleus or cell body in anterior horn cell, (iii) destruction of ventral root carrying both α- and γ-motor fibres, (iv) section of muscle nerve total.

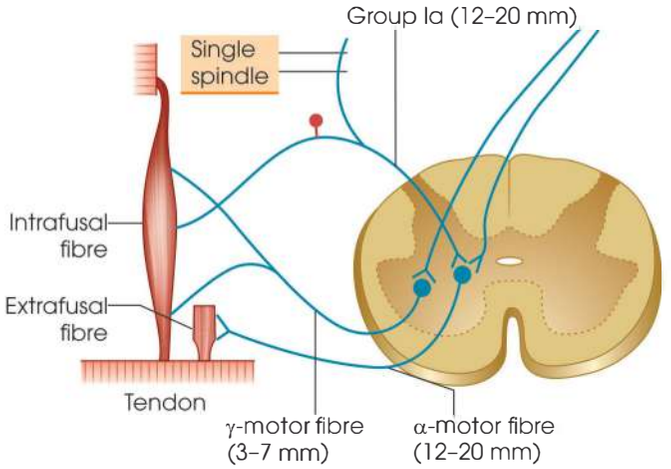

Fig. 101.1: Diagram shows the afferent and efferent mechanisms of stretch reflexes that maintain the muscle tone

5. Exaggerated muscle tone in sherringtonian decerebrate (inter-collicular) rigidity is due to excessive supraspinal drive of the γ-motor neurons, exerted by the preponderant activity of extra-pyramidal facilitatory neurons on the hindbrain. Exaggerated of the muscle tone of decerebrate animal (intercollicular) can be abolished by local application of procaine and also by chlorpromazine which selectively paralyse the γ-efferent conduction. Besides this, the muscle tone of this preparation can be abolished by cutting the dorsal roots (deafferentation), as because the exaggerated γ-efferent discharge causes stimulation of the Group Ia afferent which in turn excites the α-motor neuron.
6. Thus, muscle tone can be described as the partial tetanus of the muscle maintained by an asynchronous discharge of impulses in the motor nerve supplying the muscle. Though the tone is determined by both myotatic (stretch reflex) and non-myotatic (independent of stretch reflex) ways yet in ordinary circumstances, it is maintained by myotatic way, i.e.

through reflex activity of muscle spindle (stretch reflex).

7. Cerebellum is the important site of α, γ-linkage. In presence of cerebellum the muscle tone is maintained through α- and also by γ-activities (myotatic) but in absence of cerebellum the muscle tone is maintained by γ-activity (non-myotatic) only. In ordinary circumstances the vestibular pattern of non-myotatic component is held in check by the cerebellum.
8. The state of muscle tone is mostly depends upon the γ-motor neuron activity which, through contraction of intrafusal fibres of the muscle spindle, increases the tone due to increase of the γ-motor neuron activity, the muscle spindle is stimulated and discharges impulses which cause reflex excitation of the α-motor neuron activity. Increased α-motor neuron activity in turn contracts the extrafusal fibres causing inhibition of discharge from the muscle spindle. The α-motor neuron also excites the Renshaw cells which in turn inhibit the α-motor neuron (Fig. 101.2). In this way the muscle tone is maintained.
9. Though the muscle tone is governed by the spinal reflex arc but it is continuously being regulated or modulated by the influences coming from supraspinal centres. Thus, in an experimental preparation following spinal transection muscle tone is lowered below the section, and in with inter-collicular section muscle tone is found to be exaggerated.

POSTURE

The term posture means a subconscious adjustment of tone in the different muscles concerned, accompanying every active movement, with the purpose of:

1. Making the movement smooth and accurate
2. Maintaining the line of gravity constant (balance equilibrium).
3. It should be noted that posture is not the active movement itself (which in most cases is a voluntary process) but is the associated redistribution of tone in the different groups of related muscles.

Postural Mechanism

Being a reflex process, the postural mechanism must have:

1. Afferent impulses
2. Nuclei (centre)
3. Motor tracts.
4. In addition to this there are certain higher centres which adjust the tone and produce a correct posture.

It is the integrated activity of the multiple inputs from spinal, medullary, midbrain and cortical levels that regulate the posture of the body and make the co-ordinated movement. Smoothness and precision of movement depend upon the motor cortex as well as the cerebellum. Many of the fibres in the pyramidal system are also concerned with the control of posture.

Afferent Impulses for Muscle Tone and Posture (Fig. 101.2)

1. **Kinaesthetic impulses** are the main afferent impulses. Cutaneous impulses take no part. If a spinal animal be skinned, rigidity of muscles persists. If then the posterior roots are severed, muscles loose tone and become limp and the animal falls down.
   Impulses (kinaesthetic) from the deeper parts of 'sole' take an important part in maintaining erect posture.
2. **Vestibular impulses** play an essential part in maintaining equilibrium, tone and posture. Any defect of the vestibular apparatus seriously disturbs the process.
3. **Retinal impulses** also play some part in maintaining posture. If a subject stands on tiptoe with the eye closed, balanced becomes difficult (Romberg's sign).

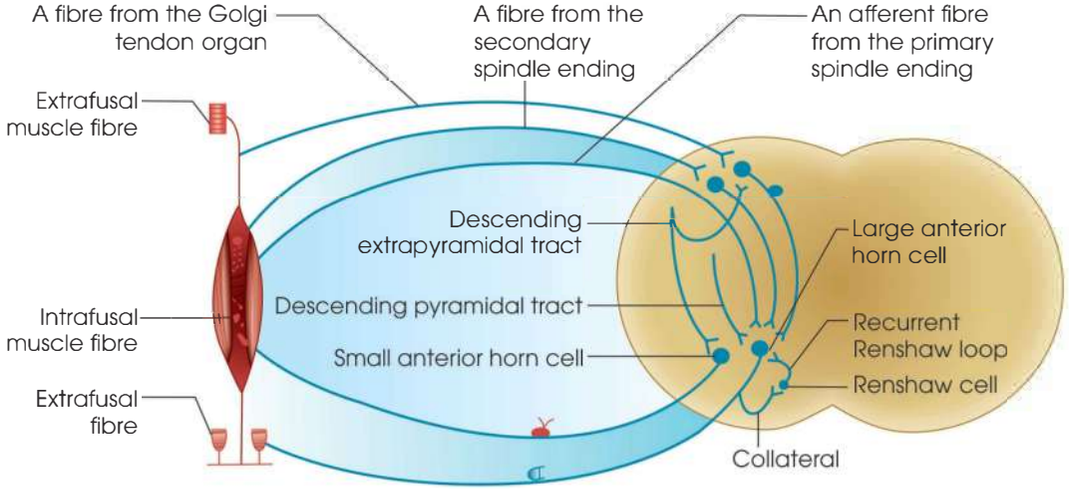

Fig. 101.2: Diagrammatic representation of the spinal reflex arcs and also of the role of Renshaw cell—inhibition in muscle tone and posture

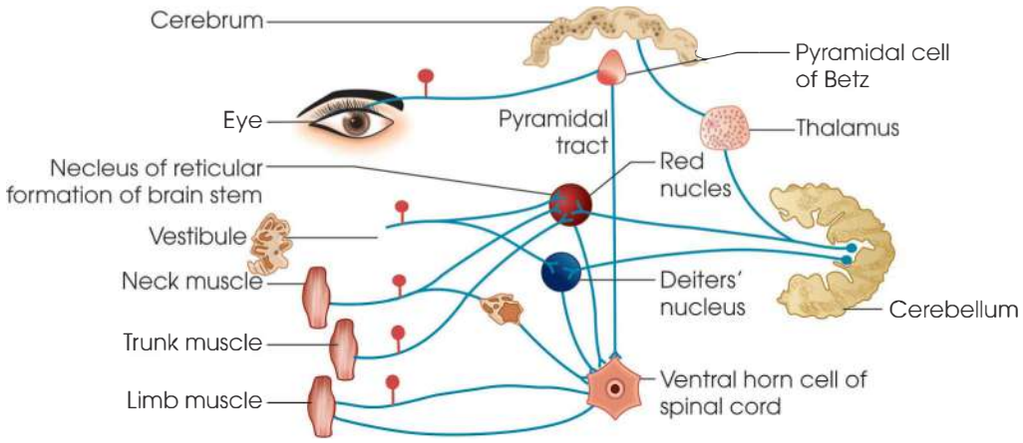

Fig. 101.3: Schematic representation of the regulation of posture (gamma-loop mechanism not shown)

HIGHER CENTRES FOR MUSCLE TONE AND POSTURE

It has been studied by noting the effects of section at different levels of brain. When section passes above the thalamus, not much disturbance of tone and posture is noticed in lower animals, e.g. dog or cat.

Effects of Lesions of the Upper Nervous System

After removal or sectioning the higher brain at a particular level, different experimental preparations can be made for studying the influence of the higher centres on the lower part of the nervous system.

Decorticate Preparation

When the entire cerebral cortex is removed the animal can stand, walk but it shows appreciable rigidity owing to the hyperactivity of the anti-gravity or extensor muscles. Decorticate rigidity is present as a result of cortical area that inhibits γ-efferent discharge via the reticular formation. Decorticate rigidity may be seen on the hemiplegic side in humans after haemorrhage or thrombosis in the arterial branch of middle cerebral artery serving internal capsule. This rigidity is commonly seen in the animal at rest.

Hopping Reaction

When a standing animal is pushed laterally, hopping movements keep the limbs in position to support the body. This response is called hopping reaction.

Placing Reaction

If one limb of a standing animal is pushed out from under it, the limb is promptly replaced on the supporting surface in position to support the body. This response is known as placing reaction.

The placing reactions are usually abolished on one side by unilateral decortication.

THALAMIC ANIMAL (*VIDE* FUNCTIONS OF THALAMUS)

Decerebrate Preparation

1. Section in between the superior colliculi and the inferior colliculi causes decerebrate rigidity (intercollicular) and this experiment was first performed by Sherrington in the cat in 1898.
2. The limbs become hyper-extended and the head is dorsiflexed (Fig. 101.4). In such decerebrate preparation the basal nuclei and cerebral cortex are removed. Respiration, swallowing and other medullary reflexes persist but temperature control and voluntary control of movements are lost. The limbs of this animal are extended, tail is raised and head is elevated (Fig.101.4A). The muscles acting against gravity become rigid and the standing position is maintained only when the rigid animal is placed with its four feet on the ground.
3. The exaggerated muscle tone is seen only in muscles that resist the effect of gravity and this tone is purely reflex in origin and γ-efferent activity is active in such preparation.
4. If dorsal roots are cut then discharge from α-motor neuron still persists though the rigidity disappears; but if the cerebellum is subsequently removed then rigidity again reappears. This rigidity is due to γ-motor neurons activity which takes place through non-myotatic way.

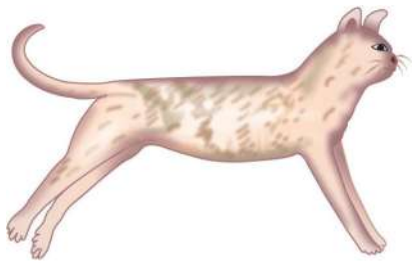

Fig. 101.4A: Decerebrate rigidity in cat (the limbs are hyper-extended and head dorsiflexed)

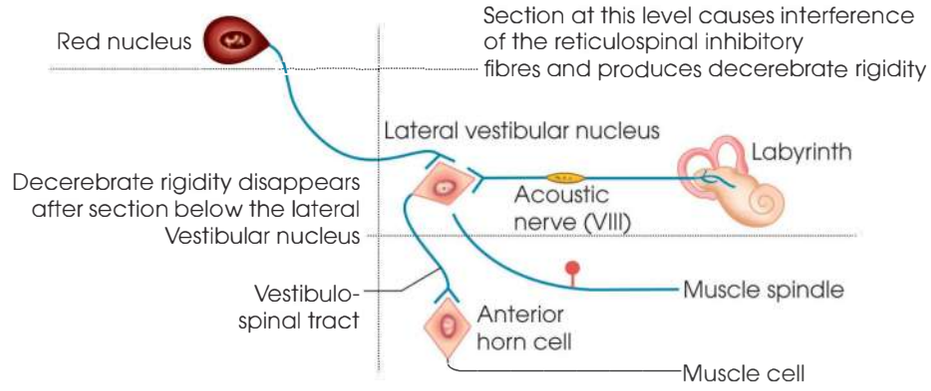

Fig. 101.4B: Decerebrate rigidity in cat and the nervous pathways involved in its production

5. Pollock and Davis (1930) produced decerebrate rigidity in animals by tying the carotid artery and basilar artery at the junction of the pons and medulla.

In such decerebrate preparation, a considerable part of pons as well as the more posterior part of the brain stem and cerebral hemispheres and about half the cerebellum becomes ischaemic and for these reasons, this type of decerebrate rigidity is called ischaemic decerebration. The cause of rigidity in this preparation is not due to γ-motor neuron activity and deafferentation does not abolish this spasticity but if the vestibular apparatus is removed or section made below the level of vestibular nucleus (Fig. 101.4B) then spasticity disappears.

Determination of Posture and Distribution of Muscle Tone

1. Thus, posture is determined by the degree and distribution of muscle tone and depends on the pattern of discharge of motor neurons that supply the muscle.
2. Motor neuron activity is reflexly regulated. Two groups of fibres arise in cells in the brain stem and descend to end in the vicinity of the spinal motor neuron. Since some cells in the brain stem are facilitatory and others are inhibitory, muscle tone and posture are under the balanced activity of the inhibitory and facilitatory areas of the brain stem reticular normal muscle tone and posture.
3. Decerebrate rigidity is the overactivity of the facilitatory areas of the brain stem reticular formation because the activity of the inhibitory areas of the brain stem becomes out of control of the higher centres (cortical areas 4, 6 and caudate nucleus) due to transection at the superior border of the pons causing isolation of the hindbrain and spinal cord from the rest of the brain (section at the level XX of Fig.101.5). Facilitatory areas of the brain stem reticular formation and also of the vestibular spinal facilitatory activating systems are excited causing exaggeration of extensor muscle tone (anti-gravity muscle) due to the γ-motor neuron activity. In such preparation the cerebellar (anterior lobe) inhibitory activity on the brain stem reticular formation as well as vestibular spinal facilitatory activity are still existing (Fig. 101.6). If the anterior lobe of this

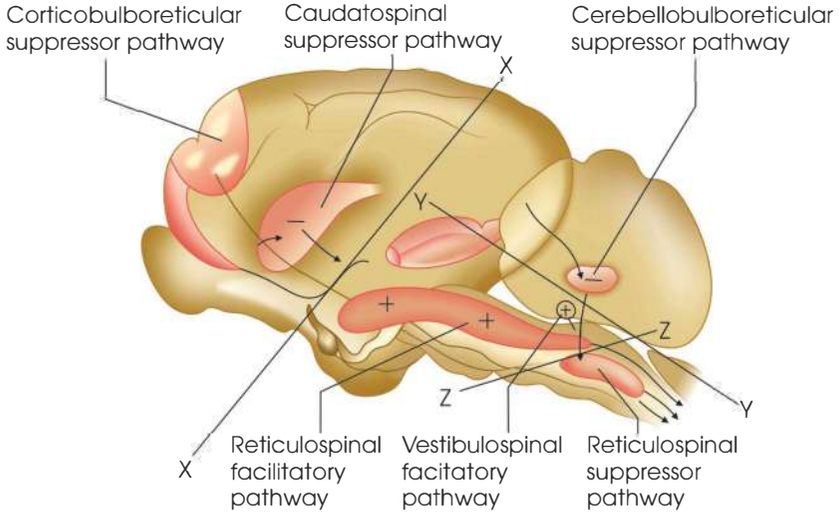

Fig. 101.5: Schematic representation of areas showing the localisation of facilitation (plus sign) and suppression (inhibition) (minus sign) of stretch reflexes (Ganong)

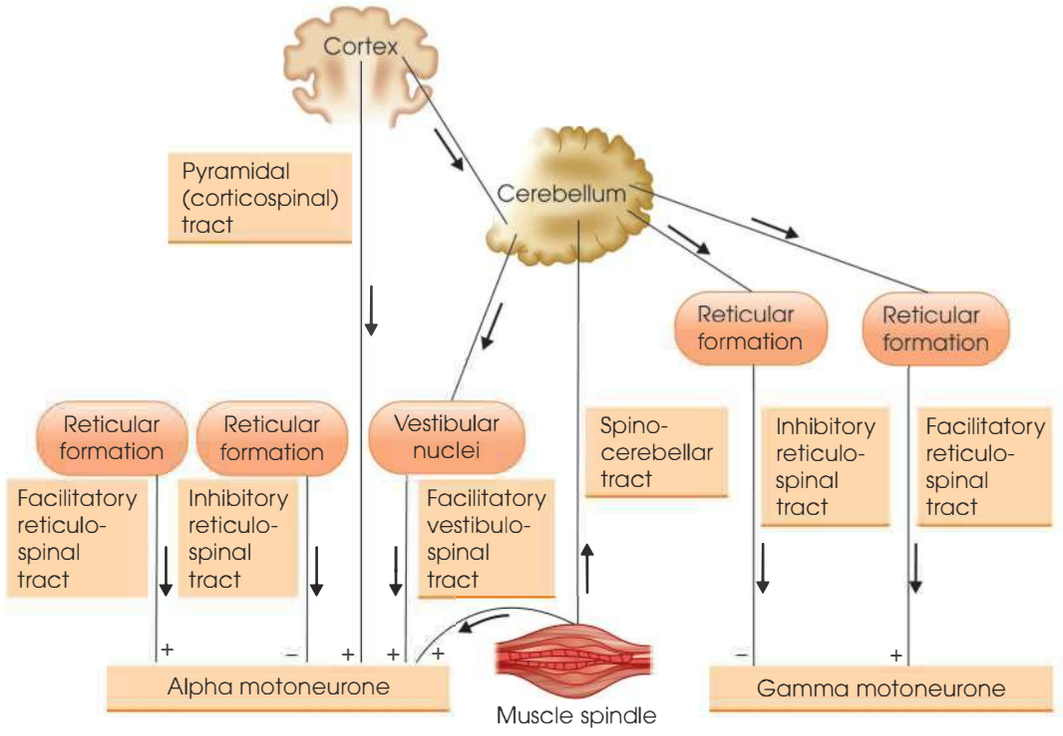

Fig. 101.6: Schematic representation of the activities of spinal alpha and gamma motor neurons and their pyramidal and extrapyramidal controls in the maintenance of muscle tone and posture

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cerebellum is removed at the level YY of Fig. 101.5 then the rigidity is further increased. This rigidity is due to increased α-motor neuron activity (Fig. 101.6). But if the brain stem is transected at the level ZZ of Fig. 101.5 then the tone is lost and muscle becomes flaccid.

4. Decerebrate rigidity is not commonly found in man and the pattern in true decerebrate rigidity is extensor in all four limbs like that in cats and dogs. Defects which produce decerebrate rigidity in man are not normally compatible with life. The actual decerebrate rigidity generally shows extensor rigidity in legs and moderate flexion in arms due to lesions of the cerebral cortex with most of the brain stem intact (Fig. 101.7).
5. *Role of reflexes on posture:* Tonic labyrinthine reflexes: Rigidity of the limb in decerebrate animals varies with the position. No righting reflexes are present and animal assumes its position in which it is put. If the animal is placed on its back then there is profound extension of all four limbs (Fig. 101.8A), but if the animal is turned on either side then the rigidity decreases. Rigidity is minimum when the animal lies in prone position. These changes in rigidity are due to the action of gravity on the otolith organs. This reflex rigidity is known as tonic labyrinthine reflexes. These reflexes can be abolished by removal of the labyrinth. Unilateral removal will cause abolition of the reflex of the same side (Fig. 101.8B). Path is the vestibulospinal tract and the centre is medulla.

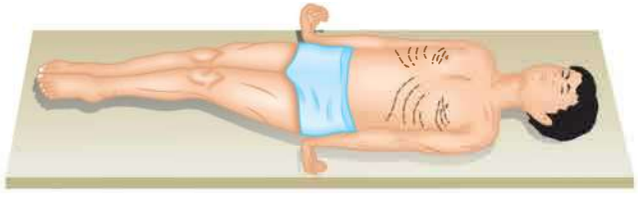

Fig. 101.7: Diagrammatic representation of true decerebrate rigidity in man (Fulton)

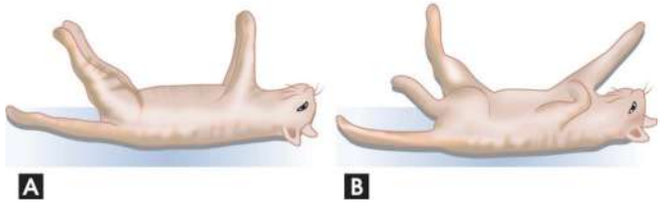

Fig. 101.8A and B: Showing the effect of position on posture of a decerebrate cat. If the animal is kept on its back (supine position) then it takes the typical posture in A. In the same animal after unilateral destruction of the vestibular nucleus, the animals assume the above posture in B

Tonic neck reflexes: If head of a decerebrate cat is turned to side, up or down then changes in rigidity are observed. This reflex is known as tonic neck reflex. For this reflex study, labyrinth is removed. If the head is turned to the right, the right limb is extended and the left limb is relaxed. If pressure is applied to the neck, then all limbs are gradually relaxed (Fig. 101.9). If the head is tilted so as to raise the nose then the forelimbs

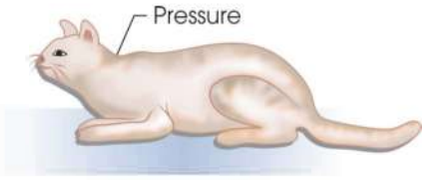

Fig. 101.9: Showing the effect of neck reflexes on the posture of a decerebrate cat. If the pressure (↓) is applied on the neck then the animal takes a typical posture

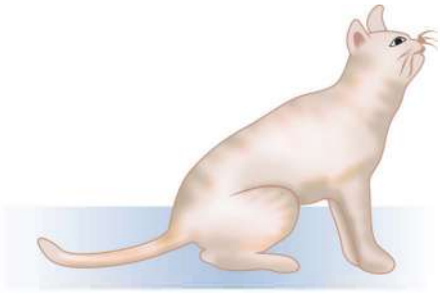

Fig. 101.10: Showing the effect of neck reflexes on the posture of a decerebrate cat. If the head is kept up keeping the nose raised then the animal takes a typical posture

are extended while the hindlimbs are relaxed (Fig. 101.10).

Autogenic Inhibition: Clasp-knife Reflex

a. If the extended limb of a decerebrate animal is forcibly flexed then initially resists, but if more force is applied then the extended limb is suddenly collapsed like a spring-loaded folding knife blade. For this reason, it is also known as clasp-knife reaction of reflex. This is also called lengthening reaction as the extensor muscles are lengthened.
b. Clasp-knife reaction or lengthening reaction takes place by the inhibitory impulses from the tendon-organ causing inhibition of the homonymous motor neuron supplying the stretched muscle. Such inhibition is also called autogenic inhibition and is a protective reflex. It protects the muscle from damaging contraction against strong stretching forces. Group Ib fibres innervating the Golgi tendon organ constitute the afferent limb of the clasp-knife reflex or autogenic inhibition. It is mediated through a disynaptic reflex arc, whereas the myotatic reflex, mediated through the Group Ia fibres is mono-synaptic.
c. Group Ia carries sensation from the annulospiral region of the muscle spindle. Threshold for excitation of the Golgi tendon-organ and of annulospiral region is different. Under moderate stretching the annulospiral region is stimulated and precipitates the myotatic reflex as in case of knee jerk but in strong stretching Golgi tendon-organ is stimulated and the impulse is transmitted through Group Ib fibres causing reflex inhibition (autogenic inhibition) through activation of the internuncial neurons.

Midbrain Component

Righting Reflexes

These righting reflexes are mostly maintained by the nuclei of the midbrain.

The purpose of the righting reflexes in humans is stabilization of the head when there is unpredictable sudden movement. Head righting reflexes (HRR) are a complex group of reactions and are the result of inputs from the vestibular, visual and somatosensory systems governs and regulates postural adjustments if the body becomes displaced from its normal vertical position.

Applied Physiology

Righting reactions in newborn develops shortly after birth since gravity is the new factor in the environment. The righting reaction become very distinguishable as the infant attains one year of age and is maintained throughout the life.

Inputs from Vestibular System

Labyrinthine Righting Reflexes

If the midbrain animal is held by its body and tipped from side to side then the animal keeps its head in level (former position). This head reflex is known as labyrinthine righting reflex. Stimulus is tilting of head which stimulates otolith organs and the centre lies within the midbrain. Midbrain animal can right his head when the body is laid on one side even after labyrinthectomy.

Inputs from somatosensory system:

1. *Body-on-head righting reflex:* Pressure on the body initiates reflex righting of the head. This is body-on-head righting reflex.
2. *Neck righting reflexes* causing righting of thorax and shoulders, then pelvis due to stretch of neck muscles are rising in the midbrain.
3. *Body-on-body righting reflexes:* Pressure on the side of the body may cause righting of body even if the head is prevented from righting. This is the body-on-body righting reflexes whose centre lies in the midbrain.

Note

Applied physiology: Flexion reflexes and regain of tone in spinal preparation in animals or spinal injury in humans.

FLEXION REFLEXES

1. The flexion or withdrawal reflex of the limb in man to a painful stimulus has already been described.
2. Flexion reflex is studied utilising chronic spinal animals where the spinal cord is severed several days before the acute experiment. The reason for delaying

the study of such preparations is to allow the animals to recover from the spinal shock.

3. Spinal shock occurs immediately after spinal cord transection and is revealed by a profound depression of reflex activity; it disappears in a few days. Some of it characteristics as seen in the cat will be described below.
4. The reflex shows a threshold; to elicit it any stimulus should reach certain intensity. When the stimulus is increased in intensity the flexion movement becomes more vigorous and more extensive.
5. Fully developed flexion reflex is accompanied by extension of the opposite leg, the ankle and knee straighten out and the limb is thrust backwards at the hip. This crossed extensor reflex has a much longer latency of 40–100 msec than a flexion reflex proper; and once it begins it takes a second or two to build up to its greatest strength (recruitment), in contrast to the rapid onset of flexion.
6. When the dorsal roots of that limb have been cut the crossed extension still occurs. The crossed extensor reflex may represent the first part of a step away from the noxious stimulus.

Spinal Preparation

Transection of the spinal cord at the midthoracic region produces flaccidity due to absence of different spinal reflex. But though animal recovers a part of its reflexes within a few days but reflex manifestation of supporting the body by the affected limb is absent (Fig. 101.11).

1. In acute spinal preparation a shock stage prevails and duration of such stage depends upon the degree of encephalisation of motor function in different species.
2. This stage lingers for a few minutes in frog, for 1–2 hours in cats and dogs, for days in monkeys and for a minimum of two weeks in man.
3. After recovery from spinal shock in animal and man or in the chronic paraplegic the withdrawal reflexes are present and threshold is greatly decreased. Stretch reflexes are heightened. The threshold stability of the withdrawal reflex is normally low in chronically quadriplegic human. Even minimal noxious stimulus may cause prolonged withdrawal of one extremity as well as flexion–extension patterns in other three limbs. Repeated flexion movement may occur for prolonged period and there is development of flexor muscle contracture. There is also hyperactivity of the stretch reflexes.

   For instance, if a finger is placed on the sole or on the palm of a spinal animal the limb commonly extends following the examining finger. This is known as positive supporting (magnet) reaction which involves proprioceptive and tactile afferents. This type of reaction transforms the limb into a rigid pillar to resist gravity in also to support the animal. After the release of magnet reaction, there is also an active phenomenon partly due to negative supporting reaction which is initiated by stretch of extensor muscles. Owing to the magnet reaction the spinal cats and dogs can be made to stand, albeit awkwardly for 2–3 minutes.
4. In such spinal animals other reflexes like reflex contraction of the full bladder and rectum occur though incompletely.
5. Sexual reflexes like erection of penis and subsequent ejaculation are also possible only after genital manipulation in male spinal animal and man. In female also irritation of the genitalia causes deviation

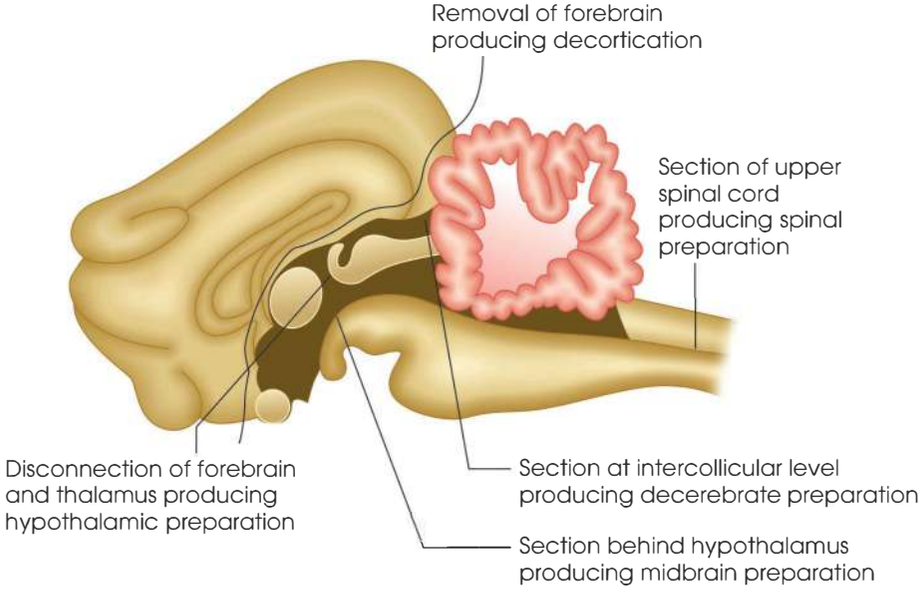

Fig. 101.11: Diagrammatic representation of sagittal section of brain stem showing different levels of transections (Carlos Eyzaguirre)

of tail along with movement of pelvis in copulatory position.

6. Besides these, there mass reflex occurs in spinal animal and man causing evacuation of bladder and rectum, sweating, pallor and raising of blood pressure due to mass irradiation of impulse in the autonomic centre.

SUPRASPINAL CONTROL OF THE STRETCH REFLEX IN RELATION TO MUSCLE TONE AND POSTURE

1. The discharge of small anterior horn cells (determining the basis of the spindle sensory end organs) and the excitability of spinal interneurons are under supraspinal control.
2. This controlling mechanism may be called the extrapyramidal system. Like muscle tone, the extrapyramidal system has been variously defined.
3. The basal ganglia, their associated nuclei and the brain stem reticular formation, together with their descending spinal pathways may also be included. The vestibular nuclei and part of the cerebellum are intimately connected functionally with this system. This total group of structures represents a functional unit.
4. The extrapyramidal system exerts its influence on spinal neurons by virtue of the descending extrapyramidal pathways. With the help of these descending pathways, the extrapyramidal system exercises its control over the stretch reflexes throughout the spinal cord, and normally set the exciting effects in each segment at a level which is most suitable for the functioning of the body as a whole. In order to compute the most appropriate setting, the extrapyramidal system requires a sufficient inflow of information. Such a concentration of information appears to occur in the brain stem reticular formation, and the descending extrapyramidal tracts take origin mainly from this region. On animals, two functional areas of the brain stem are termed as the inhibitory reticular formation and the facilitatory reticular formation. Stimulation of the inhibitory region against a background of the spinal stretch reflex activity reduces the reflex response. Stimulation of the facilitatory area enhances the reflex response. Information passes into these two regions and allows the computation of patterns of descending excitatory and inhibitory impulses. These impulses will set optimal spinal reflex excitability (Fig. 101.12).
5. The inflow of information into the smaller inhibitory reticular formation is from cortical inhibitory areas, corpus striatum (especially caudate nucleus) and the anterior lobe of cerebellum. The inflow into the facilitatory reticular formation is from the middle lobe of cerebellum and from the vestibular nuclei.
6. The brain stem reticular formation also receives collaterals from the ascending sensory pathways where impulses are used by the ascending reticular activating system.
7. This sensory information from the periphery may also be utilised by the brain stem reticular formation in determining the definite patterns of descending extrapyramidal impulses. In this way the reticular formation plays a role as a co-ordinating centre or headquarters of the extrapyramidal system, collecting inflow of information from different sources and on the basis of this information directing the distribution and extent of stretch reflexes throughout the spinal cord.
8. From this point of view, postural reflexes, viz. tonic neck reflexes, tonic labyrinthine reflexes and righting reflexes are particular examples of total activity of the extrapyramidal system.
9. With the difference these reflexes may extend further than simply altering sensitivities of the spinal reflex arcs and may lead to contraction of the extrafusal muscle fibres. However, there is no real discontinuity in the functioning of the extrapyramidal system, because the contraction of the extrafusal fibres is produced as a reflex following on imposed alterations in the length of the intrafusal muscle fibres.
10. This reveals that the descending extrapyramidal excitatory impulses increase the small anterior horn cell discharge (and hence the intrafusal muscle fibre shortening) to such a level that the discharges from spindle sensory endings are enough in activating large anterior horn cells and hence cause shortening of the extrafusal muscle fibres. This type of activity of the extrafusal muscle fibres will continue until the stretch on sensory endings (imposed by intrafusal muscle fibres) is removed, with the recurrent cessation of afferent discharges.
11. When this begins to appear to be the most common method of producing postural reflex activity in the normal subject, postural adjustments can also be obtained by direct descending extrapyramidal activation of large anterior horn cells.
12. In summary, the extrapyramidal system may be considered as the controlling mechanism determining the setting of stretch reflexes.
13. In addition to immense roles of the brain stem reticular formation and spinal cord, the following centres play an important part in the maintenance of posture, tone and equilibrium.
14. The centrencephalic system encompass the neurons from the thalamus to the medulla

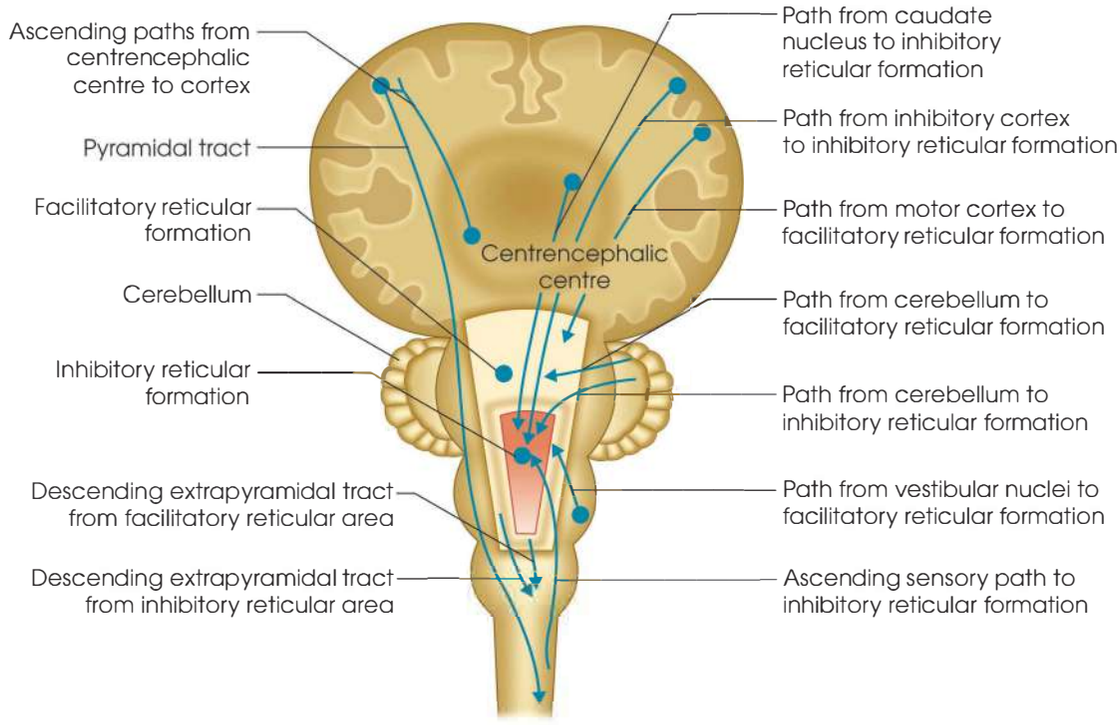

Fig. 101.12: Diagrammatic representation of a longitudinal section of the brain stem showing central organising areas and tracts

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oblongata in the central core of the brain stem and connects the two cerebral hemispheres. It integrates disparate neuronal circuits into a unified whole. It is responsible for temporal synchronization of multiple independent streams of processed information and it is influence the motor activity and influences the posture, tone and equilibrium.

15. *Role of cerebellum:* Palaeocerebellum is connected with the spinal cord and vestibular apparatus and as such, plays an essential part in equilibrium and posture. Disease or injury to this part seriously disturbs the process. Neocerebellar defects also disturb it considerably.
16. *Role of vestibular nuclei:* Role of vestibular nuclei in the maintenance of muscle tone and posture has been discussed. Unilateral destruction of the vestibular nucleus causes abolition of rigidity of the same side. Vestibular nuclei exaggerate muscle tone in ischaemic decerebration through facilitatory vestibulospinal tract acting on α-motor neuron.
17. *Role of basal ganglia:* Being an important organ for exrapyramidal control, it takes an important role in the postural mechanism. Striatal diseases (viz. Parkinson's disease) are characterised by muscular rigidity, tremor, etc. Diseases of the basal ganglia lead to abnormal movement-hyperkinetic, like chorea, athetosis and ballism. Hypokinetic disease: Parkinson's disease (paralysis agitans) is also observed.
18. *Role of cerebrum:* The cerebral cortex, in man and higher animals, with well-developed pyramidal and extrapyramidal areas exerts, immense influences on all the lower centres of brain and spinal cord, and thus exerts considerable influence on tone and posture. Injury or disease of these areas is associated with defective tone and posture. Decorticated ape or man (thalamic man) develops rigidity similar to decerebrate rigidity (legs extended, forelimbs flexed).
19. Role of 'Fast' (white or pale) and 'slow' (dark or red) muscles.

In man and monkey, most muscles are composed of slow and fast muscle fibres. The slow fibres are rich in sarcoplasm with poorly marked transverse striations, whereas the fast fibres are poor in sarcoplasm with well-marked striations. The slow or red fibres, being slow-active in nature, are suitable for maintaining posture: The fast or pale fibres, being rapid-acting in nature, are suitable for rapid phasic movements.

POSTURAL REFLEXES AND POSTURAL CONNECTION

1. All postural reflexes are strength reflex, they are divided into two groups.
   A. Static reflexes (when the body is not in locomotion)
      a. Local static reactions—confined to one limb.
      b. Segmental static reactions—confined to one segment (e.g. both hindlimbs and forelimbs).

General static reactions:
   a. Attitudinal reflexes, e.g. tonic neck and tonic labyrinthine reflexes.
   b. Righting reflexes.

B. Statokinetic reflexes (when the body is in locomotion)
   Reactions to rotation:
   a. Head reactions.
   b. Eye reactions.
   Reactions to progressive movement:
   a. Reactions of head.
   b. Reactions of extremities.

2. Though postural adjustments are very rigid to separate from voluntary movements, yet it is possible to differentiate a series of postural reflexes which include maintained static reflexes and dynamic short-term phasic reflexes.
3. The static reflexes involve sustained contraction of the musculature, whereas the phasic reflexes involve transient movements.
4. Postural reflexes not only maintain the body in an upright, balanced position but provide the constant adjustments necessary to maintain an appropriate postural background for voluntary activity.
5. Both static and phasic reflexes are integrated at various levels in the central nervous system from the spinal cord to the cerebral cortex and are affected greatly through extrapyramidal pathways.
6. At the spinal cord level, the afferent impulses produce simple reflex responses. At higher levels in the central nervous system, neural connections of increasing complexity mediate increasingly complicated motor response. Different postural reflexes with their centres are presented in Table 101.1.

Table 101.1: Postural reflexes

Reflex	*Centre*	*Receptor*	*Stimulus*	*Response*
Optical righting	Cerebral cortex	Visual cues	Opening of eyes	Righting of head
Placing reaction	Cerebral cortex	Proprioceptive, exteroceptive and visual cues	Pressure like touch, push, etc.	Limb replaced on the supporting surface in position to support body
Hopping reaction	Cerebral cortex	Stretch in muscles	Lateral pushing while standing	Movements keep limbs in position to support body
Labyrinthine righting	Midbrain	Otolith organs	Tilting of head	Compensatory contraction of neck muscles to keep head level
Neck righting	Midbrain	Stretch of neck muscles, muscle spindle	Righting of head and tilting of body	Righting of thorax and shoulders, then righting of abdomen and hind quarters
Body-on-head righting	Midbrain	Exteroceptors	Pressure on the side of body	Righting of the head even after destruction of labyrinths
Body-on-body righting	Midbrain	Exteroceptors	Pressure on the side of body	Righting of the body even if the head is prevented from righting
Tonic labyrinthine	Medulla	Otolith organs	Gravity *via* vestibulo-spinal tract	Extensor rigidity
Tonic neck	Medulla	Stretch of proprioceptors in upper part of the neck	Head turned to one side, upward and downward	Alteration in the pattern of rigidity: Extension of limbs on that idle (jaw limbs) to which head is turned. Extension of head leads to flexion of hind-limbs and extension of fore-limbs. Flexion of head causes contained extension of hind-limbs and flexion of forelimbs
Stretch	Spinal cord, medulla	Muscle spindle	Stretch	Contraction of muscles
Magnet reaction or positive supporting reaction	Spinal cord	Proprioceptors in distal flexors and tactile afferents	Pressure on sole or palm	Extension of limbs to support body
Negative supporting reaction	Spinal cord	Proprioceptors in extensors	Pressure withdrawn from sole or palm	Release of magnet reaction

RIGHTING REFLEXES AND POSTURAL CONNECTION

The body has the ability of reflexly coming back to its upright position when the erect attitude is disturbed.

This can be well demonstrated in thalamic animals. When such an animal be laid on its side, the head at once rights itself followed by the body, gradually assuming the upright position. This reflex is called righting reflex. It consists of a series of reactions with the following regular sequence.

Head righting reflex: At first the head rights itself by the following three ways:

1. *Labyrinthine righting reflex:* Position of the head being disturbed, impulses arise from the saccules and reflexly right the head.
2. *Body righting reflex:* The animal being on the ground, kinaesthetic impulses arise from the lower side due to contact with the ground. But no such impulse originates from upper side. This asymmetric series of impulses stimulate the reflex and right the head. In this way, the head can be righted even after double labyrinthectomy. The impulse must be asymmetric. If both sides be symmetrically stimulated, the head remains in the lateral position and is not righted.
3. *Optical righting reflex:* In the labyrinthless cats, dogs and monkeys, head righting reflex can still occur if the eyes are open but not when they are closed. The centre lies in the visual cortex, from where impulses pass to the neck muscles to right the head.

Neck righting reflex: The above three reflexes act primarily on the neck muscles and correct the head position. The trunk being still in the lateral position, the neck gets twisted. This generates fresh impulses and reflexly brings the thorax and then the lumbar region successively into the upright position. (If the righting of the head be prevented impulses from the body surface may cause righting of the body directly.)

Limb righting reflex: The impulses arising from the limb muscles themselves are chiefly responsible for the righting of the limbs.

The chief centre for righting reflexes lies in or near the red nucleus (Fig. 101.3).

Control or Co-ordination of Willed Movement

1. A willed movement is superimposed on a background of muscle tone and postural reflexes. A willed movement itself inevitably causes alternations in muscle tone in order that the movement may be commonly performed. In other words, a normal willed movement involves simultaneous correct functioning of the pyramidal and of the extrapyramidal system. The will to initiate a movement is believed to originate in centrencephalic area, and impulses of the nerve fibres pass from the centrencephalic area to the motor cortex. From the motor cortex nerve impulses pass down in the pyramidal tract to the anterior horn cells.
2. The centrencephalic system may call upon two primary motor cortices:
   A. Rolandic motor cortex is not the only area of the cortex responsible for giving rise to activity in the skeletal muscle while stimulated. Willed movements may also be produced from the supplementary motor area and probably from the second sensory and mesial temporal areas.
   B. Large Betz cells (area 4) give rise to only about 4–5% of fibres of the pyramidal tract, and majority of the descending fibres have small diameter and hence slowly conducting.

Key Points

Pyramidal fibres terminate either directly on the surface of anterior horn cells or indirectly via interneurons.

a. The pyramidal tract terminations might be with either large (α) motor neurons or small (γ) motor neurons. In the former case, willed contraction of the skeletal muscle might be caused by directly activating the α-motor neurons and the final common path, whereas in the latter case the contraction might be caused by a reflex following such as is stated for postural movements.
b. Under these circumstances, the descending pyramidal impulses might increase the discharge of γ-motor neurons. This will lead to intrafusal fibres shortening and a resultant increase in afferent discharge from the muscle spindles.
c. The increased afferent discharge, reaching the γ-motor neurons over the fast monosynaptic pathway, will produce a reflex (following) contraction of extrafusal fibres. The contraction of the extrafusal fibres will then be maintained as long as the increased discharge from the γ-motor neurons will be continued.
d. This type of contraction of the extrafusal fibres may be stated as a follow-up length servo, i.e. a system controlled by negative feedback. The term follow-up length servo was introduced by Merton to describe the modus operandi of α-, γ-loop mechanism. He considered the muscle spindles to serve as misalignment receptors.
e. The apparent advantage of the follow-up method will seem to be that it offer a more accurate control of the movement, since inflow of information is being fed back from the muscle spindles about the progress being made during movement. There is no inevitable evidence of such behaviour on which to decide which of these two (direct or indirect) possible mechanisms is used under specified circumstances; because a willed movement can be directly produced in deafferented limbs, though the execution of such mechanism is not precise.

Summary

The will to initiate willed movement originates in a functional, sensory, integrating area named the centrencephalic region. From this area, nerve impulses pass out to the motor cortex and to the brain stem reticular formation. The latter structure—on the basis of its sensory inflow—gives rise to a pattern of descending excitatory and inhibitory extrapyramidal impulses which set the excitability of the various stretch reflexes. The basal ganglia and lateral portions of the cerebellum (cerebrocerebellum) are parts of feedback circuit to the premotor and motor cortex that is concerned with planning and organizing voluntary movement. The motor cortex discharges, down the pyramidal tract, a pattern of impulses, which acting initially either on α- or γ-motor neurons leads to the ultimate activation of the prime mover muscles. The CNS and spinal reflexes which are influenced by the relay from proprioceptive and musculoskeletal apparatus modulates postural adjustments and maintains equilibrium.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the spinal control of stretch reflex in relation to muscle tone and posture.
2. Describe the supraspinal control of stretch reflex in relation to muscle tone and posture.

Short Notes

1. Postural reflex
2. Muscle tone
3. Righting reflexes
4. Coordination of willed movement
5. Thalamic animal
6. Postural mechanism
7. Determinations of posture and distribution of muscle tone
8. Static reflexes
9. Statokinetic reflexes
10. Spinal preparation

Chapter

102

Vestibular Apparatus

INTRODUCTION

Vestibular apparatus consists of rigid bony labyrinth which lodges a number of hollow membranous structures called membranous labyrinth (Figs 102.1 and 102.2). The bony labyrinth includes:

1. The vestibule
2. The bony semicircular canals
3. The cochlea.
   i. These three communicating cavities are filled up with perilymph which is clear fluid of high sodium.
   ii. The bony labyrinth communicates with the cerebrospinal fluid by way of the cochlear aqueduct.
4. The membranous labyrinth lies within the bony labyrinth, and consists of the cochlear duct, otolith organs—saccule and utricle and the three semicircular ducts—whole thing being situated within the vestibule as a closed system.
5. The membranous labyrinth is an endolymphatic duct ending in a depression in the petrous bone surrounded by a venous plexus and is filled up with endolymph which has high potassium.
6. The posterior and superior canals are situated in vertical planes at 90° to one another and the horizontal or lateral canal lies in a plane passing backwards and partly down.

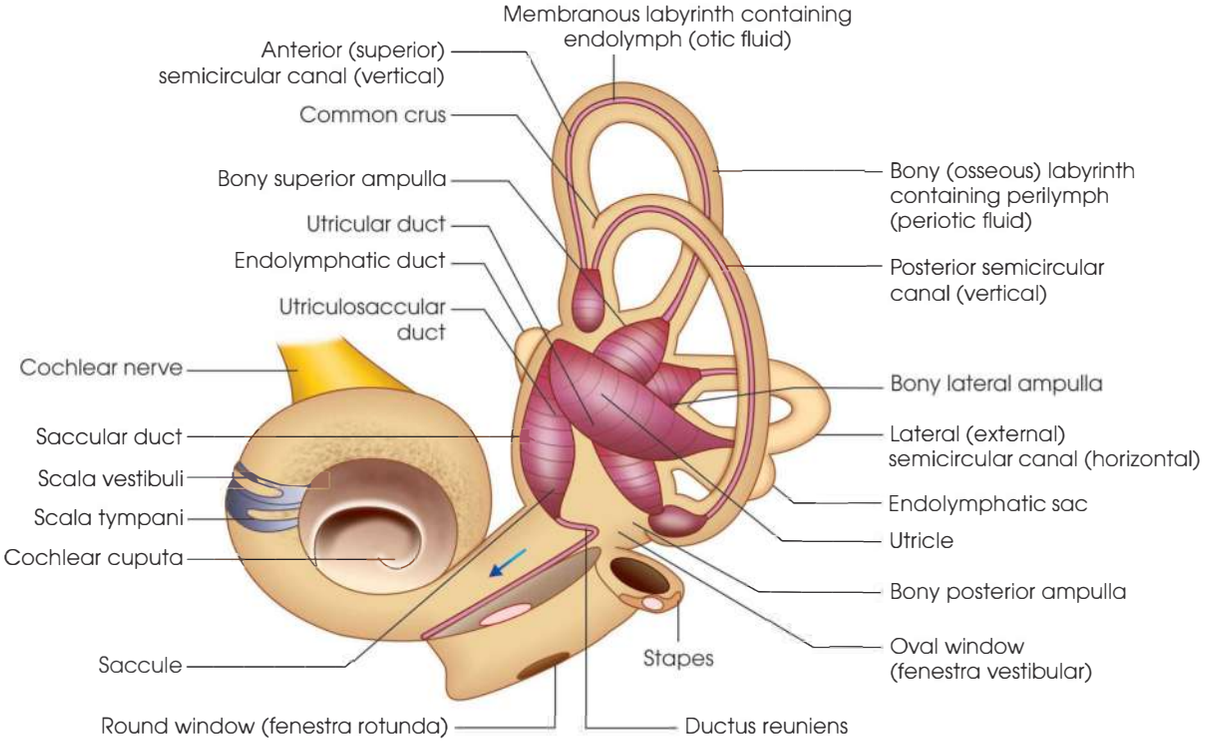

Fig. 102.1: Diagrammatic representation of bony and membranous labyrinths showing vestibular otolith organs and endolymphatic sac and duct. Oval window depicting moving stapes

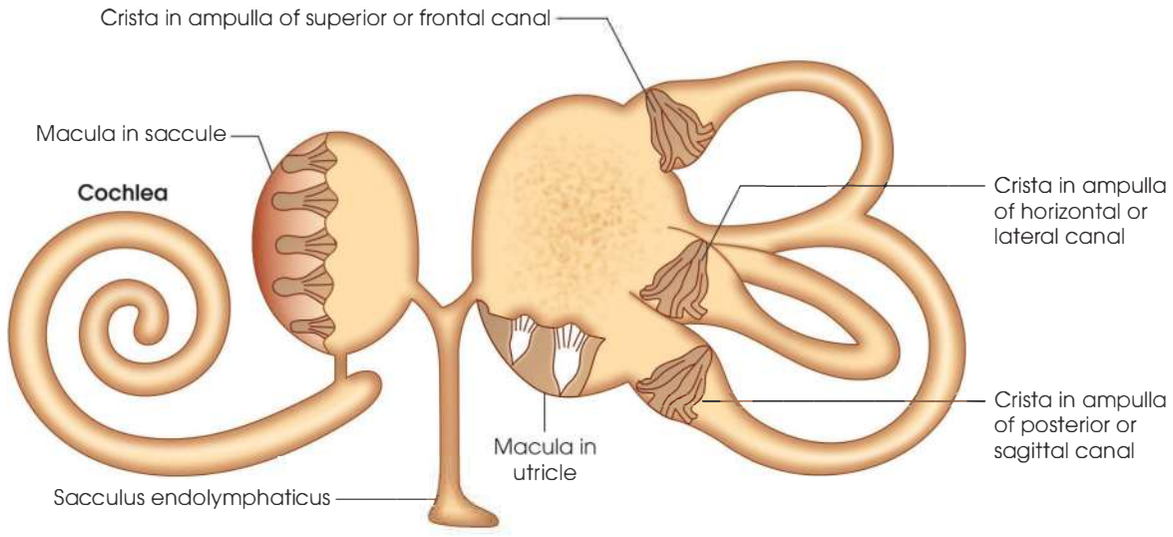

Fig. 102.2: Showing the membranous labyrinth (diagrammatic)

7. Each semicircular duct is about 15 mm long in the human and smaller in diameter than the bony semicircular canals. Each duct has a wider portion or ampulla which contains ampullary crests (cristae ampullaris). The crista is situated at the dilated end of each semicircular canal and possesses hair cells enveloped with a mass of gelatinous substance cupula.
8. Each hair cell carries numerous fine cilia about 0.2 µm in diameter with a stronger cilium nearer the utricle. The cupola comprises a network of fine fibres having a diameter of 10 nm and is embedded in a protein matrix (possibly sulphomucopolysaccharide).
9. The otolith organs (saccule and utricle) possess maculae with bottle-shaped and cylindrical hair cells separated by supporting cells and covered with a layer of jelly-like substance containing particles of otoconia (calcium carbonate).
10. When the fine nerve filaments from hair cells in the cristae and maculae pass centrally in the vestibular nerve to the vestibular ganglion and then to the vestibular nuclei become myelinated (Fig. 102.3).
11. *Fibres from these nuclei:* Some sensory fibres run in the medial longitudinal bundle to the oculomotor nuclei through which changes in position of the eyes are affected.

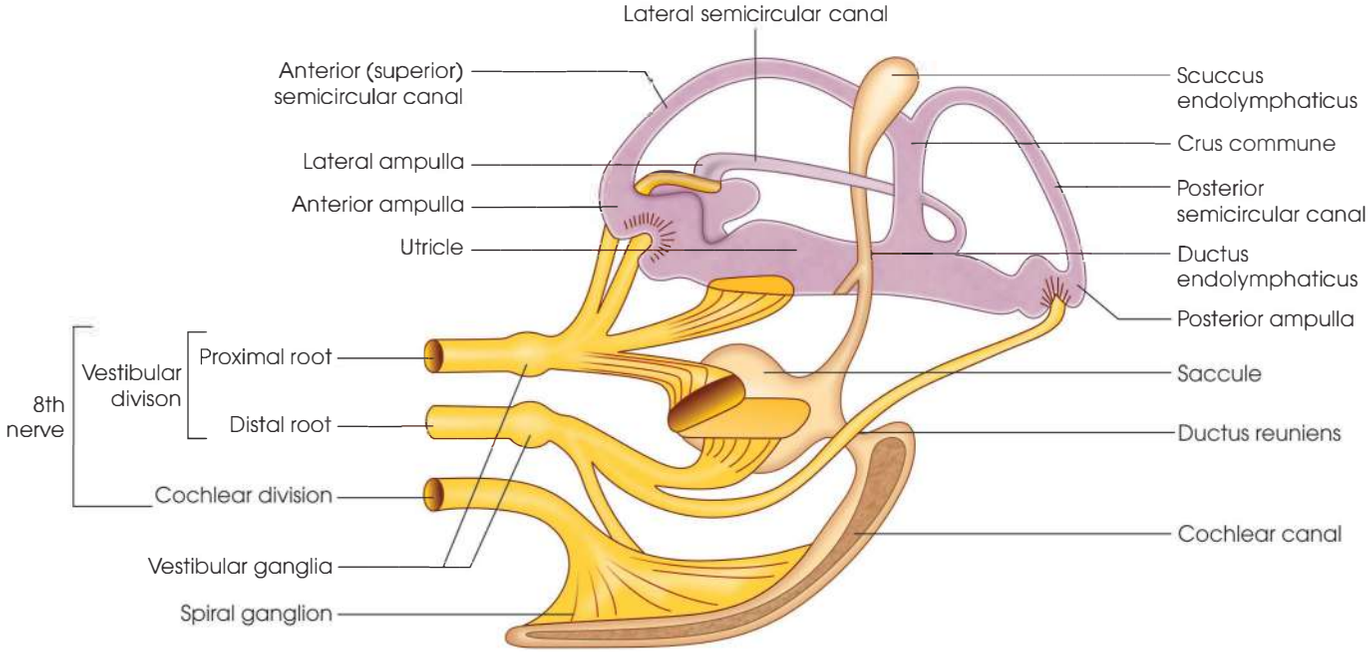

Fig. 102.3: Schematic representation of membranous labyrinth with nerve supply

This is the pathway of nystagmus and counter-rolling. A group of sensory fibres also run in the medial lemniscus to the thalamus. Other sensory fibres pass in the inferior cerebellar peduncle to the cerebellar cortex, mainly to the flocculo-nodular lobe. Some of sensory fibres go in the reticular formation. Another group of sensory fibres pass in the vestibulospinal tract. It addition to these sensory impulses, efferent impulses from the lateral vestibular nuclei reach the hair cells.

12. *Linear or horizontal acceleration:* In the erect position in man the macula of the utricle is more or less horizontal so that the hair cells project vertically upwards with the otoconia and the macula of the saccule lies in a vertical plane (Fig. 102.2). The discharge rate from nerve endings changes according to the gravitational pull on the otolith organs and it depends on the position of the head in space and signals tilting and linear acceleration.
13. *Angular acceleration:* The other type of response is rotation-controlled type, and angular acceleration produces this response and the position of the head does not affect. These impulses come from the cristae of the semicircular ducts because they are most sensitive to rotation in one particular plane. Rotational movement in the plane at right angles produces no or a little alteration of resting discharges. Rotation in the direction which displaces the cupola towards the utricle increases the frequency of discharge; rotation in the opposite direction diminishes the frequency of discharge. If a rotation which produced an increase in frequency is arrested, the rate of discharge declines and it normally takes 10–30 seconds to regain the normal resting discharge rate.

When the head is a rotated, the perilymph and endolymph in the semicircular canal lying in the plane at right angles to the axis of rotation appear to lag behind the movement of the head; the cupola is, therefore, deflected and the hair cells are stimulated. Movement of endolymph and of the cupola from the stereocilia to the kinocilium gives a drop in the potential and increases afferent discharge. Since all the hair cells are situated in the same way, all respond similarly to a certain displacement. In such a way the semicircular canals give information about the angular acceleration of the head in space. If the rotational movement is continued to reach a steady angular velocity the lymph moves with the canal the cupola comes back to its normal position and the stimulation of the hair cells ceases. However, the duration of subjective sensation of turning is related to the time taken by the cupola to regain its resting position. When the rotation of the head ceases the fluid, due to its momentum, continues to move and deflects the cupola in the opposite direction. Rotation of the head seems to produce a sliding movement rather than a deflection of the cupola.

Functions of Vestibular Apparatus

It plays an essential part in the maintenance of muscle tone, posture and equilibrium.

Reflexly

1. Adjusts the relative position of head to that of trunk and limbs.
2. Maintains the erect position of the head. Sends impulses to cortex giving information about the position (otolithic organs) and rotation of head in a particular plane (semicircular canals).

VESTIBULAR FUNCTION TESTS

Disturbance of labyrinthine function, with intermittent attacks of rotational vertigo, nausea or vomiting, and nystagmus are common, because the vestibular apparatus and the cochlea share the same circulation. The most common vestibular function test is the caloric tests. The subject lies supine with his head 30 degrees forward, to bring the lateral semicircular canal into a vertical plane with the ampulla upper most (Fig. 102.4). So, that it responds best to thermal stimulation. A stimulus of cold water 7°C, below body temperature (i.e. 30°C.); and then after an interval, a stimulus of warm water 7°C above body temperature (i.e. 44°C.) is applied through a tube directly to the tympanic membrane and so indirectly to each labyrinth. Syringing the ear with warm water causes a flow of endolymph towards the ampulla of the lateral canal and a deflection of the cupola with nystagmus to the same side. In the normal subject, this produces horizontal nystagmus lasting about 2 minutes (Fig. 102.4). Placing electrode on the skin at the outer canthi of eyes, the eye movements can be recorded and this is known as electro-nystagmography.

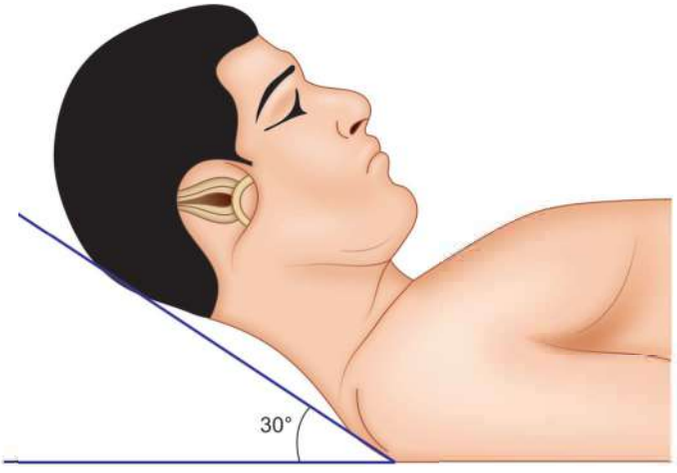

Fig. 102.4: Showing vestibular function test. The subject lies supine with his head raised 30° so that crista is horizontal

The caloric test has great value in the diagnosis of organic lesions at all levels of vestibular system and in peripheral lesions (e.g. semicircular canal paralysis, etc.).

THE SEMICIRCULAR CANALS

Anatomy

1. There are three semicircular canals lying in the three planes at right angles to one another (Fig. 102.6).
2. The canals are lateral, anterior (superior) and posterior. The lateral (external) canal is horizontal. The other two are vertical and make an angle of about 45° with the frontal and sagittal planes. The anterior canal of one side is in a plane approximately parallel to the plane containing the posterior canal of the other side. Thus, the six canals on two sides remain arranged in three planes, making three functional pairs (Figs 102.7 and 102.8).
3. Each canal begins in a dilatation called the ampulla. In the ampulla there is located the specific sense organ—the crista ampullaris. The ampullae of the corresponding canals lie facing each other.
4. The three canals open into the utricle by five apertures (not six), one aperture (common crus) being same to the two vertical canals.
5. The utricle communicates with the saccule through the utriculosaccular duct. The endolymphatic duct (ducts endolymphaticus) arises from the utriculosaccular duct and ends as a blind sac—the endolymphatic sac (saccus endolymphaticus). The saccule communicates with the duct of cochlea through ducts reuniens (Figs 102.1 to 102.3 and 102.7).

Histology (Fig.102.9)

The histological structure of ampulla shows the presence of the sense organ—crista ampullaris. It consists of a ridge of neuroepithelium and is surrounded at its base by the planum semilunatum, which is a secretory epithelium. The neuroepithelium

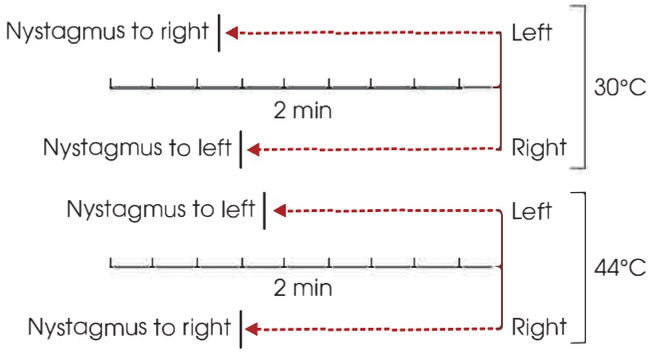

Fig. 102.5: Caloric tests. Normal average response to stimuli applied separately to each tympanic membrane. The dotted lines show the duration after nystagmus from the beginning of the stimulus

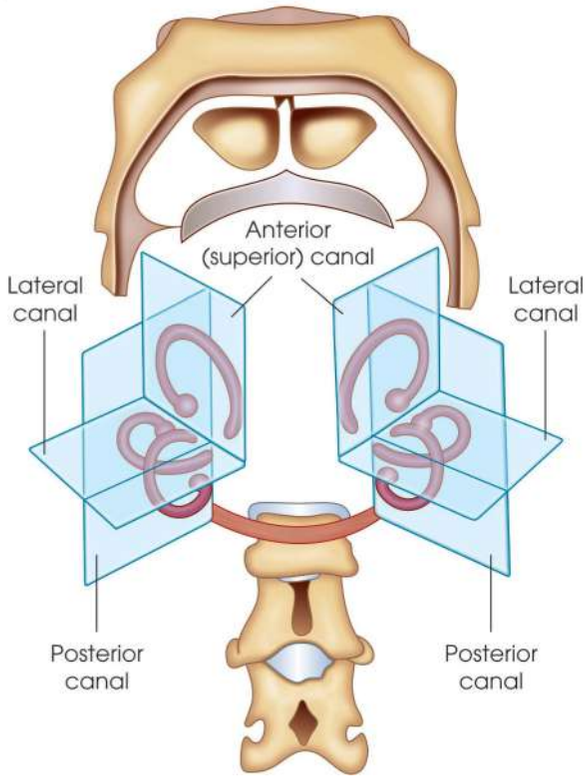

Fig. 102.6: Relative position of cochlea and vestibular apparatus on the left side (Best and Taylor)

comprises two types of hair cells—one is flask-shaped (type I of Wersall) and the other is cylindrical (type III). Both types of vestibular sensory cells bear hairs—the kinocilium (single hair) and stereocilia (40–60 hairs).

Kinocilium is thicker and single while the stereocilia are numerous and thinner (Fig. 102.10). When movement of the lymph occurs towards a kinocilium the discharge increases, and when it occurs towards the thin stereocilia the discharge declines. Between the hair cells lie the supporting cells of Retzius with their nuclei at the base and microvilli at the apices. A mucoid-gelatinous mass with its fine parallel channels encloses the long sensory hair. This soft mucoid material which is known as cupola, is a dome-shaped structure and extends upward from the crista to the roof of the ampulla. It had long been known as histological artifact but at present it has been regarded as an essential moving part in the stimulation of the hair cells. The sensory nerve endings attached to the hair cells send impulses into myelinated nerve fibres having diameter of 2 to 9 µm.

Mode of Action (Fig. 102.11)

1. Change of pressure of the endolymph (optic fluid) acts as the stimulus. Since endolymph has inertia, when the head is rotated, the endolymph lags behind. Consequently, when the rotation is from left to right, pressure in the right ampulla increases,

while that in the left falls. These opposite pressure changes stimulate the cristae which send up impulses of the brain giving information about movements of the head in that plane.

2. Semicircular canals may be stimulated in a subject by rotating him in a special chair at a quick speed (say one revolution in 2–3 seconds). If the subject is rotated to his left both eyes move slowly to the right. This is followed by a quick movement of the eyes to the left which brings the eyes back to the middle position. Another slow and quick movement takes place and so on. This phenomenon is called the vestibular nystagmus.
3. Excessive stimulation of the semicircular canals, particularly if the rotational movement is about a horizontal axis, commonly shows drowsiness, pallor, vertigo, salivation, nausea and vomiting feature of sea-sickness. There are unpleasant sensations from a conflict of sensory information. Since, the medial, vestibular nucleus is very closely situated to the dorsal vagal nucleus; there is a considerable degree of interconnection between them. When the inhibitory influence is withdrawn from the vestibular system the increased neural activity overflows to some cells in the dorsal vagal nucleus causing motion sickness. So, the vagal stimulation causes headache, pallor, perspiration, nausea and vomiting of the motion sickness.

Functions

Semicircular canals give information about the direction, degree and the plane of movement of the head (kinetic or dynamic equilibrium). In man the semicircular canals can be stimulated by angular acceleration. This angular acceleration in man can be accomplished by seating the subject on a rotating chair (Barany's chair)—producing vertigo, nausea and nystagmus. Besides this, the semicircular canal is also stimulated by:

1. Introducing cold or warm water into the ear.
2. Circuit of a direct current through the labyrinth.
3. Mechanical stimuli through compression or decompression of air.

Each functional pair gives information about its own plane. For instance:

- Right anterior and left posterior canals inform about the right oblique lane.
- Left anterior and right posterior about the left oblique plane.
- Two lateral canals inform about the horizontal plane.

If movement be complex, more than one pair will come into action.

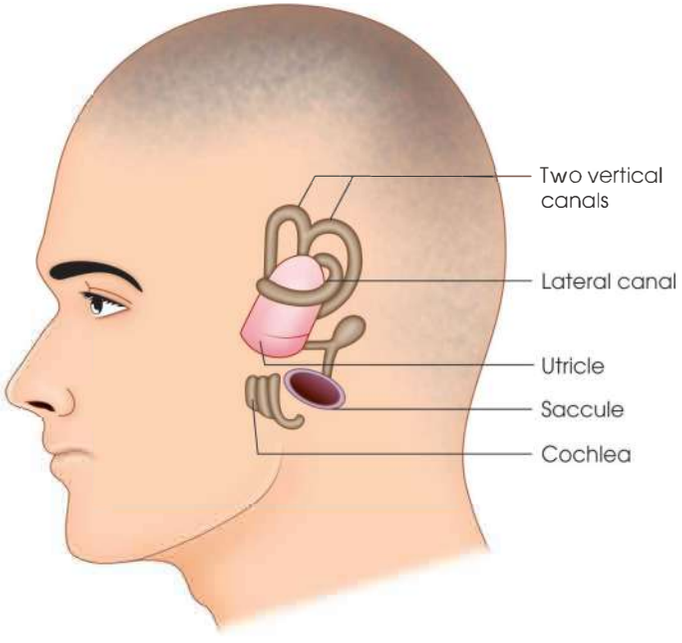

Fig. 102.7: Arrangement of the three semicircular canals in three planes at right angles (Starling)

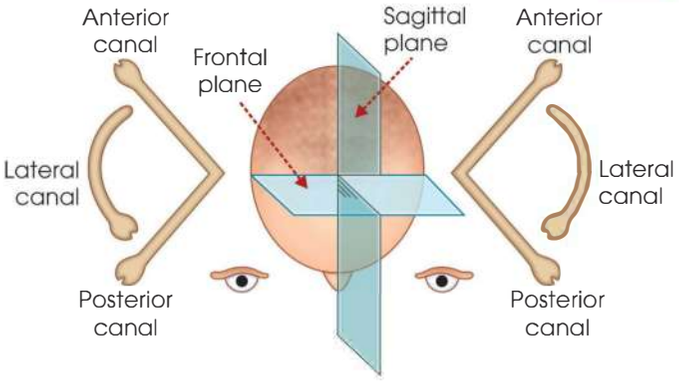

Fig. 102.8: Arrangement of semicircular canals on two sides—making three functional pairs. Anterior canal of one is in the same plane as the posterior canal of the other (Best and Taylor)

Coriolis Effects

Coriolis effect is the specific type of angular acceleration that causes major motion sickness in spacecraft due to rotation of the earth deflecting a moving mass from a north or south path. This effect is generally observed when one set of semicircular canals has equilibrated to a constant angular velocity and a head motion is made in a different plane.

THE OTOLITHIC ORGAN

Anatomy

It consists of saccule and utricle.

Histology

It consists of same three coats as the semicircular canals. A sense organ (neuroepithelium), corresponding to crista, is present both in saccule and utricle, called the macula. The macular epithelium is same as that of the

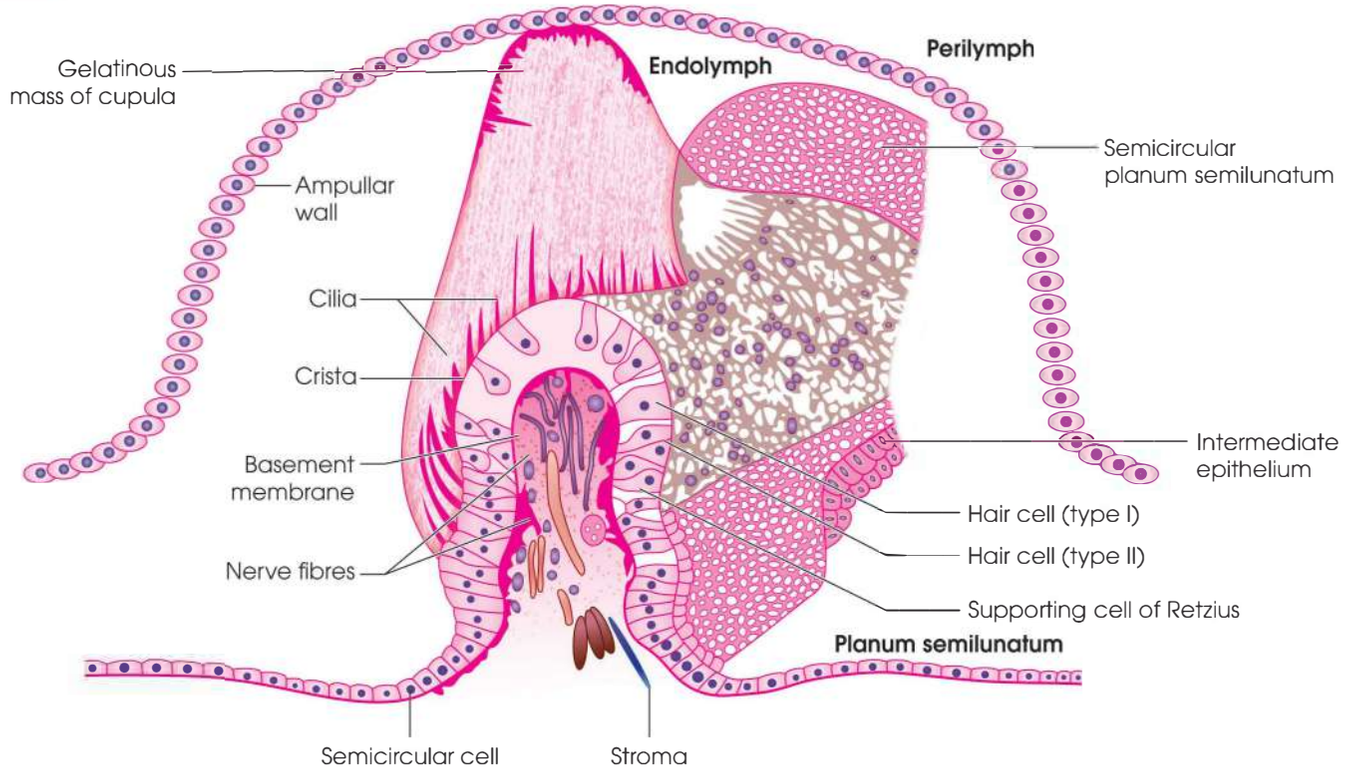

Fig. 102.9: Histological representation of one-half of an ampulla crista in a longitudinal section of a semicircular canal which passes across the crista (Carlos Eyzaguirre)

crista (Fig. 102.12). The additional feature here is the presence of small calcareous granules (otoconia otolith) embedded in the otolithic membrane. Here the cupola is replaced by the otolithic membrane which is also a gelatinous mass. When the head is in the erect position, the macula of the utricle remains in the horizontal plane with the hairs projecting upwards and the otoliths passively resting on the hairs (Fig. 102.13C). The macula

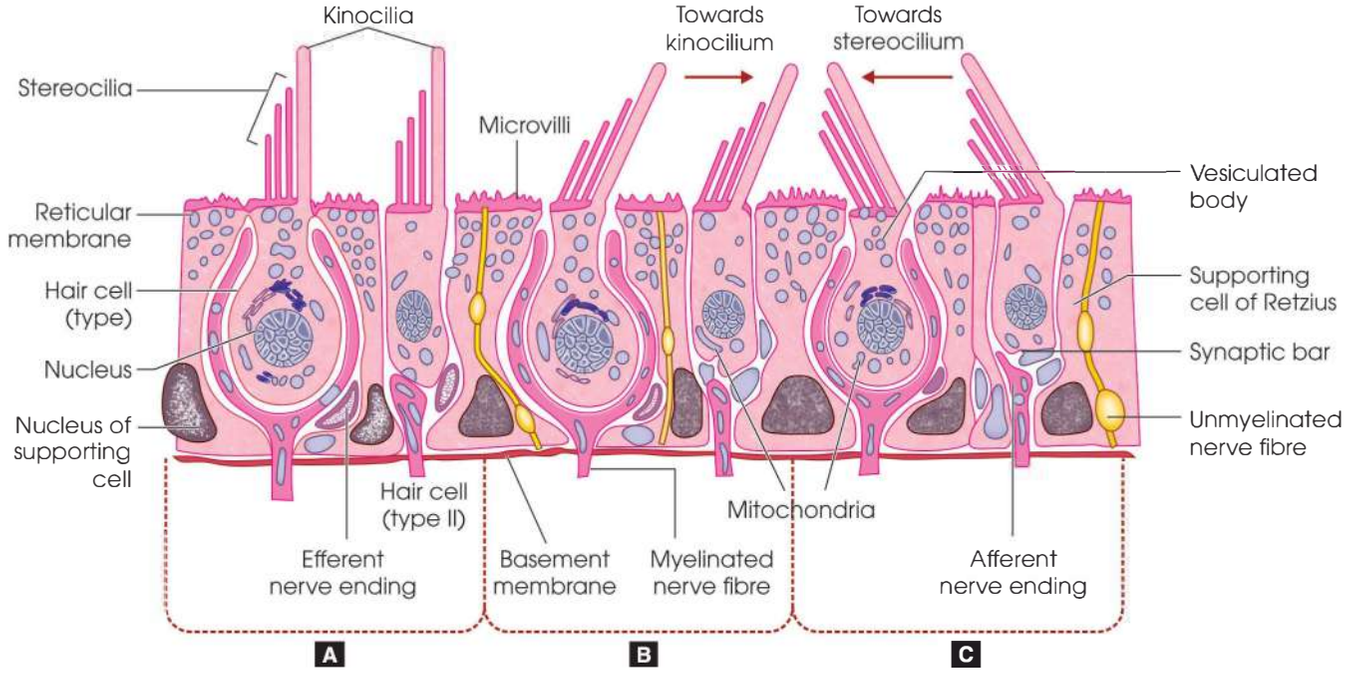

Fig. 102.10: Schematic representation of two types of hair cells showing relationships between afferent (sensory) and efferent nerves which terminate on the sensory cells and also the pattern of stimulation of and displacement of the sensory nerve fibres. (A) In resting activity, (B) in stimulation depolarisation, (C) in inhibition hyperpolarisation

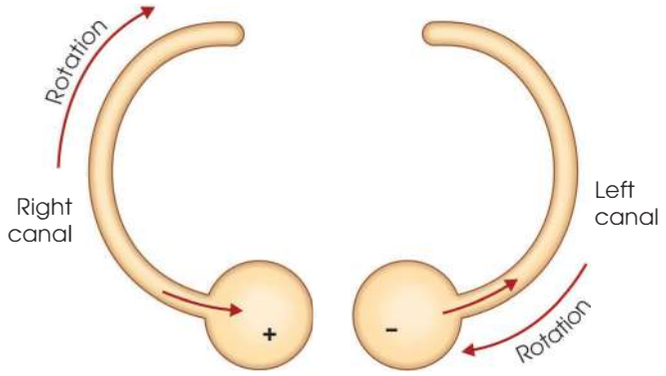

Fig. 102.11: Mode of action of semicircular canals '+' indicating increased pressure; '–' fall of pressure

of the saccule, on the other hand, lays in the vertical plane, the hairs the projecting horizontally outwards and the otoliths hanging down vertically on the outer side.

Mode of Action

1. The otolith organs act as stretch receptors. Gravity acts as the stimulus. When the otoliths hang down vertically, they exert a pulling action on the hair and produce the maximum stimulation (Fig. 102.13A).
2. When the otoliths passively rest upon the hairs, the stimulation is minimum (Fig. 102.13C). Displacement of hairs in lateral direction or sideways induces an intermediate type of stimulation (Fig. 102.13B).
3. Consequently, when the head is tilted on the left side, the otoliths of the left saccule are hanging downwards producing the maximum stimulation while the otoliths of the right saccule are simply resting on the epithelium, causing the minimum stimulation.
4. This difference of stimulation of the saccules on two sides gives conscious information about the position of the head in the lateral plane. Similarly, the utricular maculae are stimulated by antero-posterior movement of the head and give information about the position of the head in the antero-posterior plane.

Functions

The otolith organs give information about the static position of the head (static equilibrium) and not of movements. The saccules give information regarding the position of the head in the lateral plane, while utricles, in the antero-posterior plane. With all its probability, otolith organs are concerned with normal position of the head and with linear acceleration.

Unilateral Extirpation of the Labyrinths

1. In lower animals produces derangements in postural mechanism and causes nystagmus, skew deviation of the eyes, alteration of the position of the head, spiral rotation of the trunk, flexion of the limbs towards the side of the lesion and extension of the limbs of the opposite side of the lesion. The animal comes at rest with the operated side down.
2. In man a section of one vestibular nerve makes a temporary disturbance of posture and gait. This is at a minimum if the head is held steady because the

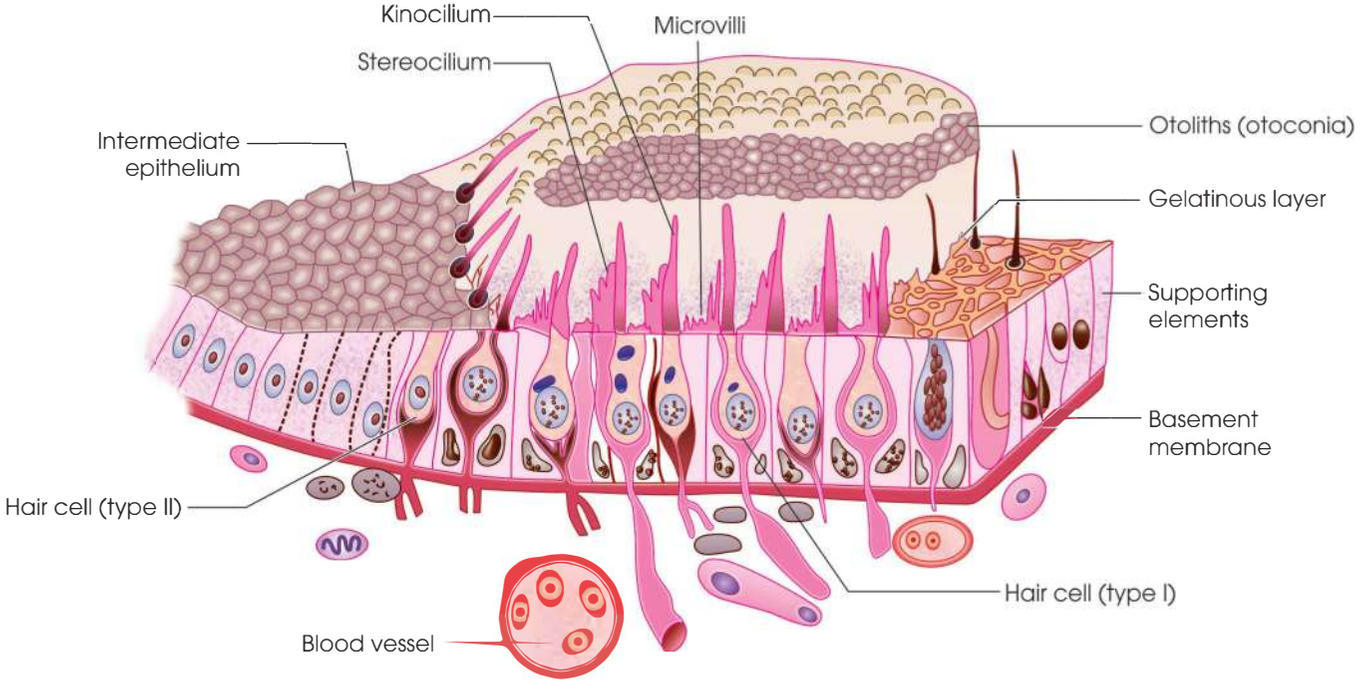

Fig. 102.12: Histological representation of a macula (Carlos Eyzaguirre)

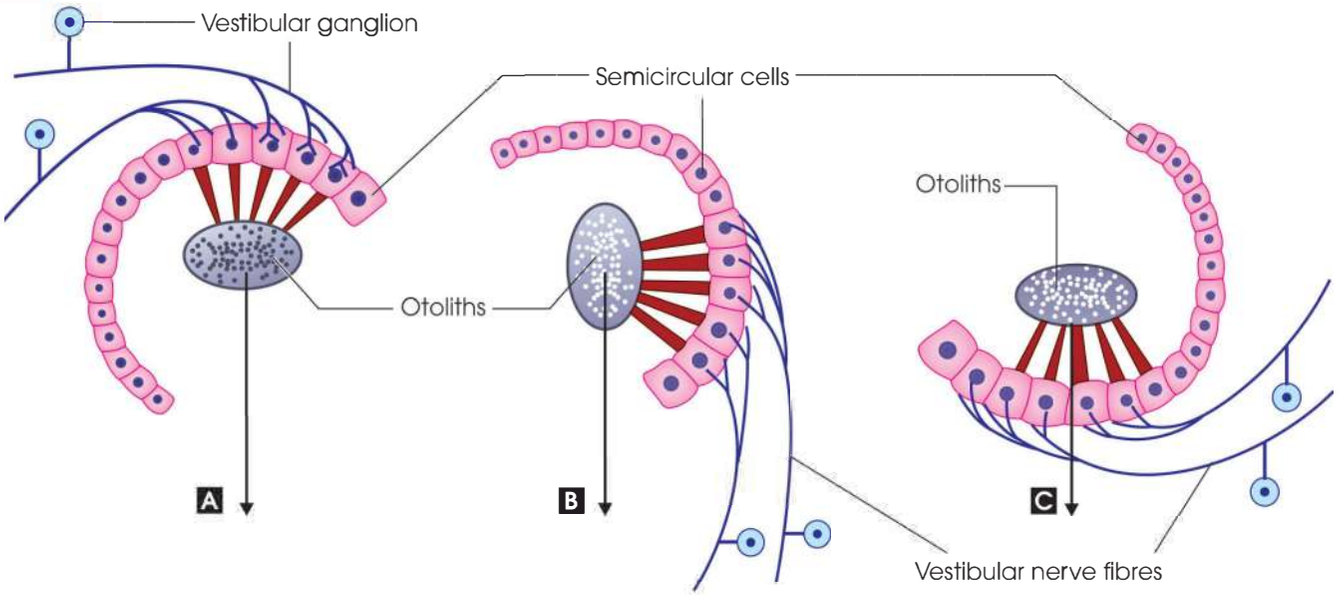

Fig. 102.13A to C: Schematic representation of the effect of different positions of the head on the otolithic organs. (A) Otolith hanging vertically from the hairs (maximum receptor stimulation); (B) Otolith pulling sideways on the hairs (intermediate receptor stimulation); (C) Otolith pressing down on the hairs (minimum receptor stimulation) (Carlos Eyzaquirre)

gaze is also steady and external objects seem to be stationary. However, if side to side eye movements are required as in crossing a street, vision is blurred and the gait appears to be unsteady. This may be caused by unilateral (i.e. asymmetrical) labyrinthine information reaching the brain. After some time these disorders disappear and the gait is maintained by the information coming from visual and muscle joint receptors.

Bilateral Extirpation of the Labyrinths

1. After bilateral extirpation of the labyrinths in lower animals there is a very unsteady posture with great loss of muscle tone and ataxia. The animals cannot stand, cannot orient itself under water and the birds are unable to fly. But in a higher animal the unsteady posture soon disappears as the animal learns to compensate for its disability by using its eyes and by proprioceptive reflexes. If the animal be blindfolded, postural unsteadiness returns.
2. These disturbances of posture produced in man by bilateral destruction of the labyrinth are after some time compensated by visual righting and proprioceptive reflexes to a large extent but the deficit can be shown by tilting him suddenly. No compensatory reactions are observed. The labyrinth is concerned in keeping the visual axes steady, in spite of head movements, so that images of external objects are fixed (or stabilized) on the retina. For instance, when such a patient is roaming or is being wheeled across rough ground his vision is jumbled.

Applied Physiology

Oculogravic Illusion (Fig.102.14)

Gravity acts on the otolith system but if any other linear force acts, then the resultant of the forces acts on the otolith system causing an illusion of the pilot

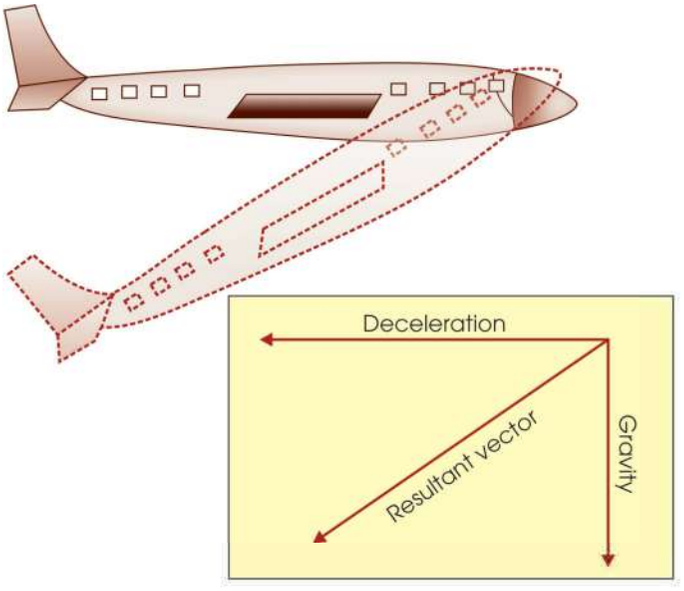

Fig. 102.14: Showing the oculogravic illusion

of a high-speed fighter plane. In a high-speed plane, linear acceleration causes a posterior shearing force on the utricular maculae of the pilot when such a plane takers off. The resultant between the deceleration and constant downward gravity vector gives the pilot an impression that the plane is 'nose up' when, it is, in reality, flying straight. If the pilot files according to his sensation and does not believe his instrument then the plane will touch the ground causing possible crash. This is the oculogravic illusion.

In space flight due to weightlessness, gravity vector fails to act on the utricle and the astronaut does not feel which is 'up' and which is 'down'.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the structural details of vestibular apparatus. Discuss the functions of vestibular apparatus.

Short Notes

1. Semi-circular canal
2. Functions of semi-circular canal
3. Otolith organ
4. Functions of otolith organ
5. Oculogravic Illusion
6. Vestibular nystagmus

Chapter

103

Path of Vestibular Impulse

INTRODUCTION

Vestibular impulses arise from the cristae of the semicircular canals and maculae of the saccules and utricles. They are carried by the dendrites of the nerve cells in the ganglion of Scarpa (first neuron). The axons of these cells form the vestibular division of the eighth cranial nerve. The nerve enters the central nervous system in the lower border of pons and terminates in the following ways (Fig. 103.1).

Some fibres enter the cerebellum on the same side through the inferior peduncle, relay in the cerebellar nuclei and end in the cerebellar cortex.

The remaining fibres terminate in the vestibular nuclei.

The vestibular nuclei can be subdivided into four ways:

1. The medial vestibular nucleus is the largest and is situated in the vestibular area of the floor of the IV ventricle, crossed dorsally by the straie medullares. It extends upwards from the medulla into the tegmentum of the pons.
2. The inferior vestibular nucleus is placed between the inferior cerebellar peduncle and medial vestibular nucleus and extends from the level of the rostral limit of the nucleus gracilis to the pontine-medullary junction.
3. The lateral vestibular nucleus (of Deiters) is situated ventrolateral to the upper part of the medial vestibular nucleus.
4. The superior vestibular nucleus (of Bechterew) is small and lies above the medial and lateral vestibular nuclei. It extends higher into the pons than the other nuclei. From here the second order neurons arise and proceed as follows.

Vestibulo-ocular tract: Some fibres (chiefly from Deiters' nucleus) constitute the vestibulo-ocular tract. They enter the posterior longitudinal bundles of sides and end round the third, sixth and fourth nuclei. These fibres are concerned with the reflex movements of the eyeballs in response to vestibular impulses. A few fibres of this bundle end in the red nucleus and also in the superior colliculus of the same side.

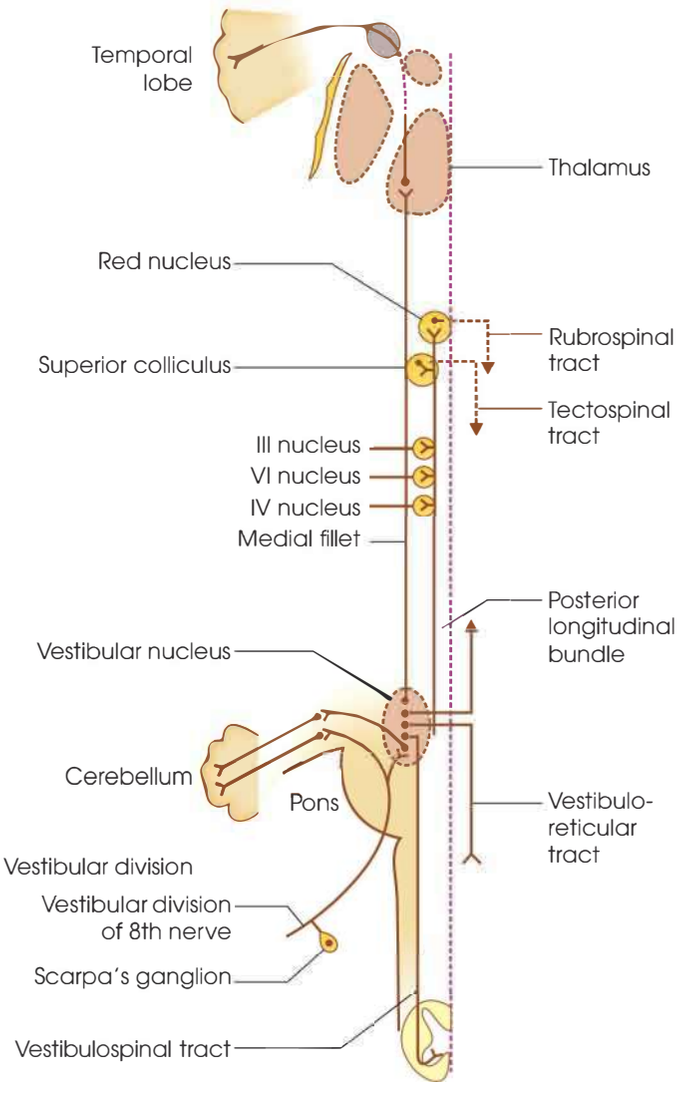

Fig. 103.1: Path of vestibular impulses

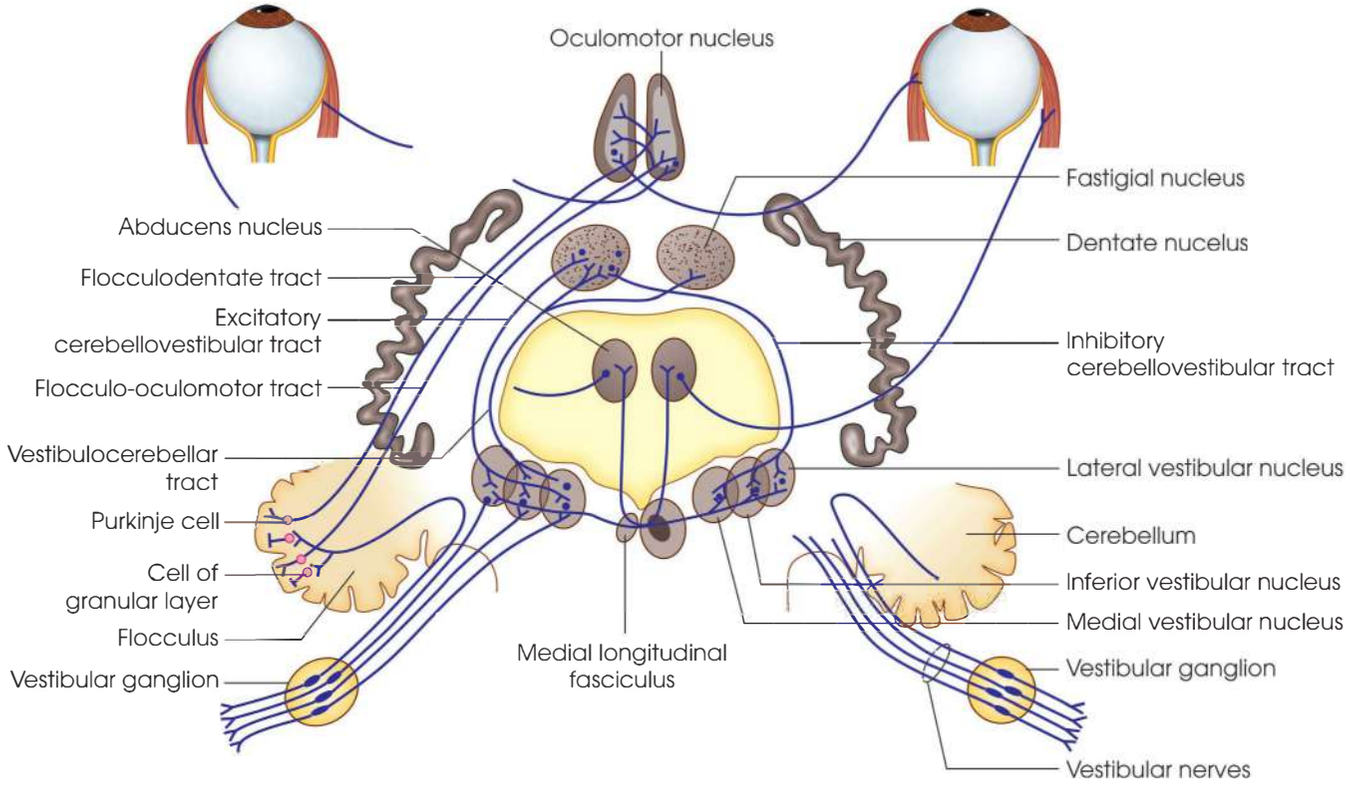

Fig. 103.2: Schematic representation of the connections between the vestibular nuclei and the cerebellum

Vestibulocerebellar tract: Some fibres enter the cerebellum through the inferior cerebellar peduncle mainly to the flocculonodular lobe of the same side and also to the fastigial nucleus of the same side (Fig. 103.2).

Vestibuloreticular tract: Some fibres end in the bulbar nuclei in the formatio-reticularis.

Vestibulocortical fibres: Some fibres (chiefly from the principal nucleus) enter the medial fillet and end in the thalamus. Here, the third neurons arise, pass with auditory fibres through the posterior limb of internal capsule and end in the temporal cortex. These fibres carry conscious vestibular sensations.

Vestibulospinal Tract (from Deiters' Nucleus)

The vestibular impulses therefore:

1. Give conscious sensations regarding the position and movements of the head.
2. Produce reflex ocular movements.
3. Control tone, posture and equilibrium.
4. Guide cerebellum and cerebrum.

Habituation

It is a process by which normal subjects adapt to complex new stimuli. With repeated exposure to vestibular stimulation, a number of individuals can develop relative insensitivity. Astronauts use to do long periods of training on centrifuges and in weightless states due to development of habituation and a depression of sickness and giddiness.

The vestibular system can perform some kind of auto-regulation which allows the CNS to perceive facts that are essential to the organism and cancel out admittance to repetitive, irrelevant or inconsequential information.

EXAM-ORIENTED QUESTION

Essay

1. Describe the path of vestibular impulse.

Chapter

104 Cerebrum

INTRODUCTION TO EVOLUTION

The cerebral hemispheres have developed from the roof of the forebrain. In the lowest vertebrates, where smell is the only special sense, cerebrum consists of the olfactory lobes only. As evolution proceeded, other varieties of special senses gradually developed. The crude sensory and motor functions hitherto carried out clumsily by the thalamus and corpus striatum respectively, were more finely organized and transferred to a large extent, to the cerebral cortex. To deal with this vast stream of sensory and motor impulses, the cerebrum had to undergo a proportional development on all sides. It is to the evolution of this part of the nervous system that the superiority of the human beings over the lower animals is due.

ANATOMY

Cerebrum consists of two symmetrical hemispheres, separated by a deep median furrow and connected by a broad band of commissural fibres—the corpus collosum. The total surface area of adult cortex is about 2200 sq cm, and is nearly three times the inner surface of the skull. Owing to this mechanical discrepancy, the cortex becomes folded upon itself producing fissures and convolutions.

Each hemisphere has five main lobes and four main fissures. The lobes are:

1. Frontal (anterior)
2. Parietal (middle top)
3. Occipital (posterior)
4. Temporal (below parietal)
5. Limbic area (at the base) (Figs 104.1 and 104.2)

The fissures are:

1. Central sulcus or rolandic fissure
2. Parieto-occipital
3. Sylvian fissure
4. Calloso-marginal fissure. Frontal lobe has four gyri—precentral (vertical), superior, middle and inferior (all three horizontal). Temporal lobe has

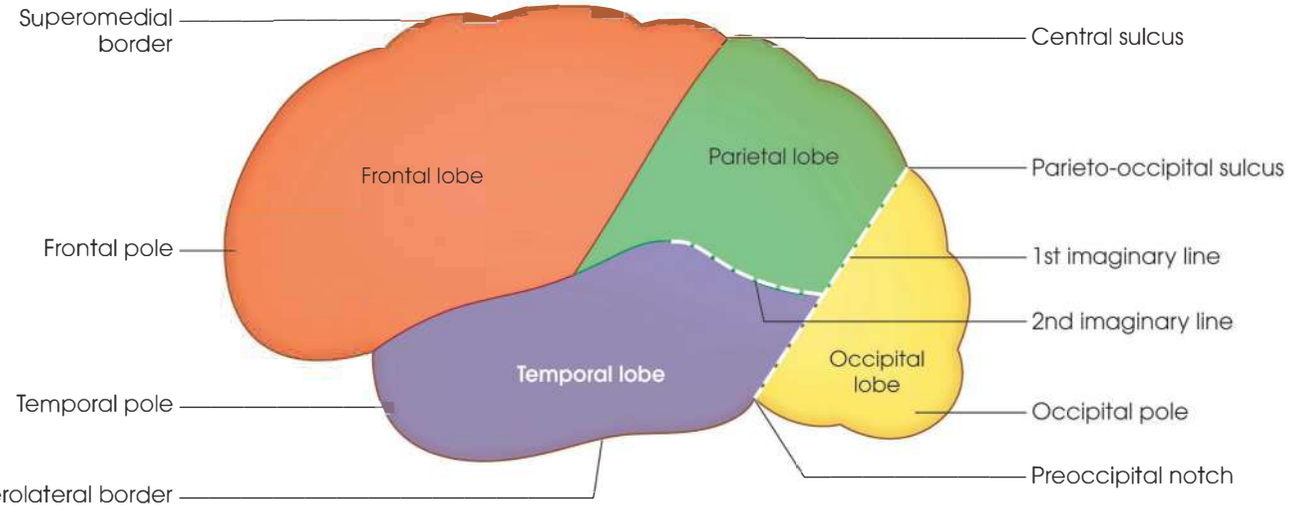

Fig. 104.1: Diagrammatic representation of the lateral surface of right cerebral hemisphere showing lobes of the brain

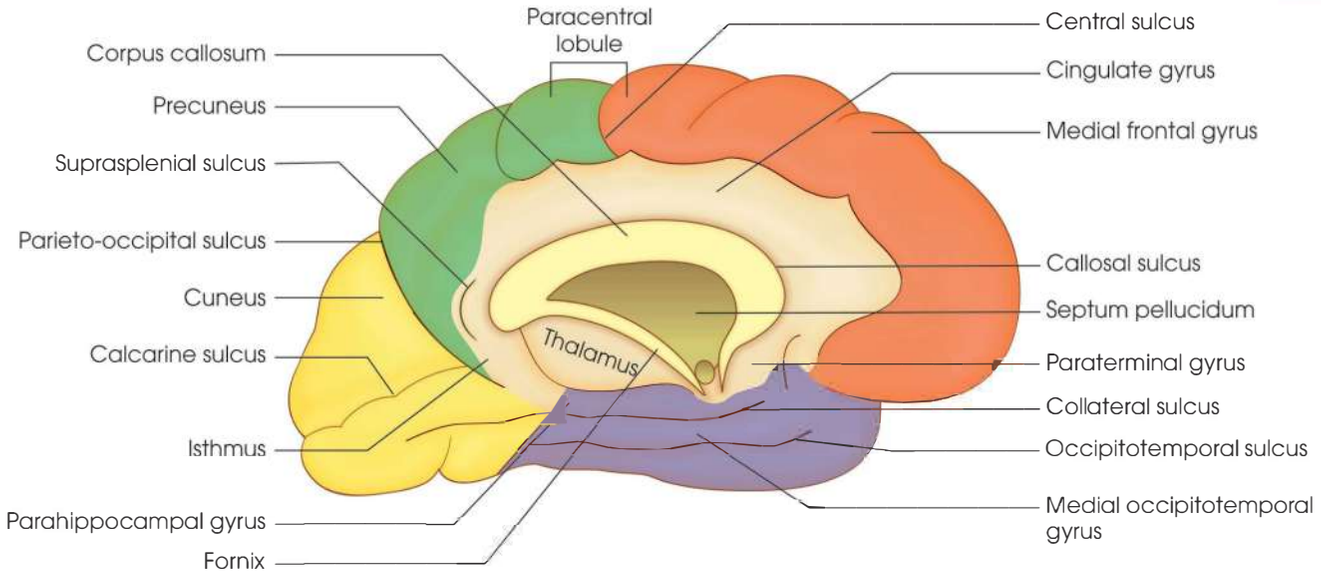

Fig. 104.2: Diagrammatic representation of the medial surface of cerebral hemisphere

three—superior, middle and inferior—all horizontal (Fig. 104.3).

Grey Matter (Cortex)

It forms the surface layer, thickest (4.5 mm) at the precentral gyrus and thinnest (1.3 mm) at the frontal and occipital poles. Average: 3.5 mm on the surface, 3 mm at the base and 2.7 mm medially. In the sulci the thickness is half that on the surface. About two-thirds of grey area remains hidden in the sulci and one-third exposed on the surface. It is composed of nerve cells, nerve fibres and neuroglia.

Roughly five types of nerve cells are:

1. **Pyramidal cells** which look like forms of pyramids or isosceles triangles and possess large vesicular nuclei and distinct. Nissl bodies. The heights of smaller and of larger pyramidal neurons are 10–12 µm and 45–50 µm respectively but in the motor area of the precentral gyrus large pyramidal cells of Betz, generally, may be more than 100 µm in height.
2. **Small stellate or granular cells** which are triangular or polygonal in size of 4–8 µm and have dark-staining nuclei and scanty cytoplasm. Resembling pyramidal cells, other larger stellate cells are known as stellate pyramidal cells or star pyramidal cells.
3. Fusiform or **spindle cells** which are generally placed vertical to the cortical surface with their long axes and are mainly found in the deepest cortical layer.
4. **Horizontal cells of Cajal** which look like pear-shaped or small fusiform cells and are found in the most peripheral layer.

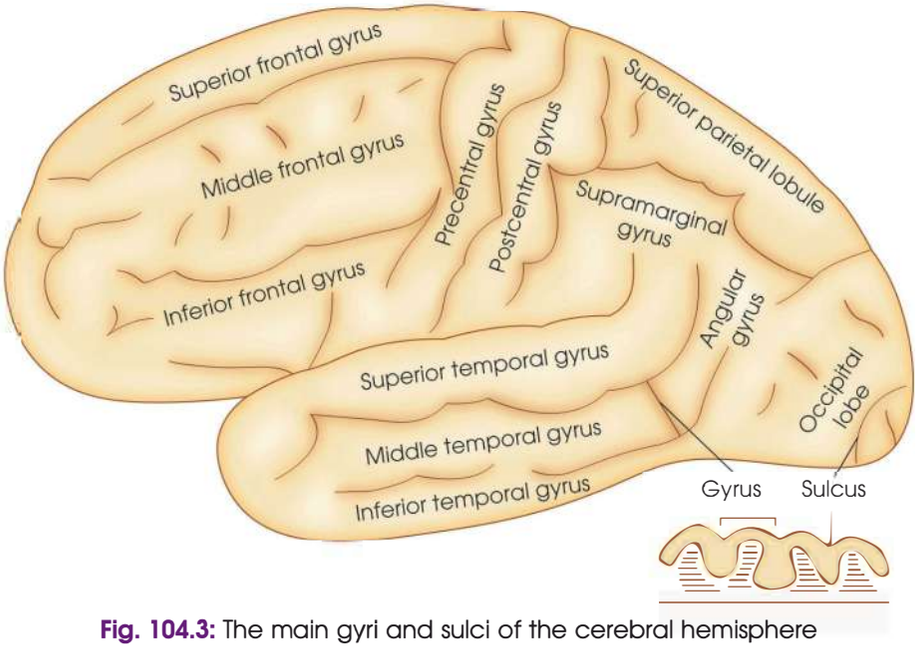

Fig. 104.3: The main gyri and sulci of the cerebral hemisphere

5. **Cells of Martinotti or cells with ascending axons** which are small triangular or polygonal and present in all layers generally.

Functionally also five types:

1. Cells whose axons come out from the base of the cells, descend toward the medullary substance and terminate in the deepest layer or enter the white matter as projection or association fibres.
2. Cells whose
   - Shorter axons ramify close to the cell body (Golgi type II)
   - Longer axons enter the medullary substance.
3. Cells whose axons emerge from middle or lower parts of the cell body and enter the white matter as projection or association fibres.
4. Cells whose axons pass horizontally for a considerable distance and arborise in the same layer.
5. Cells whose axons, facing toward the cortical surface, extend a variable distance and some of them arborise in that layer and the rest project collaterals to a number of layers.

However, pyramidal, fusiform and large stellate cells possess descending axons which leave the cortex as projection and subcortical association fibres and the entering afferent projection and association fibres terminate within the cortex. But horizontal cells of Cajal, cells of Martinotti and Golgi type II granular cells have intracortical connections. The terminal branches of the afferent projection and association fibres, axons of horizontal and granular cells, terminal branches of collateral fibres from pyramidal and fusiform cells have tangential fibres which run horizontally to the cortical surface (Fig. 104.4).

White Matter

It remains under the grey matter. Composed of three groups of medullated fibres:

Projection fibres, connecting cerebrum with extracortical areas.

Two varieties:

1. *Afferent*—thalamocortical, auditory radiation, optic radiation, cerebellocerebral, etc.
2. *Efferent*—pyramidal, frontopontine, corticonuclear, temporopontine, etc.

Association (arcuate) fibres connect different parts of same hemisphere. They are of two kinds:

1. Short association fibres which connect adjacent gyri to one another.
2. Long association fibres which connect more widely separated gyri to one another (Fig. 104.5).

Commissural fibres, unite the two hemispheres:

1. Anterior commissure—between two temporal lobes
2. Hippocampal commissure—between two hippocampal gyri.

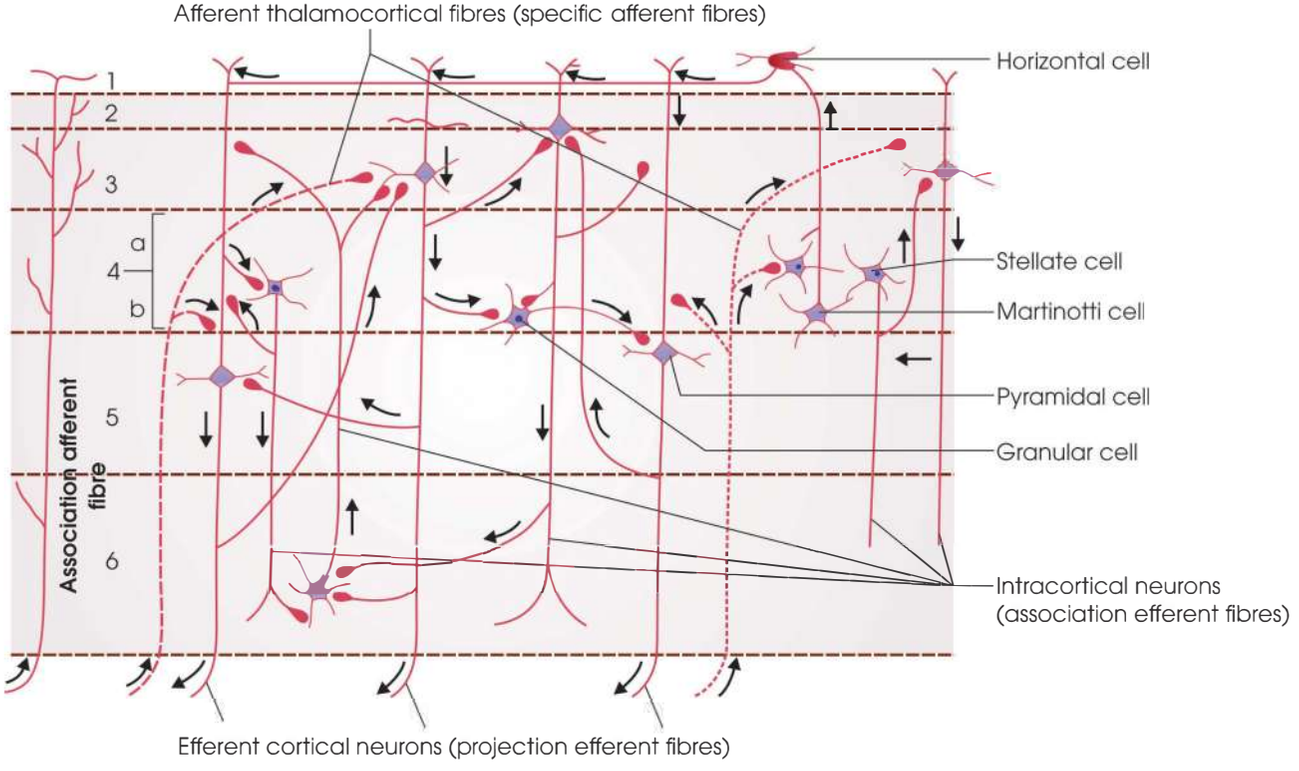

Fig. 104.4: Schematic representation of a few intracortical fibres showing synaptic junctions with loop system and termination of association afferent cortical fibres within six layers of cerebral cortex

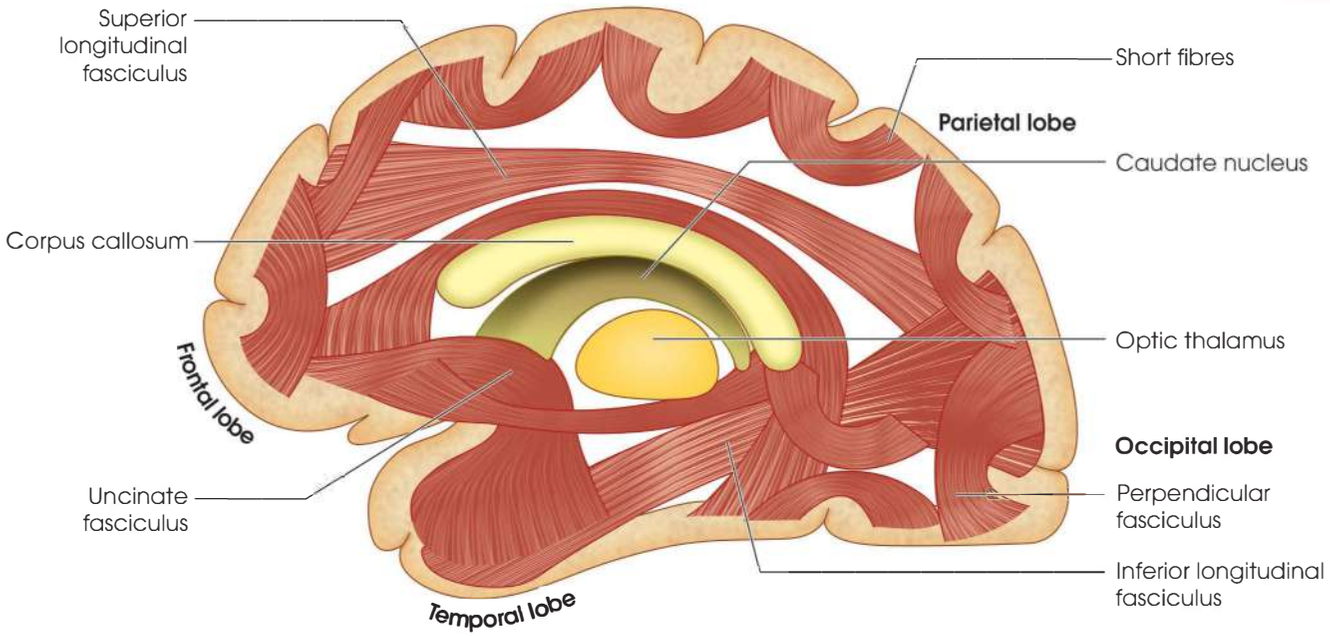

Fig. 104.5: Showing the principal system of association fibres in the cerebrum. Grey matter is stippled

STRUCTURE OF THE CEREBRAL CORTEX AND FUNCTIONS OF ITS DIFFERENT LAYERS

Histologically, cortex has three divisions:

1. **Allocortex:** Hilus of the cerebral hemisphere, comprising the olfactory area only.
2. **Isocortex (neocortex):** Cortical tissue of remaining non-limbic regions of the cerebral hemisphere.
3. **Juxtallocortex or mesocortex:** Between the allocortex and the rest of the cerebral hemisphere (isocortex) the juxtallocortex or mesocortex (cingulate gyrus) is present.

   Allocortex is primitive, having altogether a different structure. Lamination is imperfect here. For instance, in the hippocampal region, only three layers—outer molecular, external pyramidal and innermost fusiform layers. Other layers found in isocortex are not present here.

Isocortex (neocortex) has six fundamental layers of cells and fibres, with characteristic regional peculiarities. The fibres are arranged both in transverse as well as in longitudinal bands. The afferent projection fibres penetrate the deeper layers as longitudinal bundles, reaching up to the second layer and giving transverse branches which make synapses with other motor or internuncial neurons at different levels (Fig. 104.6). All pyramidal and possibly other types of cells give rise to three sets of fibres:

1. The apical dendrite passing upwards and giving transverse collaterals.
2. The basal axon passing downwards forming efferent projection fibres (may also have transverse branches).
3. A number of lateral dendrites arising from the sides of the cells and passing transversely. These tangential fibres form transverse bands.

From this arrangement the following conclusions may be drawn:

1. The cells in the different layers remain united in vertical chains which possibly act as compound functional units.
2. The afferent projection fibres, with the help of transverse collaterals, form synaptic connections with motor (or intermediate) cells at various levels and form the so-called elementary cortical unit. Through this unit, the afferent impulse is passed on to the efferent side.
3. Since the apical process of the pyramidal cell may pierce several layers, the same afferent impulse may be reach a particular pyramidal cell repeatedly from different layers.

From outside inwards the layers of cerebral cortex (Fig. 104.7) are as follows:

1. **Plexiform layer or molecular layer—a few cells, many fibres.**
   Cells
   - Neuroglia
   - Horizontal cells of Cajal.

   Fibres form a prominent transverse band.
2. **External granular layer—many small cells, a few fibres.**
   Cells
   - Granular cells—round, triangular or polygonal.
   - Small pyramidal cells.
   - External pyramidal layer-thick layer of medium pyramidal cells. Cell size increases inwards.
3. **Internal granular layer—two parts 4a (outer):**
   - Star pyramidal cells
   - Thick transverse band—outer line of Baillarger.
   - 4b (inner)—irregular stellate cells.

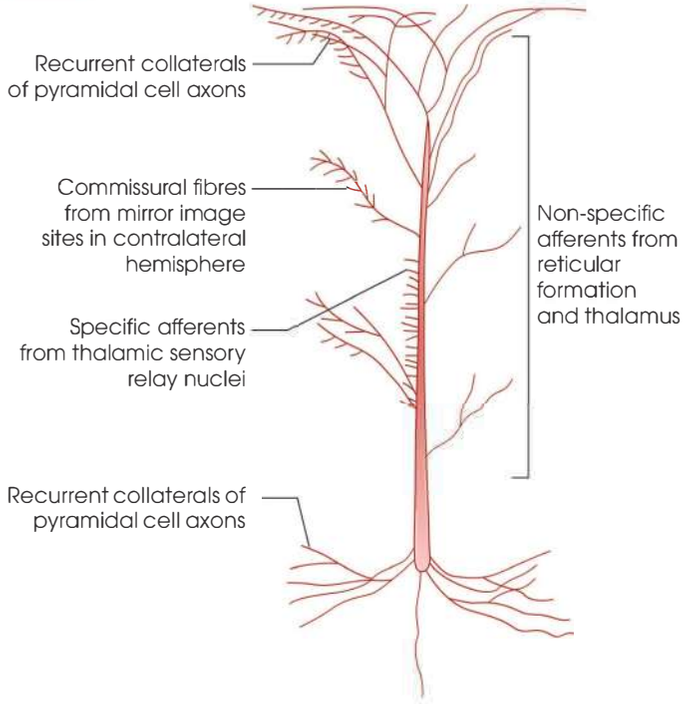

Fig. 104.6: Diagrammatic representation of cortical pyramidal cell along with distribution of presynaptic terminals (Chew and Leiman)

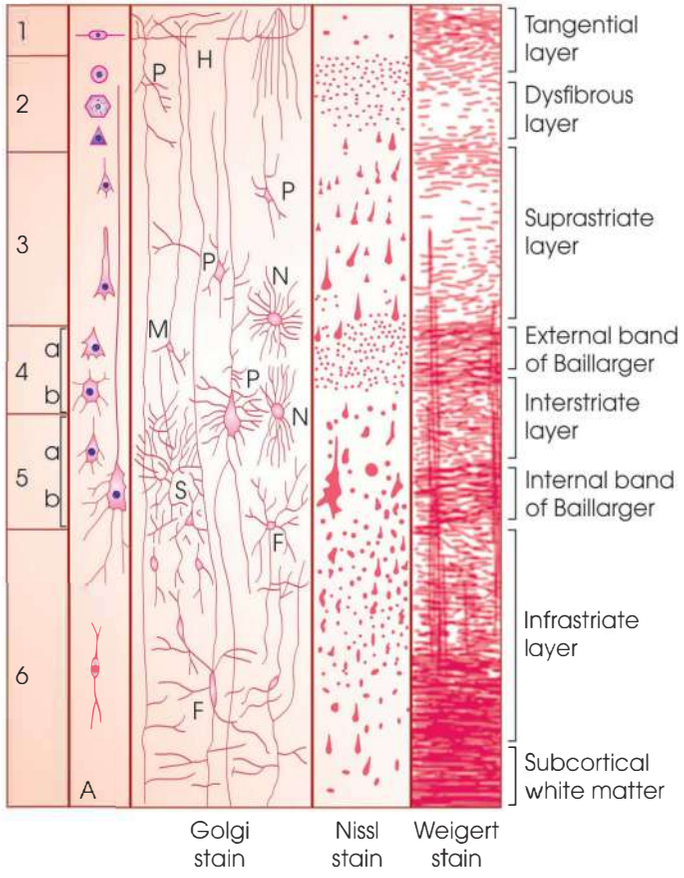

Fig. 104.7: Schematic representation of six layers of cells and arrangement of fibres of the human cerebral cortex. A—diagrammatic representation of cells

4. **Interstriate layer**
5. **Internal pyramidal layer—two parts:**
   1. 5a (outer)—small pyramidal cells
   2. 5b (inner)—large pyramidal cells (Betz cells).
   3. Inner line of Baillarger.
6. **Fusiform cell layer** thick layer of spindle-shaped cells arranged perpendicular to the surface. Fibres form thick meshwork.

Regional Peculiarities (Figs 104.8 to 104.10)

Excitomotor area (area 4: (i) 4γ, (ii) 4α, (iii) 4s—precentral gyrus, Fig. 104.8):

1. Both the granular layers are thin.
2. Characteristic layer of Betz cells. (Origin of pyramidal tract.)

Premotor area (areas 6 and 8—frontal lobe)

1. Betz cells absent.
2. Intercommunicates with area 4.
3. Efferent projection fibres arise and end in pontine nuclei (frontopontine), corpus striatum, red nucleus, superior colliculus and other extrapyramidal nuclei.

Visual area (occipital lobe—areas 17 and 18)

1. Granular layers prominent.
2. Outer pyramidal layer indistinct.
3. A few giant pyramidal cells of Meynert in the fifth layer (origin of association and projection fibres).
4. The outer line of Baillarger is very prominent and called the line of Gennari.
5. Inner line of Baillarger is indistinct.

Somaesthetic area (parietal lobe—areas 3, 1, 2 and 5, 7).

1. Granualr layers thicker and denser.
2. Pyramidal cells smaller.
3. Receives thalamocortical fibres (general senses).

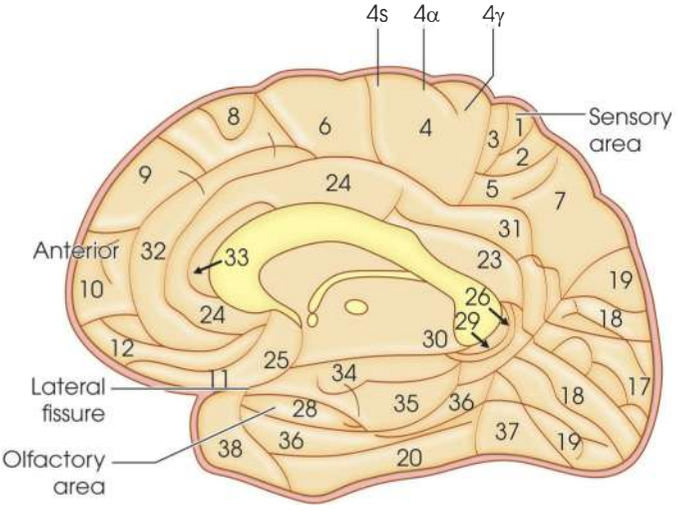

Fig. 104.8: Schematic subdivision of the medial surface of the cerebral hemisphere showing localisation of the areas according to Brodmann

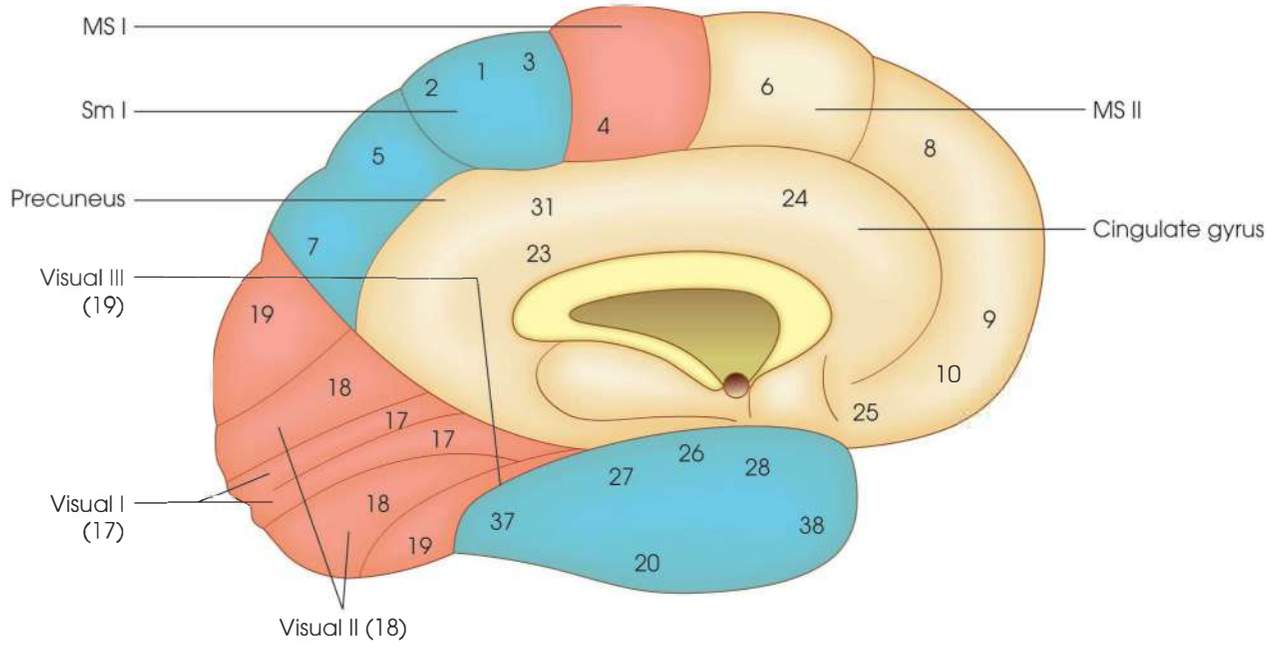

Fig. 104.9: Schematic subdivision of the medial surface of the left cerebral hemisphere showing some of the cytoarchitectural areas

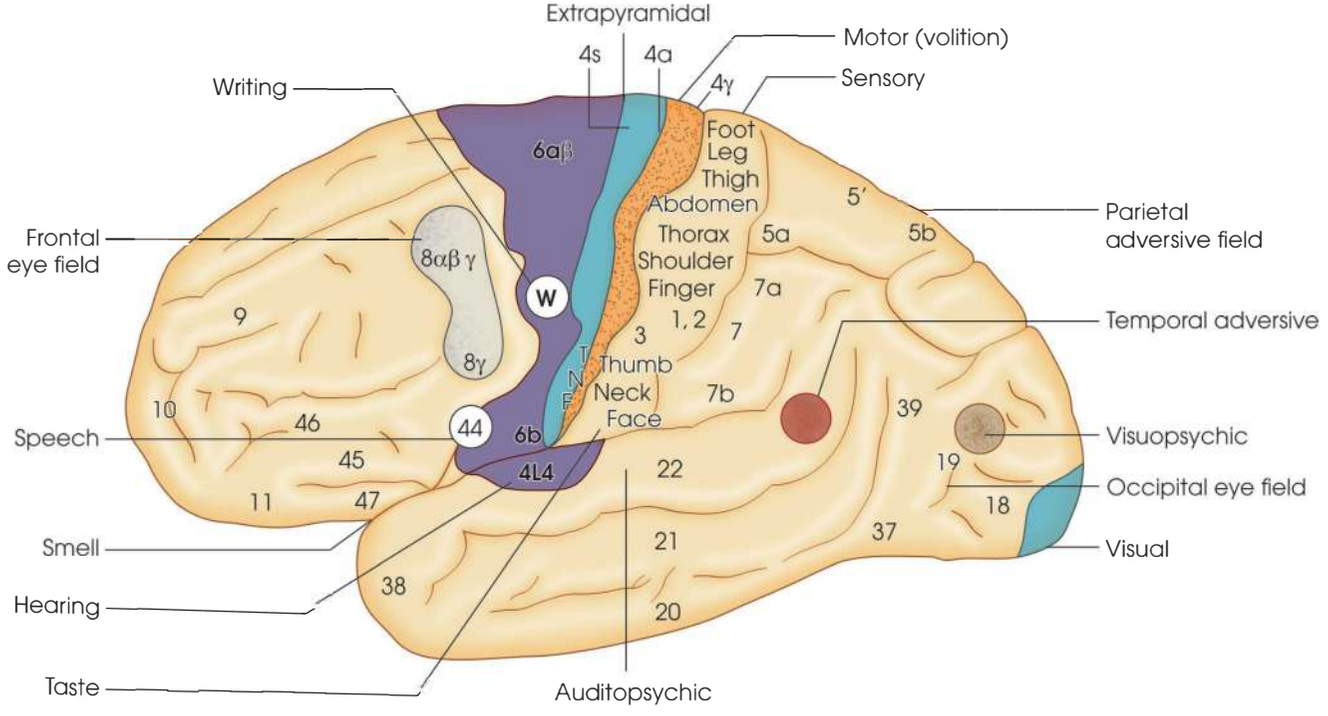

Fig. 104.10: The centres and areas in the left cerebral hemisphere

Auditory area (temporal lobe—areas 41, 42, 22, 21, 20).

1. Granular layers prominent.
2. Fourth layer rich in pyramidal and stellate cells, from which?
3. Temporopontine fibres arise.
4. Receives auditory (from external geniculate body) and vestibular afferent projection fibres.
5. Gives fibres to external geniculate body and inferior colliculus.
6. Outer line of Baillarger is prominent and is called the line of Kaes.

According to regional peculiarities economy divides isocortex into five types. Types 2, 3 and 4 differ only in detail. Types 1 and 5 have marked fundamental distinctions. Brief details are given below:

- Type 1: ***Agranular cortex*** (motor areas—4, 6, 8): Granular cells replaced by pyramidal cells. Betz cells in areas 4.

- Type 2: ***Frontal type*** (anterior two-thirds of frontal lobe, superior parietal lobule and part of temporal): Here, granular cells are triangular.
- Type 3: ***Parietal type*** (parietal lobe; junctional region between parietal, temporal and occipital lobes): Here the two granular layers are thick and dense, granular cells are round and pyramidal cells are smaller, thinner and more numerous.
- Type 4: ***Polar type*** (frontal and occipital poles): Grey matter thinnest. All layers are thinner but densely packed.
- Type 5: ***Granular cortex*** (sensory areas including special senses): Pyramidal cells replaced mostly by granular cells in layers 3 and 5.

FUNCTIONS OF DIFFERENT LAYERS OF THE CEREBRAL CORTEX (Fig. 104.11)

Pyramidal cell of the motor cortex receives impulses from many cells which convey impulses through synaptic connections. Afferent stimuli are coming from other subcortical or neighbouring cortical cells (Fig. 104.11) as shown by arrows or from collaterals of the large pyramidal cell itself.

The inner layers are concerned with organic and instinctive faculties. A little difference is seen here between man, monkey and dog. The inner layers are believed to be the fundamental layers from which the outer layers grow. This is seen both during embryological as well as in evolutional development.

Functions

1. The middle pyramidal layers are concerned with the reception of afferent impulses and their conversion into efferent.

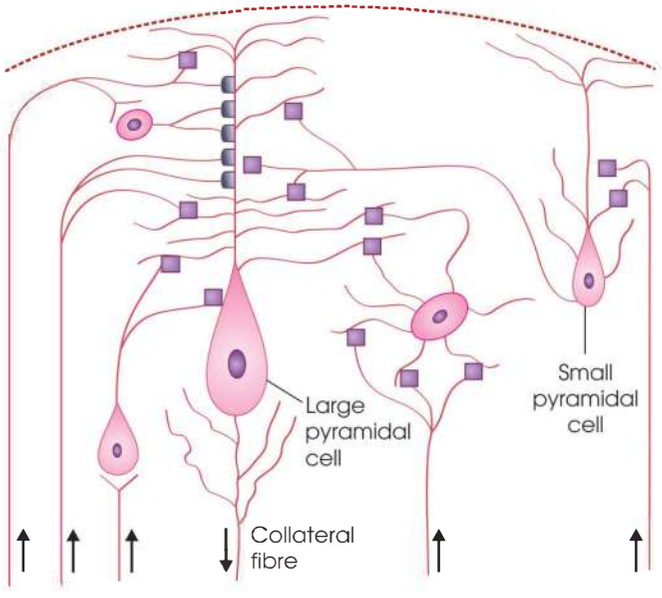

Fig. 104.11: Schematic representation of the pathways of afferent stimuli

2. The granular layers are sensory and associative in function.
3. The outer layers are concerned with intellectual and associative faculties. Various forms of amentia (poor mental development) are associated with subnormal development of outer layers.
4. Atrophy of these layers leads to dementia (mental degeneration).

LOCALISATION OF BRAIN FUNCTION

The result of various experiments on animals and close observation of effects of electrical stimulation of the cerebral cortex on the human being and clinical results of cerebral disease, physiologists have been able to localize certain areas in the brain which control motor, sensory and other activities (Figs 104.10 and 104.12). In any case, however, the control of a function is not limited to a single centre; because all mental processes involve the discharge of nervous energy from one centre to another. Change in the nervous activity of any part alters the excitability of the whole part. No one area acts alone to govern a particular function. According to Herrick "such areas are merely nodal points in an exceedingly complex system of neurons which must act as a whole in order to perform any function whatsoever".

Methods of Localisation of Functions in the Cerebral Cortex

Since cortical neurons freely intercommunicate and since injury to any part of the cortex disturbs the functions of its other parts, it was held before that brain worked as a single organ. But later investigations point out that there are particular areas in cortex serving specific functions. These special areas subserving special functions are called centres. From there facts cerebrum should not be regarded as a single organ but as a coordinated aggregate of many component organs—something like a 'union of states' in which the individual members are autonomous but interdependent—all within the framework of a common law for a common purpose.

More detailed analysis points out that even inside a centre there are special areas where functions vary in detail. Hence, for convenience of description and comparison, cortex has been mapped out into different areas each bearing a definite number, such as 3, 1, 2, etc. The following methods are commonly adopted for localising cerebral centres.

Histological study: Variety and distribution of nerve cells (cytoarchitectonics) (Figs 104.6 and 104.7) and fibres (myeloarchitectonics).

1. ***Study of myelination (Flechsig):*** Fibres in all parts of cortex do not myelinate at the same time. A regular order is seen. Myelination takes place first in the sensory areas (three months before birth), then in the

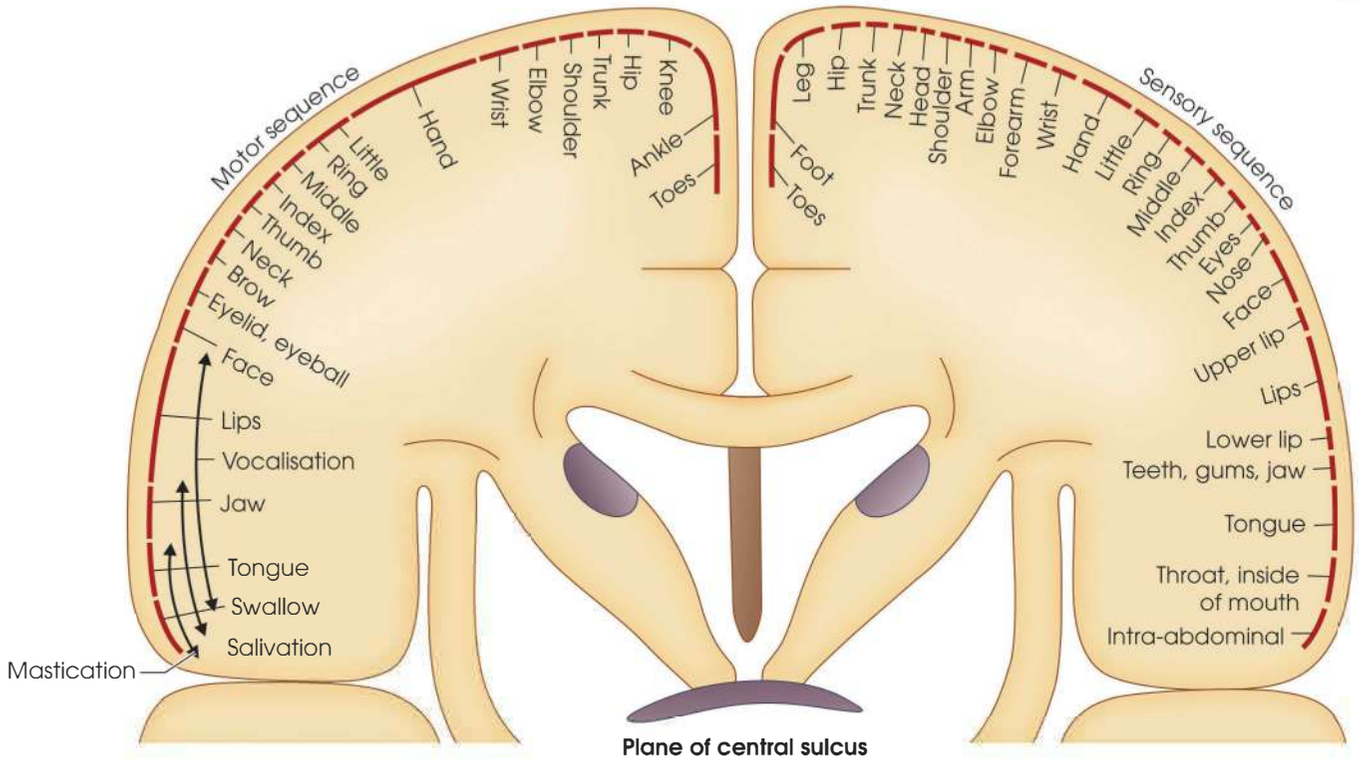

Fig. 104.12: Rasmussen and Penfield's diagram of localisation in motor and sensory cortex. The lengths of solid bars depict an estimate of average relative cortical areas from which corresponding responses are elicited

motor areas (may be several months after birth), and lastly in the association areas, where it may proceed up to 40 years.

2. ***Study of the origin and termination of the motor and sensory tracts:*** From the origin and terminations of motor and sensory tracts the functions of the related portions of the cortex may be known. Homunculus is the topographical representation of relay of sensory information which is relayed in sensory cortex. Figure 104.12 depicts the representation and relay site of sensations from foot, leg, thigh, thorax, thumb, neck, face, etc.
3. ***Effects of experimental stimulation:*** Electrical, chemical (strychnine, etc.).
4. ***Effects of removal of different regions.***
5. ***Clinical effects*** of irritative or degenerative lesions.
6. ***Establishment and abolition of conditioned reflex.*** At first, a conditioned reflex is established, say with a particular sound as the stimulus. If then removal of a particular cortical area abolishes the reflex, the area removed is obviously concerned with sound (i.e. hearing).
7. ***Electroencephalogram.*** Like other cells, activity in the nerve cells is also attended with potential changes which can be detected by electroencephalograph. If appropriate sensory stimuli be applied to peripheral parts (skin, muscles, taste, smell, vision, hearing, etc.), changes of electrical potential take place in the cortical centres concerned. In this way sensory areas can be mapped out (Fig. 104.12) (vide electroencephalography.)

Areas and Centres in the Cerebral Cortex

With the help of above methods, nearly 200 areas have been mapped out in the cortex. There are certain areas which on stimulation abolish the resting cortical potentials. The areas are called suppressor bands. They have been described along with the different areas.

104

FRONTAL LOBE

It is subdivided into two main areas:

1. The precentral cortex
2. The prefrontal cortex.

Precentral Cortex (Areas 4, 6, 8, 44)

1. ***Area 4 (4a, 4s, 4γ) (precentral motor area):*** Situation—anterior wall and lip of central sulcus (in apes also the precentral gyrus) and extends onto the medial surface of the hemisphere. 4a—constitutes the larger area of precentral gyrus. 4s—lies in front of the area. 4a, which is functionally an inhibitory area. It helps in controlling the stretch and postural reflexes. Lesion of this area causes spasticity of muscles. Spasticity of muscles in hemiplegia is due to involvement of this area. 4γ, which is situated posterior to 4a which contains giant pyramidal cells—Betz cells (Fig. 104.13).

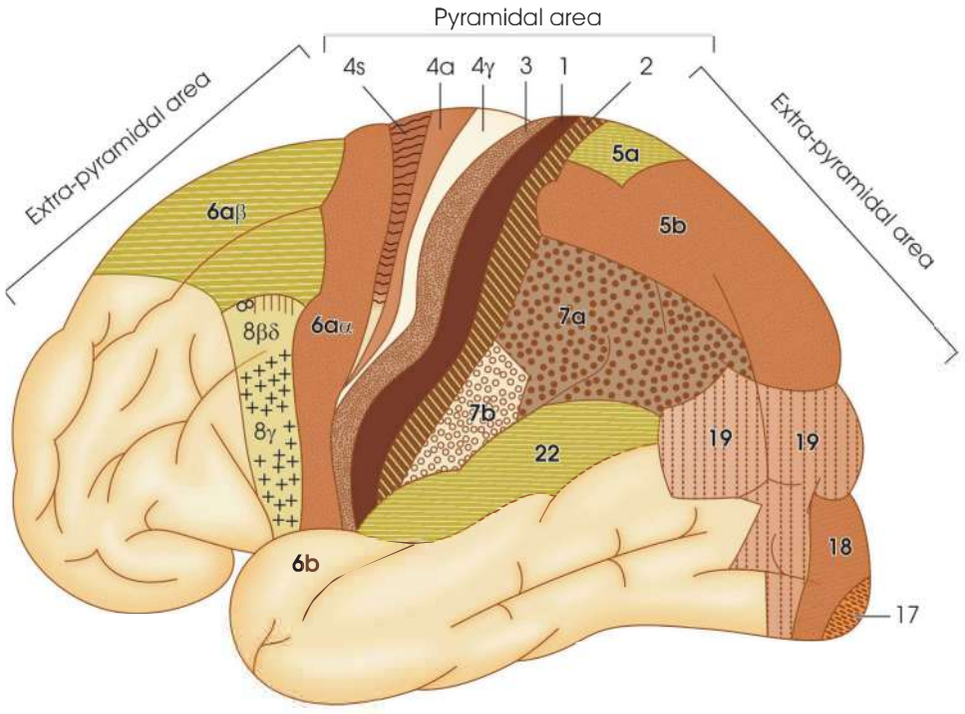

Fig. 104.13: Schematic representation of electrically excitable areas of the lateral surface of human brain showing pyramidal areas and extra-pyramidal areas

Function: Centre for volition. Centres for the various parts of body are arranged upside down, viz. from above downwards—toes, foot, leg, thigh, abdomen, thorax, shoulder, arm, hand, fingers (5, 4, 3, 2, thumb neck, face (ear, eyelids, nose, tongue, jaw, palate), larynx. This area (in apes but not in man) is interrupted by area 6aα which remains interposed between the centres for fingers and thumb.

2. ***Area 6 (premotor area):*** Situation—It is in front of area 4.

   Two parts—the upper 6a and lower 6b.

   6a: Subdivided into two parts—upper 6aβ, lower 6aα. The former is situated in the superior frontal and precentral gyri, the latter juts into the area 4 as mentioned above. Frontopontine and certain other efferent projection fibres arise from this area and control the extrapyramidal tracts.

   Functions: (a) Frontal adversive field—stimulation causes movements of eyes, head and body towards the opposite side. (b) Extrapyramidal activity—all functions attributed to the extrapyramidal tracts. (c) Writing centre: Area 6aα (on the left side in right-handed people) is believed to contain the centre for writing. 6b: Situated below area 4 functions: (a) Controls complex movements of jaws, tongue, pharynx, larynx, swallowing and also the activity of the respiratory muscles (electrical stimulation causes rhythmic movements of these parts and also respiratory changes like hiccup, grunting, etc.). (b) Extrapyramidal functions. (c) Speech centre—on the left side (in the right-handed people) it contains Broca's area (areas 44 and 45), which is the centre for speech.

3. ***Area 8 (frontal eye field).*** It is called the frontal eye field. It is situated in front of area 6aα. Two parts—upper 8aβδ in the middle frontal gyrus and lower 8γ in the inferior frontal gyrus. Corticobulbar (corticonuclear) fibres arise from this area and end round the third, fourth and sixth nuclei on the opposite side. ***Functions:*** Controls the conjugate movements of the eyeballs to the opposite side, opening and closing of the eyelids and sometimes dilatation of the pupils and lacrimation. Stimulation of this area in man causes conjugate deviation of the eyes and turning of the head to the opposite side. Bilateral lesion of this area in animal does not react to visual stimuli in normal manner.

   Area 8s: Situated in front of area 6. ***Function:*** Inhibits resting cortical potential.

4. ***Area 44.*** It is situated in the region of the posterior part of the frontal operculum in the dominant hemisphere and is the motor area (Broca's area) for speech. If this area is stimulated in conscious subject then speech is abruptly arrested.

Prefrontal Cortex (Areas 9, 10, 11, 12, 32)

It is the remainder of the frontal lobe including the orbital gyri, medial frontal gyrus and area 32. This cortex is also known as orbito-frontal cortex. Bradmann divided this cortex into different areas—9, 10, 11, 12, 13 and 14. The prefrontal lobe of the cerebral

cortex is the anterior part of the cerebrum. It remains anterior to areas 4, 6 8. Each lobe extends onto the medial surface of the hemisphere up to the anterior end of the corpus callosum and includes part of the cingulated gyrus (area 24).

Areas 9, 10, 11, 12. Situation: Anterior part of the frontal lobe.

Areas 9 and 10: On the convexity and medial surface.

Areas 11, 12: On the under surface.

Function: Seat of intelligence (i.e. highly associative). Unresponsive to electrical stimulation, hence, called silent area. Bilateral removal leads to mental impairment. Hence, it is called organ of mind.

Connections of the Prefrontal Lobes

It has got extensive subcortical and cortical connections (Figs 104.14 and 104.15).

Afferent

1. Anterior nucleus of the thalamus to cingulated gyrus (areas 23, 24, 32).
2. Medial dorsal nucleus of the thalamus to areas 8, 9, 10, 11, 12 (Fig. 104.14) and areas44, 45, 46, 47 (Fig. 104.16).

Efferent (Fig. 104.15)

1. From areas 9 and 10 to the ventral and medial dorsal nuclei of the thalamus.
2. From area 8 to the tegmentum (subthalamus) of the midbrain.
3. From the areas 9 and 10 to the reticular formation in the tegmentum (subthalamus).
4. From area 10 to the pontine nuclei.
5. From areas 8s and 24s to the caudate nucleus. From the hippocampal region to the mamillary body (hypothalamus).

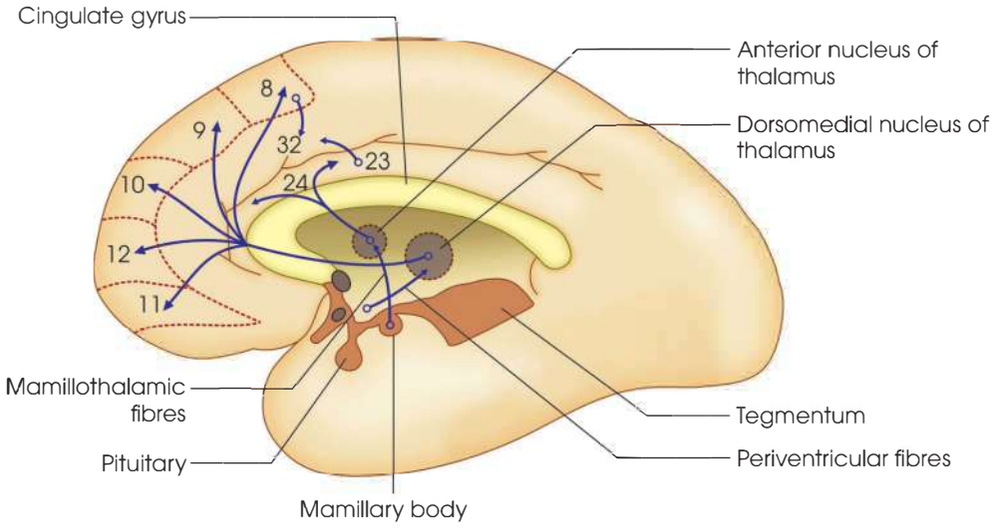

Fig. 104.14: Schematic representation of thalamocortical projections on the premotor fields of the frontal lobe (Le Gross Clark, 1948)

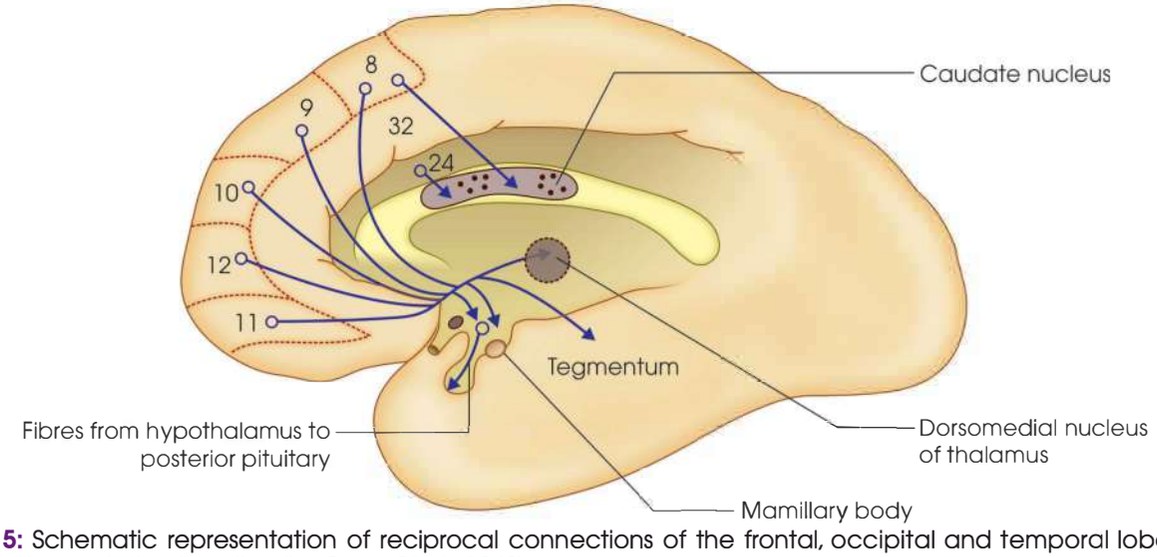

Fig. 104.15: Schematic representation of reciprocal connections of the frontal, occipital and temporal lobes through intracortical association bundles (Le Gross Clark, 1948)

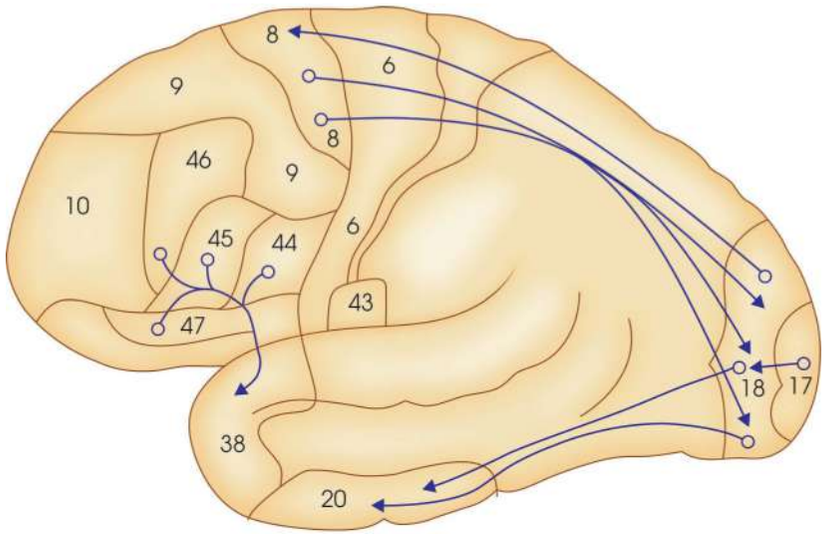

Fig. 104.16: Schematic representation of reciprocal connections of the frontal, occipital and temporal lobes through intracortical association bundles (Le Gross Clark, 1948)

Connections between Different Lobes

1. Area 8 is connected with area 18 in the occipital lobe.
2. Areas 8s, 24s, 4s, 2s and 19s are connected with area 32.
3. Areas 44, 45, 46, 47 are connected with the visual and auditory areas in the occipital and temporal lobes respectively (Fig. 104.16).

Functions of the Prefrontal Lobes

Most of the functions of the prefrontal lobes are closely associated with that of the functions of the ideomotor area or centre which is located in the supramarginal gyrus of the parietal lobe on the dominant side of cerebral cortex. The ideomotor area is under the inhibitory control of the prefrontal lobes. If the ideomotor area or centre is allowed to act independently, i.e. without the inhibitory control of the prefrontal lobes then there would have been response to every type of sensory impulses received.

1. The prefrontal lobes discriminate the sensory impulses, correlate them with the stored impression and help in the final response through the ideomotor area or centre.
2. The prefrontal lobes associate themselves with other lobes of the brain vis. parietal, occipital and temporal lobes through the association fibres and act as planning organs. Prefrontal lobes help in complex intellectual activities, e.g. working-out mathematical problems, giving judgement, etc.
3. The prefrontal lobes are connected with the thalamus, hypothalamus, tegmentum (subthalamus), visual and auditory areas. The prefrontal lobes through their connections with hypothalamus and brain stem exert their influence on the autonomic nervous system. Alteration in heart rate, blood pressure and respiration occurs after stimulation of area 13.

Applied Physiology: Effects of Removal of the Prefrontal Lobes

In expiremental study conducted in rhesus monkey to study the functions of prefrontal lobes. The prefrontal lobe was removed and the effects were studied.

The animal sits quietly with bowing of the head and remains apathetic. After a few weeks the animal becomes hyperactive and restless. There are alterations in behaviour, impairment of memory, loss of learning power, and a state of resembling sham rage phenomenon develops. After removal of the prefrontal lobes in prefrontal lobe tumour the effects have also been studied in human being. Unilateral removal of prefrontal lobes does not cause much alteration in mental processes but bilateral removal impairs moderate mental alteration.

The chief manifestations are:

1. Lack of self-control
2. Distractibility (difficulty of attention), flight of irregular linkless ideas
3. Loss of memory, especially for the recent events
4. Lack of initiative
5. Alteration in social behaviour, loss of moral and social sense
6. Disturbed orientation of time and space
7. Failure to release the seriousness of his own condition and a disproportionate sense of well-being (euphoria). Owing to these functions the prefrontal region is called the organ of mind. There will be no disturbance of voluntary movements if the excitomotor areas are not excised.

Other manifestations of prefrontal defects are:

a. The tremor

b. The disturbances in orienting the time and space

c. The increased appetite
d. The impaired control of the sphincter of the bladder and rectum.

Frontal Lobe and the Seat of Intelligence

It is of general belief that this lobe is the seat of intelligence in animal and the centre or the organ of mind. But World War II has provided an immense scope of such studies in subject having traumatic prefrontal injuries. From systematic studies in such patients it has been observed that destruction of prefrontal region does not produce any notable deficit in intelligence. From extirpation studies it do not suggest that intelligence, memory, control of behaviour, etc. are solely or even predominantly dependent upon the prefrontal cortex. This area probably represents a region of relatively high associative and synthetic capability. This area is meant for mental processes related to prediction, forecasting or to any planned activities. Housewife having loss of this area may feel difficulties in planning a meal. Mental capacity is a function of whole of the cerebral cortex and not of a particular region.

PARIETAL LOBE

Sensory Areas (Areas 3, 1 and 2)

Somaesthetic area or 'primary sensory' area or somatic sensory area (Fig. 104.17).

Areas 3, 1, 2

Situation: Posterior wall and lip of central sulcus and postcentral gyrus. Functions: Appreciation of general senses such as touch, pain, heat, cold and kinaesthetic from the opposite side of the body. The centres for the different parts of the body are arranged upside down in the same order as the motor centres in area 4.

The primary sensory area is somatic area I and somatic area II. The latter is more primitive of the two and receives crude sensation, whereas the former receives epicritic sensation. The motor centre of a particular part lies just in front of the sensory centre of the same part just like a mirror image. Central sulcus seems to be a great dividing line between motor and sensory areas. In the somaesthetic area the complete meaning of a particular sensation is understood, such as:

1. Appreciation of the size, shape, texture and weight of the objects—stereognosis.
2. Appreciation of the relative intensity of the different stimuli.
3. Tactile localisation, tactile discrimination of two points, recognition of position and passive movements of the limbs—spatial recognition.
4. Lesion of this area results in disturbances of these faculties and there will be astereognosis, loss of spatial recognition, and appreciation of the relative intensity of the different stimuli.
5. Inferior part of the postcentral gyrus contains the centre for taste and general sensations from tongue. Lesion of the inferior part of the postcentral gyrus causes loss of taste and general sensations of the opposite half of the tongue.

Area 2s

Situated in the postcentral gyrus.
Function: Inhibits resting cortical potential.

Association Area (Areas 5, 7)

Area 5: *Situation: Superior parietal lobule:* Two parts—5a (anterior), 5b (posterior). 5a is sensory association, included in the somaesthetic area. 5b is motor (described below).

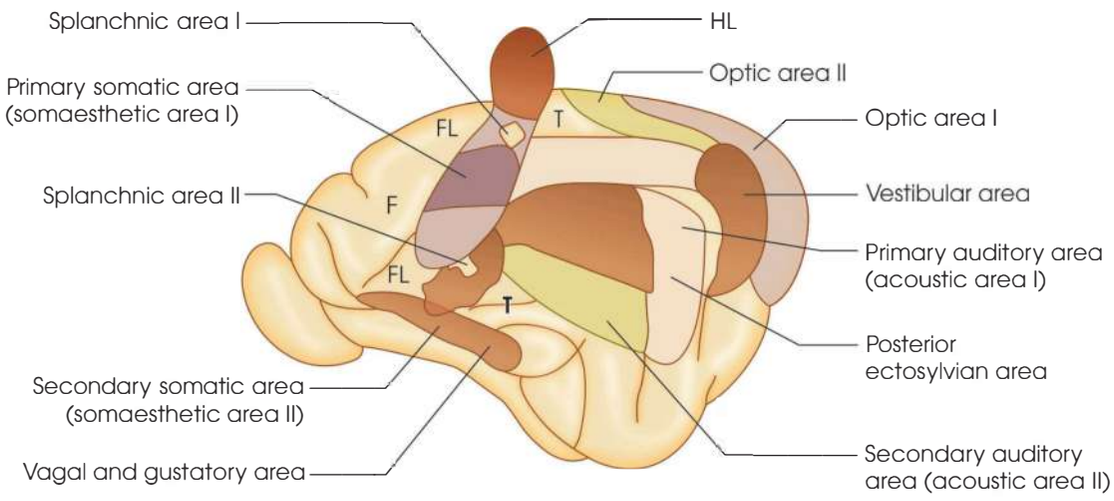

Fig. 104.17: Diagrammatic representation of the primary and secondary cortical sensory areas, primary and secondary auditory areas; visual areas; splanchnic areas, vestibular area, vagal and gustatory area and a portion of medial aspect of the brain shown above. Primary and secondary somatic areas indicating somatotrophic representation of different portions of the body showing F—face area, T—trunk, FL—forelimb, HL—hindlimb

Area 7: Situation: Supramarginal and angular gyri: Included in somaesthetic area. Two parts—7a (upper) and 7b (lower). Function: Sensory association.

In the somaesthetic area (3, 1, 2, 5, 7) not only the general senses are perceived, but their full associative meaning is interpreted.

Motor Area (Adversive)

Area 5b (parietal adversive field). Electrical stimulation causes movement of eyes, head, etc. to the opposite side. A similar adversive field is believed to be present in area 7a (angular gyrus).

TEMPORAL LOBE

Mostly sensory and association areas, viz. auditosensory and auditopsychic areas. It has minimal motor activities—adversive).

Sensory Area (Auditosensory)

Areas 41 and 42 Situation: Heschl's gyrus, mostly hidden in the sylvian fissure:

Auditosensory area: This area is grouped into auditosensory area I and auditosensory area II. In auditosensory area I the basal turn of the cochlea is projected anteriorly and the apical turn posteriorly, whereas in auditosensory area II the representation is quite reverse.

Function: Centre for hearing. Here the pitch, loudness, quality, etc. of sounds are perceived (the auditory centre also includes a small adjoining part of the superior temporal gyrus, i.e. of area 22).

Association area (auditopsychic).

Area 22: Situation: Superior Temporal Gyrus

Functions

1. A small part is included in the auditory centre.
2. Greater part acts as the auditopsychic area. The auditopsychic area is represented unilaterally. In the right-handed person it is on the left side and in the left-handed person it is on the right side.

Areas 21 and 20: Situation: Middle temporal and inferior temporal gyri respectively. Function: Auditopsychic area. Analysis, interpretation and integration of auditory impulses take place. The auditopsychic area is represented unilaterally. In the right-handed person it is on the left side and in the left-handed person it is on the right side (the speech centre is just in front of it on the anterior aspect of central sulcus).

Motor Area (Adversive)

Temporal adversive field: Posterior part of area 22.

1. Lesion of the temporal lobe results
2. Auditory disorders
3. Disturbances of smell
4. Aphasia (if the lesion is near the posterior end of the sylvian fissure): Visual hallucinations
5. Dreamy states.

Applied Physiology: Temporal Lobe Syndrome

After bilateral removal of temporal lobes along with the uncus (Fig. 104.18) and amygdale in monkeys following changes were observed.

1. Inability to recognise objects (visual agnosia).
2. Tendency to examine all the objects by putting them into the mouth (oral tendencies).

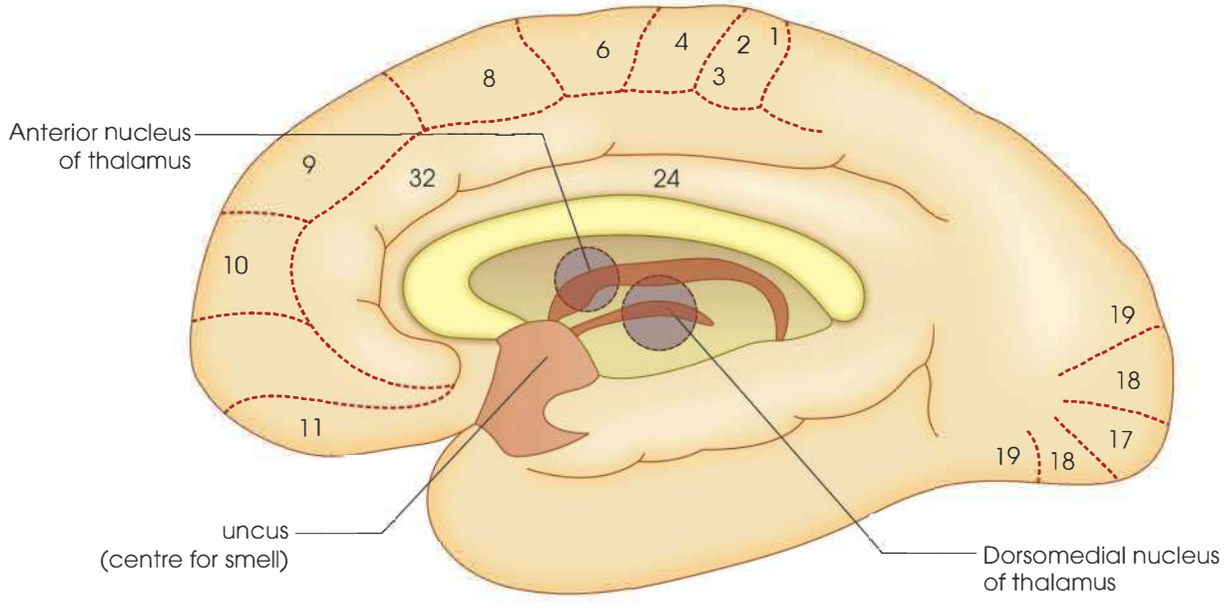

Fig. 104.18: Diagrammatic representation of the medial surface of the cerebral hemisphere showing uncus and other areas

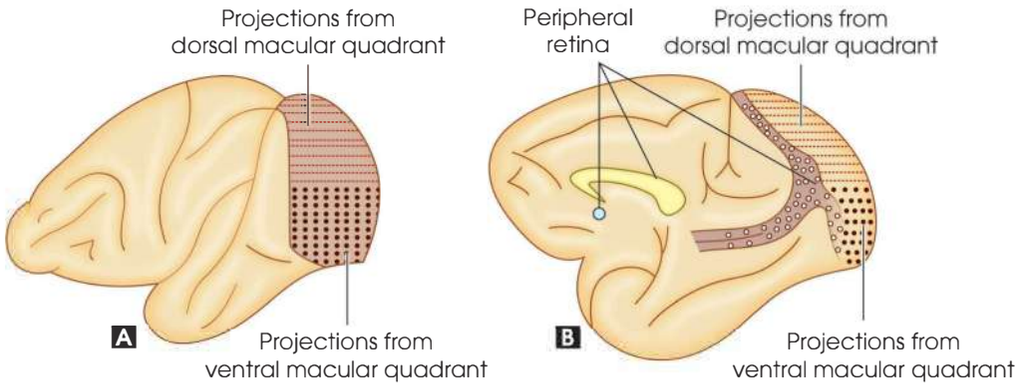

Fig. 104.19A and B: Diagrammatic representation of occipital lobe showing visual projection areas and stippled parts representing the peripheral retina. A: Lateral surface of cerebral hemisphere, B: medial surface of cerebral hemisphere

3. Peculiar attention to different objects (hypermetamorphosis).
4. Changes in emotional behaviour. The animal showed no signs offer and remained tame (tameness).
5. Striking increase in sexual behaviour and its diversity (hypersexuality).
6. Dietary habits are changed. The monkey accepts meat which is not accepted in general case.

OCCIPITAL LOBE

Mostly sensory and association areas, viz. visuosensory and visuopsychic areas. Only slightly motor-adversive.

Sensory Area (Visuosensory)

Area 17: Situation: Posterior lobe and calcarine fissure of occipital lobe—visuosensory area. Like the auditosensory area the visuosensory area, is also grouped into visuosensory area I and visuosensory area II (Fig. 104.19).
Function: It is cortical visual centre.

Association Area (Visuopsychic)

Area 18: Situation: On the convexity—just above area 17. Function—visuopsychic area: Here, the exact meaning of a visual image is interpreted and integrated, such as meaning of written language. Subjects with lesion in this area will fail to understand written language.

Motor Areas

Area 19 (occipital eye field—adversive).

Situation: It is situated just above area 18. Stimulation of this area causes conjugate deviation of the eyes towards the opposite side (same as area 8). Association fibres are believed to proceed from this area to the frontal eye field. Hence, there is conjugate deviation. These fibres are included in the path of accommodation (*vide* under accommodation).

Area 19s: *Situation:* In the occipital lobe anterior to visuopsychic area. Function—inhibits resting cortical potential.

FUNCTIONS OF THE CEREBRUM

Functions of the cerebrum may be divided into the following groups.

Motor Functions

Altogether there are three motor levels in the central nervous system. The anterior horn cells constitute the first level, the pyramidal—the second, while the extrapyramidals make up the third level. The functional difference of the three must be clearly understood.

The anterior horn cells are the basic motor units, each one controlling a few muscle fibres or almost one individual muscle. One pyramidal cell, on the other hand, controls many anterior horn cells and as such, the co-ordinated movements of a number of muscles, for instance, the extension or flexion of a limb. The extrapyramidal cortex also controls the anterior horn cells and regulates the skilled group movements of a large number of muscles, such as walking, writing, etc.

General motor function: Volitional movement—controlled by area 4.

Special motor functions:

1. Regulation of tone, posture, equilibrium.
2. Regulation of automatic and associated acts.
3. Control of autonomic nervous system (corticothalamohypothalamic). Tonic inhibitory control over lower motor centres.
4. Speech: Broca's area.
   Locations
   - In the right-handed people, situated in the left inferior frontal convolution (area 6b) in 96% individuals and 4% it is right hemisphere.
   - In the left-handed subjects—in approximately 15% in right hemisphere and in 15% no clear lateralization and remaining 70% it is left hemisphere.
5. Control of eye movements: Frontal eye field, area 8: Corticonuclear fibres arise here end round the third, sixth and fourth nuclei of the opposite side.
   - Parietal adversive field—area 5b.
   - Occipital eyefield—area 19.

- Temporal adversive field—posterior part of area 22. The adversive areas not only cause the eye movements but also those of head and body to the opposite side.

Seat of Conditioned Reflex

Cerebral cortex is responsible for the establishment of conditioned reflexes through the development of new connection with different subcortical centres. For establishment of conditioned response or reflex (CR), through specific conditioned stimuli (CS), specific cortical and subcortical centres are responsible for its development. As for example, the production of conditioned salivation reflexes, the cortical taste centre as well as the visual and auditory areas along with its subcortical centres are responsible if the CS are the ringing of bell and giving of food.

Sensory Functions

General Senses

It is involved in function of perception of touch, pain, heat, cold and kinaesthetic sensations. The location of sensory centre: Somaesthetic area (parietal lobe): Includes areas 3, 1, 2 and 5, 7. The last two act as psychic association areas, while the first three are mainly receiving areas.

In the somaesthetic area the complete meaning of a particular sensation is understood, such as:

1. Appreciation of the size, shape, texture and weight of the objects—stereognosis.
2. Appreciation of the relative intensity of the different stimuli.
3. Tactile localisation, tactile discrimination of two points, recognition of position and passive movements of the limbs-spatial recognition.

Special Senses

1. *Taste:* Inferior part of the postcentral gyrus. Here, general and taste sensations are perceived. Lesion of this area results in loss of general and taste sensations on the opposite half of the tongue.
2. *Smell:* Uncus and hippocampal gyrus (allocortex). Here, olfactory sensations are perceived.
3. *Vision*
4. *Visuosensory centre:* Occipital lobe (area 17). Here, all visual impulses are perceived.
5. *Visuopsychic area:* Area 18. Here, the exact meaning of a visual image is interpreted and integrated, such as the meaning of a written language.
6. *Hearing*
   - Auditosensory centre. Heschl's gyrus (areas 41, 42) and the adjoining part of superior temporal gyrus (area 22). Here the pitch, loudness, quality, etc. of the sound are appreciated. The centre is bilateral.
   - Auditopsychic centre. Temporal lobe (areas 22, 21 20). Here the analysis, interpretation and integration of auditory impulses take place and the complete associative meaning of a sound is recognised. It is unilateral. Like the speech centre, it is located in the left temporal lobe in the right-handed subjects.

Intellectual Functions

Cerebrum is responsible for all intellectual functions, viz. memory, intelligence, planning, judgement, etc. The so-called silent or association areas (psychic areas) are responsible for this—chiefly the prefrontal lobes. The prefrontal lobes associate themselves with other areas of the brain, viz. parietal, occipital and temporal lobes through the association fibres and act as planning organs and help in complex intellectual activities.

The development of prefrontal lobes bears a direct relation to the intelligence of the animal in the phylogenetic scale. But one must realies that these higher mental faculties cannot reside only in the prefrontal lobes. Because, intelligence depends on the ability to receive, respond and adapt. Obviously these are determined by the memory of all past impressions received through all the sensory organs. By associative faculties these sensory impressions are synthesized into various complex patterns and are stored as 'memory'. Whenever a new impression comes, its full significance is understood by analysing it in the background of this 'memory' and an appropriate motor response is accordingly organized. This whole process is called intelligence. Mental capacity will, therefore, depend not only on a particular lobe, but on the co-ordinated activity of the brain as a whole. The special value of prefrontal lobe lies in its high associative abilities.

ELECTRICAL ACTIVITY OF THE CEREBRAL CORTEX

The electrical activity of the brain and cerebral cortex is complicated and of different types from those of single nerve fibre or neuron. This is due to a large number of neurons, synapses and various properties of synapses, such as inhibition, summation, facilitation, etc. are integrated together to give rise rhythmic electrical potential changes which can be recorded through suitable instruments like electroencephalograph or cathode ray oscilloscope. The electrical activity of the cerebral cortex is of mainly two types—spontaneous and evoked. The spontaneous electrical activity of the brain is the electroencephalogram which is described below.

ELECTROENCEPHALOGRAPHY

Like other cells, nerve cells also show changes of electrical potential during activity. With an instrument called electroencephalograph, the waves can be

detected, amplified and recorded. Such a record is called electroencephalogram. Hans Berger who was a German scientist, first introduced the term electroencephalogram (EEG). Berger in 1929 recorded changes in the electrical potential by placing electrodes on the scalp of the human beings. These electrical potentials were later investigated by Adrian and Matthews. Electrocorticogram is the term sometimes used to denote the record obtained with electrodes on the pial surface of the cortex. Berger also detected the changes by placing minute electrodes on the surface or within the substance of the cerebral cortex in animals (electrocorticogram).

Applied Physiology: Electroencephalogram (EEG)

Spontaneous Electrical Activity

The spontaneous electrical activity from the brain as recorded by the electroencephalographic machine with the help of scalp electrodes through the lead is called electroencephalogram which has been most effectively studied in human beings.

Electroencephalogram

Electroencephalographic records may be bipolar or unipolar and consists of different types of rhythmic waves. Bipolar is the record of potential fluctuations between two cortical electrodes, whereas the unipolar electrode is the record of potential differences between a cortical electrode and an indifferent electrode placed on some part of the body.

Alpha, beta, theta and delta waves: In normal human subjects four types of waves are recorded, e.g. alpha (α), beta (β), theta (θ) and delta (δ) (Fig. 104.20).

Alpha Waves

Alpha waves (rhythm) are the most prominent synchronised rhythmic potential changes, found with eyes closed or in dark, when the brain is under quiet rest (Fig. 104.21). Usually found in the occipital cortex,

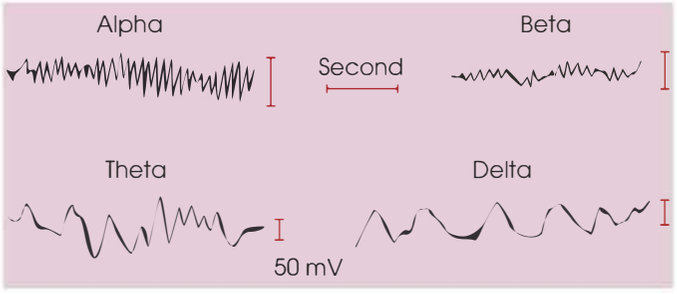

Fig. 104.20: Diagrammatic representation of normal electroencephalographic alpha, beta, theta and delta waves

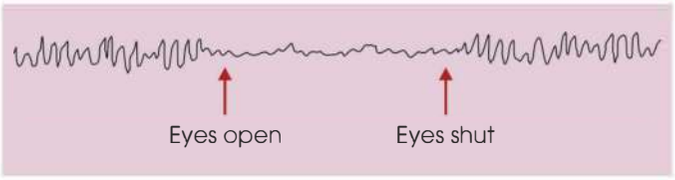

Fig. 104.21: Diagram shows the changes of alpha rhythm after opening and closing the eyes

but also obtained in frontal and parietal regions. This rhythm is marked in occipitoparietal region. Any mental exertion, even with closed eyes, will disturb. The alpha waves disappear when eyes remain open. This alpha wave is disappeared with a replacement of fast, irregular and low voltage activity without any dominant frequency just after opening the eye. This phenomenon is known as α-block. This α-block is due to desynchronisation of regular (synchronised) α-rhythm by any kind of sensory stimulation. This desynchronisation response is also called arousal or alerting response (Fig.104.21). Visual stimuli, mental concentration, etc. abolish alpha waves. During deep sleep, the alpha waves disappear entirely and with a specific mental activity of alpha waves are replaced by asynchronous high frequency low-voltage waves.

The dream is accompanied by alpha waves. The alpha waves cannot occur without the connection of the reticular activating system. It is postulated that the reverberation between thalamus and cerebral cortex and also the recruiting response of the thalamus are responsible for the cause of the periodicity of the alpha waves. Rate: 8–12 cycles per second. Amplitude—highest-average 50 microvolts.

Beta Waves

Usually found in the parietal and frontal regions of the scalp.

Rate

It is about 18 cycles per second and maximum 60 cycles per second.

Types

Beta I waves have a frequency about twice that of alpha waves and disappear during reaction of mental activity, but such waves are replaced by asynchronous low-voltage waves. Beta II waves appear during tension or during intense activation of the central nervous system.

Amplitude

5–10 microvolts (less than alpha wavers)—two voltage fast waves (Fig. 104.22).

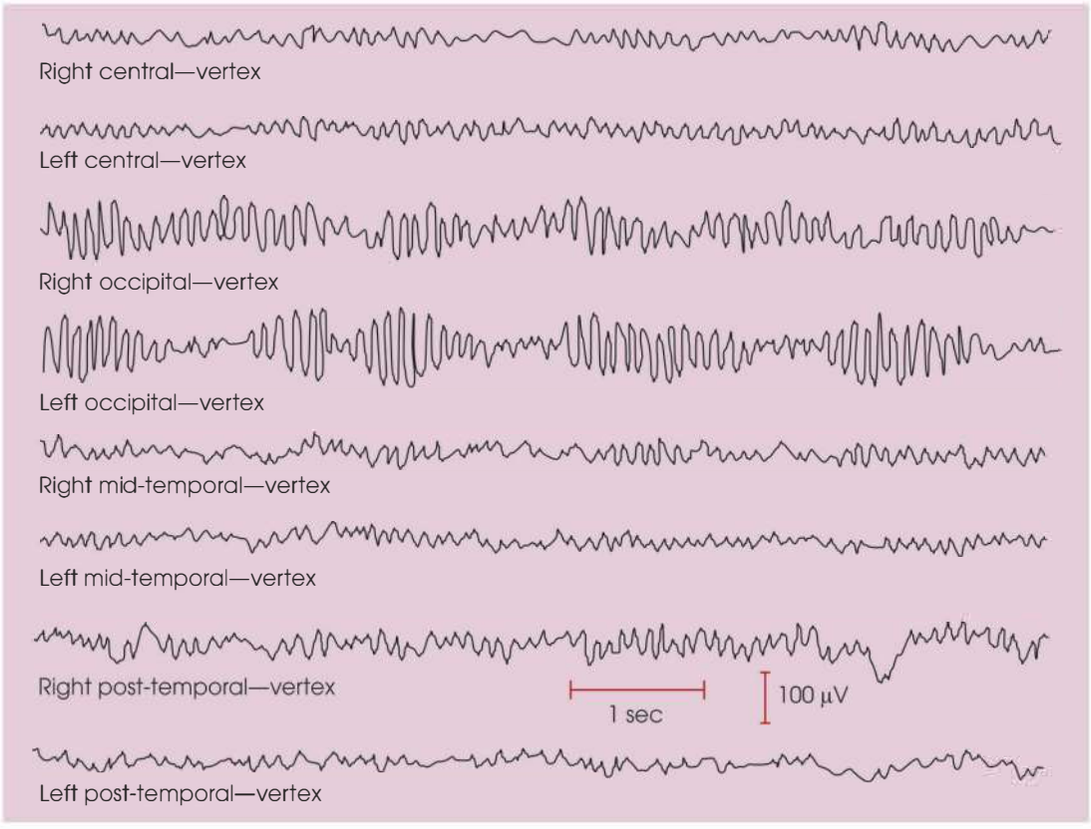

Fig. 104.22: Normal electroencephalogram from different cortical areas in man showing alpha and beta waves during awake with eyes shut. (*Courtesy*: Dr TK Ghosh, MD (Cal), Head, Department of Neurology, University College of Medicine, Calcutta)

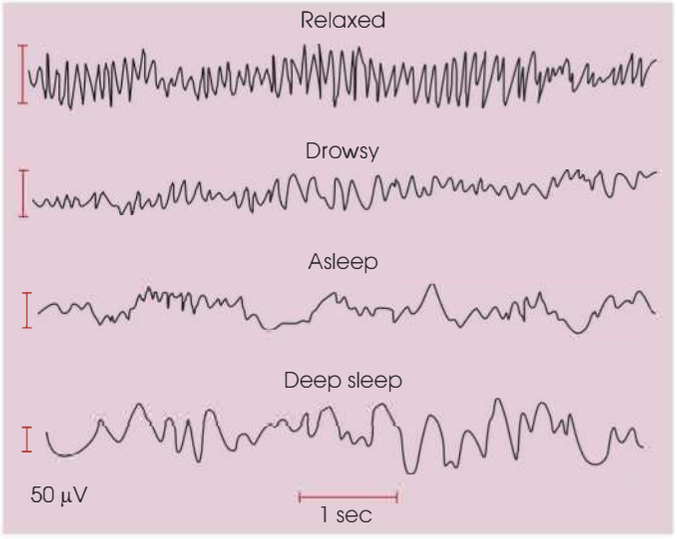

Fig. 104.23: EEG patterns under certain conditions (Ganong)

Theta Waves

Usually found over the parietal and temporal regions. In children between the ages two and five year's theta waves are prominent.

Rate

4–8 cycles per second.

Amplitude

10 microvolts.

Delta Waves

It is postulated that the delta waves occur due to separation of the cerebral cortex from the reticular activating system. Rarely found in normal adults during waking periods, but usually found during deep sleep and in serious organic brain disease (Fig. 104.23). In severe hypoxia and also in hypoglycaemia δ-waves appear frequently. In infancy, it appears both during deep sleep and waking.

Rate

Minimum, 0.5–3.5 cycles per second.

Amplitude

Variable 20–200 microvolts—high voltage slow waves.

Conditions that Alter the Electroencephalogram (EEG) Pattern

Different factors may alter the EEG pattern. These are discussed below:

Age: Dominant EEG rhythm may vary with age. α- and θ-waves are the characteristic features of infancy and

childhood. In infants, there is fast β-like activity but with the advent of adolescence gradual α-pattern appears.

Blood-glucose level: Blood sugar level has got profound influence on the EEG pattern. (Hypoglycaemia decreases the frequency of α-rhythm and even causes appearance of δ-rhythm but the α-rhythm is not totally abolished. Hyperglycaemia has got a little effect on cortical potential.

Hypoxia: Mild hypoxia initially slowers the rhythm but if the state is severe then causes appearance of δ-waves.

Effect of CO_2: High arterial CO_2 tension may cause slowing of the frequency of α-rhythm. Washing out of CO_2 is used clinically to bring out latent EEG abnormality.

Temperature: Lowering of body temperature may sometimes decrease the frequency of α-rhythm.

Sensory stimulation: Any type of sensory stimulation alters the EEG pattern. Pattern of α-rhythm is altered with attention and mental concentration. But in full mental rest, there is appearance of α-wave but with attempt of solving a mathematical problem it is abolished by fast and irregular low voltage activity. Sleep and EEG: As soon as a subject gets relaxed, he feels drowsy and gradually falls asleep. α-pattern of EEG is replaced by slower and larger waves. In deep sleep there are often irregular δ-waves having frequency less than 4 per second (Fig. 104.22).

The EEG pattern of deep sleep is sometimes replaced by low voltage and high frequency irregular waves along with eye movements. This type of sleep is known as paradoxical sleep and for the associated movements of eyes it is also called rapid eye movement sleep (REM sleep) (Figs 104.23 and 104.24).

Sleep having high voltage (spindle) slow wave EEG pattern but unassociated with eye movement is also called slow-wave sleep or non-rapid eye movement sleep (NREM sleep). REM sleep occurs at about every 90 minutes of sleep period.

Narcotics: With narcotics the α-waves are replaced by δ-waves. The rhythm of α-waves is deceased by low glucose level, lowered body temperature, anaesthesia or analgesia, sleep, etc.

Electroencephalogram in Various Diseases

Changes in the electroencephalogram have been noted in the following diseases.

Increased intracranial pressure: Berger demonstrated slow δ-waves with amplitude up to 100 microvolts and a frequency of 3 cycles per second during the rise of intracranial pressure due to cerebral tumours, concussion, meningitis, etc.

Cerebral tumours: Berger also demonstrated similar slow δ-waves arising from the affected region of the brain. The tumours cause progressive destruction of cortical tissue and as a result abnormally large slow δ-waves will arise from the damaged cerebral cortex (Fig. 104.25).

Epilepsy: It is a disorder, characterized by an abnormal and severe discharge of nervous energy from either a part of the central nervous system, usually the cerebral cortex or all of it.

There are mainly two types of epilepsy:

1. Generalised epilepsy
2. Partial epilepsy.

The generalised epilepsy is of three types—grand mal, petil mal and psychomotor (Fig.104.26). In the grand mal type there is generalised convulsions along with abrupt loss of consciousness. This seizure lasts for three seconds to as long as four minutes and is characterized by postseizure depression of the entire nervous system. The grand mal attack is presumably due to increased activities of the mesencephalic (midbrain) part of the reticular activating system.

The petit mal epilepsy occurs in two different forms:

1. The myoclonic form
2. The absence form.

In the myoclonic petit mal epilepsy, the subject exhibits a single violent muscular jerk (head or arms) and it lasts only for a few seconds. In the absence petit mal epilepsy, it is characterised by 4 to 22 seconds of unconsciousness along with several twitch-like contractions of the muscle usually in the head region. The electroencephalographic record shows spike and dome pattern (Fig. 104.25). In petit mal attack large but slow and irregular waves are recorded just before the attack.

A sharp spike deflection follows the large wave. An increase in the number of these spike waves often precedes a grand mal attack and indicates the onset of convulsion. The seizure waves in grand mal attack are sharp spikes occurring at 25 to 30 cycles per second and in petit mal attack there are sharp spikes alternating with slow round waves at 3 cycles per second.

Fig. 104.24: Sequential changes of EEG in a subject during alert, drowsy, slow wave sleep and paradoxical sleep

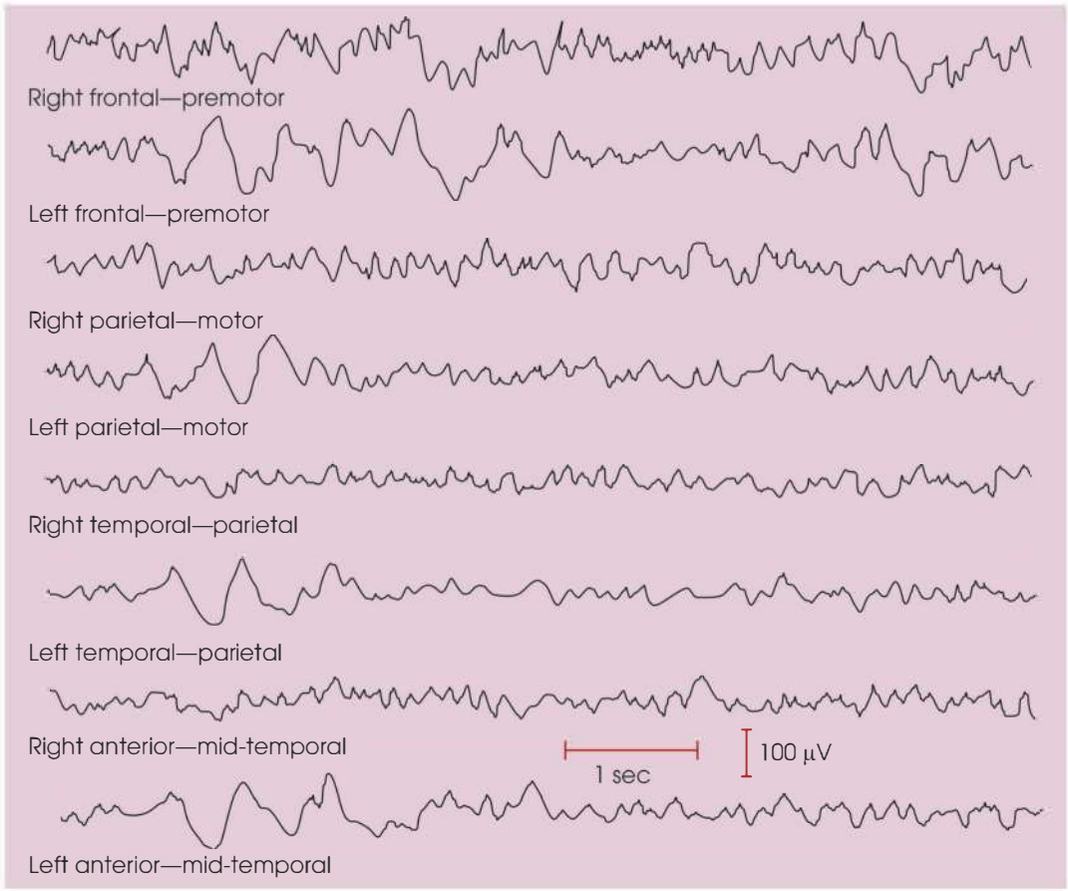

Fig. 104.25: Electroencephalogram of brain tumour in left parietotemporal regions showing delta waver. (*Courtesy*: Dr. TK ghosh, M.D. (Cal.), Head, Department of Neurology, University College of Medicine, Calcutta)

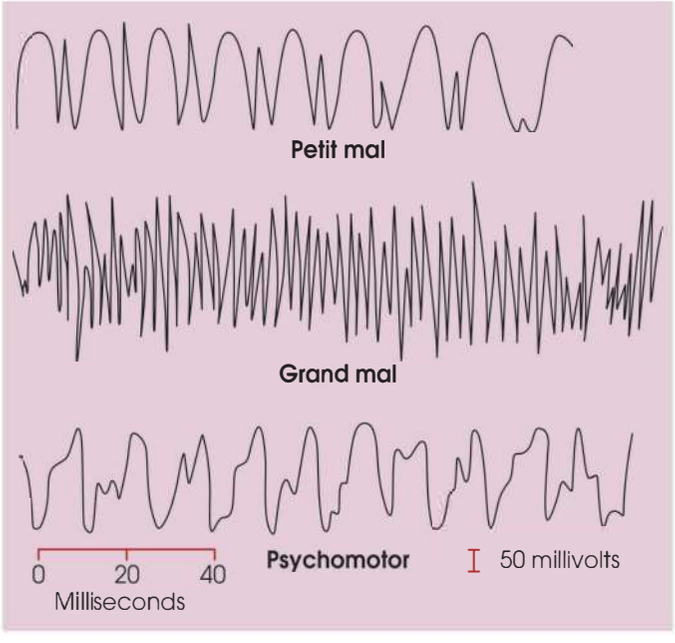

Fig. 104.26: Electroencephalograms of different types of epilepsy

Psychomotor is characterised by the automatic movements, i.e. chewing, smacking of lips, etc. along with a dreamy feeling of unreality. It is said that this type of psychomotor seizure is commonly due to disturbances in the temporal lobe. The hypothalamic tumour may cause the outbursts of autonomic phenomena. During a psychomotor attack there is a low frequency of rectangular wave with the frequency of 2–4 cycles per second and with the fast frequency of 14 cycles per second. This type of epileptic attack may cause an attack of abnormal range, a short period of amnesia, a moment of incoherent speech, sudden anxiety or fear or discomfort.

Partial epilepsy or localised epilepsy is often of different forms and generally referred to as jacksonian epilepsy.

Motor jacksonian epilepsy involves any localised area of the cerebral cortex or deeper structure of the cerebrum or the brain stem. The seizure is characterised by turning of the head and eyes towards the side opposite the lesion in the brain (anterior part of the precentral motor cortex and also of the medial surface of temporal lobe).

The partial epileptic attack may the confined to a single area of brain, but in several cases it excites brain stem reticular activating system so greatly that may initiate grand mal epileptic attack, cerebral tumours,

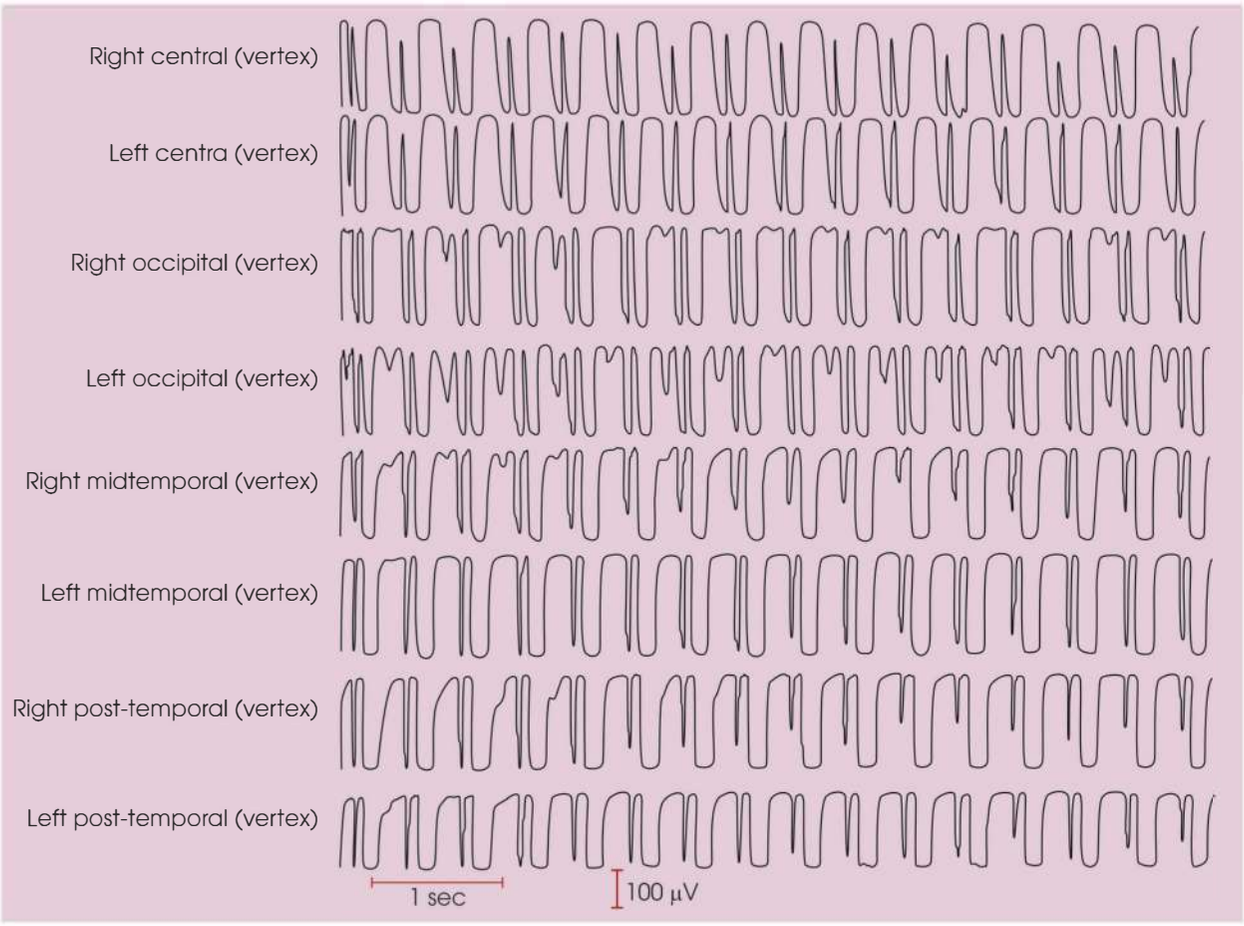

Fig. 104.27: Electroencephalogram of epileptic seizures (petit mal) showing spike and dome pattern. (*Courtesy*: Dr TK Ghosh, MD (Cal.), Head of the Department of Neurology, University College of Medicine, Culcutta)

abscesses, traumatic scars, vascular abnormalities, etc. are the commonest cause of this attack.

Idiopathic or cryptogenic epilepsy is that type of epilepsy whose cause is unknown and cannot be explained with demonstrable lesion in the brain.

CONCLUSION

Electroencephalography is now widely accepted as a reliable method of studying the electrical changes occurring in the cerebral cortex during normal and abnormal conditions. It is helpful in localising the exact site of cerebral tumours, abscesses, etc. It is of special importance in investigating the presence of epilepsy and the types of fits that occur in the epileptic subjects. Besides, it is also helpful in the diagnosis and investigation of impaired cerebral functions in various diseases of cerebral cortex, head injury, brain death, etc:

PHYSIOLOGICAL BASIS OF EEG

Source of EEG

Originally it was of opinion that EEG waves are the summated action potential of cortical cells discharging in a volume conductor. But present concept is changed and it is due to current flow in the fluctuating dipoles formed on the dendrites of the cortical cells and cell bodies. Cortical dendrites are the forest of densely units placed in the superficial layers of the cerebral cortex (Fig. 104.28). Dendrites are the sites of non-propagated hypopolarising and hyperpolarising local potential changes in the excitatory and inhibitory axodendritic synapses. Dendrites are not the processes for conduction and do not propagate action potentials. Action potentials are propagated through the axonic terminals. When the excitatory axodendritic synapses are activated, current flow into and out in between the cell body and axodendritic endings, causing a wave-like potential fluctuation in the volume conductor. Thus, EEG is the potential fluctuation in volume conductor, but not the action potential that is conducted through the axon only.

Thus, the dipole formed in between the dendrites and the cell bodies fluctuates constantly due to the excitatory and inhibitory axodendritic synapses.

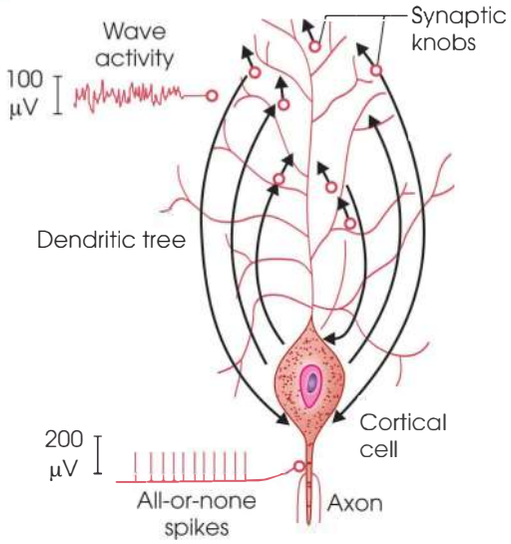

Fig. 104.28: The dendritic tree or cortical superficial neurone showing the development of wave pattern by current flow to and from active synaptic knobs on the dendrites (Bickford's Computational Aspects of Brain Function and Ganong)

Mechanism of Desynchronisation and Synchronisation

Definite pattern of α-rhythm is due to synchronised activity of the many dendritic units. When the synchronised activities of the dendritic units are disturbed by incoming different sensory impulses, the synchronised pattern of α-rhythm no longer persists and is replaced by desynchronised pattern of irregular low voltage activity.

For the genesis of synchronised wave pattern, two factors are responsible, such as: Synchronising effects of two parallel nerve fibres. The influences of impulses from the thalamus and the brain stem. The characteristic feature of α-wave indicates that the activities of many dendritic units are synchronised. Large bilateral lesions in the non-specific projection nuclei of the thalamus abolish the EEG synchrony. Desynchronisation of EEG pattern with irregular low voltage activity can be produced by stimulating the specific sensory input up to the level of the midbrain.

High frequency stimulation of the reticular formation in the midbrain tegmentum and of the non-specific projection nuclei of the thalamus desynchronises the EEG pattern.

EVOKED CORTICAL POTENTIALS

Evoked activity in the cerebral cortex is elicited by stimulating directly the cortical surface (direct cortical response—DCR) or by stimulating the peripheral sense organ like retina—by photo stimuli, ear—by auditory click or the peripheral sensory nerve endings or fibres. A characteristic response is seen in each case which is greatly influenced by the effect of narcotics, drugs, physiological conditions like sleep, etc.

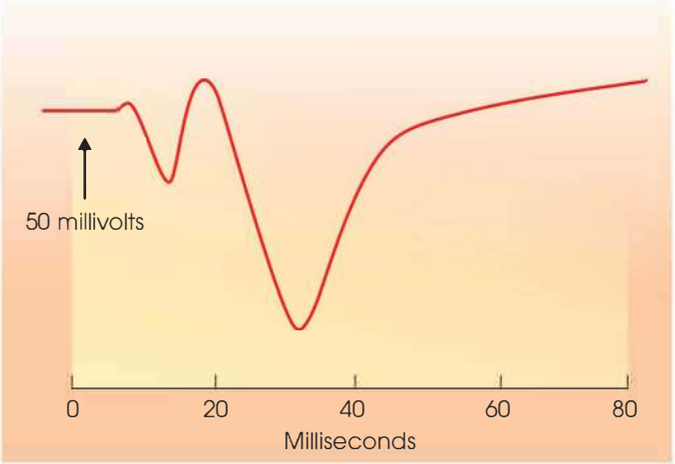

Fig. 104.29: Graphical representation showing response evoked in the contralateral sensory cortex by stimulation of the sciatic nerve

The waves consist of surface positive, followed by small negative and then by a larger more prolonged positive deflection (Fig. 104.29). The first positive–negative waves sequence is the primary evoked response; the second one is the diffuse secondary response. Evoked and spontaneous electrical activities can be recorded directly from the cerebral cortex through either extracellular or intracellular recording with the help of microelectrodes (Fig. 104.30).

OTHER TYPES OF ELECTRICAL ACTIVITY IN THE CEREBRAL CORTEX

Direct Cortical (DC) Potentials

During recording of the spontaneous electrical activity, the cerebral cortex shows certain changes in DC

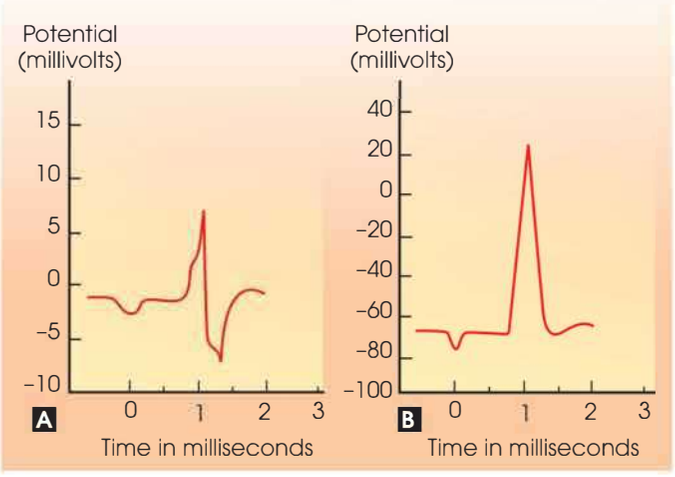

Fig. 104.30: Diagram showing discharge of Betz cells of the motor cortex stimulated by electrode at the cortical surface. (A) Recording extracellularly, (B) recording intracellularly

potentials which can be recorded through non-polarisable electrode, sometimes recorded from the scalp also. The steady potential (SP) level of the cerebral cortex is originated from the polarisation state of the cortex and apical dendrites. A marked change is seen in the steady potential following asphyxiation. There is often a marked increase in electrical impedance (resistivity) of the cortex following asphyxia.

Spreading Depression (SD)

During recording of the spontaneous electrical activity, the cortical region very often shows temporary or transient inhibition of these rhythmic waves and this is believed to be due to the spreading depression.

A depression phase slowly spreads from the occipital region to another part of the frontal cortex at 2.5 mm per minute and successively invades one area after another followed by immediate recovery. This depression is the function of the apical dendrites and recovery requires the expenditure of metabolic activity. Release of potassium or glutamic acid is involved in the genesis of spreading depression.

Applied Physiology

1. *Blindness or dyslexia:* The individual is unable to interpret the words he sees. This condition is due to lesion in angular gyrus and damaged area no 39. The Wernicke's area which lies in close proximity, Wernicke's area is intact.
2. *Aprasia:* It is in inability to correctly and sequentially perform any tasks or movements. In speech, aprasia person is unable to have a coherent and sequential
3. *Cerebral palsy:* The head injury leading to damage to the motor cortex during intrauterine foetal life, birth or during infancy may lead to cerebral palsy. The pathological manifestation included loss of muscle control and incordination of muscular activities. The common causes are exposure to radiation in foetal life, rubella virus infection causing measles in newborn, infants with hydrocephalus and hypoxic damage to brain during delivery.

Korbinian Brodmann is a German Neurologist who demarcated the cerebral cortex into 52 distinct regions from their cytoarchitectonic characteristics.

1868–1918

EXAM-ORIENTED QUESTIONS

Essay

1. Descibe the structure and functions of cerebral cortex.
2. Descibe the structure and functions of frontal lobe.
3. Descibe the structure and functions of occipital lobe.
4. Descibe the structure and functions of temporal lobe.
5. Describe the waves of EEG and their significance.

Short Notes

1. Blindness or dyslexia
2. Cerebral palsy
3. Evoked cortical potential
4. Petit mal epilepsy
5. Grand mal epilepsy

Chapter

105

Limbic Lobe and Limbic System

INTRODUCTION

Limbic lobe is the phylogenetically old palaeocortex and is called allocortex. Between the allocortex and the rest of the cerebral hemisphere there is a transitional type of cortex which is known as juxtallocortex or mesocortex (Fig. 105.1). The allocortex is developed in association with the chemical senses and thus known as olfactory cortex or rhinencephalon and phylogenetically, having six characteristic layers (Fig. 105.2) are described as neocortex (isocortex).

The neocortex sits astride the limbic system like a rider on a horse without reins. But the rhinencephalon or olfactory cortex is a more restricted term and it includes only those portions of the brain which receive projections from the olfactory bulb. Specifically, the limbic lobe includes the subcallosal cingulated and parahippocampal gyri as well as the underlying hippocampal formation (hippocampus, dentate gyrus, indusium griseum or supracallosal gyrus and the longitudinal striae).

The limbic system is a more generic term and includes all of the limbic lobe and the associated subcortical nuclei such as the amygdaloid complex, septal nuclei, hypothalamus, epithalamus (pineal body, habenular nucleus, stria medullaris, and epithelial roof of the third ventricle), anterior thalamic nuclei, parts of the basal ganglia and midbrain reticuar formation (Fig. 105.3). The olfactory centre is situated in the uncinate part of the hippocampal gyrus.

In 1958, Penfield and Milner observed that there was loss of recent memory after bilateral removal of hippocampal gyrus and hippocampus (hippocampal formation) in a patient. In human being the hippocampus, fornix, cingulate gyrus, are well developed and so it has been suggested that beside olfaction they subserve more important functions in the body.

AFFERENT AND EFFERENT CONNECTIONS OF LIMBIC SYSTEM

The main connections of the limbic system have been represented in Fig. 105.3. The fornix connects the hippocampus with Ammon's horn to different hypothalamic nuclei and the mamillary bodies of the hypothalamus are connected to the anterior nucleus of

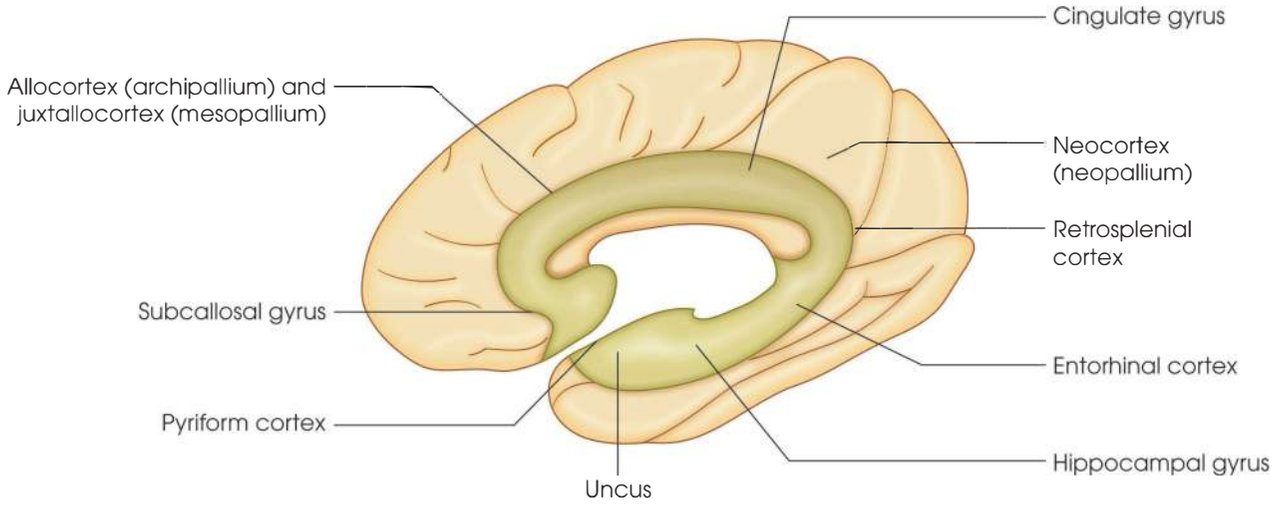

Fig. 105.1: Diagram showing the anatomical relationship of the limbic cortex with the rest of the cortex in human beings

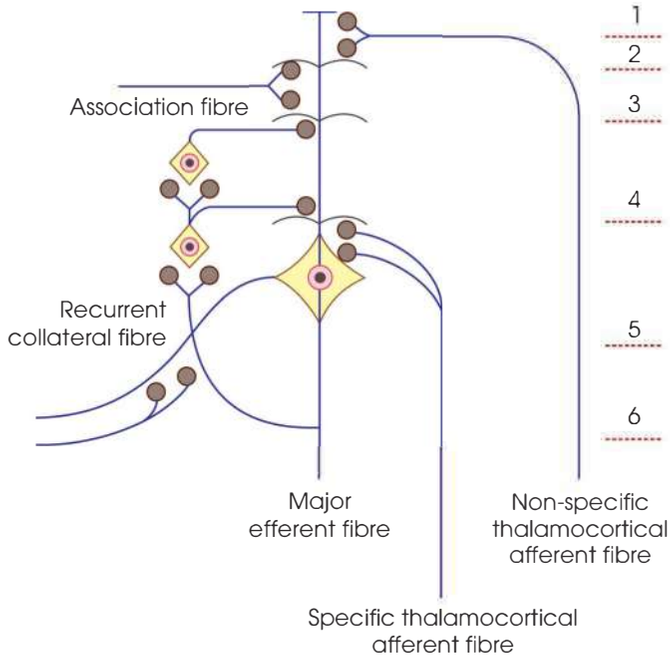

Fig. 105.2: Diagrammatic representation showing the connections of neocortical neurons. Descending axons of the giant cell give off collateral fibres in the pyramidal cell layer. These collaterals send feedback through association fibres to the cellular dendrites. Recurrent collateral fibres connect to adjacent cells and a few recurrent collaterals end on inhibitory neurons. Specific thalamocortical afferent fibres end in the fourth layer and non-specific thalamocortical afferents end in the first layer (Ganong)

the thalamus through the mamillothalamic tract. The anterior nucleus of the thalamus sends fibres to the cingular (cingulated) cortex (areas 23, 24, 29, 32). The hippocampus and the septal region thus project to the hypothalamic nuclei mainly through the fornix. The caudate nucleus receives fibres from the cingular gyrus and the intralaminar nuclei of the thalamus.

The lateral hypothalamus receives fibres from the following:

1. Hippocampal and septal zones
2. Olfactory tubercle
3. Head of the caudate nucleus
4. Prepyriform and periamygdaloid cortex (Fig. 105.4).

However, the different parts of this system are closely connected with one another and, on the other hand, with secondary sensory areas and association areas of the isocortex, i.e. medial surfaces of the frontal, parietal, temporal and occipital lobes.

Interconnection

The parts of limbic system are connected to each other. The main interconnections include:

1. Amygdala to hippocampus
2. Hippocampus to septum.

Functions of the Limbic System

1. Limbic system plays an important role in learning, and memory by influencing the endocrine system

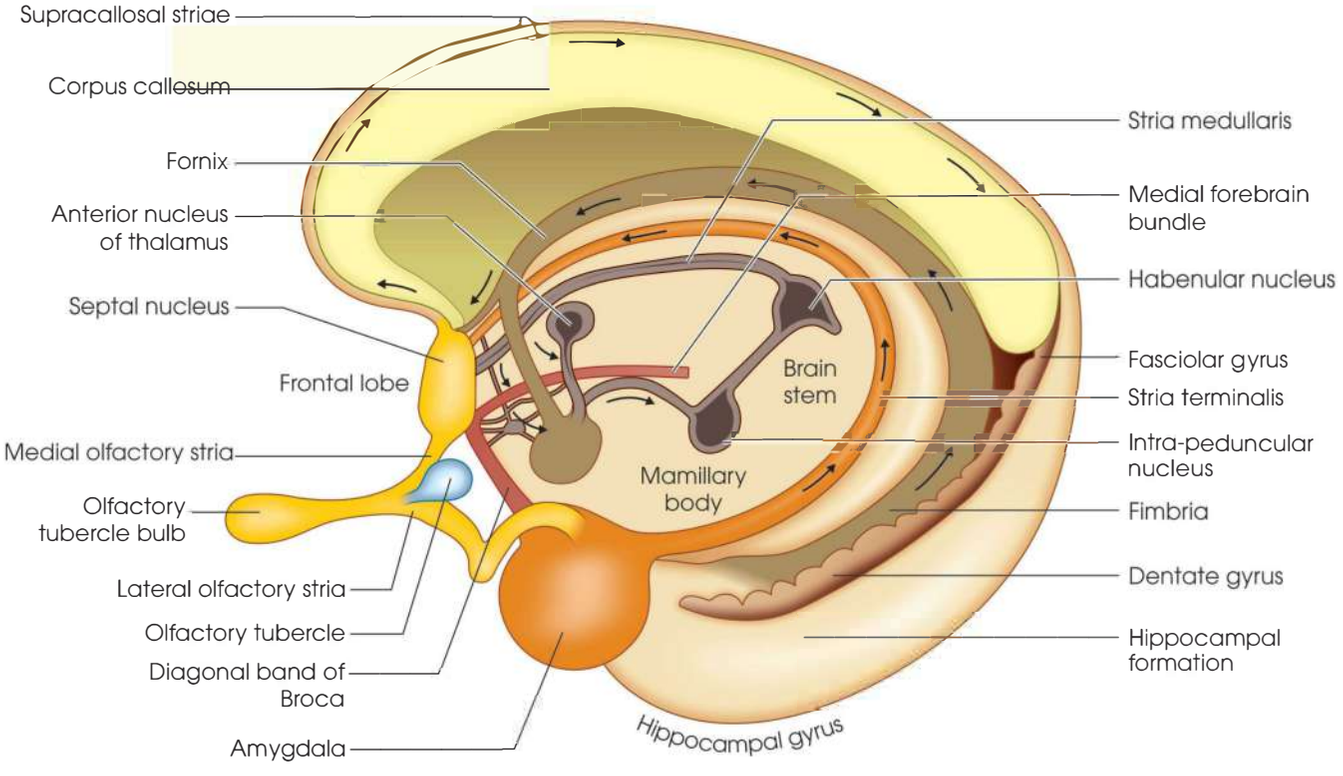

Fig. 105.3: Diagram showing the main connections of the limbic system

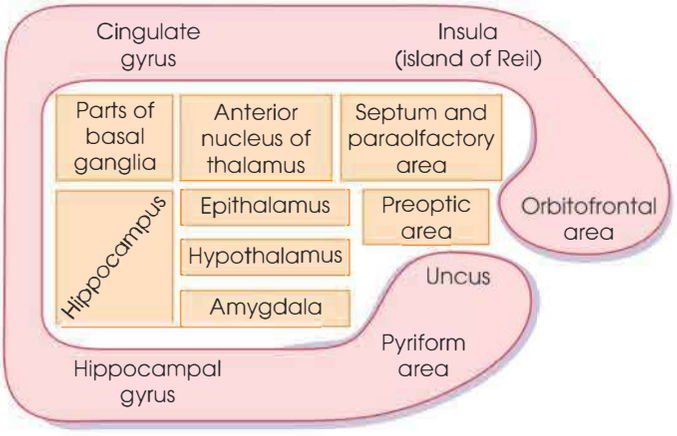

Fig. 105.4: Simplified diagram of the limbic system (Guyton)

and the autonomic nervous system. Amygdala is responsible for the associative learning process and fear conditioning. The hippocampus plays a role as a memory indexer and helps in the formation of new memories about experiences of past.

2. It has interconnection with the nucleus accumbens and via this interconnection which is modulated by dopaminergic projections; it influences the sexual arousal mechanism.
3. The sensory input pertaining to emotions and the regulation of aggressive behaviour is influenced by cingulated gyrus of the limbic cortex.
4. The hypothalamus and thalamus influences and control hanges in emotional reactivity. Thus, limbic system plays a role in emotion and memory.
5. It is also responsible for adding sensory experiences.
6. Nucleus accumbens is involved in psychological outcome of reward, pleasure, addiction, fear, aggression and the placebo effect.
7. The orbitofrontal cortex which forms the part of the limbic cortex is involved in the process of decision-making.
8. It regulates autonomic processes. Hypothalamus is connected with the thalamus via the mamillothalamic fasciculus, with the frontal lobes, septal nuclei and reticular formation via the medial forebrain bundle, with the hippocampus via the fornix and there by it regulates the autonomic response.

Thus, to conclude the limbic system is concerned with emotional reaction, visceral, somatic, behavioural changes, motivation, biological rhythms, and respiratory, circulatory and endocrine changes.

Applied Physiology

Damage to structures of limbic system also leads to Klüver-Bucy syndrome which results due to bilateral lesions of the medial temporal lobe including amygdaloid nucleus. Klüver-Bucy syndrome presents with symptoms of hypersexuality, hyperorality, hyperphagia, visual agnosia, and docility.

> Gustav Molaison a 27-year-old male had undergone bilateral removal of almost all of his hippocampus to prevent fatal kepileptic seizures in 1953. The symptoms exhibited by him were fading of semantic and episodic events within minutes, never reached or able to recall his long-term memory, but emotions, unconnected from the details of causation, were many a time retained. Dr. Suzanne Corkin reported this tragic "experiment" in her 2013 book. He volunteered to be a subject for thousand of studies conducted regarding limbic system functions.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the afferent and efferent connections and functions of limbic system.

Short Note

1. Klüver-Bucy syndrome

REFERENCE

1. Geoff Watts. 'Obituary Suzzane Corkin.' The Lancet 2016; 388 (10042):336.

Chapter

106 Speech

INTRODUCTION

Speech is the production of articulate sounds, always bearing a definite meaning. It is one of the highest faculties of brain brought about by the co-ordinated activity of different motor, sensory and psychic centres. Speech, reading and writing (written speech) are closely allied. When a sound is verbally reproduced and that is what we call speech. If it be expressed by visual symbols, that is known as writing. If visual symbols (written) are expressed verbally, that becomes reading.

CENTRE

One curious finding is that in the right-handed people the sensory, psychic and motor areas concerned with speech and is chiefly located in the left cerebral hemisphere. While in the left-handed people it may be the reverse. Speech centre lies in the left inferior frontal convolution area (6b). The writing centre is believed to be in the left middle frontal convolution area (6aα).

DEVELOPMENT OF SPEECH

Like all complex motor processes, speech depends on the co-ordinated activities of a number of sensory, psychic and motor areas. When the baby learns speaking, it at first hears the sound of a spoken word (Auditosensory area), then it tries to understand the full meaning of the sound with the help of other sensory and associative impressions (auditopsychic area). For instance, the word 'Papa' becomes linked up with a particular man. The baby then tries to organise the necessary motor impulses in a particular area called the speech centre (Broca's area). Thus, organised, the stream of impulses are passed onto the adjoining pyramidal area, which control the movements of lips, tongue, larynx, pharynx, respiration, etc., i.e. those concerned with articulation. The impulses then travel down the pyramidal tracts to the motor centres of the corresponding nerves. In this way, the child produces the first sound. The first attempt naturally becomes defective. The defective sound is compared with the memory of the correct sound (auditopsychic area). The child recognises the fault and tries again. Thus, after a long period of 'trial and error' (lisping) the sound becomes accurate. In this way, speech develops. For speech, therefore, hearing is essential. A child who is born deaf is also born dumb (unless special methods are adopted).

Writing is a very similar process. At first the visual impressions of the letters are received (visuosensory area) and then their full meaning understood (visuopsychic area). Then it is linked up with the centre for the complex movements of fingers and hands (writing centre—area 6aα) and thus the hand 'writes'. Hence, vision is important for writing (in blind schools,

For speech

'A' 'B'

Ear → auditonsensory → auditopsychic → speech centre → excitomotor centre → speech

For writing

'C' 'D'

Eyes → visuosensory → visuopsychic → writing centre → excitomotor centre → writing

For reading

Eyes → visuosensory → visuopsychic → speech centre → excitomotor centre → reading

↓ ↓

Auditopsychic

raised letters are used and thus alphabets are taught through tactile and kinaesthetic sensations).

Reading is also a similar but a little more complicated process. The visual impressions of the letters and the auditory impressions of their sounds become manually linked up in the corresponding psychic areas and are then associated with the speech centre. The following scheme summarises the three processes.

Applied Physiology: Aphasia

Various types of speech defects occur due to lesions of the sensory, psychic or motor areas responsible for speech, particularly. Broca's area and neighbouring areas. The term aphasia is applied to those defects of speech which result from the disorders of higher nervous mechanism underlying the understanding of various sensory impulses (auditory, visual, kinaesthetic, etc.), the use of symbols (words, letters, figures), the organisation of adequate motor impulses. In other words, the defect lies in the psychical field. Those, resulting from paralysis of the muscles of articulation, are not true aphasias.

Classification of Aphasia

1. ***Expressive aphasia:*** It is also known as "motor aphasia" or "Broca's aphasia", the characteristic features of expressive aphasia is halted, fragmented, effortful speech with well-preserved comprehension. The damage is in the anterior portion of the left hemisphere, particularly Broca's area that is being affected in Expressive aphasia.
2. ***Receptive aphasia:*** It is also known as "sensory aphasia" or "Wernicke's aphasia", the characteristic features of receptive aphasia is fluent speech, but it is difficult to understand words and sentences. The receptive aphasia is associated with damage to the posterior left temporal cortex, prominently Wernicke's area.
3. ***Transcortical motor aphasia and transcortical sensory aphasia:*** These are similar to Broca's and Wernicke's aphasia respectively, but mainly the ability to repeat words and sentences is disproportionately preserved.
4. ***Nominal aphasia (blindness)*** (alexia, visual aphasia, nominal aphasia): Inability to understand written or printed words. Cannot read or name the symbols, printed or written letters. But can speak or write spoken words. Lesions are centred on lower part of the posterior parietal lobule, angular gyrus, adjoining to occipital visual area, i.e. at the level of 'C' (Scheme given above on this page).
5. ***Auditory aphasia (deafness):*** 3 in Fig. 106.1 (auditory aphasia, syntactical aphasia). Inability to understand spoken words, but able to read and write although the reading is incoherent. The lesions are involved at the levels of superior and middle temporal convolutions adjacent to cortical area for hearing. Since the subject does not understand the meaning of his own words, he cannot rectify the faults of his speech. The subject is voluble and there is jargon speech. Alexia (visual aphasia) and auditory aphasia are collectively known as agnosis (semantic aphasia).

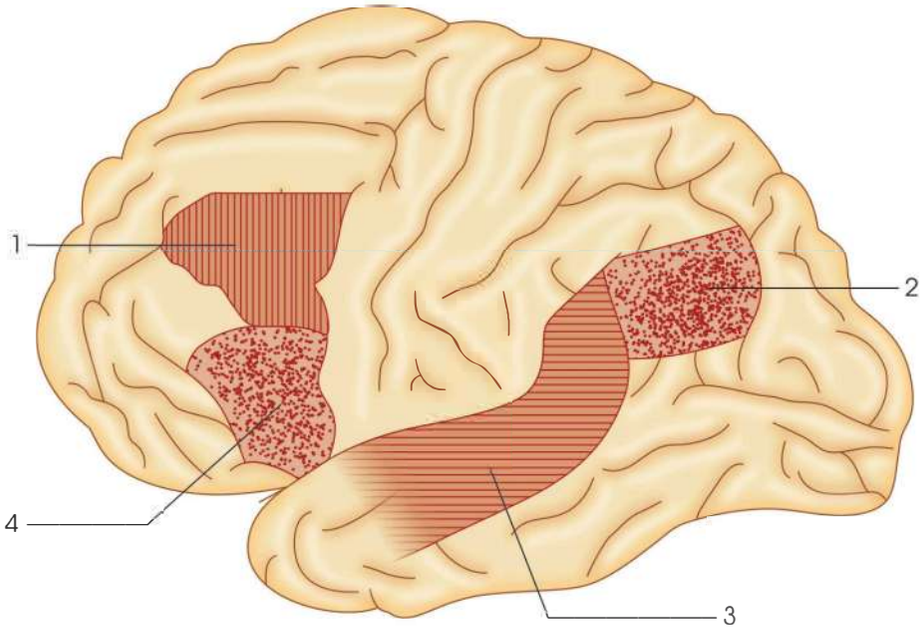

Fig. 106.1: Diagrammatic representation showing localisation of language functions. Lesion at 1 resulting difficulty in expressing ideas in writing (agraphia); Lesion at 2 causing difficulty in understanding written words (blindness); Lesion at 3 resulting difficulty in understanding spoken words (deafness); Lesion at 4 causing difficulty in expression (pure motor aphasia) (Ruch and Patton)

These are commonly associated with mental defects.

6. ***Agraphia:*** Inability to express the thoughts in writing although the muscles of hand are intact. Can read and speak. Injury lies at the finger region of premotor cortex (1 in Fig.106.1), i.e. at the level of 'D' (Scheme given above on this page).
7. ***Cortical aphasia:*** For alexia, auditory aphasia, apraxia and agraphia. Lesions are subcortical affecting the association fibres only. Hence, not much intellectual defect. But lesions of cortical grey matter disturb speech function as a whole and always cause intellectual defect. Lesions affecting the posterior parts disturb the receptive and psychical processes, while those situated anteriorly disturb the motor phenomena.

Head's Classification of Aphasias

Head has classified aphasias into four types: (a) Nominal aphasia; (b) Verbal aphasia; (c) Syntactical aphasia; (d) Semantic aphasia.

Nominal aphasia: Difficulty in naming an object or inability to find suitable words to express the meaning of an object.

Verbal aphasia: Inability to utter individual words of all types and to express thoughts in words although motor mechanism remains intact. It resembles pure motor aphasia.

Syntactical aphasia: Inability to understand spoken words, but able to read and write although the reading is incoherent. The subject is voluble and there is jargon speech. The speech is in short phrases and defective.

Semantic aphasia: Failure to understand one's own utterances and inability to grasp the meaning which it conveys.

Pierre Paul Broca conducted extensive research on Broca's area and this area in the frontal lobe has been named after him. It is involved in language development. He found out that lesion in a particular part of the cortex, in the left frontal region leads to aphasia. Broca's scientific work led to the development of physical anthropology, thereby advancing the science of anthropometry.

Pierre Paul Broca
1824–1880

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the mechanism of formation of speech. Add note on aphasia.
2. Define aphasia. Classify aphasia and explain their types in brief.

Short Notes

1. Nominal aphasia
2. Motor aphasia
3. Semantic aphasia
4. Syntactical aphasia
5. Cortical aphasia
6. Receptive aphasia
7. Transcortical motor aphasia
8. Transcortical sensory aphasia

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Chapter

107

Neurophysiology of Learning and Memory

INTRODUCTION

Learning

Learning is the most characteristic attributes of man and also of higher animals and by the process of learning the individual can change his behaviour by experience. Learning and memory are mediated by the nervous system. It is sometimes assumed to be the function of the cerebral cortex but it occurs in animals which have got no cortex. Learning is possible even in lower animals like worms and even in unicellular animals. Learning occurs in subcortical and spinal levels.

Different processes have been adopted for the study of the neurophysiological basis of learning, these are:

- Classical conditioning of Pavlov (pavlovian conditioning)
- Instrumental conditioning or learning discrimination learning.

CLASSICAL CONDITIONING OF PAVLOV

The term conditioning is often used to represent all learning. We deal with conditioning in a much more limited sense. It means for us the acquisition of conditioned responses. Thus, the term is used to represent a relatively simple aspect of the learning process. The response to be conditioned is already in the organism's repertoire. Therefore, a conditioned reflex is a reflex response to a stimulus, which did not elicit the response previously, but acquired after repeated application with another specific type of stimulus that normally evoked such response.

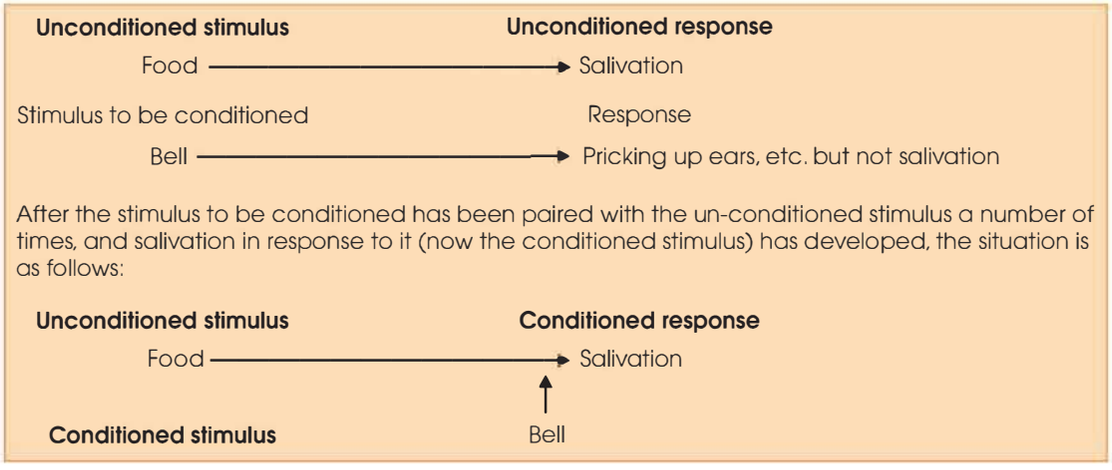
As mentioned before reflexes are of two classes:

1. Inborn or unconditioned reflex (UR)
2. Acquired or conditioned reflex (CR).

The characteristics of conditioned reflexes are:

1. It is acquired and developed as course of learing in life. It:
   - Depends on previous experience
   - Can be established or abolished
   - Not transmitted by heredity
2. Conditioned reflexes are established primarily upon some pre-existing unconditioned reflexes.
3. Cortical and subcortical centres are responsible for it.

Example: Food stimulates salivary secretion. This is an unconditioned reflex. Now, if a second neutral stimulus, viz. ringing of a bell or flash of light, be applied just before or during the giving of food for some



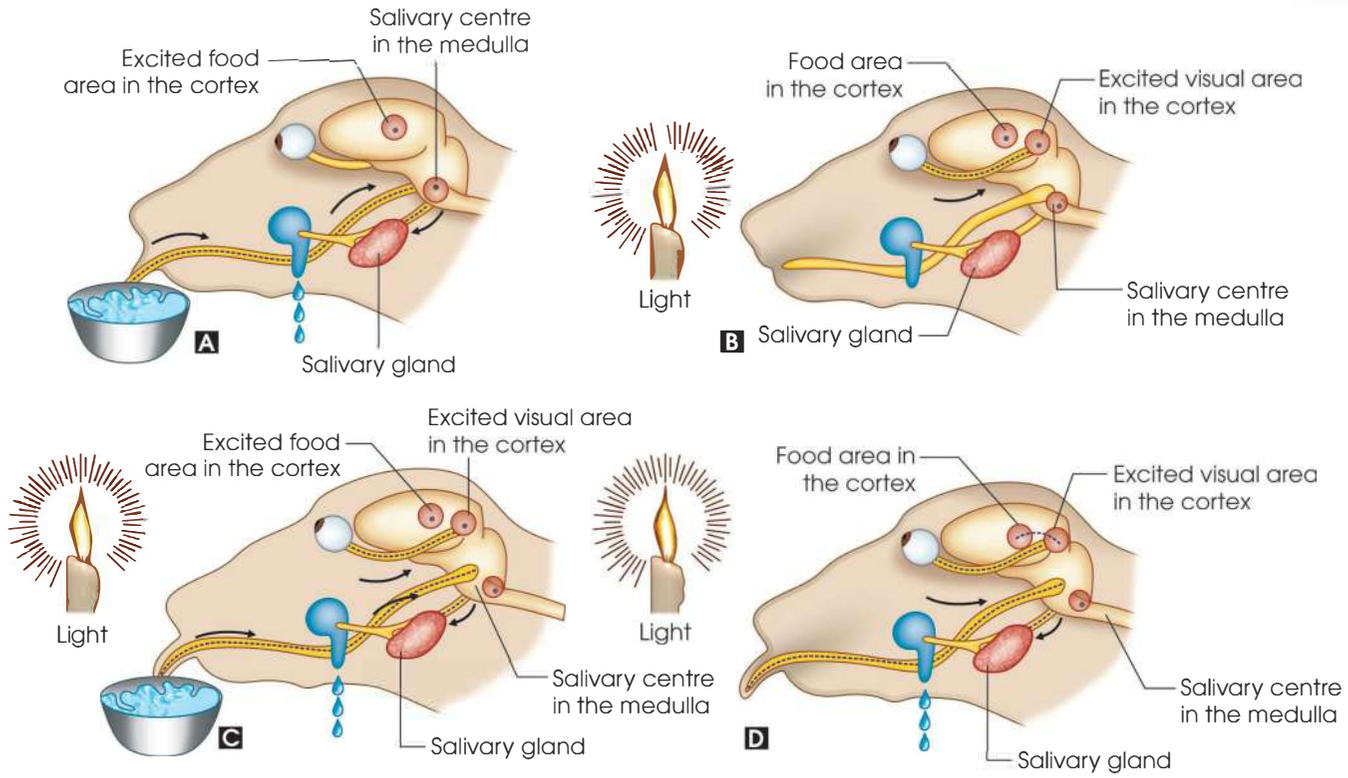


Fig. 107.1: Diagrammatic representation of the formation of conditioned salivary reflex. (A) Showing unconditioning salivary reflex (food); (B) Showing application of conditioning stimulus (light) before establishment of conditioning reflex where the visual area of the cortex excited but there is no conditioned response (CR); (C) Representing application of a conditioning stimulus (light) with an unconditioning stimulus (food) visual area and food area in the cortex excited simultaneously; (D) Showing establishment of CR by giving conditioned stimulus (CS) (light) only and the arrow indicates resultant momentary connection between visual area and food area in the cortex

days, the bell sound or flash of light itself will be able to elicit the salivary reflex, even if no food be given at all (Fig. 107.1). Such a neutral stimulus is called conditioned stimulus. Pavlov (1906) had carried this experiment in the dog, the dog associates the bell sound with the giving of food and starts salivation in anticipation. A good lot of mental analysis and association is required for the establishment of this reflex. This reflex has been termed by Pavlov as conditioned reflex (Fig. 107.2). The conditioning process may be represented schematically in such a way as to show the S-R relationships. Thus, before the salivary response is conditioned to a bell, the situation is as follows.

The previously neutral or ineffective stimulus, as well as the unconditioned stimulus, now elicits salivation, i.e. salivation elicited by the bell alone is a conditioned response.

Pavlov confined his attention to dogs and, in those, to the salivary secretion. But Bekhterev extended the conditioned response technique to human subjects. In his work with dogs and human beings, Bekhterev used an electric shock as unconditioned stimulus and reflex withdrawal of the shocked limb as unconditioned response. Various kinds of conditioned stimuli were

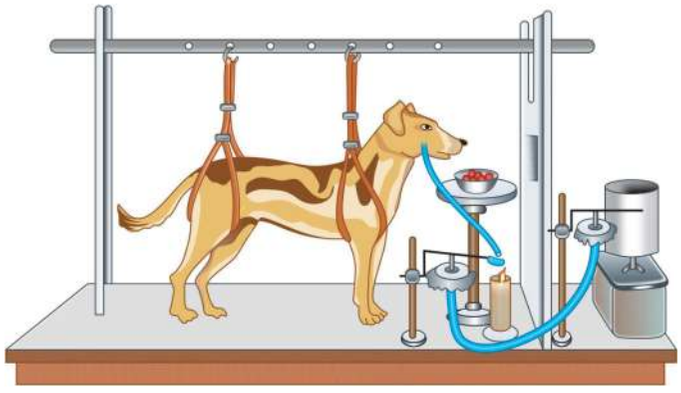


Fig. 107.2: Experimental procedure for demonstration of conditioned reflex or response (CR) in a dog (Pavlov). Here the conditioned response (salivary secretion) has been recorded graphically by cannulating the salivary duct

used, including the beating of a metronome. The subject conditioned with this method gets the shock whether or not it responds to the conditioned stimulus. Bekhterev (1932) termed the response to the new stimulus an associative reflex, but later workers with this and related methods have adopted Pavlov's terminology.

The cerebral cortex is responsible for establishment as well as retention of learned habits; because after establishment of conditioned habits, if the cerebrum is removed then the habit is no longer present. But in absence of cerebral cortex, certain conditioned reflexes can be established in presence of subcortical centres only. The subcortical centres gain the power of retaining the learned habits in absence of cortical centres, but in presence of cortical centres the subcortical centres have got a little power of retention of learned habits. Most of our habits are nothing but conditioned reflexes. A habit may, therefore, be described as an automatic response to a fixed set of conditions, acquired and established by infinite repetitions.

Development of Conditioned Reflexes

1. Conditioned reflex always develops on the basis of an unconditioned reflex.
2. Speed of development is fairly quick, taking only a few days.
3. The unconditioned stimulus must accompany or just precede the conditioned stimulus.
4. Any stimulus (general or special senses) may be transformed into a conditioned stimulus.
5. The animal or the subject must be conscious and must co-operate.

Classifications

1. Positive or excitatory.
2. Negative or inhibitory.

Conditioned Excitatory Reflexes

Experimental Facts

Summation

When same response is obtained by two conditioned stimuli, the response will be bigger if two stimuli are simultaneously applied.

Irradiation

When a conditioned reflex is established by stimulating a particular area of skin, the response will be lesser if a neighbouring area be stimulated. Greater the distance from the actual spot, lesser is the effect.

Specificity

The stimulus is more or less specific. If a conditioned reflex be established with a particular sound, a note with a different pitch will be ineffective, provided the animal has the power to recognise the difference.

Discrimination

This is another way of testing the law of specificity. If one sound be associated with the 'giving of food' and another with 'no food', then by using a set of gongs whose vibrations lie somewhere between the two sounds, the range of discrimination by the animal can be tested.

Decay

If a conditioned reflex be not elicited for several months it undergoes decay (unresponsive) due to disuse.

Reinforcement

A decayed reflex may be fully revived by applying the same conditioned stimulus several times. It is easily formed if the unconditioned stimulus is associated with a pleasant or an unpleasant effect. Stimulation that follows with reward system is called positive reinforcement and when it is associated with avoidance system or a painful shock is termed negative reinforcement.

Linking

A second stimulus may acquire a conditioned value if it can be linked up with the first conditioned stimulus. Suppose salivary reflex is established by using a gong sound as the primary conditioned stimulus. If now, a second neutral stimulus, such as a flash of light, be applied just before 10 seconds of the gong sound and if this procedure be repeated for a number of days, then the second stimulus only will elicit the conditioned response. Similarly, an endless series of stimuli can be linked up establishing secondary, tertiary, reflexes, etc. (If the second stimulus be simultaneous it will have inhibitory effect.)

Trace Phenomenon

Trace reflexes can be established by applying unconditioned stimulus (food) after an appreciable interval following stimulus (sound). When established, the reflex response follows the conditioned stimulus after the same interval. According to the length of the interval the trace reflexes may be short or long.

Extinction

If the conditioned stimulus be repeated several times the unconditioned stimulus reflex becomes extinct. Repeated disappointment crates a state of cortical inhibition so that no response occurs.

Induction

A positive conditioned response induces a state of increased inhibition. Similarly, an inhibitory conditioned reflex creates a state of increased excitation. When the conditioned excitatory stimulus is applied immediately after the conditioned inhibitory stimulus, the positive effects of the former are enhanced. This is called positive induction. The reverse changers are known as negative induction.

Conditioned Inhibitory Reflexes

Like excitation, a conditioned reflex may also have inhibitory effects. Inhibition may be of two types:

- External
- Internal

External Inhibition

Definition: A positive conditioned reflex is weakened or inhibited by a simultaneous excitatory process. It has two types:

1. ***Temporary:*** A sudden noise or fear or any other emotion, distracts the attention of the subject and inhibits the conditioned reflex. Here, inhibition arises in a part of the brain other than that where the conditioned reflex is initiated. As soon as the distraction is off, the reflex returns.
2. ***Permanent:*** If the distraction or disturbance be lasting the inhibition may also last long, at least as long as the disturbance persists.

Internal Inhibition

Definition: The stimulus sets up an inhibitory state in that part of the cerebral cortex which initiates the conditioned reflex. The following types of inhibitory phenomena are seen.

Differential inhibition: If a conditioned reflex be established with a sound, say, of 800 vibrations per second, tones a little higher or lower, at first acquire some positive conditioned value (period of generalisation). If, however, the original stimulus be repeated (reinforced) and not the others, a time comes when the other tones not only become ineffective but exert an inhibitory effect on the primary stimulus (period of differential inhibition). For instance, suppose a primary sound produces, say, five drops of saliva. If then a lower or higher tone be applied (unreinforced) just before the primary tone, the effects of the latter will be inhibited and will produce less saliva. Repetition of the allied tones will increase the degree of inhibition (summation of inhibition).

Extinction by inhibition: As mentioned above the phenomenon of extinction is due to the development of an inhibitory state in the cortex. Because, during the progress of extinction, other pre-existing conditioned reflexes based on other inborn reflexes are also inhibited.

Conditioned inhibition: Suppose salivary reflexes are established to the beat of metronome. If then a bell is rung along with the metronome, but is not followed by food, it is seen that the metronome alone will elicit the reflex but metronome plus bell is ineffective. The bell sound here acts as conditioned inhibitor. To have an inhibitory effect, the additional stimulus must overlap the primary stimulus at least to some extent.

Inhibition of delay: If the conditioned stimulus be short and be immediately followed by the unconditioned stimulus, the response starts as soon as the conditioned stimulus begins. In other words, the reflex has a short latent period (simultaneous reflex). But if the conditioned stimulus be continued for some length of time (1, 2, 3 minutes, etc.), the response comes after the termination of the stimulus, i.e. the latent period lengthens in proportion to the duration of the stimulus.

Functions of Conditioned Reflexes

Most of our habits are conditioned reflexes. Hence, it is of immense personal and social importance. It has a great applied value in clinical and psychological medicine. With the help of conditioned reflexes cerebral centres can be localised.

Effects of Drugs upon Conditioned Reflexes

1. Caffeine and strychnine increase the effects of positive conditioned stimuli and diminish internal inhibition.
2. Bromide increases internal inhibition.
3. Alcohol, in moderate doses, weakens internal inhibition.
4. Hypercalcaemia (overdose of parathormone or vitamin D) increases inhibitory process and accelerates the extinction of positive or excitatory conditioned reflexes. Caffeine antagonises.

Operant Conditioning

Apart from the classical conditionings, this is a form of conditioning in which the animal is taught to perform some task in order to obtain a reward or punishment.

Condition Avoidance or Avoidance Conditioning

If conditioned reflex (CR) is established in an animal by a conditioned stimulus (CS) like bell or light followed by giving a electroshock, then sometimes the animal gives response as for instance moving the leg even before feeling or even application of the second unpleasant stimulus like electroshock. This reflex is developed only to avoid the second unpleasant stimulus. This is known as condition avoidance. In Russia, it is known as defensive conditioning, conditioning of the second type or type II conditioning.

The operant conditioning differs from the classical and avoidance conditioning in the following features:

1. No specific unconditioned stimulus becomes necessary.
2. The animal is free to respond at any time as per its own will during operant conditioning which rarely occurs in other two varieties.

Instrumental Conditioning or Learning

Many years after the development of pavlovian classical conditioning technique, Konorski (1950) and Skinner (1938) applied the term conditioning to a still different learning procedure. In such procedure an instrument is used. Upon such instrument the animal performs some work and the response or behaviour is termed an Instrumental response. Skinner box (Fig. 107.3) is a versatile instrument of such learning. Another problem box is the maze box which is also used widely: In Skinner box the hungry animal like rat is put and the animal learns how to get a pellet in the food magazine below by pressing the lever. Each pressing is recorded mechanically. In this case food is the unconditioned stimulus (US) and pushing lever is the conditioned reflex or response (CR). It differs from the classical and avoidance conditioning in that it does not possess any specific conditioned stimulus (CS); and pushing the lever, (CR) is not originally an unconditioned reflex (UR) to the food (US). In maze learning the animals must learn to make several turns so as to receive a food reward. However, maze learning is a trial and an error learning while the Skinner box learning is a kind of conditioning.

Discrimination Learning

In addition to the classical conditioning of Pavlov and of instrumental conditioning animals can learn to differentiate different types of stimuli and can make differential responses. In such discrimination learnings, instrumental learnings are employed and the animals choose between two stimuli presented simultaneously and receive a reward for making a correct choice.

Discrimination learning includes

A. Somaesthetic discrimination, such as:
   1. Thermal discrimination
   2. Kinaesthetic discrimination
   3. Roughness discrimination
   4. Form discrimination

B. Auditory discrimination and visual discrimination.

Physiological Basis of Conditioned Reflexes and Learning

Conditioned reflex is the process of learning through the formation of a new functional connection in the nervous system of both cortical and subcortical centres. Repeated application of new sensory stimulus is followed by gradual development of specific cortico-subcortical pathways. New connections between different organs, centres and neurons are established. During maturation of learning, certain parts of the nervous system as well as the muscle possibly excite some attractive influences on the growth of the new neural fibres and if the new pathway is developed then it is so rigidly fixed that it cannot be abolished so easily. It has been observed that in the mammals there are so many events going on during development of conditioned reflexes and learning. For getting a conditioned response (CR) through both conditioned stimulation (CS) and unconditioned stimulation (US) there require motivation and attention.

An attentive subject learns earlier than a subject whose attention wanders. Beside this, a hungry rat learns to run a maze for food more readily than a well-fed rat. Limbic–midbrain circuit of Galambos and

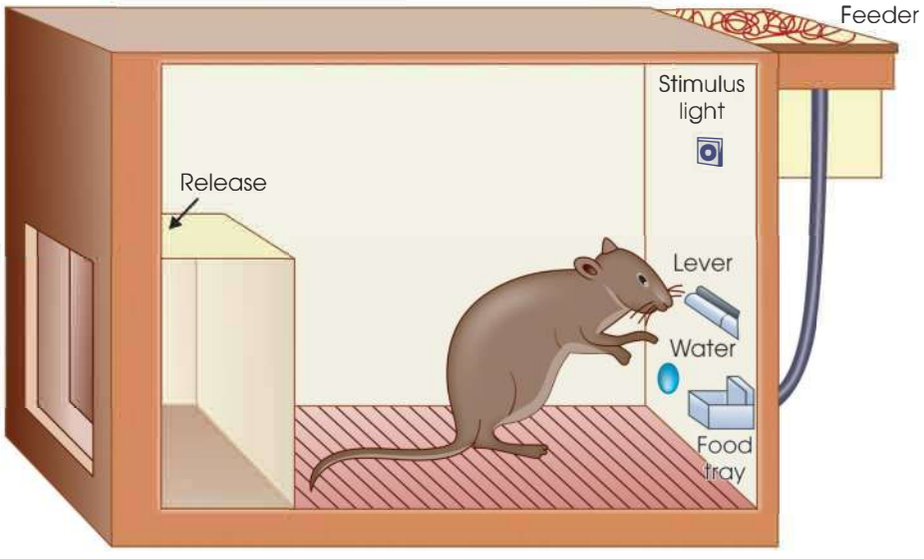


Fig.107.3: Showing the apparatus which is just big enough to permit free movement of a rat (diagrammatic) used by Skinner in his studies of instrumental conditioning. Cutting away one side of the chamber in which the animal (rat) is released though the door at the left. As soon as the hungry rat depresses the lever, the apparatus behind the panel at the right automatically releases a pellet of food into the tray from the feeder, or deliver a drop of water

Morgan makes a reverberatory link in between the limbic system and midbrain reticular formation. The midbrain reticular formation transmits and modifies the impulses to and from the cerebral cortex (Fig. 107.4).

Drugs that Facilitate Learning

Certain drugs have been proved to help in learning process in animals. Such drugs are caffeine, physostigmine, amphetamine, nicotine, picrotoxin, strychnine and metrazol (pentylenetetrazol). It has been reported that pentylenetetrazol has got effect in improvement of memory in senile human. Pemoline also facilitates learning process in animals. This compound also stimulates RNA synthesis.

Memory and its Neurophysiological Basis

Memory is a special faculty of brain which retains the events developed during the process of learning. Memory may be of three types: Sensory, recent memory and remote memory.

Types of Memory

1. ***Sensory memory:*** The ability to retain impressions of sensory information after the stimulis withdrawn. There are three types of sensory memories:
   a. *Iconic memory:* The fast decaying store of visual information perceived for a small duration is iconic memory.

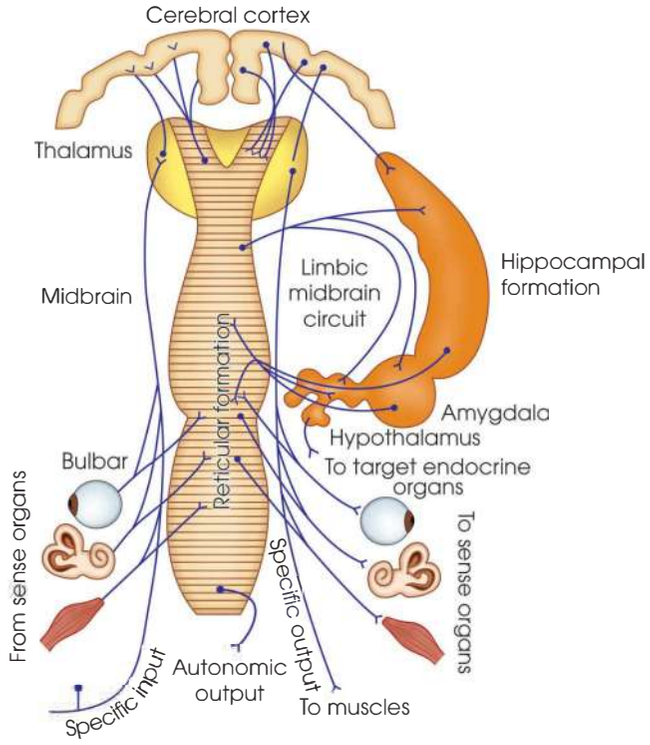


Fig. 107.4: Diagram represents the simplified anatomical plan of neural connections involved during establishment of conditioned reflex or unconditioned reflex (CR or UR) and learning (Galambos and Morgan)

   b. *Echoic memory:* The fast decaying store of auditory information perceived for short durations is the echoic memory.
   c. *Haptic memory:* The type of sensory memory representing database for touch stimuli is the haptic memory.
2. ***Short-term memory or recent memory:*** It is a working memory allowing recall for a period of several seconds to a minute. It may be lost frequently with neurologic disease but the remote memory is remarkably resistant and may persist even in severe brain damage. It is claimed that hippocampus is related with recent memories as because electroshock on the hippocampus causes abolition of recent memories. Bilateral destruction of the hippocampus causes striking defects in recent memories but not remote memories. Several drugs that affect recent memories also alter the function of hippocampus considerably.
3. ***Long-term memory or remote memory:*** It can store much larger quantities of information for potentially unlimited duration. It has been suggested that activation of a synapse during learning process may induce a dendritic growth or new formation of the axonic boutous terminaux that strengthens the connections between two neurons and stabilizes neural connections widely spread throughout the brain. The hippocampus plays an important role for learning new information, and it also consolidates the information from short-term to long-term memory, although it does not store information itself.

   The other types of memory are:
   i. ***Recognition memory:*** Persons are able to indicate whether they have encountered a similar stimulus (example: Picture or a word) before.
   ii. ***Recall memory:*** Person is able to retrieve previously learned information.
   iii. ***Declarative memory or explicit memory:*** It involves conscious recall of some previous incidence or any stored information. The information which is explicitly stored is retrieved and hence it is called explict memory.
   iv. ***Procedural or implicit memory:*** This type of memory does not relie on the conscious recall of information, but on implicit learning.
   v. ***Flash bulb memory:*** It is a memory recall of a critical or heart rendering event where a person still perceives the event as snap short.
   vi. ***Logical memory:*** When things are learnt logically the memory is consolidated as long-term memory.
   vii. ***Rote memory:*** When things are learnt without understanding or logical reasoning. Example: Cramming and mugging up information before examination.

Experimental Evaluation: Memory Consolidation and Storage

1. The morphological and biochemical changes are associated with memory consolidation and storage.
2. The morphological changes include formation of newer neuronal connection in cerebral cortex (especially Wernicke's area of memory), increase in size and number of presynaptic terminals and also increase in number of dendritic spines.
3. Other than structural changes, biochemical changes have been suggested in relation to the process of learning and memory. As the remote memory is not lost even after electroshock and brain concussion, it has been suspected that memory may be stored as an actual biochemical change in the neurons. This fact has come from the work on planarians—the flat-worms having rudimentary nervous system and remarkable ability to regenerate from cut pieces. These worms can be taught to avoid certain visual stimuli. If these trained worms are cut into two pieces then the regenerated worms from piece, head or tail can retain previous (learned) response (Fig. 107.5). This has been explained on the basis of changes in RNA of cells. Through the process of learning, there is a stable change in the RNA which is presumably transferred to the new parts of the regenerated parts. It is further supported that if ribonuclease is administered into the cut pieces of conditioned planarians cannot retain previous condition response due to destruction of RNA. Besides this, if trained planarians are ground up into powder and fed to untrained planarians then the fed planarians become trained up earlier than those of the control (unfed) one. Protein synthesis has got relation with the process of memory and learning. Drugs that inhibit protein synthesis affect the memory and learning. Puremycin which inhibits protein synthesis also disrupts recent memory.

Mechanism of Memory Encoding, Consolidation and Storage

1. ***Encoding:*** Attentive perception which is regulated by the thalamus and the frontal lobe for memorable event causes associated neurons to fire more frequently, this makes the experience more intense and increases the chances of the event being encoded as a memory. The decoding of perceived sensation occurs in the associated varied sensory areas of the cortex, and further comprehended in the hippocampus into a single experience. The hippocampus

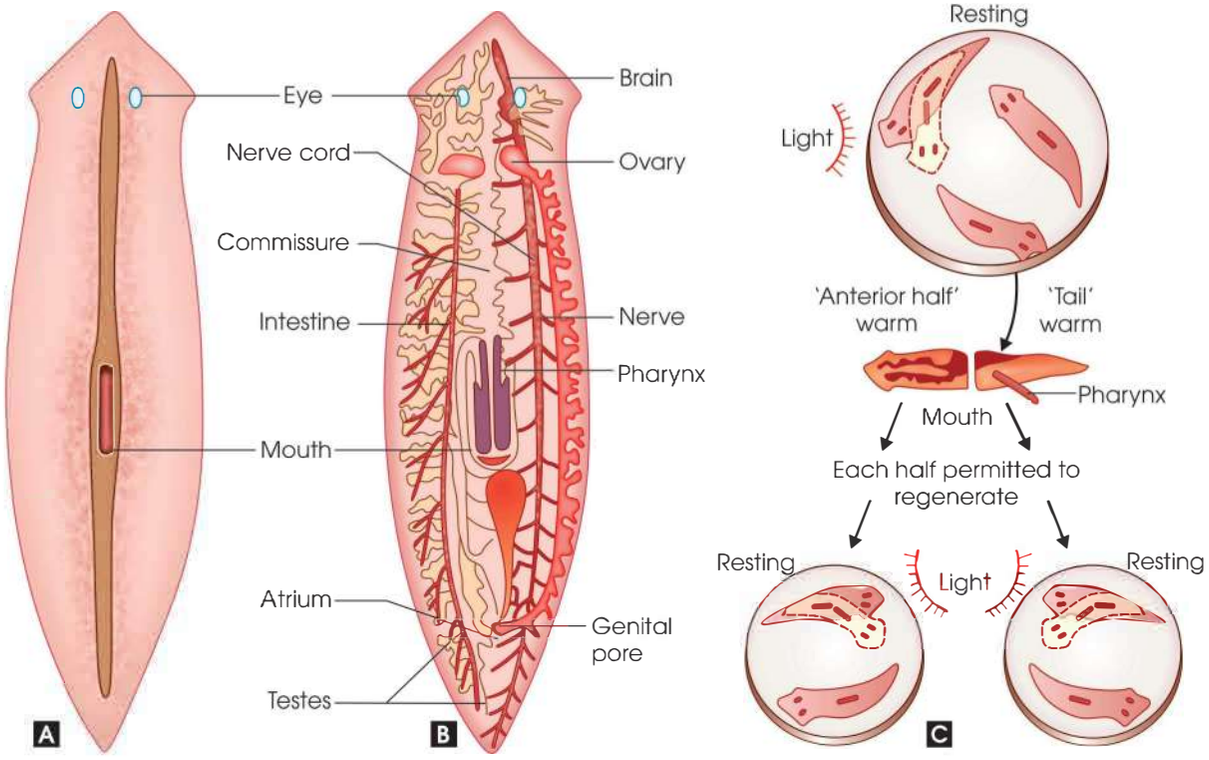


Fig. 107.5A to C: Planarian, a free-living flat-worm. (A) Showing external features; (B) General structure (diagrammatic), on its right side testes, vas deferens and digestive tract are omitted and on its left side nerve cord, yolk glands and oviduct are omitted; (C) Illustrates regeneration. When exposed repeatedly to bright light at intervals, of a minute or so, it will react only to the first few bursts. When exposed repeatedly to mild electroshocks, it continues to react (contract). When such a trained worm is cut in half and each half is permitted to regenerate, both worms react to light, because memory is somehow stored throughout the body

analyzes these inputs and finally decides whether or not the event is to be committed to long-term memory.

2. ***Consolidation:*** The long-term potentiation is the process involved in consolidation of memory. The synchronous firing of neurons is termed as potentiation while in long-term potentiation the same group of neurons fire together and as a result are permanently sensitized to each other. The new experiences and episodes accumulate creating more and more interneuronal connections and pathways. These interneuronal connections are morphologically re-routed and re-arranged for long lasting changes to occur in the efficiency of synaptic transmission. This process of enhancement of synaptic transmission is known as synaptic plasticity or neural plasticity. Thus, memory is consolidated.
3. ***Storage of memory:*** Following consolidation the permanent or remote or long-term memories are stored throughout the brain as groups of neurons which are primed for compact firing in the same pattern that created the original experience, and each component part of a memory gets stored in the brain area that initiated it.

Applied Physiology

1. ***Alzheimer's disease:*** The characteristic features of Alzheimer's diseases include loss of synapses and neuronal connections in the cerebral cortex and associated subcortical regions. This causes degeneration of neurons in the parietal lobe, cingulated gyrus, temporal lobe, brain stem nuclei like the locus coeruleus and parts of the frontal cortex. The degenerative changes lead to gross atrophy of the affected regions. The common symptoms associated with the disease are loss of short-term memory, mood swings, no motivational drive, language disorientation, self-neglect and behavioural alteration. Further deterioration in physiological functions leads to death.
2. ***Korsakoff's syndrome:*** It is also known as Korsakoff's psychosis. It is an organic brain disease affecting memory by widespread shrinkage or loss of neurons within the prefrontal cortex.
3. ***Autism:*** It is a neurodevelopmental disorder. The characteristic symptoms in this disease condition include impaired verbal and non-verbal communication, restrictive, repetitive and introvert behaviour and patient prefer being in social isolation. The signs of the disease are often noted and reported by the parents in the first two years of childhood. These signs are manifested gradually. Autimism is a complex disorder and the genetic, cognitive, and neural levels for autism's form the characteristic triad of symptoms.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the physiological basis of conditioned reflexes and learning.
2. Define memory. What are the various types of memory. Add note on Alzheimer's diseases.
3. Describe the mechanism of memory encoding, consolidation and storage.

Short Notes

1. Alzheimer's diseases
2. Conditioned reflex
3. Discriminating learning
4. Korsakoff's syndrome
5. Autism
6. Classical conditioning

Chapter

108 Sleep

INTRODUCTION

Sleep and wakefulness occur alternately within 24 hours during whole of the lifespan of the individual. Inspite of tremendous work for unveiling the cause of this natural event, it has not yet been possible to find out the correct cause of sleep. During sleep, organs like kidney, heart, lung, gastrointestinal tract, etc. remain active. Similarly, brain also remains active during sleep and it undergoes an active reorganisation rather than real inhibition. So, it can be assumed as an active phenomenon. It is also sometimes assumed to be of passive phenomenon as the same ensues during withdrawal of the activation process of reticular activating system (RAS).

Definition: Sleep can be defined as a state of consciousness that differs from alert wakefulness by a loss of critical reactivity to events in the environment with a profound alteration in the function of the brain. It is also noteworthy that sleep is not a uniform phenomenon and it varies greatly in nature and depth from time to time in the same person and between individuals as well.

Sleep Rhythm

Animals and man show one sleep period in 24 hours. It depends on habit. Night, commonly being the period of rest, is used for sleep. But in night workers, day-sleeping is the habit.

Sleep Requirement

It varies inversely with age. The sleep requirement is as follows: For the newborn baby: 16–20 hours; children 12–14 hours; adults 7–9 hours; old age 5 hours.

Depth of Sleep

It follows a characteristic curve:

1. In adults, maximum depth of sleep occurs at the end of first hour.
2. In children, two maximum depth of sleep periods are seen: One between first and second and the other between eighth and ninth hours.
3. Deep sleep NREM type is not attended with dreams.
4. Sleep does not affect all the senses equally. Smell and taste are most depressed. Pain, touch and hearing are least affected. Hence, a sleeping man can be more easily aroused by the latter stimuli.
5. Abnormal wakefulness or inability to sleep is called insomnia.

Physiological Changes During Sleep

During sleep somatic activity is greatly decreased. Threshold of many reflexes is elevated and responsiveness is also lessened. Man cannot remember the events occurring during sleep. Basal metabolic rate being least; all tissues and organs perform the least work.

The physiological changes during sleep are given below:

1. *Circulatory system:* Pulse rate, vasomotor tone and blood pressure are reduced.
2. *Respiratory system*
   a. It may be costal or periodic, especially in children.
   b. Tidal volume, rate of respiration and, therefore, pulmonary ventilation are lowered (sometimes rate may be unchanged or even high due to shallow breathing).
3. *Basal metabolic rate:* It is reduced by 10–15%.
4. *Urine:* Urine volume is less, reaction variable, specific gravity and phosphates are raised.
5. *Secretions*
   a. Salivary and lacrimal secxretions are reduced
   b. Gastric secretion is unaltered or raised
   c. Sweat secretion is raised.
6. *Muscles:* Relaxed (tone minimum).
7. *Eyes*
   a. Eyeballs—roll up and out—due to flaccid external ocular muscles (may take up any position.)

b. Eyelids—come closer, specially due to the drooping of the upper lids.
c. Pupils—constricted.

8. *Blood:* Volume increased (plasma diluted).
9. *Nervous system*
   a. Electroencephalogram: Appearance of δ-waves.
   b. Deep reflexes—reduced.
   c. Babinski—extensor.
   d. Superficial reflexes—unchanged.
      - Vasomotor reflexes—more brisk.
      - Light reflex—retained.
10. Electroencephalographic changes during sleep. The EEG pattern changes at different stages from normal waking state to sleep—depending upon the degree of sleep.

Behavioural and EEG Changes during Sleep

a. *Relaxed awake:* α-rhythm is observed when person is relaxed and eyes are closed.
b. *Relaxed drowsy* (state): α-wave gradually diminished in amplitude and is followed by in sleep cycle.

NREM sleep

c. *Stage I: Light sleep:* There is decrease in frequency and amplitude of α-wave.
d. *Stage II: True sleep:* This stage is characterised by 14 cycles per second spindle bursts associated with low voltage δ-wave background.
e. *Stage III: Medium sleep or sleep deepens:* When δ-wave frequency becomes lower with greater amplitude associated with disappearance of spindle burst.
f. *Deep sleep:* In this stage, δ-wave becomes more prominent with higher amplitude and longer duration.

REM sleep

g. It is the deepest phase of sleep cycle and desynchronized activites of EEG are observed.

The above changes in the EEG pattern occurs sometimes in sequences as per (a) to (g) stages but in between the two, any other stage may supervene during the sleep.

TYPES OF SLEEP

According to the EEG pattern the sleep is divided into:

1. ***Rapid eye movement sleep*** which is often associated with rapid wandering eye movement, and is called rapid eye movement (REM sleep or rhombencephalic sleep). Also called paradoxical sleep as sleep is deep yet EEG is like awake state.

   The characterstic features of REM sleep are:
   a. There is decrease in generalized motor tone.
   b. Rapid wandering eye movement
   c. High incidence of penile erection and grinding of teeth (bruxism) occur in the subjects.
   d. The long-term structural and chemical changes in brain during this phase of sleep enhance learning and memory.
   e. It is produced by discharge of norepinephrine from locus coeruleus and neurons in pontine reticular nucleus and by discharge of cholinergic neurons via PGO spikes transforms NREM to REM sleep.
2. ***Non-rapid eye movement sleep or deep sleep:*** On the other hand, non-rapid eye movement (NREM sleep or slow wave sleep) is generally associated with spindle or synchronised slow wave.

   The characteristic features of NREM sleep are:
   a. Muscle tone progressively decreases.
   b. Slow eye rolling movements
   c. It is not associated with dreaming.
   d. There is pulsatile release of gowth hormone and gonadotrophin during this phase of sleep.
   e. It is produced by synchronizing discharges from reticular activating system and rhythmic discharge from thalamus.

Normal Sleep

With synchronised electrical activity in the thalamus and cortex depends upon neural and neurohumoral mechanisms—specially on a serotonergic substrate—the raphe nuclei that extend from medulla to midbrain. According to Jouvet, lesions of raphe nuclei reduce normal sleep and partly paradoxical sleep. Concentration of serotonin is found to be increased in midbrain, around the aqueduct and in the hypothalamus during normal sleep.

Effects of Prolonged Sleeplessness in Man

It is observed on subjects kept awake for 60–114 hours. Objective changes are few, viz. Babinski—extensor. Equilibrium is disturbed, neuromusclular—fatigue, etc.

Subjective symptoms are chief, viz.

a. Mental concentration difficult and inaccurate.
b. Threshold for pain lowered. If very much prolonged, collapse and death. Cortical nerve cells undergo shrinkage and chromatolysis. The lethal period of sleeplessness in man is not known. In dogs, it is about 14 days.

THEORIES OF SLEEP

There are several theories for explaining the cause of sleep, but none is quite competent.

1. ***Pavlov's theory:*** Sleep is a special manifestation of conditioned inhibition. It is due to spread of an internal inhibitory process and is considered the concomitant sleep as a symptom of the cortical inhibition.
2. ***Biochemical basis of sleep:*** The humoral and chemical substances which induced sleep are acetylcholine, norepinephrine, hypotoxin, 5-hydroxytryptamine antagonist, and adenosine and sleep producing peptides.

3. ***Kleitman's theory:*** Due to reduction of muscle tone and discharge of less afferent impulses, the cerebral cortex remains inactive. Fatigue of the muscle with consequent reduction of transmission of afferent impulses to the cerebral cortex and thereby keeping it inactive seems to be a plausible factor in the production of sleep. Kleitman also observed that reticular formation plays an important role in the production of sleep. The afferent impulses, carried through the peripheral nerves and the spinal cord, activate the reticular formation. Activity of the reticular formation causes wakefulness. But in sleep, the reticular formation remains inactive.
4. ***Neural mechanism:*** The decreased activity of reticular activating system initiates and produces sleep while stimulation of raphe nucleus, sensory cortex and reticular activating system produces wakefulness.

Feedback Theories of Wakefulness and Sleep

Sleep is a passive process (*vide* central neural mechanisms). Sleep is an active process (*vide* central neural mechanisms).

Sleep depends upon conditioned reflex: Sleep can be described as the activation process of the reticular activating system (RAS). Because certain conditioned stimuli causing activation of reticular formation may induce sleep. Baby is sometimes induced sleep with conditioned stimuli like typical cradle songs, tapping over the head and body, softly brushing the hair and so on. Even in adult certain conditioned stimuli like reading, massaging, brushing, softly pulling hairs, induce sleep.

Applied Physiology

The common sleep disorders are:

1. ***Bruxism:*** The individual involuntarily grind or clench there teeth during sleep.
2. ***Hypopnea syndrome:*** In this condition the patient exhibit signs of abnormally shallow breathing or decreased respiratory rate during sleep.
3. ***Insomnia:*** The primary insomnia is a disorder in which patients are unable to fall asleep and no associated etiological cause could be traced. Insomnia can also be secondary to other disease condition.
4. ***Kleine-Levin syndrome:*** The characterstic features of this disorder are persistent episodic hypersomnia and cognitive or mood changes.
5. ***Narcolepsy:*** It is daytime sleepiness (EDS) and the individual may fall asleep spontaneously but unwillingly at any time of the day. These individuals may have a sudden weakness in the motor muscles due to which the fall over but they are full conscious and aware and this episodic behaviour is termed as catalepsy.
6. ***Nocturia*:** The individual has a frequent urge to urinate at night, but he does not arouse from sleep, and empty the bladder in the bed.
7. ***Periodic limb movement disorder* (PLMD):** It is a sudden involuntary movement of arms and or legs while sleeping. It is also known as nocturnal myoclonus.
8. ***Sleep apnea*:** It is also known as obstructive sleep apnea and is due to obstruction of the airway during sleep, and is accompanied by snoring.
9. ***Sleep-walking or somnambulism*:** It involves various activities like walking, eating, dressing up being carried by individual who is sub-conscious and in sleep.
10. ***Somniphobia*:** The individual has fear of falling asleep or going to bed and may suspect that he may die during sleep. This may cause anxiety and panic attacks prior to sleep and during attempts to sleep.

Hans Berger (1873–1941) was a German Psychiatrist, is known as the inventor of electroencephalography (*EEG*) in 1924.

Sleep Research

Nathaniel Kleitman (1895–1999) was a physiologist recognized as the father of modern sleep research. He authored the famous book *Sleep and Wakefulness in 1939*.

Eugene Aserinsky, William Dement and Michel Jouvet identified rapid eye movement and linked it to dreams in 1953.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the physiological, behavioural and EEG changes during sleep.
2. Describe the physiological changes during sleep. Describe the theories of sleep.
3. Describe the physiological changes during sleep. Describe in brief various clinical disorders associated with sleep.

Short Notes

1. Rapid eye movement sleep (REM sleep)
2. Non-rapid eye movement (NREM or non-REM sleep)
3. Insomnia
4. Narcolepsy
5. Somniphobia
6. Somnambulism
7. Periodic limb movement disorder (PLMD)
8. Kleine-Levin syndrome

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Chapter

109

Emotion

INTRODUCTION

It is a kind of psychophysiological phenomenon. It is a multifaceted form of behaviour involving:

1. Different somatic reactions like smiling, laughing, crying, screaming, running in flight and so on.
2. A variety of autonomic responses like pallor of fear, fainting, decrease or increase of heart rate and so on.

It has been defined by neuropathologist, Vonderahe (1944) as follows: "Emotion is a way of feeling and a way of acting. It may be defined as a tendency of an organism towards or away from an object, accompanied by notable bodily alteration. There is an element of motivation—an impulsion to action and an element of alertness, a hyperawareness or vividness of mental processes. There is of course the opposite, a depression of movement".

Emotion has got four aspects, such as (i) cognition, (ii) expression, (iii) experience, and (iv) excitement.

1. ***Cognition:*** It is such faculty which determines what emotion in kind and degree is appropriated to a given situation. For this, the situation must be perceived in relation to past experience and accordingly evaluated before emotion occurs.
2. ***Expression:*** It is expressed outwardly in the form of somatic and autonomic activities like facial expression, lacrimation, vocalisation, flashing or paling, laughing, fighting or flight. Emotions are also expressed internally as in the form of visceral and vascular changes by the activities of autonomic nervous system.
3. ***Experience:*** It is the subjective aspect of emotion. Psychologist divides the experience into two categories by affect, such as pleasant or unpleasant.
4. ***Excitement:*** It is nothing but an experience or expression of emotion which may be delight or distress. Besides this, emotion may be classified into three categories, such as pleasure, fear and anger. Fear and anger are disquieting reaction and involve tension and disturbance of the organism's responses, both internal and external. Fear is a flight or fright reaction and anger is a fight reaction. Pleasure is a quieting or calming reaction; it is practically relief from fear and anger.

While discussing the development of emotion in children, Bridges (1932) has described that first expression of emotion is one of general excitement. Figure 109.1 illustrates the classification of emotional behaviour in early childhood in which excitement is the stem from which different kinds of emotions are gradually differentiated. Excitement initially differentiates into distress and delight and each of which is gradually differentiated.

BEHAVIOURAL CHANGES IN EMOTION

1. In emotion there are different types of behavioural changes. Such changes are somatic reactions which include smiling, laughing, crying, screaming, running in flight, startle responses to sudden loud sounds and other various facial expressions of distress and delight. In animals, such somatic reactions are snarling, purring, yelping, tail waging, baring of fangs, hissing and other types of facial and bodily reactions.
2. In animals and men, emotional outbursts are always associated with a variety of autonomic responses. During pallor of fear, blood may tend to leave the head. There is increase and decrease of blood pressure and heart rate. Fainting may be associated with circulatory changes. Glandular secretions may be decreased or increased resulting changes in cellular metabolism.
3. During emotional outburst there is activation- of sympathetic and parasympathetic systems. In fear motor activities of bladder and rectum are increased and these activities are under the control of parasympathetic system. Crying is under the control of parasympathetic.

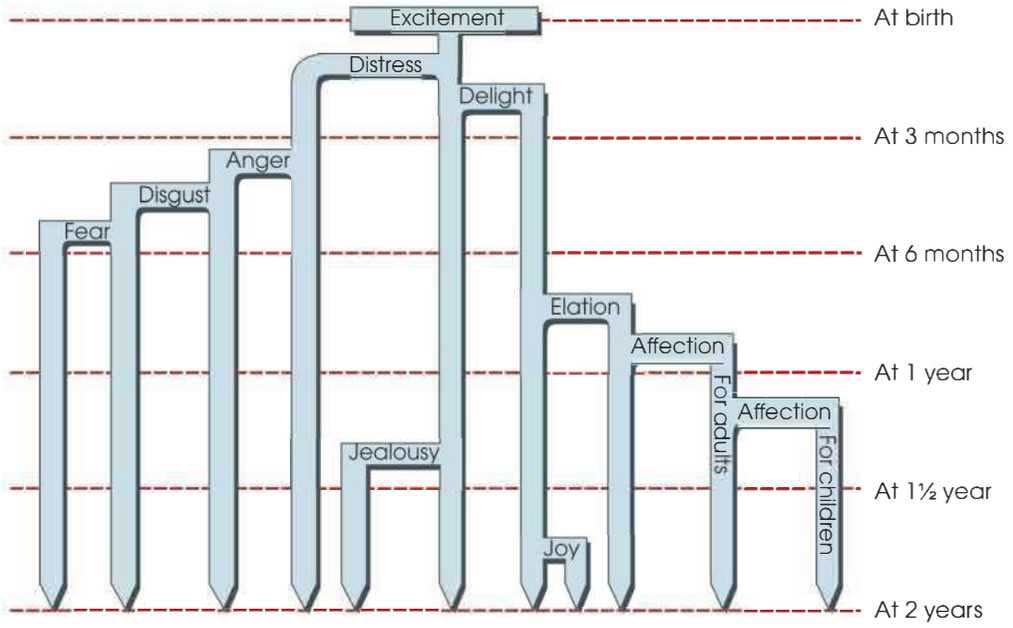

Fig. 109.1: Approximate ages of differentiation of emotion in early childhood (from Bridges, KMB, 1942)

4. In emotional disturbance there are often changes in respiration and also profound vasodilatation.
5. Cardiac abnormality leading to death may be associated with emotional stress. These effects are precipitated due to autonomic imbalance.

NEURAL CONTROL OF EMOTION

Hypothalamus

Hypothalamus is often considered as the seat of emotion. Though this term is misleading, yet hypothalamus is the principal centre in which various components of emotional reactions are organised into definite pattern. It is the focal point for emotional expression as by stimulation of the hypothalamus shows different emotional reactions. There are evidences that hypothalamus is responsible for elaboration and execution of complex reactions, characteristics of anger or rage. This type of rage is excessive in animal having no amygdaloid complex.

Thalamus

It has been observed directly and indirectly that thalamus is also concerned with different emotional reactions and emotional experiences as well. Different areas implicated are:

1. Anterior nuclei
2. Dorsomedial nucleus
3. Posteroventral nucleus.

Cerebral Cortex and Limbic System

In earlier experiments, in which total decortication leading to removal of amygdaloid complex was done, animals exhibited profound anger and rage. These facts indicate that cerebral cortex or certain portions of forebrain held in check the mechanisms that are responsible for the bodily expression of anger. It has been observed by Bard and Mountcastle (1947) that decortication, keeping the amygdaloid nucleus intact does not alter the emotional behaviour of the animal (cats and dogs) but as soon as the amygdaloid nucleus on both sides are removed, the animals become furious. This indicates that amygdaloid nucleus exerts an influence which inhibits the activities of brain stem that is concerned with anger and rage. It has been further observed that projection fibres from the amygdala to the ventromedial nuclei of the hypothalamus, causes inhibition of rage induced by hypothalamus as because selective destruction of ventromedial nucleus of hypothalamus causes calm and quiet animal to a condition of rage.

Papez Circuit: Physiological Basis of Emotion

1. The first interpretation of the limbic or 'internal' brain as a visceroemotional mechanism was reported by Bavarian neuropathologist Christfried Jakob in the year 1907 and 1908. He identified limbic structures associated with emotions on basis of degeneration experiments conducted by hom on apes and dogs as well as his studies on neurodegenerative diseases in humans.
2. James Papez in the year 1937 further clarified the role of limbic system in emotions. Papez conducted studies on cases of rabies and noticed that this disease causes high levels of aggression. He observed that this heightened aggression was correlated with damage to the hippocampus. Papez concluded that

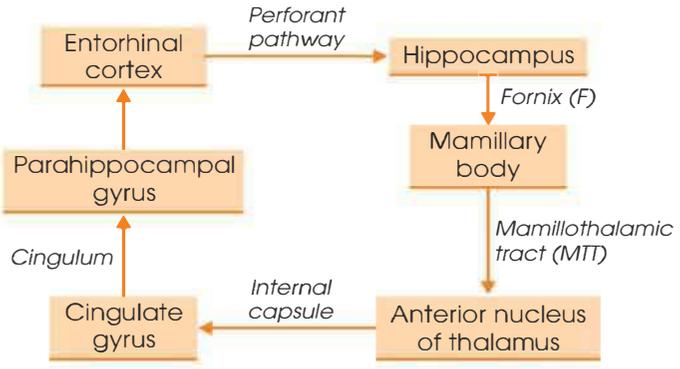

Fig. 109.2: Papez circuit

hippocampus is responsible for the expression of emotion as it is connected to the autonomic nervous system. He also observed that various stimuli (taste, smell, pain, etc.) produce emotional responses in which apart from the hippocampus other brain structures were stimulated. His theory suggested that brain structures worked in union as the emotional control centre in the brain and consequently designed the Papez circuit and opined that the Papez circuit was the cortical control of emotion.

Thus, the cohesive collective and connective role of hippocampus, mamillary body, anterior nucleus of thalamus, parahippocampal gyrus and entorhinal cortex brought over emotions in human (Fig. 109.2).

3. In 1952 Paul D. MacLean proposed a modified version of the Papez circuit, emphasizing not only the hippocampus, but also the role of amygdala and septum in emotions.
4. The hippocampus, amygdala, and septum form the rhinencephalon (frontotemporal portion of the brain). The limbic lobe and the visceral brain make as a unit forms the limbic system. The visceral brain feeds the visual, auditory, olfactory, and various other external sensory inputs associated with emotions.
5. Thus, limbic system palys an important role in expression of behaviour, motivation, and olfaction.

Applied Physiology

1. ***Semantic dementia:*** The destruction or damage in the ventral anterior nucleus, ventral lateral nucleus and mamillary bodies leads to semantic dementia. The characteristic features of this disorder are mainly defects in all semantic memory functions. The patient is unable to comprehend word and thoughts, remember names and has impoverished general knowledge.
2. ***Transient global amnesia:*** It is a very rare clinical disorder. These patients have a selective disorder of episodic memory. The patient is unable to recall events and information learned several to 48 hours prior and fails to learn new information. The damage to the medial lobe structures in the Papez circuit and hippocampus results in reduced or lost episodic memory.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the physiological basis of emotions. Discuss the neural control of emotions.

Short Notes

1. Papez circuit
2. Role of cerebral cortex in emotion
3. Behavioural changes in emotion

Chapter

110

Cerebrospinal Fluid

INTRODUCTION

It is a modified tissue fluid present in the cerebral ventricles, spinal canal and subarachnoid spaces thus bathing the entire nervous system. The central nervous system is devoid of lymphatics. Cerebrospinal fluid (CSF) replaces lymph here.

Character

1. It is a clear, colourless, transparent fluid, does not coagulate on standing.
2. Reaction alkaline and contains about 5 lymphocytes per cu mm.
3. Specific gravity 1.004–1.006.
4. Volume—about 150 ml in adults.
5. Pressure 110–130 mm H_2O (1 drop per second through the lumbar puncture needle). Pressure rises on standing, coughing, sneezing, crying, etc. Compression of internal jugular veins increases pressure (Queckenstedt's sign).

Composition

It resembles colloid-free plasma with certain variations of crystalloid content.

The average composition is compared with that of plasma is given below.

1. *Proteins:* 20–30 mg per 100 ml (alb/glob = 1/1)—much less than plasma.
2. *Amino acids:* 1.5–3.0 mg per 100 ml—much less than plasma.
3. *Cholesterol:* 0.06–0.22 mg per 100 ml—much less than plasma.
4. *Glucose:* 50–80 mg per 100 ml—almost same or less than plasma.
5. *Chloride:* 700–750 mg per 100 ml—much above plasma (550–630 mg per 100 ml). Sodium 330 mg per 100 ml—same as plasma.
6. *Calcium:* 5.3 mg per 100 ml (all in ionic form)—half of the total but same as the ionic calcium of plasma.
7. *Potassium:* 12 mg per 100 ml—less than plasma.
8. *Phosphate (inorganic):* 1.8 mg per 100 ml—less than plasma.
9. *Sulphate:* 0.6 mg per 100 ml—less than plasma.
10. *Magnesium:* 3.0–3.6 mg per 100 ml—more than plasma.
11. *Bicarbonate (CO_2—volume percent):* 40–60 mg per 100 ml—same as plasma. Urea: 10–30 mg per 100 ml—almost same or slightly less than plasma.
12. *Uric acid:* 0.5–2.2 mg per 100 ml—less than plasma.
13. *Creatinine:* 0.5–2.2 mg per 100 ml—almost same.
14. *Lactic acid:* 8–27 mgm per 100 ml—less than plasma.

Bile pigments are not usually present. But in severe jaundice of long duration the bile pigments are found in the cerebrospinal fluid. Certain drugs, bacteria and toxins do not freely pass. In certain diseases of the central nervous system, characteristic changes take place in the cerebrospinal fluid. There presence is of a great diagnostic value.

FORMATION OF CEREBROSPINAL FLUID

Two-thirds of CSF is formed by choroid plexuses in the ventricles, specially the lateral ventricles. The remaining proportion of CSF is produced by the surfaces of the ventricles and by the lining surrounding the subarachnoid space. Choroid plexuses are tuft of capillaries covered by ependyma. The endothelial cells of the capillaries are not flat as elsewhere, but are granular and cubical with mitochondria and vacuoles. This arrangement indicates active metabolic processes in the cells. Hence, not a passive filter. The sodium secreted from ependymal cells moves into the lateral ventricles, thereby creating osmotic pressure and drawing water into the CSF space. The negatively chloride also moves with the positively charged sodium thus maintaining neutrality. CSF, therefore, contains a higher concentration of sodium and chloride and less potassium, calcium, glucose and protein as compared to plasma.

Rate of Formation

As seen with lumbar puncture, the rate in adults is about 20 ml per hour or 500 ml per day.

Circulation

1. From the lateral ventricles (first and second) the fluid passes through the foramina of Monro (right and left interventricular foramina) to the III ventricle, thence through the midbrain as aqueduct of Sylvius (cerebral aqueduct) to the IV ventricle in the medulla.
2. From the IV ventricle the fluid follows three routes—central one, the foramen of Magendie ending directly into the cisterna magna and two lateral ones, the foramina of Luschka ending into the cisterna points on the basal aspect of the brain stem to the subarachnoid space.
3. From the IV ventricle it also passes into the central canal of the spinal cord (Fig. 110.1).
4. The ciliary movements of the ependymal cells help in the circulation of the cerebrospinal fluid.

Nervous and Humoral Factors Controlling the Formation and Circulation of the Cerebrospinal Fluid

1. Numerous nervous and humoral factors are concerned in the formation and circulation of cerebrospinal fluid.
2. Sympathetic stimulation alters the formation and circulation of cerebrospinal fluid. Sympathetic stimulation of the cervical sympathetic nerve reduces the production and pressure of the cerebrospinal fluid by increasing the tonus of the pial vessels.
3. Chloroform, ether, chloral, alcohol all stimulate in the production of cerebrospinal fluid, whereas the posterior pituitary extract and caffeine reduce its formation. Hypertonic glucose solution also decreases the cerebrospinal fluid pressure.

Absorption

It is absorbed into the cranial venous sinuses through the arachnoid villi. Small amounts are absorbed by the perivascular spaces and the spinal veins. Arachnoid villi are small finger-like processes projecting into the venous sinuses. The larger ones are called pacchionian bodies or arachnoidal granulations. Clumps of specialised cells, known as meningocytes are found in the arachnoid villi (also abundant in the lining of subarachnoid space) (Fig. 110.1). They belong to the reticuloendothelial system and act as phagocytes.

Mechanism of Absorption

Two factors: (1) filtration and (2) osmosis.

Filtration: Pressure of the cerebrospinal fluid is higher than that of venous blood in the cranial sinuses. Hence, the cerebrospinal fluid is filtered out into the veins.

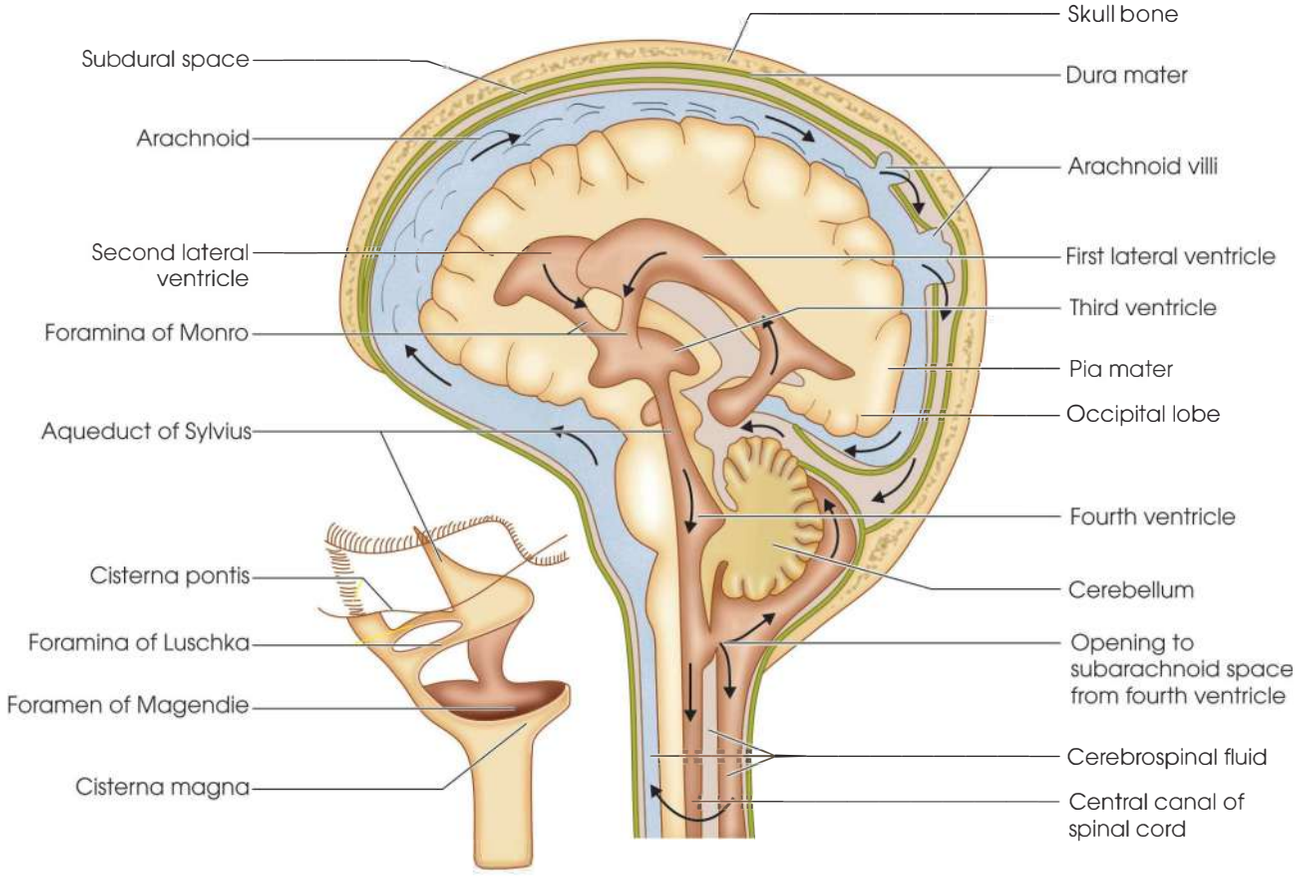

Fig. 110.1: Ventricles of the brain and the central canal of the spinal cord (lateral view) through which the cerebrospinal fluid circulates

Osmosis: Colloidal osmotic pressure of plasma is 25 mm of Hg. That if the cerebrospinal fluid is negligible. Hence, cerebrospinal fluid is drawn into the sinuses.

FUNCTIONS OF CEREBROSPINAL FLUID

1. ***Protection:*** CSF is a protective barrier and protects the brain tissue from injury when hit especially during vehicular accident or fall. It acts as a mechanical buffer. Remaining inside and outside the central nervous system it equalises mechanical pressure, thus acts as cushion between the soft and delicate brain substance and the rigid cranium. Any change of pressure is equally distributed and thus mechanical injury is prevented. If intracranial pressure tends to rise, cerebrospinal fluid is pressed out. If the pressure tends to fall, more cerebrospinal fluid is retained.
2. ***Drainage of metabolites:*** CSF via brain's lymphatic system plays a vital role in flushing metabolic toxins or waste from the brain's tissues, cellular interstitial fluid. Beta amyloid which is produced during state of awakefullness is cleared by CSF during sleep.
3. ***Prevention of brain ischaemia:*** Decreasing the amount of CSF via drainage system in the limited space inside the skull prevents brain ischaemia and related damages. Thereby the total intracranial pressure is decreased facilitating blood perfusion.
4. ***Chemical stability:*** CSF circulates through the ventricular system in the brain and is also absorbed back into the blood thereby aiding in removal of metabolic waste from the central nervous system via the blood–brain barrier. This also promotes homeostatic regulation of neuroendocrine factors in circulation in brain.
5. ***Buoyancy:*** The net weight of the brain suspended in the CSF is equivalent to a mass of 25 gm though the actual weight of human brain is 1400 gm. Brain maintains neutral buoyancy thus maintaining its density otherwise reduced density would cut off blood supply and damage cerebral neurons.

Applied Physiology: Lumbar Puncture

Cerebrospinal fluid can be collected from the subarachnoid space by introducing a special needle between the third and fourth lumbar spines. This procedure is called lumbar puncture. This lumbar puncture technique is of a great clinical importance for diagnostic purposes of meningitis, increased intracranial pressure, syphilis, intracranial tumours and cerebral haemorrhage and for therapeutic purposes of relieving pressure in meningitis, convulsions in children, hydrocephalus and rarely for introduction of sera, i.e. anti-meningitis serum or drugs and for spinal anaesthesia.

VENTRICULOGRAPHY

The size, shape, position, etc. of the ventricles can be studied under X-ray—after injecting air or a radio-opaque substance, viz. thorotrast, into the lateral ventricle (3.0 ml thorotrast in each lateral ventricle) by a fine needle introduced through a trephine hole and passing through the silent area. Equivalent amount of cerebrospinal fluid is withdrawn before introduction of thorotrast. This is of considerable clinical help in certain diseases of brain, e.g. in the localisation of cerebral tumours.

HYDROCEPHALUS

It is due to abnormal accumulation of cerebrospinal fluid. It occurs due to any of the following factors:

1. Increased secretion of the cerebrospinal fluid which gives rise to symptoms of pressure, viz. headache, slow pulse, slow respiration and complete or partial unconsciousness.
2. Obstruction in the passage of the cerebrospinal fluid, e.g. in the foramina of Monro, or in the aqueduct of Sylvius; or in the IV ventricle, or in the foramina of Magendie and Luschka.
3. Retardation of absorption of the cerebrospinal fluid through the arachnoid villi.
4. Hydrocephalus may be internal or external. In internal hydrocephalus the circulation of cerebrospinal fluid is blocked, the fluid accumulates within lateral and III ventricles. Whereas in external hydrocephalus the fluid accumulates in the subarachnoid space around the brain due to blockade of cerebrospinal fluid drainage from the subarachnoid space.

BLOOD–CSF AND BRAIN BARRIER (Fig. 110.2)

The composition of the cerebrospinal fluid mostly depends upon the nature of flow of materials from the perivascular spaces into the fluid spaces and vice versa through diffusion. Therefore an exchange of materials between the intracellular fluids of brain parenchyma and the cerebrospinal fluids and vice versa will also alter the fluid composition. The knowledge of the nature of transformation of different materials from the blood to the cerebrospinal fluid and thence to the brain parenchyma and vice versa is not only of great academic interest but also of clinical importance. Because certain materials can diffuse through spaces but others do not. Generally it is assumed that there are the existences of three barriers: (a) Blood–cerebrospinal fluid barrier, (b) blood–brain barrier, and (c) cerebrospinal fluid–brain barrier.

Blood–Cerebrospinal Fluid Barrier

The transfer of materials from the blood into the cerebrospinal fluid apparently takes place very slowly,

because there is a blood–cerebrospinal fluid barrier. Lipid soluble substances may pass from the blood to the cerebrospinal fluid more easily than a less lipoid soluble material. Ions, active compounds and drugs alter the brain–cerebrospinal fluid barrier. Epinephrine and calcium decreases the permeability of the above barrier. Theophylline, on the other hand, increases the permeability of the blood–cerebrospinal fluid barrier. The blood–cerebrospinal fluid barrier is associated mainly with the endothelia of the choroid plexus and also in part with those of the meningeal capillaries of the pia.

Blood–Brain Barrier

The blood–brain barrier is a controlling mechanism as membrane–barrier system which allows selectively some substances from the capillary blood to enter the brain. The blood–brain barrier is due to presence of tight junctions between endothelial cells in blood vessel of central nervous system and this restricts the passage of solutes. The tight junctions consist of transmembrane proteins such as claudins and occludin. The blood–brain barrier is present in all part of the brain except area postrema, the roof of the third and fourth ventricles, capillaries in the pineal gland, some areas of hypothalamus; and circumventricular organs.

Morphological Characteristics of Blood–Brain Barrier

1. The high electron density of endothelial cytoplasm
2. Thicker basement membrane
3. Absence of perivascular connective tissue
4. Complete covering of the endothelial surface by astrocytic processes
5. Small number or absence of cytoplasmic vesicles in endothelial cells.

Morphologically, blood–brain barrier is constituted by the layer of astrocytic end feet. Lateral zonulae occludentes of the capillary endothelium force solutes to pass through the cytoplasm of astrocyte which restrains the passage of molecule through its plasma membrane.

The blood–brain barrier allows the passage of small molecules or hydrophilic molecules like oxygen, carbon dioxide, water and lipid soluble substances like anaesthetics and alchol. The electrolytes like sodium, potassium, etc. can also permeate through this barrier.

Functions of Blood–Brain Barrier

1. The blood–brain barrier protects the brain from bacterial pathogens.
2. Because of its selective permeability nature it helps to maintain constancy in environment of the cortical neurons.

Applied Physiology: Blood–Brain Barrier

The blood–brain barrier permeability increases during inflammation. Thus, brain becomes potently susceptible to bacterial and viral infections. The bacterial pathogens which may penetrate the barrier are toxoplasma gondii (producing toxoplasmosis), Group B streptococci (causing meningitis in newborns) and *Treponema pallidum* (causing syphilis).

Cerebrospinal Fluid–Brain Barrier

The cerebrospinal fluid–brain barrier is located in the layer glial fibres lining the outer surface of the brain or in ependyma that lines the ventricles. Between the cerebrospinal fluid and brain the exchange rate is faster than its exchange across the cerebral capillaries of choroid plexus. But water-soluble materials of large molecular weight cannot pass easily the cerebrospinal fluid–brain barrier.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the composition, formation and functions of cerebrospinal fluids. Add note on hydrocephalus.

Short Notes

1. Blood–brain barrier
2. Cerebrospinal fluid–brain barrier

Chapter

111

Autonomic Nervous System

INTRODUCTION

General Considerations

Autonomic system is that part of nervous system which controls the activity of viscera.

Autonomic nervous system can be classified in three ways:

1. ***Anatomical:*** According to the situation of outflow:
   a. Craniosacral (cranial [tectobulbar] III, VII, IX, X and sacral: 2–4).
   b. Thoracolumbar (thoracic: 1–12 and lumbar 1–3).
2. ***Functional:*** According to the nature of function.
   a. Sympathetic—same as thoracolumbar.
   b. Parasympathetic—same as craniosacral.

   The parasympathetic reactions are usually localised reactions and the sympathetic reactions are concerned with mass reactions. The parasympathetic activity results for instance, in slowing of the heart and increase in the peristaltic and glandular activities of the gut; these conserve the body energies. Sympathetic activity results, for example, in constriction of the cutaneous arteries (with consequent increase in the blood supply to the heart, brain and muscle), acceleration of the heart and increase of blood pressure, contraction of the sphincters and lessening of the peristalsis of the gut; these mobilise body energies for dealing with emergencies.

   These two are functionally opposite. Broadly speaking, functions of sympathetic are anabolic, while those of parasympathetic are, anabolic in nature.
3. ***Chemical:*** According to the chemical substances liberated (Fig. 111.1).
   - *Adrenergic:* Those producing norepinephrine or epinephrine at the nerve endings. Include only the

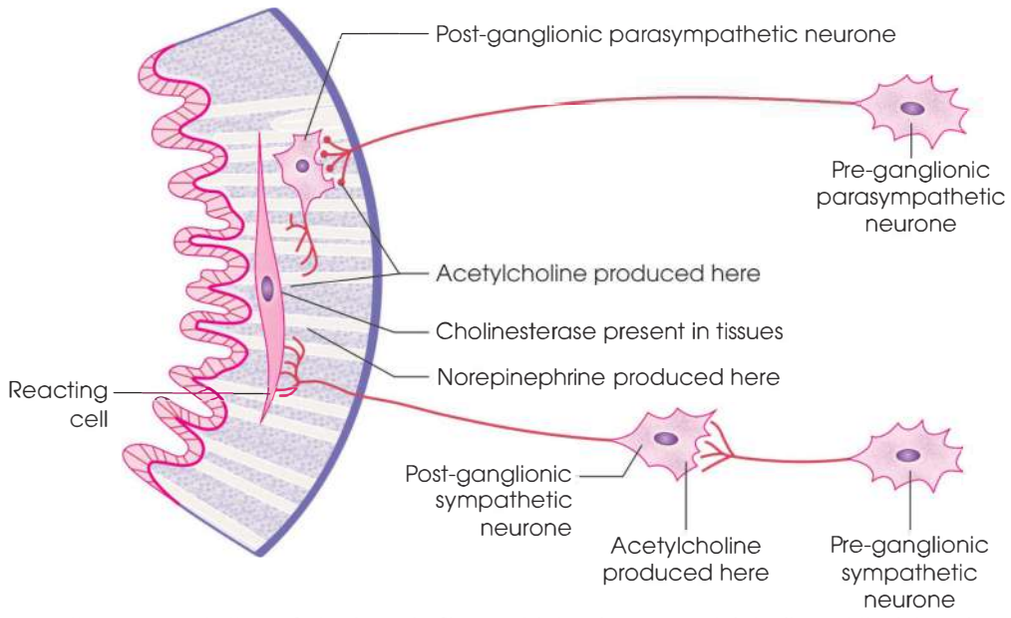

Fig. 111.1: Diagrammatic representation of cholinergic fibres which release acetylcholine at their terminals and adrenergic fibres those release norepinephrine (noradrenaline) and some epinephrine (adrenaline) at their terminals

postganglionic fibres of sympathetic except to sweat glands

- *Cholinergic:* Those producing acetylcholine include:
  - The whole of parasympathetic—both pre-ganglionic and post-ganglionic fibres
  - All pre-ganglionic sympathetic fibres
  - Those post-ganglionic sympathetic fibres which supply the sweat glands.

It is to be noted that the adrenergic fibres produce epinephrine or norepinephrine at the nerve endings, whereas cholinergic fibres produce acetylcholine both at the synapses (ganglia) as well as at the nerve endings. The parasympathetic receptors may be excitatory, as in glands and in smooth muscle cells of the alimentary canal, or inhibitory, as in the heart. Sympathetic receptors in blood vessels (when present) are not innervated, but in other kinds of receptor cell, such as the heart, they are thought to be innervated and may be excitatory.

General Arrangement (Fig. 111.2)

1. Autonomic reflexes are very important in the control of the viscera. Like some of the somatic reflex arcs the autonomic reflex arc also contains three neurons, e.g. afferent, connector and efferent (excitor or effector) neurons.
2. In the somatic system the afferent neurons lie in the posterior root ganglia (or their cranial homologues). In the autonomic system they also lie in the posterior root ganglia.
3. The connector neurons in the somatic system are found in the posterior horn cells. But in the autonomic system they are found in the lateral horn cells.
4. In the somatic system the effector neurons are situated in the anterior horn cells. But in the autonomic system they are not present in the central nervous system at all.
5. They lie outside the central nervous system in the form of various ganglia. The presence of peripheral ganglia is the characteristic feature of the autonomic

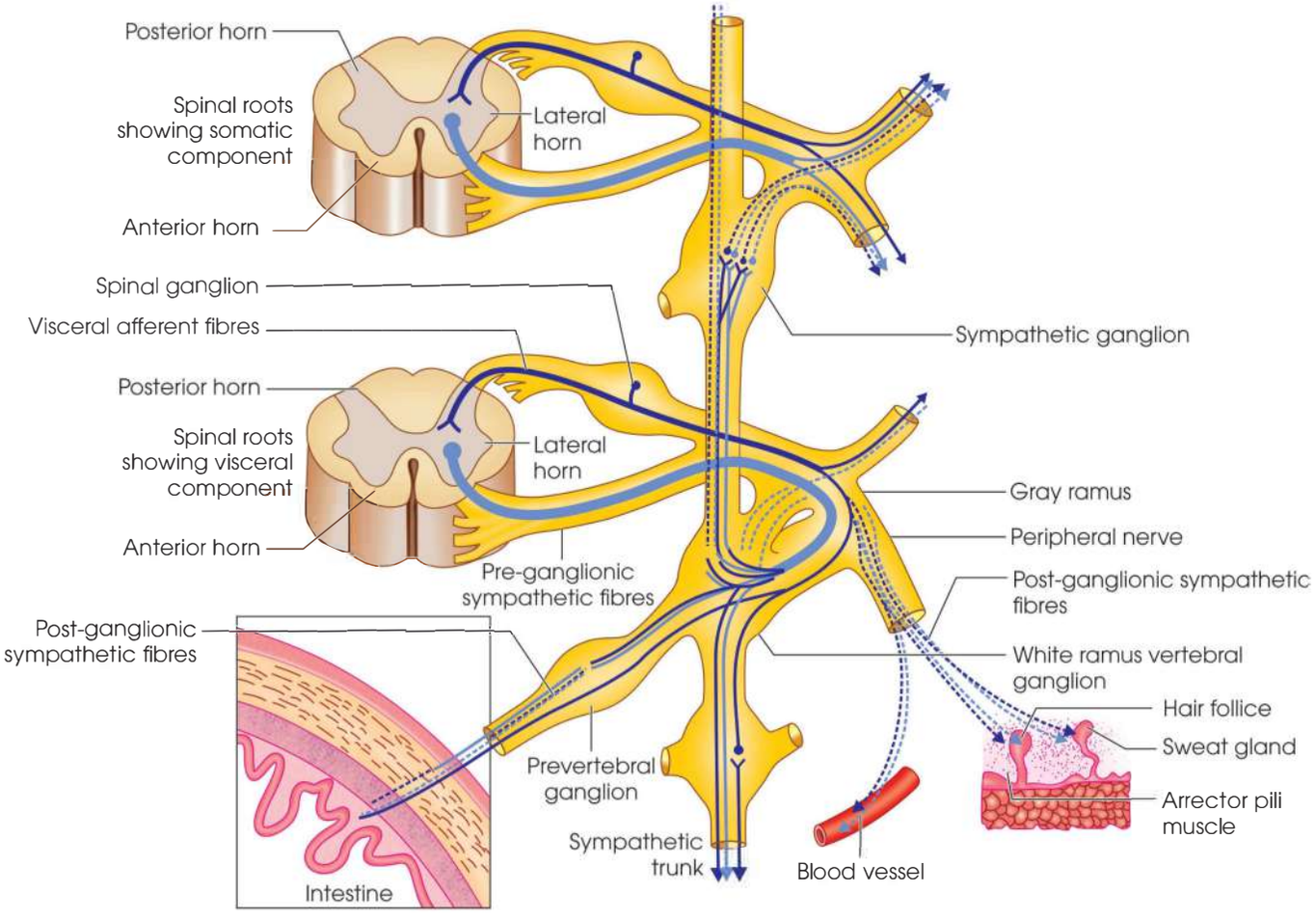

Fig. 111.2: Diagram shows the constitution of a typical spinal nerve. The upper part shows the somatic components and the lower part, the visceral components. Red solid lines representing motor efferent somatic and preganglionic visceral fibres; black solid lines indicating afferent somatic and visceral fibres: red dotted lines showing post-ganglionic visceral fibres

system. In the sympathetic system the ganglia lie away from viscera supplied. But in the parasympathetic system they lie in or near the viscera (exception—Meckel's ganglion and otic ganglion). Hence, the parasympathetic system exerts a more localised action than the sympathetic system.

6. Autonomic functions like the control of the elasticity of blood vessels, sweating, gastrointestinal, genitourinary, respiratory and cardiac functions are reflexly maintained.
7. Autonomic reflexes are qualitatively similar to somatic ones and mostly they are polysynaptic. However, because of the interneuron located in the spinal cord, the integrity of the spinal cord is essential for regulating the autonomic reflex arcs.

Functional Significance

1. Efferent post-ganglionic fibres that run in grey rami communicantes to the spinal nerves innervate vasoconstrictor fibres to blood vessels, motor fibres to the arrectores pilorum muscles in the areas supplied by the corresponding spinal nerves, and secretomotor fibres to the sweat glands.
2. Those efferent post-ganglionic fibres accompany motor nerves to voluntary muscles are presumably distributed only to blood vessels supplying the muscles. Those fibres which run in the viscera and other structures are related to vasoconstriction, dilatation of pupils and of bronchioles, movements of the alimentary tract and the urinary bladder (relaxation of muscle walls and contraction of sphincters), glandular secretion, and so on.
3. A certain pre-ganglionic fibre synapses with the post-ganglionic neurons supplying one effector system only, dissociation sympathetic actions, viz. vasomotor and sudomotor activities, can take place.
4. While the actions of the sympathetic and parasympathetic systems are generally antagonistic on the viscera they supply, in the case of the urinary bladder, for example, the normal emptying and filling of the viscus are controlled only by the parasympathetic system.
5. The sympathetic system is mainly being concerned with blood supply of the organ. Some of afferent sympathetic fibres mediate pain impulses.
6. On the other hand, afferent parasympathetic fibres are concerned with visceral reflexes which operate under normal conditions of life. In most cases, afferent sympathetic fibres are probably concerned with unusual or pathological reflexes.

Dual Supply

1. Most of the organs in the body are supplied both by sympathetic (thoracolumbar) and parasympathetic (craniosacral) nerves, exerting antagonistic actions. But some structures are supplied by sympathetic alone, e.g. adrenal medulla, most arterioles, ureters, uterus, Fallopian tubes, vesicles, etc. While there are certain other structures having parasympathetic supply alone, e.g. oesophagus, gastric glands, pancreas including the islets of Langerhans, lacrimal glands, etc.

SYMPATHETIC (THORACOLUMBAR) SYSTEM

1. As mentioned before, sympathetic outflow takes place from the thoracic and lumbar regions. The connector cells lie in the lateral horn cells situated only in the thoracic and upper three lumbar segments (T1 to L3).
2. Since the effector neurons lie outside the central nervous system, the axons of the lateral horn cells of the spinal cord (intermediate lateral tract) pass out through the anterior root and enter the anterior divisions of the mixed spinal nerve. These fibres are thinly medullated (β), hence white. They leave the nerve in the form of a branch called the white ramus communicans and enter the sympathetic ganglion.
3. It may end in this ganglion or may simply pass through it to other ganglia up or down the sympathetic chain or even to other distant ganglia.
4. The effector fibres (postganglionic) arising from the ganglion of sympathetic chain is non-meduallated, hence grey. They run back to join the spinal nerves in the form of another branch called the grey ramus communicans, and are ultimately distributed either along the blood vessels or the spinal nerves. It is to be noted that all the spinal nerves possess grey rami, but only the thoracic and lumbar nerves have white rami.
5. As noted before, the cell bodies of the afferent neurons lie in the posterior root ganglia or their cranial equivalents. The dendrites collect impulses form the viscera, pass through the white ramus and end in the cell body. The axons transmit impulses to the lateral horn cells (Fig. 111.3).

Sympathetic Ganglia

Three classes of sympathetic ganglia:

1. ***Vertebral ganglia:*** Consist of about twenty-two ganglia, lying by the side of the vertebral bodies and connected together by nerve fibres in the form of a chain. It extends from the base of the skull to the front of the coccyx. As a rule, there is one ganglion for each segment. But they show a tendency to coalesce. For instance, the eight cervical ganglia become fused into there—the superior, middle and inferior cervical ganglia. In the thoracic region there are from ten to twelve ganglia on each side. The first thoracic ganglion in man sometimes fuses with the inferior cervical ganglion forming the stellate ganglion. In the lumbar region there are usually four.

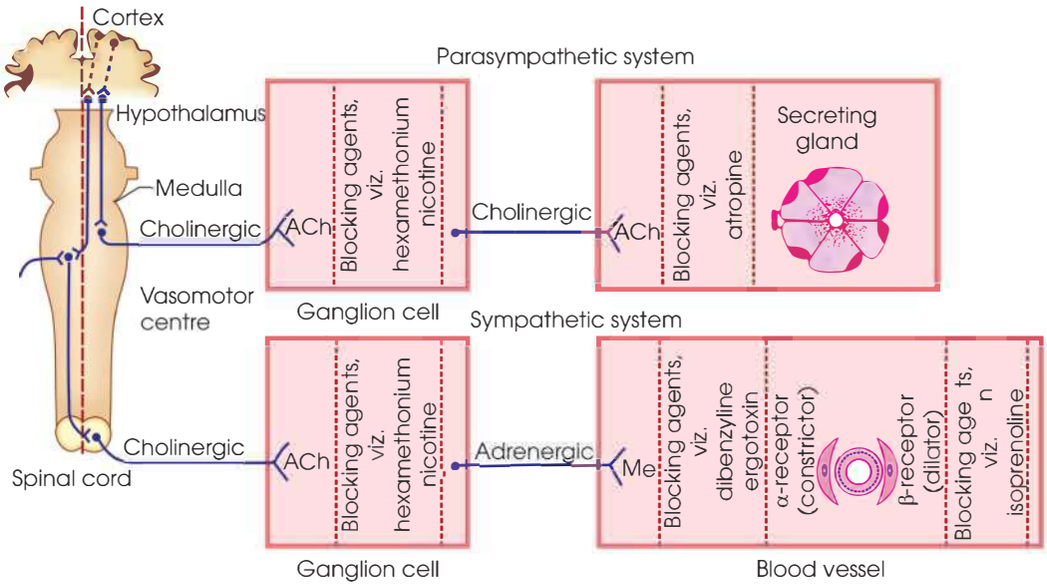

Fig. 111.3: Schematic representation of chemical transmission in the autonomic nervous system and distribution of cholinergic and adrenergic neurons. Where a secreting gland is taken as a typical effector organ innervated from the parasympathetic system; and the smooth muscle in a blood vessel as a typical effector organ innervated from the sympathetic system

In the sacral, four to five, which in the coccygeal region the terminal portions of the two sympathetic chains fuse together and form a single ganglion in front of the coccyx (coccygeal ganglion).

2. ***Collateral ganglia*** (prevertebral ganglia). Lie in the thorax, abdomen and pelvis in close relation with aorta and its big branches. For instance, the coeliac (solar or semilunar), superior mesenteric, inferior mesenteric, etc.
3. ***Terminal ganglia.*** They are situated in close relation to organs of supply.

SYMPATHETIC OUTFLOW (Fig. 111.5)

Head and Neck

Afferents connectors (pre-ganglionic): T1 and T2. Effectors (post-ganglionic) are superior cervical ganglion.

Eye: Post-ganglionic sympathetic fibres pass from the superior cervical ganglion to internal carotid artery (internal carotid plexus) and ophthalmic artery to the orbit. These supply:

1. Vessels of eyeball, retina, ciliary body and dilator muscle of the pupil (dilatation of pupil).
2. Smooth muscles of the upper and lower lids (retraction of lids).
3. The retro-ocular plain muscles of Müller (protrusion of eyeball). In man, the latter is rudimentary.

Skin structures: Postganglionic sympathetic fibres pass from superior cervical ganglion to upper 4 cervical nerves (Fig. 111.4). Join the brachial plexus and finally pass along the branches of external carotid artery.

Throughout the whole body, the skin structures supplied by the sympathetic are:

1. Sweat gland—secretory fibres (cholinergic)

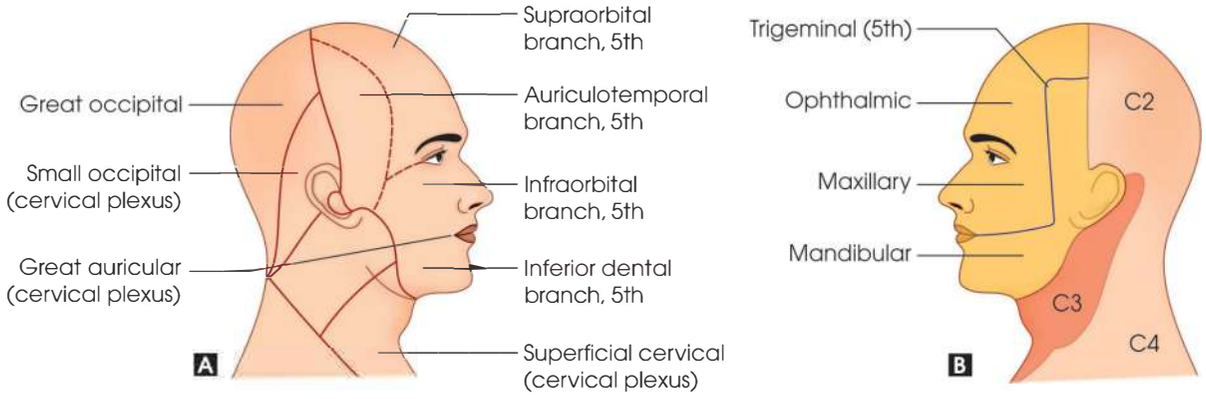

Fig. 111.4: (A) Shows the distribution of sensory nerves of the head; (B) Represents lateral view of skin areas innervated by fifth cranial nerve and second, third and fourth cervical segments

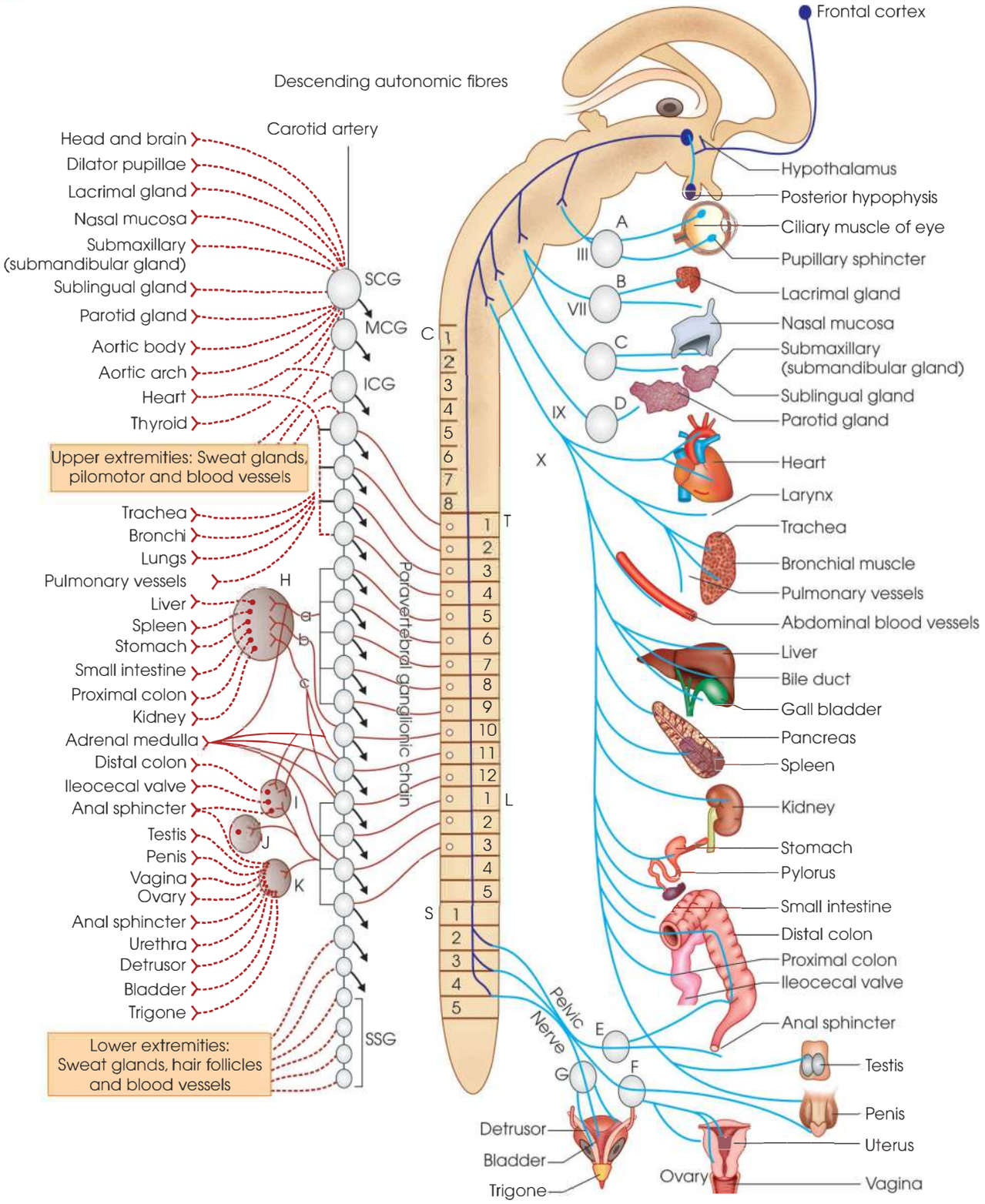

Fig. 111.5: Diagrammatic representation of the autonomic nervous system (*see* text)

2. Plain muscles—arrectores pilli (which erect hairs and produce an appearance in man as goose skin), those around the orifices of the body (anal sphincters and vagina) retractor penis, dartos, etc.
3. Blood vessels—vasoconstrictors, may be some vasodilators.

Black solid lines designate preganglionic sympathetic fibres; Black dotted lines represent post-ganglionic sympathetic fibres. Red solid lines show pre-ganglionic parasympathetic fibres; Red dotted lines indicate post-ganglionic parasympathetic fibres. A: Ciliary ganglion, B: Sphenopalatine ganglion,

C: Submaxillary (submandibular) and sublingual ganglion, D: Otic ganglia, E and K: Hypogastric plexus, F: Inferior hypogastric plexus, G: Vesical plexus. SCG: Superior cervical ganglion, MCG: Middle cervical ganglion, ICG: Inferior cervical ganglion, SSG: Sacral sympathetic ganglion, H: Coeliac ganglion, I: Superior mesenteric ganglion, J: Inferior mesenteric ganglion,a: Greater splanchnic nerve, b: Lesser splanchnic nerve, c: Least splanchnic nerve. C: Cervical cord, T: Thoracic cord, L: Lumbar cord, S: Sacral cord.

Glands

1. Buccal, parotid, sublingual, submaxillary (submandibular) and lacrimal glands receive both vasoconstrictor and trophic sympathetic fibres along the blood vessels.
2. Thyroid—from middle cervical ganglion along the blood vessels, probably vasomotor.

Carebral blood vessels: From superior and inferior cervical ganglia passing along internal carotid and vertebral arteries respectively.

Thoracic Viscera

1. Connectors from T3 and T4. Effectors from the three cervical ganglia.
2. Heart—acceleration.
3. Coronary vessels—dilatation.
4. Bronchial muscles relaxation. Bronchi dilate. Pulmonary vessels constriction.

Forelimb: Connectors—T59. Effectors are first, second thoracic, middle and inferior cervical ganglia. Joins brachial plexus and passes along the spinal nerves. supply:

1. Skin structures
2. Vessels in skeletal muscles (dilators), etc.

Hindlimb, Connectors—T10–12 and L1–3. Effectors are from lumbar and sacral ganglia. Post-ganglionic sympathetic fibres join the lumbosacral plexus, pass along the spinal nerves and supply in the same way as the forelimb.

Thoracic and abdominal wall: Connectors—T1–12. Effectors are from the ganglia of the thoracic chain. Finally supply through the intercostal nerves.

Abdominal and pelvic viscera: Connectors arise from T5 to L3, pass through the vertebral ganglia without relay, and form the splanchnic nerves (pre-ganglionic). There are greater, lesser and least splanchnic nerves. The greater splanchnic nerve arises from the fifth to ninth thoracic segments, the lesser splanchnic nerve from the twelfth thoracic segment. The greater splanchnic nerve ends in the upper part of the coeliac ganglion.

The lesser splanchnic nerve ends in the lower part of the coeliac ganglion and the least splanchnic nerve joins the renal plexus and ends in small ganglia from where post-ganglionic sympathetic fibres arise and supply the kidney and ureter. The fibres arising from the first and second lumbar segments end in the inferior mesenteric ganglion (in animal) or in the hypogastric ganglion (in man). From here post-ganglionic sympathetic fibres arise and supply the viscera along the blood vessels.

Gastro-intestinal Tract

1. Oesophagus—no sympathetic supply.
2. Whole of large and small intestines and stomach with all the sphincters in them, receive sympathetic supply (body of stomach—doubtful). Action-tone reduced, movements inhibited, sphincters constricted.
3. ***Splanchnic vessels:*** Richest vasoconstrictor supply. (Some vasodilators have also been demonstrated.)
4. ***Urinary bladder:*** Movements inhibited. Sphincters constricted
5. ***Adrenal medulla:*** Sympathetic supply only (secretomotor).
6. ***Spleen and gall bladder:*** Contraction.
7. ***Ureters:*** Both motor and inhibitory fibres from the sympathetic. Parasympathetic absent.
8. ***Kidney:*** Constriction of glomerular arterioles, specially efferent.
9. ***Uterus, fallopian tubes and vas deferens:*** Both motor and inhibitory fibres from sympathetic.
10. ***Liver:*** Glycogen mobilised.

PARASYMPATHETIC (CRANIOSACRAL) SYSTEM
(Figs 111.6 and 111.7)

Parasympathetic outflow takes place from the cranial and sacral regions. This connector cells of the cranial outflow lie in the cranial nerve nuclei (Fig. 111.7). The connector cells of the sacral region lie in the lateral horn cells.

The presence of the peripheral ganglia is also a characteristic feature but unlike the sympathetic system the ganglia lie in or near the viscera except Meckel's ganglion and otic ganglion. Hence, the parasympathetic system exerts a more localised action than the sympathetic system.

PARASYMPATHETIC OUTFLOW

Cranial Outflow

Take place through four cranial nerves: Oculomotor (III), facial (VII), glossopharyngeal (IX), vagus (X).

They are briefly described below.

1. ***Oculomotor*** (third cranial nerve). Connectors arise from the most cranial part of oculomotor nucleus (Edinger-Westphal nucleus), relay in the ciliary ganglion, from where post-ganglionic

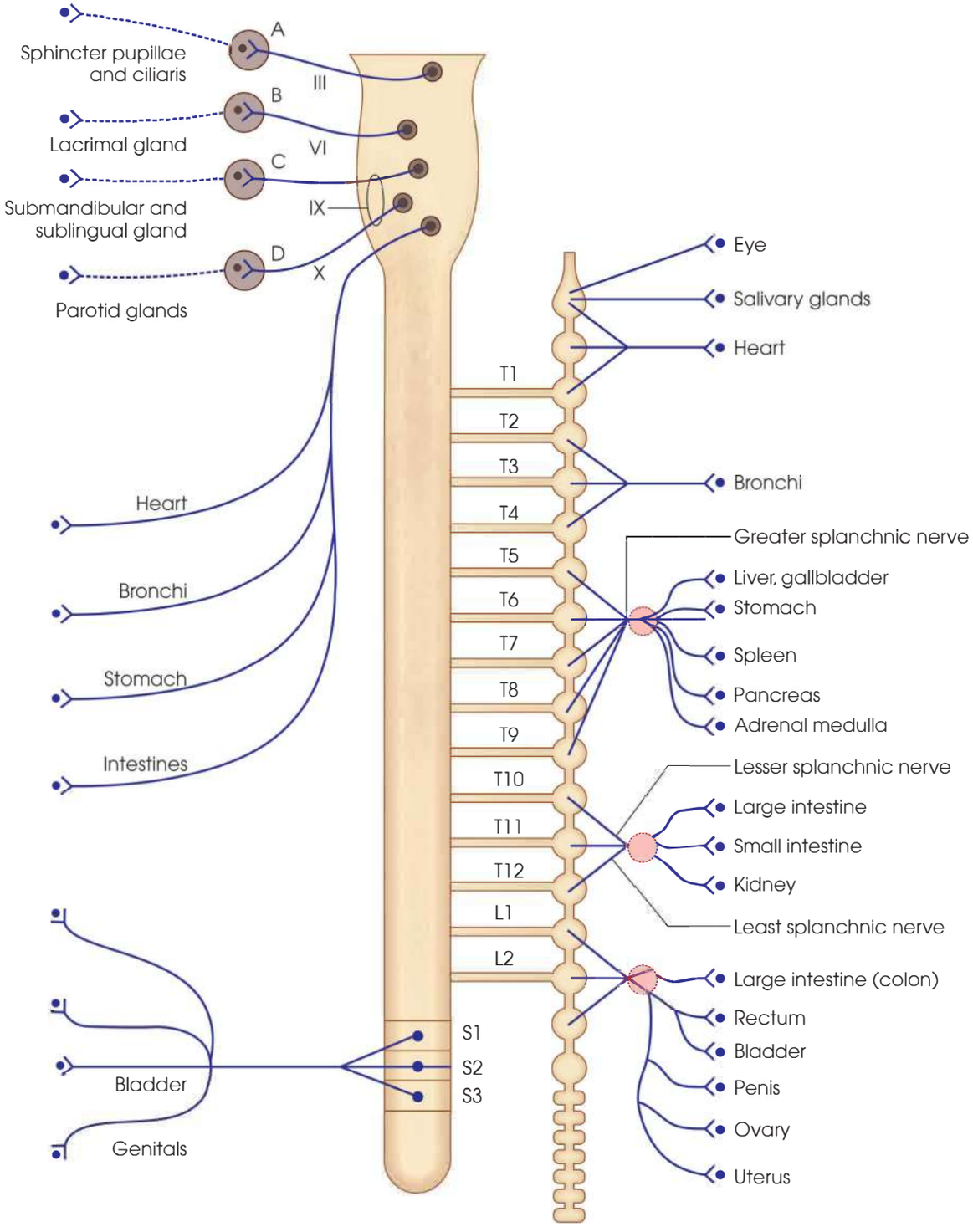

Fig. 111.6: Diagrammatic representation of projections of visceral afferent nerves showing spinal cord and brain stem centres. A: Trigeminal ganglion (geniculus gasseri); B: Geniculate ganglion (geniculus geniculi); C: Petrosal ganglion; D: Nodose ganglion

parasympathetic fibres arise, pass in the short ciliary nerve and supply the ciliary muscles and sphincter pupillae. This nerve is also included within the midbrain outflow or tectal outflow.

2. ***Facial nerve*** (seventh cranial nerve). Connectors arise from the dorsal nucleus (superior salivary nucleus) and pass out in two ways:

- One group passes through greater superficial petrosal nerve to the sphenopalatine ganglion (Meckel's ganglion) from where post-ganglionic parasympathetic fibres arise and supply the lacrimal glands, plain muscles, blood vessels and glands of plate and naso-pharynx.

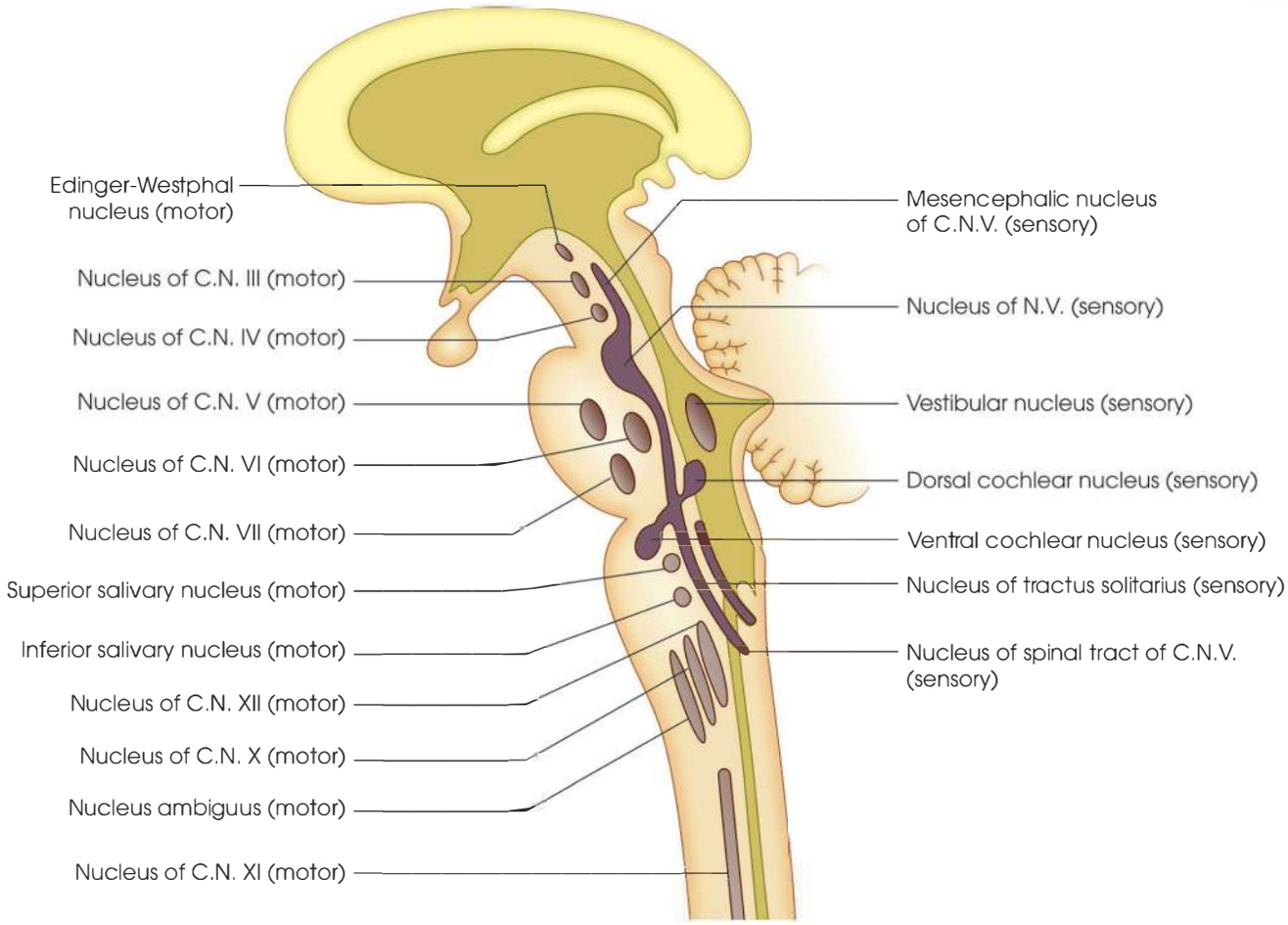

Fig. 111.7: Diagram represents the anatomical position of the different cranial nerve nuclei.

- Another group passes in the chorda tympani, then joins the lingual nerve and at the floor of the mouth the chorda tympani fibres separate from the lingual nerve and end in the ganglia (sublingual ganglion and submaxillary ganglion) close to the submaxillary and sublingual glands (*vide* Volume 1). Post-ganglionic parasympathetic fibres arise from these ganglia and supply secretory and vasodilator fibres to the glands. (Taste fibres form the anterior two-thirds of tongue also end in this nucleus forming a reflex arc for salivation. Hence, the name superior salivary nucleus.)

3. ***Glossopharyngeal nerve*** (ninth cranial nerve). Connectors lie in the dorsal nucleus (inferior salivary nucleus), pass along the tympanic nerve and the lesser superficial petrosal nerve to the otic ganglion. Here, the post-ganglionic parasympathetic fibres arise, pass along the auriculotemporal nerve and supply secretory and vasodilator fibres to the parotid gland. (Taste fibres form the posterior one-third of tongue end in this nucleus and form a reflex arc for salivation. Hence, the name inferior salivary nucleus.)
4. ***Vagus*** (Tenth cranial nerve). The vagus is the most important parasympathetic nerve, widely distributed and carries the parasympathetic fibres practically everywhere in the body except the limbs. Connectors arise from the small—celled part of the dorsal nucleus known as the nucleus intercalates (Staderini's nucleus). Fibres pass out in the vagus trunk (pre-ganglionic), end in ganglia-in or near the viscera, from where post-ganglionic parasympathetic fibres arise and supply the viscera as mentioned below.
5. ***Heart:*** Post-ganglionic parasympathetic fibres arise from the ganglion cells near the sinoatrial and atrioventricular nodes. Supply inhibitory fibres to the junctional tissues and cardiac muscles and dilator fibres to coronary vessels.
6. ***Lungs:*** Constrictor fibres to the bronchial muscles.
7. ***Gastrointestinal tract:*** Supply the tract from the oesophagus up to caecum. Post-ganglionic parasympathetic fibres arise from Auerbach's plexus and Meissner's plexus. Fibres from the former supply the muscle coats, stimulate intestinal movements and inhibit the sphincters. Fibres from the latter supply vasodilator fibres and secretomotor fibres to the gastrointestinal glands and mucosa.

8. ***Pancreas:*** Supplies secretory fibres to the pancreatic alveoli as well as to the islets of Langerhans.
9. ***Gall bladder:*** Action reverse of the sympathetic fibres.
10. ***Liver and kidney:*** No appreciable effect.

Sacral Outflow

Connectors from S2 and S4, pass out through corresponding anterior roots and unite to form a single nerve on each side called nervi erigentes (preganglionic). They relay in the hypogastric ganglia, from where post-ganglionic parasympathetic fibres arise and supply urinary bladder, prostate and the whole of large intesline except caecum.

Actions

1. Movements stimulated and sphincters inhibited (reverse of the sympathetic).
2. Also supplies dilator fibres to the blood vessels of external genitalia. This vasodilatation is an important factor for causing erection of penis (hence, the name nervi erigentes).

Spinal Parasympathetic

Posterior spinal nerve roots contain certain fibres which on stimulation produce vasodilatation. These fibres are said to be parasympathetic as their action, unlike that of other vasodilator nerve, is not abolished by atropine. These fibres are also known as antidromic vasodilator fibres as their impulses pass out against the general afferent impulses of the posterior nerve roots and extend up to posterior root ganglion. Local stimulation by irritants applied to the skin produces vasodilatation through these fibres. This is known as axon reflex. The vasodilatation is produced due to liberation of acetylcholine at the nerve endings.

HIGHER AUTONOMIC CENTRES

These activities of higher centres in the brain influence peripheral autonomic nervous system. The parts of the brain especially concerned have been described in the CNS and include some of the nuclei in the hypothalamus and certain areas of the cortex of the frontal lobe. The activities of the cerebral cortex in relation to the autonomic nervous system indicate a close relationship between mental states and visceral and somatic activities.

FUNCTIONS OF SYMPATHETIC AND PARASYMPATHETIC SYSTEMS

In summary, the sympathetic and parasympathetic system, by acting oppositely, take part in maintaining the body temperature mechanism in response to changes in external or internal environments. The sympathetic system directs to strengthen the subject's ability to adapt itself following a change in its internal environment, such as fall in hear rate, blood sugar, blood pressure, etc. and in external environment for securing foods and protection whereas the parasympathetic system is concerned with restoring and conserving energy. In most instances the parasympathetic system takes part in inhibiting or slowing down the different bodily processes.

CONCLUSION

Though the actions of the sympathetic and the parasympathetic system are antagonistic, i.e. if one system inhibits a function, the other activates it, but it is not always true. Because it depends upon the efficacy of transmitters released by either system and on the area of innervation. For example, the sympathetic stimulation markedly enhances peripheral vascular resistance, but it is not altered appreciably by the activity of parasympathetic system. In general, most of the vessels involoved in the control of blood pressure are innervated only by the sympathetic nerve fibres and these fibres are continuously active. The parasympathetic nerve fibres which serve blood vessels normally are restricted to small areas of the body, and vasodilatation in these areas does not contribute appreciably to systemic blood pressure. So, to decrease blood pressure, it is more significant to paralyse the continuous sympathetic activity (tone) than to elicit the parasympathetic action. Further informations on the function of the peripheral autonomic system have been discussed on the digestive system, the circulatory system and endocrinology.

Sympathetic and parasympathetic anatomical and physiological aspects are summarized below.

- The salient anatomical features of the sympathetic nervous system.
- The salient anatomical features of the parasympathetic nervous system.
- The effects of stimulation of autonomic adrenergic and cholinergic nerves are summarised below and many of these effects are discussed in more detail in other sections of the text.
- Physiological functions and responses of autonomic nervous system.

CONTROL OF THE AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system is controlled in the following ways.

Nervous Control

1. ***Hypothalamus:*** As detailed in chapter of hypothalamus.
2. ***Cerebral cortex:*** In spite of the fact that decorticate animals maintains almost normal autonomic functions, following facts suggest that cerebrum

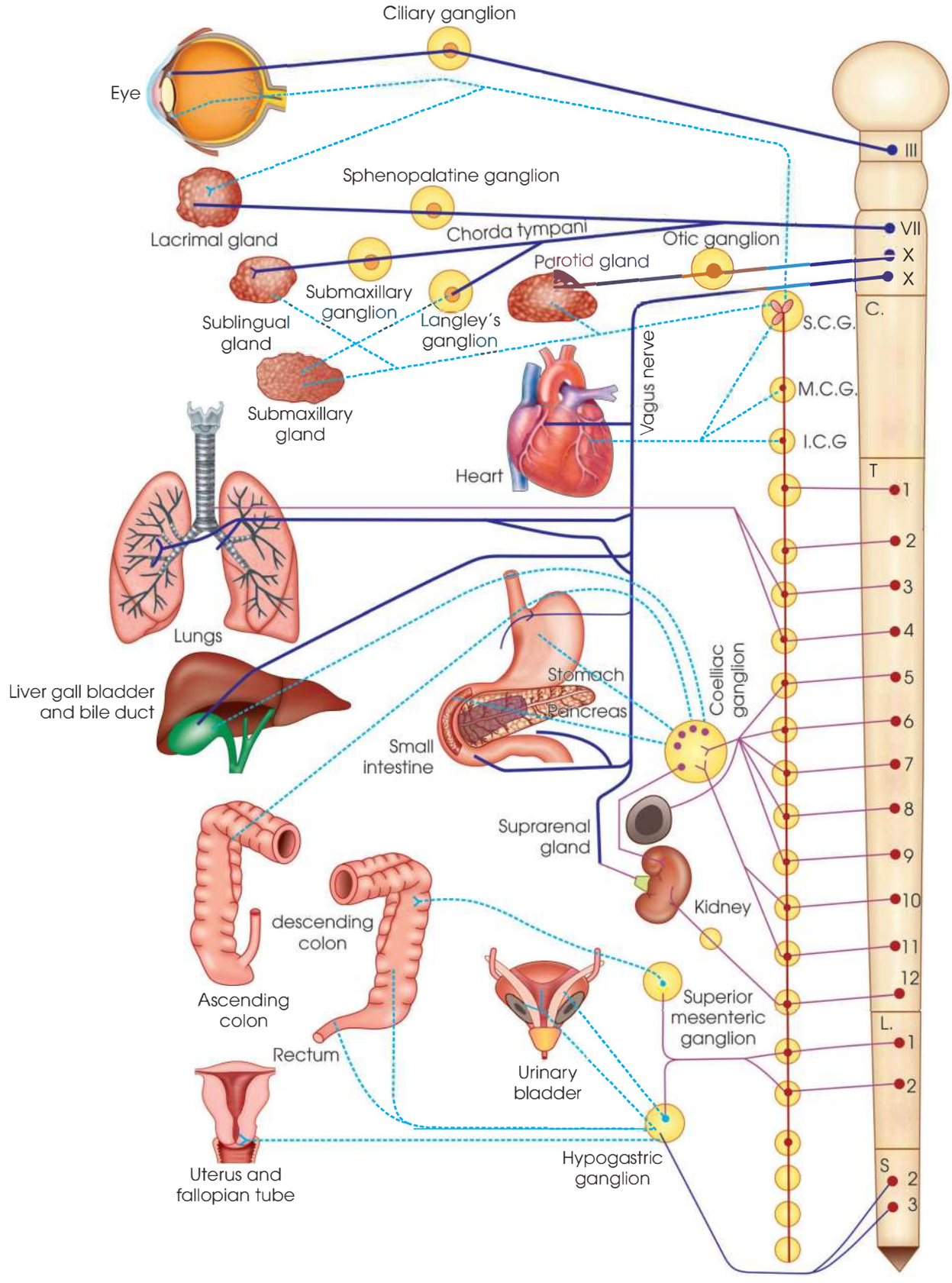

Fig. 111.8: Diagrammatic representation of some of the chief conduction pathways of the autonomic nervous system. Black solid lines—preganglionic sympathetic fibres; Black dotted lines—postganglionic sympathetic fibres; Red solid lines—preganglionic parasympathetic fibres; Red dotted lines—postganglionic parasympathetic fibres; SCG—superior cervical ganglion. MCG—middle cervical ganglion; ICG—inferior cervical ganglion; C—cranial segments. T— thoracic segments L—lumbar segments; S—sacral segments

Preganglionic cell bodies in the CNS nuclei	*Postganglionic cell bodies in peripheral ganglia*	*Organs supplied*
Intermediolateral nucleus in cord segments C8–T2 (T3 sometimes)	Superior cervical ganglion and scattered along carotid plexus	Iris of eye
Intermediolateral nucleus in cord segments T1–T2	Superior and middle cervical sympathetic ganglia	Lacrimal gland
Intermediolateral nucleus in cord segments T1–T3 (T4 sometimes)	Superior and middle cervical sympathetic ganglia	Submandibular and sublingual glands
Intermediolateral nucleus in cord segments T1–T3 (T4 sometimes)	Superior and middle cervical sympathetic ganglia	Parotid gland
Intermediolateral nucleus in cord segments T1–T3	Superior, middle and inferior cervical sympathetic ganglia	Sweat glands of head and neck
Intermediolateral nucleus in cord segments T1–T5	Inferior cervical and thoracic (T1 –T5) sympathetic ganglia	Lungs and bronchi
Intermediolateral nucleus in cord segments T1–T5 (T6, T7 sometimes)	Superior, middle and inferior cervical and thoracic (T1–T6) sympathetic ganglia	Heart
Intermediolateral nucleus in cord segments T1–T6	Thoracic sympathetic T4–T6 (T1–T6) ganglia	Oesophagus
Intermediolateral nucleus in cord segments T5–T11	Celiac and superior mesenteric ganglia	Stomach, small intestine, ascending and transverse colon
Intermediolateral nucleus in cord segments T12–L3	Lumbar and inferior mesenteric sympathetic ganglia	Descending colon and rectum
Intermediolateral nucleus in cord segments T10–L2	Lumbar, sacral and inferior mesenteric sympathetic ganglia	Sex organs
Intermediolateral nucleus in cord segments T12–L2	Lumbar and inferior mesenteric sympathetic ganglia	Urinary bladder
Intermediolateral nucleus in cord segments L1–L2	Lumbar and sacral sympathetic ganglia	Sweat glands and blood vessels of lower extremity

Preganglionic cell bodies in the CNS nuclei	*Postganglionic cell bodies in peripheral ganglia*	*Organs supplied*
Edinger-Westphal nucleus of midbrain (cranial part of III nerve nucleus)	Ciliary ganglion	Sphincter pupillae ciliary muscle
Superior salivary nucleus in pons varolii (dorsal nucleus of CN VII)	Pterygopalatine ganglion	Lacrimal gland
Superior salivary nucleus in pons varolii (dorsal nucleus of CN VII)	Submandibular ganglion	Submandibular and sublingual glands
Inferior salivary nucleus in medulla (dorsal nucleus of CN IX)	Otic ganglion	Parotid gland
Dorsal motor nucleus of vagus (CN X)	Ganglia of pulmonary plexuses	Lungs and bronchi
Dorsal motor nucleus of vagus (CN X)	Intracardiac ganglia of atria	Heart
Dorsal motor nucleus of vagus (CN X)	Myenteric (Auerbach's) and submucous (Meissner's) plexuses	Oesophagus
Dorsal motor nucleus of vagus (CN X)	Myenteric (Auerbach's) and submucous (Meissner's) plexuses	Stomach, small intestine, ascending and transverse colon
Dorsal motor nucleus of vagus (CN X)	Submucous (Meissner's) plexuses	Pancreas: Endocrine and exocrine cells
Autonomic nucleus of intermediate grey column in cord segments S2—S4	Ganglia of haemorrhoidal myenteric and submucous plexus	Descending colon and rectum
Autonomic nucleus of intermediate grey ramus in cord segments S2–S4 *Nervi erigentes*	Ganglia along branches of aorta and inferior iliac arteries (e.g. ovarian, uterine)	Sex organs
Autonomic nucleus of intermediate grey ramus in cord segments S2–S4 *Nervi erigentes*	Ganglia along vesical branches of inferior iliac artery	Urinary bladder

Adrenergic impulses		*Cholinergic impulses*	*Effector organs*
Receptor type	*Responses*	*Responses*	
α	Contraction (mydriasis)		*Eye:* Iris radial muscle
		Contraction (miosis)	Iris circular muscle (sphincter pupillae)
β	Relaxation for far vision (slight effect)	Contraction, accommodation for near vision	Ciliary muscle
	Lid retraction		Lid smooth muscle
β	Increased heart rate (tachycardia)	Decreased heart rate (bradycardia), vagal arrest	*Heart:* SA node
β	Increased contractility and conduction velocity	Decreased contractility and (usually) increased conduction velocity	Atria
	Increased conduction velocity	Decreased conduction velocity; AV block	AV node and conduction system
β	Increased contractility and conduction velocity; Increased irritability; extrasystoles		Ventricles
α	Constriction		*Blood vessels:* Coronary
β	Dilatation		
α	Constriction		Skin and mucosa
α	Constriction	Dilatation	Skeletal muscle
β	Dilatation		
α	Slight constriction		Cerebral
α	Constriction		Pulmonary
α	Constriction		Abdominal viscera
β	Dilatation		
α	Constriction	Dilatation	Salivary glands
α	Constriction		Renal
β	Relaxation	Contraction	*Lung:* Bronchial muscle
		Stimulation of mucous secretion	Bronchial glands
β	Usually decrease	Increase	*Stomach:* Motility and tone
α	Usually contraction	Usually relaxation	Sphincters
	Inhibition	Stimulation, especially enzymes	Secretion
α, β	Decrease	Increase	*Intestine:* Motility and tone
α	Usually contraction	Usually relaxation	*Sphincters*
		Stimulation	Secretion
	Relaxation	Contraction	*Gall bladder and ducts*
β	Usually relaxation	Contraction	*Urinary bladder:* Detrusor
α	Contraction	Relaxation	Trigone and internal sphincter
	Usually increase		*Ureter:* Motility and tone
α, β	Variable (responses influenced by stage of menstrual cycle, amount of circulating oestrogen and progesterone, etc. and by pregnancy)	Variable	*Uterus*
	Ejaculation in male	Vasodilatation and erection (penis, clitoris)	*Sex organs*
α	Contraction		*Skin:* Arrectores pili
α	Slight, localised secretion (on palms and in other locations adrenergic sweating)	Generalised secretion	Sweat glands
α	Contraction		*Spleen capsule*
		Secretion of epinephrine and norepinephrine	*Adrenal medulla*
β	Glycogenolysis		*Liver*
αβ	Inhibition of insulin secretion	Insulin secretion	Islets
	Insulin secretion		
		Secretion	*Salivary glands:* Parotid
α	Thick, viscous secretion	Profuse, watery secretion	Submaxillary
		Secretion	*Lacrimal glands*
		Secretion	*Nasopharyngeal glands*
		Stimulation	*Autonomic ganglion cells*
β	Release of FFA (lipolysis)		*Adipose tissue*
β	Renin secretion		*Juxtaglomerular cells*

probably exerts a controlling effect on the autonomic nervous system.

- Stimulation of area 13 (on the under surface of the frontal lobe) causes cardiac acceleration, etc.
- From areas 6 and 13 of the cerebral cortex afferent impulses are projected to the hypothalamus. Stimulation of same areas of the cerebral cortex increases blood pressure, while stimulation of other foci has the opposite effect. Both the sympathetic and parasympathetic systems are represented in the cerebral cortex and stimulation of certain cortical areas may result the continued effect of both the two systems. Lacrimation can be observed by stimulation of cortical eyefields; also salivation may appear by stimulating the motor representation of the face and tongue. Cardiovascular reactions can be obtained by electrical stimulation of motor areas 4 and 6.

  Disturbances of sweat secretion may result from stimulation of area 6, while ablation of this area abolishes some sweating reflexes.

3. ***Centres in the brain stem and medulla:*** The medullary centres for the autonomic reflex control of circulation, heart, respiration, vomiting, coughing, sneezing, etc. are called the vital centres. The afferent fibres connecting to these centres originate from the visceral receptors located at the particular sites like carotid and aortic bodies, stretch receptors, etc. The motor or effect or pathways originating from the medulla pass through either sympathetic or parasympathetic pathways. The details of these reflexes such as:
   - Vasomotor centre (*vide* Volume 1)
   - Cardiac centre (*vide* Volume 1)
   - Pupil-dilating centre situated in the medulla, controls the pupil-dilating sympathetic fibres, etc. are discussed in the respective chapters.
4. ***Hormonal control:*** Epinephrine, norepinephrine and also acetylcholine control the autonomic nervous system through the activation of the certain hypothalamic nuclei.

Applied Physiology

Dysautonomia encompasses group of disorders which include multiple system atrophy, postural orthostatic tachycardia syndrome (POTS), autonomic neuropathy and also may lead to autonomic failure. Dysautonomia is most often a type of neuropathy affecting the autonomic nervous system especially the nerves that carry information from the brain and spinal cord to the heart, sweat glands, pupils, and blood vessel bladder, intestines. The patient presents with symptoms of sympathetic and parasympathetic imbalances.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the physiological functions and responses of sympathetic nervous system.
2. Describe the physiological functions and responses of parasympathetic nervous system.

Short Notes

1. Control of autonomic nervous system
2. Dysautonomia
3. Anatomical features of the sympathetic nervous system
4. Anatomical features of the parasympathetic nervous system.

Chapter

112 Hypothalamus

INTRODUCTION

Hypothalamus (basal part of diencephalon)

1. It is the highest centre for the autonomic nervous system (Fig. 112.1).
2. The diencephalon comprises the thalamus and the hypothalamus.
3. The hypothalamus is derived from the basal plate (ala ventralis) of the diencephalon as ventral part of it and forms a complexity of nuclei and fibres which are connected with higher and deeper levels of the central nervous system. So, the hypothalamus is the higher projection centre of visceral afferent impulses.
4. The hypothalamus has got close connection with the hypophysis and is concerned with a complex neurohormonal regulatory apparatus. The posterior lobe of the hypophysis develops from the ventral part of the infundibulum, whereas the anterior lobe of the hypophysis originates from the so-called Rathke's pouch.
5. *Anatomical position of hypothalamus:* The hypothalamus forms the lower part of the lateral and the anterior wall of the third ventricle and is situated at the interpeduncular space somewhat anterior to and below the thalamus. The hypothalamic sulcus separates it from the thalamus. Anterolaterally the hypothalamic sulcus continues in the paraterminal gyrus and the paraolfactory part of the frontal lobe. Anteriorly and medially it is continuous in the optic chiasma and the supraoptic commissures on the floor of the third ventricle. It is seen from the base that the cerebral peduncles and optic fasciculus circumscribe the hypothalamus.

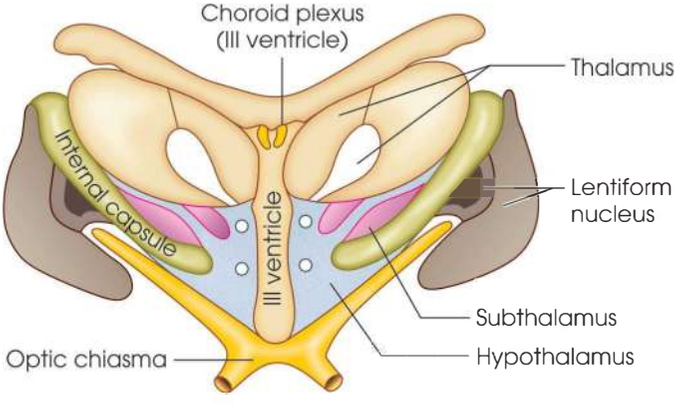

Fig. 112.1: Schematic representation of frontal section through the diencephalon and related structures

NUCLEI OF HYPOTHALAMUS

It consists of following nuclear masses (Fig. 112.2):

Anterior group: In relation with optic chiasma:

1. Medial preoptic nucleus
2. Lateral preoptic nucleus and supraoptic nucleus
3. Suprachiasmatic nucleus and paraventricular nucleus
4. Anterior hypothalamic nucleus.

Middle group: Situated in close relation with infundibulum and tuber cinereum (nucleus tuber):

1. Ventromedial hypothalamic nucleus
2. Dorsomedial hypothalamic nucleus
3. Lateral hypothalamic nucleus
4. Posterior hypothalamic nucleus
5. Arcuate nucleus.

Posterior group: In close relation to the wall of the third ventricle and mamillary body.

1. Nucleus intercalates (Staderini's nucleus)
2. Premamillary nucleus
3. Supramamillary nucleus
4. Medial mamillary nucleus
5. Lateral mamillary nucleus.

Connections of Hypothalamus (Fig. 112.3)

Hypothalamic nuclei receive a number of projections from different parts of the brain.

Afferent

1. *Corticomamillary fibres:* Area 6a and cingulated gyrus (areas 23, 24) project on the mamillary body, and also

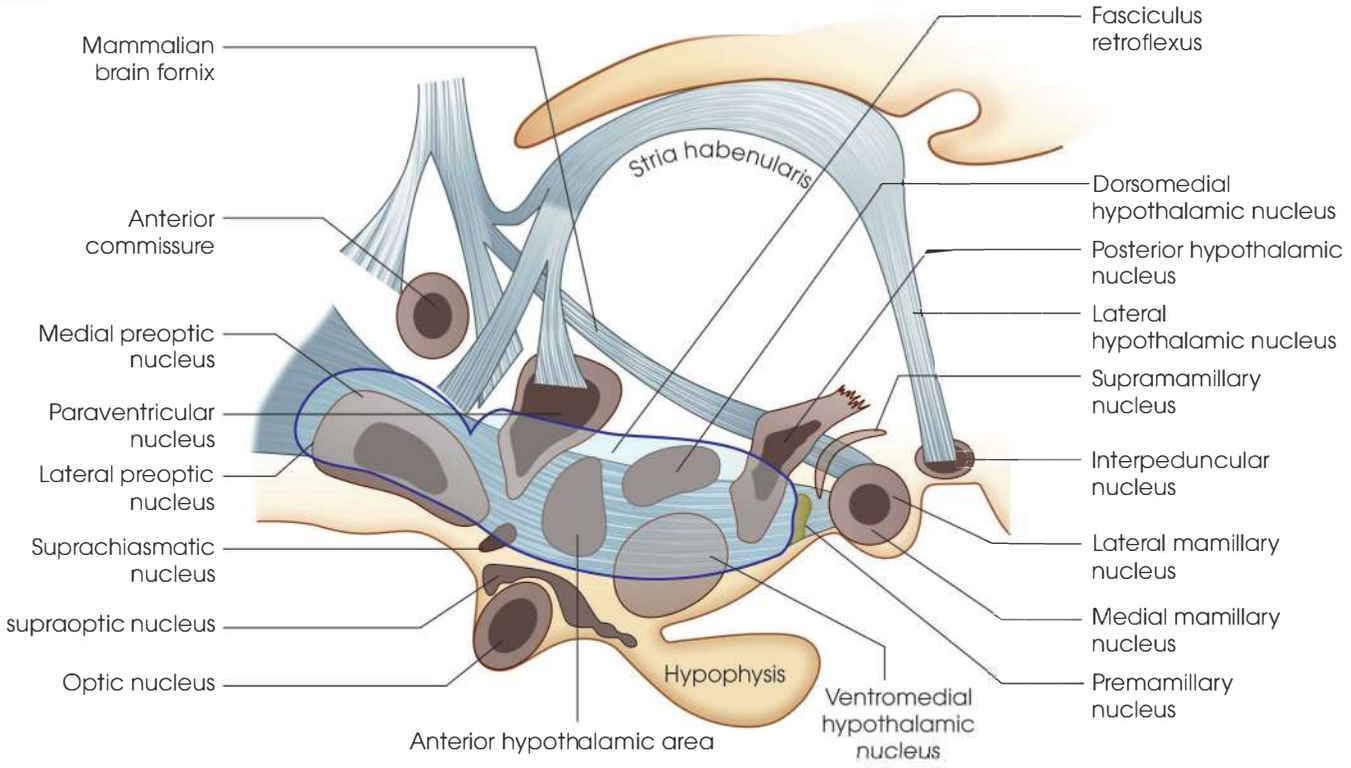

Fig. 112.2: Diagrammatic representation of relative positions of different hypothalamic nuclei (sagittal section) (Le Grass Clark)

the hippocampus to the mammillary nuclei through the fornix.

2. *Fibres from medial thalamic nuclei:* From the dorsomedial thalamic nucleus and also from the midline nucleus to the hypothalamus through the thalamohypothalamic fibres.
3. *Mesencephalic reticular formation:* From the mesencephalic reticular formation to hypothalamus through the reticulohypothalamic fibres.
4. *Olfactohypothalamic fibres:* From the olfactory bulb and the anterior perforated substance to the hypothalamic nuclei through the medial forebrain bundle.
5. *Globus pallidus:* From the globus pallidus to the hypothalamus (pallidohypothalamic tract) via the medial forebrain bundle and the ansa lenticularis.
6. *Precentral motor area:* From precentral motor area 6 and prefrontal areas of the cerebral cortex to the supraoptic and paraventricular nuclei through the corticohypothalamic fibres. Area 6 is also projected bilaterally on the ventromedial nucleus of pars tuberalis. Areas 8 and 10 activate the supraoptic nucleus whereas areas 10, 46 and 47 activate paraventricular nucleus.
7. *Orbital lobe projections:* Area 13, the posterior part of the orbital cortex projects partly on the ventromedial hypothalamic nucleus and also projects on the supraoptic and paraventricular nuclei.

Efferent

The hypothalamus sends in turn, a number of projections to different areas:

1. Mamillothalamic tract—from the medial mamillary nucleus to anterior nucleus of thalamus.
2. To the dorsomedial thalamic nucleus and thence to the areas 11, 12, 10, 9, 8, 45, 46, 47 (Figs 112.2 and 112.3) of the cerebral cortex (periventricular projection).
3. Efferent fibres of hypothalamus are projected mainly to the anteroventral group of the thalamus and thence it is projected to the areas 23 and 24.
4. *Hypophysis hypothalamic hypophyseal tract:* From the supraoptic, paraventricular and tuberal nuclei to the posterior pituitary. Majority of the fibres end in the pituicytes of the pars nervosa. Some fibres also end in the pars intermedia. This connection is made up of a number of very thin unmyelinated fibres which by anastomosis end around capillary vessels of neurohypophysis.
5. From the lateral hypothalamic nucleus to the reticular formation of the tegmentum and autonomic nuclei in the brain stem and lateral horn cells of the spinal cord. Fibres controlling parasympathetic system originate from the middle hypothalamic nuclei. Those for the sympathetic system arise from posterior hypothalamic nuclei.

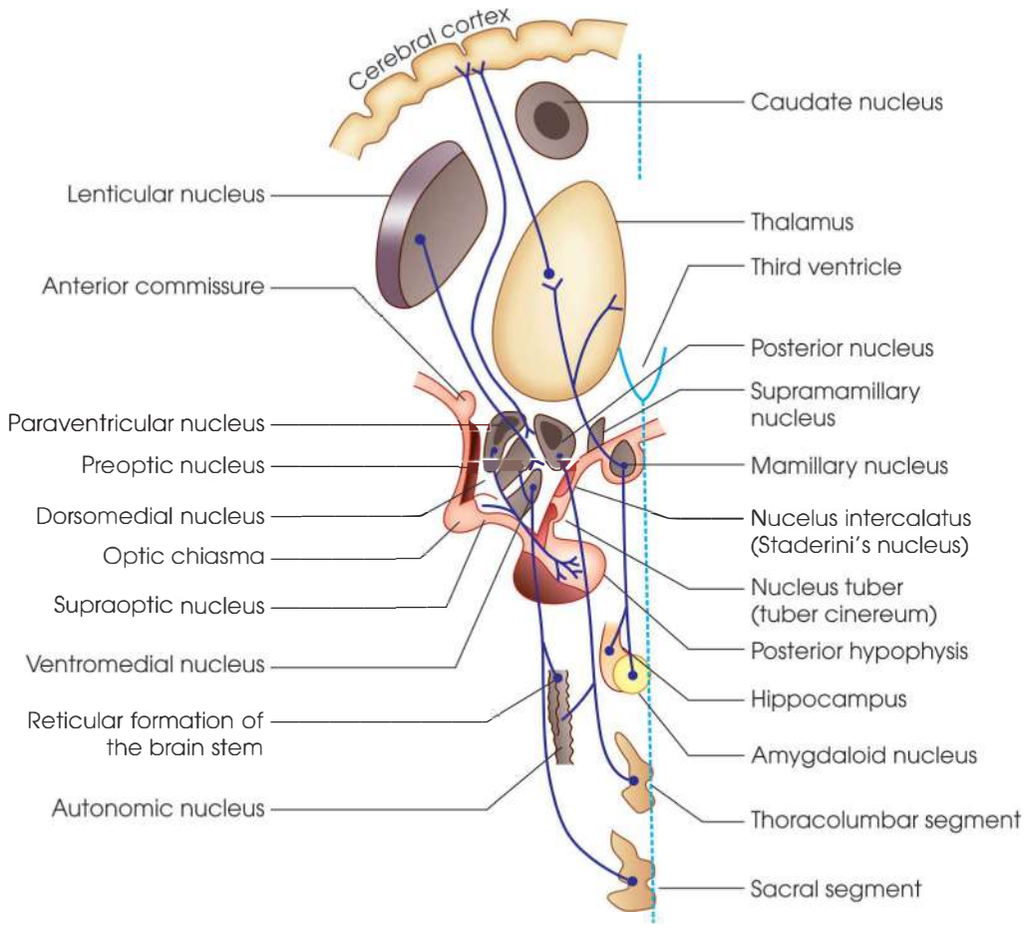

Fig. 112.3: Diagrammatic representation of some connections of hypothalamus. Red—efferent; Black—afferent. Free interconnections also exist between various hypothalamic nuclei

FUNCTIONS OF HYPOTHALAMUS

The functions of the hypothalamus have been studied both by stimulating electrically certain parts of the hypothalamic nuclei or by ablating or making selective lesion of the hypothalamus. The major functions are given below. In general, the posterior hypothalamus contains predominantly sympathetic representation, while the middle and anterior nuclei contain parasympathetic representation. Some of the functions related with those groups of nuclei may appear clear cut, while majority of the functions include complex behavioural and emotional reactions.

1. Controls the Autonomic Nervous System

a. ***Sympathetic nervous system:*** The posterior and lateral nuclei of the hypothalamus are particularly concerned with this function. Stimulation of these nuclei raises blood pressure, increases epinephrine secretion, causes tachycardia, vasoconstriction, dilatation of pupils, inhibition of intestinal movements, etc. Lesions of posterior nuclei produce lethargy, hypothermia and Horner's syndrome. Experimental decortications in animals produce signs of sympathetic hyperactivity. This is a release phenomenon—hypothalamus being released from cortical control.

Controls parasympathetic nervous system: The anterior and middle hypothalamic nuclei are mainly concerned with this function. Stimulation of these nuclei causes parasympathetic hyperactivity, viz. slowing of the heart rate, contraction of pupils, etc. These effects were called by Hess as trophotropic effects and are mediated through trophotropic or parasympathetic system (Fig. 112.4). The trophotropic system is related to protective mechanism. The drugs reserpine and serotonin stimulate the trophotropic system.

2. Takes Part in Regulation of Body Temperature

a. Stimulation of the posterior nuclei of the hypothalamus produces vasoconstriction, shivering, struggling and also raises blood pressure. Lesion of the posterior part of the hypothalamus abolishes shivering, vasoconstriction, etc. and the animal cannot respond to cold and cannot protect itself from the increased environmental temperature.

b. Lesion of the anterior part of the hypothalamus abolishes vasodilatation, sweating, panting, etc.

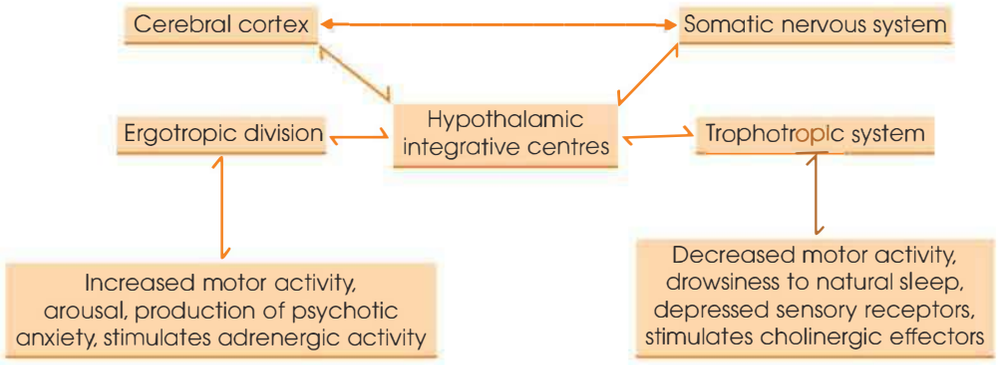

Fig. 112.4: Hypothalamic integrative mechanism indicating a hypothetical balance between ergotropic and trophotropic systems. The degree of behavioural response depends upon the amount and/or frequency of stimulation of that system

when the animal is exposed to high temperature. These experiments prove that the heat-regulating centre is situated in the hypothalamus.

c. *Conclusion:* It is clear from the above observations that there are two separate temperature-regulating centres—one mostly occupying anteriorly and the other posteriorly in the hypothalamus. The anteriorly placed nuclei mostly regulate temperature during overheating by sweating, panting, vasodilatation, etc. and the posteriorly placed hypothalamic nuclei regulate body temperature during extreme cold by shivering, piloerection, vasoconstriction, epinephrine secretion, etc. Thus, the hypothalamus plays as thermostat which maintains normal body temperature by the co-ordinated activities of the above two different systems.

d. It is claimed that for the functions of thermostat mechanisms, two receptive mechanisms are playing. One such is the peripheral cutaneous thermoreceptors which constantly feed impulses to the hypothalamic thermoregulatory centre with the change of environmental temperature. Other such is the centrally located thermodetectors which respond to changes in intracranial temperature.

3. Controls Emotions

Hpothalamus is important reflex centre for emotional expression. Hypothalamus as part of Papez circuit (mamillothalamic tract) and that of limbic cortex influences expression of emotions which is mediated via autonomic nervous system. The cohesive collective and connective role of hippocampus, mamillary body, anterior nucleus of thalamus, parahippocampal gyrus and entorhinal cortex brings over emotions in human.

Experimental Studies

a. Goltz, Britton and Cannon have shown that removal of the cerebral hemispheres and a large part of the thalamus in dogs and cats produced the following phenomena, immediately after recovery from the anaesthesia, i.e. erection of the hairs dilatation of pupils, lashing of the tail, growling, sweating, etc. (Sham rage). Hess has shown that by stimulation of the anterior part of the hypothalamus in animals also causes outbursts of mental excitation (rage phenomenon).

b. Bard found that when the entire cortex was removed, the animals failed to show rage reactions when attacked. Some researchers have found that destruction of the amygdalas produces placid animals, and other researchers have reported that the operation produces savage animals.

c. Limbic structures exert an inhibitory effect over the hypothalamic centre causing rage phenomenon. The rage reactions that occur in the decorticate animal disappear in lesion of the hypothalamus.

4. Related to Hunger Feeding, Obesity and Thirst

a. The satiety center is located in the ventromedial nucleus of thalamus. The lesion in ventromedial nucleus leads to hyperphagia. The stimulation of this area in experimental study found sense of satiety in experiment animal.

b. The lateral hypothalamic nucleus is the known centre for feeding. It is tonically active. Ingestion of food increases activity in satiety centre thereby inhibiting feeding centre.

c. The various theories associated with food intake are:

Glucostatic theory: The glucoreceptors are located in the satiety centre. Increase glucose level post-food intake stimulates satiety centre and which eventually inhibit feeding centre.

Lipostatic theory: The neurons of satiety centre are also stimulated by circulating levels of amino acids and fatty acids. The peptide hormone leptin is a product of fat metabolism. It is mainly produce in the adipose cells. The hormone leptin by its action on its receptor located in arcuate nucleus of hypothalamus decreases neuropeptide Y secretion thereby decreasing food intake. The leptin receptors are located in various

tissues of body and adipose cells. Leptin plays a role in feedback loop controlling the body fat depot. The genetic defecy in leptin receptor is responsible for producing obesity.

Thermostatic theory: Increase in body temperature decreases food intake and vice versa.

Gut peptide theory: The presence of food in gastro-intestinal tract releases cholecystokinin, GRP, glucagon and somatostatin which acts on feeding centre inhibiting them.

Note

The hypothalamic hormones which increase food intake are ghrelin, orexin A and orexin B, neuropeptide Y and melanocyte concentrating hormone while corticotrophin releasing hormone, alpha melanocyte stimulating hormone and cocaine and amphetamine regulated transcript decreases food intake.

5. Controls Circadian Rhythm

The biological clock of day night cycle influences secretions of growth hormone, gonadotrophins, catecholamines, etc. The suprachiasmatic nucleus of hypothalamus synchronizes information received via eyes and lateral geniculate nucleus and is responsible for initiating hormonals and neuronal signals which thus govern the biological clock.

6. Controls Sleep Wakefulness Cycle

The sleep facilitatory centre in hypothalamus is located in venterolateral preoptic nucleus. The neurons release neurotransmitters GABA and galanin. These sleep facilitatory centres which are active during sleep inhibits wakefulness centre. The waking centre is located in tuberomammillary nucleus of hypothalamus. They inhibit the activity of venterolateral preoptic nucleus.

7. Maintenance of Homeostasis

With the help of its functions hypothalamus maintains the physical and chemical constancy (homeostasis of Cannon) of the internal environment. Milieu interieur of Claude Bernard which is essential for the normal life processes of the organism. Just as somatic nervous system adjusts the body against external environment, so the autonomic nervous system combats all forces that try to alter the internal environment and thus, helps to keep the latter constant.

8. Regulation of Water Balance

a. It has been described earlier that hypothalamus plays an important role in the maintenance of water-balance of the body through the liberation of antidiuretic hormone (vasopressin) from the posterior pituitary. The antidiuretic hormone promotes the reabsorption of water through the renal tubules and thus limits the water loss from the body. If the supraoptic nucleus and paraventricualr nucleus or median eminence are damaged, they produce diabetes insipidus—the condition which enhances excretion of water from the body. Antidiuretic hormone secretion is modified under different conditions such as water deprivation, plasma hyperosmolarity, changes in blood volume and pressure, negative pressure respiration, positive pressure respiration, haemorrhage and changes in blood volume.

b. Stimulation of thirst: The decrease in extracellular fluid volume with increased plasma osmolarity stimulates thirst. The decreased extracellular fluid volume stimulates renin-angiotensin-aldosterone secretion which further activates organum vasculosum of lamina terminalis (OVLT) in circumventricullar organ of the brain thereby initiating feeling of thirst and desire to intake water.

c. Beside these, osmoreceptors are present in the hypothalamus within lateral preoptic areas. The receptors are stimulated by the increase of plasma osmolarity (increased blood NaCl concentration). This stimulates the thirst mechanism.

9. Regulation of Posterior Pituitary Gland Activity

Antidiuretic hormone secretion: Hypothalamic nuclei, supraoptic and paraventricular, are connected with the posterior pituitary through unmyelinated hypothalamic hypophyseal tract (Fig. 112.5). Posterior pituitary hormones are formed in the hypothalamic nuclei and transported to the posterior pituitary through the hypothalamic hpophyseal tract. The antidiuretic hormone promotes the reabsorption of water through the renal tubules and thus limits the water loss from the body.

Oxytocin secretion, like ADH, the oxytocin is also secreted from the hypothalamus and thence transported to the neurohypophysis. Oxytocin is important in parturition and milk ejection. Stimulation of supraoptic hypophyseal tract causes liberation of oxytocin.

10. Regulation of Pituitary Gland Activity

Anterior pituitary functions: Regulation of adeno-hypophyseal functions (Fig. 112.6). Hypothalamus being the guardian of the pituitary regulates the secretory functions of the anterior pituitary. It has been reported with substantial evidences that hypothalamic axons which end in the capillary loops in the median eminence liberate multiple hypothalamic hormones or factors.

The hypothalamic regulatory hormones control the secretion of the anterior pituitary hormones (Fig. 112.5). These hormones are:

1. Corticotrophin releasing hormone or factor (CRH or CRF).

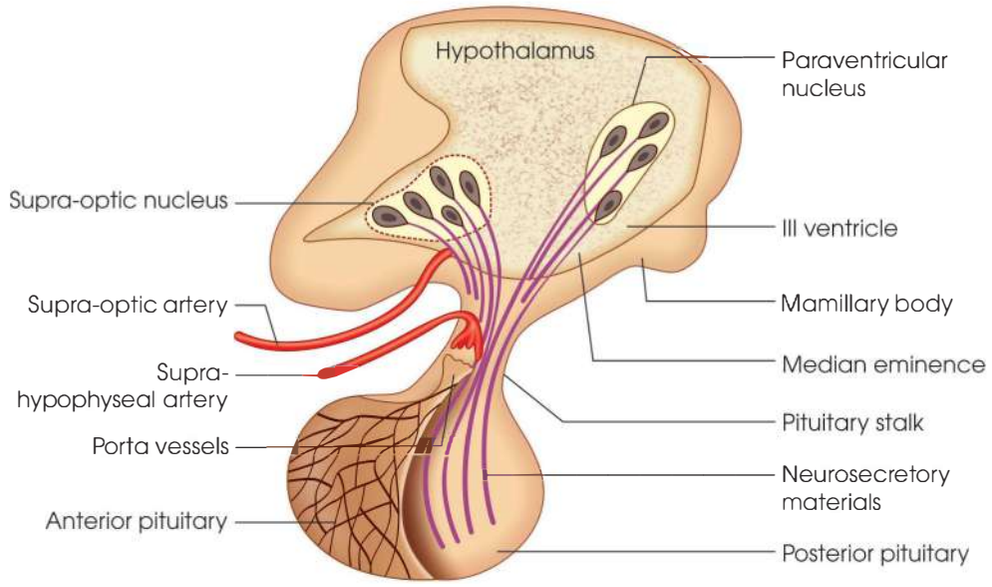

Fig 112.5: Diagrammatic representation of the functional relationship between the hypothalamus and hypophysis

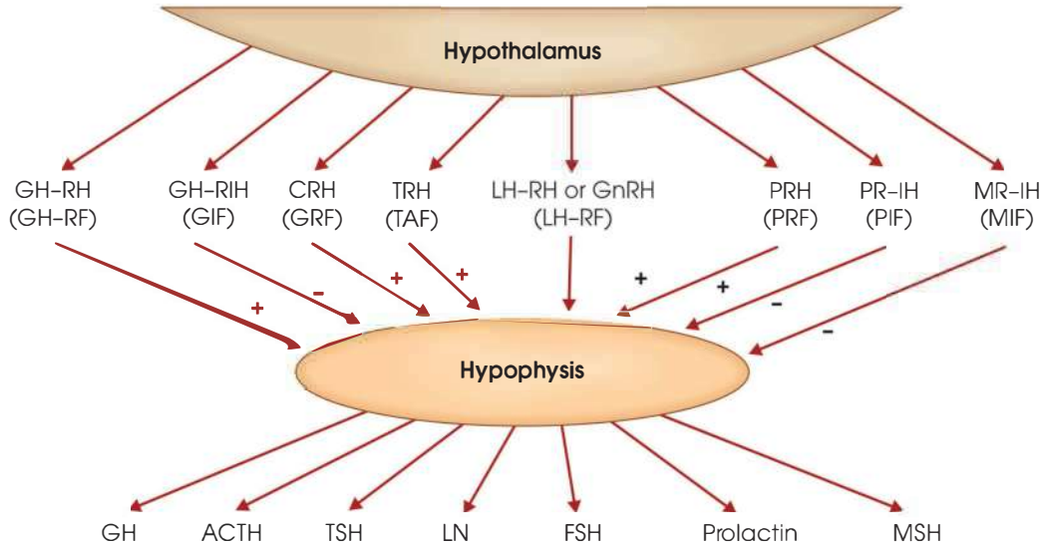

Fig. 112.6: Diagrammatic representation of the functional relationship between the hypothalamus and hypophysis in mammals

2. Thyrotrophin releasing hormone or factor (TRH or TRF).
3. Gonadotropin releasing hormone or factor (GnRH or LH-RH or LHRF).
4. Growth hormone release-inhibiting hormone or factor (GH-RIH or GIF).
5. Prolactin release-inhibiting hormone or factor (PR-IH or PIF). Prolactin releasing hormone or factor (PRH or PRF).
6. Melanocyte-stimulating hormone release-inhibiting hormone or melanocyte-inhibiting factor (MR-IH or MIF).

Hypothalamic lesions have been found to interfere with hypophyseal functions. If the median eminence is damaged so that the vascular link in between the hypothalamus and pituitary is cut off then certain hypophyseal secretory function is permanently lost with the exception of LTH, MSH and SRF which are secreted in large amounts.

11. Cardiovascular Regulation

Hypothalamus being the higher centres of the autonomic nervous system regulates the heart rate, blood pressure, circulation and also takes part in vasomotor adjustment under any condition like increased blood pressure, decreased blood pressure, haemorrhage, hypoxia, etc. Beside these, adaptive cardiovascular adjustment under fear, anger and rage takes place through the hypothalamo-sympathetico-adrenal activity.

12. Relation with Stress through Neurohormonal Mediation

In any condition of stress, hypothalamus plays a prime role in combating the syndrome through the activation of adrenal-pituitary axis. The stress factors may act directly on the hypothalamus and indirectly on the adrenal cortex. The stress syndrome is thus combated through the mediation of hypothalamic-sympathetic-adrenal system and the hypophyseal-cortico-suprarenal system (Fig. 112.7).

Applied Physiology

1. *Hypopituitarism*

The hypothalamus and pituitary gland have integrative role in physiological functioning of the human body. Hypothalamic disease, damage to hypothalamus or lesions in hypothalamus may affect the secretion of following hormones: Growth hormone thyroid-stimulating hormone, adrenocorticotropic hormone, follicle-stimulating hormone, beta-endorphin, luteinizing hormone, and melanocyte-stimulating hormones. The hypopituitarism is treated with hormone replacement therapy.

2. *The Common Causes of Hypothalamic Dysfunction*

1. Birth defects (e.g. holoprosencephaly, septo-optic dysplasia)
2. Genetic disorders (e.g. Prader-Willi syndrome, growth hormone deficiency)
3. Tumors (e.g. craniopharyngiomas, gliomas, ependymomas, germinomas, meningiomas and gliomas of the optic nerve)
4. Head trauma (due to injury, birth trauma, etc.)
5. Secondary to malnutrition
6. Exposure of cranium to radiation
7. Surgical complications
8. Autoimmune disorders (e.g. sarcoidosis)

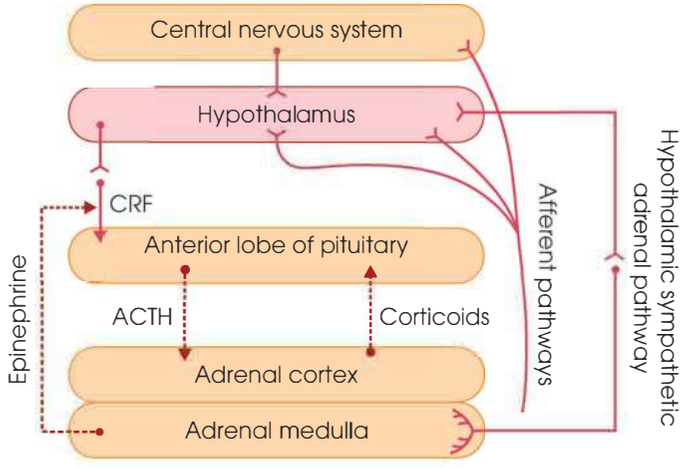

Fig. 112.7: Schematic representation of interactions of hypothalamus, anterior pituitary and adrenal medulla

Recent Advances

Hypothalamus and Odour Response

The research study conducted by Berglund, Lindström, and Savic using positron emission tomography (PET) in 2004 and 2006 revealed hypothalamus response to smelling common odours, the scent of testosterone found in male sweat, and the scent of estrogen found in female urine. The hypothalamus of both homosexual females and heterosexual males respond to estrogen while the hypothalamus of both homosexual males and heterosexual females responds to testosterone. Moreover, the hypothalamus of all four groups illicited no response to the common odours, which generates a normal olfactory response in the brain.

Nobel Prize in Physiology or Medicine 2017

Jeffrey C. Hall, Michael Rosbash and Michael W. Young received the Nobel Prize in Physiology or Medicine for 2017 for their discoveries of molecular mechanisms controlling the circadian rhythm.


Jeffrey C. Hall


Michael Rosbash


Michael W. Young

Reference

"The 2017 Nobel Prize in Physiology or Medicine—Press Release". The Nobel Foundation. October 2, 2017.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the hypothalamic connections. Discuss the functions of hypothalamus.

Short Notes

1. Role of hypothalamus in feeding and satiety.
2. Role of hypothalamus in regulation of posterior pituitary gland activity
3. Role of hypothalamus in regulation of anterior pituitary gland activity
4. Circadian rhythm
5. Common causes of hypothalamic dysfunction
6. Role of hypothalamus in regulation of body temperature
7. Role of hypothalamus in thirst mechanism
8. Hypopituitarism

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Chapter

113

Neurosecretion

INTRODUCTION

Modern Concept of Neurosecretion

The modern concept of neurosecretion has come from the studies on the vertebrate hypothalamo-neurohypophyseal complex (HNC). According to the definition neurosecretions are neurohormones, polypeptide in nature and are sequestered within membrane bound vesicles of diameter greater than 1000 Å. Electron microscopic studies have revealed the presence of electron dense granules—the neurosecretory granules (NSG) having diameter 1000 to 3000 Å. Neurosecretory material is the aggregates of neurosecretory granules. The cell body of the neuron synthesises and packages the neurohormones within NSG. The neurosecretory granules are aggregated into neurosecretory materials and transported through the axoplasm along the axon to the region of the nerve terminals and are discharged into the bloodstream.

Nature of Neurosecretory Cells

Neuronal characteristics: The neurosecretory cells are nothing but specialized neurons having the ability to synthesise and to secrete hormones. Like ordinary neurons there are axons and dendrites extensively developed endoplasmic reticulum, Golgi complex, neurofibrils, etc. But these cells do not have synaptic connections with other neurons.

Glandular characteristics: The neurosecretory cell is an endocrine cell directly involved with the control of endocrine activity. The glandular characteristic of the cell is due to direct contact of the cell apex with the basement membrane through which secretory materials are discharged out. Like other endocrine cells (pancreas, pituitary), these cells are capable of synthesizing protein hormones and thus are well equipped with the organelles taking active part in synthesizing the protein for the hormones. These organelles—the endoplasmic reticulum and Golgi bodies are well developed. Thus, the neurosecretory cells differ from the ordinary neurosecretory cells by the presence of electron dense materials with Golgi membranes.

Significance of Neurosecretory Cells

The fundamental significance of the neurosecretory cells is the final common path upon which a vast array of neural information is channelled to endocrine organs and by which neural inputs are translated into endocrine function. Bodily systems such as somatic and visceral system are under the dual control of the nervous system and endocrine system. The endocrine system is the effector arms of the nervous system and the functional status of the endocrine system is under the control of the nervous system.

EXAM-ORIENTED QUESTION

Short Notes

1. Nature of neurosecretory cells
2. Significance of neurosecretory cells

Chapter

114

Cranial Nerves

INTRODUCTION

There are 12 pairs of cranial nerves arising directly from the brain (Fig. 114.1). These cranial nerves are: I cranial nerves—olfactory, II cranial nerves—optic, III cranial nerves—oculomotor, IV cranial nerves—trochlear, V cranial nerves—trigeminal, VI cranial nerves—abducens, VII cranial nerves—facial, VIII cranial nerves—vestibulocochlear or acoustic, IX cranial nerves- glossopharyngeal, X cranial nerves-vagus, XI cranial nerves—spinal accessory, and XII cranial nerves are hypoglossal (Table 114.1).

Among the cranial nerves described above, the olfactory, optic and vestibulocochlear are sensory in function, the hypoglossal and spinal accessory are motor in function, and the oculomotor, trochlear, trigeminal, abducens, facial, glossopharyngeal and vagus are motor and sensory in functions for anatomical positions of different cranial nerve nuclei.

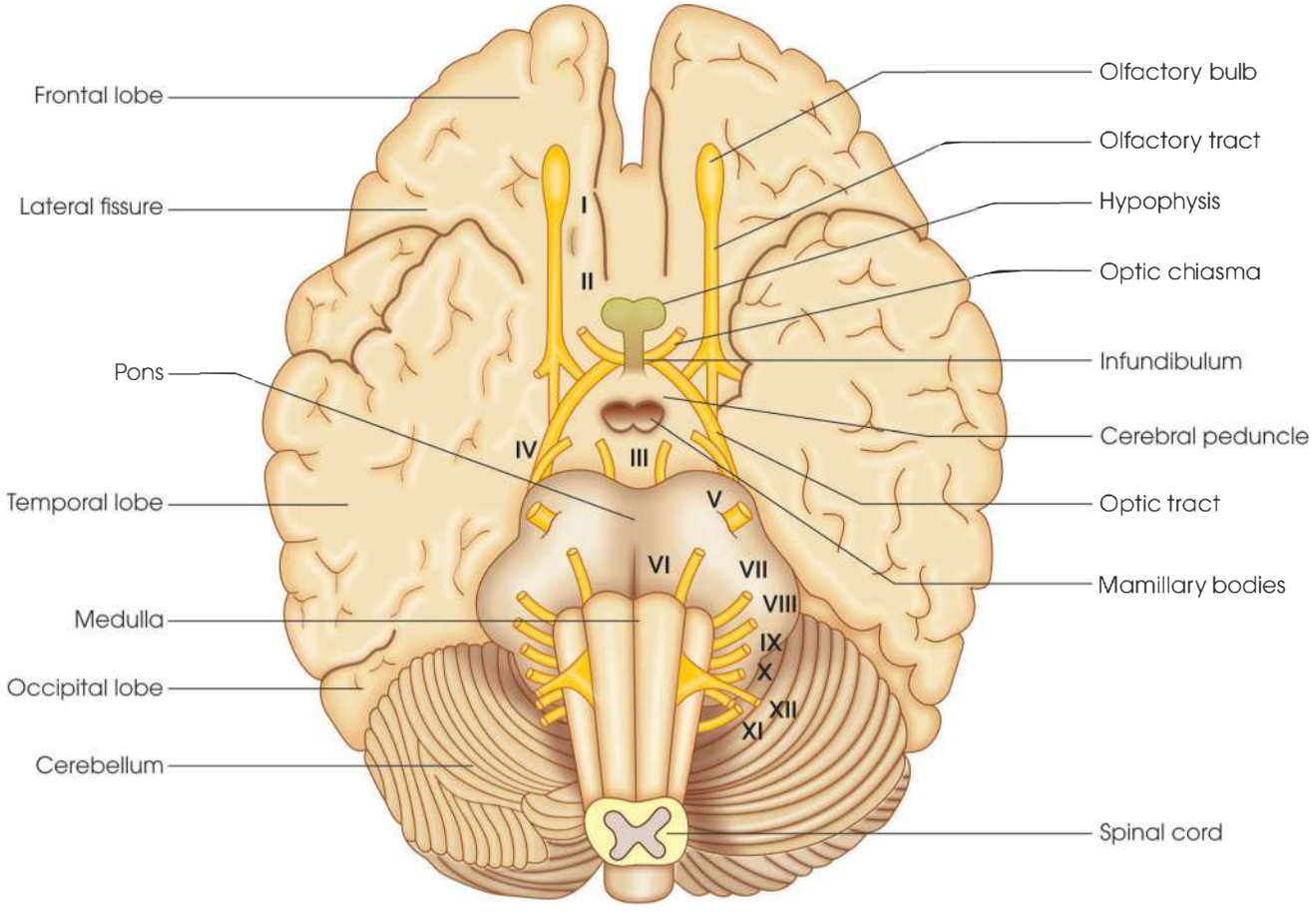

Fig. 114.1: Diagrammatic representation of the undersurface of the brain. The numerals show the cranial nerves

Table 114.1: Origin, innervation and function of cranial nerves

Common name (modality)	*Components or types of fibres*	*Origin*	*Organs innervated*	*Central connection*	*Functions*
I—Olfactory	• Special somatic sensory (afferent)	• Nasal mucous membrane	• Olfactory epithelial cells	• (i) Olfactory bulb (ii) Parts of rhinencephalon	• Sense of smell
II—Optic	• Special somatic sensory (afferent)	• Ganglionic layer of retina	• Retina	• (i) Lateral geniculate body (ii) Visuosensory cortex (area 17) (iii) Superior colliculus (iv) Pretectal nucleus	• Visual sensation
III—Oculomotor	• Somatic motor (efferent)	• III cranial nerve nucleus	• Medial rectus, inferior rectus and inferior oblique muscles	• Frotnal eye fields (areas 4, 6, 8) and areas 17, 18, 19	• Eyeball movements
	• General somatic sensory (afferent)	• Mesencephalic nucleus of trigeminal nerve and bipolar cells along oculomotor nerve	• Ciliary muscles	• (i) Thalamus, (ii) Gerebellum (iii) Post-central gyrus (areas 3, 1, 2)	• Proprioception of muscles of eyeball
	• General visceral motor (efferent)	• Edinger-Westphal nucleus	• (i) Sphincter pupillae (ii) Levator muscle of upper eyelid (iii) Superior rectus muscle of the eyeball	• Pretectal nucleus and cerebral cortex	• (i) Contraction of pupil (ii) Accommodation
IV—Trochlear	• General somatic sensory (afferent) • Somatic motor (efferent)	• Mesencephalic nucleus of trigeminal nerve and bipolar cells along trochlear nerve • IV cranial nerve nucleus	• Superior oblique muscle of eyeball	• (i) Thalamus (ii) Cerebellum (iii) Post-central gyrus (areas 3, 1, 2) • Middle frontal gyrus (areas 6)	• Proprioception of superior oblique muscle of eyeball • Movements of eyeball
V—Trigeminal (trifacial)	• Special visceral (branchial) motor (efferent) • General somatic sensory (afferent) • Do • Do	• Motor nucleus of V cranial nerve • Trigeminal ganglion • Trigeminal ganglion • Mesencephalic nucleus of V cranial nerve	• Pinna of the ear, lower part of the face, teeth and gums of the mandible • Cornea, ciliary body and iris, acrimal gland, conjunctiva, part of mucous membrane of nasal cavity, skin of eyelid, eyebrow, forehead and nose • Dura mater, forehead, lower eyelid, lateral angle of orbit, upper lip, gums, teeth of upper jaw, mucous membrane and skin of cheek and of nose • Muscles of mastication, mucous membrane of the anterior part of tongue with the lingual nerve	• Pre-central gyrus (area 4) • (i) Thalamus (ii) Post-central gyrus (areas 3, 1, 2) (iii) Nucleus of spinal tract • (i) Thalamus (ii) Principal sensory nucleus of V cranial nerve (iii) Post-central gyrus (areas, 3, 1, 2) • (i) Post-central gyrus (areas 3, 1, 2) (ii) Thalamus (iii) Cerebellum	• Movement of mandible. • Painful and thermal sensibility of skin, of face and scalp, of mucous membrane, of nose and mouth • Tactile and pressure sensibility of skin, of face and scalp, of mucous membrane, of nose and mouth • Proprioception of muscles of mastication

(*Contd.*)

Table 114.1: Origin, innervation and function of cranial nerves (*Contd.*)

Common name (modality)	*Components or types of fibres*	*Origin*	*Organs innervated*	*Central connection*	*Functions*
VI—Abducens	• General somatic sensory (afferent) Somatic motor (efferent)	• Mesencephalic nucleus of trigeminal nerve. Small nucleus beneath floor of IV ventricle. Bipolar cells along abducens nerve • VI cranial nerve nucleus	• Lateral rectus (fibres from III nucleus communicate with VI nucleus to co-ordinate activity of lateral and medial recti of two sides) • Lateral rectus muscle of eye	• (i) Cerebellum. (ii) Post-central gyrus (areas 3, 1, 2) (iii) Thalamus • Middle frontal gyrus (area 6)	• Proprioception of lateral rectus (co-ordination is affected by fibres in medial longitudinal fasciculus) • Lateral movement of the eyeball
VII—Facial	• General somatic sensory (afferent) • Special visceral (branchial) motor (efferent) • Special visceral sensory (afferent) • General visceral motor (efferent)—secretomotor (parasympathetic)	• Geniculate ganglion on the facial nerve • VII cranial nerve nucleus • Geniculate ganglion on the facial nerve • Superior salivary nucleus Lacrimatory nucleus	• External ear and middle ear and mastoid region • Muscles of face, neck, pinna and part of scalp • Taste buds of anterior two-thirds of tongue • Sublingual and submaxillary salivary glands Lacrimal glands	• Post-central gyrus (areas 3, 1, 2). Thalamus Cerebellum • Pre-central gyrus (area 4) • (i) Postcentral gyrus (areas 3, 1, 2) (ii) Thalamus, (iii) Nucleus of tractus solitarius • (i) Nucleus of spinal tract (ii) Nucleus of V cranial nerve	• Proprioceptive (facial muscles, etc.) • Facial expression and elevation of hyoid bone • Taste • Secretion of saliva Lacrimation
VIII—Vestibulocochlear • Cochlear • Vestibular	• Specific somatic sensory (afferent) • Special somatic sensory (afferent)	• Spiral ganglion of cochlea • Vestibular ganglion of internal auditory meatus	• Organ of Corti • Semicircular canals, utricle, saccule	• (i) Auditory cortex (areas 22, 41, 42) (ii) Cochlear nuclei (iii) Inferior colliculus (iv) Medial geniculate body • (i) Cerebellum (ii) Flocculonodular lobe (iii) Vestibular nucleus	• Hearing • Maintenance of equilibrium
IX—Glossopharyngeal	• General visceral sensory (afferent) • Special visceral sensory afferent) • General somatic sensory (afferent) • Special visceral (branchial) motor • General visceral motor (efferent)	• Inferior ganglion • Inferior ganglion • Superior ganglion • Nucleus ambiguus • Inferior salivary nucleus	• Mucous membrane of pharynx and posterior third of tongue • Taste buds of posterior third of tongue • Stylopharyngeal muscles Muscle of palatine tonsil and adjacent part of soft palate carotid body, carotid sinus • Muscles of larynx • Secretory fibres to the parotid gland	• Solitary nucleus • (i) Thalamus (ii) Nucleus of tractus solitarius (iii) Post-central gyrus (areas 3, 1, 2) • (i) Cerebellum (ii) Post-central gyrus (areas 3, 1, 2) (iii) Thalamus • Pre-central gyrus (area 4) • Inferior salivatory nucleus	Sensation for taste • Taste • Proprioception • Elevation of larynx in deglutition • Secretion of saliva

(*Contd.*)

Table 114.1: Origin, innervation and function of cranial nerves (*Contd.*)

Common name (modality)	*Components or types of fibres*	*Origin*	*Organs innervated*	*Central connection*	*Functions*
X-Vagues and cranial root of accessory	• Special visceral sensory (afferent) • General visceral sensory (afferent) • Special visceral (branchial) motor (efferent) • General visceral motor (efferent) • General somatic sensory (afferent)	• Inferior ganglion (nodose ganglion) • Inferior ganglion (nodose ganglion) • Nucleus ambiguus in the medulla • Dorsal nucleus of X cranial nerve • Superior ganglion (jugular ganglion)	• Mucosa of epiglottis • Mucous membrane of larynx, trachea, lungs, oesophagus, stomach, intestine, heart, gall bladder and aortic body • Muscles of pharynx, larynx, trachea, oesophagus, stomach, small intestine, ascending colon, inhibitory fibres to heart, secretory fibres to gastric and pancreatic glands, trachea, spleen, kidneys, liver, pancreas • Mucous membrane of stomach and small intestine • Central cutaneous part of auricle and external acoustic meatus	• (i) Post-central gyrus (areas 3, 1, 2) (ii) Thalamus (iii) Nucleus of tractus solitarius • (i) Nucleus of tractus solitarius (ii) Frontal area • Pre-central gyrus (area 4) • Posterior orbital gyrus (area 13) • (i) Thalamus (ii) Postcentral gyrus (iii) Cerebellum (iv) Nucleus of spinal tract of V	• Taste • Sensation • Swallowing; Phonation; Intestinal or gastric movement; Visceral reflexes for heart and lung • Movements • Cutaneous sensibility
Spinal Accessory	• Special visceral motor (efferent)	• Lateral part of anterior grey column of spinal cord (C1–C5)	• Muscles of neck and shoulder	• Precentral gyrus (area 4)	• Movements of head and shoulder
XII—Hypoglossal	• Somatic motor (efferent)	• Hypoglossal nucleus of XII cranial nerve	• Muscles of tongue	• Precentral gyrus (area 4)	• Movement of tongue

For convenience, the origin, distribution and functions have been presented in the following tabular form.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the origin, distribution and functions of cranial nerves.

Short Notes

1. Describe the origin, distribution and functions of optic nerve
2. Describe the origin, distribution and functions of trigeminal nerve
3. Describe the origin, distribution and functions of facial nerve
4. Describe the origin, distribution and functions of auditory nerve
5. Describe the origin, distribution and functions of hypoglossal nerve
6. Describe the origin, distribution and functions of glossopharyngeal nerve.

CLINICAL CASE SCENARIOS

Central Nervous System

Q1. A 22-year-old male was diagnosed as a case of Wilson's disease. What is cause for the same? What are the clinical features in the disease?

Ans. Wilson disease is a rare, inherited, autosomal recessive metabolic disorder. This disease is characterized by deposition of copper particularly in the brain, liver and cornea. The excess of copper deposition in the brain produces lesions of the lenticular nucleus, including the putamen and pallidum resulting in progressive rigidity, intention tremor and mental deterioration.

Q2. A 50-year-old male complained of loss of memory, inability to concentrate and remember events and unable to relate person, place and things. What is the diagnosis? What is the cause?

Ans. The patient is suffering from Alzheimer's disease. The cholinergic nerve terminal in hippocampus and cerebral cortex degenerates and causes Alzheimer's disease.

Q3. A 32-year-old male was examined for the motor and sensory changes as he was a case of hemi-section of spinal cord due to traumatic injury. The physician opined that the patient exhibits sighs of Brown-Séquard syndrome. What is the cause for developing Brown-Séquard syndrome?

Ans. Brown-Séquard syndrome results in paralysis and loss of proprioception on same side of lesion and loss of pain and temperature on opposite side of lesion. The causes of Brown-Séquard syndrome are spinal cord tumor, trauma to spinal cord due to gunshot injury of cervical or thoracic spine, infectious disease such as multiple sclerosis or tuberculosis or ischaemic damage.

Q4. A 14-year-old child complained of nausea, giddiness and vomiting after travelling in ship during an entertainment visit to the beach shore. What kind of sickness is the child suffering after travelling in ship? What is the reason for the same?

Ans. The child is suffering from seasickness. The ship vowels and due to irregular movements and sea saw movements due to turbulence stimulate the labyrinth extensively producing seasickness and the observed symptoms.

Q5. CT scan and MRI imaging revealed blockage of posterior cerebral arteries in the thalamo-geniculate branch. What are the signs and symptoms will be observed in such cases?

Ans. The blocked thalamo-geniculate branch of posterior cerebral arteries may lead to loss of kinaesthetic sensation. Hyperreactive response to any pain inducing stimulation with loss of tactile localization, discrimination and stereognosis are the signs and symptoms observed in such cases.

Q6. An 18-year-old student was punished for regularly sleeping in classes. Later he was diagnosed as a case of narcolepsy. Describe this clinical condition.

Ans. This is a disease in which there is uncontrolled urged to sleep during the day and aetiology for it is not yet known.

Q7. A 60-year-old male presented to the medical specialist with signs of flexion attitude, pill rolling movement of thumb over fingers, resting tremor, mask-like face and festinating gait. What is the likely diagnosis? What is the cause for the same?

Ans. The patient is suffering from Parkinson's disease. The degeneration of globus pallidus and or substantia nigra leads to decreased dopamine secretion in the nigrostriatal systems leading to signs and symptoms of Parkinson disease. This disease is also known as paralysis agitans.

Q8. A 24-year-old male medical student was having BMI 30 and was identified as obese during medical check up. Genetic study in patient revealed abnormality in leptin receptor gene. Discuss the role of leptin in obesity.

Ans. Leptin which is secreted from brown adipose tissue and other tissues of body decreases the release of neuropeptide Y from hypothalamus. The neuropeptide Y acts on satiety centre and thereby decreases intake of food physiologically.

Q9. A 51-year-old male patient was diagnosed as case of locked in syndrome. Explain this clinical disease syndrome. What are the causes for this condition?

Ans. The patient of locked in syndrome is in state of total paralysis of the voluntary muscles of body except eyes but is in conscious state. The few likely causes for development of locked in syndrome are traumatic

brain, amyotrophic lateral sclerosis, poisoning due to neurotoxic venous, multiple sclerosis, etc.

Q10. A 10-year-old female patient was diagnosed as a case of Tourette syndrome. Explain the basis of this disorder.

Ans. Tourette syndrome is a neuropsychiatry inherited disorders which occurs in children and manifest as motor tics and phonic verbal tics. These ticks may be provisional, transient and persistent. The exact aetiology of disease is not yet known.

Q11. A 21-year-old male was diagnosed as a case of fatal familial insomnia. What is the cause for the disorder?

Ans. Fatal familial insomnia is disorder in which there is degeneration of thalamus and patient progressively finds it difficult to sleep leading to condition of total insomnia and death. It is also called prion's disease.

Q12. Differentiate between Friedreich ataxia and spinocerebellar ataxia.

Ans. *Friedreich ataxia:* It is an autosomal recessive disorder due to gene mutation especially in the gene code of mitochondrial protein fraxin. The reduced levels of fraxin lead to impaired mitochondrial function and iron overload in mitochondrion. The clinical features of the disease include unsteady gait, upper extremity ataxia, paresis and dysarthria.

Spinocerebellar ataxia is autosomal dominant disorder affecting numerous locations of peripheral and central nervous system. The clinical symptoms include ataxia, dystonia, facial twitching, parkinsonism, ophthalmoplegia and bulging of eyes.

Q13. Identify a clinical disorder which is genetic, an origin and associated with lack of sense of smell and failure to start or complete puberty.

Ans. This clinical disorder is Kallmann syndrome and is due to failure of hypothalamus to release gonado trophin releasing hormone.

Sir Charles Bell was an anatomist, neurologist, and philosophical theologian. He is noted for discovering the difference between sensory nerves and motor nerves in the spinal cord. He is also noted for describing Bell's palsy.

Sir Charles Bell
1774–1842

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Grzybowski, Andrzej; Kaufman, Matthew H. (2007). "Sir Charles Bell (1774–1842): contributions to neuro-ophthalmology". Acta Ophthalmologica Scandinavica. 85 (8): 897–901.

Nobel Prize in Physiology or Medicine in 2014: Space representing cell and positioning system in the brain.

John O'Keefe, an American-British neuroscientist shared the Nobel Prize in Physiology or Medicine in 2014 together with May-Britt Moser and Edvard Moser for their work regarding the grid cells in the entorhinal cortex, as well as several additional space-representing cell types in the same circuit that make up the positioning system in the brain. John O'Keefe is also known for his discovery regarding specialized brain networks for memory and cognition". Moser discovered types of cells that which are vital for determining position (spatial representation) close to the hippocampus, an area located in the centre of the brain.

John O'Keefe
1939

May-Britt Moser
1963

Edvard Ingjald Moser
1962

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O'Keefe J, Burgess N. Geometric determinants of the place fields of hippocampal neurons". Nature. 1996; **381** (6581): 425–428.
Moser E.I. and Moser M.B. Seeing into the future. Nature. 2011; 469:303–4.

Stanley Benjamin Prusiner
1942

Prion Research 1998 Nobel Prize for Physiology and Medicine
Stanley Benjamin Prusiner an American neurologist and biochemist received 1994 Nobel Prize in Physiology or Medicine in 1997 for prion research. A **prion** is an infectious agent composing of protein material, called PrP (prion protein) fold in multiple, structurally distinct ways at least one of which is transmissible to other prion proteins, leading to disease. They are suspected to be the cause of transmissible spongiform encephalopathies (TSEs) among other diseases.

Reference
Prusiner SB. Molecular biology of prion disease. Science. 1991; 252 (5012): 1515–1522

Section

XI

Special Senses

Chapter

115

Introduction to Special Senses

INTRODUCTION

To fight out the environment, general sensations are essential but not enough; because unless the offending agent actually falls on the body, general sensations will fail to give any information to the organism. Hence, a special information service must be created, by which the existence of an object may be known from a distance. Out of this necessity the special senses evolved.

The organs of special senses have got special end organs for the reception of specific types of stimuli. The sense impressions are carried by sensory nerves to the brain where the sensation is received and interpreted. The particular type of sensations is carried by the sensory nerve from each specified organ. There are five varieties of special senses, viz.

1. Taste
2. Smell
3. Vision
4. Hearing

The first two are collectively known as chemical senses. The senses like balance, kinaesthetic sensation, pain and temperature are other modalities of senses.

GENERAL CHARACTERS

All are located in the head. Two advantages:

1. Better protection.
2. Quicker response—being nearest the centre.
3. It is subserved by special receptive apparatus; Situated in special regions and; is highly developed.
4. Fine discriminations are possible.
5. Greater part of the impulse goes to cerebral cortex and is conscious. A small part used for reflex purposes.
6. Excepting taste, all are projected outside the body, onto the source of the impulse. Such as, light is localized not on the retina but on the luminous object. Sound is localised not on the ear but on the source of the sound. Obviously, taste is an exception to this rule.

TASTE (GUSTATION)

The senses of taste and smell are closely interrelated and there is probably no such thing as a pure taste. They are mainly concerned with nutrition. In the nose and mouth, common chemical sensibility is closely associated with senses of smell and taste respectively. For example, smells of the vapours of onions are caused by stimulation of the olfactory apparatus and by stimulation of the V nerve endings subserving common chemical sense. Sensation of taste does not evolve solely from the stimulation of taste buds. It is also due to sensation of common senses like heat, cold, touch and especially of olfaction. In the absence of olfaction taste sensation is remarkably altered. Discrimination of taste is attributed to the palate by the help of olfaction. Flavour is the complex sensation of taste, odours, hotness or coldness, pungency or blandness, roughness or smoothness.

Tongue is mainly concerned with taste sensation. Taste buds are the end organs of taste.

Primary Taste Sensations (Fig. 115.1A)

Four primary tastes:

1. Sweet
2. Bitter
3. Sour (acid)
4. Salt

Some hold that there are two others:

1. Metallic
2. Alkaline

Taste sensations often become complicated due to three factors:

- Blending of two or more primary tastes
- Blending with general sensations in the mouth
- Blending with the sensation of smell.

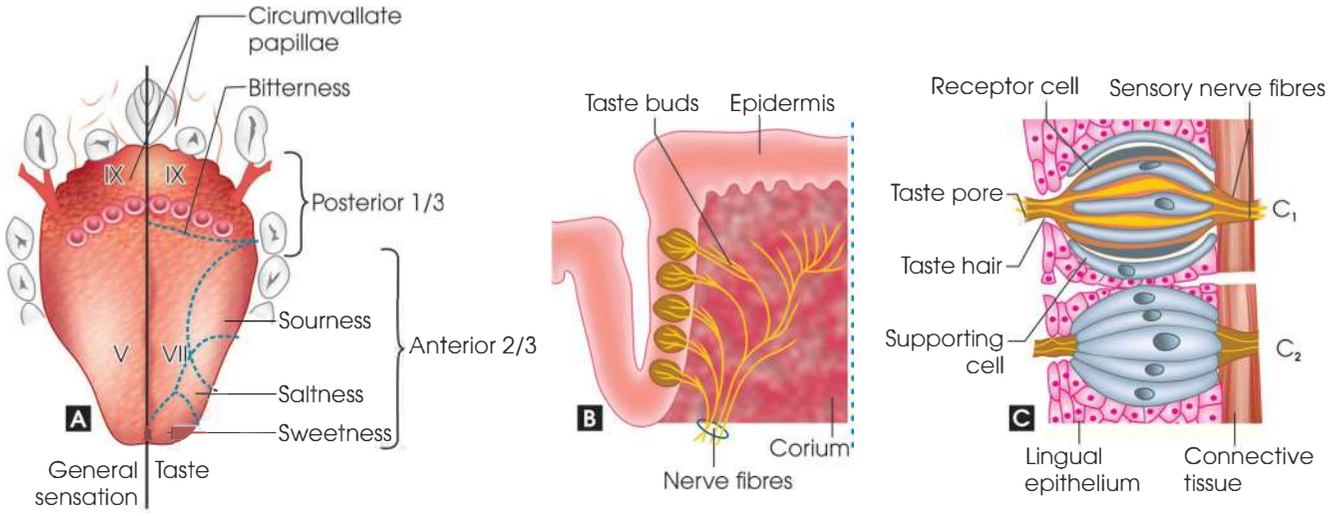

Fig. 115.1A to C: (A) Diagrammatic representation of chief distribution of primary taste sensations on different areas of tongue. Impulses from taste receptors carried by V, VII and IX cranial nerves. The sides and tip of the tongue are served by facial (VII) and trigeminal (V) nerves, whereas glossopharyngeal (IX) nerve serves the back and sides; circumvallate papillae cut lengthwise, (B) depicts nerve innervations to the taste buds; C1 and C2 depict sectional representation of taste bud showing taste cell, (C) taste pore and taste hair that protrude from the free surface of the taste cell

TONGUE

Papillae and Histology of Tongue

Discussed under general outline of digestive system.

Taste Buds

Taste buds are the end organs of taste. These are located in the mucosa of the epiglottis and pharynx and in the lateral walls of the fungiform and vallate papillae of the tongue. There are about 10,000 taste buds in man. In old age it decreases in number.

Histology

They are oval, about 70 µm long and 50 µm broad, with the long axis perpendicular to the surface. Vessels and nerves enter through the bottom.

Taste buds were formerly classified into two—gustatory or taste cells and supporting or sustentacular cells on the basis of shape, size and staining properties. But recent electron microscopic studies have shown that many of the cells are transitional in character and this is due to different stages of development of the taste buds. The taste cells are developed from the epithelial cells around the taste buds and during the process of maturity the cells thus migrate towards the centre of the bud and then degenerate. Each taste cell has got microvilli that are projected in the taste pore.

Each bud contains a number of receptor cells whose apical tips project through a pore in the surface epithelium. Nerve fibres enter the base of the taste bud, lose their myelin sheaths and either invaginated the receptor cells or lie between them.

Distribution

Taste buds are located mainly on the tongue. Circumvallate and fungiform papillae contain taste buds. Taste buds are also located in:

1. Soft palate
2. Pharynx, epiglottis
3. Inner surface of arytenoid process
4. Anterior pillars of fauces, etc.

Varieties

Probably there are as many varieties of taste buds as there are primary taste sensations.

Proof: Based on experimental studies

Differential distribution of taste on the tongue:

1. Decoction or chewing the leaves of Gymnema Sylvestre selectively abolishes at first the sweet and then the bitter sensations, leaving sour and salt unaffected.
2. Cocaine abolishes at first the bitter, then sweet, then salt and lastly the sour.
3. Some substances produce different taste sensations according to the area of tongue stimulated, e.g. magnesium sulphate tastes salty in front but bitter behind.
4. *Action potentials:* Three types of nerve fibres were identified in the cat by Pfaffmann. Action potentials were detected only when acid, salt and bitter substances were placed over the tongue. Other workers recorded action potentials when sweet substances were placed over the tip of the tongue.

Nature of Stimuli

The substance to be tasted must be in solution. Normally saliva acts as the solvent.

Receptor Stimulation

Taste receptors are considered as chemoreceptors that respond to substances dissolved in the oral fluids bathing them. Receptors have microvilli covered with a polyelectrosurface film. Binding of ions to this film causes a distortion of the film with initiating the generator potential which would in turn depolarise the sensory nerves. The sensation of taste is mediated by nerve fibers which innervate the taste buds. The anterior two-thirds of the tongue is innervated by the lingual nerve and the posterior third of the tongue is supplied by the glossopharyngeal nerve.

Basic Modalities of Taste

There are about four basic modalities of taste, viz. sweet, sour, bitter and salt. Sweet chiefly at the tip, salt on the dorsum anteriorly, sour at the sides, and bitter at the back of the tongue (Fig. 115.1A). Mid-dorsum has got no taste sensation. The taste buds in each of these areas are not histological different from those in other areas.

Electrophysiological studies have shown that the taste receptor cells do not always belong to basic types corresponding to the basic taste qualities. Individual sensory cells are differentially sensitive to chemicals as for instance a receptor cell can be excited by low concentrations of sodium chloride or by high concentrations of sucrose. Thus, any taste cell is capable of stimulation to a varying degree by different chemical stimuli.

Chemical Constitution Related to Taste

Sweet taste is caused by some organic compounds, e.g. sugars, certain polysaccharides, alcohols, aldehydes, ketones, saccharine, chloroform, etc. But certain inorganic substances also arouse sweet sensations, e.g. lead acetate, highly diluted alkalis, etc. It is proven that every sweet substance possesses two radicals. One is called glucophore and the other auxogluc. Any stuff having both the radicals will taste sweet.

Salty taste is caused by inorganic compounds, such as chlorides, sulphates, bromides, iodides, etc. The saline sensation is attributed to the anions of these compounds. Certain organic compounds also give saline taste, e.g. hydrochlorides of monomethyl and dimethyl amine.

Sour taste is caused by acids or acid salts. It is attributed to the hydrogen ion concentration upon which the acidity depends. Curiously enough, certain organic acids (with a little ionisation), such as acetic acid, has more acid taste than mineral acids, e.g. HCl. This is due to greater power of penetration of acetic acid.

Bitter taste is caused by some organic compounds, such as alkaloids (strychnine and quinine), certain glucosides, bile salts, etc. Some inorganic substances also produce bitter taste, e.g. salts of magnesium, ammonium and calcium. The bitterness of these inorganic compounds is attributed to the cations, that of the organic compounds is somewhat related to the NO_2 group.

Threshold of Primary Taste Sensations

It is the minimum concentration of different substance necessary to arouse a primary taste sensation. Taste buds are most sensitive to bitter and least to salt. The threshold concentration, for HCl is at a pH of about 4 and for NaCl the least concentration is about 0.12%. (0.02 M). On the other hand, for strychnine the threshold concentration is about 0.00006% and the least concentration of cane sugar is about 0.5%, but for saccharin is only about 0.001%.

Successive Contrast

After taking bitter, sweet taste is enhanced. So, the bitter taste enhances the sweet taste sensation. Similarly, sweet taste enhances the bitter taste sensation.

Simultaneous Contrast

After applying salt on one border of the tongue, other border of the tongue becomes hypersensitive to sweet.

Factors Influencing Taste Sensations

Area

Intensity of taste sensation depends upon the total surface area stimulated, as for instance stimulation of a single papilla by a drop of solution produces weaker sensation that does tasting of the same solution by the whole of tongue.

Temperature

Taste sensation is modified with temperature and in a range of 30°–40°C maximum sensation is observed.

Olfaction

Taste sensation depends upon olfaction. In condition of diseases of olfactory receptors, the acuity of taste sensation is defective.

Individual Variation

There is individual variation of taste sensation. A concentration of a substance which can be tasted by one individual may not be detected by another. These differences are usually quantitative but can be qualitative.

The most interesting example of qualitative variation is the ability to taste PTC (phenyl thiocarbamide). The human race can be divided into those who cannot taste this at all and those to whom it tastes sour. The ability to taste it is inherited as a Mendelian recessive trait.

Adaptation

Taste sensation is quickly adapted and threshold of stimulus for a particular substance is increased. As for instance after taking sweets if anyone takes tea with usual sugar then the sweet sensation is somewhat decreased.

Path of Taste Impulses

From anterior two-thirds of tongue taste sensations are carried by the VII cranial nerve, from posterior third by the X cranial nerve (Fig. 115.2).

1. From the anterior two-thirds, the sensory taste fibres first enter the lingual nerve, then the chorda tympanic branch of the facial (VII) nerve and then join the trunk of the facial in the aqueductus Fallopius. Their cell station is situated in the geniculate ganglion (first-order neurone). The axons of these cells enter the pars intermedia and end in the dorsal nucleus of the VII cranial nerve (upper part of the nucleus of tractus solitarius). The chorda tympani also contain efferent fibres for salivation. The taste sensations are carried by VII cranial nerve. From the region of anterior 2/3rds of the tongue the general sensations are carried by V cranial nerve.
2. From the posterior third, including the vallate papillae, taste fibres pass along the glossopharyngeal (IX) nerve and enter their cell station in the petrous ganglion (first-order neuron). The axons of these cells pass along the IX cranial nerve and end in the dorsal nucleus of the IX cranial nerve (lower part of the nucleus of tractus solitarius).

   The greater superficial petrosal nerve supplies gustatory fibres to the palate. Taste buds near the epiglottis are innervated by the vagus.
3. From the nucleus of tractus solitarius, second-order neurons arise, cross the middle line, pass through the medial lemniscus or fillet and end in the posterior ventral nucleus of the thalamus. Here, third-order neurons arise, pass through the posterior limb of internal capsule and end in the inferior part of the postcentral gyrus of the cerebral cortex.

The sensations of touch, hot, cold, pain (common sensibility) are carried by the lingual branch of the V cranial nerve (cell bodies which are situated in the semilunar ganglion) and pursue the similar course and end in the inferior part of the postcentral gyrus.

Electrical stimulation of the inferior part of the postcentral cortex can produce hallucinations of taste and destructive lesions of this area reduce gustatory and tactile sensibility of the tongue. When a taste-evoking substance is placed on the tongue, it (e.g. quinine) produces changes in the electrocorticogram of the inferior part of the postcentral cortex (sensory area).

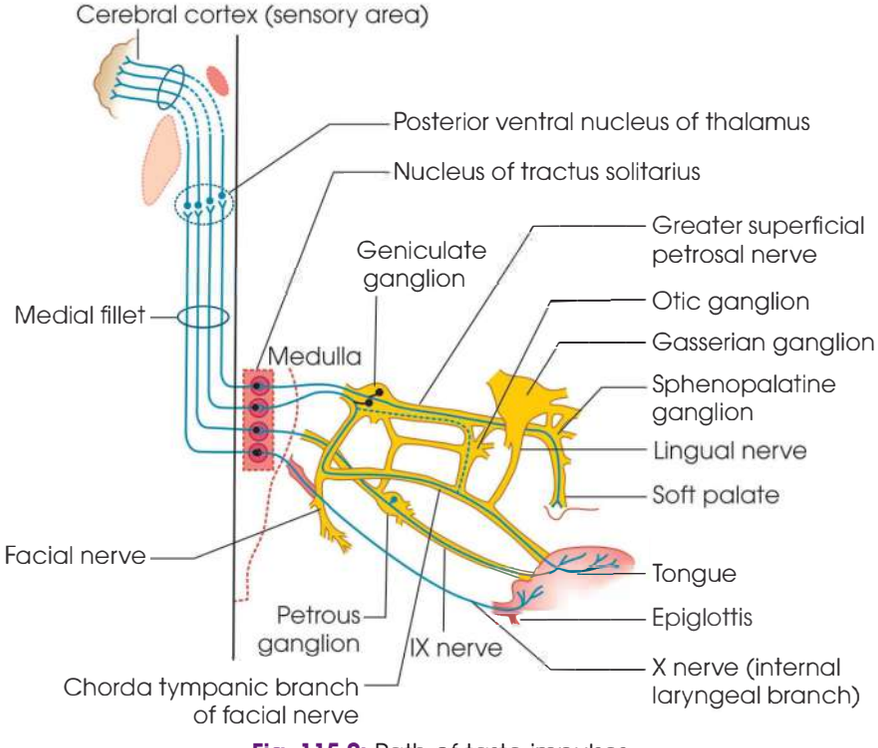

Fig. 115.2: Path of taste impulses

Applied Physiology

1. *Familial Dysautonomia*

There is a widespread familial disorder of sensation, in which the subject cannot identify even a saturated solution of NaCl by taste.

2. *Selective Taste Blindness*

In this case the subject does lose taste sensation of a particular substance and however does not lose completely. Threshold for stimulation is increased. The subject possesses normal taste sensation of other modalities and thus this defect is less selective. Caucasians are affected by this type of disease.

3. *Acceptance and Rejection of Foods*

Taste sensation is also related with food habit. Someone likes sweet and other likes salt. Besides this, certain substances may be accepted or may be rejected. Sweet is mostly accepted by all but the noxious substances are rejected. Acid and salt in mild concentration is accepted but in higher concentration is rejected. Rejection and acceptance are also dependent upon the metabolic states of the individual. Hypoglycaemic patients want to take more sugar. Subject having adrenocortical insufficiency wants much salt.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the various modalities of taste sensation, factors influencing taste sensations and taste pathway.

Short Notes

1. Taste buds
2. Familial dysautonomia
3. Selective taste blindness
4. Path of taste impulses.

Chapter

116

Sense of Smell (Olfaction)

INTRODUCTION

Like taste, smell is also a chemical sensation. For taste, the substance must be in liquid form; for smell it must be in gaseous form. Volatile substances have generally strong odours. After reaching the nose the vapour gets dissolved in the local secretion and stimulates the olfactory epithelium.

Olfactory sensation is the most primitive of all special senses and is much more acute than taste. A man can detect mercaptan and artificial musk in a dilution of one part in several billion parts of air. In many animals the sensation of smell is much more acute than in man. Such animals are called macrosmatic. In macrosmatic animals the olfactory sense plays an important role in protecting the animals from enemies; search for food and in the reactions of sex. In comparison to them man is microsmatic.

Smell sensations are often blended with simultaneous taste and general sensations and thus often become a complex admixture, viz. sweet smell (chloroform), pungent smell (ammonia), etc. An instrument called olfactometer is used to determine the minimum identifiable odour (MIO) of a substance.

Olfactory Mucous Membrane (Fig. 116.1)

The olfactory receptors are located in a small specialised portion of the nasal mucosa which is called the olfactory area. This area differs from the rest of the nasal mucosa both in its gross appearance as well as in its histological structure. The dog is a macrosmatic animal and its olfactory area is large. The human being is microsmatic and his olfactory area is comparatively very small.

Olfactory epithelium: The olfactory epithelium is that part of nasal epithelium which is sensitive to smell and confined to the nasal mucosa of the olfactory area. Smelling sensation is developed mainly from the stimulation of receptors in the yellow brown olfactory mucosa that lines the surface of the superior turbinate and the upper third of the nasal septum. In man, the total area of olfaction on each side is about 250 mm^2. The olfactory area is formed by the superior nasal concha, the upper part of the septum and the roof of the nose (Figs 116.1 and 116.2).

The olfactory epithelium (Fig. 116.3) is composed of mainly two types of cells. These are supporting (sustentacular) cell and receptor cell. There is a third

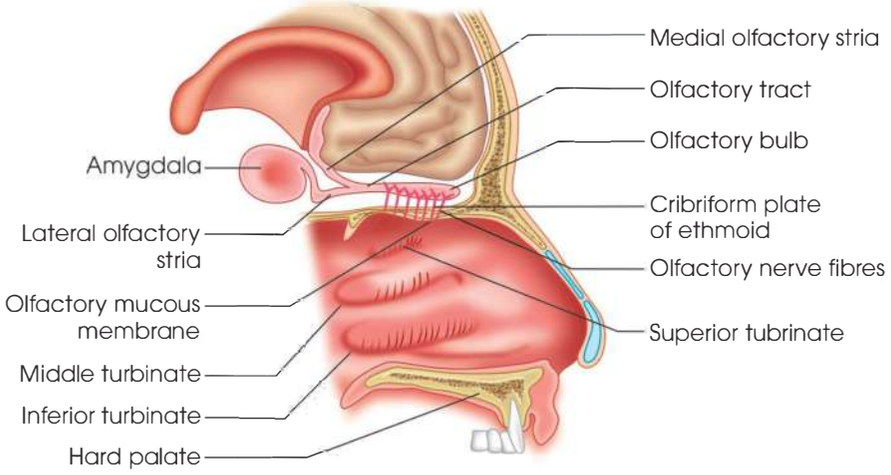

Fig. 116.1: Diagram represents the anatomy of the olfactory mucous membrane

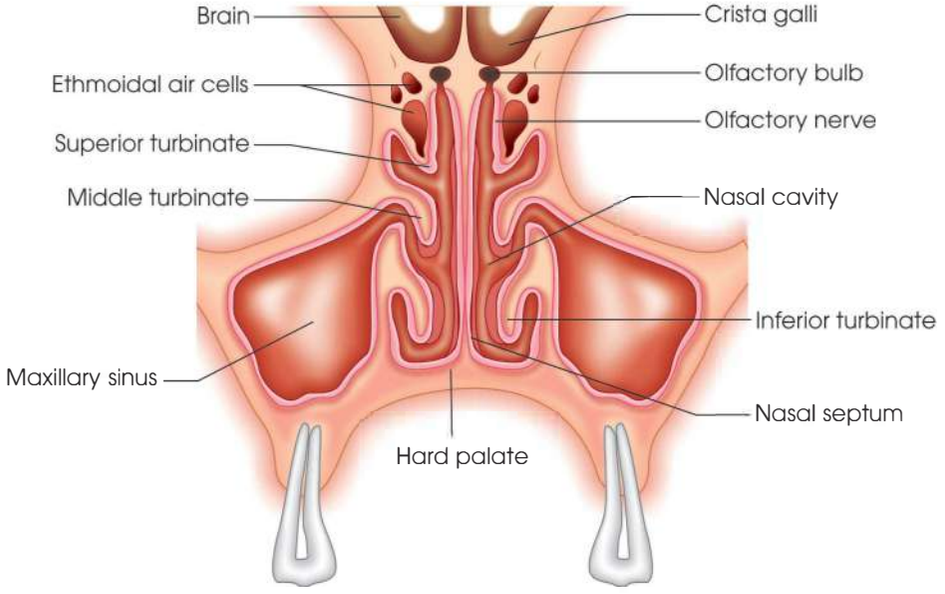

Fig. 116.2: Anatomical position of the receptors for the sense of smell in the interior of the nose in between the median nasal septum and the superior turbinate (Crellmen)

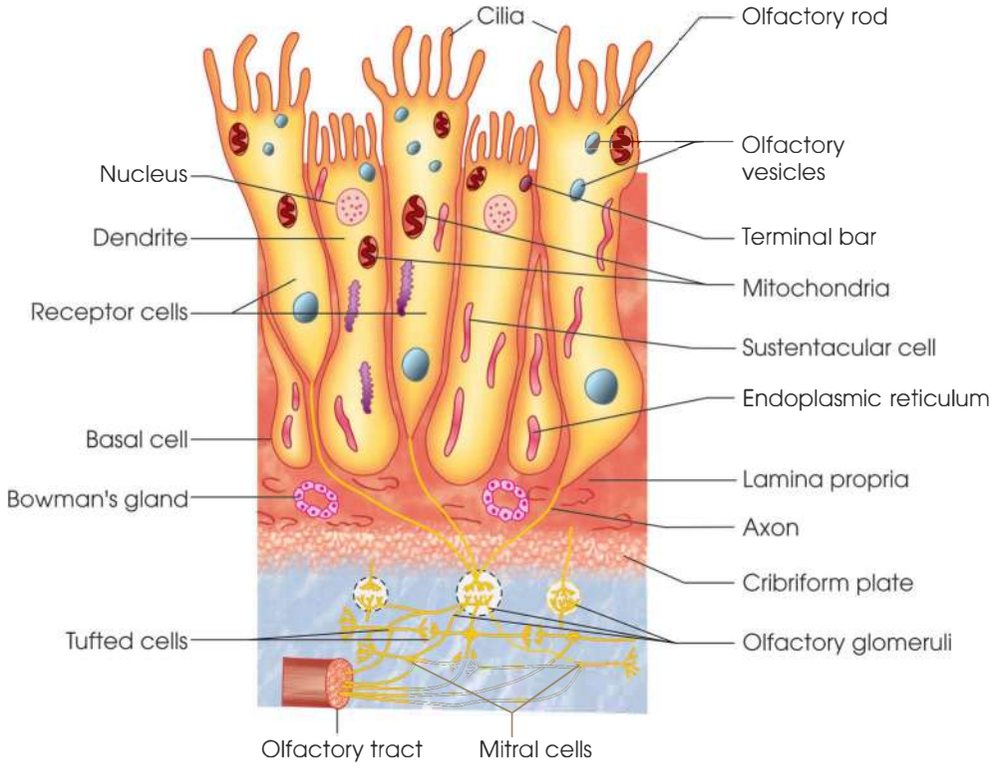

Fig. 116.3: Histological representation of the olfactory epithelium and connections of olfactory nerve fibres (diagrammatic)

type of cell which is called the basal cell. This basal cell is not numerous but mainly parent cell and gives rise to supporting cell. The supporting cell is highly columnar with large oval nuclei and ends in microvilli that secrete mucus. Cytoplasm contains granules of a golden-brown pigment that gives the golden-yellow colour of the nasal mucosa. Bowman's glands also secrete golden-yellow pigment.

Olfactory receptors: The olfactory receptors cells are supported by tall sustentacular cells. The receptor cells are bipolar neurons and are about 10–20 millions in number in man. They function both as receptor and ganglion cells. Dendrite arises from superficial pole and the axon arises from the deeper pole of the fusiform receptor cell. These axons are very fine having about only 0.2 µm in diameter and several run together within

a single Schwann cell sheath. Because of this, it is very difficult to record from single axons and it is debatable whether this has ever been done successfully. The axons pass through the cribriform plate to reach the olfactory bulb. Beside these, the lamina propria contain certain glands—Bowman's glands, which secrete fluid containing the watery and oily substances (Fig. 116.3).

Olfactory Bulb

The dendrite projects out through the space in between the supporting cells and expand slightly to form the olfactory rods. In the olfactory bulb there are a large number of nerve cells called granules intermingled in an interlacement of nerve fibrils, mitral cells and tufted cells with their dendrites and axons forming the layer of olfactory glomeruli. The olfactory rods contain numerous vacuoles, mitochondria as well as vesicles. Unmyelinated cilia project out from the rod. There are about 10–20 cilia per receptor cell.

The two main cell types tufted and mitral cells (Fig. 116.3) give off innumerable bushy dendrites on the side nearest the bulb surface and it is with these dendrites that the olfactory nerve axons make connections. The tufted cells send their axons via the medial olfactory tract to the opposite side of the brain. The mitral cell axons enter the lateral olfactory tract which is primarily ipsilateral.

OLFACTOMETER

The most well-known method of investigation of the olfactory sensation is the olfactometer of Zwaardemaker (Fig. 116.4). This instrument consists of a glass-tube sliding over another tube. The inner tube A is graduated into 10 equal divisions of 0.7 cm each. Both ends of the inner tube are open but one outer end C is curved and tapering. This tapering end is introduced into the nostrils. The inner wall of the outer tube B contains the odorous substance. The subject inhales the substance as he breathes within the tube because other nostril is kept closed. The intensity of smell is increased with the gradual withdrawal of the outer tube because this process facilitates the dilution with increasing concentration in the inspired air. This method gives only an approximate result.

Another method is the blast method of Elsberg and Levy. Here a controlled volume of odour-laden air is forced into the nose. Blast of such air is given successively so as to just perceive the odour. The minimum volume of odour-laden air necessary for identification is called the minimum identifiable odour (MIO) or the olfactory coefficient. This method has been a great aid in localisation of tumours in the anterior part of the skull.

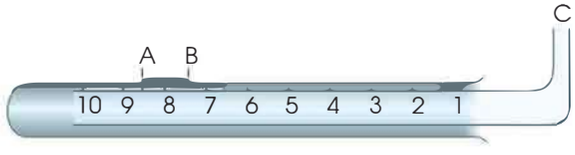

Fig. 116.4: Diagram showing Zwaardemaker's olfactometer

Classification of odours by Zwaardemaker

S.no.	*Class*	*Subdivisions*
I	Alliaceous	Arsine
		Chlorine
		Hydrogen sulphide
II	Ambrosial	Amber
		Musk
III	Aromatic	Bitter almond
		Camphor
		Clobes
		Lavender
		Lemon
IV	Caprillic	Cheese
		Rancid fat
V	Empyreumatic	Benzene
		Coffee
VI	Ethereal	Beeswax
		Ether
		Fruit
VII	Fragrant	Flowers
		Vanilla
VIII	Nauseating	Carrion
		Faeces
IX	Repulsive	Bedbug
		Belladonna

Physiology of Olfaction

The substances which remain in the gaseous state, e.g. turpentine, essential oil, etc. produce strong odours, whereas non-volatile substances, viz. the heavy metals, etc. are in-odorous. The odoriferous substances after inhalation do not reach the olfactory areas immediately but remain in the middle of the nose, e.g. below the level of the superior concha. The odorous particles of molecular size emitted by the odoriferous substances ascend upwards through the air and reach the olfactory areas either by eddy current or by diffusion. Diffusion is a slow process and so eddy current is the main factor. After reaching the olfactory area the odorous particles get dissolved in the fluid secreted by Bowman's glands. The secretion of Bowman's glands contain both water and oil. The odoriferous substances, which are soluble in water and oil, produce strong odour. The high solubility in oil is of greater importance than that of water-solubility for olfactory stimulation. The odorous particles after getting into solution become adsorbed on the surface of the cilia. There is some specificity or selectivity in the adsorption of odorous substances onto the olfactory receptors. After the odorous substances being adsorbed onto the olfactory mucosa, generator

potentials of 4–6 second durations are developed. These generator potentials when reached to its threshold value, initiates action potential which is then propagated along the axons to the olfactory bulb.

The odour producing molecules react with chemical groupings on the surface protein film of the receptor thereby increasing the surface area of the proteins which would distort the receptor surface and thus a generator potential is initiated.

Olfactory Discrimination

Man can distinguish between 2000 and 4000 different odours, and different parts of the olfactory mucous membrane respond differently to the same odours and receptors. Classification according to the different odours is still unsuccessful.

Olfactory Adaptation

The olfactory receptors become insensitive to a particular odorous substance after exposure to a specific period of time. As for instance the odour of the oil of lemon is not perceptible after an exposure varying from 2.5 to 10 minutes.

This is due to sensory adaptation. It is partly a central phenomenon, but it is also due to a change of the receptors themselves.

Threshold of olfactory sensation

It is the minimum concentration of different odorous substances to arouse olfactory sensation. Artificial musk, iodoform, butyric acid, etc. are perceptible in minimum concentration.

Chemical Compounds and their Relation to Olfactory Sensation

The intensity of olfactory sensation varies with different chemical compounds. If the chemical compounds belong to homologue series then the intensity of stimulation will increase from the lower members to higher one. In alcoholic series the odours increase in strength (from lower to higher one), i.e. from methyl, ethyl, propyl, butyl to amyl.

Relation of Odorous Substances

Weaker odours are masked by the stronger ones. If the odorous substances are of equal strength then the odours of both are perceived. Some of the odorous substances are antagonistic to each other, e.g. iodoform antagonises balsam of Peru.

Pathways of Olfactory Impulses

Key Points

1. Bipolar nerve cells of the olfactory epithelium are the first-order neurons. Each receptor cell gives rise to only one axon which joins with those derived from other receptors forming collectively the fila olfactoria or the olfactory nerves. The olfactory nerves are unmyelinated and have got neurolemmal sheath. The sheath is continuous with the subarachnoid space.
2. The nerves pierce the cribriform plate of the ethmoid bone and enter the olfactory bulb. Here, the axons make synapses with the dendrites of the mitral cells and the tufted cells to form the complex globular structures which are known as olfactory glomeruli.
3. Approximately 26,000 receptor cells converge on each glomerulus and each glomerulus again passes impulses to about 24 mitral cells and 68 tufted cells. The mitral and tufted cells are the second-order neurons and their axons constitute the olfactory tract.
4. The olfactory tract proceeds towards the anterior perforated substance and divides in the olfactory trigone into well-defined olfactory striae—medial, intermediate and lateral (Figs 116.5 and 116.6).
5. The axons of the tufted cells leave the tract and most probably end in the opposite bulb via the anterior commissure through the medical olfactory stria. This tract after entering the anterior commissure passes bilaterally to the nucleus of the stria terminalis; olfactory tubercle and to amygdaloid nuclear complex.
6. The axons of the mitral cells pass through the lateral olfactory stria and ends in the anterior olfactory nucleus. Cortical and medial portions of the ipsilateral amygdaloid nucleus and in the prepyriform cortex and periamygdaloid cortex.
7. The prepyriform cortex and the periamygdaloid cortex are the primary olfactory cortex. Entorhinal

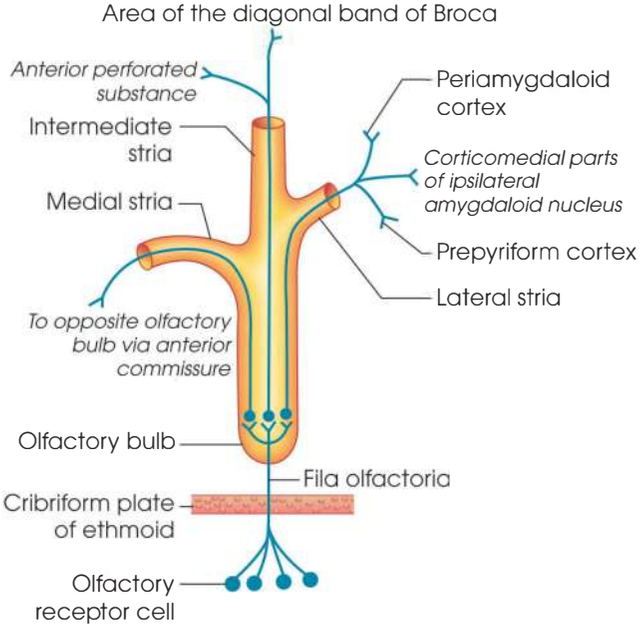

Fig. 116.5: Diagrammatic representation of path of olfactory impulses showing olfactory rods (receptor cells) and supporting cells in the olfactory mucosa

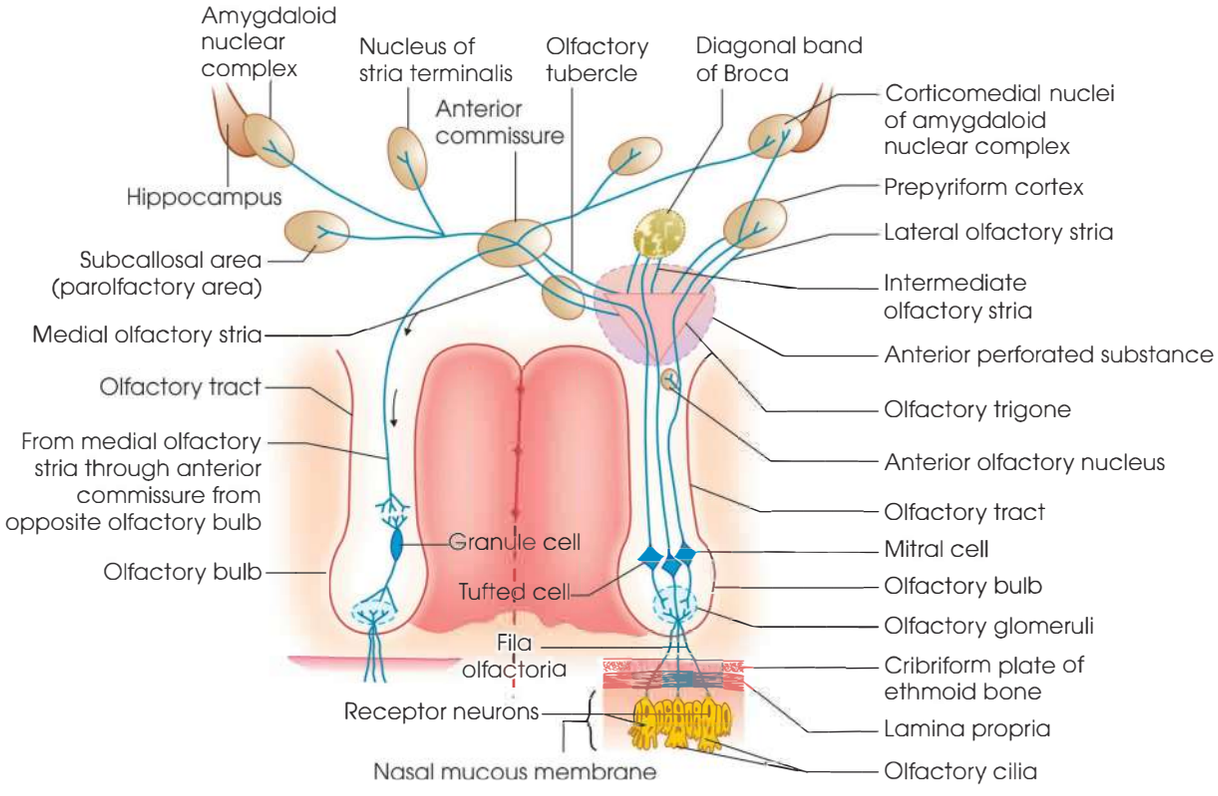

Fig. 116.6: Simplified diagram of the olfactory bulb and its connections

cortex (area 28) is the secondary olfactory area because it receives fibres from primary olfactory cortex or adjacent neocortex. There is no thalamic representation to the olfactory system.

8. Another groups of fibres which are less significant in man pass through the intermediate stria and ends within the anterior perforated substance and the area of the diagonal band of Broca.

Abnormalities of Olfactory Sensation

1. ***Anosmia:*** The loss of the sense of smell is known as anosmia. It occurs due to congenital abnormalities of olfactory bulbs or nerves.
2. ***Hyposmia:*** The decreased sensitivity to smell is hyposmia. During inflammation of nasal mucosa there is temporary loss of smell.
3. ***Hyperosmia*** is the morbid sensitiveness to odours. It occurs in hysteria, in raised intracranial pressure, etc.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the physiology of olfaction. Describe the pathways of olfactory impulses.

Short Notes

1. Olfactory pathway
2. Olfactory bulb
3. Anosmia
4. Hyposmia
5. Hyperosmia

Chapter

117

Physiology of Vision

INTRODUCTION

Human eyeball (Figs 117.1 and 117.2) is roughly spherical, being a little flat from above downwards (25 mm horizontal, and 23.5 mm vertical). The optic nerve enters the eyeball (Fig. 117.3), a little inside the posterior pole, through the optic disc.

Tunics

From outside inward, the wall has three coats:

1. Fibrous coat
2. Vascular coat
3. Nervous coat.

Fibrous coat: It has two parts:

1. Posterior (5/6ths) is opaque and called the sclera.
2. Anterior (1/6th) is transparent, called the cornea.

The vascular coat (uvea, or uveal tract)

Three parts: From behind forward:

a. The choroid—remains just behind the retina forming the posterior 5/6ths of the middle coat. Composed of numerous blood vessels and pigmented cells containing melanin. Hence, its colour is dark. Its function is to convert the eyeball into a dark chamber.

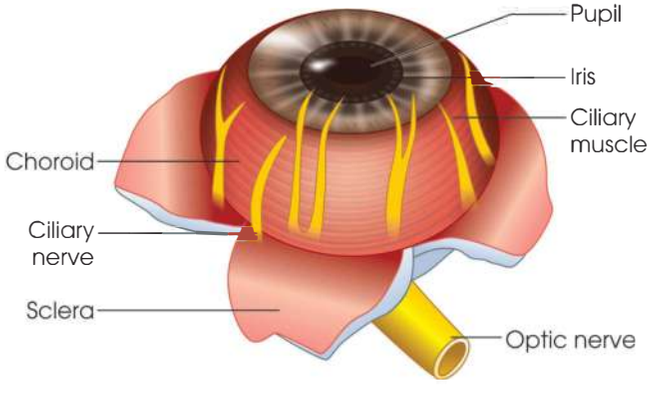

Fig. 117.1: Showing the eyeball, sclera cut and turned back, pupil, iris, ciliary muscle, choroid, ciliary nerves and optic nerve

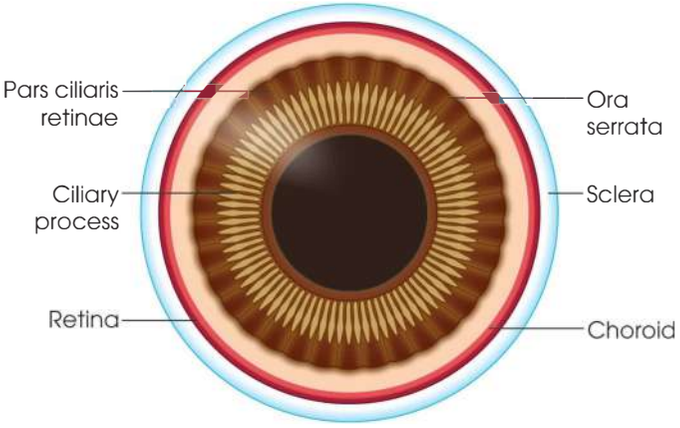

Fig. 117.2: Diagrammatic representation of the interior of the anterior half of the eyeball

b. The ciliary body includes orbicularis ciliaris, ciliary processes, and ciliaris muscle.
c. The iris (vide later).

Nervous coat: The nervous coat is called the retina. It contains the photosensitive receptors, where the visual impulses are generated.

CONJUNCTIVA

The exposed part of the eyeball is covered by a thin stratified mucous membrane which is reflected onto the inner surface of the eyelids. It is called conjunctiva. Its function is protection and lubrication.

LACRIMAL APPARATUS

The lacrimal gland is an almond-shaped racemose gland remaining inside the upper and outer parts of the orbit and secreting a watery fluid, the tears. Smaller accessory glands are common (Fig. 117.4). The secretions are delivered into the conjunctival sac through six to ten fine ducts. The movements of the eyelids help to spread the tears over the conjunctival surface.

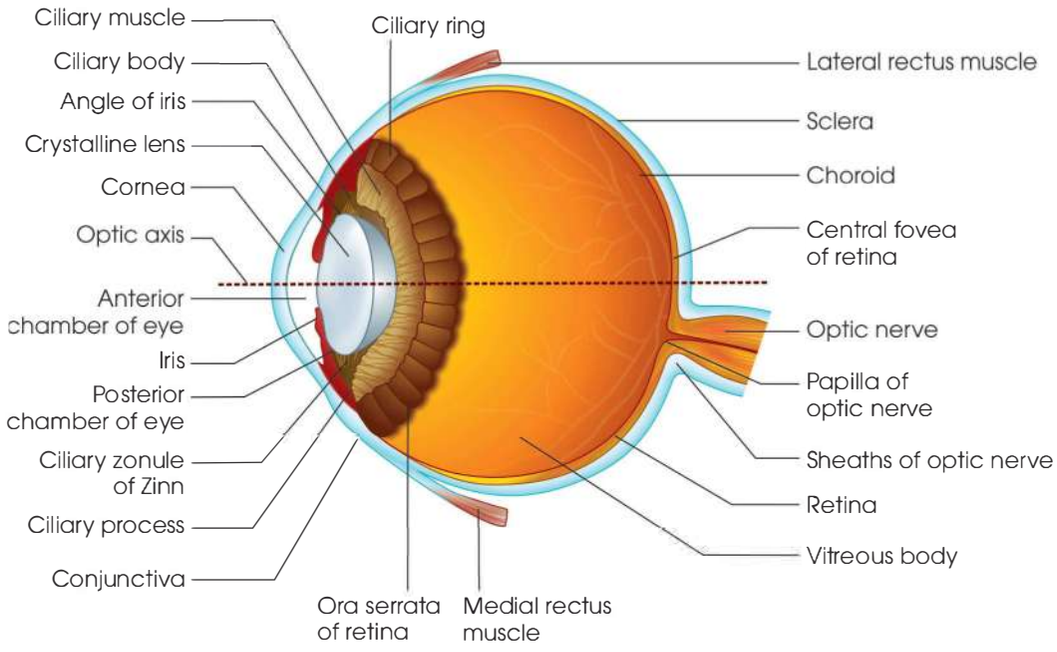

Fig. 117.3: Anatomical representation of the structure of the eye

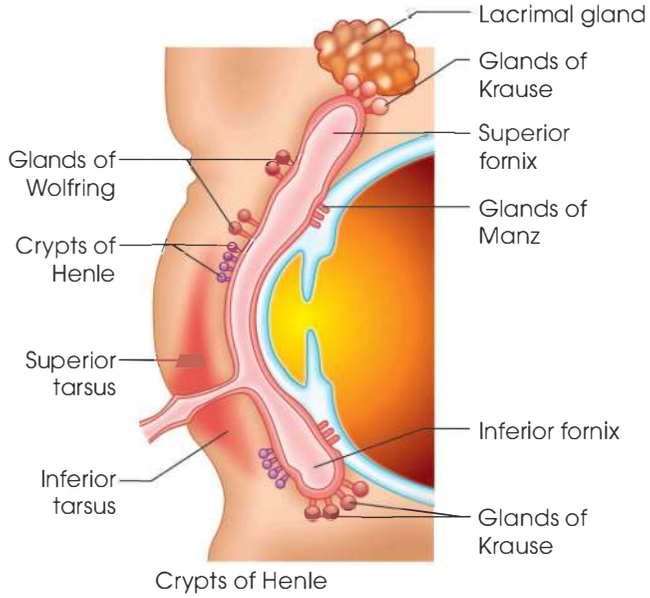

Fig. 117.4: Sectional representation through eyelid and eyeball showing the conjunctival sac and positions of its glands (Adler)

The tears ultimately collect into a small triangular area (lacrimal lake) at the inner angle of the eye. From here the fluid passes through puncta lacrimalia and is carried through two small lacrimal canaliculi into the lacrimal sac inside the nose, where the sac opens (Fig. 117.5). The normal function of tears is to keep the exposed surface moist. Irritation or emotion increases secretion.

Nerve supply: Sympathetic from superior cervical ganglion, parasympathetic from the facial.

Composition of tear: Closely resembles aqueous humour.

Water—98.2%; solids—1.8%; organic elements: Protein—0.67%; sugar—0.65%; NaCl—0.66%; NPN—0.05%; urea—0.03%; other mineral elements—sodium, potassium and ammonia—0.79%.

Electrophoretic Analysis of Tears

It shows three types of proteins—albumin, globulin and lysozyme. The lysozyme can dissolve many air-borne saprophytes rapidly and completely. Lysozyme along with other unidentified labile agents seems to inhibit the growth of many pyogenic cocci (Staphylococcus, haemolytic Streptococcus, Diplococcus pneumoniae, etc.).

EYEBALL

Its interior is divided into two compartments by a partition. The centre of this partition is occupied by the lens. The peripheral part, by which the lens remains attached to the wall of the eyeball, is called the suspensory ligament.

The posterior compartment contains vitreous humour (vitreous body). The anterior compartment contains aqueous humour. Aqueous humour and vitreous humour create the intraocular pressure. This pressure tends to hold the eyeball round and firm (Fig. 117.6). The anterior compartment is further subdivided by the iris into an anterior and a posterior chamber. Both contain aqueous humour. Intraocular pressure is 25–30 mm of Hg. It varies with general blood pressure. Pressure on the ocular veins or on eyeball from outside, disturbed drainage of aqueous humour and exposure to darkness raises the pressure.

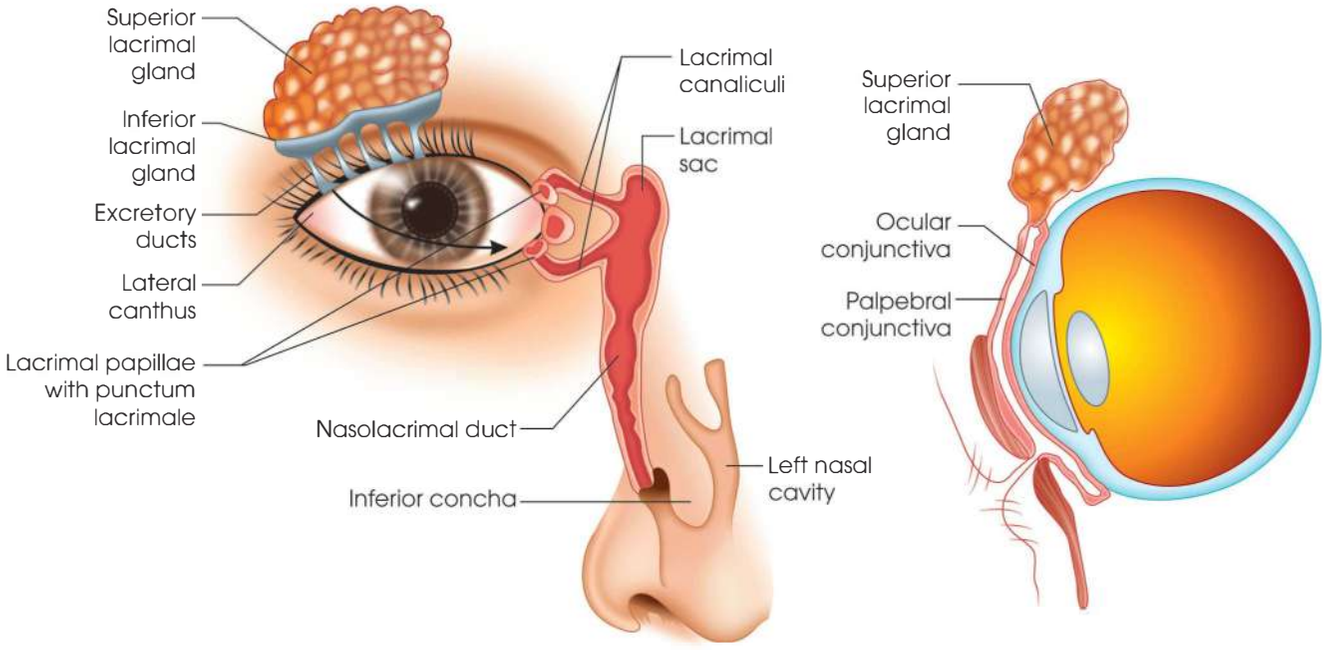

Fig. 117.5: Diagrammatic representation of the lacrimal apparatus. Left-sided diagram showing the direction of drainage of lacrimal fluid from the excretory ducts of the lacrimal glands across the eye to the nasolacrimal duct via lacrimal sac and right-sided diagram representing relation of the lacrimal gland to conjunctival surfaces with the eye closed (Langley and others)

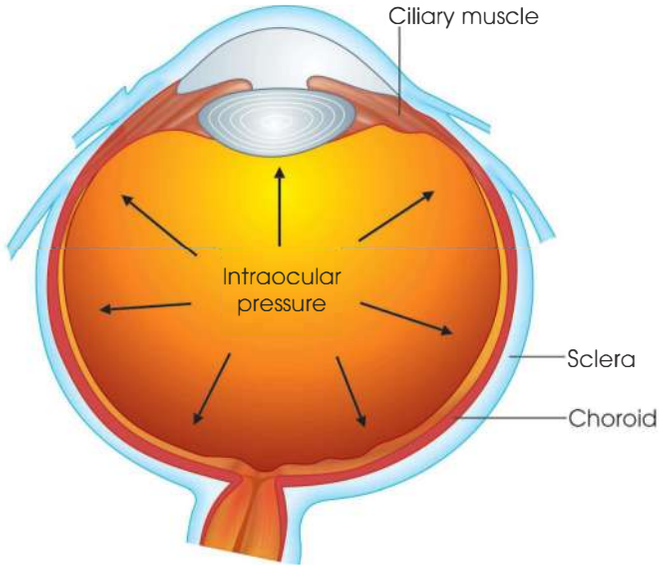

Fig. 117.6: Diagrammatic representation of the mechanism of the intraocular pressure (Langley and others)

Refractive Media of the Eyeball

Physics of Vision

1. Light is a form of radiant energy. This energy travels in waves through air at a speed of about 3,00,000 km per second. The wavelength of light visible to the human eye differs from about 3850 to 7200 μm.
2. *Refraction* denotes 'to bend' or 'to turn aside'. As the speed of light is different from one medium to another medium; hence the beam of light travels more slowly in glass than in air.
3. *Refractive index* is a relative measure of transmission of light. This measure is relative to the rate of light ray in air. If light travels through a medium at a rate of 1,50,000 km per second, this medium is said to have a refractive index about 2.0 (3,00,000 ÷ 1,50,000). As the lens of the human eye transmits light at the rate of about 2,14,285 km per second, it has a refractive index of about 1.40.

   If a transparent medium be at a right angle to its surface there is no bending of light rays. Therefore, the degree of refraction depends upon the difference between refractive indices of two media and the angle at which the beam of light traverses the interface between the media.

   A *lens* is a transparent substance. This substance bends rays of light and causes rays to converge or diverge. Man-made lens (Fig. 117.7) is generally of glass.
4. If the rays of light are parallel to the axis (line through the middle) of a lens (or curved mirror) they come to the *principal focus*. If the lens has sufficient

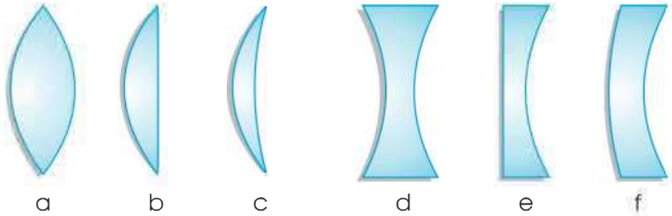

Fig. 117.7: Various types of lenses. a—biconvex, b—planoconvex, c—concavoconvex, d—biconcave, e—planoconcave, f—convexoconcave

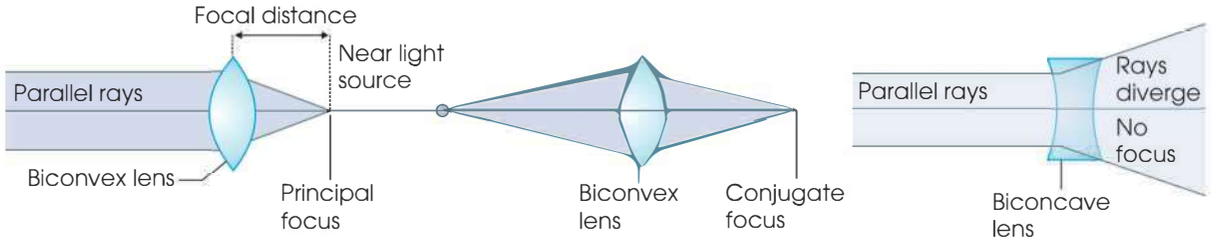

Fig. 117.8: Diagram showing refraction of light rays by biconvex and biconcave lenses (Langley and others)

convexity, these diverging rays of light will be bent and ultimately converge on a *conjugate focus* (Fig. 117.8). Therefore, the distance to the conjugate focus is greater than to the principal focus for any lens.

5. The *power of a lens to bend light* depends upon the refractive index of the lens and the curvature of the surfaces.
6. Refractive power of a lens is expressed in *diopters* and *focal distance* is the distance between a biconvex lens and its principal focus. Thus, the dioptre is the refractive power of the lens which is determined by the focal distance between a biconvex lens and its principal focus.
7. The shorter the focal distance greater the refractive power of the lens will be. When the focal distance is 100 cm, the lens is said to get a power of one dioptre (100 ÷ 100). And, when the focal distance is 20 cm, a lens has a power of 5 diopters (100 ÷ 20). As the parallel rays of light are caused to diverge by a biconcave lens and there is no focal point, the power of a biconcave lens would be expressed in terms of its ability to counteract converging ability of a biconvex lens. Therefore, the power of a biconvex lens is termed in *plus diopters* and the power of a biconcave lens is expressed in *minus diopters* (Fig. 117.9).

Optical Arrangement of the Eye

The beams of light first strike the cornea and then pass through the aqueous humour. Afterwards these strike the lens, then vitreous humour and finally the retina. The normal eyeball acts as a camera. Inverted images of external objects are formed exactly on the retina, and generate appropriate visual impulses. These impulses are carried through the optic nerves to the brain where visual impressions are produced. There are four refractive media in the eye which help to converge the light rays and focus them on the retina. The media are:

1. Cornea
2. Aqueous humour
3. Crystalline lens
4. Vitreous humour.

Maximum refraction occurs at the air—corneal surface: 42 diopters; at lens: 20 diopters, and during accommodation it varies between 13 and 26 diopters. The media are briefly described below.

CORNEA

It is the round, transparent convexity in the anterior part of the eyeball.

1. *Diameters*: 11 mm (vertical) × 12 mm (lateral).
2. *Thickness:* 0.5–1 mm.
3. *Nerve supply:* They are rich and non-medullated. Only free nerve terminals—subserving pain. There are no other sensations and no other endings.
4. *Nutrition*—from the aqueous humour.
5. *Refractive index:* 1.336.

Functions

1. Allows free entry of light.
2. Acts as a refractive medium.

Intraocular pressure or tension—the aqueous humour is under a pressure of 25 to 30 mm of Hg. The tension of the eyeball can be felt by palpating the eyeball with two fingers. The pressure is measured with the help of tonometer. The intraocular pressure becomes high in glaucoma.

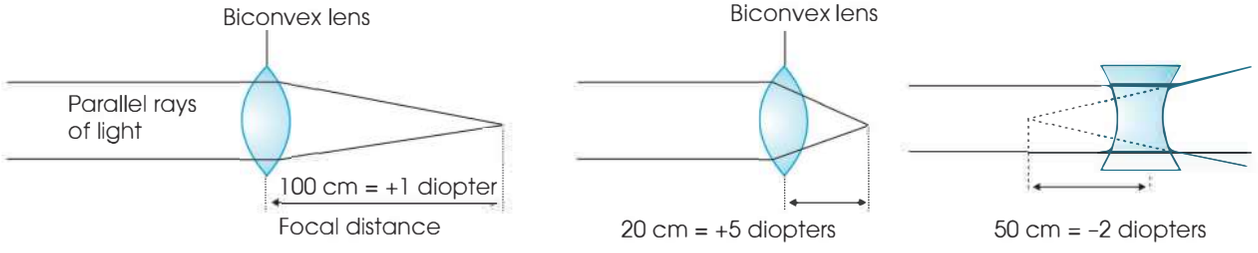

Fig. 117.9: Diagrams representing the refractive power of the lenses in diopters

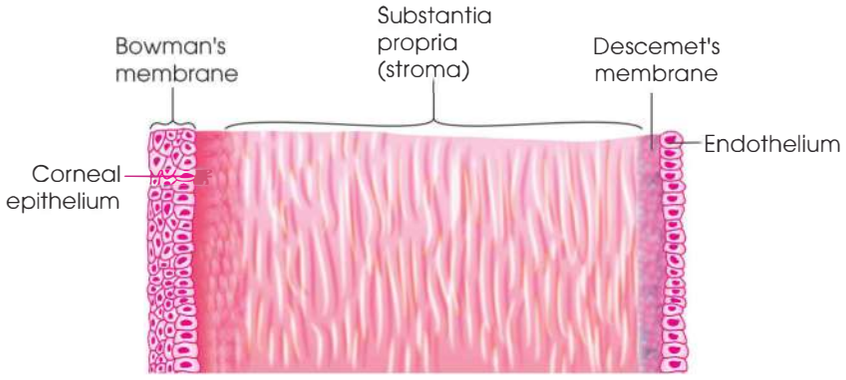

Fig. 117.10: Showing meridional section through the cornea

Histology (Fig. 117.10)

From outside inwards there are as follows:

- Corneal epithelium or external stratified epithelium: This layer is about 50 µm thick. Several layers of cells continuous with the conjunctiva:
- The superficial four or five layers are stratified squamous.
- The deepest (basal) layer is columnar.
- The intermediate two or three layers are polyhedral.

Bowman's membrane or anterior elastic lamina: This layer consists of the presence of a network of relatively fine collagenous fibres with an irregular arrangement. This homogeneous layer is 5–10 µm thick.

Substantia propria or corneal stroma: 90% thickness of the cornea is dependent upon this layer. It is composed of connective tissue fibres and cells. This layer is held together by mucoprotein and rich in keratin sulphate. As the fibres and mucosubstance have the refractive index and are highly hydrated, the whole cornea is transparent.

Descemet's membrane or posterior elastic lamina: This homogeneous layer is about 5–10 µm thick.

Corneal endothelium or Innerlayer of squamous epithelium: A single layer of endothelial cells that extends over the inner surface of Descemet's membrane and is continuous with the epithelium covering the anterior surface of the iris.

Nutrition of Cornea

It is avascular and its living materials like epithelium, corneal corpuscles and endothelium get nutrition from aqueous humour and from superficial marginal plexus of blood vessels. Nutrition of the cornea depends upon the diffusion of substances into it from the film of tears covering its epithelial surface, from capillaries in the tarsal conjunctiva when the lids (Fig. 117.11) are closed, from the limbal capillaries and from the aqueous humour bathing its endothelial surface.

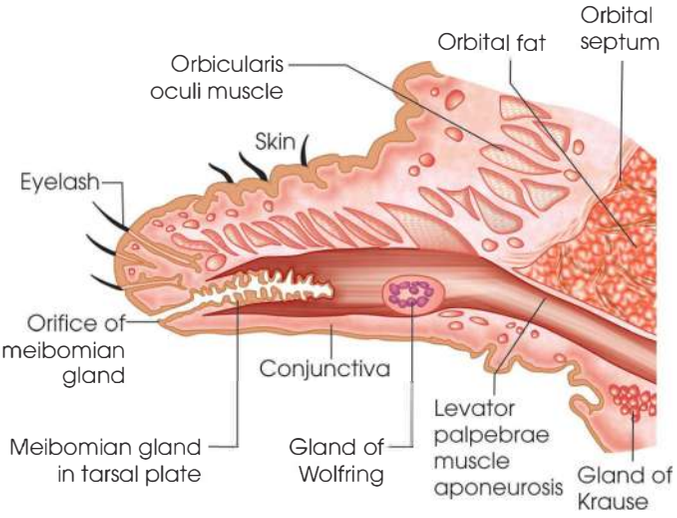

Fig. 117.11: Showing transverse section of the upper eyelid

AQUEOUS HUMOUR

It is a clear watery fluid occupying both the anterior and posterior chambers of the eye. It is known to be the only secretory product of epithelium covering the ciliary body. It is not a stagnant fluid but continuously circulates (Fig. 117.12).

The ophthalmic artery gives rise to all arterial branches and venous drainage is through the cavernous sinus and pterygoid plexus—secreted and passed over the lens through the pupil into the anterior chamber and then drained into the vascular system—the anterior ciliary veins (Figs 117.12 and 117.13).

Composition: Water—98.69% and solids—1.31%. Further details, as compared with serum, are as follows:

1. The diffusible, non-ionisable substances, viz. urea, NPN, sugar, etc. same as in serum.
2. Colloids—only traces, i.e. much less than serum.
3. Chlorides—much higher than serum.

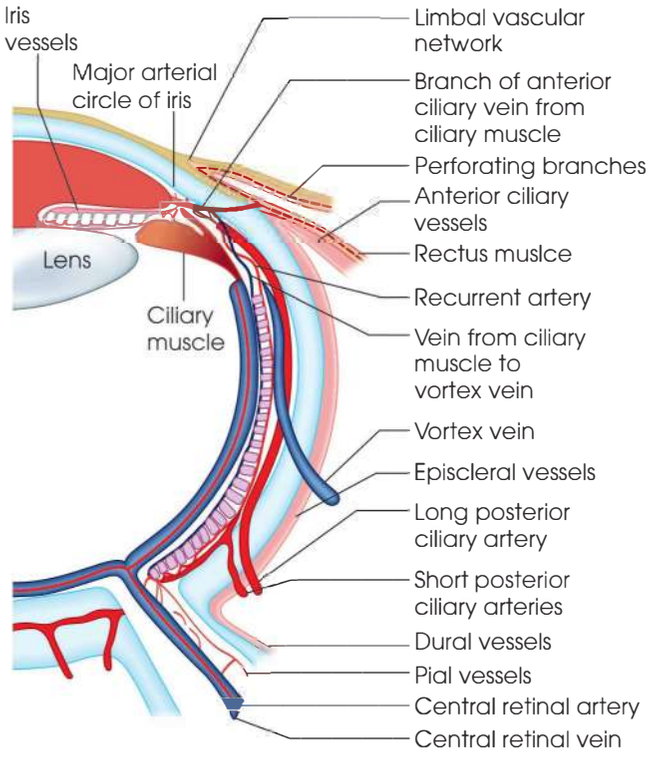

Fig. 117.12: Diagram showing vascular supply to eye

Chemical composition of aqueous humour

1. *Protein:* The most obvious chemical difference between aqueous humour and blood plasma is to be found in the protein contents of two fluids. In the plasma it has the order of 6.0–7.0 gm/100 ml, whereas in the aqueous humour it is only 5.0–15.0 mg/100 ml in man and about 50.0 mg/100 ml in the rabbit.
2. *Non-colloidal constituents:* The crystalloidal composition of the aqueous humour is similar to that of plasma. But the concentrations of ascorbate (vit. C), pyruvate and lactate are much higher than in plasma, whilst those of urea and glucose are much less.

Blood-aqueous barrier: Like cerebrospinal fluid, the aqueous humour also maintains a blood-aqueous barrier. Because large water-soluble molecules like penicillin, sucrose, P-aminohippurate, etc. cannot pass from blood to the aqueous humour or if pass, it is very slow indeed.

Formation: Formed by the enzymatic activity of the ciliary processes.

FLOW OF AQUEOUS HUMOUR

Aqueous humour flows from the posterior chamber into the anterior chamber through the pupil. From the anterior chamber, the aqueous humour gets exit chiefly at the so-called iridocorneal or filtration angle (Fig. 117.14). At the filtration angle, the aqueous humour comes in contact with the trabecular tissue and makes its way through the meshwork to react the canal of Schlemm (Fig. 117.13). From here it goes to the sclera and episcleral venous plexus and thence to the aqueous veins and out of the eye.

Furthermore, the increased formation of aqueous humour is readily compensated by a rapid escape through the canal of Schlemm.

A small amount may pass through the suspensory ligament to the anterior surface of the vitreous, then through the hyaloids canal to the optic disc and then

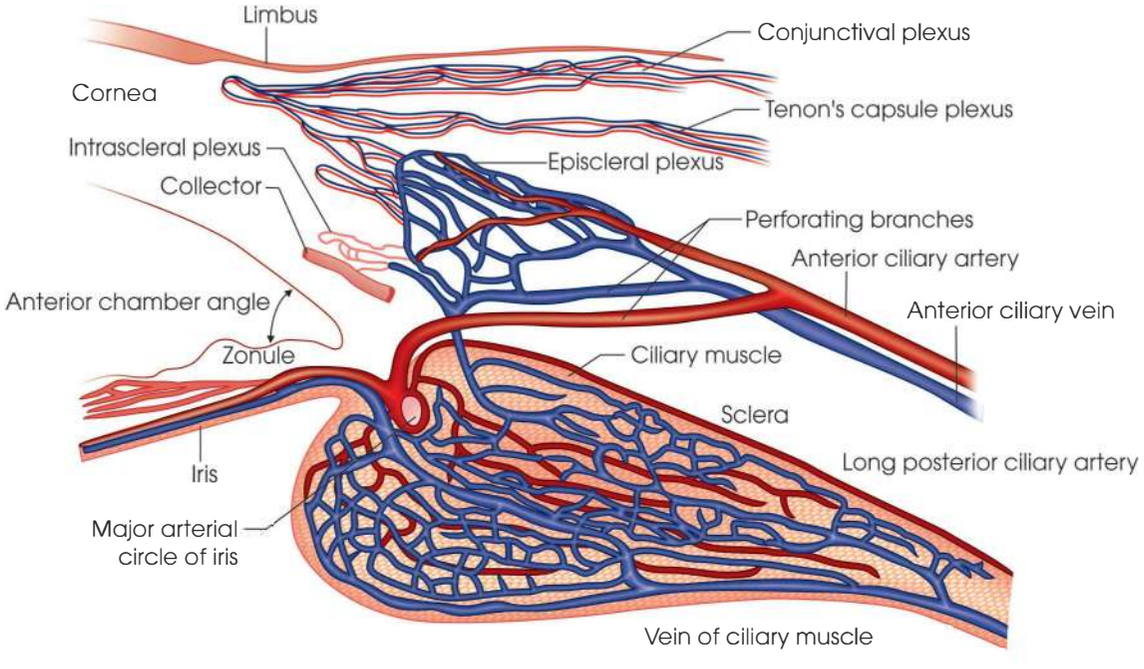

Fig. 117.13: Plexuses of antero-posterior segment of the eye and its venous drainage (Dauson)

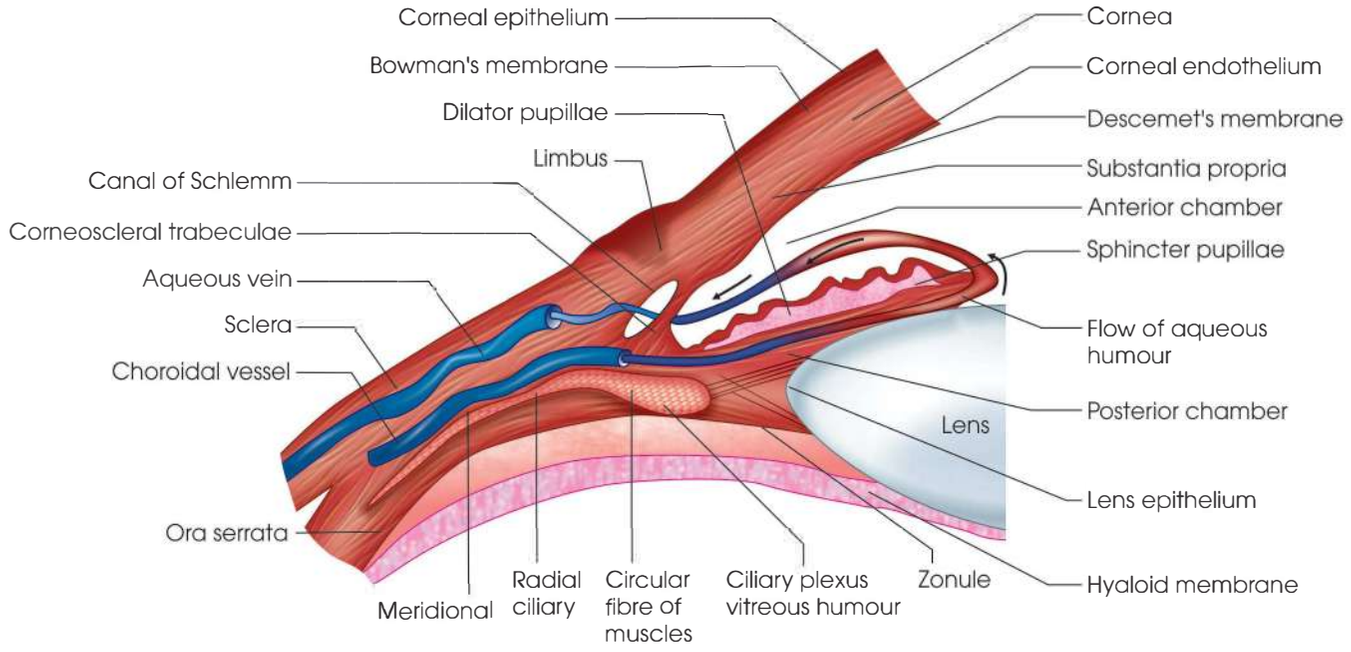

Fig. 117.14: Diagram shows sectional details of anterior segment of the human eye and also flow of the aqueous humour

drains away through the perineurial lymphatics of the optic nerve. A little may be absorbed through the veins and lymphatics of the interior of the eyeball (Fig. 117.13).

Functions

1. Maintains intraocular pressure and the shape of the eyeball.
2. Acts as a refractive medium.
3. Supplies nutrition to drains the metabolites from the surrounding structures.

Aqueous Veins

In 1942 Ascher, when examining the superficial vessels of the globe with the slit-lamp microscope, observed what appeared to be empty veins but they turned out to be full of aqueous humour, and he called them aqueous veins. Usually one of these veins could be followed till it joined a blood vessel, in which event the contents of two vessels, aqueous humour and veins did not mix immediately but often ran in parallel streams constituting a laminated aqueous vein (Fig. 117.15). If the blood vein beyond the junction was compressed, either the blood drove the aqueous humour out of its channel or the aqueous humour drove the blood out (Fig. 117.16).

Autonomic Regulation of the Formation of the Aqueous Humour

The innervations of the ciliary processes are both sympathetic and parasympathetic running mostly along the vessels. Stimulation of the parasympathetic accelerates whereas stimulation of the sympathetic depresses the formation of aqueous humour. The

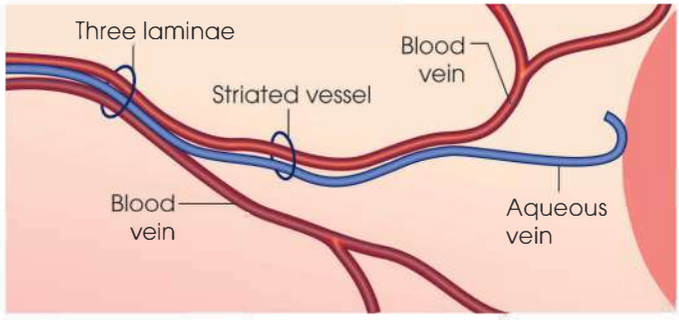

Fig. 117.15: Diagrammatic representation of formation of laminated aqueous vein

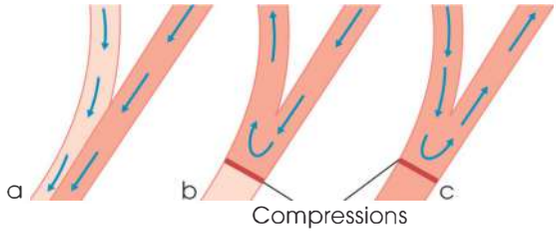

Fig. 117.16: Diagrammatic representation of aqueous veins (a) shows the formation of laminated vein, (b) blood drives aqueous humour from its vessel, (c) due to compression of laminated vein (Starling)

sympathetic stimulation constricts the filtering and secretory parts of the ciliary process and thus the intraocular pressure is reduced.

Autonomic Regulation of the Outflow of the Aqueous Humour

1. The rate of outflow is mostly facilitated by the contraction of the iris and the ciliary muscle.

Dilatation of the trabecular network and canal of Schlemm also facilitates the outflow.

2. Following sympathetic stimulation the rate of flow is decreased because the intraocular pressure falls due to vasoconstriction in the filtering and the secretory parts of the ciliary process. But the outflow from the anterior chamber remains unaltered either by sympathetic stimulation or by administration of sympathomimetic drugs.
3. Parasympathetic stimulation increases the outflow from the anterior chamber and the rate of flow is increased.
4. Parasympathomimetic drugs like pilocarpine and physostigmine also increases the outflow mechanism; through contraction of the ciliary muscle; dilatation of the trabecular network of Schlemm's canal and of the episcleral veins. These drugs are very important in the treatment of glaucoma.
5. Parasympatholytic drug like atropine has got opposite effect. It affects the outflow of the aqueous humour and thus the intraocular pressure is elevated.

CRYSTALLINE LENS

It is the chief refracting medium of the eyeball. It is a transparent, elastic and biconvex lens, enclosed in a capsule. Posteriorly, it is more convex. It is circular, about 11 mm in diameter. The thickness at the centre is about 3.6–3.9 mm. Refractive index: 1.40 at the centre. It is less in the periphery. It is held *in situ* by the suspensory ligament.

Histology (Fig. 117.17)

It is composed of concentric layers of elongated modified cells. The peripheral parts are soft and nucleated, while the central part forms a dense non-nucleated mass with a higher refractive index. A single layer of columnar epithelial cells lies on the anterior surface, just behind the capsule. From the central part of the anterior surface to the equator of the lens, the columnar cells undergo a gradual transition into the attenuated cells of the lens.

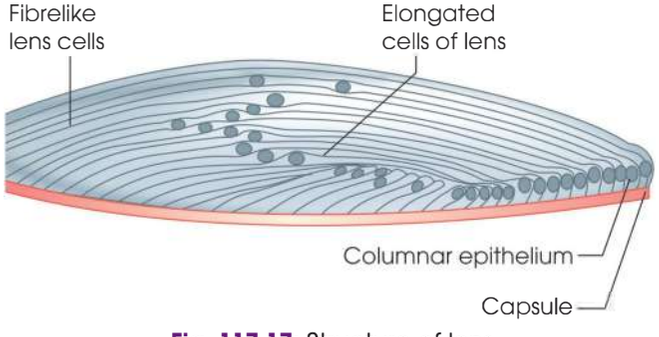

Fig. 117.17: Structure of lens

Function

To refract light and focus it exactly on the retina.

Metabolism of Lens

Isolated lens, when placed in a suitable micro-spirometer, can be shown to use O_2 and eliminate CO_2. Oxygen lack, CO_2 excess and other pathological conditions cause degenerations of the lens. In the young, the lens is rich in cystine, which may be a part of glutathione, necessary for local tissue oxidation. As age advances, the cystine content falls.

Nutrition of Lens and Cataract

Nutrition of the lens is maintained by the aqueous humour over the lens. Transparency of the lens is maintained by the normal nutrition and if this nutritional status is altered due to some dietary deficiencies then there comes a certain pathological changes in the lens leading to opacity. This condition is known as cataract. Glutathione content in the cataract lens is greatly decreased and has got direct relationship with the degree of opacity in the lens.

VITREOUS HUMOUR (VITREOUS BODY)

It is a jelly-like material covered by a homogeneous membrane, the hyaloid membrane, and occupying the posterior compartment. It is made up of a series of lamellae arranged concentrically round the hyaloid canal (Fig. 117.18). The lamellae are composed of flat cells. The spaces between the lamellae are filled up with fluid.

The composition of the vitreous humour is mostly similar to that of the aqueous humour except (i) its glucose content is considerably less than that in either aqueous humour or plasma, and (ii) its concentration of pyruvic acid and lactic acid are higher than that in the aqueous humour. Retina liberates these acids greatly.

Refractive index: 1.34.

Functions

1. Maintains shape and pressure of the eyeball
2. Acts as a refractive medium.

Retinal detachment is the cause of localized liquefaction of the vitreous body and as a result a part of the retina floats in the vitreous cavity.

Blood-vitreous Barrier (Fig. 117.19)

The vitreous body comes into equilibrium with blood much more slowly than the aqueous humour and it may be attributed to blood-vitreous barrier. The vitreous body presumably receives material from the choroidal and retinal circulations. But, with many substances, equilibrium with plasma takes a long time to be

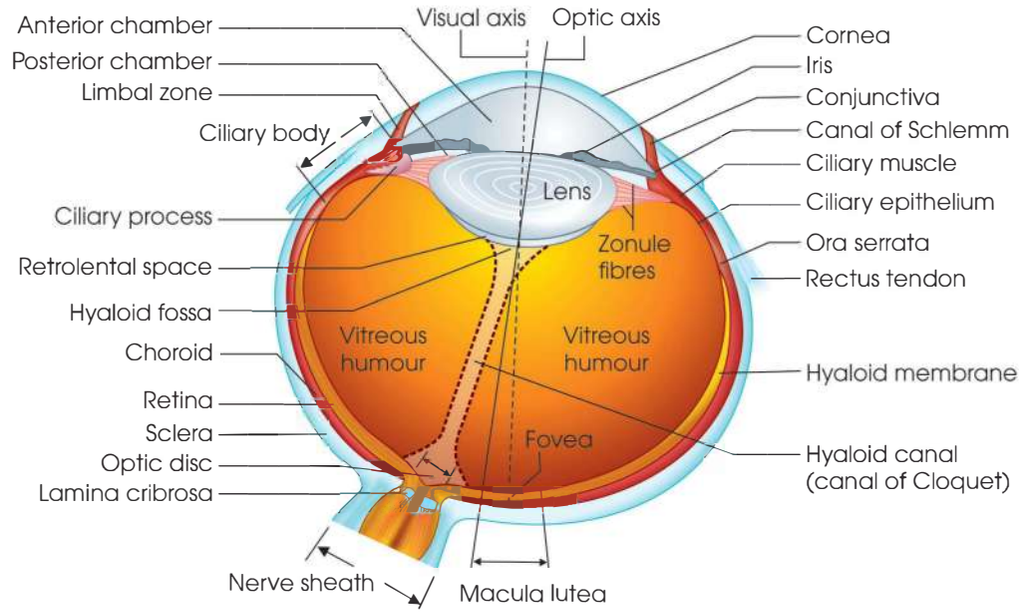

Fig. 117.18: Diagram represents the horizontal section of right human eyeball showing hyaloid canal, fovea, hyaloid fossa, retrolental space, etc.

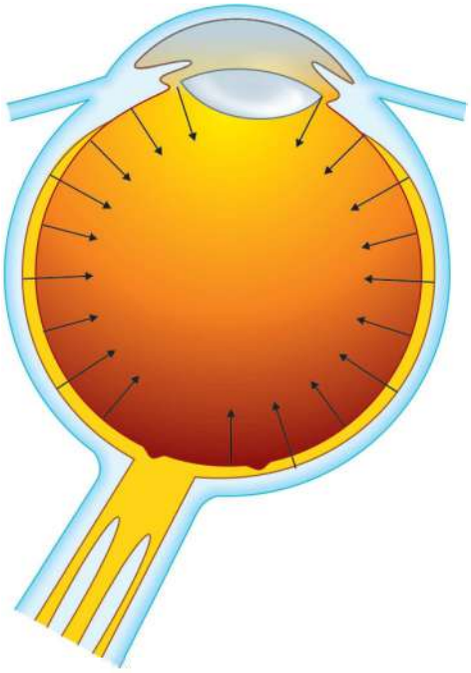

Fig. 117.19: Showing the blood-vitreous barrier (Davson)

achieved. The vitreous body must also receive material from the aqueous humour in the posterior chamber, the concentration tending to be higher in this fluid. Thus, the blood-vitreous barrier is complex.

Control of Eye Movement

There are six external ocular muscles for the movement of each eyeball (Figs 117.21 and 117. 22). Their names, nerve supply and actions are:

Muscle	*Direction*	*Interconnection*
Medial rectus or internal rectus	Inward	Oculomotor (C.N.III)
Lateral rectus or external rectus	Outward	Abducens (C.N.VI)
Superior rectus	Up and in	Oculomotor (C.N.III)
Inferior rectus	Down and in	Oculomotor (C.N.III)
Superior oblique	Down and out	Trochlear (C.N.IV)
Inferior oblique	Up and out	Oculomotor (C.N.III)

Co-ordination of Eye Movements

The external ocular muscles move the eyeballs in such a way that the two images are formed on the

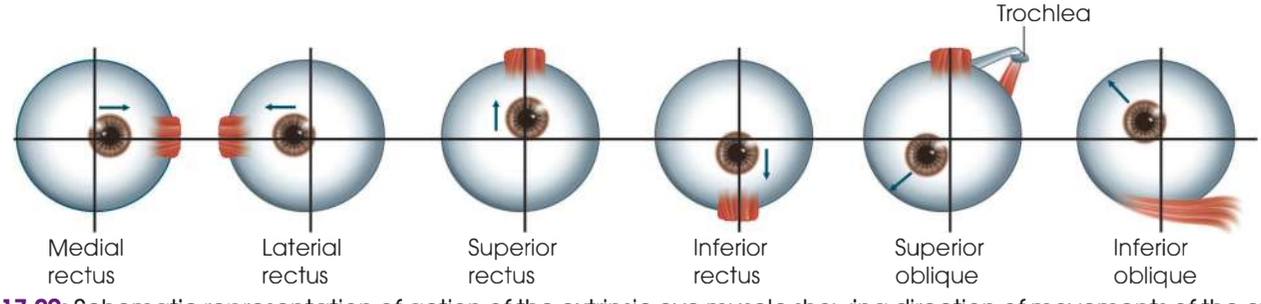

Fig. 117.20: Schematic representation of action of the extrinsic eye muscle showing direction of movements of the eyeball by arrows (Langley and others)

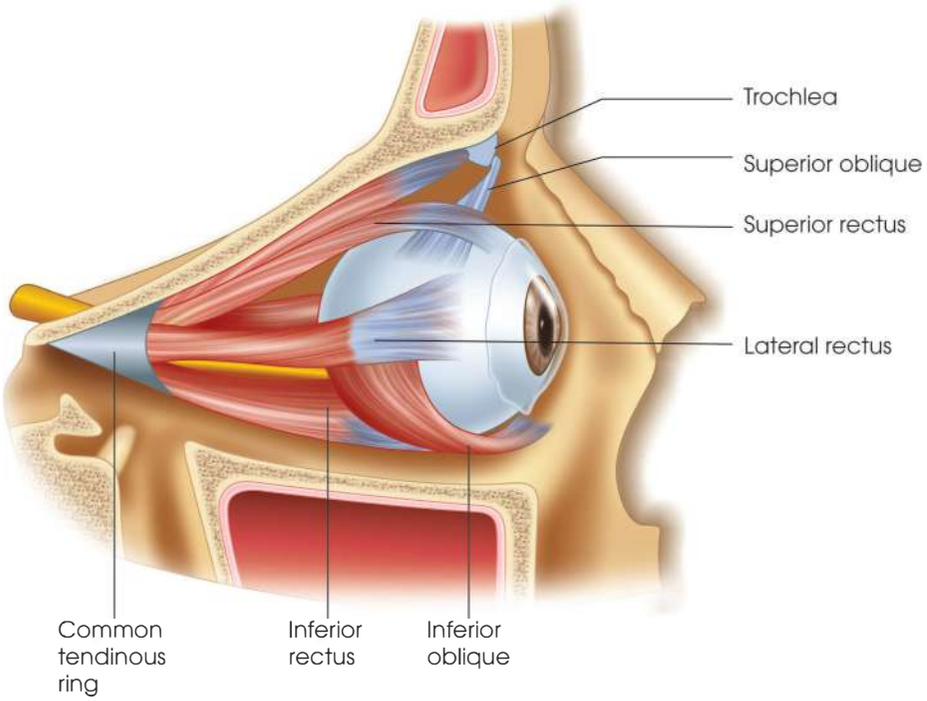

Fig. 117.21: Schematic representation of the localisation of specific extraocular muscles which are innervated by cell groups within oculomotor nuclei (Warwick)

physiologically corresponding points on the retina, so that only one visual impression is produced.

These movements may be either voluntary or reflex.

Ocular movements are of three kinds:

1. Those in which the eye axes move to the same side, e.g. right, left, up, or down.
2. Those in which the axes move in opposite directions, e.g. convergence or divergence.
3. Those in which the eyeballs rotate round their axes clockwise or anticlockwise (Figs 117.20, 117.22 and 117.23).

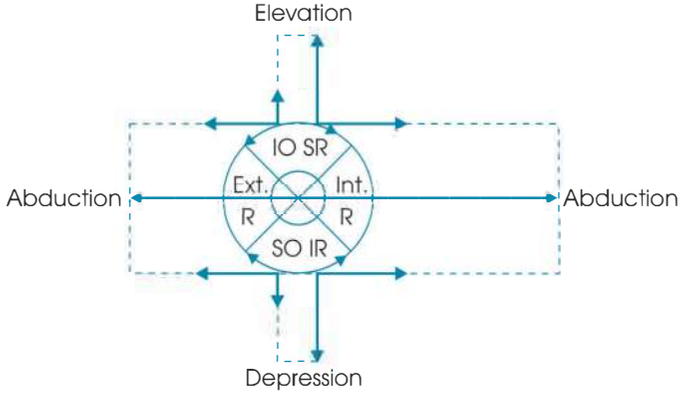

Fig. 117.22: Action of ocular muscles. SR—superior rectus; IR—inferior rectus; Ext. R.—external or lateral rectus; Int. R.—internal or medial rectus; IO—inferior oblique; SO—superior oblique (Best and Taylor)

Nervous Control

The co-ordinated movements of the eyeballs are controlled in several ways:

Bilateral nerve supply: Nerve of one side may supply muscles on both sides. For instance, internal and inferior recti and the inferior oblique muscles of one side receive fibres from III cranial nerve nucleus of both sides.

Intercommunications: Between the different parts of the III cranial nerve nucleus and between the III, IV and VI cranial nerve nuclei of the same and opposite side (Fig. 117.24).

Intercommunication of the III, IV and VI Cranial Nerve Nuclei

The III cranial nerve nucleus is supposed to contain seven component nuclei four for the four external ocular muscles it supplies, and one each for the levator palpebrae superioris (upper lid), ciliary muscles (accommodation) and constrictor pupillae (Edinger-Westphal nucleus).

The chief intercommunications are as follows:

1. Nuclei for lateral rectus of one side and medial or internal rectus of other (Fig. 117.25) (conjugate deviation).
2. Nuclei for constrictor papillae, ciliary muscles and internal rectus (accommodation).
3. Nuclei for superior rectus of both sides (Fig. 117.26) upward movement.

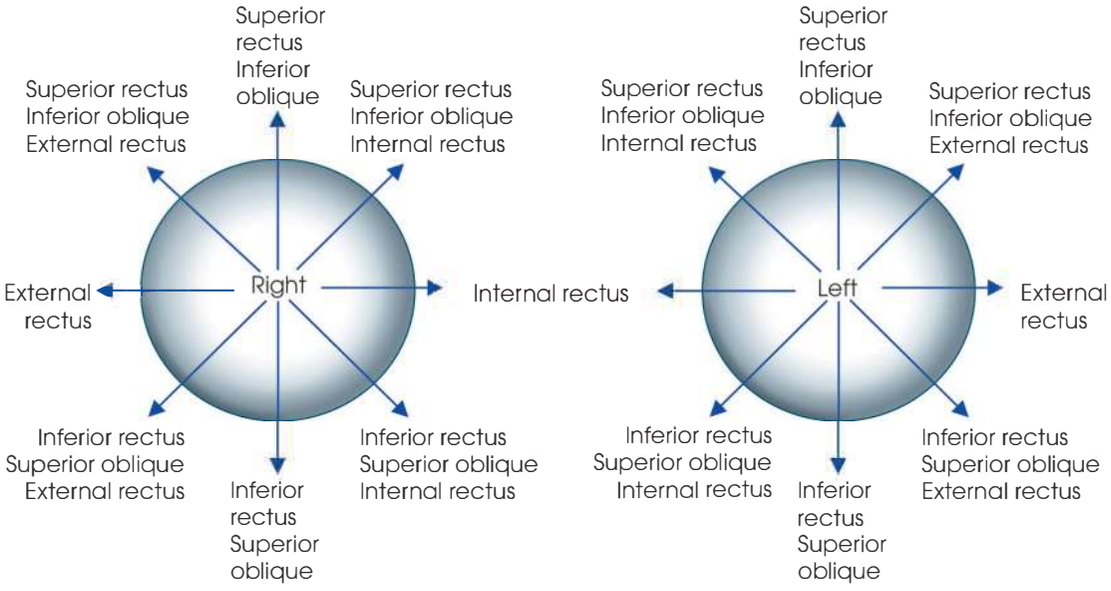

Fig. 117.23: Illustrates the action of the different ocular muscles and co-ordinated movements of the two eyeballs (Savill)

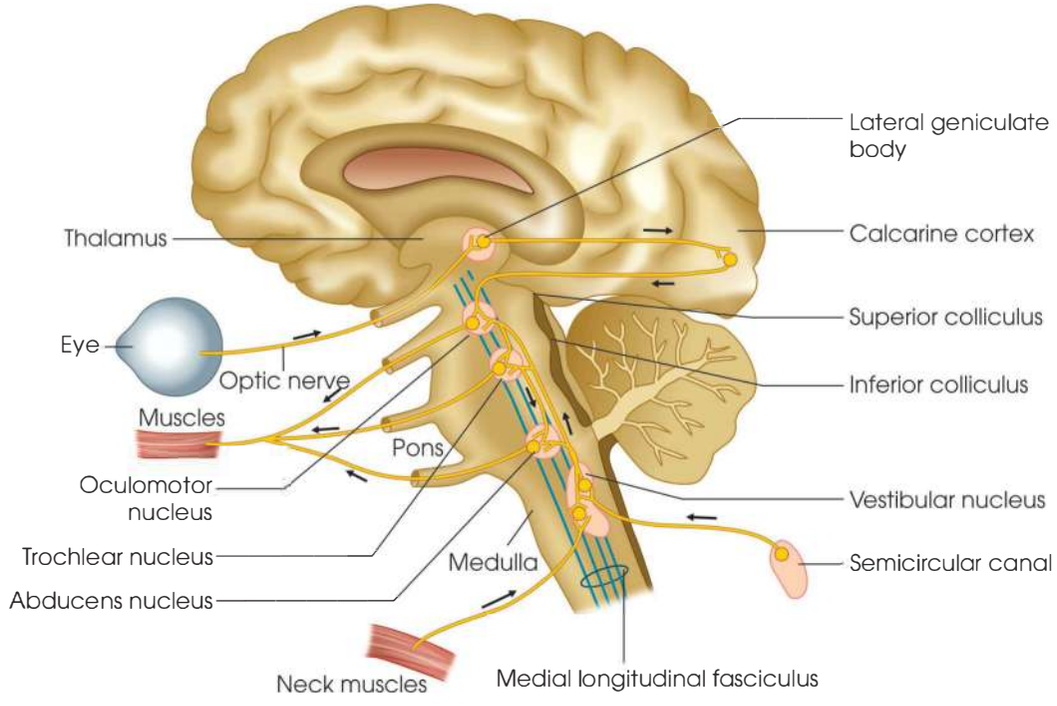

Fig. 117.24: Diagrammatic representation of reflex innervations of the ocular muscles

4. Nuclei for inferior rectus of both sides (Fig. 117.27) downward movement.
5. Nuclei for superior oblique of one side and inferior oblique of other (conjugate rotation).
6. Nuclei for superior rectus and inferior oblique of same side (Fig. 117.28B) (deviation of one corrected by other).
7. Nuclei for inferior rectus and superior oblique of same side (Fig. 117.28A) (deviation of one corrected by other).
8. Nuclei for superior rectus and levator palpebrae superioris of same side (raises the lid when eyes move up).

Squint or strabismus: Anatomical or functional defects of external or lateral ocular muscles cause various types of squint.

Cerebellar control: Through vestibular nuclei and posterior longitudinal bundle.

Midbrain control: Through superior corpora quadrigemina and possible others.

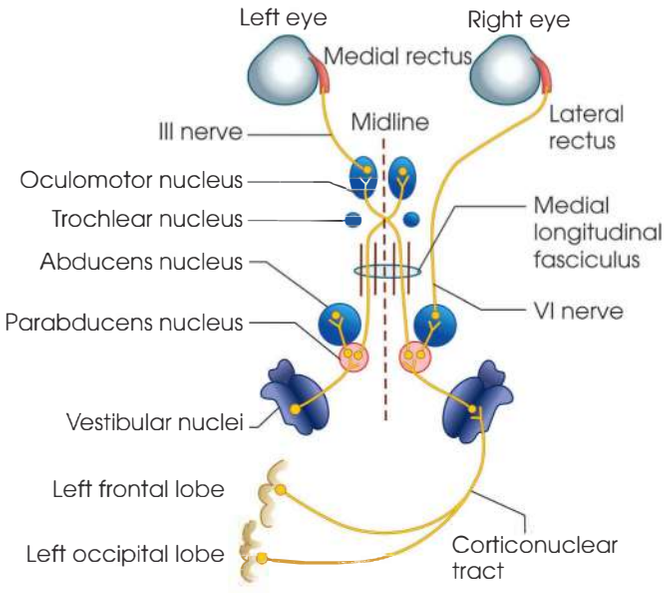

Fig. 117.25: Showing conjugate right gaze. Impulses for conjugate movements in the left frontal lobe (voluntary) and the left occipital lobe (involuntary)

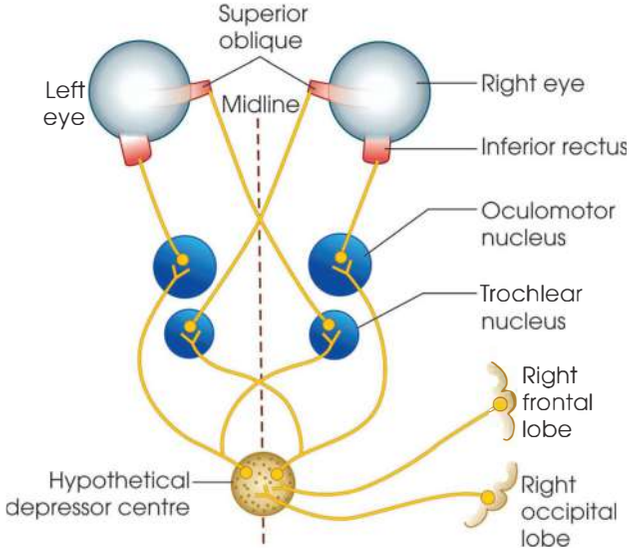

Fig. 117.26: Showing central organisation for conjugate elevation of eyes

Cerebral control (Fig.117.29): Concerned with both voluntary and reflex eye movements. It co-ordinates the action of antagonistic muscles (reciprocal innervation).

Effects of Section of III Cranial Nerve

Muscles supplied by the III cranial nerve will be paralysed.

Effects

1. Ptosis (drooping of the upper lid)
2. External strabismus
3. Crossed diplopia

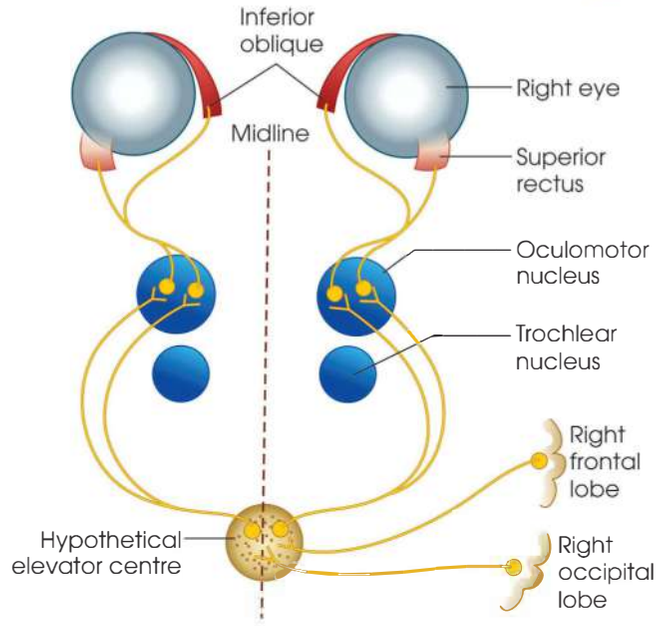

Fig. 117.27: Represents central organisation for continuous depression of eyes

4. Slight protrusion of the eyeball
5. Loss of accommodation
6. Dilatation of pupil
7. Loss of light reflex
8. Inability to move eyeball inwards. Downward and upward movements are also restricted.

Effects of Section of VI Cranial Nerve

1. Internal strabismus
2. Homonymous diplopia
3. Inability to move the eyeball outwards.

Effects of Section of IV Cranial Nerve

1. Slight upward deviation of cornea due to the rolling up of the eyeball.
2. Homonymous diplopia while looking downwards.

IRIS

1. Iris is a circular partition just in front of the lens. It has a central round aperture-pupil. The diameter of pupil can be altered (2 mm to 8 mm) and in this way iris acts as an adjustable diaphragm. The centre of the pupil is exactly against the centre of the lens.
2. Iris has got two types of muscles—the sphincter pupillae and the dilator pupillae. These two muscles along with the ciliary body, comprise the intrinsic muscles of the eye. The sphincter is innervated by the parasympathetic, whereas the dilator pupillae is by the sympathetic. The efferent fibres subserving light reflex are lying in the parasympathetic division of the autonomic nervous system.
3. The parasympathetic nerve fibres supplying the sphincter papillae originate from the oculomotor

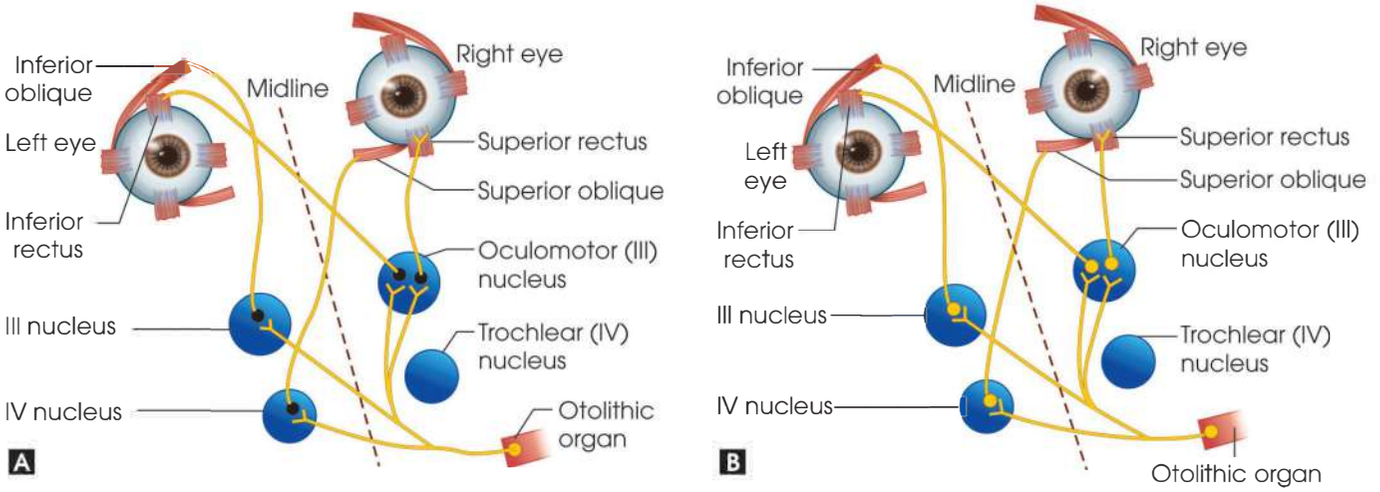

Fig. 117.28A and B: (A) Represents effects of head tilting towards the right shoulder. Due to lack of any compensating mechanism, the vertical meridians of the corneas are tilted towards the right; (B) Shows the otolithic organ which compensates for this and the vertical meridians become perpendicular (Adler)

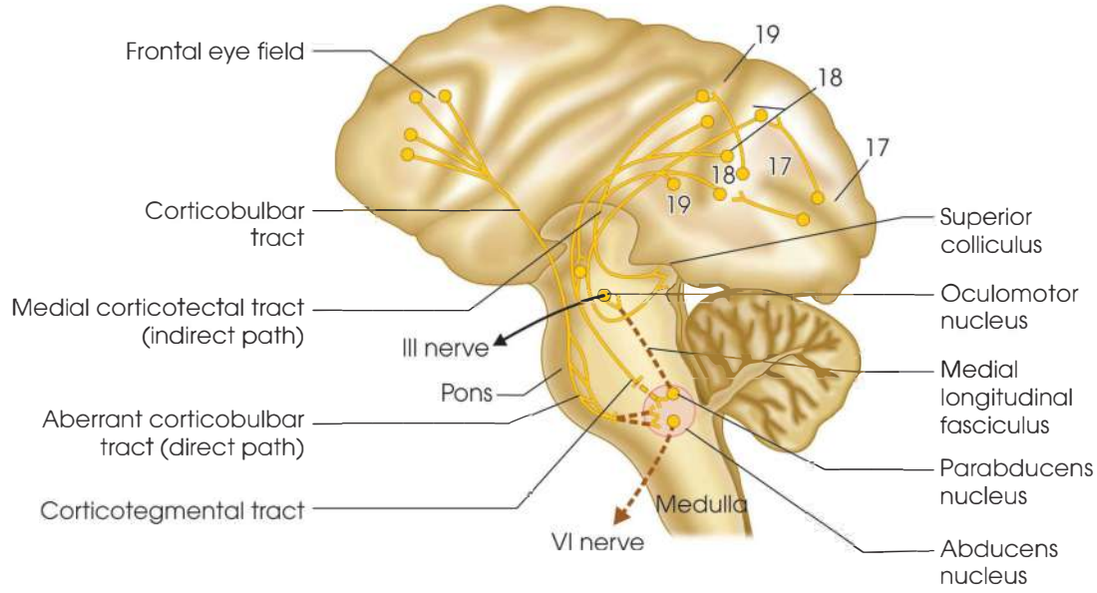

Fig. 117.29: Diagram showing the pathways for the cortical control of eye movements (Crosby and Davson)

nucleus (probably the Edinger-Westphal nucleus) and run via the III cranial nerve, ciliary ganglion and short ciliary nerve (Fig. 117.30).

4. Sympathetic fibres supplying the dilator pupillae originate from the first and second thoracic segments of the spinal cord and sometimes from the eighth cervical or the third thoracic segment. From here the fibres, through white rami, pass into the cervical sympathetic chain and end in the superior cervical ganglion. From here the post-ganglionic fibres arise and run along the internal carotid artery and via the Gasserian ganglion and nasociliary branch of the first division of the V cranial nerve ultimately end in the dilator papillae in the long ciliary nerve.
5. Contraction of the sphincter pupillae alone or in association with relaxation of the dilator pupillae causes constriction of the pupil. Constriction of the pupil is called miosis. Contraction of the dilator pupillae along with relaxation of the sphincter pupillae causes dilatation of the pupil.
6. The dilatation of the pupil is called mydriasis. Drugs that cause constriction of the pupil are called miotics (Fig. 117.31). Parasympathomimetic substances are miotics. These are acetylcholine, eserine, prostigmin, pilocarpine. Drugs that dilate the pupil are mydriatics. Mydriatics are:
   a. Parasympatholytic drugs—atropine, homatropine and scopolamine.
   b. Sympathomimetic drugs—catecholamines, norepinephrine like substances, such as paredrine, amphetamine and amine oxidase inhibitor—cocaine.

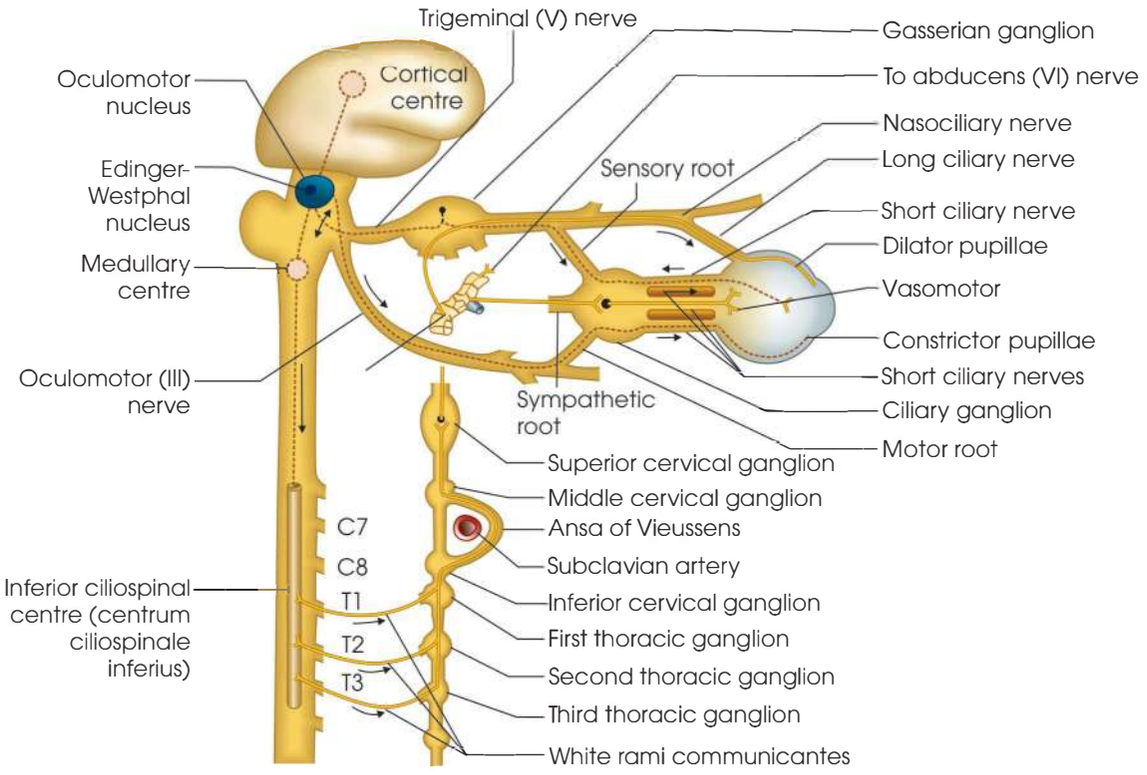

Fig. 117.30: Diagram showing ciliary ganglion with its connections and also origin and course of sympathetic and parasympathetic nerves supply to the muscles of the iris (Adler)

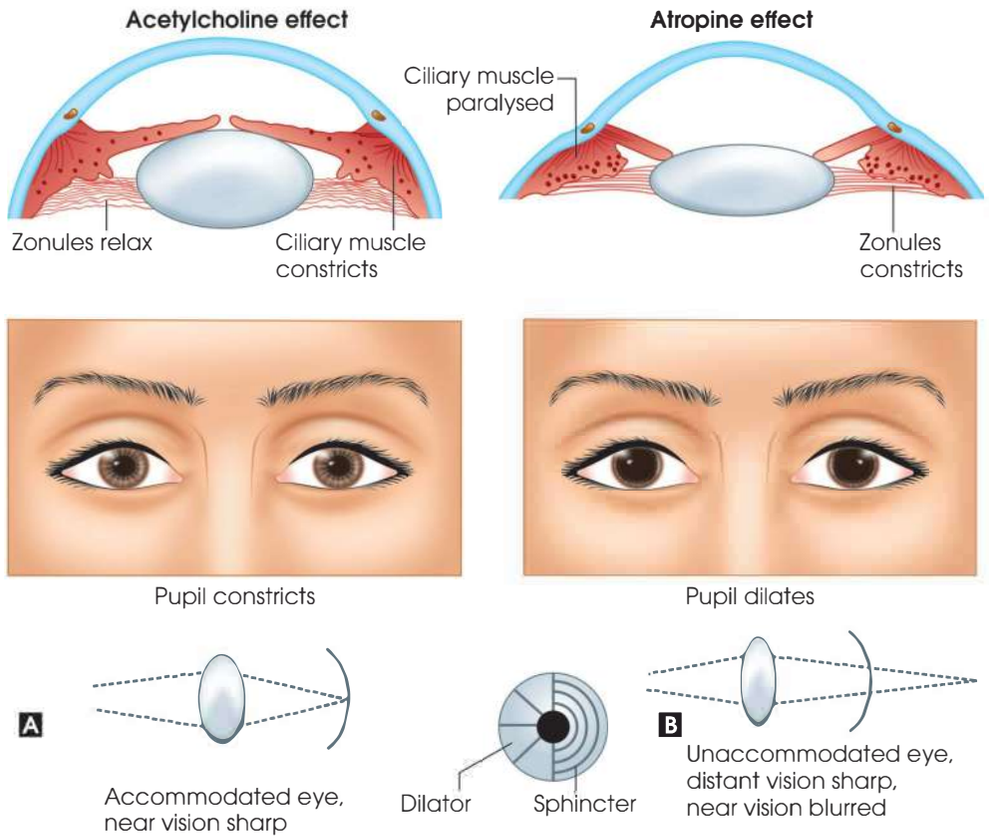

Fig. 117.31A and B: Diagram shows accommodation. (A) The eye is shown with the ciliary muscle and the sphincter muscle of the pupil relaxed by atropine; (B) The ciliary and the sphincter muscles are contracted by a cholinergic drug or by parasympathetic nerve activity

Effects of Sections

Effects of sections of the nerves at different levels produce:

1. Ptosis
2. Ptosis and narrowing of the pupil
3. Enophthalmos (theoretically)
4. Symptoms of Horner's syndrome as shown in Fig. 117.32.

Functions of Iris

1. It adjusts the amount of light falling on the retina.
2. By cutting off the peripheral rays it helps to avoid errors of refraction (such as spherical aberration), and thus produces better definition of the image.
3. Increases the depth of focus.

PUPIL

Pupil, the central round aperture of the refractive system of the eye; is controlled by the iris. The iris behaves like a diaphragm. The normal size of the pupil is 3–4 mm. The size of the pupil varies with ages. It is small in newborn infant. In childhood and also in adolescence the pupils are at maximum size and in advanced age it is often miotic. Besides this, the pupil in woman is larger than that in man.

If the two pupils are unequal then the condition is described as anisocoria. Anisocoria is harmless but should not be considered as normal. Unilateral or bilateral lesions may produce anisocoria.

Functions of Pupil

There are three main functions of the pupil:

1. Pupil modifies the amount of light entering the eye. The amount of light that enters the eye is directly proportional to the area of the pupil. In nocturnal animals, pupil size is of great importance in permitting proper light during night and daytime.
2. Pupil controls the depth of focus of the optical system of the eye. Smaller pupil increases the depth of focus (Fig. 117.33).
3. Acuity of vision is dependent upon pupillary size. Spherical aberrations are minimised by the reduction of the pupillary size.

Different factors may alter the size and appearance of the pupil and these have been presented in the following tabular form.

Pupillary Reflexes

Reflexes Constricting the Pupil

1. *Light reflex:* If bright light falls on the eye and the intensity of illumination is increased gradually and reaches above a threshold value then pupils constrict. This is known as light reflex. Light reflex is of two types, such a direct and consensual (indirect).
2. *Direct light reflex*: Constriction of the pupil due to fall of light directly on the eye is the direct light reflex.
3. *Consensual light reflex:* This is also called indirect light reflex.

If light is directed on one eye then constriction also occurs on the other eye. This is dependent upon fibres

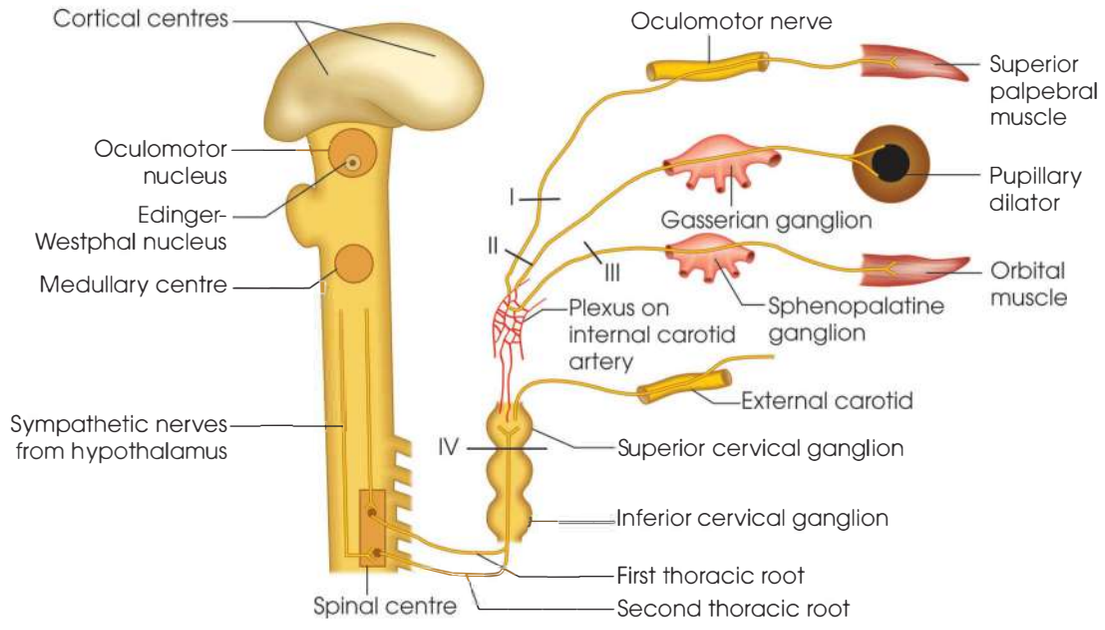

Fig. 117.32: Distribution of the cervical sympathetic nervous system. Lesions at I—ptosis, II—ptosis and narrowing of the pupil, III—enophthalmos (theoretically), and IV—symptoms of Horner's syndrome produced (Adler)

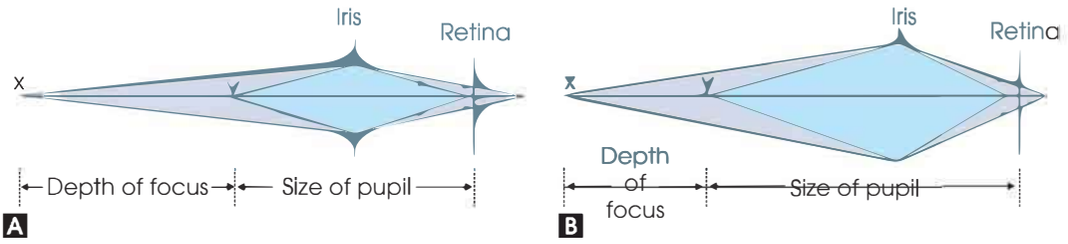

Fig. 117.33A and B: Showing the influence of the size of the pupil on the depth of the focus. Smaller pupil increases the depth of focus (A) and a larger pupil decreases the depth of focus (B)

which cross to the pupillary constrictor centre of the opposite side.

Nerve path (Fig. 117.34): Visual impulses arise in the rods and cones, pass through the different layers of retina, and enter the optic nerve and then the optic chiasma. Here the nerve partially decussates and the fibres enter the optic tracts of both sides. From the optic tract fibres pass out and end in the pretectal area (some hold—superior colliculus), where a new relay arises (colliculonuclear fibres), crosses both in front and behind the aqueduct and ends in III cranial nerve nucleus (most anterior part—Edinger-Westphal nucleus). Fibres of III cranial nerve relay in the ciliary ganglion from where postganglionic fibres arise and supply the sphincter pupillae through short ciliary nerves.

The reflex arc for the direct and indirect light reflexes has been presented in Fig. 117.34.

Functions of Light Reflex

1. To adjust the amount of light entering the eye.
2. To prevent spherical aberration by cutting off the peripheral rays.
3. To increase the depth of focus:
   a. *Near reflex (accommodation-convergence reaction):* Constriction of the pupil during focussing on a near object. This is a part of the mechanism of accommodation to near vision. This is also accompanied by convergence of the eyes onto a near object and accommodation of the lens. All the reactions—pupillary constriction (miosis),

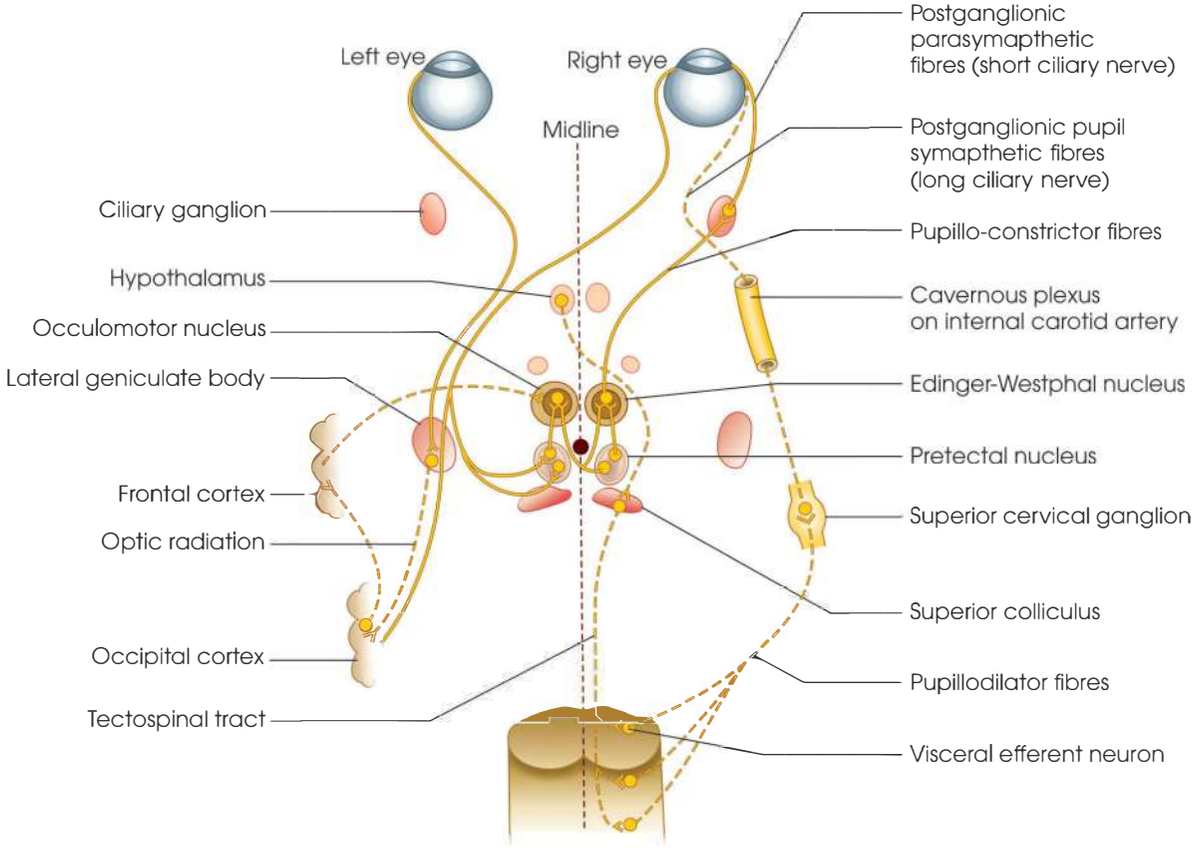

Fig. 117.34: Illustrates pupillary reflexes. Plain lines indicate pupillo-constrictor reflex. Thin dotted lines show path of near reflex from lateral geniculate body of the thalamus to the cortex and oculomotor nucleus. Deep dotted lines represent pupillo-dilator reflex

convergence and accommodation are mediated by the oculomotor nerve (C.N. III).

b. *Lid-closure reflex:* It is also called orbicularis reflex. Constriction of the pupil occurs when the effort for closure of the eyelid is made though the eyelids are kept open. The mechanism is central in origin and oculomotor nucleus may be a factor in the reflex.

c. *Oculopupillary reflex* (*oculosensory reflex*). It is also called trigeminal reflex. Pupil is constricted if the conjunctiva or cornea is irritated. The pathway for this reflex is the ophthalmic branch of the trigeminal nerve (CNV) to the Gasserian ganglion and the nucleus of V cranial nerve, by way of medial longitudinal bundle, connecting fibres finally run to the sphincter nucleus.

The constriction of the pupil sometimes happens due to reflex vasodilatation of the iris capillaries through local axon reflex.

Reflexes Dilating the Pupil (Fig. 117.34)

1. *Psychosensory reflex:* Emotion like fear and anxiety may cause dilatation of the pupil. It is caused by stimulation of the sympathetic nerve.
2. *Withdrawal reflex:* Withdrawal of light from the eyes causes dilatation of the pupil.
3. *Labyrinthine pupillary reflex:* Dilatation of the pupil due to rotation of the body around its long axis. This is due to stimulation of the labyrinthine receptors.

Argyll Robertson Pupil

1. It is a condition when light reflex (direct or indirect) is lost, but the near reflex (accommodation-convergence reflex) is retained.
2. A bilateral lesion affecting the pathway from the cortex to the centre for accommodation in the oculomotor nucleus will cause a loss of the near reflex, but light reflex (direct and indirect) will remain intact. This is just the reverse of the Argyll Robertson pupil. It happens sometimes in post diphtheritic paralysis. Just the reverse condition is called Wernicke's hemianopic pupillary reaction—where light, falling on the blind half of retina, elicits light reflex but not accommodation reflex.

Accommodation

Definition

1. Adjustment of the optical apparatus so as to change the refractive power of the eye, when the image of a near object is brought into focus on the retina is described as accommodation. Such mechanisms involve an increase in dioptric power of the lens.
2. The normal resting eye (emmetropic) is set for parallel rays (20 ft or beyond-far point) and is capable of focussing the distant object without accommodation. But from nearer objects are divergent and unless the refractive power of the media be adequately raised, they will not be focussed on the retina but behind it. Normally, this is done by increasing the curvature of the lens and thus raising its refractive power.
3. Accommodation is not a pure reflex process. It is to some extent a 'willed' movement. Because, the object must be intentionally looked at before the changes can occur. Hence, it is called accommodation reaction (convergence-accommodation reaction).
4. If object is brought closer to closer than a point is reached at which in spite of strong contraction of the ciliary muscle the object is not focussed. The rays from the object are so divergent that the object cannot be focussed.
5. In normal emmetropic eye parallel rays are focussed on the retina from infinity (more than 20 ft) without accommodation (rest). Thus 20 ft is the far point of the normal eye. The 'far point' of the eye is at infinity (6 m or 20 ft and beyond). The 'near point' varies from 9 to 50 cm (average 6 inch) according to age. As age advances, the power of accommodation becomes lowered and the near point recedes.
6. The difference between far and near points is called the range of accommodation. The difference of refractive powers between a resting eye and a fully accommodated one is called the amplitude of accommodation.

> Presbyopia or old-sightedness is the loss of accommodative power of a near object. This is detected only when reading is interfered with at the age of 40–45 years (Fig. 117.35). The nearest point at which the subject is clearly focussed with full accommodation is the near point. Distance between the near point and the eyes increases with age. It is increased very rapidly in early forty and then slowly in after fifty.

Mechanism of Accommodation

Near Response

When a person looks at a near object, his pupil constricts and along with the accommodation the visual axes converge. There are three responses:

1. Pupillary constriction
2. Convergence
3. Accommodation—together three are called the near response.

Following changes take place:

1. Constriction of pupils—caused by the contraction of the sphincter pupillae by the III cranial nerve.
2. Convergence of two optical laxes—due to internal rotation of eyeballs caused by contraction of internal recti by the III cranial nerve (Fig. 117.32).
3. Accommodation: Increased curvature of lens: When the eyes are accommodated for distant vision, the

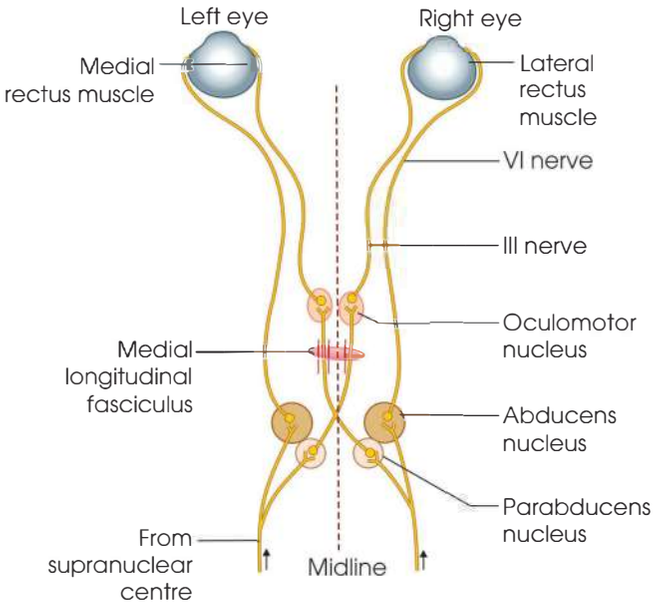

Fig. 117.35: Mechanisms of convergence and divergence (diagrammatic)

ciliary muscle is relaxed; and the choroid, due to its elastic property, recoils and pulls the suspensory ligament peripherally (Fig. 117.36C). Due to peripherally directed traction of the suspensory ligaments, the anterior surface of the lens is flattened and the object is correctly focussed on the retina.

When the eyes are accommodated for near vision contraction of ciliary muscles draws the choroid inward, causing relaxation of the suspensory ligaments. As a result there is relaxation of the capsule of the lens. Due to relaxation of the capsule, the lens assumes a more convex form (Fig. 117.36B). The anterior surface bulges more than the posterior, because the latter is prevented by the vitreous humour. There is increased curvature of the anterior surface of the lens and the object is correctly focussed on the retina.

Nerve Path for Accommodation Reflex (Fig. 117.39)

1. The nerve pathway for the accommodation reflex consists of the optic nerve, optic tract, and lateral geniculate body of the thalamus, optic radiation and the visual area of the cerebral cortex.
2. From the occipital cortex impulses are relayed to the frontal eye field (area 8) by the superior longitudinal association tract, when nerve fibres descend through the anterior limb of the internal capsule to the oculomotor nuclei of the opposite side.
3. From the Edinger-Westphal nucleus nerve fibres pass to the ciliaris and sphincter pupillae relaying in the ciliary ganglion and from the ventral nucleus of the oculomotor nuclei supply the medial recti for the action of convergence.

The changes in the curvature of the lens, i.e. the increased convexity of the lens during accommodation can be determined by the phakoscope of Helmholtz (Fig.117.37). With the help of this instrument following experiment can be performed. When a lighted candle is kept on the outer side of a subject's eye, three images [Purkinje-Samson images (Fig. 117.38)] of the flame within the subject's pupil are seen by an observer.

1. A small, erect and bright image formed by the cornea.
2. A larger, erect and less distinct image formed by the anterior convex surface of the lens.
3. A smaller, indistinct and inverted image formed by the posterior surface of the lens which acts like concave mirror.
4. When the eye is focussed to a near object the second image (b) becomes smaller and moves towards the first (Fig. 117.38 B). The second image again becomes larger when the eye is focussed to a far point (Fig. 117.38A). There is no change of the first and third images. This experiment thus shows that during accommodation no change occurs either in the curvatures of the cornea or in the posterior surface of the lens, but there is increased curvature of the anterior surface of the lens.

Common Errors of Refraction

The normal eye with correct refraction is called emmetropic. Emmetropic eye is capable of focussing the distant object without accommodation. Thus parallel rays from distant objects are brought to focus on the retina when the eye is at rest. Any deviation from the condition of emmetropia is called ammetropia. But refraction may be defective in a number of ways. They are briefly given below.

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1. Hypermetropia (Long-sightedness) (Fig.117.40)

It can see distant objects but not near ones. Because, parallel rays [from distant objects: 6 metres (20 ft) or beyond] are focussed on retina, but divergent rays (from near objects) behind the retina. Two varieties:

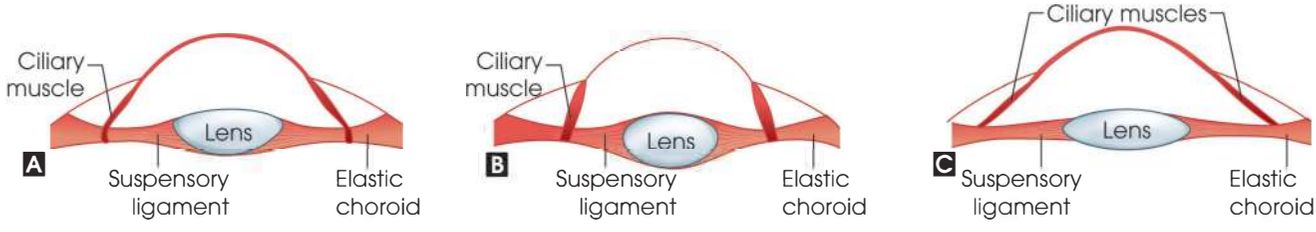


Fig. 117.36A to C: Changes in the curvature of the lens during unaccommodation and accommodation for objects. (A) Representing state of unaccommodation; (B) Showing accommodation for near vision; (C) Indicating accommodation for distant vision

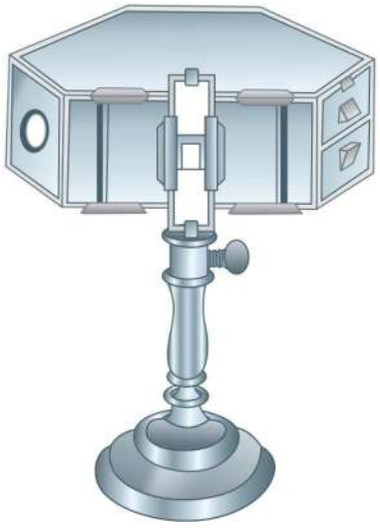


Fig. 117.37: Helmholtz's phakoscope

1. The childhood variety. Here the eyeball is very short. Because, the optical system sometimes develops much faster than the size of the eyeball. As the child grows, the eyeball becomes longer and the defect disappears (in a few cases it persists).
2. The old age variety (between 40 and 45 age group) or presbyopia. Due to reduced power of accommodation; caused by less elasticity of the lens and weakness of the ciliary muscles.

Remedy: Convex glasses (convergent-positive power).

2. Myopia (Short-sightedness) (Fig. 117.41)

It can see near objects but not distant ones. The eyeball is elongated, so that parallel rays are focussed in front of retina but divergent rays are focussed on it.

Remedy: Concave glasses (divergent-negative power).

3. Astigmatism

Astigmatism (Gr. a-, privative or negative; stigma, a point) is the condition, where the rays of light are not brought into sharp focus at the retina. It is the refractive error of the lens system of the eye due to irregular or oblong shape of the cornea (commonest) (Fig. 117.42) or also of the lens (Fig. 117.43).

The curvature of an astigmatic lens along one plane is not similar with the curvature at other plane. For this reason light rays falling on one plane or on other plane of an astigmatic lens do not fall at a common focal point. In an astigmatic lens with greater curvature in vertical plane (A-C) and lesser curvature in horizontal plane (B-D) (Fig. 117.44), light rays in the vertical plane are refracted more greatly than in the horizontal plane. Thus, the light rays passing through astigmatic lens do not converge on a common focal point due to the unequal curvature as well as unequal refractive power of the lens at different planes.

Remedy: Astigmatism may be corrected by a cylindrical lens or by combination of spherical and cylindrical lenses of such strength and so placed that they equalise the refraction in the meridians of the greatest and least curvature.

Spherical Aberration

The peripheral rays in a convex lens are focussed at a nearer point than the central rays, so that the margins of the image become blurred.

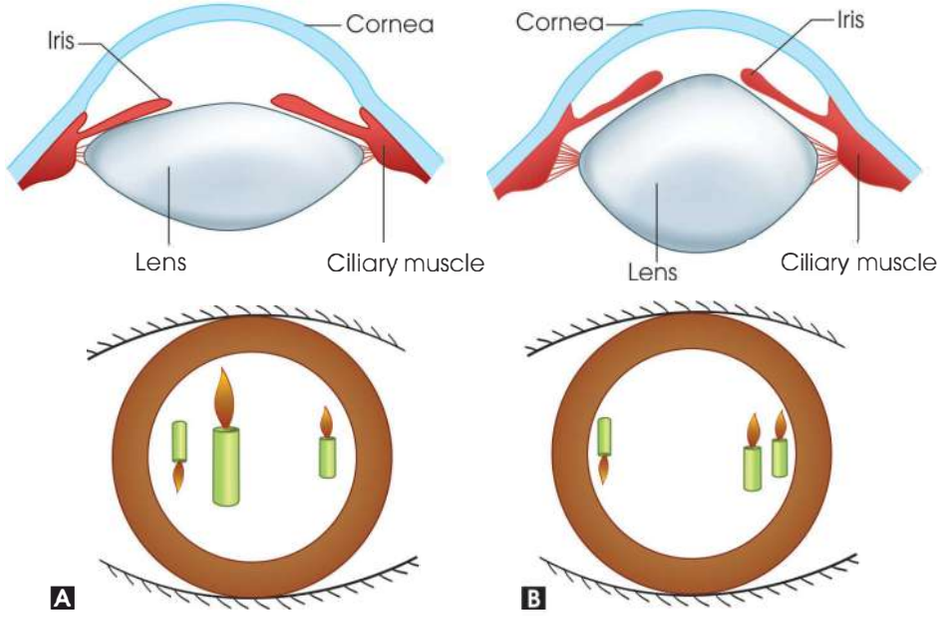


Fig. 117.38A and B: Purkinje-Samson images: (A) Showing the reflections of a candle in the pupil with the subject looking at a distant subject; (B) Also same at a near object

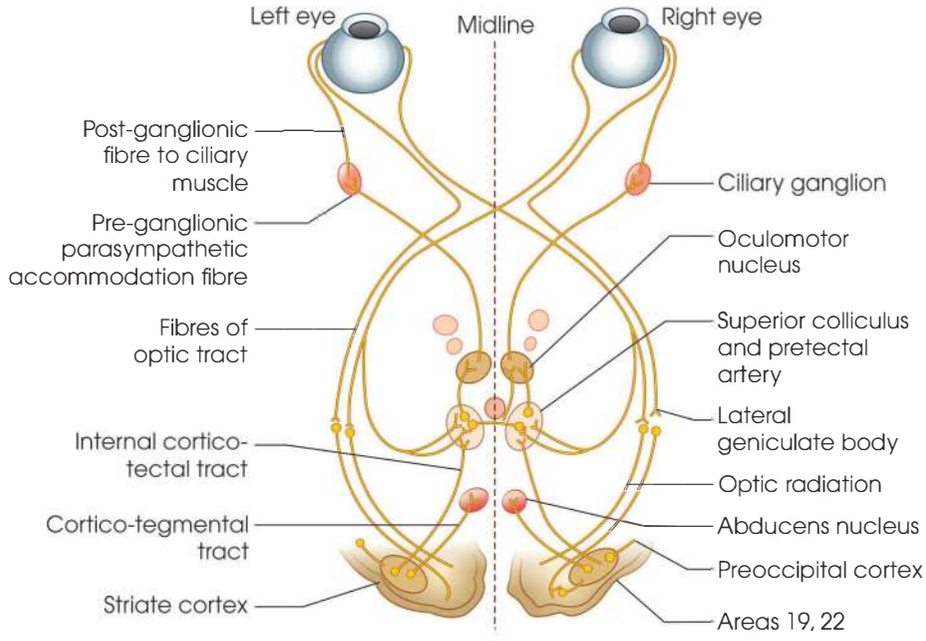


Fig. 117.39: Showing nerve pathways for the accommodation reflex (diagrammatic)

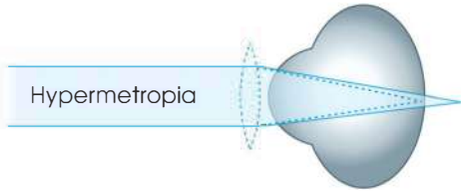


Fig. 117.40: Hypermetropia—correction by converge lens

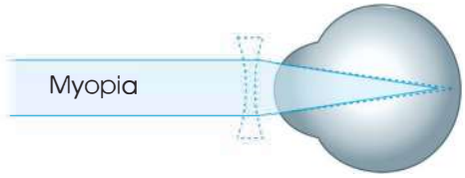


Fig. 117.41: Myopia—correction by concave lens (Winton and Bayliss)

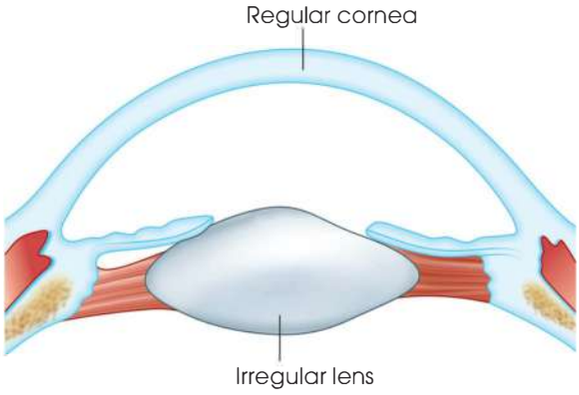


Fig. 117.43: Schematic representation of astigmatism from an irregular lens

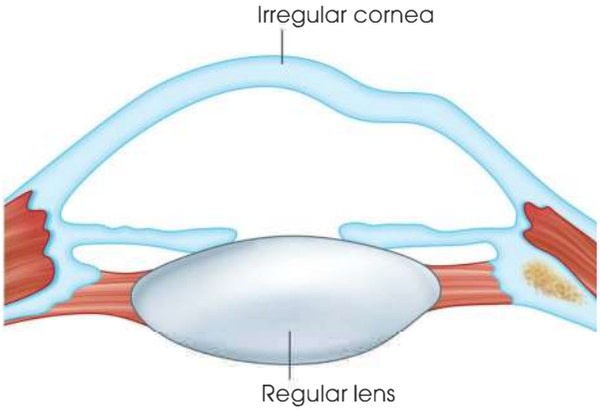


Fig. 117.42: Schematic representation of astigmatism from an irregular cornea

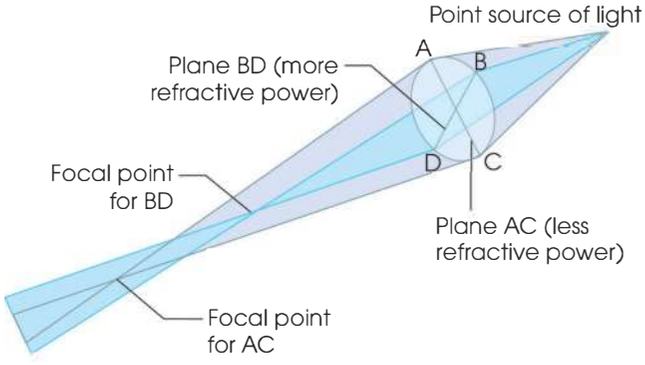


Fig. 117.44: Diagram showing rays of light focus at one focal distance in one focal plane and at another focal distance in the plane at right angles (Guyton)

In the normal eye it is corrected in two ways:

1. The iris shuts off the peripheral rays.
2. The central portion of the lens has a higher refractive power than the peripheral portion. Hence, all the rays are brought to the same focus.

Chromatic Aberration

Lights of different colours (e.g. of different wave lengths) undergo different degrees of refraction. Red light (shortest) is refracted least. Violet rays (longest) are refracted most. Hence, the margin of the image may show rainbow colours. The lens of the human eye has the same defect. It is normally rectified in two ways:

1. The difference of refractive powers of the various refractive media of the eyeball partly rectifies it.
2. The colour fringes are ignored by the brain.

Applied Physiology: Contact Lens

It consists of a glass shell fitted close opposition to the cornea and sclera, and accompanies the eye in its movements. It has got different portions. The corneal segment which covers the cornea corrects optical defects by eliminating the cornea as a refracting surface and, in effect, replacing it by a perfectly spherical one. The common principle of the use of a contact lens is indicated in Fig. 117.45.

Advantages of a Contact Lens

Apart from the cosmetic value, the contact lens is of prime importance in correcting the irregular astigmatism. It is also very important in correcting hypermetropia without producing retinal image of different sizes in subjects having unilateral aphakia (conditions having unilateral removal of the lens).

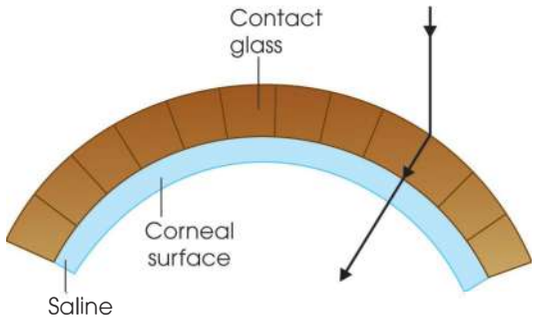


Fig. 117.45: Refraction of a ray by an afocal contact glass

RETINA

Anatomy

It is the light sensitive nervous layer situated between the choroid and vitreous. It ends just behind the ciliary body in a serrated border—the ora serrata. But the pigment layer is prolonged further onto the inner surface of the ciliary body and the iris. Opposite the pupil, lies the yellow spot (macula lutea) having a central depression (0.44 mm)—the fovea centralis. The yellow colour is due to a pigment which is bleached by light. A little medial to the macula (3.5 mm) lays the optic disc. It is a pinkish-white oval area (1.5 mm average) through which the optic nerve fibres pass out.

Histology (Figs 117.46 to 117.48)

Retina is composed of one pigment layer, seven nervous layers and two limiting membranes—external and internal. The layers of the retina from the choroidal side towards the vitreous humour are as follows:

1. ***Pigment layer:*** The retinal layer just near the choroid is known as pigmented layer. This layer

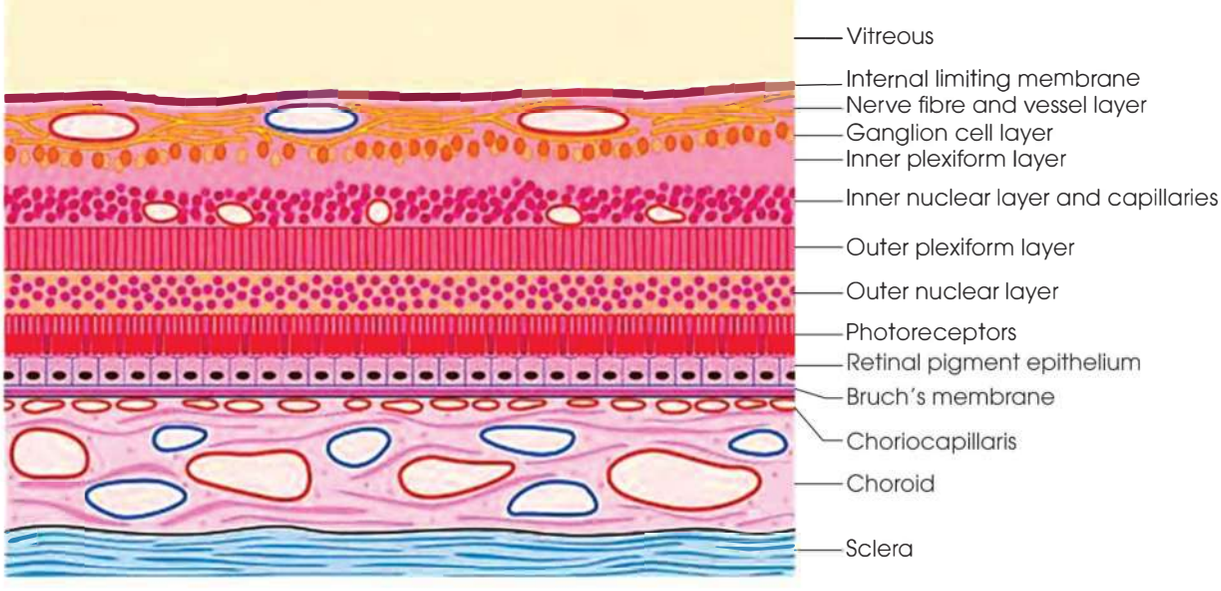


Fig. 117.46: Histological structures showing panoramic view of layers through the thickness of the retina and the choroid (diagrammatic)

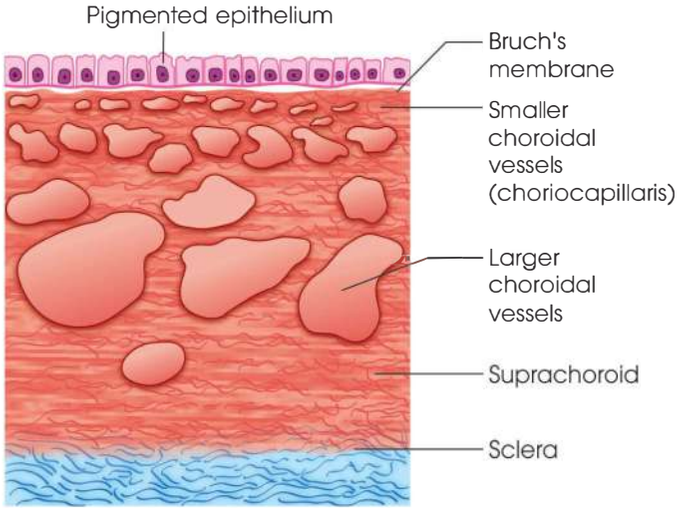


Fig. 117.47: Showing cross-section of the choroid (diagrammatic)

consists of large hexagonal epithelial cells. The cells send processes in between rods and cones. The pigment layer contains pigment which is the inert derivative of tyrosine, melanin. This black melanin pigment in the pigment layer and also in the choroidal layer acts like a black paint inside a camera. This black pigment prevents reflection of light throughout the eyeball and it is very important for acute vision. Bruch's membrane is present immediately against the basement membrane of the pigment epithelium (Fig. 117.47).

2. ***Layer of rods and cones:*** Rods and cones are the photoreceptors and are separated from one another by radially arranged glial fibres (Müller's fibres). Cones are pyramidal in shape; rods are cylindrical. The cones vary in shape in different parts of the retina. In the fovea they are long, narrow and rod-shaped and in the periphery they are shorter and broader. The elongated projected parts of the rods and cones extend beyond the external limiting membrane. The cones are concerned with bright light vision, acuity of vision and colour vision. The cones contain a pigment known as iodopsin. The rods contain a pigment called rhodopsin and are concerned with dim light vision. Both are set perpendicular to the surface and possess a smaller outer segment and a larger inner segment (*vide* under 'Rods and Cones').
3. ***External limiting membrane:*** This is a thin sieve-like membrane formed by the lateral processes of the radially arranged glial fibres at the bases of the rods and cones. The glial cells are very rich in glycogen.
4. ***External nuclear layer:*** This layer is composed solely of nuclei of rods and cones (also called rod granules and cone granules). The rod nuclei are smaller, round and are stained intensely whereas the cone nuclei are larger, oval and are stained faintly. They constitute the first-order neurons in the path of visual impulses. Their axons form synapse in the next layer.
5. ***External plexiform layer:*** It consists of synapses formed by the axons of the rod cell and cone cell and the dendrites of the bipolar cells. Here the several rods make connection with dendrites of one bipolar cell but case of cones, one cone axon is connected with a single bipolar cell—separately in the region of fovea (Fig. 117.49).
6. ***Internal nuclear layer:*** This layer contains the cell bodies and nuclei of the bipolar cells—the second-order neurone of the visual pathway. Beside this

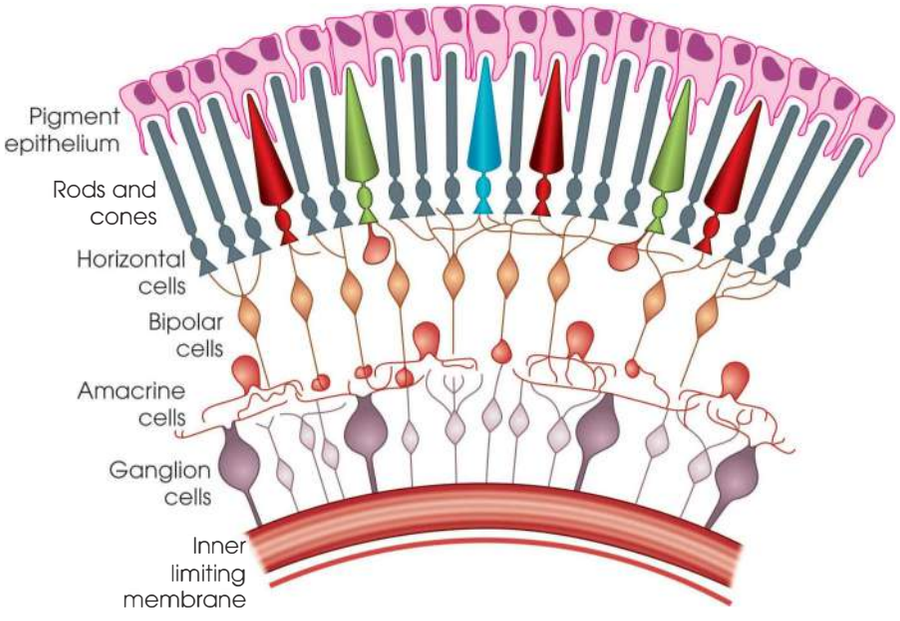


Fig. 117.48: Diagrammatic representation of the layers of the retina and choroid in detail

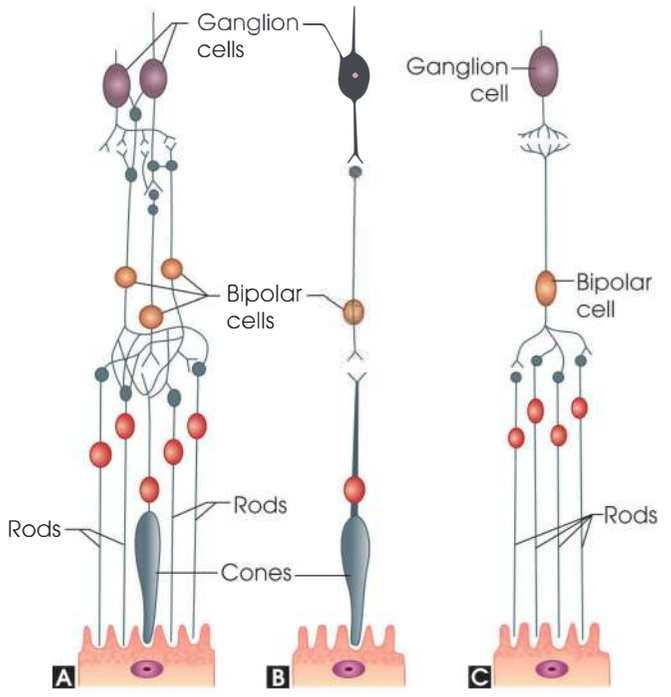


Fig. 117.49A to C: Simplified diagram showing three probable connections between rods and cones and the ganglion cells. (A) Showing connections of 4 rods and 1 cone via 3 bipolar cells to 2 ganglion cells; (B) Representing connections of 1 cone via a midget bipolar cell to a single ganglion cell; (C) Indicating connections of 4 rods via one bipolar cell to a single ganglion cell (Bradbury)

bipolar cell there are certain association neurones—the horizontal cells and amacrine cells. These cells serve to interconnect various regions of the retina and play an important role in the integration and summation of the responses.

7. ***Bipolar cells are of two types.*** Most common one is the diffuse, polysynaptic rod and cone bipolar cells. This type of cell receives axons from multiple rods and also of a cone. The another type is the individual, monosynaptic cone cell or midget bipolar cell. This type of bipolar cell only connects one cone cell (Fig. 117.49).
8. ***Internal plexiform layer:*** This is composed of synapses formed by the axons of the bipolar cells and the dendrites of the ganglion cells and also processes of amacrine cells.
9. ***Layer of the ganglion cells:*** This layer consists of large pyriform cells with Nissl granules. Their axons form the stratum opticum and dendrites pass into the inner plexiform layer. Ganglion cells are also of two types: One is the diffuse type and connects with many bipolar cells. Another type is the monosynaptic or individual ganglion cell which connects synaptic connection by way of midget bipolar cells with only one or two cone cells. This type is only seen in the foveal region, hence foveal vision is very accurate.
10. ***Stratum opticum or optical nerve fibre layer:*** This is made up of axons of the ganglion cells which converge at the optic disc and form the optic nerve. On the inner side of this layer lies the internal limiting membrane. Retinal blood vessels are also present here.
11. ***Internal limiting membrane:*** This layer separates the retinal layer from the vitreous humour. It is formed by the apposition of the glial fibres. It is thus the inner-most layer of the retina. The light rays falling on the eye pass through cornea → pupil → aqueous humour → lens → vitreous humour → blood vessels → nerve fibres and cell bodies to reach photoreceptor cells—the rods and cones. The rods and cones are the first-order neurons and then electrical impulses from these neurons proceed, in reverse direction of rays of light, to the bipolar cells (second-order neurons) and hence to the ganglion cells (third-order neurons) and finally through the optic nerve.

Regional Peculiarities of the Retina

1. *Fovea:* At the posterior pole of the eye there is a yellowish pigmented spot—called the macula lutea in which the fovea centralis is situated (Fig. 117.50).
2. This is very thin (0.1 mm), due to the absence of stratum opticum, ganglion cell, inner plexiform, inner nuclear, and outer plexiform layers.
3. Rods—absent. Only cones present.
4. Cones are highly developed, longer, thinner and closely packed. They are set obliquely so that their fibres communicate with bipolar cells at the margin of the fovea.
5. One cone communicates with one bipolar cell and one ganglion cell.
6. Pigment layer—highly developed and thus the reflected light is well suppressed in the fovea. It is the point where visual acuity is maximum.
7. There are no blood vessels that cross the fovea.

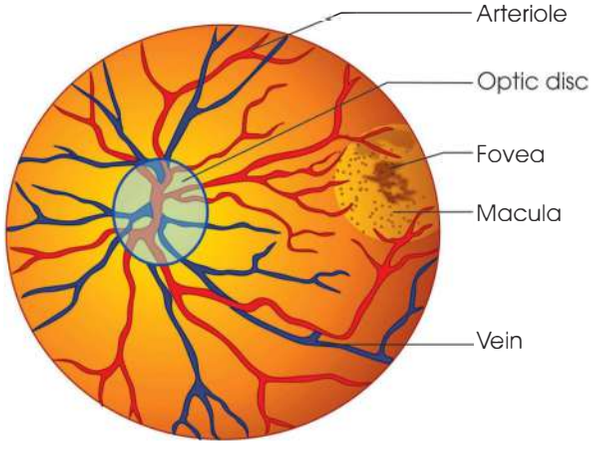


Fig. 117.50: Diagrammatic representation of the retina seen through the ophthalmoscope in a normal human eye

8. Peripheral retina: Chiefly rods. From the fovea to the periphery—cones diminish and rods increase in number. Hence, in the periphery—only twilight vision and no colour vision.

Optic disc: The optic nerve leaves the eye and the retinal blood vessels enter through a point 3 mm medial to and slightly above at the posterior pole of the globe. Through the ophthalmoscope this region is visible as optic disc. There are no photoreceptors in this area and hence no vision (Fig. 117.51). Thus, he called it blind spot (Fig. 117.51).

Blood Supply of the Retina

The retinal blood supply is maintained through retinal circulation and choroidal circulation. The central artery forms the retinal circulation. It enters the eye at the optic disc and gives off smaller branches that course over the retinal surface. Corresponding veins return over the retinal surface to form the central retinal vein and then leaves the eye at the optic disc (Fig. 117.52). The major retinal blood vessels, artery and vein run mostly in pairs. Capillaries of the retinal circulation are present at different retinal levels and deepest capillary plexus is seen in the outer margin of the inner nuclear layer.

The choroidal circulation is maintained by the vessels that penetrate the sclera to one side of the optic disc. A rich capillary plexus, lying immediately against the basement membrane, is called the choriocapillary. This is derived from the choroidal circulation.

Functions of the Retina

1. *Vision:* Retina reacts to light of wavelengths between 390 mμ and 750 mμ. Fovea due to the presence of cones is responsible for acuity of vision, bright light or daylight or photopic vision and colour vision. The peripheral retina due to preponderance of rods is responsible for dim light or twilight or scotopic vision. The duality of the retinal receptors has been collectively known as duplicity theory of vision.
2. *Reflexes:* It is concerned with various reflexes:
   a. Light reflex
   b. Accommodation reflex
   c. Fixation reflex
   d. Visuospinal reflex, etc.

Fig. 117.51: Illustrates the presence of blind spot. Hold the book at about 22 cm from the eye and look at the cross with the right eye only. The white disc will not be visible because the image falls on the blind spot (Winton and Bayliss)

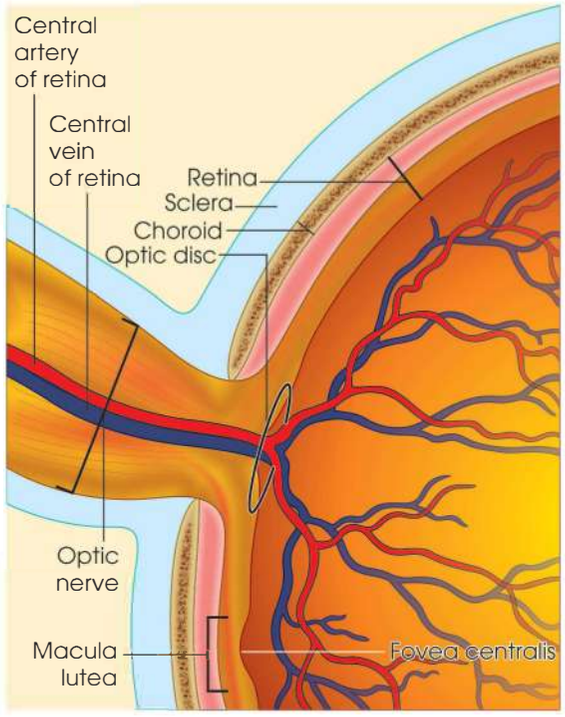


Fig. 117.52: Diagram showing the structure in the region of the optic disc and the entrance of the optic nerve and blood vessels

3. Tone, posture and equilibrium. Retinal impulses also help to maintain tone, posture and equilibrium.

Rods and Cones

The cones which are responsible for colour vision and the rods which cannot detect colour are not evenly distributed over the retina. Each eye contains well over 100 million rods and about 7 million cones. The cones are most densely packed in the fovea. There are no rods in the fovea and the cones themselves are finer than the cones found elsewhere. On moving out from the fovea the proportion of cones to rods gradually diminishes until at the edge of the retina no cones are found.

Fine Structure

1. Actually, photosensitive cells (rods and cones) are situated in the outermost layer of the retina next to the pigment epithelium. Light reaching the photoreceptors first passes through the other layers of the retina, except in the foveal region.
2. Over most of the retina, rods and cones are found side by side, although in the central fovea there are only very closely packed (rod-shaped) cones while in most peripheral regions of the retina, where the receptors are markedly separated, very few cones are found.
3. Rods and cones form synaptic connections with bipolar cells and they in turn connect with ganglion cells. The ganglion cells give rise to optic nerve fibres

that run toward the optic nerve head as the innermost layer of the retina.

4. Ganglions cells and to lesser extent bipolar cells possess quite extensively spreading dendrites so that the activity or a large number of rods and cones influences each ganglion cell. Amacrine cells and horizontal cells mediate further lateral interactions (Fig. 117.53).
5. Photoreceptors of the retina are situated just inside the stratum pigmenti. The principle underlying the generation of visual impulses seems to be that, these receptors contain certain photosensitive pigments which are changed on exposure to light. These chemical changes stimulate the nerve cells to produce visual impulses. When light is withdrawn these pigments are quickly resynthesized. They are briefly described below.

Rods (Fig. 117.54)

1. *Function:* They are responsible for dim light vision and not colour vision.
2. *Number:* About 110–25 million.
3. *Distribution: Vide* above.
4. *Size:* 40–60 µm long and about 2 µm in diameter.
5. *Parts:* Consist of outer segment and inner segment.
6. *The outer segment consists of two parts*
   a. Outer part—thin cylindrical and transversely striated. Composed of a myelin-like substance and contains rhodopsin.
   b. Inner part is broad (thickness double) with longitudinal striations and is protoplasmic. The inner segment is thinner and consists of a nucleus and a long fibre terminating in end bulb of a spherule. The outer segment is the most sensitive part and contains the visual purple of the photosensitive pigment which absorbs light and the inner segment is concerned with the metabolic activity of the rod cell.
7. *Neural connections:* 10 to 100 rods are connected with one single optic nerve fibre.

Cones (Fig. 117.54)

1. *Function:* It is concerned with bright light vision, colour vision and acuity of vision.
2. *Number:* About 6–7 millions.
3. *Distribution:* Fovea—only cones. Periphery—only rods, intermediate—both.
4. *Size:* 28–85 µm long and 2–5 µm in diameter.
5. *Parts:* Consist of outer and inner segments. The outer segment consists of two parts:
   a. Outer part—smaller and transversely striated.
   b. Inner part—larger and longitudinally striated.
6. The inner segment is thinner and consists of a nucleus and a fibre.
7. Neural connections: In the central part of the retina one cone is connected with one optic nerve fibre.

> There is a structural difference in between the outer segments of the rods and cones.

The electron microscope observations have revealed that the outer segments of the rods and cones consist of flattened vesicles or sacs and the inner segments contain metabolic enzymes, e.g. succinic dehydrogenase and large number of mitochondria known as ellipsoid. There is a plasma membrane covering the

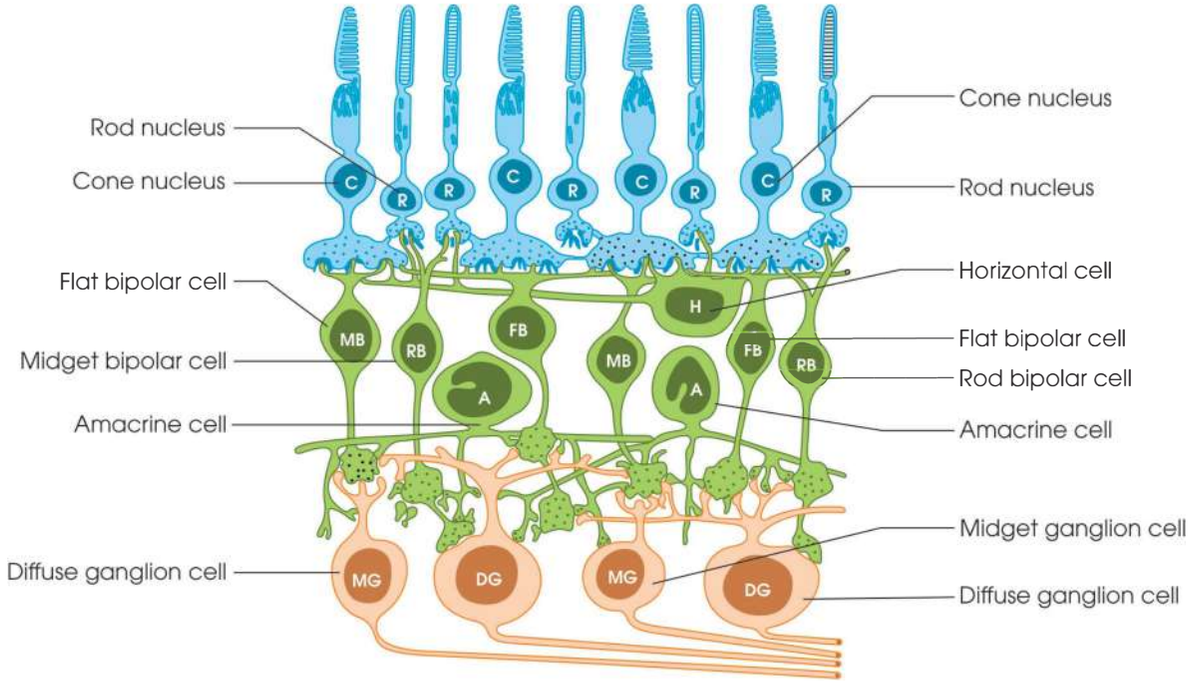


Fig. 117.53: Diagrammatic representation of the contacts in the retina (Baycott and Dowling)

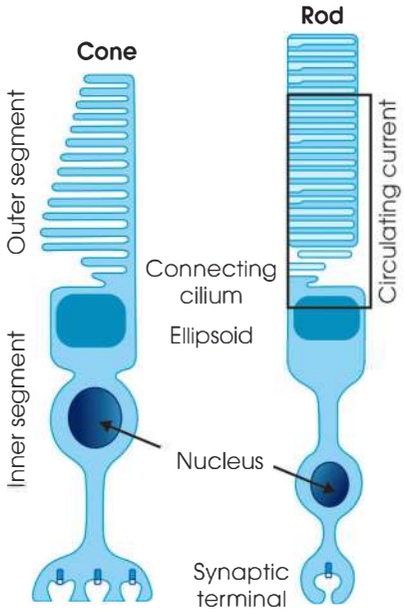


Fig. 117.54: Diagrammatic representation of a retinal rod (on the left), a cone (on the middle) and cones in the fovea centralis (on the right) indicating their components parts; and ellipsoid which is the aggregation of mitochondria in the inner segment

outer and inner segments. The outer segment is connected with the inner segment by the cilium.

In the outer segment of the rod (Fig. 117.55), the double layer discs—the sacs are arranged one above the other like a stack of plates and all are enclosed within the plasma membrane. The double layer sacs look like a rim. The discs or sacs are cut into lobules by longitudinal fissures (Fig. 117.56 C and D).

a. In the outer segment of the cone there are certain differences. The plasma membrane is repeatedly infolded on the side opposite from the cilium to give the double layer disc (sac) structure. This double layer disc structure does not look like a rim and the cone lacks the fissures and lamellar micelles (Fig. 117.56 A and B).
b. The outer segments of the rods which contain the visual purple or rhodopsin absorb light and due to the piling up of the sacs this photochemical reaction takes place over a wider area. In the cones the pigment is iodopsin. Presence of xanthophyll has been demonstrated in the cytoplasm of the cones.
c. Rod cells have got smaller nuclei without definite nucleoli. The nuclei of the cone cells are found near the external limiting membrane and each nucleus has got a nucleolus.
d. The rods have got knobs at their endings where they make synaptic connections with the bipolar cells whereas the cones have got 'pedicles' at their endings. Since there are approximately 6–7 million cones, 110–25 million rods in the retina of each eye and about 0.4–1.0 million nerve fibres in each optic nerve of the human being—main convergence of receptors takes place through bipolar and ganglion cells.

Formation of an Image on the Retina

Rays of light which traverse through the centre of the convex lens fall on the retina without any bend, but rays from the peripheral region of the pupil are bent back to a focus on the retina. The image that is formed in the retina is inverted. The cerebral cortex interprets the inverted image on the retina as an upright one.

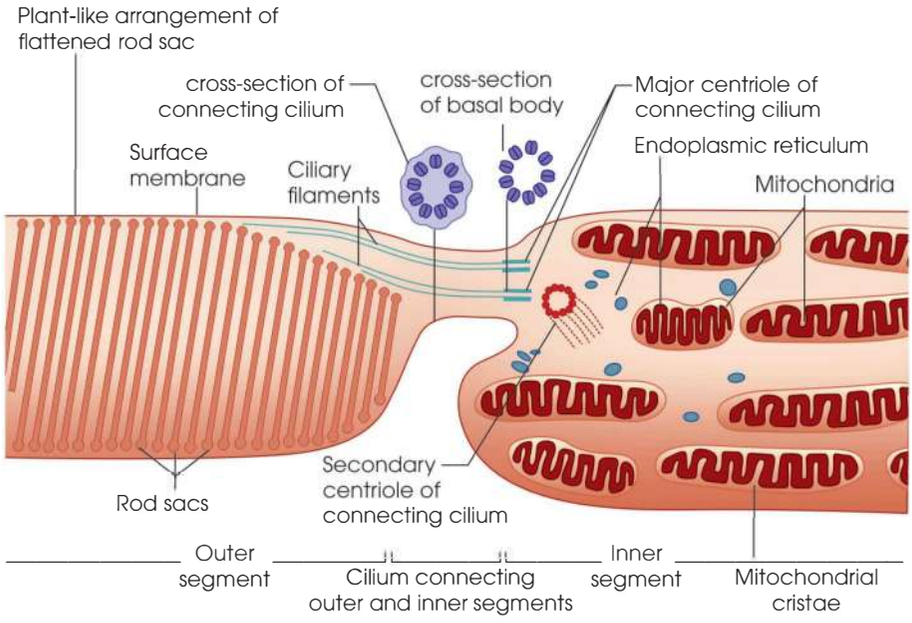


Fig. 117.55: Electron microscopic structure showing connecting zone (diagrammatic) between the inner segment and the outer segment of rod (Mountcastle)

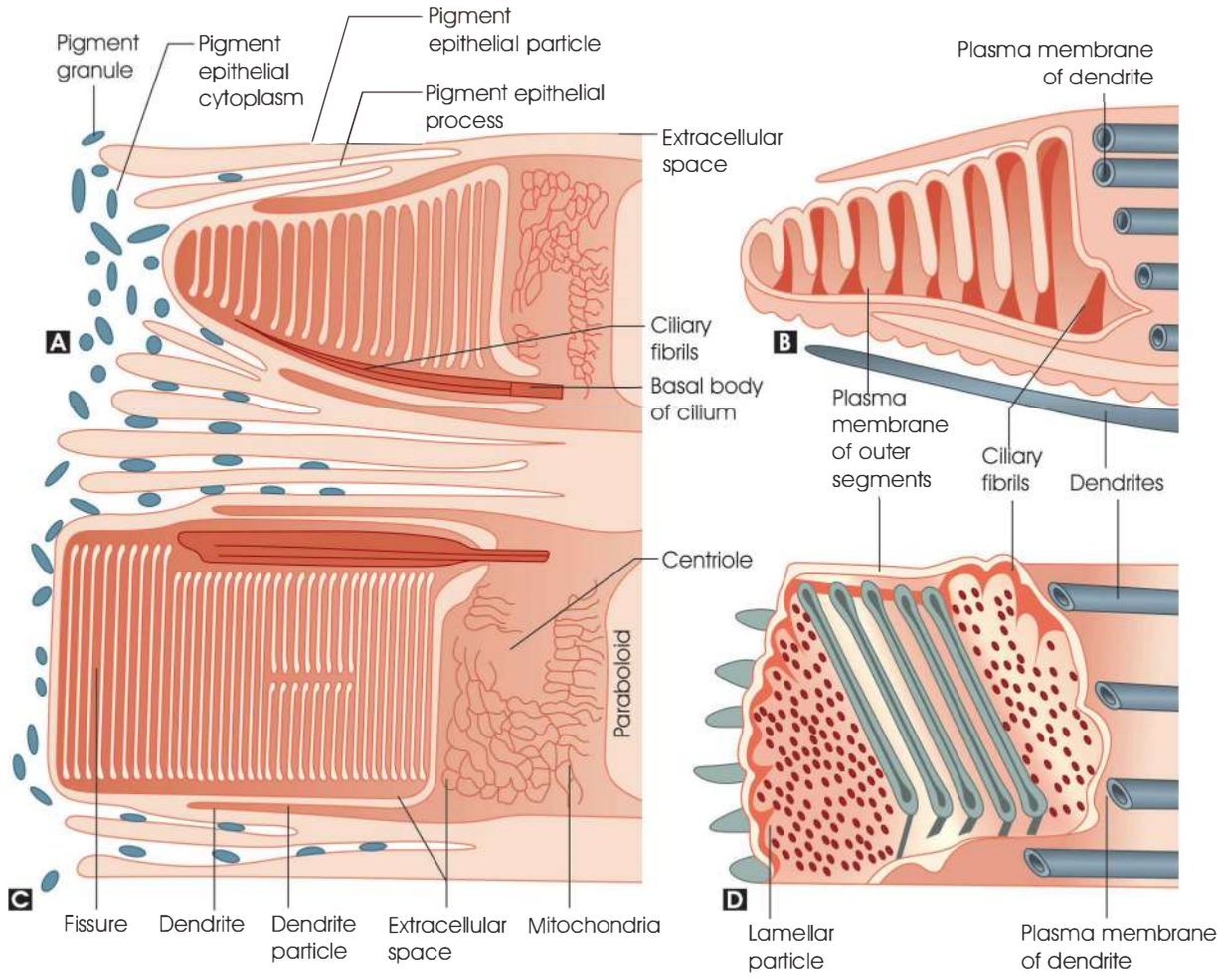


Fig. 117.56A to D: Electron microscopic structure indicating relations between rods (C and D) and cones (A and B), C and D show the cut discs or sacs arranged in stack and covered by a separate plasma membrane. A and B represent infolding of repeated common plasma membrane on the side opposite from the cilium (Best and Taylor)

Effects of Light on the Retina

When light falls in the retina following changes take place.

Photochemical Changes

Key Points

Visual purple or rhodopsin is a chromoprotein containing a carotenoid pigment (chromophore group) as a prosthetic group. This group is the specific part of the molecule and is a derivative of vitamin A. It is present in the outer segments of the rods only. It is bleached on exposure to light. Its main steps have been described in Fig. 117.57.

1. When light falls on the retina, the rhodopsin passes rapidly through several stages. It is first converted into lumirhodopsin and then to metarhodopsin. The metarhodopsin is then split into retinene-1 (retinene) and opsin. Retinene-1 is the oxidative product of vitamin A_1 (vitamin A). Opsin is the protein of rhodopsin.

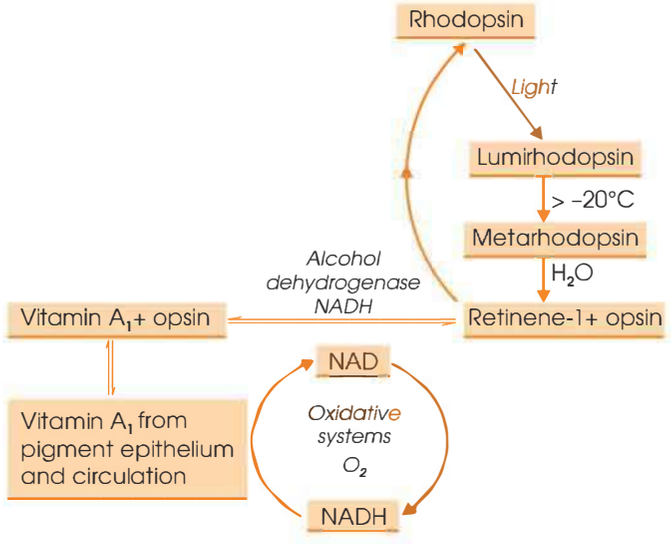


Fig. 117.57: Bleaching and synthesis of rhodopsin

2. The retinene is then reduced to vitamin A_1 by enzyme alcohol dehydrogenase (retinene reductase) in presence of NAD. Vitamin A_1 is then stored in the

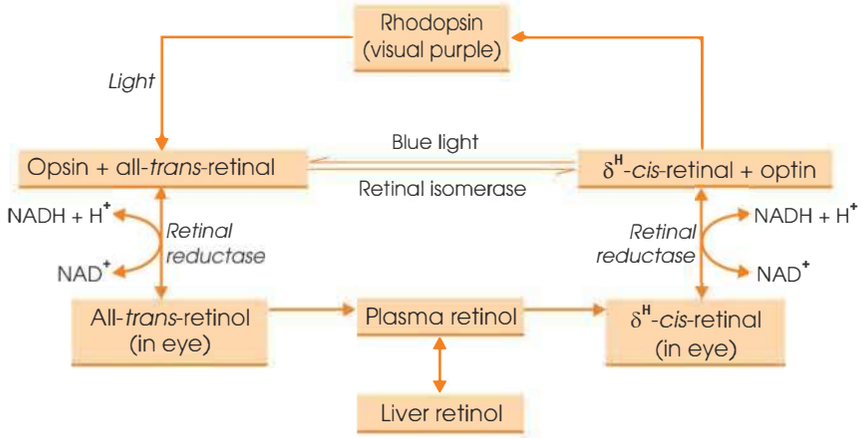


Fig. 117.58: Showing the visual cycle

pigment epithelium. The photopigment must be regenerated after being bleached by light so as to prepare for another response.

3. *Visual cycle* (Fig. 117.58): The *trans*-form of vitamin A (retinol), which is abundant in the liver and the blood, is the most active isomer in all physiological roles of the vitamin other than that of the vision. For vitamin A to give rise to a visual pigment, it must be converted in the eye to a *cis*-isomer or retinal by retinal reductase and retinal isomerase.
4. The *cis*-retinal combines with opsin to form rhodopsin. Light falling on the retina splits retinal from opsin by isomerising it to the *trans*-configuration. The liberated *trans*-retinal then either may be changed back to the *cis*-form by the enzyme retinal isomerase to regenerate rhodopsin after completion of an isomerisation cycle in the eye or may be reduced vitamin A by retinal reductase (Fig. 117.58).
5. Like rhodopsin system the all-*trans* retinene-2 is reversibly converted to neo-b retinene-2 (11-*cis*-isomer) by the specific isomerase. Neo-b retinene-2 and all-*trans* retinene-2 are also reversibly transformed into neo-b vitamin A_2 and all-*trans* vitamin A_2 respectively by alcohol dehydrogenase in presence of NAD. The porphyropsin system has been presented in Fig. 117.59.

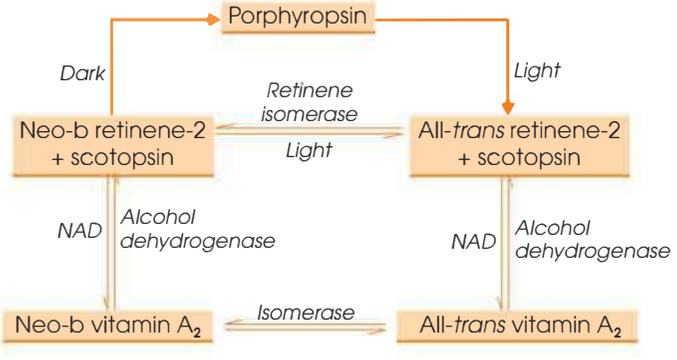


Fig. 117.59: Diagram showing porphyropsin system (Field, et al.)

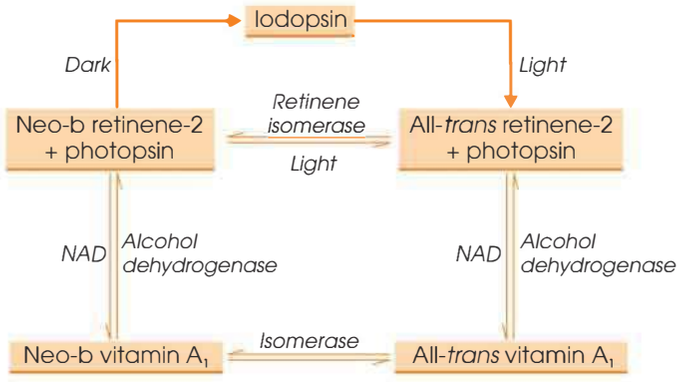


Fig. 117.60: Diagram showing the series of changes in the photochemical substances of cone after absorption of light (Field, et al.)

6. In the cone there is photosensitive pigment which is known as iodopsin. Iodopsin to undergo the same series of changes which happen in case of rhodopsin after absorption of light. Only the difference is in its opsin. Cone opsin is called photopsin (Fig. 117.60).

In summary, it can be described that vitamin A_1 (vitamin A) takes part in the synthesis of rhodopsin or iodopsin, whereas vitamin A_2 takes part in the synthesis of porphyropsin or cyanopsin (Fig. 117.61).

NEUROPHYSIOLOGY OF VISION

Electrical Activity in the Retina

1. When the photopigment absorbs light in a retinal rod or cone, light causes the cell membrane to become hyperpolarised. The light decreases the permeability of the cell membrane to sodium ions. This change in permeability is directly related to the light-induced change in the structure of photopigment because the photopigment is a constituent of the membrane of the outer segment of the photoreceptor cells (rods and cones).
2. The potential changes which are generated in the outer segment of a photoreceptor are transmitted

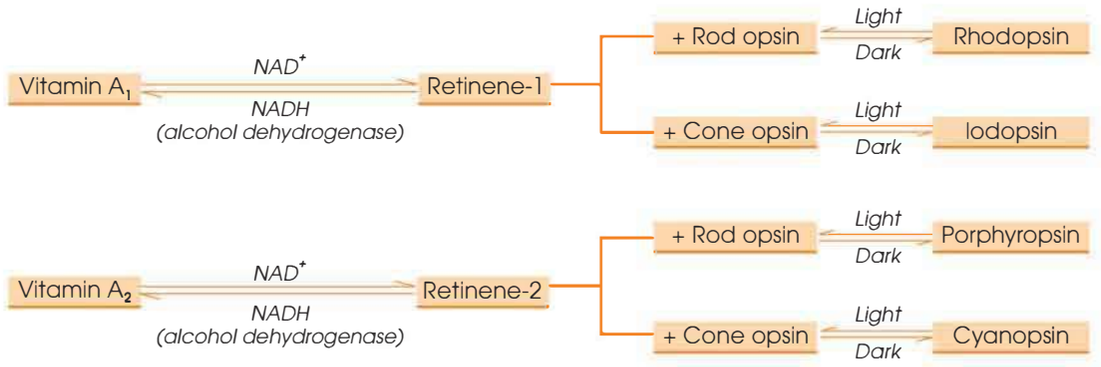


Fig. 117.61: Recapitulations of visual system in the synthesis and breakdown of different photosensitive pigments and vice versa through interactions of rod opsin or cone opsin, with vitamin A-retinene system in presence of enzyme alcohol dehydrogenase (Field, et al.)

electronically to synapses on both bipolar and horizontal cells.

3. The bipolar cells in turn transmit a graded electrical signal to the ganglion and amacrine cells with which they are in contact. On the other hand, the horizontal cells may be capable of spreading an inhibitory effect to surrounding photoreceptors.
4. In the ganglion cells the generated action potential passes along optic nerve fibres and optic tract fibres to the lateral geniculate body and the superior colliculus.

Electrophysiological Changes

Sequence of potential changes in the retina occurs when light strikes the eye. This record of the sequence of potential changes is known as electroretinogram (ERG). The most conventional method of recording the ERG is to put an electrode in contact with the retina and an indifferent electrode on the back of the eye. Responses recorded by this method are very small in amplitude and give only a summated response of the whole retina but not of its individual layer.

The ERG shows different waves.

Analysis of ERG

Since human retina contains both rods and cones, analysis of ERG through recording each from rod-dominated area and also from cone-dominated area is essential. Figure 117.62 shows the ERG recorded through microelectrode technique by from rod and from cone area separately.

1. The c-wave has been omitted from both rod and cone analyses as the same wave are originated from the pigment epithelium.
2. Each component of general ERG except the c-wave can be analysed and explained by the three major

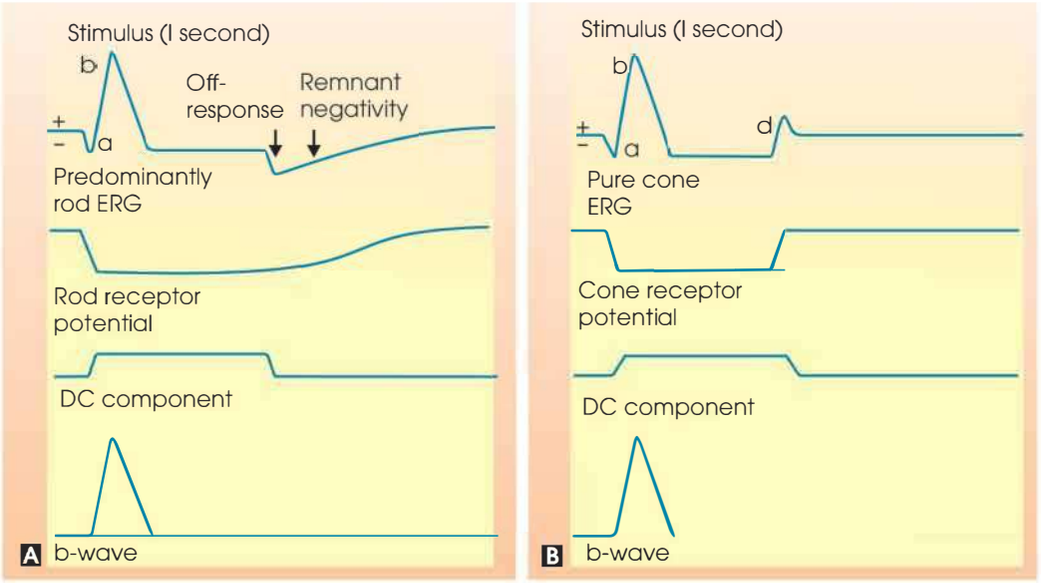


Fig. 117.62A and B: Component of analysis of electroretinogram. (A) Showing ERG from rod; (B) Indicating ERG from cone. 'Off-response' means the stimulation is discontinued (Brown, 1968)

neural components (the receptor potential, DC component, and b-wave).
3. The rod receptor potential recorded directly from the rod has a rapid onset but with a very slow decay at the termination of the stimulus.
4. The DC component is so named as it looks like a direct current pulse and is originated from the inner nuclear layer.
5. The b-wave also arises from the nuclear layer.
6. The a-wave is due to the rising phase of rod receptor potential and the rise of wave is abruptly terminated by the onset of the DC component and large b-wave.
7. The DC component and b-wave have got opposite in polarity to the receptor potential. The b-wave maintains its positivity only for a short period and becomes negative within short period and maintains this stage though the stimulus is continued. This abrupt onset of negativity is due to the negative receptor potential having larger amplitude than the positive DC component.
8. After discontinuing stimulation the DC component abruptly terminates and gives a negative deflection called the 'off-response' accompanied by a slowly decaying negativity. This slowly decaying negativity is known as remnant negativity which is due to very slow decay of the rod receptor potential.

The cone ERG is more or less similar to that of the rod ERG until the stimulus is terminated. The pure cone ERG shows d-wave which occurs just after termination of the stimulus. This d-wave has got both positive and negative waves and there is no remnant negativity. The cone receptor potentials decay very abruptly after termination of the stimulus. Thus the main differences in form of the cone and rod ERGs appear to be the differences in rates of decay of the rod and cone receptor potentials.

Spectral Sensitivity: Scotopic Vision and Photopic Vision

1. Scotopic (dim light) vision and photopic (daylight) vision are the function of the rods and cones respectively. The sensitivity of the eye to a flash of light varies with the wavelength of the light.
2. The colour of light depends upon its wavelength and the visible spectrum extends from wavelength 400 to 750 μm. Thus, the eye responds to light of wavelength from 400 to 750 μm.
3. Beyond this range the receptors are not stimulated. For this reason ultraviolet rays (below 400 μm) and infra red (above 750 μm) are not visible.
4. In scotopic vision, maximum luminosity is observed at a wavelength of 507 μm (blue-green) and in photopic vision the maximum luminosity is observed at a wavelength of 550 μm (yellow-green). The rods are much more sensitive than the cones (Fig. 117.63).

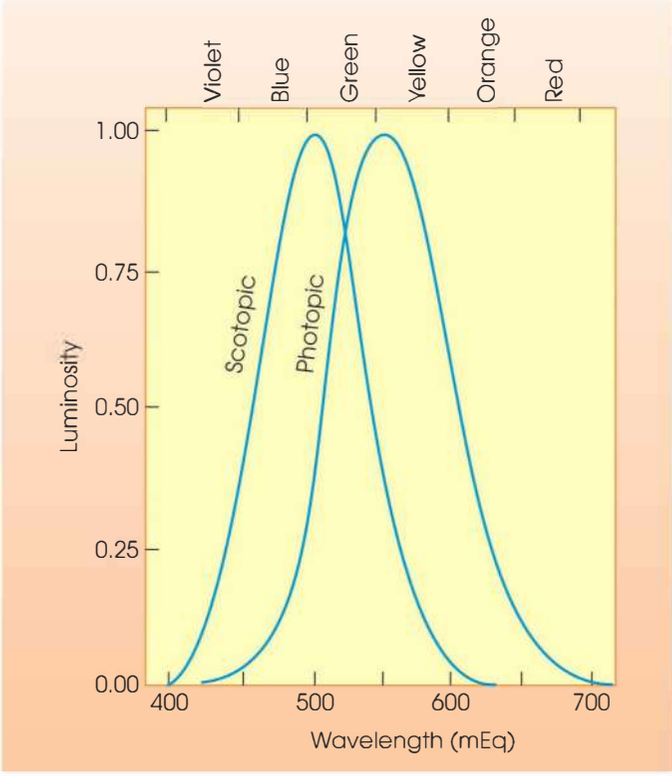


Fig. 117.63: Sensitivity curves for scotopic (rod) and photopic (cone) vision

This shows that the yellow-green photopic function is shifted towards longer wavelength than the blue-green scotopic function. This shift of spectral sensitivity was first observed by Purkinje in 1825 and is thus known as Purkinje shift and the phenomenon is known as Purkinje phenomenon. He also noted that in bright illumination the yellow colour appears brighter than other but in dim light or fading light blue-green colour appears brighter than other.

In the garden with gradual advent of dark, the red and blue flowers look equally bright only before the light fades but after then red flowers appear black and the blue flowers are seen only as coloured objects.

As the scotopic vision is due to rod and photopic is due to cone, Purkinje's shift can also explain partly the duplicity theory of vision.

Light and Dark Adaptation

If the eye, after being exposed to dark, be rapidly exposed to strong light or vice versa, the eyes take a little time to get adapted. Thus, there are two types of adaptation:

1. Light adaptation (photopic eye)
2. Dark adaptation (scotopic eye).

Dark adaptation involves two separate processes:

A. Removal of after-images from the retina.
B. Resynthesis of the bleached visual purple in the rods.

1. In strong light, the first method predominates. In dim light, the second method is the chief process.

2. Time taken for dark adaptation is directly proportional to the intensity of light in duration of exposure and inversely proportional to vitamin A content.
3. Dark adaptation is not possible in vitamin A deficiency and as a matter of fact, depressed dark adaptation is taken as the most sensitive test for vitamin A deficiency.
4. It is a common experience that after entering from brightly illuminated area into a dark area, the vision at first is very poor but after sometimes the vision is improved. This is known as dark adaptation.
5. The dark adaptation can be studied quantitatively by determining the time interval that requires for dark adaptation of a subject who was previously exposed to bright light, now in the dark.
6. Dark adaptation is completed within an hour. Figure 117.64 shows the course of dark adaptation when a person is exposed to total darkness after having been exposed to bright light for several hours. The curve has got two distinct phases with a kink in the middle. The first phase of the curve is due to dark adaptation of the cone, because if this test is made with the foveal retina then the similar curve is obtained and no kink is observed. The second curve is due to dark adaptation of the rod.
7. This shows that at first the sensitivity of vision rises quickly to reach a fairly steady value within 4–5 minutes and maintained this state for another 5–6 minute (cone adaptation). After that the sensitivity is further increased though slowly but with much greater degree (rod adaptation). This shows that both cones and rods take part in dark adaptation. The cone adapts earlier than the rod.
8. In deficiency of vitamin A or in congenital absence of rod, this secondary increased sensitivity (rod adaptation) is not observed. Dark adaptation is very slow if the subject is previously exposed to intense bright light. The radiologist, pilot, etc. use red goggles only to avoid bleaching of visual purple because the rod is insensitive to wavelength of above 640 μm. The red goggles allow light having longer wavelength (650 to 750 μm)

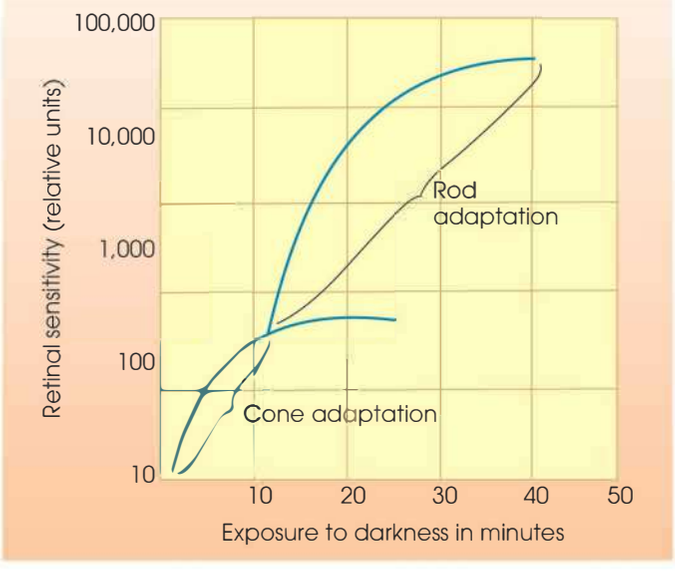


Fig. 117.64: Graphical representation of relative retinal sensitivity during dark adaptation

Light Adaptation

If a person suddenly passes from a dim to brightly illuminated environment, intense and uncomfortable light is felt by the subject but after a while (5 minutes) this stage is passed over and the visual threshold rises. This is known as light adaptation. The light adaptation is nothing but the disappearance of the dark adaptation.

VISUAL ACUITY

1. The visual acuity is the power of the eye to resolve two stimuli separated in space. It is the sharpness to which the details and contours of objects are perceived. The visual acuity is usually defined in terms of minimum separable or resolution threshold—the shortest distance by which the two lines will be perceived separately.
2. The visual acuity depends upon the sensitivity of retina to light, illumination of the surface, the time of exposure and ability to recognise the distance of parallel rays.
3. Visual acuity helps in determining shape, form, outline and minute details of the surroundings. It is expressed as the reciprocal of the angle subtended at the nodal point of the eye—visual angle.
4. The visual angle is generally one minute (60 seconds) when the retinal images are separated by 4.5 μm.
5. Visual acuity is found to be maximum at the fovea centralis where there are large number of cones; and minimum at the peripheral part of the retina where the number of cones are very few.
6. The visual acuity increases with monochromatic light. Errors of refraction reduce the visual acuity.

In testing the visual acuity for fitting of glasses, Snellen's test type is most commonly employed.

Snellen's Test Type

Clinically Snellen's test is employed to measure the ability of the subject in discriminating different letters which are constructed so that their details (as for instances in Fig. 117.65), subtend a known angle at a given distance from the eye. This test type is devised upon the basis that two points or lines separated by a space having a visual angle of 1 minute can be resolved by the average normal eye. This test comprises nine rows of block letters printed in black upon a white background. The rows of these letters are arranged in

Fig. 117.65: Illustrates Snellen's test chart reduced in size (Starling)

descending order of size from above down. The width of the lines forming the letters of the first row subtends an angle of 1 minute at 60 metres from the eye, whereas that of the letters in the two to nine rows, have a visual angle of 1 minute at 36, 24, 18, 12, 9, 6, 5, and 4 (not shown) metres respectively. The top letter is constructed in such a fashion that its details subtend 1 minute at 60 metres. The subject stands at a distance of 6 metres (20 ft) and reads these letters with one eye closed. The acuteness of vision is expressed by a fraction of which the numerator is 6 (distance of 6 metres from the letters) and the denominator is the distance at which the smallest letters can be read by the eye. It the subject cannot read beyond '12-metre' line then his visual acuity is said to be 6/12. The normal visual acuity is 6/6 and subject having 6/5 visual acuity is considered to be better than normal vision. A subject having 6/30 visual acuity is considered to be subnormal vision.

OPHTHALMOSCOPY

The retina of the living eye can be examined with the aid of an instrument known as ophthalmoscope which allows light to be projected into the eye through the pupil along the visual axis of the observer's eye. The term ophthalmoscopy is applied for the process by which the condition of the retina (fundus) itself is examined to see whether it is healthy or diseased.

When light enters our eye through the pupil, a portion of it is reflected back and traces its original course. If the observer and the source of light are in the same position, rays reflected from the fundus will now be received by the observer and the pupil of the subject appears as a red glow, which is called fundus reflex.

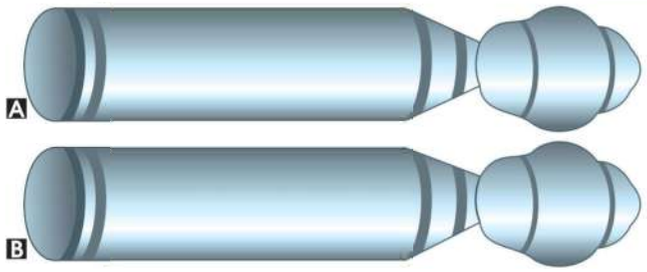


Fig. 117.66A and B: Modern ophthalmoscope; (A) Showing anterior view; (B) Posterior view. '+' indicates the power of convex lenses. '–' indicates the power of concave lenses (*Courtesy:* Dr. Gopal Sen, M.D., D.O. M.S)

The above principle is taken advantage of in ophthalmoscopic examination. In ophthalmoscopy light from a source is reflected from a plane or concave mirror into the subject's eye. If the observer's eye is placed just behind a hole in the mirror, then the rays of light travelling from the subject's eye reaches the observer's eye and the observer sees the fundus glow. In ophthalmoscopy the details of the fundus oculi are seen.

The modern ophthalmoscope, as in the Fig. 117.66, is a self-illuminating one; the illumination is made by dry battery cells. A condenser condenses the light which passes through the lens. The lens forms an image of the source of light at the top of the half mirror. The light then passes through the subject's eye and the observer can see the details of the fundus oculi by placing different powers of lenses behind the sight hole (as described in Morton's ophthalmoscope).

1. The first thing to look is the optic disc. The subject is asked to look at a distance with his accommodation fully relaxed. Normal optic disc is circular with 1.5 mm in diameter. The colour of the disc is pinkish. The centre of the disc is slightly white and the vessels emerge from the centre of the disc.
2. Retinal blood vessels divide into numerous branches after emerging from the centre of the disc. Veins are slightly broader than the arteries which are narrower.
3. The next is to look at the macula luteal which is situated about 3 mm from the temporal side of the optic disc. The area is slightly redder than the general fundus and in the centre of macula; there is a very bright reflex which is called foveal reflex. The macula is brought to focus by asking the subject to look at the light of the ophthalmoscope.

RETINOSCOPY

Retinoscopy is a process by which the refractive error of an eye is detected.

The theory of retinoscopy is based on the principle that if a point of light is placed in front of an eye, the rays of light entering the eye through the pupil are brought to a focus on the retina so that a circular area

of the fundus will be illuminated. In the practice of retinoscopy the subject and the observer are one metre distance away. The examination is carried out in the dark room with the source of light behind the subject, so that the face is not illuminated. The observer stands or sits at a distance of one metre and holds a plane mirror, so that the rays of light reflected from the plane mirror enter the subject's eye through the pupil.

The observer notes a circular red glow of the fundus. In practice when the mirror is tilted to the right and the illuminated area moves in the same direction as the mirror, the eye is hypermetropic, emmetropic (normal) or myopic whose refractive error is less than 1D. If the movement is in opposite direction, the myopia is more than 1D. Retinoscopy is done with or without mydriatics.

FIELD OF VISION

Definition

On looking straight ahead, with the eyeball fixed, that part of the external world which can be seen with each eye is called the visual field of that eye.

Extent

Laterally, it extends up to 104° (i.e. 14° behind the horizontal plane), on the nasal side about 65°. In front there is a cone-shaped area in which the two fields overlap and enjoy binocular vision. The visual fields for blue, red and green are progressively smaller.

Mapping of the Field of Vision (Perimetry)

1. It is done by perimeter (Fig. 117.68). It consists of a metal piece-shaped like an arc of a circle, the centre of which is always marked by a fixed pointer attached to the base of the instrument.
2. The subject's head is supported on the chin rest and the eye to be examined is placed very close to the metal point indicating the centre of the arc. The other eye is covered.
3. An index mark, white in colour with a diameter of about 2 mm, is made to slide along the arc to find the limits of visual field in that meridian. The index mark can be blue, red or green to find out the corresponding colour fields.
4. The arc can be rotated around a horizontal axis through a full circle, and at each new situation the test is repeated to find out the field in that meridian. These results when plotted give the visual field.

BINOCULAR VISION

Although we have two eyes, two optic nerves and two visual centres yet we do not see two objects. This phenomenon of seeing one object with two eyes is called

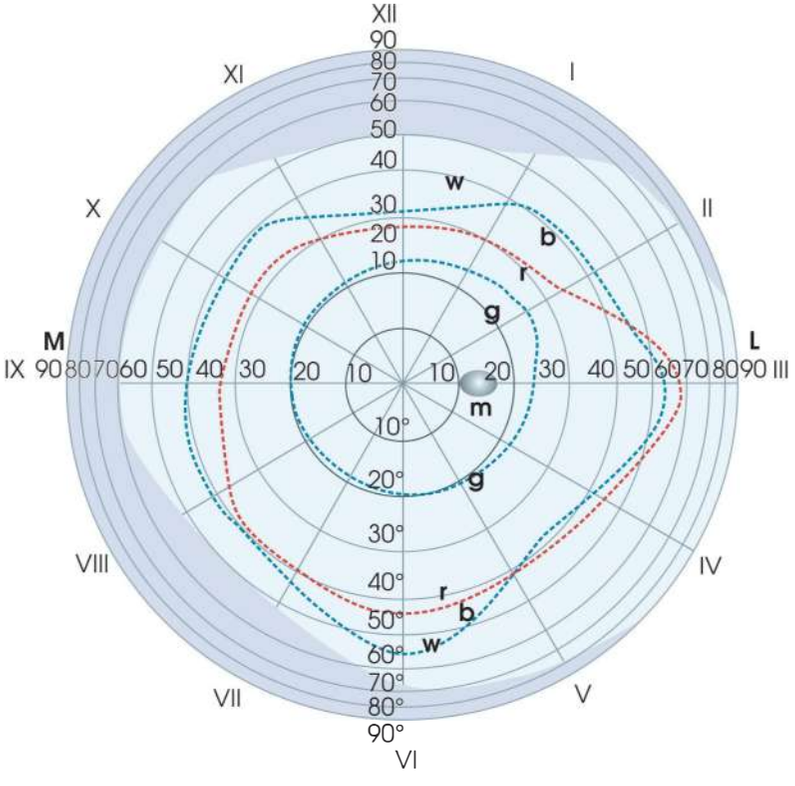


Fig. 117.67: Field of vision of left eye. m—blind spot; w, b, r, g—fields for white, blue, red, green respectively (Best and Taylor)

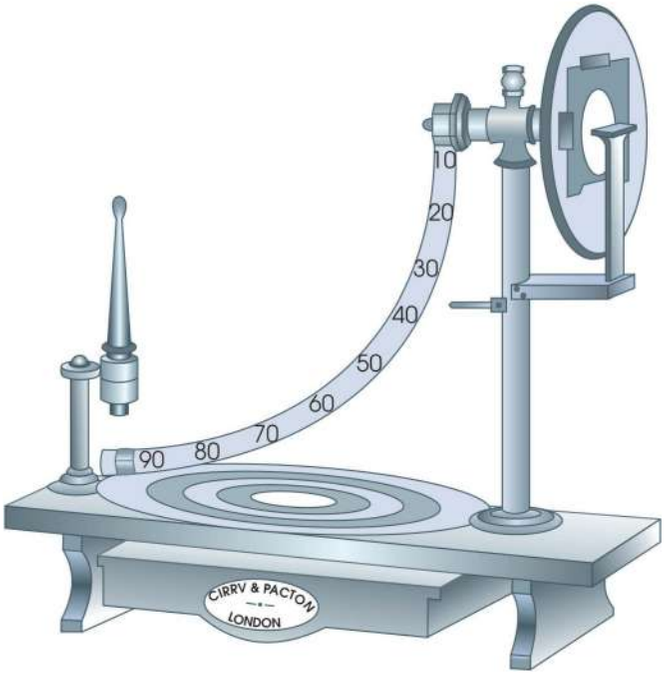


Fig. 117.68: Perimeter (Priestley Smith)

binocular vision. The impulses set up by light rays from an object when transmitted from the two retinae are simultaneously fused at the cortex into single image.

Conditions for Binocular Vision

The two visual fields must overlap (Fig. 117.69). Approximately similar images must be formed on the two retinae. The retinae must possess physiologically corresponding points so that images formed on them may cause a single visual impression.

The external ocular muscles must contract in such a way that the axes of the two eyeballs converge on the object to be seen. The oblique muscles must rotate the eyeballs, so that the physiologically corresponding points of retina may occupy the corresponding meridians.

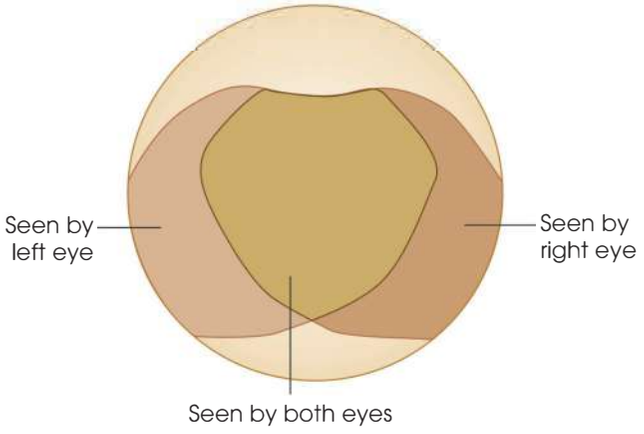


Fig. 117.69: Monocular and binocular visual fields. Heart-shaped common area (seen by each eye) is occurred with binocular vision

Advantages of Binocular Vision

Optical defects of one eye are corrected by the other.

The combined field of vision of two eyes is much wider than that of single eye.

Binocular vision provides a very accurate perception of depth, size and distance (stereoscopic vision).

Monocular Depth Perception

People with one eye can also judge accurately the length, breadth and thickness (depth or distance) of an object. Monocular depth perception depends on the following factors:

The apparent size of known objects: The farther away the object, the smaller will be the size. Consequently, if the size be known, the distance can be judged.

1. The apparent change of colour of an object at a distance. Distance modifies colour. For instance, green trees appear blue at a distance. Colours of many other objects appear to fade more and more as the distance increases. The details of their outlines also become dim. These changes help to guess the distance.
2. Partial blocking of a distant object by a nearer object also gives idea of depth.
3. The distribution of light and shade is an important factor.
4. The shadows which one plane casts upon the other and upon its surroundings are also very helpful.
5. Mathematical perspective, for instance, parallel lines running to a distance seem to be convergent.
6. Parallax. When the head moves in one direction, the nearer object moves in the opposite direction, while the distant object moves in the same direction.

Stereoscopic Vision

Stereoscopic vision is binocular perception of depth. All the factors mentioned under monocular vision, are involved here. The following additional factors are also involved:

1. Convergence of the eye axes to produce images on the fovea simultaneously.
2. There must be some dissimilarity between the two images formed on the retina.

If a man looks at an object with one eye at a time, he will easily note the difference. This difference is of a great help for stereoscopic vision.

Applied Physiology

Strabismus or squint: Binocular vision requires a co-ordinated action of the eye muscles of both the eyes to move the eyeballs in one direction under united

direction. If this balance is lost or the co-ordinating mechanisms are damaged owing to the disease, injuries or congenital abnormalities, the visual axes from both the eyes are not united upon the object or point looked at—this condition is called strabismus or squint. Such defects of long-standing cases or caused by any actual muscle weakness may be remedied by careful surgical shortening of some of the eye muscles or by use of proper prismatic glasses which would direct the light upon the fovea.

THE VISUAL PATHWAY

Optic Nerve and Tract

1. Visual impulses arise in the rods and cones which remain in the posterior part of retina. So, light has to pierce the whole depth of retina before it can arouse visual impulses. The impulse then passes through the different layers of retina towards the ganglionic layer. The rod and cone cells constitute first-order neurons, the bipolar cells—second-order neurons, while the ganglion cells—third-order neurons.
2. It is the fibres of ganglion cells which congreate to form optic nerve. The impulses then pass through the stratum opticum and enter the optic nerve and nerve of sight (Fig. 117.70).
3. In the optic nerve, the impulses from different quadrants of retina occupy the corresponding quadrants.
4. The optic nerve traverses around to optic chiasm. In the optic chiasma, partial decussation takes place. Fibres coming from the temporal halves of retina (nasal field) remain uncrossed, while those from the nasal halves (temporal field) cross. The macular fibres also decussate in the same way. After decussation they form the optic tract.
5. When each optic tract passes between the anterior perforated substance and the tuber cinereum, the tract becomes flattened and winds round the upper region of the cerebral peduncle. Here it is hidden from view on the basal surface of the brain by the uncus and the parahippocampal gyrus. When the tract reaches the lateral geniculate body, its course is divided into a medial and a lateral root. The lateral root comprises commonly the afferent fibres which arise in the retina and undergo partial decussation in the optic chiasma. But the lateral root contains a few fine efferent fibres which are passing forwards to terminate in the retina. Most of the fibres of the lateral root end in the lateral geniculate body, and some sweep medially below the pulvinar and reach the superior colliculus and the pretectal nucleus. The macular fibres end superiorly.
6. New fibres arise from the cells in the lateral geniculate body and pass through the posterior root of the internal capsule.
7. Emerging from the capsule as the optic radiation, the fibres curve backwards and medially to reach the cortex of the occipital lobe, where the higher visual centres are situated.
8. Some fibres in the optic radiation take an opposite course, arising from the cells of the occipital cortex and passing to the superior colliculus. Therefore, the superior colliculus receives retinal as well as cortical fibres. From the superior colliculus new fibres arise and travel through the tectobulbar and tectospinal tracts to reach the nuclei of the oculomotor (III), trochlear (IV), abducent (VI) and superior spinal accessory (XI) nerves and the anterior gray column of the spinal cord. So, the superior colliculus forms a lower visual centre. This lower visual centre is concerned, through its cortical fibres, with the reflex movements of the head and eyes, which occur in response to visual stimuli.
9. The visual cortex is located in the occipital lobe and is subdivided into primary visual cortex (striated cortex (V1) and secondary cortex (V2). Primary visual cortex represents areas 17, 18 and 19 forms secondary or also known as associated visual cortex. In these central structures the image formation processes take place.

To conclude: Fibres of the optic tract terminate in three ways:

a. One set ends in the pretectal area from which fresh relay arises, crosses both in front and behind the aqueduct of Sylvius and ends round the III cranial nerve nucleus of the opposite side. This pathway subserves light reflex.
b. Some fibres end in the superior colliculus and are known as mesencephalic root of the optic tract. From here tectospinal and tectobulbar tracts arise. This pathway mediates tone, posture and equilibrium and also visuospinal reflexes (eye protection movements). Superior colliculi are considered as the highest visual centres in sub-mammalian forms. In fishes and birds these structures are large as that of cerebral hemisphere.
c. The main set of fibres (diencephalic root) ends in the lateral (external) geniculate body and subserves vision. Hence, the lateral geniculate body is called the primary visual centre. The macular fibres as a whole terminate here.

> The lateral geniculate body has six layers of nerve cells. Fibres coming from the retina of the contralateral side end in layers 1, 4 and 6. Those from equivalent spots of the ipsilateral retina end in same region but in layers 2, 3 and 5.

Visual Signal Processing

1. The photoreceptors, rods and cones have high basal release of glutamate. Nearly hundred and twenty-five millions photoreceptor cells synapse with nearly ten millions bipolar cells within the

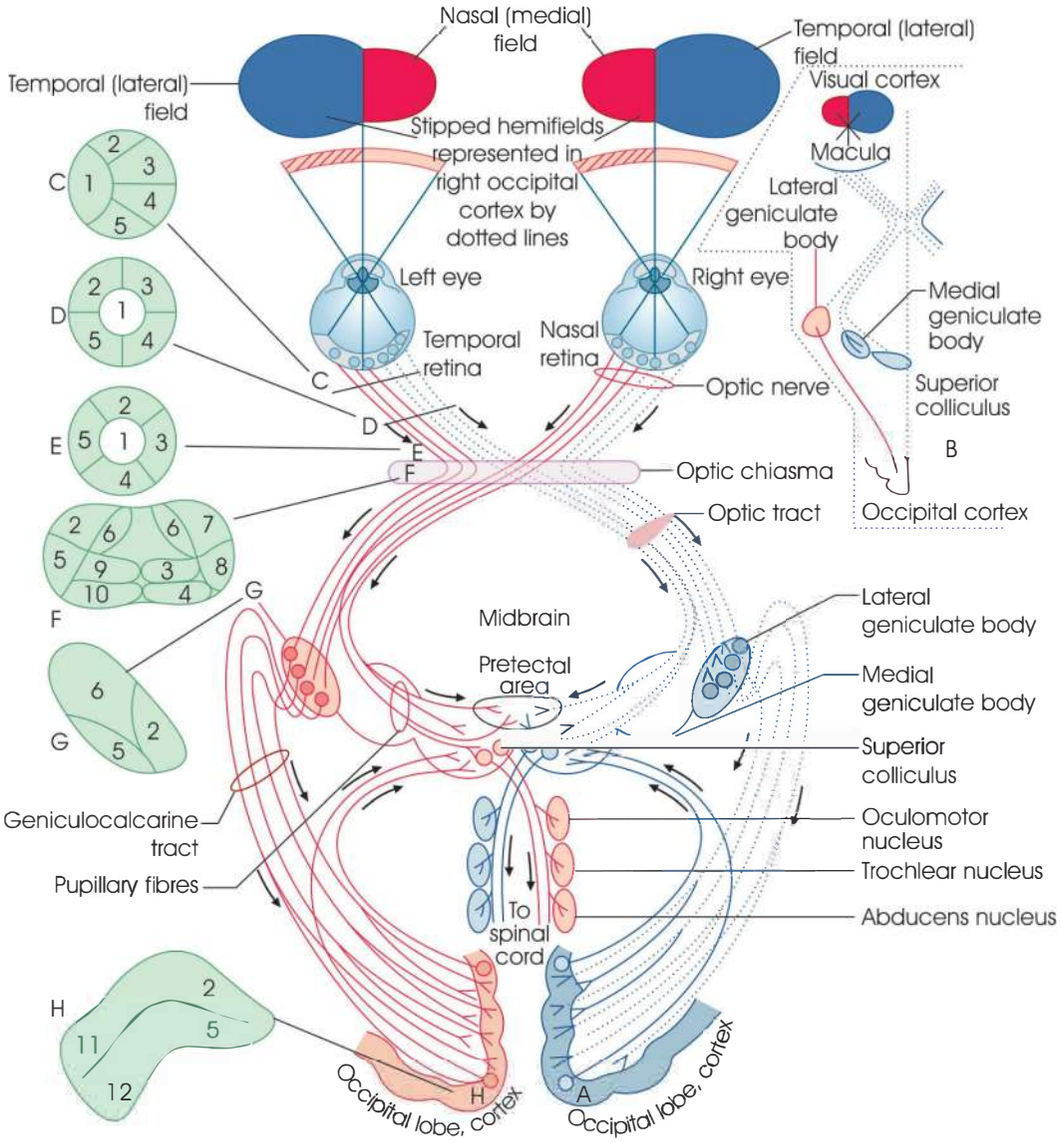


Fig. 117.70: Diagram of the central visual pathways. Fibres from the nasal retina, including the nasal half of the macula, decussate in the chiasma to join the uncrossed fibres of the temporal half of the retina (A&B). The broken lines in A represent nerve fibres from the retina to the occipital cortex that carry visual and pupillary afferent impulses from the left half of the visual field. Insets C-H showing distribution of the nerve fibre bundles at different levels of the visual pathway. C = optic nerve behind the eye. D = optic nerve behind the entrance of the central vessels into the nerve. E = optic nerve in front of its entrance into the optic chiasma. F = optic chiasma. G = lateral geniculate body. H = calcarinc cortex. 1—fibres from macula, 2—fibres from the temporal superior quadrant of the extramacular retina, 3—fibres from the nasal superior quadrant of the extramacular retina, 4—fibres from the nasal inferior quadrant of the extramacular retina, 5—fibres from the temporal inferior quadrant of the extramacular retina, 6—fibres from the temporal half of the macula, 7—fibres from the temporal superior quadrant of the extramacular retina of the other eye, 8—fibres from the temporal interior quadrant of the extramacular retina of the other eye, 9—fibres from the nasal superior quadrant of the extramacular retina of the other eye, 10—fibres from the nasal inferior quadrant of the extramacular retina of the other eye, 11—fibres from the temporal superior quadrant of the macula, 12—fibres from the temporal inferior quadrant of the macula

outer plexiform layer of the retina when photoreceptor cell is encountered by light the biochemical process in photoreceptors starts in them reducing the release of glutamate from its axon terminal.

2. The glutamate influences the activity of the bipolar and horizontal cells, which synapse with the photoreceptor. The visual information is transmitted from the eye to the visual cortex by the photoreceptor cell, bipolar cell and ganglion cell. The synaptic activity of receptor cells is modulated by the horizontal cells and thereby it modulates the transmission of visual information by bipolar cells.

3. The bipolar cells synapse with retinal ganglion cells and amacrine cells. The two types of bipolar cells which respond to glutamate are on and off bipolar cells. Glutamate depolarizes off bipolar cells and hyperpolarize on bipolar cells. The dendrites of horizontal cells mainly laterally inhibit bipolar cells. The axon terminals of bipolar cells synapse on the dendritic processes of amacrine cells and ganglion cells. The bipolar cells release glutamate, which is excitatory to most ganglion cells (i.e. depolarizes ganglion cells).
4. Amacrine cells synapse with ganglion cells and bipolar cell. They increase the centre-surround effect in ganglion cell receptive fields by producing the rapidly adapting response of the Type M ganglion cells. Amacrine cells also connect rod bipolar cells to cone bipolar cells, due to which the ganglion cells are able to respond to the entire range of light from scotopic to photopic. Amacrine cells are accountable for modulating the synaptic activity of the retinal bipolar and ganglion cells, thereby controlling the transmission of visual information by the ganglion cells.
5. Retinal ganglion cells are the final link in the direct pathway from the eye to the brain. They carry visual information for some distance from the eye. They have voltage-gated sodium channels in their axonal membranes and generate action potentials when they are depolarized by the bipolar cells. The off-bipolar which synapses with the retinal ganglion cells depolarizes when it is dark on its centre cones and releases glutamate when centre of its receptive field is dark. This produces depolarization of the retinal ganglion cells generating action potentials by these ganglion cells. As a result the retinal ganglion cells have off-center/on-surround receptive fields and are called off-ganglion cells. Similarly, the on bipolar cell which synapses with the retinal ganglion cells depolarizes when there is light on the centre of its receptive field. This depolarizes the retinal ganglion cells and produces action potentials. As a result they have on-centre/off-surround receptive fields and are called on-ganglion cells. To conclude the receptive fields of the bipolar cells determine the receptive field configuration of a retinal ganglion cell. The retinal ganglion cells provide information important for detecting the shape and movement of objects.
6. The two types of retinal ganglion cells, Type M and Type P cells and it processes information about different stimulus properties. The axons of the M and P retinal ganglion cells travel in the retinal optic nerve fibre layer to the optic disc where they exit the eye. There the axons travel to and terminate in the lateral geniculate nucleus of the thalamus.
7. The axons of the retinal ganglion cells traverse as the optic nerve and carries impulses to the visual cortex via lateral geniculate nucleus.
8. Although the cells of the lateral geniculate body are influenced by impulses in many fibres of the optic tract, they are usually very strongly influenced by discharges from one specified ganglion cell. Like ganglion cells they possess concentrically organised receptive fields of different sizes many of which have colour-specific centre and surround regions. Lateral geniculate body receives afferent nerve fibres from both eyes, but stimulation of one eye can only excite individual cells.
9. *Feedback mechanism:* Lateral geniculate body: Traditionally the lateral geniculate body has been regarded as a relay-station from the retina to the cerebral cortex, and as such, doing a little more than passes the visual information on. However, the message is modified, and this modification is effected not only by the activity in the part of geniculate cells but also corticofugal fibres, i.e. by fibres originating in the occipital cortex which, by either excitatory or inhibitory activity, modify the responses of the geniculate cells to the retinal impulses. By this feedback arrangement the cortex is able to modify and control the information it receives.

   Inhibition of geniculate cells following light stimuli may also be achieved by activity on the part of the geniculate cells themselves. The principal cell, activated by an optic tract fibre, sends its message up to the cerebral cortex but also, by a collateral fibre, it activates a short axon neurone in the lateral geniculate body, and this in turn inhibits the activities of neighbouring principal geniculate cells. The lateral geniculate body continues a process that has already been begun in the retina itself (Fig. 117.71).

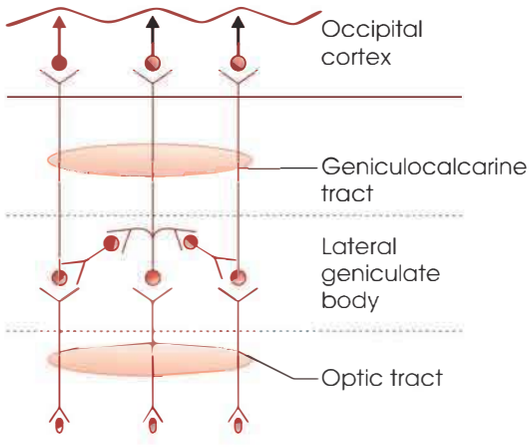


Fig. 117.71: Illustrates inhibition within the lateral geniculate cells relays an excitatory influence to the cerebral cortex, and to short-axon inhibitory cells which inhibit the neighbouring geniculate cells (Davson)

10. *Central representation of visual fibres:* From the lateral geniculate body the fourth-order neurons arise and constitute the optic radiations. These fibres pass through the posterior limb of internal capsule and end in the granular layer of the occipital cortex. The granular layer is also known as striate area (area 17). Area striate forms the walls and lips of the calcarine fissure on the medial aspect of the occipital lobe. The different retinal areas project on the definite area of the cerebral cortex and there is a point-to-point projection onto the striate area. The nasal (medial) half of the right retina and the temporal (lateral) half of the left retina are projected onto the left occipital cortex. The nasal half of the left retina and the temporal half of the right retina are projected onto the right striate area. Macula is represented bilaterally on the visual cortex since macular vision of both eyes is relieved even after extensive lesion of an occipital lobe (*vide* macular sparing). Small lesions in the striate area lead to blindness.
11. *Activity of cells in the visual cortex*
    a. Like other parts of the cortex, the visual cortex appears to contain six layers of cells. It is also called the striate cortex because, on taking a section at right angles to the surface, a white layer can clearly be seen. This is due to the almost complete absence of large pyramid-shaped cells. Most of the axons from the lateral geniculate nucleus end in fourth layer on cells which then make connections with other layers. The cells of third and fifth layers send their axons out of the visual cortex. Most of the connections are perpendicular to the cortical surface. The ability of cortical cells to respond rather selectively to particular spatial stimulus patterns is probably determined by the interplay of excitatory and inhibitory influences from various regions of their receptive fields.
    b. The primary visual cortex projects to area V3A and MTV5 which receives information regarding motion of an object, area LO recognizes larger object area V8 identify colour vision details while functions of V7 is not yet known.
    c. The visual association areas 18 and 19 receive visual impulse information from primary visual cortex. The main function is to aid in perceive finer details of texture of an object such as location, form, shape, depth, etc. The area 8 which is frontal eyelid controls saccadic eye movements.

Though one eye is commonly dominant, most cells in the visual cortex can be excited by stimuli applied to either eye. Simultaneous records from both eyes after stimuli have shown that the response of the cell may be much greater than when either eye is stimulated alone. The stimulus pattern must be appropriately positioned on both retinas in order to obtain maximum response. When both eyes are in their normal positions, the optimal positioning of both retinal images of a real object can only be achieved if the object is at a certain distance from the eyes. Probably different cortical cells respond best to objects at different distances, thus providing a basis for stereoscopic vision which depends upon the presence in the visual cortex of cells responding specifically to retinal images with particular degrees of disparity.

Effects of Injury at Different Levels of Visual Path (Fig. 117.72)

1. Injury to optic nerve at the level I blindness of the affected eye.
2. Crossed fibres at the level II bitemporal hemianopia.
3. Uncrossed fibres at the level III binasal hemianopia.
4. Optic tract before light reflex fibres leave at the level IV.
    a. Homonymous hemianopia.
    b. Light reflex lost.
5. Optic tract after light reflex fibres leave at the level V
    a. Homonymous hemianopia.
    b. Light reflex persists.
6. Optic radiation at the level VI same as V.
7. Area striata of one occipital lobe causes homonymous hemianopia. Injury at the level VII to the upper or lower part of the area striata on one side causes quadrantic homonymous hemianopia.

Macular Sparing

When there is intact macular vision but peripheral vision is lost. This is common with occipital lesion (at the level VII) because the macular representation is wide (bilateral) enough to cover very large fields of the occipital lobe.

Bilateral destruction of the occipital cortex causes complete blindness in human beings.

COLOUR VISION

1. Appreciation of colour is a function of the light-adapted eye and is entirely the property of cones. A normal man can easily distinguish the seven colours of spectrum and an infinite number of intermediate shades.
2. The human eye can recognise as many as 160 different colours in the visible spectrum (400–750 μm) and difference of less than 3 μm wavelength can be detected.
3. The limiting wavelengths of commonly named colours are:
    - White means a colour mixture in which the seven component colures remain in the same proportion as in the sunlight.
    - Black is the sensation caused by the withdrawal of light. It is a sensation connected definitely with retinal activity and one must have a retina in order

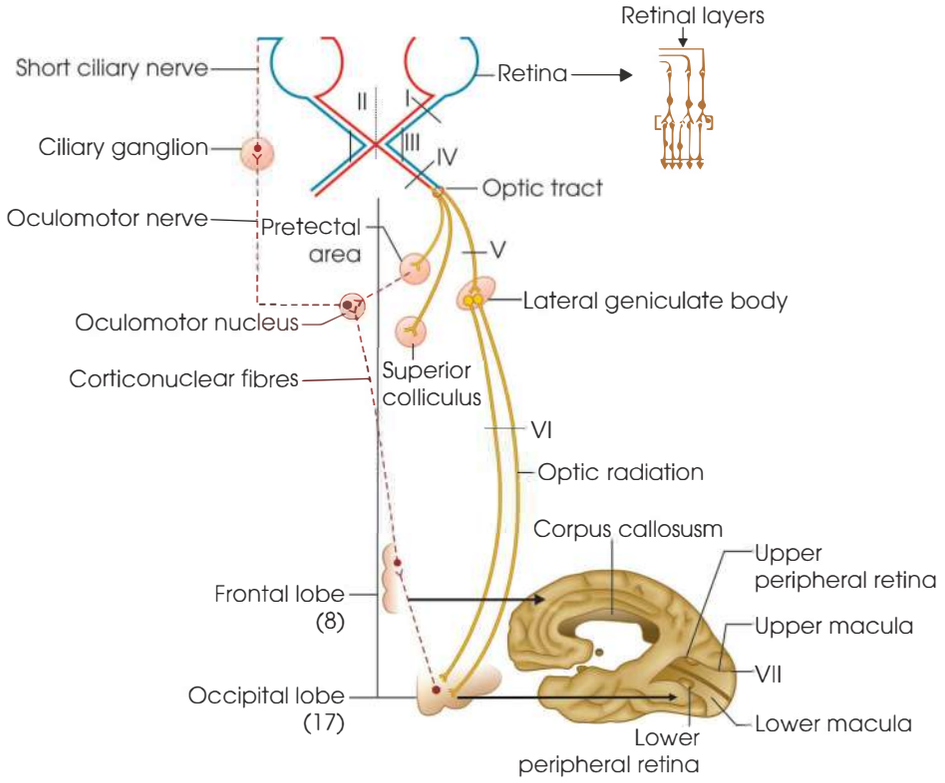


Fig. 117.72: Visual pathways in the CNS and the effects on the visual fields of lesions (I, II, III, IV, V, VI, VII) at various points

to see the black because in the blind spot where there is no retinal receptor one sees not black but nothing.

4. When the intensity of light is gradually reduced, at first the red objects lose their colour, then the yellow, then the green and lastly the blue in the dim light, the surroundings appear to have no definite colour and seem to be of various shades of grey or bluish-black.
5. All the colours of spectrum can be obtained by the fusion of the following three colours in varying proportions—red, green and violet. These are termed the primary colours.
6. Complementary colours are those:
   a. Which appear in the negative after-image.
   b. Which when blended in proper proportions, give the grey impression. Red and green, yellow and blue, black and white are complementary pairs. The same colour may be primary as well as complementary to another colour. The field of vision for the different colours in different.

Violet	397–424 μm
Indigo	424–455 μm
Blue	455–492 μm
Green	492–575 μm
Yellow	575–585 μm
Orange	585–647 μm
Red	647–723 μm

In colour fusion one colour more or less may extinguish another colour, viz. fusion of yellow and blue produces white. Maxwell's coloured disc, with rotating device is used for demonstration of the fusion of colours. If a piece of blue paper is placed against a yellow paper then intensity of colour becomes heightened (colour contrast).

Theories of Colour Vision

There are number of theories, but none can explain the full details. The first important theory (trichromatic theory) explaining the colour vision was that of Young in the year 1801. In the middle of the same century Helmholtz elaborated colour vision in detail.

1. *Young Theory of Colour Vision*

Trichromatic theory of colour vision: This theory holds that there are three types of cones with three fundamental sensations—red, green and violet. These three types of cones contain three photochemical substances corresponding to the three fundamental colour sensations. The theory also suggests the presence of specific nerve fibres and specific cortical cells corresponding specifically to each photochemical substance for each colour sensation—red or green or violet. The different photoreceptors, after being stimulated, transmit different types of messages to the visual cortex.

2. *Helmholtz Theory*

a. The theory of Helmholtz also describes that though the photochemical substances excite the nerve fibre

but the quality of sensation developed depends on the ending of the fibre in the brain. It is assumed that each of the photoreceptors is stimulated to some degree by all of the spectral frequencies but for a particular colour sensation, the specific photoreceptor is chiefly affected by the specific wavelength.

b. The sensations of many colours are produced by combined stimulation of the three receptors at different intensities. White sensation arises when all the three are equally stimulated.

c. Young and Helmholtz trichromatic theory of colour vision also states that any colour can be matched in terms of three stimuli. Figure 117.73 represents the spectral mixture curves indicating the relative amounts of three primary colours that are required for matching any spectral wavelength. From the three curves we can get the amounts of red, green and blue required to match any spectral hue.

As for example (Fig. 117.74), for a blue at 5000A, the relative contributions of green will be 0.33 unit, that of blue 0.01 unit (actual value in the figure is 0.1 but it has divided by 10 only because the luminosity value is very low and has been multiplied by ten) and of red 0.05 unit. The relative contributions of three primary colours for green of 5500A will be 0.88 unit green, 0.12 units red and –0.001 unit blue (approximately).

3. *Granit's Modulator and Dominator Theory*

a. Granit in 1945 inserted micro-electrode into the single ganglion cell and investigated the sensitivity to light of different wavelengths. He obtained the sensitivity curve in the light-adapted eye and also in the dark-adapted eye similar to that in photopic and scotopic visibility respectively.

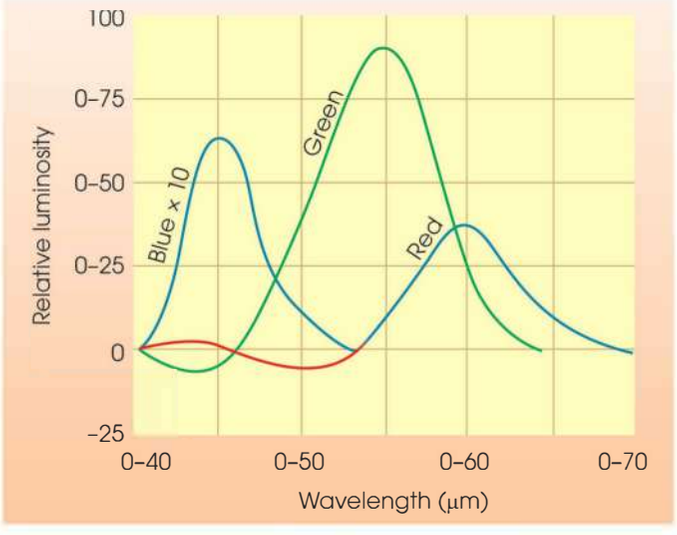


Fig. 117.73: Graphical representation of spectral mixture curves indicating the relative amounts of the three primary colours for matching any spectral hue (Wright)

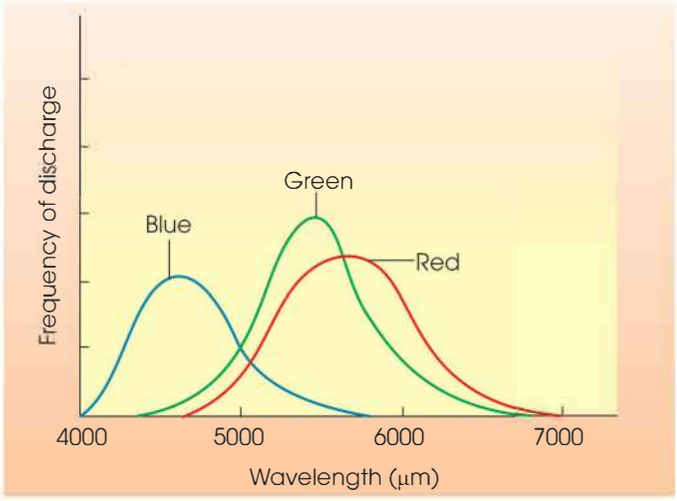


Fig. 117.74: Wavelength response curve of three receptors sensitive maximally to red, green and blue respectively (Davson, 1963)

b. The shift of scotopic curve to photopic curve suggests that as the rods and cones converge on the single ganglion cell, then the rod will possibly cease functions at light intensities which will stimulate the cones.

c. On the basis of his findings Granit has described that there are ganglion cells which are stimulated by the whole of the visual spectrum. These are described by him as dominator. There are two types of dominator—dominator for cone and dominator for rod.

d. In light-adapted eye the dominator cones in general give broad sensitivity curve with maximum response around wavelength of 550 μm. In dark-adapted eye the dominator rods only response and give maximum response at wavelength of 500 μm. The dominator cone indicates intensity of light, but not the colour. Dominator rod is probably related to the sensation of brightness.

e. In the light-adapted eye Granit found also certain ganglion cells which are stimulated only at a narrow wavelength band. These are described as modulators and are of three groups. One group is affected by blue light of wavelength 450–470 μm, one that are affected by green light of wavelength 520–540 μm, and other is affected by red-yellow light of 580–600 μm (Fig. 117.75).

f. Granit has also described that during light adaptation, the modulators also come into action. The spectral composition of light stimulus determines at what degree the three groups will be stimulated. As for example, if the green light falls on the retina then the green modulators will be stimulated maximally while the red and blue modulators will be affected little. Thus, the modulators are concerned with different colour sensations.

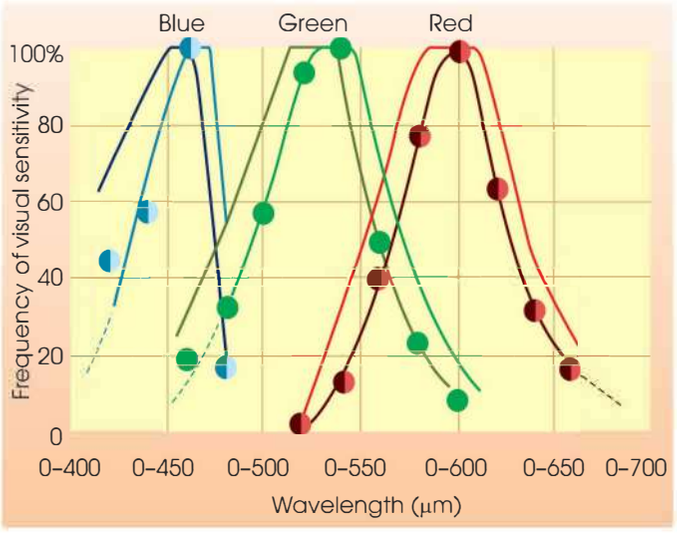


Fig. 117.75: Graphical representation of the sensitivity curves for blue, green and red receptors (Granit)

Photochemical substance	*Retinal process*	*Sensation*
White-black	Breakdown	White
	Resynthesis	Black
Red-green	Breakdown	Red
	Resynthesis	Green
Yellow-blue	Breakdown	Yellow
	Resynthesis	Blue

4. *Hering Theory*

Though the Hering theory is antagonistic to that of Young and Helmholtz yet it is simply the modification of the latter. Hering also assumes the existence of three photochemical substances in the retina but they are of such a nature as to give six different qualities of sensations. According to this theory the photochemical substances (white-black, red-green and yellow-blue) give one sensation on breakdown and a different one on resynthesis.

According to this theory, the complementary colours become antagonistic to its respective primary colours. This theory also does not accept the presence of specific nerve energies because it assumes that the same fibre can carry two different sensations to the brain.

Cortical Representation of Colour Sensation

Recent evidences suggest that the colour sensation of the retina is largely concerned with cerebral cortex. But the rod function is not so dependent on the cortical function. In destruction of the cortex, the cone function is greatly affected, but the rod is totally unaffected. The visual impulses are carried from the different types of cones to the occipital cortex. The primary visual cortex projects to area V8 which is responsible for identification of colour vision. It is in this area the differentiation of the visual impulses takes place and there is perception of various coloured lights. The perception of complementary colours also takes place in the same area.

Colour Blindness

Colour blindness means defect or lack of appreciation of one or more colours. About 8% of males and 0.4% of females show some defect of colour vision.

Classification

Different ways of classification: But none is completely satisfactory. Because:

Classification depends upon one or the other theory of colour vision, hence varies widely.

Various anomalous types are often found which may not fit in with a particular classification.

The following classification depending upon Young-Helmholtz theory of colour vision is widely accepted. According to this theory, normal colour vision depends upon the presence of three primary colour substances—red, green and blue. So, that the colour blindness is divided into three following broad classes:

Anomalous trichromatism: This is the commonest variety: 5.6%. Anomalous trichromats can see all the three colours, but appreciation of one particular colour is subnormal. For instance, to match a particular shade of red, green or blue he will require a greater amount of that particular colour than a normal subject. This class has three subclasses:

1. Protanomaly (partial protanopia): 1% red vision is subnormal. Generally hereditary.
2. Deuteranomaly (partial deuteranopia): Green vision is subnormal. Commonest variety: 4.6%, generally hereditary.
3. Tritanomaly (partial tritanopia): Subnormal blue vision. Rarest form: 0.0001%. An instrument, called anomaloscope, is used for testing these defects.

Dichromatism: Less common than the first group: 2.6%. Dichromats can see two colours but fail to see one. Consequently, there are three types:

1. *Protanopia* or red blindness—1.2%.
2. *Deuteranopia* or green blindness—1.4%.
3. *Tritanopia* or blue blindness. The first two types are generally hereditary, whereas tritanopia is the rare form and is generally acquired. It is found in detachment of retina, in jaundice (bilirubin in the eye absorbs all blue colour), heavy doses of santonin, etc.

Monochromatism: This is the reverse of night blindness, where the rods are all right but the colour sensation of the cones is lost. It may be regarded as total colour blindness. In the daytime the surroundings appear to be dark, grey or pale bluish-white (rod vision).

Tests for Colour Blindness

This test is essential for members of those professions who have to distinguish between different colours, such as drivers, signalmen, seamen, air pilots, etc. The following three types of tests are generally employed:

1. ***Spectroscopic test:*** In this test, the limits of visibility of spectrum, distinction between different spectral colours, their exact positions, etc. are tested.
2. ***Colour-matching test (Holmgren's wool test):*** The subject is given a set of coloured wools. He is required to select from the set only those specimens which will match another given sample of a particular colour.
3. ***Use of pseudo-isochromatic plates (Ishihara's test):*** These plates consist of a series of cards on each of which is printed a coloured background in spots of different sizes. A letter, figure or a number is printed against this background—also in spots of same size. These spots are of such a colour that it is likely to be confused with the colour of the background. To a normal subject the figure or letter at once becomes clear, but the colour-blind subject fails to distinguish it from the background. The numerical figures are read correctly by a normal subject, but the colour-blind subject may read these differently.
4. ***Green and red light test:*** This device is in practice for testing the engine-drivers, signalmen, etc. The subject has to identify the green and red light focused from a small illuminated area.

Visual impressions persist even after the removal of the object. This is called after-image. After-image may be of two types: Positive and negative.

a. ***Positive after-image:*** If after looking at an object the eyes be closed or turned to a dark surface or the object is quickly removed, the image of the same object with the same colours can be seen for a brief while. It is due to the continuation of the physicochemical changes in the rods and cones even after the stimulus is removed. This phenomenon is also called persistence of vision. It is due to this phenomenon that rapidly intermittent stimuli (as in the cinema) become fused into a smooth continuous visual impression.

b. ***Negative after-image:*** After looking at a coloured object if the gaze be turned against a white background, the image of the same object will be seen but with the complementary colour. If the object be white, red or yellow, the image will be black, green or blue respectively.

Young-Helmholtz theory holds that fatigue of one or more of the three varieties of cones (for three primary colours) are caused by the first stimulus and these fatigued cones will not respond for a brief while to a second stimulus of the same type. When the subject looks against a white surface, the white light stimulates the whole retina except the tiered cones and so that the negative after-image of a white object will be black. If the original object was coloured, the white light will fail to stimulate the tired cones but will stimulate the others, giving the complementary colours.

Contrast Phenomenon

There are two types of contrast: Simultaneous contrast and successive contrast.

1. ***Simultaneous contrast.*** When an object with a particular colour is viewed against a background of the complementary colour, such as red against green, blue against yellow, black against white—both the colours appear to be more vivid. This is due to negative after-image.
2. ***Successive contrast.*** If one looks for some time at a coloured object in strong light and then at another object with the complementary colour, the latter appears brighter. For instance, if after looking at a red object a green object is seen, the colour of the latter seems to be more intensified. This is also due to negative after-image.

Thomas Young was a Physician who made notable scientific contributions to the fields of vision, light, solid mechanics, energy, physiology, language, musical harmony, and Egyptology. He described the theory of colour vision.

1733–1829

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the visual pathway. Describe the effect of lesion at various locations of visual pathway.
2. Define colour vision. Discuss regarding the theories of colour vision.
3. Discuss the test for colour blindness. Describe the anomalies related to colour blindness.

Short Notes

1. Refractive errors of refraction
2. Pupillary reflexes
3. Dark adaptation
4. Accommodation reflex
5. Visual acuity
6. Comparison between rods and cones
7. Photo transduction
8. Colour blindness
9. Argyll Robertson pupil
10. Cortical representation of colour sensation.

Chapter

118 Hearing

ANATOMY (Figs 118.1 and 118.2)

Ear has three parts: External ear, middle ear, internal ear.

External Ear

It consists of two parts: Pinna and external auditory meatus.

1. Pinna collects and reflects sound waves into the meatus.
2. The external auditory meatus is a tortuous canal, about 2.54 cm long looking at first inwards forwards and upwards and then inwards forwards and downwards. It is shut off medially by the tympanic membrane (Fig. 118.3). It transmits the sound wave perpendicularly to the membrane. A straight rod will hit the roof. Thus, tortuosity of the canal prevents mechanical injury to the tympanic membrane from outside.

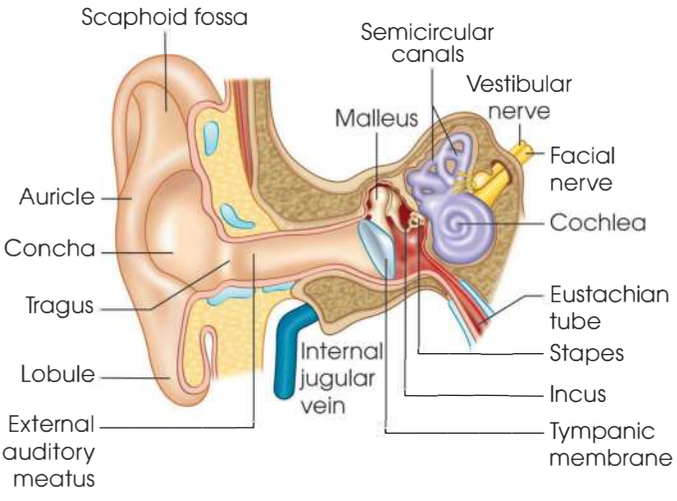


Fig. 118.1: Diagram of the ear showing the external ear, middle ear and internal ear and also showing the communication of the middle ear with the nasopharynx by means of the eustachian tube

Middle Ear

It contains air, auditory ossicles, tensor tympani muscle (fifth cranial nerve) and stapedius muscle (seventh cranial nerve).

1. Tympanic membrane (Figs 118.3 and 118.4) forms the outer wall being elliptical (10 mm vertical × 9 mm horizontal) and set obliquely, downwards, inwards and forwards. It is concave from outside (Fig. 118.7). The point of maximum concavity is called umbo. To this point the handle of the malleus is attached on the inner side.
2. In the medial wall there are two windows: The oval window (fenestra ovalis) and the round window fenestra cochleae or rotunda). The latter is closed by a membrane. To the former is fitted the footplate of the stapes and sealed in by means of a membrane. The posterior wall communicates with air cavities in the mastoid process. The largest cavity being known as the mastoid antrum.
3. Through the anterior wall two canals pass. The upper one lodges the tensor tympani (attached to the handle of the malleus), the lower one is known as the eustachian tube, which opens into the pharynx (Fig. 118.1).
4. The eustachian tube normally remains closed, but opens during chewing, yawning and sneezing. Its main function is to equalise pressure on the two sides of the eardrum (the tympanic membrane). Any imbalance of the static pressure affects the transmission of the middle ear structure. This effect is generally felt while landing an aircraft. During diving or going up in an aeroplane, there is change of air pressure and this may produce a considerable stress on the tympanic membrane if the pressure in the middle ear is not equalised with the outside pressure. This is achieved through the eustachian tube.
5. The auditory ossicles are three minute bones, known from outside inwards as malleus (hammer), incus (anvil) and stapes (stirrup) (Fig. 118.5). The stapedius

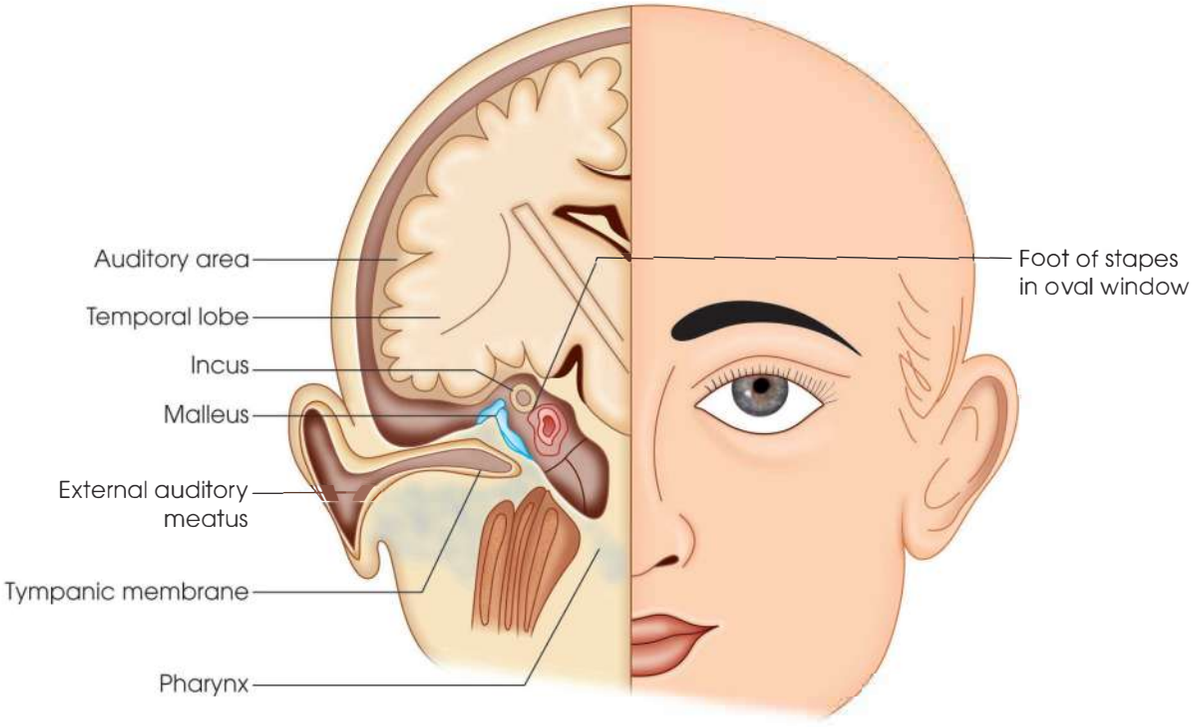


Fig. 118.2: Showing the principal features of the human ear. The external ear consists of the pinna and external meatus. The tympanic membrane is situated at the medial end of the meatus. The middle ear is situated within the temporal bone between the tympanic membrane and the lateral bony wall of the internal ear. The middle ear communicates with the pharynx through the eustachian tube. The internal ear is embedded deeply in the petrous portion of the temporal bone

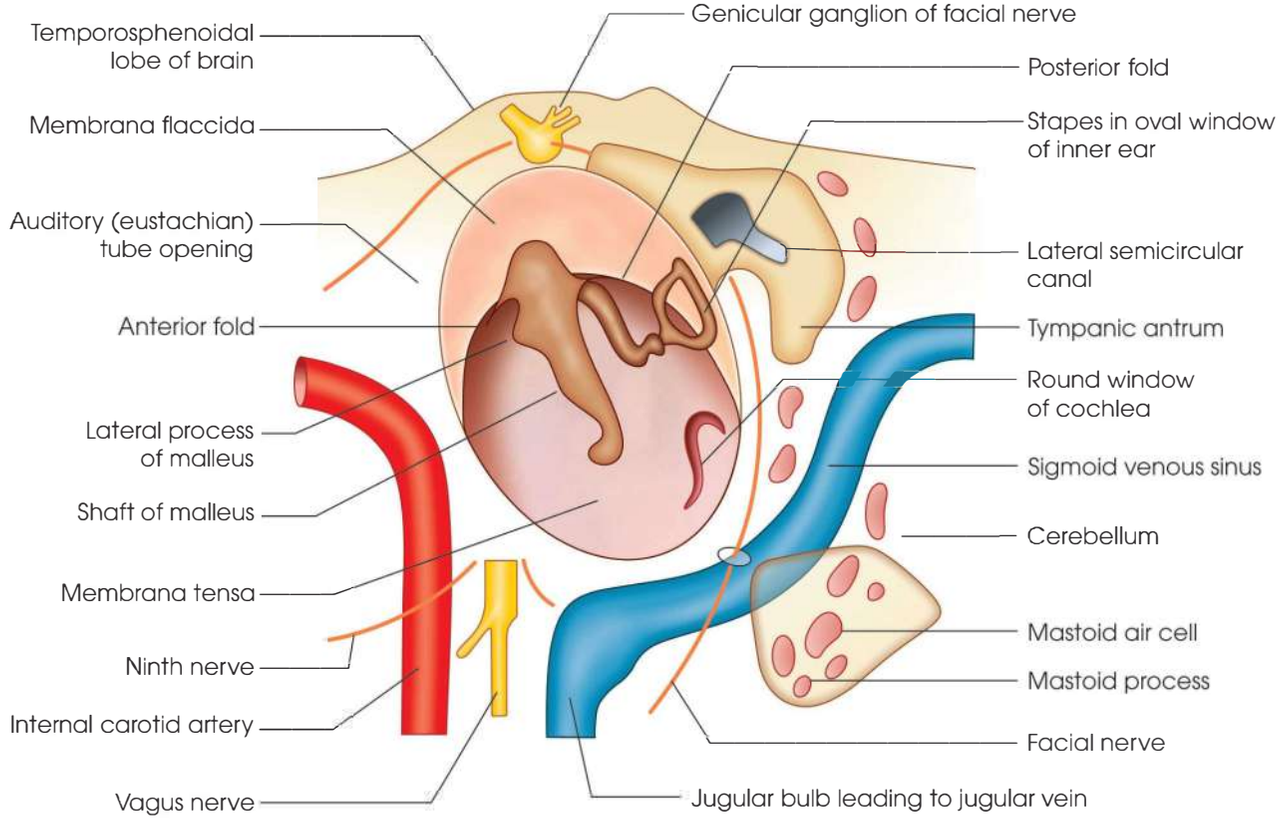


Fig. 118.3: Diagrammatic representation of the tympanic membrane and important anatomical structures around the middle ear

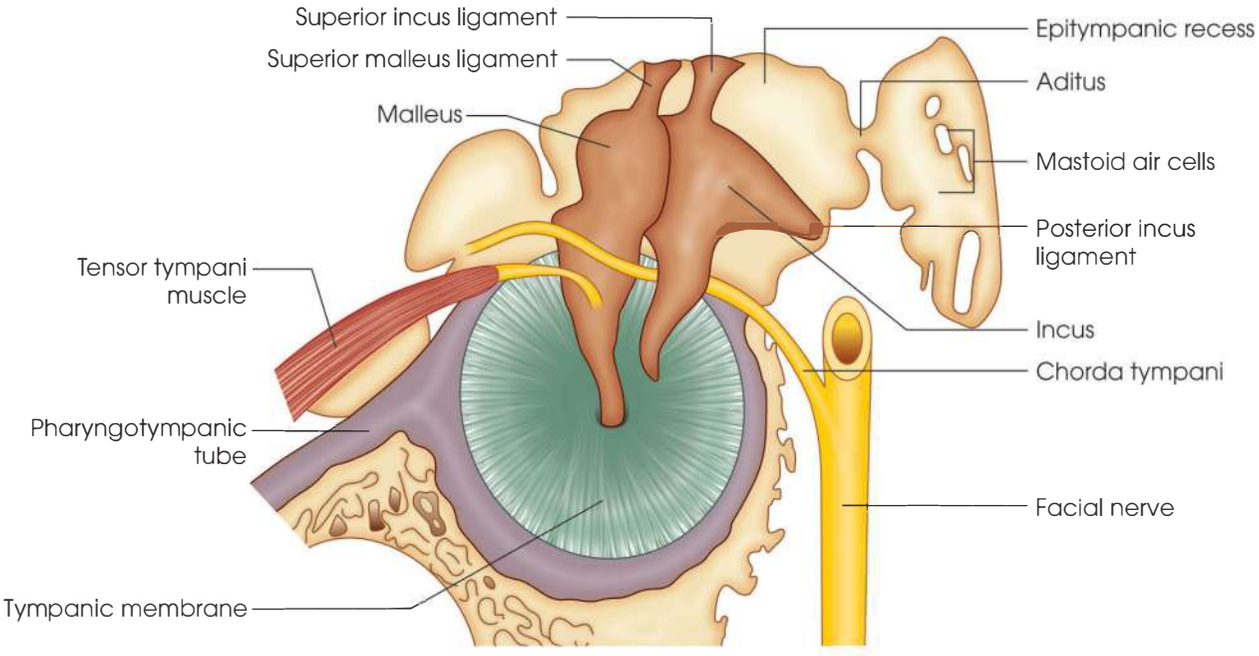


Fig. 118.4: Diagrammatic representation of the tympanic membrane and its attachment with the malleus

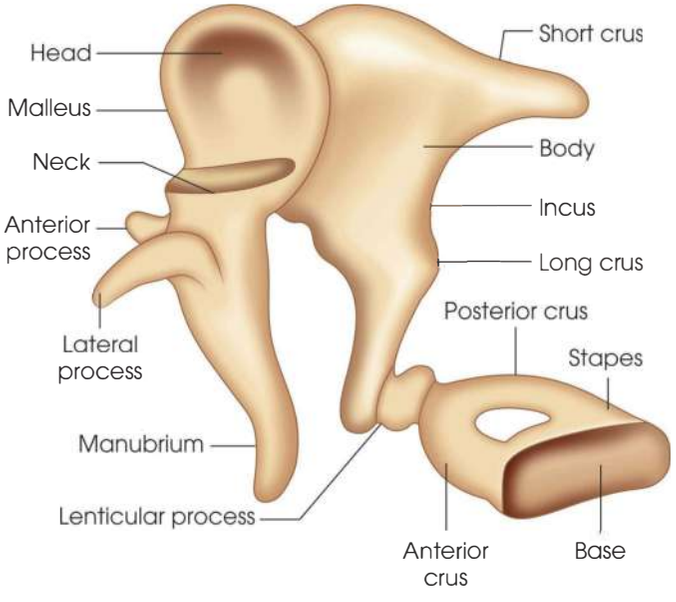


Fig. 118.5: Schematic representation of the ossicles of the ear showing the attachment of malleus, uncus and stapes

muscle remains attached to the stapes. The remain articulated together forming a complex system of levers stretching across the middle ear—the handle of the malleus remaining attached to the tympanic membrane and the foot plate of the stapes fitting into the oval window in the internal wall. The malleus, incus and stapes are bound by ligaments.

6. When the sound waves impinge on the tympanic membrane, these chains of ossicles vibrate as a single unit. Figures 118.6 and 118.7 show the link between the inner side of the tympanic membrane to the liquid-filled cochlea at the oval window. The mechanical joint and bearing systems of the single unit of the bony ossicles are such that displacements at the tympanic membrane by air will be three times higher in the oval window. Thus, it acts like a hydraulic press. The force in the oval window is spread over an area of 3.2 mm^2 but at the tympanic membrane this is spread over 65 mm^2. Accordingly the pressure changes in the liquid of inner ear just inside the oval window will be greater than that of outside the tympanic membrane. The base of the stapes produces rocking rather than push-pull movement. Tensor tympani and stapedius muscles modify the transmission of sounds of different intensities and provide a protective mechanism.

Internal Ear

It consists of two parts: Cochlea—in front and vestibular apparatus—behind (Fig. 118.8).

1. *Cochlea*

a. It is made up of a bony canal, arranged spirally (two—and three-fourths turns) like the shell of a snail (hence, the name cochlea). The spirals wind round a central bony pillar, the modiolus, through the axis of which passes the auditory nerve.

b. A tape-like bony projection winds round the modiolus like the edges of a screw and makes an incomplete partition. It is completed by the basilar membrane extending from the tip of the spiral lamina to the outer wall of the canal.

c. A second membrane, Reissner's membrane stretches from the upper surface of the spiral lamina to the bony wall of the canal a little above the attachment

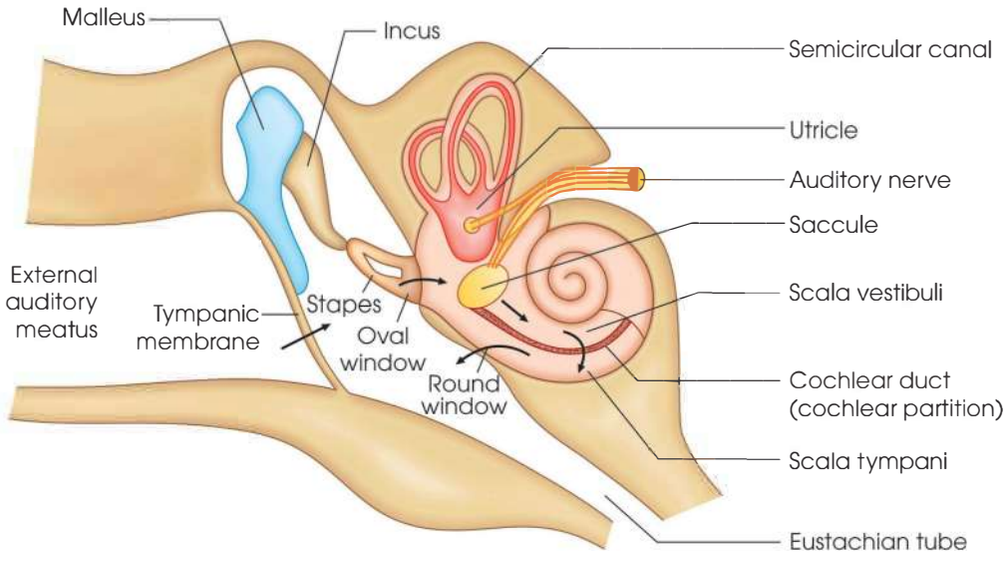


Fig. 118.6: Schematic representation of the link between the inner side of the tympanic membrane to the liquid - filled cochlea at the oval window and also the paths of acoustic transmission

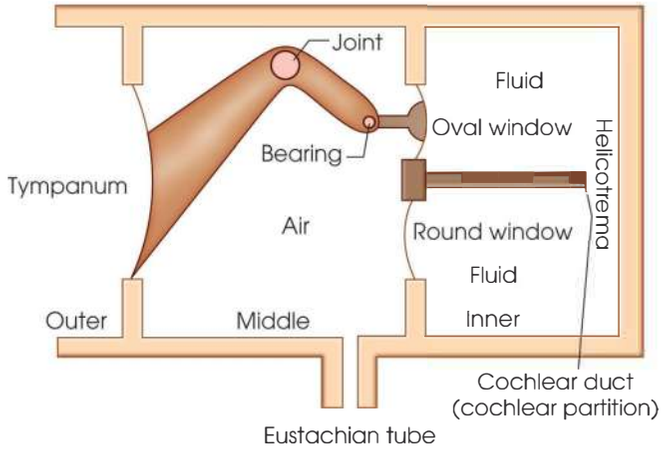


Fig. 118.7: Schematic representation of vibration from the external ear to the internal ear

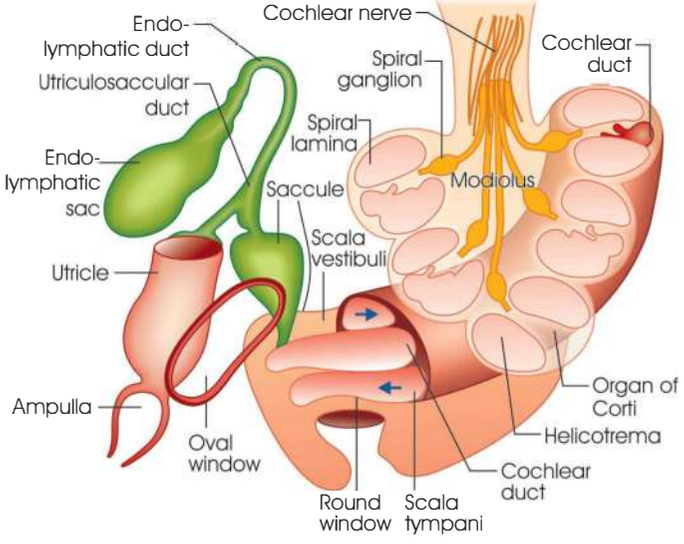


Fig. 118.8: Diagrammatic representation of the connection of the cochlea and the vestibular apparatus and directions of arrows showing transmission of sound waves

of the basilar membrane. Reissner's membrane and the stria vascularis, is called cochlear duct or cochlear partition (Fig. 118.9).

d. Thus, the bony cochlea is partitioned down its length by the triangular duct, the cochlear duct into two halves: (i) Scala vestibuli and (ii) scala tympani. This partition is actually containing sense organs situated on the basilar membrane and other accessory organs and endolymph.

e. The length of the cochlear partition (duct) in man from its origin between oval window and round window to the helicotrema is roughly about 35 mm. The cochlear partition has been regarded as the mechanical frequency analyser of the ear.

f. Thus, the original bony canal is subdivided into three spiral canals. That below the basilar membrane is called the scala tympani, that between the two membranes, is called the scala media (canal of cochlea), and that above Reissner's membrane the scala vestibuli. The scala media (membranous cochlea) are filled up with endolymph. It ends at the apex in a blind sac, but at the base it communicates with the vestibular apparatus through the duct of Hensen (canalis reuniens). The scala vestibuli and scala tympani are filled up with perilymph and communicate with each other at the apex through a small opening, the helicotrema (Fig. 118.10).

g. On the basilar membrane lies the organ of Corti which is the sense organ for hearing. The basilar membrane is about 32 mm long. It is composed of fibres that run laterally from the osseous spiral lamina to the spiral ligament. It is narrower at the base (0.17 mm) and broader at the apex (0.47 mm). It is not under tension. It consists of parallel fibres in a gelatinous sheet. The number of parallel fibres in man is about 24,000. The range of fibre length lies

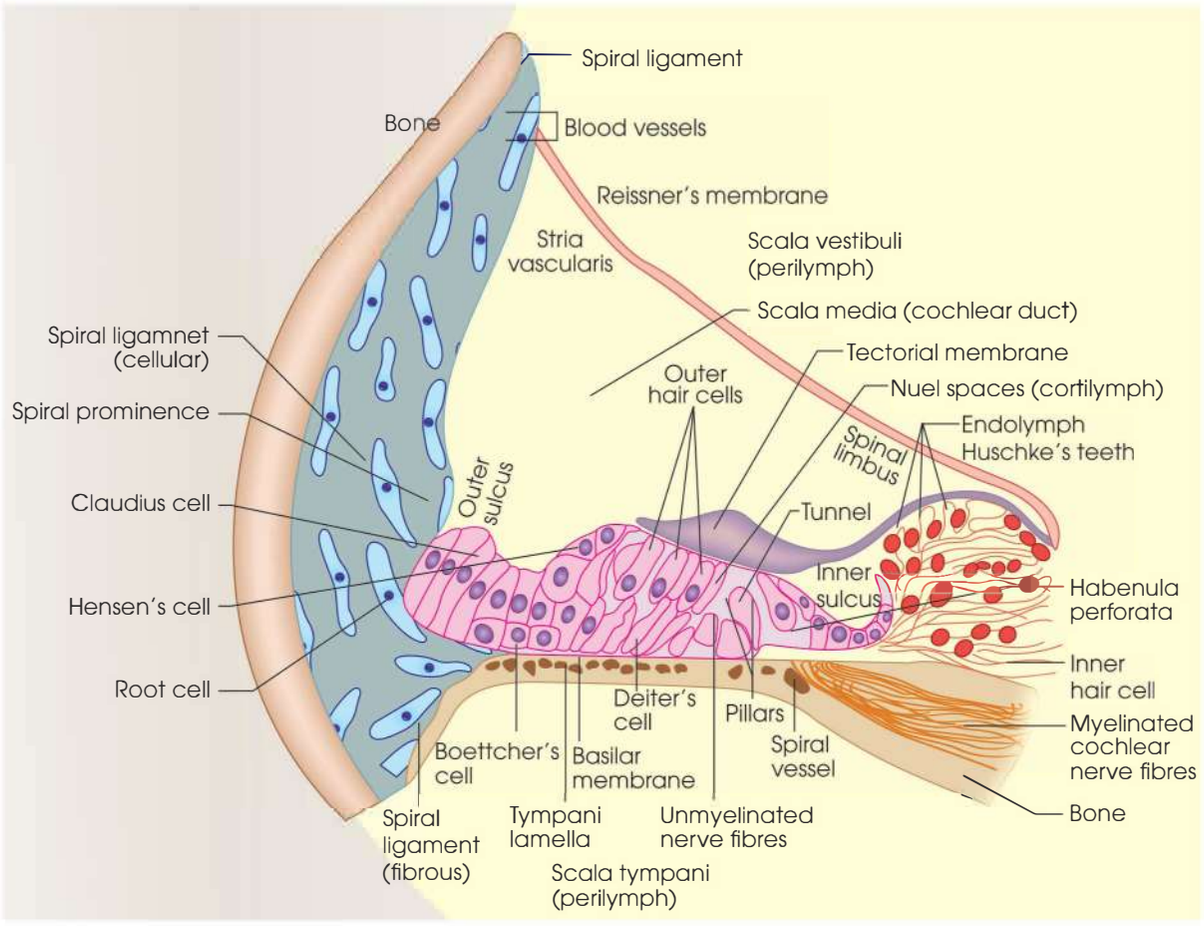


Fig. 118.9: Diagram showing cross-section of cochlear partition of the guinea-pig in the lower part of the second turn (Best and Taylor)

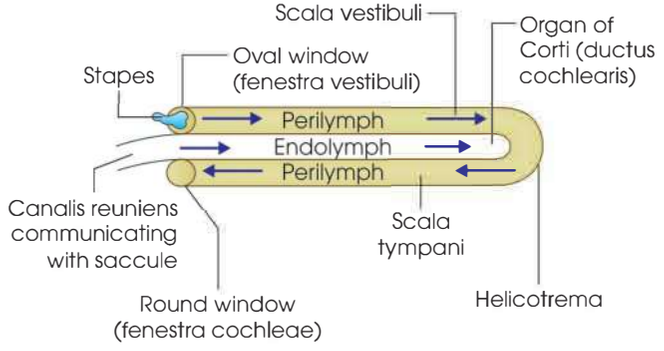


Fig. 118.10: Diagrammatic representation of the bony and membranous cochlea, uncoiled. End organ of Corti projecting into the endolymph contained in the membranous cochlea. The perilymph indicated above the endolymph occupies the scala vestibuli. The perilymph in the lower compartment lies in the scala tympani

between 64–128 μm (basal) and 352–480 μm (apical). These fibres act as resonators.

h. The vibration of higher frequency causes the maximal amplitude of vibration of the basal fibres. The vibration of lower frequency causes the maximal amplitude of vibration of apical fibres. The vibration of the basilar membrane takes the form of wave and may be compared with that of arterial pulse wave.

2. *Vestibular Apparatus*

Organ of Corti

a. It is situated on the basilar membrane and consists of hair cells, separated into two rows by the tunnel of Corti (Figs 118.11 and 118.12). Tunnel of Corti is formed when the inner rods of Corti and outer rods of Corti unite at apex.

b. Thus, the tunnel of Corti separates the hair cells into a single row of inner hair cells and three or four rows of outer hair cells, each cell having about twenty tiny hairs. There are about all total 3500 inner hair cells and 20,000 outer hair cells.

c. Outer hair cells are much more specialised in their structure than inner hair cells.

d. Inner hair cells resemble mostly type I cells in the vestibular labyrinth. The cells are flask-shaped (Fig. 118.13) and contain numerous mitochondria cells of Hensen stereocilia. Located as the apex of hair cells are stereocelia which are non-motile cilia. Stereocilia contact the tectorial membrane. The nucleus is larger than that of an outer hair cell and situated at the base. The flask-shaped cells are enclosed from its constricted neck inferiorly with a chalice-like nerve terminal. The hairs of the inner hair cells are arranged on the cell

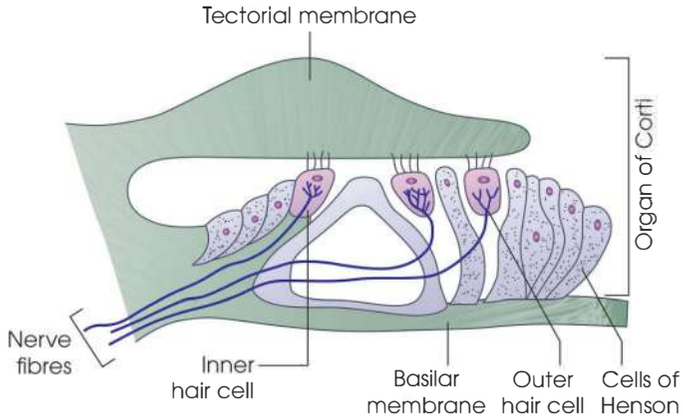


Fig. 118.11: Diagrammatic representation of the sensory portion of the organ of Corti under various electron microscopic studies in monkey and man (Ham)

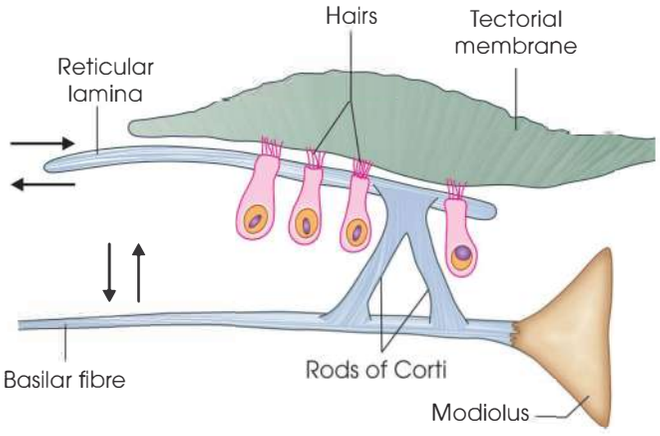


Fig. 118.12: Diagrammatic representation of inner and outer pillars of the organ of Corti (Bloom and Fawcett)

apex in the form of a letter W or U with the base of the letter directed towards the centrioles.

e. Outer hair cells are not flask-shaped and nuclei are mostly situated at the centre. Mitochondria are also

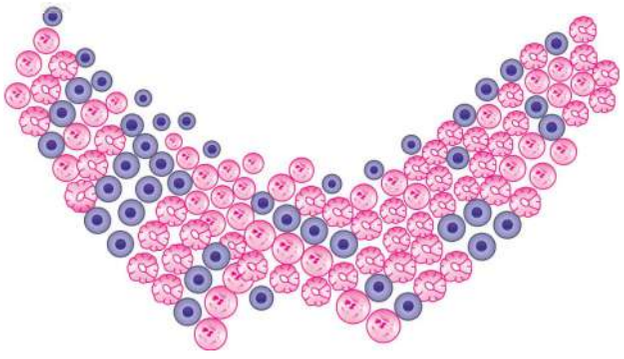


Fig. 118.14: Electron microscopic structure of the W configuration of the hairs on the external sensory cells of the human organ of Corti (Bloom and Fawcett)

aggregated at the base. Like inner hair cells, only the base of this outer hair cell, are enclosed by the afferent nerve endings. Stereocilia present and hairs are arranged on the apex of the cells in a more distinct form of a distinctive 'long-horned W' pattern (Fig. 118.14). Here there are more rows of hairs and the length of the hairs varies from long at the periphery to the short centrally (Fig. 118.15).

f. In between the hair cells lie the supporting cells of Deiters, their phalangeal processes project upwards and form part of the reticular lamina (Fig. 118.16). The hairs of the hair cells project through the pores of the reticular lamina. Overhanging the hair cells lay the membrana tectoria.

g. Membrana tectoria is attached to the outer border of the spiral lamina. It is made up of gelatinous substance. The outer hair cells are surrounded by the supporting cells of Hensen (Fig. 118.11). These cells also send off processes which help in the formation of reticular lamina. Cells of Claudius remain on the outer side of the Hensen cells. At the base of each hair cell two types of cochlear nerve endings are present—smaller and larger. The smaller

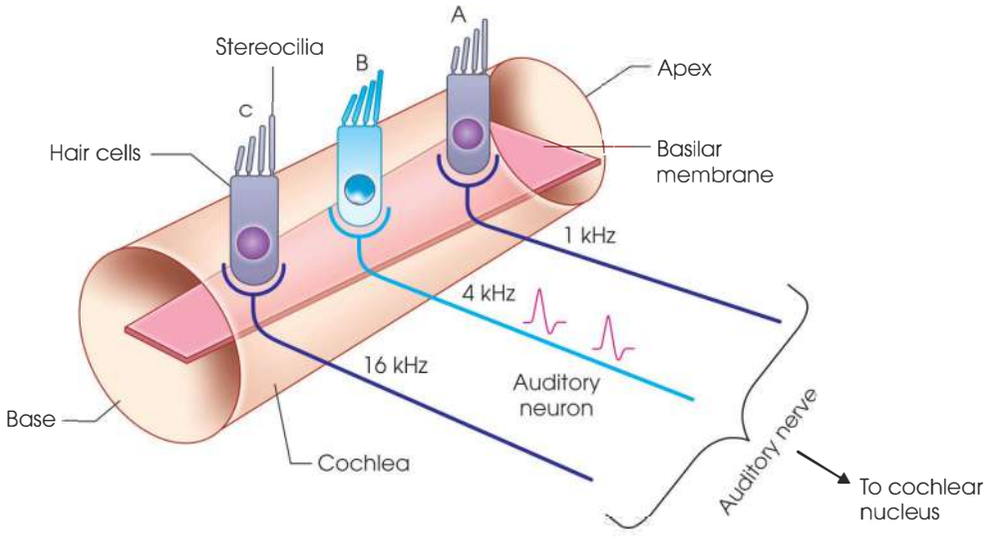


Fig. 118.13: Schematic diagram of inner hair cells

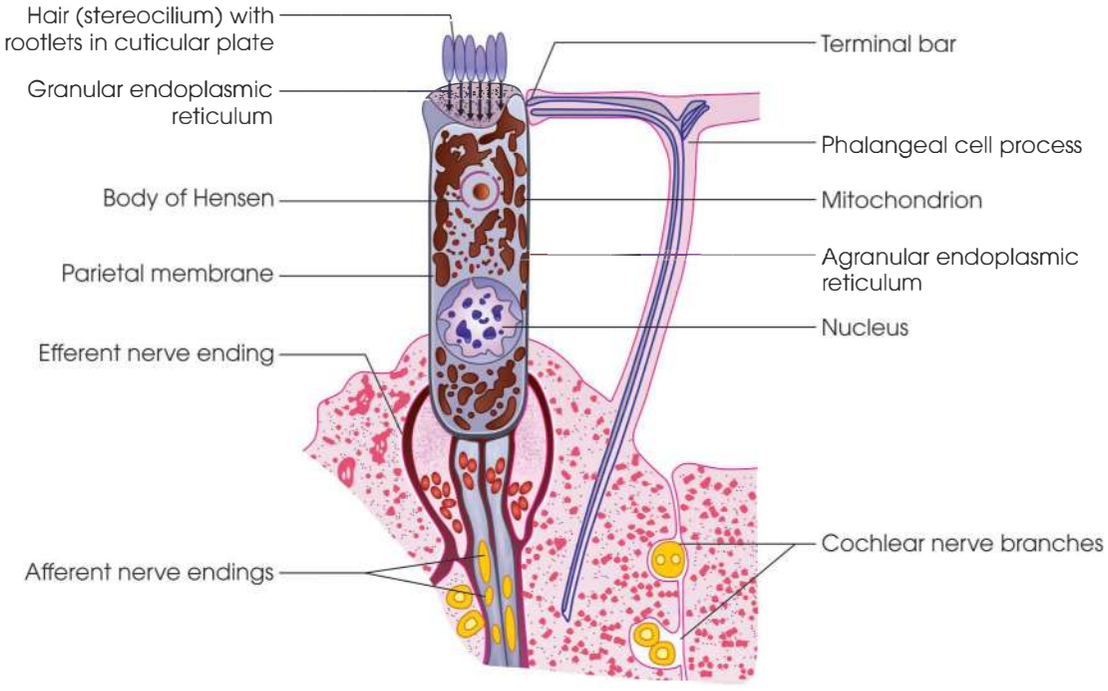


Fig. 118.15: Schematic drawing of an outer hair cell

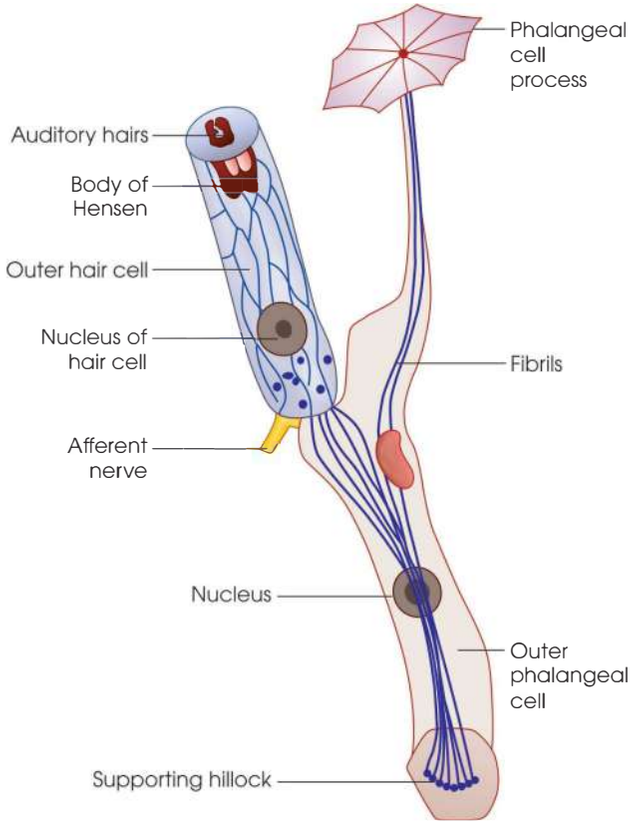


Fig. 118.16: Showing the supporting cells of Deiters and the associated outer hair cells (Bloom and Fawcett)

nerve endings are thinner and less granulated. The large ones are thicker and densely granulated.

h. The cochlear nerve fibres after losing their sheaths enter the organ of Corti. The nerve fibres from the outer hair cells cross the tunnel of Corti and meet the nerve fibres from the inner hair cells and reach the bipolar cells of the spiral ganglion situated on the osseous spiral lamina. Auditory impulses arise in the hair cells and carried by the auditory nerve.

PROPERTIES OF SOUND AND RANGE OF HEARING

Sound Waves

1. Sound is the vibration of air molecules, i.e. alternate phases of condensation and rarefaction of the molecules, when these air molecules strike the tympanic membrane sound is heard.
2. The vibrations imparted to the conducting medium by the sound producing mechanism are generally spoken of as sound waves, which comprise a series of alternate condensations (compressions) and rarefactions in the air propagated in a pendular manner in all directions (Fig. 118.17).
3. When these alternating compressed and rarefied portions of the atmosphere strike the eardrums, they cause them to vibrate at the same rate as the iron rod, and the sound is heard. Thus, a sound wave in air consists of an abnormal distribution of air molecules in which compressed regions alternate with regions of partial vacuum. When a normal distribution of air molecules exists, no sound waves are travelling through the air.

Properties of Sound

1. In an electronic device, a sound wave can be seen in the form of a sine wave (Fig. 118.18). Amplitude of

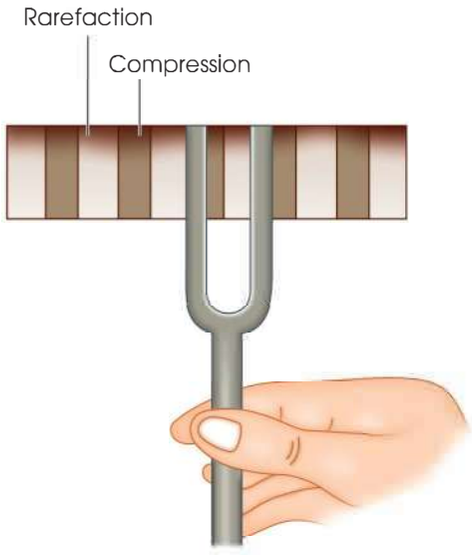


Fig. 118.17: Sound waves as produced by a tuning fork or vibrating rod showing the production of condensations (compressions) and rarefactions

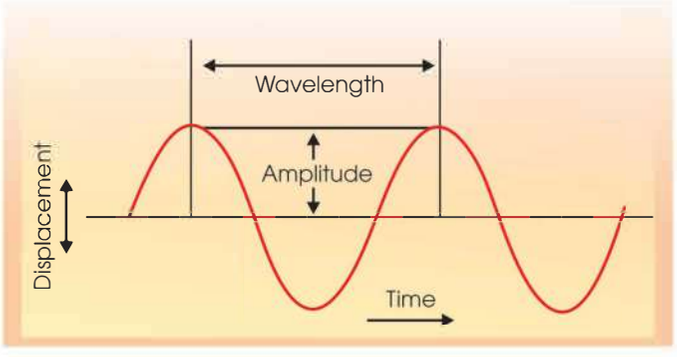


Fig. 118.18: Diagram showing the longitudinal oscillation of air molecules during passage of a sound wave. The loudness of sound is determined by the amplitude of vibration and the frequency of oscillation determines the pitch of the sound

the waves determines the intensity of the sound and the pitch of the sound is determined by the frequency of the waves.

2. Frequency also plays a part in subjective sensation of loudness because threshold of sound which the ear can just detect varies with frequency. Sounds of same intensity but of different frequencies, one may be heard and other may not be heard. One may be louder, other may not be.
3. The amplitude of a sound is generally compared with a standard sound and the relative scale commonly used is the intensity of a sound in bel which is logarithm of the ratio of the intensities of that sound and a standard sound.

$$1 \text{ bel} = \log \frac{\text{intensity of sound}}{\text{intensity of standard sound}}$$

4. The bel is a large unit and so decibel (one-tenth of a bel) is generally used. Acoustic Society of America has adopted the standard sound reference level corresponding to 0 decibel at a pressure level of 0.000204 dyne per sq cm, a value which is just at the auditory threshold for the average human subject.
5. In the decibel (dB) scale the faintest audible sound is taken as the unit, and called 0. All other sounds are measured as multiples of 0. Briefly the scale is as follows:

	Decibels
Faintest audible sound	0
Whisper at 122 cm (4 ft)	20
Quiet street	30
Average office	40
Noisy street	60–80
Pneumatic drill	80
Boiler shop	100
Loud motor-horn at 7 m (23 ft)	100
Thunder	120
Limit of endurance	130
Jet engine	140

It is to be noted that the actual scale is logarithmic. For instance, 1 bel is 101, i.e. 10 times 0, 2 bels are 102, i.e. 100 times 0, 3 bels are 103, i.e. 1000 times of 0, and so on.

Quality—same note produced by different instruments varies in quality. It depends on the peculiarity of the waves.

Range of Hearing

It extends over 10–11 octaves. Limits of audibility lie from 20 to 20,000 cycles per second. Frequencies outside this range are not usually audible. But there are wide individual variations. The range is wider in certain animals.

AUDITORY ACUITY

Threshold of Audibility

If the intensity of sound is gradually decreased then it reaches a certain value, when there will be no sound. The lowest intensity which will just give a sound sensation is known as threshold of audibility. It varies considerably with its frequency. Sound frequencies well above 20,000 cycles per second (c/s or CPS) are audible in dog, but not in man. If the intensity of sound is increased gradually above the threshold value then the magnitude of sensation is increased and it is not only heard but felt by the ear often with a painful sensation. It is called the threshold of feeling.

Difference or Discrimination Threshold

Small differences between the frequencies of two tones can be detected by a normal individual. The minimum perceptible difference is known as absolute difference threshold. It is about 3 cycles per second independent

of the frequency up to about 500 cycles per second. This will also rise more or less in proportion to the frequency above about 1000 cycles per second. The ability of discrimination between sounds of different frequencies improves with the gradual increase in the intensity of sound. Again the acuity of the ear for differences in sound frequency is higher than its acuity for differences in sound intensity.

Localisation of Sound

In man, the power of localisation of sound is poorly developed. But in animals this power is well developed, because the animals can localise the source of sound by moving the pinna towards the sound. In human being, the localisation of sound is higher where the direction of sound is in vertical plane. In the horizontal direction, this localisation of power is less as the head acts as a shadow. In horizontal direction of sound wave, one ear gets sound earlier than the other ear. Besides this, the sound of high frequency is felt by one ear facing the sound at higher intensity than the other ear due to shadowing effect of the head.

Auditory Fatigue

It is the transient loss of sensitivity due to prolonged hearing of a loud sound. This loss of sensitivity is known as auditory fatigue. The fatigue is binaural because if one ear is subjected to prolonged sound the other is not, then both the ears suffer the loss of sensitivity. If the frequency of sound is 1000 cycles per second or above, then it produces fatigue more intensely than that of frequency below.

Noise

It is described in psychological terms as a sound which causes disturbance or annoyance. If the auditory apparatus is exposed to continued noise, the mechanism of hearing is seriously affected and this may lead to loss of hearing. The degree of loss of hearing depends upon the frequency value of the noise. After continued exposure to industrial noises the sensitivity of hearing is found to be diminished or lost.

Masking

In a railway train journey unless the voice is louder one cannot hear it. The loudness of the voice can be revealed when the train stops. Weaker sounds may be completely inaudible in presence of louder sounds. This phenomenon is called masking. The degree of masking to which one component is masked by the other is measured by finding the threshold. The sounds of almost same frequency cause fluctuations in loudness. Bekesy observed that about whole length of the basilar membrane is affected by low tones, where as a limited region is affected by high tones and that is why the low tones are more effective in masking.

Deafness

The primary acoustic centre is in the temporal lobe of the cerebrum. Removal of both temporal lobes is followed by complete deafness and of one temporal lobe is followed by impairment of hearing. This holds that some fibres from each ear cross at some point in their afferent pathways and terminate in the opposite cortex. This is similar to the partial decussation of visual fibres occurring in the optic chiasma.

Deafness may be of two types, viz.

1. Conductive deafness
2. Nerve deafness.

In conductive deafness there is interference with the passage of sound waves through the external ear and middle ear.

1. *External ear obstruction:* The conductive deafness occurs due to entrance of foreign bodies, or due to hard or dry wax in the external ear. The damage or perforation of tympanic membrane may be the cause of failure of conduction.
2. *Middle ear disease:* Any condition which prevents the normal functioning of the ossicles. The condition is frequently observed in nasal catarrh, otosclerosis, etc.

The nerve deafness is due to loss of function of organ of Corti and also due to interference of transmission of impulses by the auditory nerve. The temporary nerve deafness occurs after exposure to a very loud sound. The main causes are:

1. Due to bacterial or viral infection as in meningitis in children.
2. Due to acoustic trauma as in boiler-makers.
3. Due to toxic action of the drugs, viz. streptomycin, quinine, measles, etc.
4. Due to pressure of a tumour at the junction of cerebellum and pons.

The nerve deafness is also found in Meniere's syndrome which occurs in adult and is accompanied by vertigo. This is due to increased hydrostatic pressure in the endolymph. There may be also hereditary nerve deafness.

Test for Deafness

Rinne's test: The base of a vibrating tuning fork is placed over the mastoid process of the subject. When the sound fades away (bone-conduction ceases) the prongs of the fork are brought towards the external auditory meatus. If there is no abnormality in the tympanic membrane and ear ossicles, the air-conducted sound is heard for a longer period by the subject and the test is said to be positive. If the sound is heard longer by bone-conduction the test is said to be negative and indicates conductive deafness (Fig. 118.19C). In case of internal ear disease affecting the nervous conduction the test is said to be positive and indicates perceptive deafness (Fig. 118.19B).

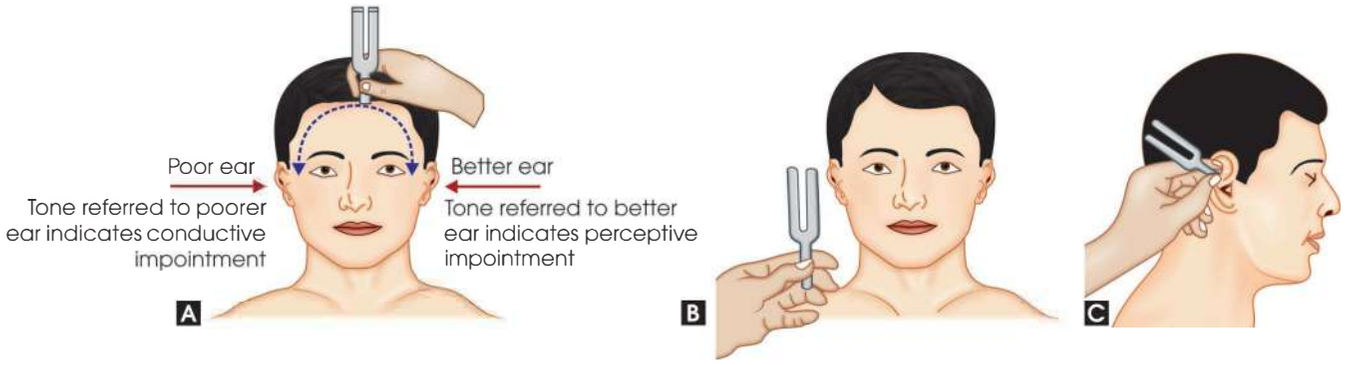
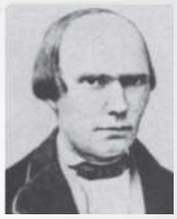


Fig. 118.19A to C: (A) The Weber test furnishes only a comparison of two ears. If a subject has nerve deafness which is worse in one ear than the other, the tone will be heard best in the better ear. The tone will be heard in the poorer ear if the subject has asymmetric conductive deafness; (B) Tone heard longer by air conduction—Rinne positive; (C) Tone heard longer by bone conduction—Rinne negative

Weber's test: The base of a vibrating tuning fork is placed over the midline of the vertex of the subject (Fig. 118.19A). The sound is heard equally in both ears. In unilateral middle ear disease affecting the conductive system, the sound is better heard in the diseased ear and Weber's test is said to be positive. In case of unilateral internal ear disease affecting the nervous conduction the sound is better heard in the normal ear. Rinne's and Weber's tests help to differentiate middle ear or conductive deafness from internal ear or perceptive deafness.



Heinrich Adolf Rinne
1819–1868

Rinne described the conductive process of the tympanic membrane and the ossicles of the middle ear in the year 1855. He formulated the Rinne test. The Rinne test is a hearing used to compare a patients' hearing via air conduction (normal process) or by way of bone conduction (sound to the inner ear through the mastoid) using a tuning fork. He reasoned that if a person hears a sound for a longer period of time through bone conduction than through air conduction, a disease is present somewhere in the conduction apparatus.

TRANSMISSION OF SOUND WAVE

The ear apparatus conducts sound wave from air to bone and to fluid and ultimately transforms into action potentials in the auditory nerves.

Functions of the External Ear and Middle Ear

1. The external ear due to its shape and mobility helps in the reception of sound. In human being although the pinna of the external ear is not mobile but it also receives the sound of shorter wave lengths and transmits it into the external auditory meatus.
2. The length and shape of the external auditory meatus not only transmits the sound but also acts as a protective organ. Through the external auditory meatus sound waves fall on the tympanic membrane. Part of the sound energy is reflected by the tympanic membrane and part of the sound energy is transmitted from the tympanic membrane to the ear ossicles. In response to the sound wave on its external surface, the tympanic membrane moves in and out. The membrane seems to function as resonator and stops vibrating soon after the cessation of sound waves.
3. Bekesy found that at all frequency of the sound upto 2400 cycles per second (CPS) the central conical part of the tympanic membrane and the handle of the malleus moves as a single unit. When the frequency of the sound is over 2400 cycles per second (CPS), the tympanic membrane vibrates in segments.
4. The malleus and incus are closely bound together and suspended by elastic ligaments. They move as a single unit. The axis of rotation is through the anterior and lateral processes and transmits the vibrations to the head of the stapes. The footplate of the stapes shows a rocking movement which is marked at its posterior margin. If the intensity of the low frequency tone rises above a critical level, the footplate rotates in its long axis. The ossicles thus function as lever system converting mechanically the resonant vibrations of the tympanic membrane into movements of the stapes against the posterior edge of the oval window. The vibrations are transmitted through the oval window to the perilymph in the scala vestibuli (Figs 118.6 and 118.7).
5. The muscles of the middle ear also play an important role. The muscles contract reflexly to sound. Due to contraction of the tensor tympani the handle of the malleus along with the tympanic membrane is pulled inwards. Due to contraction of the stapedius the footplate of the stapes is pulled outwards. The contraction of these muscles checks

the movement of the ear ossicles and protects the ear against intense sounds. The total effective area of the tympanic membrane is about 13 times greater than the area of the footplate of the oval window. So, due to reduction in area the pressure increases at the oval window (impedance matching). Further the handle of the malleus is longer than the long process of the incus so the pressure exerted at the oval window by the footplate increases further (17 times greater).

6. Conduction of sound waves from the external ear and the middle ear to the cochlear fluid is regarded as ossicular conduction. Sound waves may be conducted in the cochlear fluid through the membrane of round window (secondary tympanic membrane). This type of conduction is known as air conduction and is not normally required. Third type of conduction into the fluid of the cochlea is possible through transmission of vibration of the bones of the skull. Tuning fork or vibrating reed applied directly to the skull, considerable conduction may occur. The movements of the footplate of the stapes produce series of travelling waves which bring the cochlear duct or partition into oscillation. There are several theories regarding the transmission of sound wave in the cochlea and the mechanism of hearing.
7. Helmholtz by his resonance theory suggested that the rods of Corti act as resonators. Later he suggested that fibres of the basilar membrane act like strings of a piano, each one resonating to a particular tone. The longer fibres (apical) respond to lower tones, while the shorter ones (basal) to higher tones (Fig. 118.20). Sound waves transmitted to the internal ear set up vibrations of particular fibres of the basilar membrane and thus stimulate the overlying hair cells.
8. Rutherford by his telephone theory suggested that cochlea acts like a telephone transmitter. None of these theories could explain the mechanism of frequency analysis of sound.
9. Later came the place theory of pitch discrimination which was widely accepted. According to this theory the cochlea is said to be a tuned structure which helps in the frequency analysis of sound.
10. Ernest Wevers (1949) proposed the resonance-volley theory. He had combined the resonance theory of Helmholtz and telephone theory of Rutherford so as to explain the response of the whole cochlea to low frequencies by the latter and to explain the cochlear analysis of higher frequencies by the former.

FUNCTIONS OF THE COCHLEA (THEORIES OF HEARING)

The role of the cochlea in the mechanism of hearing has been investigated by Helmholtz, Rutherford, etc.

This theory is based on two facts: Mechanism of the basilar membrane and electrical potentials in the cochlea.

A. The basilar membrane and the organ of Corti respond to different frequency of sound waves. A particular region of the basilar membrane resonates to a particular frequency of sound waves. The longer (apical) fibres of the basilar membrane respond to lower tones, while the shorter ones (basal) to higher tones.
B. The hair cells being situated over the basilar membrane will consequently vibrate to different tones. The hair cells at the apex of the cochlea respond to lower tones while those at the base respond to higher tones.
C. There is bending of the hairs due to a shearing motion between the reticular lamina (membrane) and membrana tectoria.
D. When the hair cells are stimulated the nerve endings over their surface are also stimulated and carry the auditory impulse through the auditory nerve.

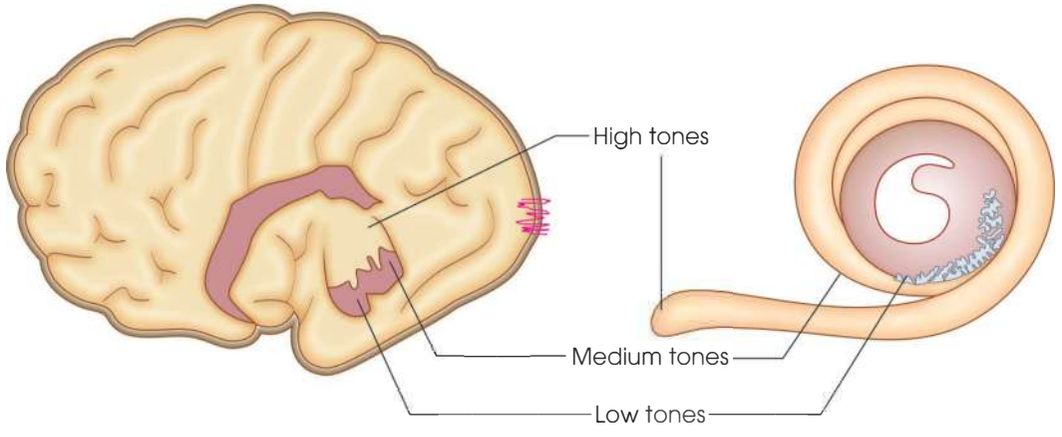


Fig. 118.20: Showing the relationship between the cochlea and acoustic area of the cortex and interpretations of sound in the brain

However, both principles have got some solid basis as evident from the study of:

1. Mechanics of the cochlear partition
2. Electrical potentials of the cochlea.

1. Mechanics of the Cochlear Duct (Cochlear Partition)

a. Present-day knowledge of the ear physiology comes mostly from the work of von Bekesy who obtained the Nobel Prize in 1961. He has proved by studying the physical properties of the cochlear partition, the patterns of movements of the cochlear partition and the basilar membrane as well under microscope through stroboscopic illuminations that the place theory has got some scientific basis.

b. The cochlea has been considered as frequency analyser of sound. It is a tuned structure and this tuning is partly due to gradually increasing width of the basilar membrane from the basal end of the cochlea to the helicotrema and partly due to increase in mass of the organ of Corti in the same direction.

c. Beside these, the basilar membrane has graded stiffness, increasing greatest towards the stapes and lowest towards the apex. Basilar membrane can be considered as a gelatinous mass covered by a homogeneous layer of fibres and forming a continuous structure with organ of Corti.

   The basilar membrane is not under tension. Due to gradation of stiffness of the cochlear partition, the resonant frequency is greatest towards the stapes than in the apical side.

d. Von Bekesy by measuring the amplitude and phase of vibration at a number of positions on the cochlear partition has found that each position shows a maximum displacement for a certain frequency of sound. He has observed that with increased frequency, maximum displacement is observed towards the stapes, but with decreased frequency, maximum displacement occurs towards the apex. Figure 118.21 shows the amplitude of displacement (envelope of vibration) of the cochlear partition at different frequencies. High-pitched sounds create waves that reach maximum height near the base and the low-pitched sounds create waves that reach maximum height at the apex.

e. Travelling waves are akin to pulse wave and are generated because the cochlear partition near the stapes is the stiffest and the waves being transmitted rapidly towards the flexible portions. The cochlear partition near the stapes vibrates in response to all frequencies and the wave moves at increasing amplitude towards the apex reaching its maximum height where the natural frequency of the cochlear partition is the same as the driving frequency. The amplitude declines abruptly beyond this point. Figure 118.22 shows the travelling waves pattern on the basilar membrane with increasing amplitude as they proceed towards the apex but decline abruptly near the apex.

f. Thus, the movements of the foot plate of the stapes set up a series of travelling waves in the perilymph and the cochlear partition. In the cochlear partition, the whole organ comprising the basilar membrane, organ of Corti, tectorial membrane and usually Reissner's membrane, all move in phase with one another.

g. As the basilar membrane bulges upwards and downward, then the stiff reticular lamina tends to rock on the support of rods of Corti around an axis at the attachment of the basilar membrane to the bony modiolus.

h. The tectorial membrane also begins to swing resulting in shearing action between the tectorial membrane and the reticular lamina. Figure 118.23 represents that the shearing action between two structures—the tectorial membrane and the reticular lamina, bends the hairs of the hair cells (Fig. 118.23B).

i. Under microscope, von Bekesy has examined in detail the nature of movements in different tissues relative to the basilar membrane. Figure 118.24 represents that on stapes side where the vibration is maximum; the movement of the ends of the hair cells under the tectorial membrane and of the cells of Hensen is in a radial direction. The inner and outer hair cells show vertical vibration at the region of maximum vibration but at the direction of the helicotrema the vibration becomes longitudinal. But how these shearing forces on the hair cells lead to excitation of the fibres of the eighth (VIII) cranial nerve is not known and requires further investigations though electro-physiological studies of the cochlea may throw some light on it.

2. Electrical Potentials of the Cochlea

Wever and Bray in 1930 proved that the electrical potentials recorded from the auditory nerve reproduced the frequency and the amplitude of the sound waves reaching the ear. The observer's findings supported Rutherford's telephone theory. But several electrical potentials of the cochlea have been demonstrated in order to find out the actual mechanism of hearing. These are described below.

Cochlear Microphonic (CM) Potential

a. Microphonic potential originates in the cochlea and spreads into neighbouring structures. It is produced due to acoustic stimulation.

b. CM is generated by deformation of the processes of the hair cells, and is linearly proportionate to the magnitude of the displacement of the basement membrane.

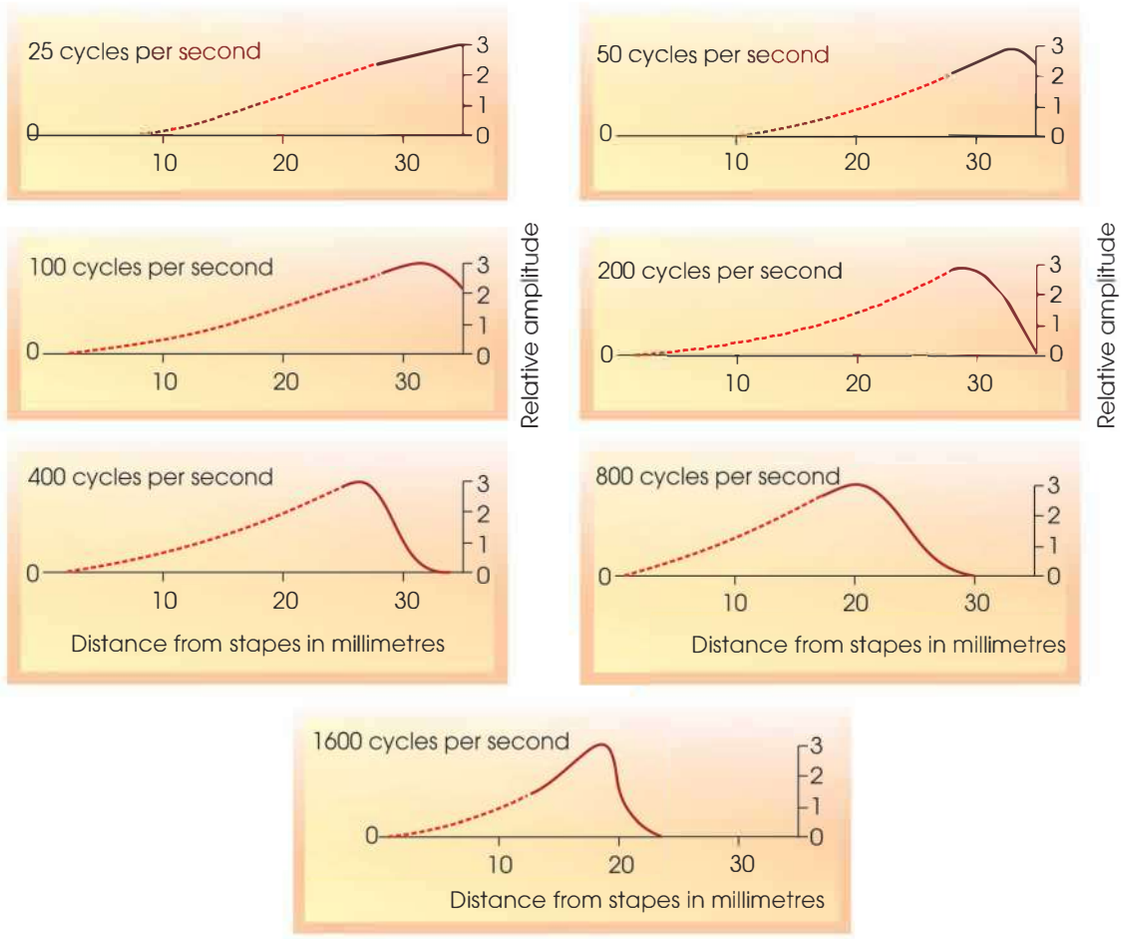


Fig. 118.21: Amplitude of displacement of the cochlear partition at different frequencies (Bekesy, 1949)

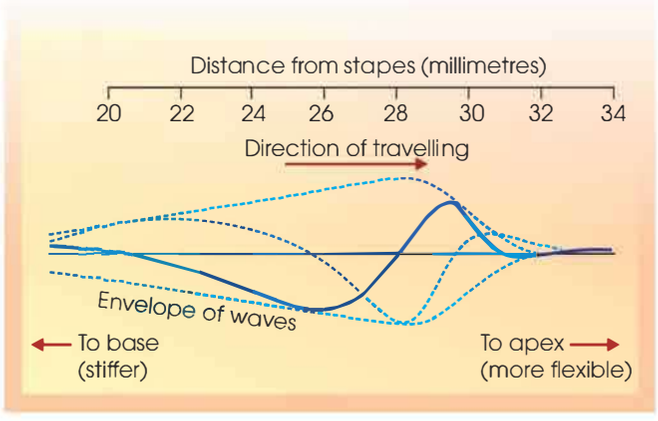


Fig. 118.22: Diagram shows the travelling wave patterns on the basilar membrane (Davis)

c. When the tectorial membrane vibrates and the hair cells bend, there is alteration of the DC endolymphatic potential which helps in the development of the cochlear microphonic potential. It can be recorded by placing one electrode in the scala media and another in the scala tympani.

d. The intensity of the stimulus is directly proportional to the amplitude of the response. It is developed by deformation of the processes of the hair cells and is linearly proportionate to the magnitude of the displacement of the basement membrane. It also increases linearly with increase in the pressure of the applied sound wave to a maximum of 2 mV, and decreases with further increase in sound pressure.

e. The increase in current flow associated with the cochlear microphonic potential stimulates the terminal non-medullated auditory nerve endings. Increased negativity in the scala media is associated with the current flow outwards across the membrane of the nerve fibres. Unlike nerve action potential, the CM is highly resistant to drugs, anaesthesia, cold and fatigue.

f. *Summating potential* (*SP*): Two additional potentials—the negative and the positive summating potentials have been recorded in response to acoustic stimulation. These potentials are the changes in the endolymphatic potentials in response to acoustic or mechanical stimulation. Summating potential is either an increase or a decrease of endolymphatic potentials. Those potentials appear where the cochlear microphonic potential is non-linear. The positive summating potential (SP+) has been though to originates in the outer hair cells, whereas the negative summating potential (SP–) has been regarded to originate from the inner hair cells.

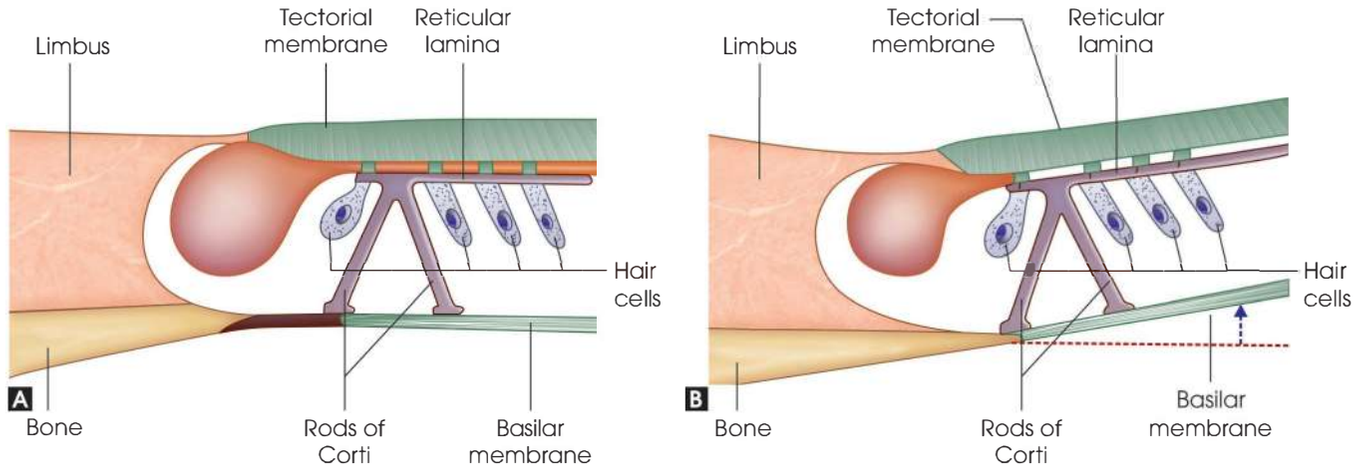


Fig. 118.23A and B: Diagram showing the mechanism of stimulation of the hairs of the hair cells through the shearing actions between two stiff structures, the reticular lamina and the tectorial membrane. (A) During rest, (B) during activity (Davis, 1957)

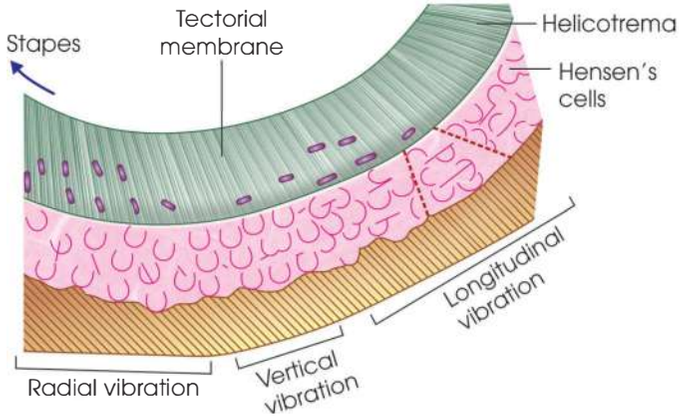


Fig. 118.24: Distribution of radial and longitudinal vibrations along organ of Corti as seen through Reissner's membrane (Bekesy)

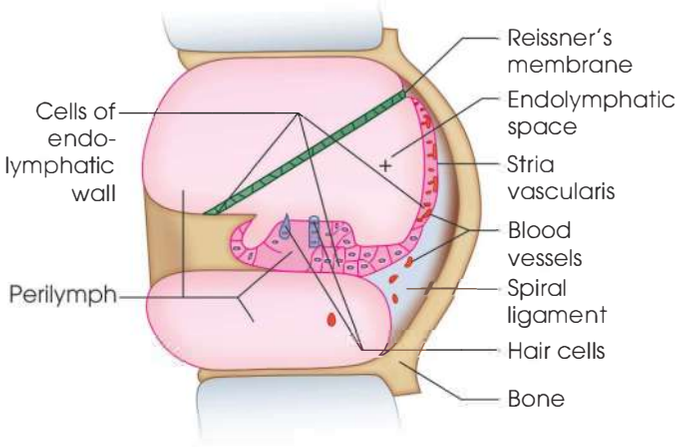


Fig. 118.25: The distribution of positive endocochlear potential. It is positive (+) relative to the perilymph (Tasaki, et al.)

g. *Endolymphatic potential* (*EP*): Positive electrical potential is recorded from the endolymph in the cochlear duct introducing a micro-electrode into the cochlea. At rest there is a steady +80 mV potential in the scala media with respect to the scala tympani, scala vestibuli or the tissues of the head (Fig. 118.25). The endolymphatic potential (endocochlear potential) is not only dependent upon ionic composition but also upon oxygen supply. In asphyxia it decreases. Metabolic activity of the stria vascularis probably forms the source of the endolymphatic potential. The potential is increased when the basilar membrane moves towards the scala tympani by the inward movement of the stapes. The outward movement of the stapes causes diminution of the potential.

Corti Lymphatic Potential

If the micro-electrode is introduced into the organ of Corti, then the –20 mV to –80 mV potentials are recorded in respect to perilymph. This negative potential is known as Corti lymphatic potential.

Action Potential from the Auditory Nerve

The cochlea, both mechanically and electrically, behaves like an acoustic analyser. The analysis is coded in terms of all-or-none activity in single auditory nerve fibres and is subsequently transmitted to the CNS. Tasaki (1954) has recorded response from single fibre of auditory nerve to tonal pips of different frequencies and intensities. He has shown that the frequency of the action potential in single auditory nerve fibre is proportionate to the loudness of the sound stimuli. At threshold intensity the nerve endings give response only to a narrow range of frequencies. With the increase of intensities, the nerve endings respond to an increasingly wide range of sound frequencies which lie below that to which they maximally respond. But there is a little if any impulse discharge to frequencies above that of maximal responsiveness. Figure 118.26 demonstrates the responses of a single auditory nerve fibre to tones of different frequencies.

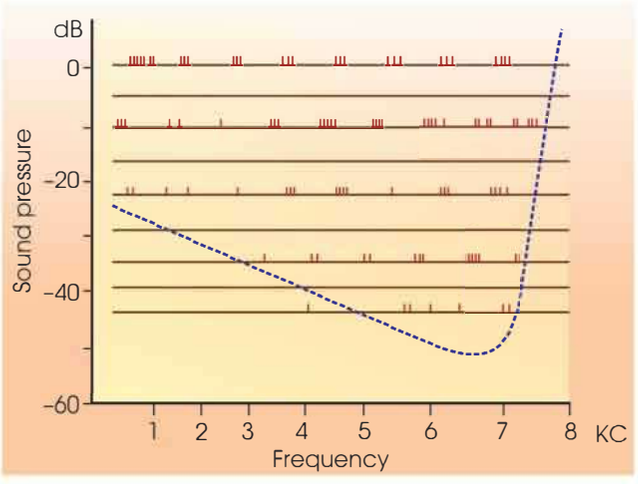


Fig. 118.26: Frequency response range of a single auditory unit becoming narrower as the sound intensity decreased. Sound intensity is expressed in decibels (dB) below an arbitrary standard

Path of Auditory Impulses

1. The cells of the spiral ganglion constitute the first - order neurons (Figs 118.27 and 118.28). Their short dendrites terminate round the hairs cells of the organ of Corti and carry the auditory impulses to the ganglion cells. The axons of these cells constitute the cochlear division of the eight.
2. At the lower border of the pons the nerve divides into two parts—one part ends in the dorsal cochlear nucleus and the other in the ventral cochlear nucleus, lying dorsal and ventral to the restiform body respectively. From these nuclei the second-order neurons arise:
   A. From the ventral nucleus a transverse band of fibres arises, called the corpus trapezoideum. Its fibres have three fates:
      a. A few end round the superior olivary nucleus and trapezoid nucleus of the same side.
      b. Most of the fibres cross and join the lateral fillet on the opposite side.
      c. Some remain uncrossed and join the lateral fillet on the same side.
   B. Fibres from the dorsal nucleus pass along the floor of the fourth ventricle towards the midline forming a conspicuous band of fibres called the medullary striae or acoustic striae. These fibres also have similar three fates:
      a. Most of them cross the midline sharply turn forwards and join the lateral fillet on the opposite side.
      b. Some fibres remain uncrossed and enter the lateral fillet on the same side.
      c. A few fibres terminate in the superior olivary nucleus on the same side.
3. The lateral fillet on each side, therefore, is composed of auditory fibres of both sides. It ascends through the pons and midbrain and ends in many fibres:
   1. In inferior colliculus.
   2. In the medial geniculate body.

   The two medial geniculate bodies remain united by commissural fibres, forming Gudden's commissure. The cochlea receives efferent innervations from the olivocochlear bundle. They are often called the efferent inhibitory pathway to the cochlea and play an important role in the regulation of the sensory output from this organ.
4. From the medial geniculate body the third-order neurons arise and constitute the auditory radiations. The fibres pass through the posterior limb of internal capsule and end in the auditory centre in the temporal lobe. The centre is situated in Heschl's

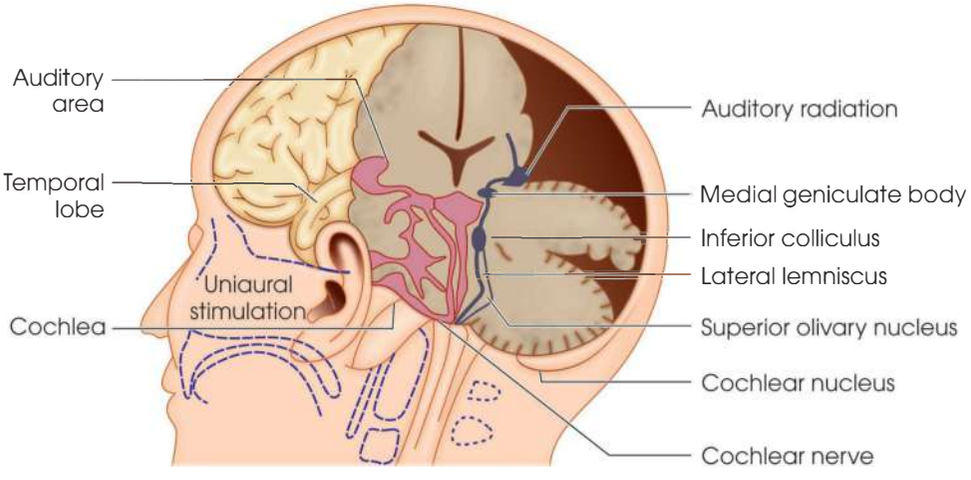


Fig. 118.27: An anatomical representation of auditory pathway. The impulses generated by displacement of the hair cells of the organ of Corti are carried along the corresponding nerve fibres to the auditory area of the cortex where they are resynthesized to produce sound (diagrammatic)

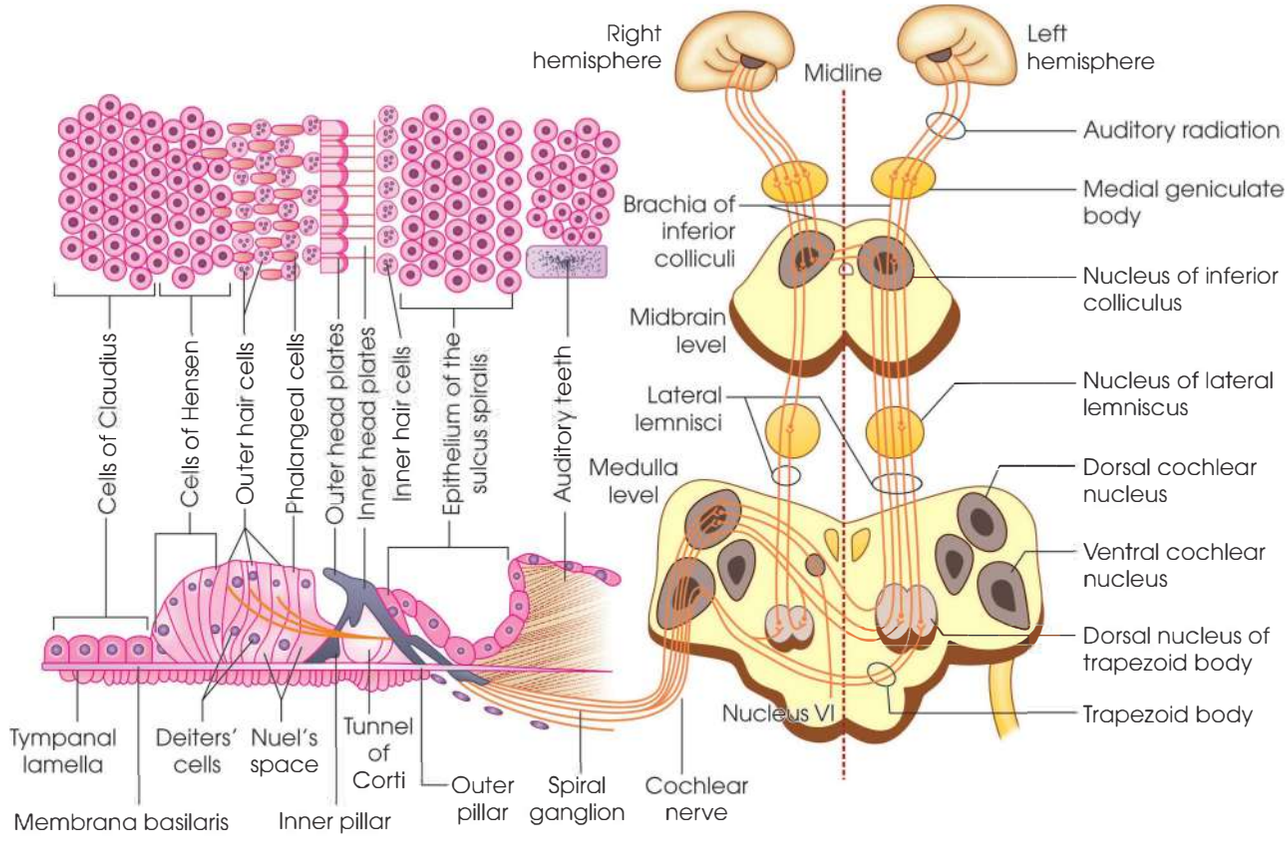


Fig. 118.28: Path of auditory impulses

gyrus and superior temporal gyrus (areas 41, 42, 22). There is a regular, point-to-point representation of the basilar membrane, at first in the medial geniculate body and then in the auditory centre (same as with vision). The apex of the cochlea is represented in the anterior end; the basal parts in the posterior end the intermediate region in the middle of the centre.

5. The audiopsychic centre remains close to it, occupying the superior, middle and inferior temporal gyri (areas 20, 21, 22); here the full meaning of a particular sound is interpreted. The auditory impulses from each ear project to the auditory centres of both cerebral hemispheres so unilateral removal of tone auditory cortex will not produce deafness.

EXAM-ORIENTED QUESTIONS

Essay

1. Describe the theories of hearing and mechanism of hearing. Add note on Rinne's test.
2. Describe the mechanism of hearing and auditory pathways. Add note on Weber's test.

Short Notes

1. Functions of middle ear
2. Cochlea
3. Cochlear potential
4. Place theory of hearing
5. Travelling wave theory
6. Endolymphatic potential (EP)
7. Audiometry

CLINICAL CASE SCENARIO

Special Senses

Q1. An 18-year-old male had a vehicular accident as he crossed the signal on traffic square and did not stop. The parents enquired from traffic police that he drove down the lane in spite of red colour signals were on. On treatment in casualty for injury he was also diagnosed as colour blind having protanopia coincidentally. Discuss regarding the diagnosed condition.

Ans. The 18-year-old male is suffering from colour blindness. It is chromosome linked genetic disorder. The patient is having protanopia means he is unable to identify and appreciate red colour. He is colour blind for red colour.

Q2. A 32-year-old soldier reported of inability to hear after reporting from war field where he had experienced massive bomb blast.

Ans. The patient is having conductive damage as a result of damage to tympanic membrane and ossicular system.

Q3. A student was asked to describe the five-type taste sensations and the taste modified portion. What answer is accepted as correct answer? What is miraculin?

Ans. The five-type taste sensations are sour, salty, bitter, sweet and umami. The umami taste is characteristically sweat and gives a pleasant experience. Miraculin is a known taste modifying protein. Miraculin when applied on tongue gins a sensation of sweetness instead of acidic taste.

Q4. A patient was diagnosed as a case of nerve deafness. If you are asked to perform Rinne test and Weber test, how would you interpret the findings?

Ans. A normal or positive Rinne test indicates that air conduction (AC) is greater/louder than the bone conduction (BC) (AC > BC normal), and if the patient is unable to hear the tuning fork post-mastoid test it is interpreted that his/her bone conduction is greater than air conduction. In sensorineural hearing loss the ability to sense the tuning fork by both bone and air conduction is equally diminished and the sound stops much earlier. Weber test: A vibrating tuning fork (256 or 512 Hz) is placed in middle of the forehead of patient.

In case of normal Weber's test patient report of hearing sound equally on both side. In case of conductive deafness the defective ear hears the sound louder while in sensorineural deafness sound is better heard in normal ear.

Q5. Enlist the common causes of blindness and visual impairment keeping in mind that you have to plan community base studies for prevalence of blindness and visual impairment in general population.

Ans. The common pathological conditions leading to blindness are cataract, glaucoma trachoma, trachoma, diabolic retinopathy, childhood blindness and age related macular degeneration, etc. The associated conditions leading to visual impairment are errors of refraction, cataract, glaucoma, macular degeneration associate with aging, childhood blindness, undetermined cause, etc.

Q7. A child of 7 years with history of loss of vision was diagnosed as case of amblyopia. Explain the condition. What are the causes for the same?

Ans. Amblyopia is a ocular disorder in which there is either loss of vision or impairment of vision because of failure of development of visual system and is associated in children having history of past illness of measles, or in patients of vitamin A deficiency, congenital rubella syndrome or meningitis.

Q8. As a medical student who is instructed to interpret for effect of lesions in visual pathway. Discuss the effect of lesions along the course of optic nerve.

Ans. The site of lesion and visual field defects are as follows:

Lesion	*Field defects*
1. Partial optic nerve	Ipsilateral scotoma
2. Complete optic nerve	Blindness in that eye
3. Optic chiasm	Bitemporal hemianopia
4. Optic tract	Homonymous hemianopia
5. Optic radiation	Homonymous hemianopia
6. Visual cortex	Homonymous hemianopia
7. Bilateral macular cortex	Bilateral central scotoma

Q9. Describe the various syndromes associated with hearing loss.

Ans. The common syndromes are:

a. *Ushers syndrome:* It is genetic disorder in which patient suffer from impairment of vision and loss of hearing. It is the most common cause of deaf blindness.
b. *Stickler syndrome:* Its genetic disorder affecting connective tissue and its characteristic features are facial abnormalities, visual disturbances, loss of hearing and joint associated pathology.
c. *Waardenburg syndrome:* It is a rare genetic disease in which patient suffer from varying degrees of deafness, pigmentation, anomalies and defects in structures arising from neural crest.
d. *Alport syndrome:* It is a genetic disease. The characteristic features of this disease are glomerular nephritis, end-stage renal disease and hearing loss.
e. *Neurofibromatosis type 2:* There are symmetric non-malignant brain tumours in the auditory vestibular nerve.

Q10. A patient was found to be having distortion of sense of taste. What can be the causes for the same?

Ans. The distortion of sense of taste is called parageusia or dysgeusia The common cause for dysgeusia are: Drug induced dysgeusia in patients on chemotherapy drugs such as cyctophosphamide, cisplatin and etoposide.

Nobel Prize 2004: Olfactory receptors

Richard Axel and Linda Brown Buck were awarded 2004 Nobel Prize in Physiology or Medicine for their work on olfactory receptors. Both of them described the family of about one thousand genes for odorant receptors. Independent studies conducted by both the Nobel Prize recipient also clarified the olfactory system, from the molecular level to the organization of the cells.

Richard Axel (1946)

Linda Brown Buck (1947)

Richard Axel, New York, USA, and Linda Buck, Seattle, USA, published the fundamental paper jointly in 1991, in which they described the very large family of about one thousand genes for odorant receptors. Axel and Buck have since worked independent of each other, and they have in several elegants, often parallel, studies clarified the olfactory system, from the molecular level to the organization of the cells.

Reference: Press Release 'The 2004 Nobel Prize in Physiology or Medicine'. Nobel Prize.org.

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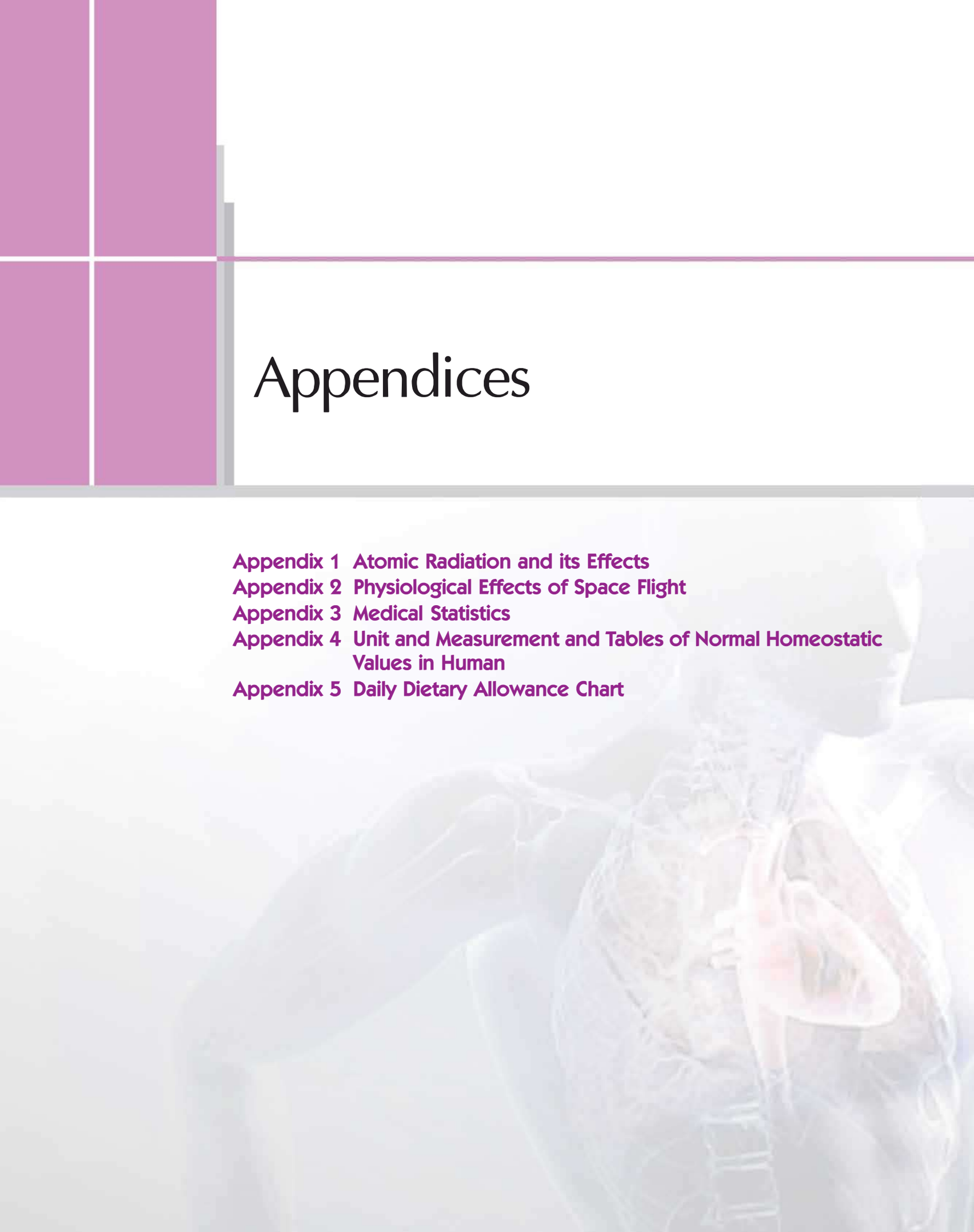
Appendices



Appendix

1

Atomic Radiation and its Effects

INTRODUCTION

Atoms were supposed to be the smallest particles existing in nature but now it has been established that still smaller particles exist. Atom consists of these smaller particles, e.g. electrons, protons, neutrons, positrons, etc. Electrons are very small particles and remain around the nucleus of each atom. The electron particles are negatively charged and can move from one atom to another. The protons exist in the nuclei of the atom. They are positively charged. Electrons and proton when get united, neutron is formed. The neutron has got no electrical charge. The positrons are positively charged. Radioactivity is due to disparity between the number of protons and neutrons in the nucleus. When radioactive disintegration occurs fast moving subatomic particles, electrons are emitted. These beams are called beta rays. When a positron strikes an electron there is release of gamma rays. Gamma rays and X-rays are practically of the same nature. The term gamma ray is used when the radiations are emitted by radioactive substances and X-rays are called when they are produced in special high voltage equipment. Radioactive atoms like helium on disintegration discharge alpha particles. Helium contains proton and neutron.

NUCLEAR REACTIONS

In the nuclear reaction there is released excess amount of energy and nuclear re-arrangement. When the two nuclei are brought into contact by some artificial procedure, at first a large nucleus is formed which undergoes disintegration. There may be fission of the large nucleus, or there may be release of gamma rays, or beta rays, or alpha rays, neutrons, protons or positrons, etc.

ATOM BOMB

In recent years the atom bomb has become lethal weapon in modern warfare. In making an atom bomb radioactive substances such as uranium 235 or uranium 233 and plutonium 239 are used. In the atom bomb reaction there is nuclear fission, i.e. the nuclei of uranium or plutonium split up and liberate neutrons. Again each of the neutrons helps splitting up of another uranium atom. Ultimately disintegration of the whole mass of uranium occurs. In the atom bomb very small masses of uranium are put together in a suitable container for explosion.

IONISING RADIATION

Since 1945 when the atomic bomb was dropped on Hiroshima and Nagasaki the conscious people of the world became alert about the hazards of atomic radiation. What we mean by 'radiation'? When we use the word radiation we commonly refer to 'ionising' radiations. Ionising radiations cause serious damage to living tissues and are so-called because they cause each atom they hit to lose an electron, the atom thereby being converted to a positively charged ion. The freed electron is incorporated in another atom which therefore becomes a negatively charged ion. When each electron lost from one atom is gained by another atom, the number of positively charged ions is equal to the number of negatively charged ions.

Ionising radiations include electromagnetic waves of very short wavelength (X-rays and γ-rays, and high energy particles—α-particles, β-particles, and neutrons). X-rays, γ-rays, and neutrons have great penetrating power but α-particles can invade soft tissues to a depth of only a fraction of a millimetre and γ-particles only up to a few millimetres in such tissues. Alpha and beta particles are extremely important if they are emitted from a radioactive substance which is actually inside the body.

The amount of radiation received by irradiated tissues is often called the 'dose' of radiation, which is measured in terms of rads and rems. The rad is a measure of the amount of any ionising radiation which is actually absorbed by the tissues and the rem is a convenient unit as it is a measure of any radiation in terms of X-rays. One rad is equivalent to 100 ergs of

energy absorbed per gram of tissue and one rem of radiation is that absorbed dose which produces in a given tissue the same biological effect as one rad of X-rays.

Sources of Ionising Radiations

Sources of ionising radiations are natural (background) and artificial. The amount of radiation from natural sources has remained the same since life first appeared on this planet. This natural source of radiation consists of cosmic rays, external radiation from radioactive materials in certain rocks, and internal radiation from radioactive materials in our tissues.

Cosmic rays originate from outer space and consist of high energy particles, mostly protons and small amounts of alpha particles, carbon, nitrogen, oxygen and iron. The effects of cosmic radiation in man are perhaps negligible but in the future the hazards to aircrews that operate at very high altitudes for considerable periods of time may be significant. The effects on persons involved in interplanetary space travel will have to be stupid. The intensity of cosmic radiation depends not only on altitude but also on latitude being greater at the poles than at the equator. The dose of radiation is expressed in relation to the amount received by the gonads. The gonad dose of radiation is often expressed as the amount received in 30 years. In the case of cosmic radiation the dose to the gonads is about 0.90 rem per 30 years.

A number of natural radioactive elements, namely thorium, uranium, radium and an isotope of potassium (^{40}K) are widely distributed over the earth's surface. The amount of radiation received by man from these sources varies considerably in various parts of the world. An average dose to the gonads from radiation from naturally occurring radioactive materials external to the body; amounts to about 50 mrems per year or 1.50 rems in 30 years. For example, in parts of the state of Kerala in India the average level of radiation is as high as 2800 mrems per year and in the state of Espirito Santo in Brazil it is about 500 mrems per year. Common natural radioactive materials are constituents of the breathing air, the eating food, and the drinking water. These radioactive materials include minute quantities of uranium, thorium and related substances, and isotopes of potassium (^{40}K), strontium (^{90}Sr), and carbon (^{14}C). The radiation from these elements within the body amounts to about 20 mrems per year.

The hazards and dangers from radioactive fallout resulting from the testing of nuclear weapons has become usually a political issue in many countries. On the average, the world population at present is exposed to less radiation from fallout from nuclear explosions than from medical radiology.

When a nuclear device is implied, it releases a tremendous amount of energy in the form of heat, light, ionising radiations, and many radioactive substances. Among the most important of these radioactive substances are isotopes of carbon (^{14}C), iodine (^{131}I), cesium (^{137}Cs), strontium (^{90}Sr), ^{137}Cs and ^{90}Sr are considered most important. Because the 'half-life' of ^{90}Sr is 28 years and that of ^{137}Cs is 30 years. This means that the radioactive of ^{90}Sr is reduced by a half in 28 years, by three-quarters in 56 years and by seven-eighths in 84 years. The hot gases of a nuclear explosion carry these radioactive substances into the atmosphere and stratosphere where they remain for some time before falling back to the earth (fallout). ^{137}Cs and ^{90}Sr are lodged on water which is later drunk or on vegetation which is either eaten by man or by cattle. The radioactive materials may also be passed onto man in the meat of cattle or in their milk. In man, ^{187}Cs is widely distributed throughout the body but is commonly abundant in muscle, whereas ^{90}Sr becomes almost solely localised in bone. Moderately large numbers of workers are engaged in medical radiology and atomic energy projects. The use of X-rays for detecting flaws in castings and for the examination of other commercial products has introduced potential hazards in industry. The use of radioactive isotopes has increased greatly in many spheres of activity from biologists using titrated thymidine in studies of chromosome replication to engineers interested in the combustion of motor fuels. Obviously persons in technologically advanced countries will be exposed to the greatest amount of radiation from man-made sources.

Effects of radiation: Ionising radiation acts upon the cells of the body and the sex cells; they have somatic and genetic effects. The immediate somatic effects of acute 'whole' body irradiation were seen in those individuals close to the centre of the atomic explosions in Japan in 1945: Among those who were not killed immediately by the blast, many suffered from the effects of having received an enormous dose of radiation. Some died within 10 days, others were ill for several weeks. Those exposed lost their hair and their bone marrow activity was greatly reduced so that the number of circulating leucocytes was considerably decreased and their resistance to infection was therefore severely impaired. Among those who recovered from the immediate effects; and some later developed leukaemia. One of the possible hazards of radiotherapy is an increased risk of developing leukaemia or other neoplastic diseases. Experiments on animals have shown that exposure to ionising radiation leads to a reduction in the lifespan; but so far there is no proof of this in man. There is good evidence in man that irradiation of the foetus, particularly during the early weeks of pregnancy, is associated with an increased risk of microcephaly and malignant disease in childhood. For this reason it is suggested that X-ray examination of the lower abdomen should be carried out within 10 days following the first day of the last menstrual period when it is most improbable that the woman could be pregnant. The somatic effects of a high

dose of radiation to a 'localised' volume of tissue are seen in patients being treated for malignant tumours and in persons involved in accidents with radioactive materials. The result may be local tissue necrosis (radiation burn) and general malaise with some nausea and vomiting (radiation sickness). Sufficient exposure to radiation will result in sterility but since it requires several hundred rads to destroy the sex cells, if this amount of radiation were received by the whole body it would probably be fatal. The somatic effects of radiation are extremely important to those involved in radiotherapy and the handling of radioactive materials.

In 1927, HK Müller demonstrated that exposure of colonies of Drosophila to X-rays resulted in an increase in the number of mutations in excess of those occurring spontaneously. He thus showed that X-rays are mutagenic. In the field of radiation genetic mutations are chromosome aberrations and point mutations. The chromosome aberrations are gross structural changes of the chromosomes such as deletions and breakages which are caused by high doses of radiation. Point mutations involve such a minute amount of chromosome material that they produce no visible change microscopically. It seems that ionising radiations and other mutagenic agents (exposure to high temperatures, ultra-violet radiation, and certain chemicals have been shown to be mutagenic in animals) bring about their effects by changing the arrangement of the atoms within a localised region of the DNA molecule. Mutations are usually harmful.

Sometimes a new mutation is beneficial. Plant and animal breeders are continually on the lookout for new mutations which have economic importance, Examples include strains of barley with higher protein contain: varieties of cattle with increased milk yield. There is no doubt that these mutations are beneficial to man, but it is a moot point whether, under natural conditions, such mutations are necessarily of benefit to the organism possessing them. In man, a new mutation is much more likely to be recognised if its effect is detrimental rather than if it confers some increased resistance to infection or leads to a slightly longer survival time.

Sequences of events of first atom bomb blasts during the last World War are:

Release of huge quantity of gamma rays in all directions is due to nuclear reaction.

Disintegration of the atom bomb into a gaseous mass; generates a very high temperature. The gaseous mass due to its very high temperature emits electromagnetic radiations, e.g. heat and light rays. These heat rays cause burning of the skin of the body. Excessive heat produced due to atom bomb blast makes a shock wave which travels at quite a high speed. This shock wave is so powerful that it will destroy all the animate and inanimate objects in its path up to a distance of about 3 kilometres. Emission of gamma rays which may kill a person even if he may remain about 3 to 5 kilometres away from the place of atom bomb blast. A person being exposed to atom bomb blast may die due to shock wave or due to burns within a few hours to a few days or due to effects of gamma rays which produce its deleterious effects on the different tissues of the body.

The effects of gamma rays on the different systems of the living body are as follows:

Cell division: Mitosis is blocked completely or almost completely after exposure to gamma rays or any other ionising radiations. Some cells in the body must be formed anew at different intervals according to their span of life. So, if there is blocking in mitosis, the specific functions carried out by these cells will be hampered due to their complete or partial disappearance.

1. *Blood*
2. *Leucopenia.* Both the granulocytes (function against invading organisms) and the lymphocytes (responsible for antibody formation) are diminished. As a result of leucopenia, the body is prone to infection and often there is septicaemia.
3. Anaemia occurs at a later stage as the lifespan of red blood corpuscles is approximately 120 days. It is due to inhibitory effect of gamma rays on the bone marrow. As a result of the inhibitory effect production of red blood corpuscles is reduced.
4. *Digestive system:* Inhibition of secretion of the epithelial and glandular cells of the gastrointestinal tract. The inhibition of secretion is due to cessation of mitotic division of the cells. As a result of these changes, symptoms like nausea, vomiting, diarrhoea, bleeding, and ulceration within a few days or weeks.
5. *Skin:* The germinative layer of the skin is prone to attack by the gamma rays. Mitotic division of the cells of this layer is inhibited. The skin is gradually atrophied and it may be extensively ulcerated within a few days or weeks.
6. *Eyes:* Cataract in some cases may develop (delayed effect). This is the late effect of gamma rays. The cells of the anterior part of the lens are destroyed.
7. *Gonads:* The germinal cells of the testes and ovaries are markedly affected. As a result the genes of the sperms and of the ova may become mutated and it is likely that the mutated offspring might be produced.
8. *Cellular changes:* Due to changes in the genes of some of the cells there is rapid proliferation of these cells and ultimately they may develop into cancer.
9. *Other organs:* As the various muscles and the nervous tissues do not depend upon rapid mitosis, they are least affected by gamma rays or other ionising radiations. The greatly depressed mitosis may be returned to normal after a few hours or several months which depend upon the degree of exposure. So, if the patients can overcome this depressed mitotic condition (i.e. maintain the life process until the mitosis returns to normal), they may return to normal physiological activity after several months.

Appendix

2

Physiological Effects of Space Flight

INTRODUCTION

Problems that have to face in space flight are hazards due to X-ray and gamma radiations, linear acceleration, weightlessness, survival in a sealed cabin and lastly the temperature in space. In space flight the subject does not have angular acceleration as the spacecraft cannot make rapid turns. But he has to withstand the take-off acceleration and landing deceleration. During take-off in 'three-stage spaceship', he has to face linear acceleration as high as 9G at first stage booster and as high as 8G at second stage booster. As the subject stays within the spacecraft in a semi-reclining position, transverse to the axis of acceleration, the subject can withstand the G effect easily. When the spacecraft re-enters the atmosphere, problems arise due to deceleration.

ARTIFICIAL CLIMATE IN SPACE CRAFT

In the outer space there is no atmosphere and for this reason artificial atmospheric climate condition atmosphere is to develop within the spacecraft. In such spacecraft sufficient O_2 is provided to the astronaut and suitable arrangement is made for absorption of CO_2. Besides this, food and water are provided according to the need. The gas mixture that is provided to the spacecraft is one of almost pure O_2 at 200 to 240 mm of Hg.

RADIATION HAZARDS

Cosmic particles in a large quantity are bombarding the earth. Some cosmic particles are coming from the sun and some are coming from the outer space. Magnetic field of the earth traps many of these cosmic particles at two major belts—inner and outer—around the earth—the Van Allen radiation belts (*see* Volume 1). The inner belt ranges from about 480 to 4800 km (300 to 3000 miles) from the earth and the outer belt from about 9650 to 32000 km (6000 to 20,000 miles) from the earth. Possibilities of the radiation hazards at two belts are high-energy electrons in the outer belt, and electrons and protons in the inner belt.

WEIGHTLESSNESS IN THE SPACE

Weightlessness is an acute problem in the space due to negative G. Posture has got a little effect on blood pressure and the subject may have a condition of red-out.

Temperature in the Space

In the ionosphere of several miles from the earth, the kinetic energy of atmosphere molecules, atoms and ions is very extreme. For this reason, the temperature of atmosphere is about 3000°C at an altitude of about 350 miles. But the spacecraft does not experience such temperature because of the sparsity of these particles.

ACCELERATION OF EXPOSURE

During space flight the space vehicle and crew must attain a velocity of 8000 msec to enter the earth orbit and attain an escape velocity of 11,6000 msec, to leave the earth's gravitational field. The Advisory Group for Aerospace Research and Development Space Medical Panel has used certain terminology, and symbols for different acceleration forces. On the basis of such terminology, the terminology in order to express the different acceleration forces are detailed in Fig. A2.1). Acceleration forces and resulting inertial forces are always opposite in direction. The distance through the body from front to back is designated by subscript x, the distance across the body from side to side is denoted by subscript y, and the length of the body is expressed by subscript z. G vector notations and descriptions* have been classified in Table A2.1.

*From Annual Review of Physiology, Volume 37, 1972: Physiological Problems of Space Travel by Robert W. Bullard and adapted from Von Gierke.

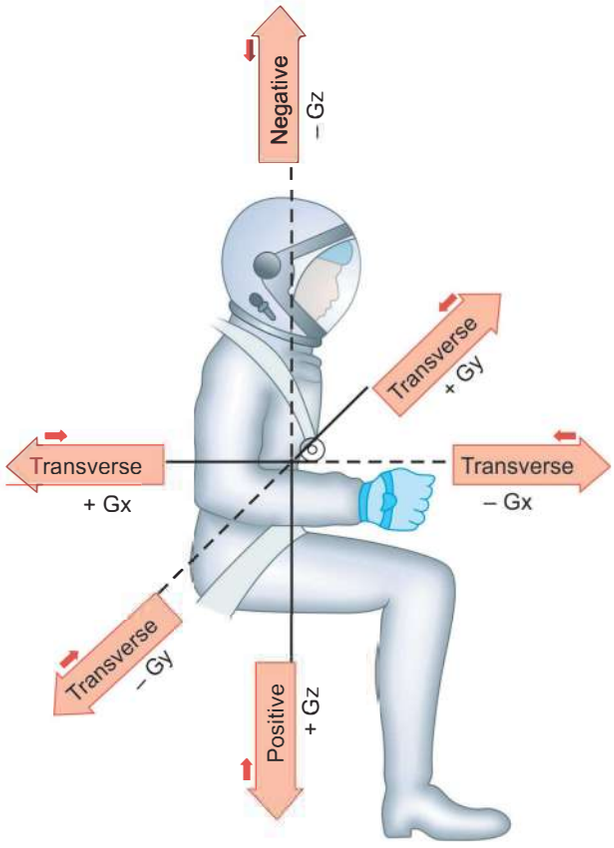


Fig. A2.1: Showing the various notations of acceleration as followed by Wunder (1966). Solid arrows depicting acceleration forces; open arrows denoting resulting internal forces always opposite in direction

Physiological changes in bodily processes are as follows:

Cardiovascular system: The main factors that play during space flight are due to positive G (+ Gz) for linear acceleration and due to negative G (– Gz) for absence of effect of gravity at space. Hydrostatic factors the **pgh** mainly govern the pressure and flow in the vascular system. p is the density of fluid (gm/ml), g is the acceleration of gravity (980 cm/sec) and h is the depth (cm). When a subject remains in horizontal position the blood pressure will be same all throughout the body but when the subject will be in erect position the blood pressure will be different (Fig. A2.2). Pressure at head level will be lower than those of the heart and foot levels. This is due to the effect of **pgh**. Furthermore if the G force is increased several times as in case of acceleration; then the pressure in the head will be so decreased that a condition black-out may be developed in the subject under such acceleration forces (Fig. A 2.1). Besides this, if the acceleration forces go opposite the force of gravity then the pressure will be alerted. Under such state, G effect will be nil and the subject feel weightlessness. Postural effect on blood pressure will both be observed and all throughout the body there will be uniform blood pressure. Thus, this opposite acceleration force exceeding the G force will raise the blood pressure in the brain above normal causing a condition known as red-out. Within the physiological limits, the body homeostasis can withstand against these effects of G. Human limit of tolerance against G is about 3G. Different vascular reflexes play an important role in maintaining the flow and pressure in the brain at such acceleration forces. Subjects having less active vascular reflexes cannot withstand such acceleration forces and become unfit for aviation or space flight.

Cardiovascular effects that have been studied during acceleration forces are an increased incidence of cardiac arrhythmias, alterations in the electrocardiograph, cardiac output, blood flow, blood pressure, etc. Incidence of arrhythmias is very, common under + Gz and + Gx accelerations. High incidence of premature ventricular contractions has been reported by many under + Gx acceleration. Flattening of T-waves in standard II and III leads, aVF and V4 and V6 were observed by many under + Gz and + Gx acceleration forces. Increase of heart rate with acceleration is also a common factor. But excessive G forces may decrease heart rate.

Hemodynamic changes with increased gravitational force vary greatly with the direction, magnitude and duration of the applied forces.

In experimental animals under + Gx acceleration has been observed to decrease cardiac output. Stroke volume is decreased greatly under acceleration forces from 5, 10 and 15 + Gx. Marked increase in arterial pressure has been observed by Sandler (1966). He has observed increase of pressure from 130 to 220 mm of Hg at 15 + Gx. Intraventricular pressure is increased under acceleration forces. Venous pressure and atrial pressure are also increased. These above pressures are increased greatly under transverse acceleration. Regional blood flow is greatly decreased under + Gx acceleration. Tissue fluid flows are decreased in renal

Table A2.1: G vector notations and descriptions classification

Vector	*Linear motion*	*Direction relative to body*	*Eyeballs of the pilot*	*Classic physiological description*
+ Gx	Forward	Chest-to-back: *Toward spin*	*In*	Supine G
– Gx	Backward	Back-to-chest: *Toward sternum*	*Out*	Prone G
+ Gy	To right	Lateral: *Toward left*	*Left*	Lateral G
– Gy	To left	Lateral: *Toward right*	*Right*	Lateral G
+ Gz	Upward	Head-to-feet: *Toward feet*	*Down*	Positive G
– Gz	Downward	Foot-to-head: *Toward head*	*Up*	Negative G

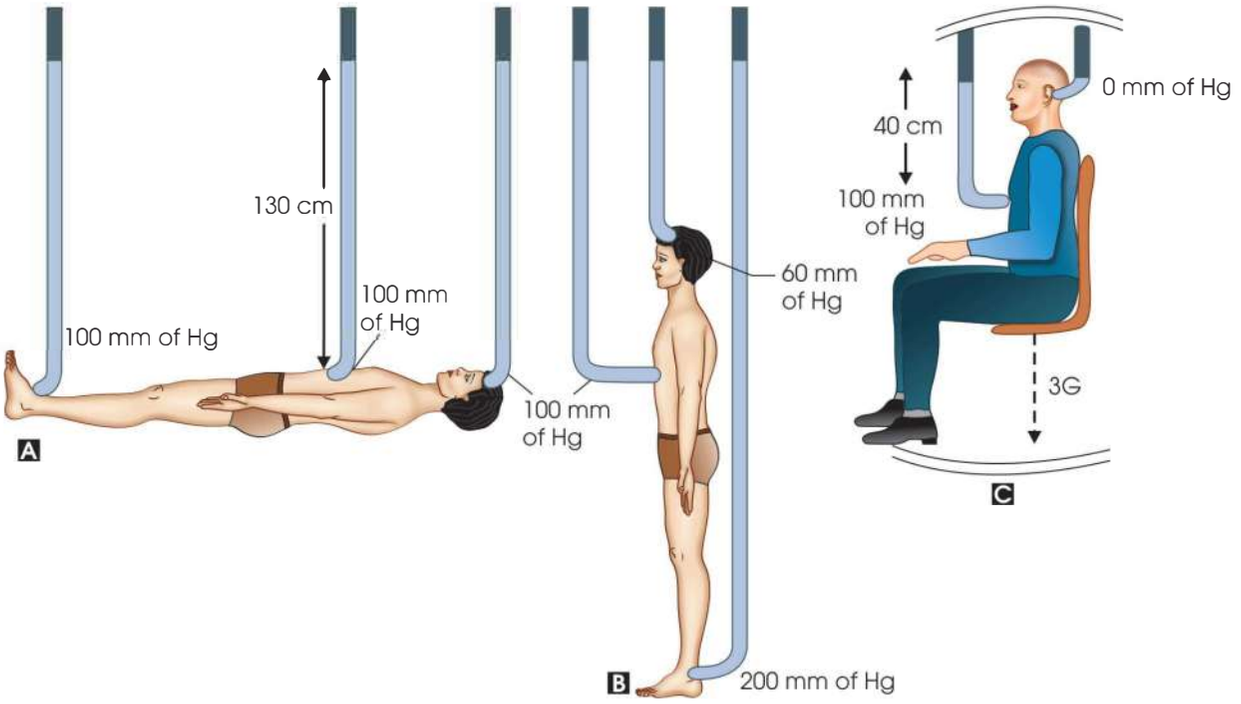


Fig. A2.2: Demonstrates the role of hydrostatic factor **pgh** on systemic blood pressure. (A) Subject in supine position; shows uniform pressure all throughout the body. (B) Subject in standing posture shows unequal pressure in head, chest (heart level) and in feet. (C) Subject in sitting posture is under acceleration of 3G directed towards the feet. It shows the fall of pressure in the head level due to effect of increased G. Cannulae inserted into aorta and arteries of brain and foot would support columns of blood to heights shown

cortex, adrenal gland and in small intestine. Blood in left coronary artery (circumflex) and common carotid artery has been measured. Blood flows through both the vessels are increased under 15 + Gz. Very recently it has been reported that prolonged space flight may alter the size of the heart. Heart weight is reduced after space flight.

Respiration: Extreme failure of respiration during space flight and also in space is the great problem. Respiratory structures are greatly affected due to displacement and distortion of the circulatory system. Major respiratory distresses are atelectasis, airway closure, increased transudation of fluids from capillaries and marked variations in ventilation–perfusion ratios. Marked distortion of pulmonary structure causes increased effect upon ventilation. Up to 4–6 + Gx, the musculature can lift the increased weight of the thoracic cage and the abdominal viscera. There is an increased rate of respiration of about 30/min. Tidal volume is decreased. Hyperventilation as well as apnoea is also encountered.

Blood volume: Blood volume is decreased by 7–15% in 4–8-day missions. In this brief period, loss of red cell volume appears to be very great.

Kidney function and body fluid regulation: Increased gravitational forces affect the kidney function and the regulatory mechanisms of body fluid. Vary greatly. At 6 + Gz renal blood flow is decreased along with diminution of arterial pressure and oliguria starts. This reduction in renal blood flow is attributed to intrarenal vasoconstriction medicated by α-receptors.

When human beings are centrifuged in + Gz axis; then changes in haematocrit ratio and plasma-protein concentration occurs. Free water clearance decreases with an increase in G load to 3 + Gz. Ability to excrete action of anti-diuretic hormone (ADH). Research studies have indicated mean rise in ADH of blood in subjects under 30-minute exposures of 2 + Gz acceleration. Besides this, aldosterone secretions as well as renin secretion are also enhanced due to acceleration forces.

Weightlessness: Weightlessness is the great problem in space. Many sorts of hazards that have to face are the nausea, anorexia, disorientation, sleeplessness, fatigue, restlessness, euphoria, hallucination, gastrointestinal disturbances, diuresis, urinary retention, muscular atrophy, bone demineralisation, red-out. Prolonged weightlessness resulted in subjective feelings of heaviness of head, limbs and body as reported on the 18-day flight mission of Soyuz 9.

Bone and electrolyte metabolism: Demineralisation is the problem of space flight. This effect has been predicted to be of prolonged weightlessness. This part has been neglected however the Gemini programme included the measurement of bone density. Decrease of bone density in Gemini flight was observed.

Electrolyte metabolism is greatly alerted. During entire flight potassium excretion is reduced and this

effect is unrelated with aldosterone. Aldosterone excretion in the urine is not detectable in the early four days of flight, but later on it is increased above the pre-flight level. For each forty-eight hours of flight, urine sample indicates retention of sodium paralleled by a similar decrease in chloride secretion. Calcium excretion is increased.

Work capacity: Work capacity is altered during space flight. Marked decrement in exercise capacity following a prolonged space flight is encountered when pre-flight and post-flight exercise tolerance is compared. Muscle tone of the legs is decreased. Walk and posture are not normal until ten days after flight.

Metabolic problems: Energy metabolism under absence of G has not been studied so clearly. The basal requirements for an average man of about 1.85 m^2 body surface have been estimated to be about 1700 kcal/day. The energy cost of movement will probably be somewhat reduced in absence of G. But attempt of movement in free space or within the capsule will certainly alter the energy expenditure. It is suggested that the energy expenditure in space will probably be less than that of in the earth. However, other factors like psychic problems, changes in hormonal level, adverse temperature, etc. may have some influence energy metabolism.

Appendix

3

Medical Statistics

Sometimes we want to explore new information about facts present in the universe. Any information regardless of its motive depends partly on real observations and partly on reasoning. The inference drawn either from observation or reasoning or from both is named as hypothesis. This hypothesis or inference in any case cannot be treated as an absolute result or value. In a large population it is not possible to observe all the items. Therefore, statistical methods have been developed to estimate the error or deflection from the true or real value when we are taking inference from a sample for a population.

The statistical methods are utilised in interpreting the results which are at the mercy of numerous influences and obtained from different experimental procedures. The object of the statistical analysis is to isolate and measure the effects of individual influences. To get a correct statistical analysis we have to see that we are comparing groups like with like that means we have not overlooked any relevant factor which is not present in anyone of the two groups.

Experiment with biological material is much more complex. Most of the biological parameters are interrelated and influenced by many other factors. When we measure a parameter, the readings are scattered over a wide range, even when we think that the affecting conditions are constant. Again when the readings are taken after altering some of the affecting conditions, the range of the readings often overlap the former instead of being a completely separate one. Under such circumstances, statistical assessment can help in several ways:

1. To choose a value of parameter of representatives of each group of readings.
2. To describe what is the nature of the variability within the group.
3. To decide whether a difference between two groups is a real one or it could have occurred by chance.

PROBABILITY

When we are conducting some experimental observations, first of all we have to consider that whether the result is obtained only due to chance or coincidence, or it is appearing as the real of true one. To meet this query, we have to find out the natural probability. First, say, where n is the number of all possible results of some action, which are of equal possibility to occur and r is the number or results which will satisfy some particular necessity or condition, then the probability of satisfaction of the requirement will be (r/n). As for example, a dice can fall with any of its six sides ($n = 6$) keeping uppermost. If the necessity is such that the side marked with 4 should come uppermost then only one of the six sides will satisfy the requirement, i.e. $r = 1$. So, in this case the probability is (1/6). When we consider r and n for an ideal dice then any of the numbers from 1 to 6 is equally likely to come upwards. In that case the P is equal to (1/6). This type of presumed probability is named as a *priori probability*. But the probability may also be obtained by actual throwing of the dice for a number of times (more the number of throwing better or more nearer will be the P value to the ideal one). The probability obtained with this process is named as a posteriori probability. In practice, this is a more complex process than the priori probability. So in the case of a dice a priori probability is (1/6), i.e. (r/n) but a posteriori probability is (r_x/n_x) which may not be exactly equal to (1/6).

Probability of More than One Event

The probability of occurring multiple events at a time is same as above, i.e. in case of a single event (r/n), when n is the possible way in which all the combinations of events can occur and r the number of combinations that fulfils the requirement. These multiple events may be dependent or independent of each other.

Probability of Mutually Dependent Events

When the requirement is so that any of the mutually exclusive results (events) satisfy then the individual probabilities are to be added together to get the final probability. In other words, when individual probabilities are (1/6), (1/6), (1/6) for appearing upwards anyone of the numbers more than three of a dice, i.e. 4, 5 and 6 respectively; then probability of appearing anyone number more than three in a dice is (1/6) + (1/6) + (1/6) = (3/6). In summary, this can be stated as-if either *a* or *b* or *c*, add the probabilities of *a*, *b* and *c*.

Probability of Independent Events

If the requirement is so that the concurrence of two or more events, each of which can occur independent of the other then the probability or concurrent events can be obtained by multiplying the individual probabilities. Say for example, when one coin and one dice are tossed together and the requirement is that the head of the coin and the side of the dice containing number 4 should come upward; then individual probabilities are (1/2) and (1/6) respectively; and the probability of concurrence of these events is (1/2) × (1/6) = (1/12). In short this may be stated as-if only a as well as *b*, as well as *c* will satisfy the requirement, then multiply the probabilities of *a*, *b* and *c*.

Calculation of *n* and *r* to Find out the Probability of Larger Systems

In larger complicated systems it is more convenient to calculate *n* and *r* by the method or formula of permutation and combination.

All possible different arrangements which can be made out of *n* things by taking some (*m*) or all (*n*) of them at a time is called their permutation (^nP or ^nP) respectively, which is stated as:

$$^nP_m = n(n-1)(n-2)...(n-m=1)$$

$$^nP_m = {}^nP_n = n = n! = (n-1)(n-2)...3.21, \text{when } n = m$$

Now again, when each combination of *m* objects from *n* objects differs only of content and not of inner arrangement, it is called combination (^nC_m).

$$^nC_m = \frac{^nP_m}{m!} = \frac{n!}{m!(n-m)!}$$

For example, the number of ways by which any four cards can be drawn from a packet of playing cards is $^{52}P = 52 \times 51 \times 50 \times 49 = 64, 97, 400$ when the inner arrangement or order is considered:

$$^{52}C_4 = \frac{^{52}P_4}{4!} = \frac{52 \times 51 \times 50 \times 49}{4 \times 3 \times 2 \times 1} = 2,20,725$$

when the inner arrangement or order is not considered.

So, the probabilities of getting 4 jacks together, with or without considering the inner order are (1/64, 97, 400) or (1/2, 70, 725) respectively (as here $r = 1$ in both the cases and n = 64,97,400 and 2,70,725 respectively).

Now in practice, more the number of repetitions of the experiment the *P* value will be more nearer to the theoretical or ideal one. Smaller the number of repetition larger will be the discrepancies which can also be calculated with the following formula:

$$P = \frac{n!}{r!(n-r)!}.p^r.(1-p)^{n-r}$$

when *p* is the probability of a positive result in some situation, the probability, *P* of getting *r* positive results in *n* trails.

For example, in case of coin, the probability of getting four times head upwards in 8 trails will be as follows:

$$P = \frac{8!}{4!(8-4)!}.\left(\frac{1}{2}\right)^4.(1-\frac{1}{2})8-4$$

$$= \frac{8!}{4!4!}.\left(\frac{1}{2}\right)^4.\left(\frac{1}{2}\right)^4 = \frac{8!}{4!4!}.\left(\frac{1}{2}\right)^4 = \left(\frac{35}{128}\right)$$

Much of statistics involves the use of test to work out what is the probability of a particular difference in events occurring by chance. Then with an arbitrary definition it can be stated that the result is whether or not statistically significant. When $P \leq 0.05$, i.e. one in twenty trials, is significant and $P \leq 0.01$, i.e. one in hundred trials, is taken as highly significant. Still $P \leq 0.01$ does not mean that there is a real difference between two sets of results but only that such a difference can occur one in hundred trials by chance.

FREQUENCY DISTRIBUTION

The experimental observations may be divided mainly into two groups, quantitative, dealing with some property or change of property in quantity and qualitative, some sort or property (quality). Generally the number of observations is smaller when dealing with qualitative observations, and very large when dealing with quantitative observation. When experimental results are obtained, they appear as mere collection of data. In many cases, it is therefore, advisable to prepare smaller groups of them by dividing the range of data into smaller subdivisions according to some standards and then to obtain a frequency distribution. So, frequency distribution of a set of data is the frequency of occurring of the data in different smaller subdivisions of the range of data.

Preparation of a Frequency Distribution Table

The frequency distribution table (Table A3.1) can be prepared by jotting down all the numerical values in

Table A3.1: Preparation of frequency distribution chart

Actual range of groups	*Mean value*	*Occurrences*	*Total*
1.48–1.50	1.49	I	1
1.50–1.52	1.51	IIII	4
1.52–1.54	1.53	IIII‖	7
1.54–1.56	1.55	IIIII‖I	9
1.56–1.58	1.57	IIIII	6
1.58–1.60	1.59	III	3
		Total number of data is 30	

order of increasing size which are represented in the series of measurements in the first column, next the mean value of each range. In the occurrence column one vertical stroke is marked for each occurrence of the value against the respective range of subgroup and a group of five is made with four such vertical strokes and a diagonal one across the first four (Table A3.1).

As for example, the results obtained by measuring the height (in metres) of 30 human adults of age group 20–25 years: 1.51, 1.54, 1.55, 1.59, 1.48, 1.50, 1.55, 1.53, 1.50, 1.55, 1.55, 1.52, 1.53, 1.54, 1.53, 1.56, 1.52, 1.57, 1.53, 1.57, 1.52, 1.54, 1.51, 1.54, 1.55, 1.56, 1.57, 1.56, 1.59, 1.59.

The frequency distribution table is prepared with these results by dividing into smaller ranges as 1.48, to 1.50; 1.50 to 1.52, etc. along with a mean value in each case and the frequency of occurring the results in different subgroups are found.

Frequency Polygon

The frequency polygon (Fig. A3.1) is nothing but the graphic representation of the frequency distribution table. The graph is to be drawn with the mean values of the range of subgroups along the abscissa and the frequency distribution along the ordinate.

If we increase the number of results and divide into smaller subgroups then the polygon will be more accurate and smoother one which is then named frequency distribution curve. When the frequency is equally distributed on the both sides of the midpoint (highest frequency) the curve will be bell-shaped and named as normal, Gaussian or symmetrical distribution curve (Fig. A3.2A). if there are only two possible alternatives for a parameter (e.g. head and tail of a coin; Rh+ and Rh–) and we can precisely state the number of times one or the other occurs. In such a case the distribution is named is binomial which may be symmetrical or asymmetrical. When the slope of the curve is less at the positive side (right side)—it is asymmetrical, positively skewed (Fig. A3.2B), the reverse one is the asymmetrical, negatively skewed (Fig. A3.2C) distribution.

When the frequency polygon is tending to approach a J-shape, i.e. frequency tends from infinity to zero but remains finite as measurement increases, it is J-shaped or poissonian distribution (Fig. A3.2D). When it is infinite to infinite U-shaped (Fig. A3.2E), i.e. at both the highest and lowest values of the parameter the frequency is infinite. When the frequency is equal throughout the groups of data, then the curve will be parallel to the horizontal axis—rectangular (Fig. A3.2F).

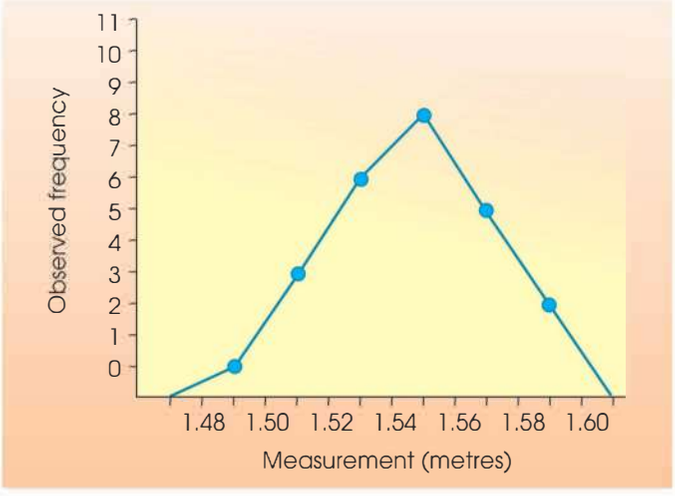


Fig. A3.1: Frequency polygon

Frequency Histogram

The frequency with which each of the values in the series occurs is therefore qualitative statistics, in other words, each refers to the number of individual measurements falling into a class having well-defined limits. The graph can be done by putting the ranges in place of the measurements, e.g. 1.51 metres = 1.50–1.52 metres and forming a rectangle with the frequency, i.e. the rectangle is formed with the range as the base and the frequency distribution as the height. This type of graphic representation is named as frequency histogram (Fig. A3.3). The probability of occurring any individual measurement that lies within any specific limits can be inferred from the frequency polygon or histogram drawn from a set of data. The probability is proportional to the frequency for each of the stated values representing the midpoint of the range in case of the frequency polygon. But in case of the histogram the probability is proportional to the rectangle made of the range of values and frequency observed. Now normally the ranges of values are equal to each other and then, the probability is proportional to the frequency observed.

AVERAGES (Fig. A3.4)

Arithmetic Mean

When several readings are obtained from the same parameter (object) or of the similar kind of objects, then

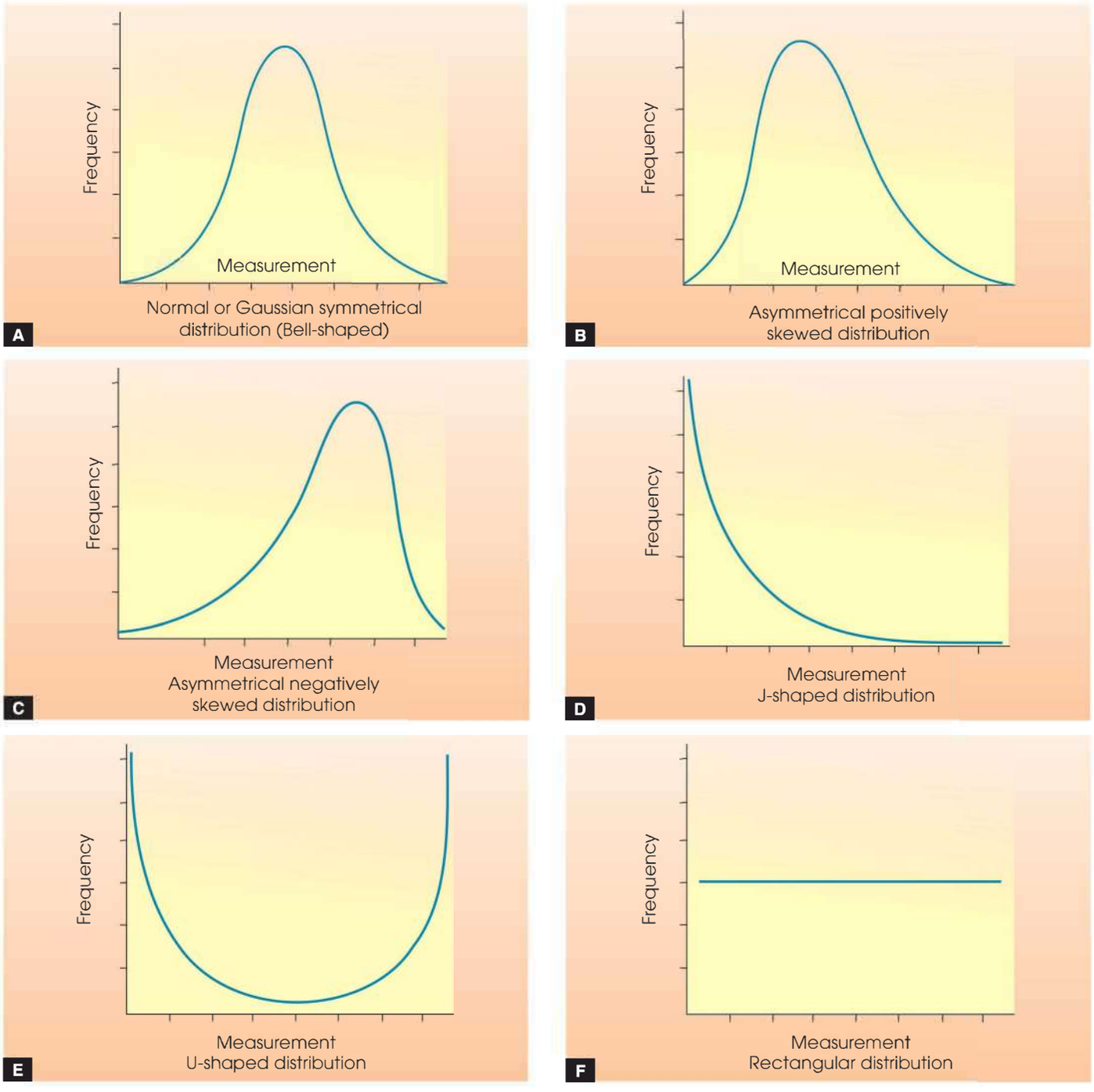


Fig. A3.2A to F: Frequency distribution curve

usually an average (mean) is taken from all the readings. One of such averages which is most commonly used is the arithmetic mean. Generally the term 'average' or 'mean' is used for the arithmetic mean. Now for example when the set of data is $x_1, x_2, x_3, ..., x_n$; n being the number of data (readings); $\Sigma(x)$ stands for summation of the whole set of data (i.e. $x_1 + x_2 + x_3 + ... + x_n$); then the arithmetic mean ($\bar{x}$) can be obtained with the following formulas:

$$\bar{x} = \frac{(x)}{n}$$

Mode

There are some conditions (requirements) where the arithmetic mean does not serve the purpose. Say for example, one businessman wants to stock ready-to-wear garments of standard size which will fit maximum number of customers. In this case he will be interested of the size of customers most frequently occurring in the population and not in the arithmetic mean. So, the mode is the most frequently occurring value of x; in other words, the mode is the highest point of the frequency polygon.

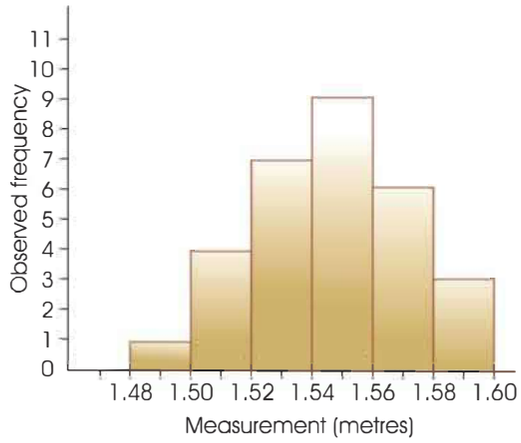


Fig. A3.3: Frequency histogram

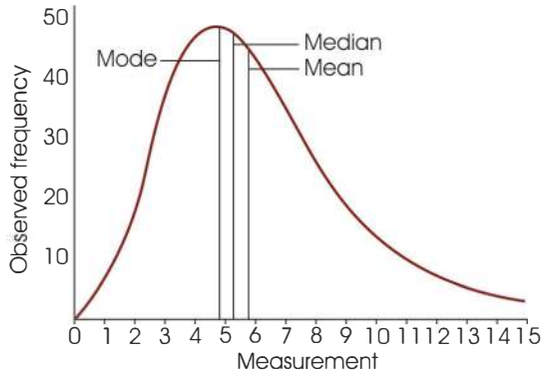


Fig. A3.4: Mode, median and mean of a skewed distribution

Median

It is the third kind of average which divides a set of data into two equal halves, one containing the values lower than this value and the other containing the higher values. The formula to find out the position of the median is $\{(n + 1)/2\}$, in other words $\{(n + 1)/2\}$ value of x. For example, there are 107 items in a set of data, then $\{(107 + 1)/2\} = 54$th value in the range of data is the median.

If the distribution of the frequency is a symmetrical one then the median coincides with both the mean and the mode. If it is a positively or negatively skewed one then the median will lie in between the mode and the mean. The mode is the peak of the curve and the mean towards the long tail end.

Geometric Mean

This kind of average is used when dealing with ratios, indices or any such other relative numbers.

$$M_{\bar{g}} = \sqrt[n]{x_1 \times x_2 \times x_3 \times \ldots \times x_n}$$

Harmonic Mean

This is used when dealing with rates and speeds.

$$M_{\bar{h}} = \frac{n}{(1/x)}$$

In summary, an average can have a variety of proportions, but it is not always possible to show all of them in one value. It may be the one nearest to all experimental values (arithmetic mean), or the value that divides the experimental values into two equal halves of larger and smaller values (median), or the value that occurs most frequently (mode).

Average of Averages

Sometimes it needs to have a grand average of the averages obtained from smaller groups or samples. To get the grand mean the size of each sample must be considered when the sample size is not constant for all of them. Say for example, there are r sets of samples, having means as $m_1, m_2, m_3, \ldots, m_r$ with $n_1, n_2, n_3, \ldots, n_r$ number of values respectively. Then {as $S(x) = m.n$} the sum of the results of the first sample m_1. n_1; the sum of all the results of all the samples is

$S(mn) = m_1n_1 + m_2n_2 + m_3n_3 + \ldots + m_rn_r$.

Total number of results or data of all the samples together is

$$S(n) = n_1 + n_2 + n_3 + \ldots + n_r.$$

The grand arithmetic mean (M) is then

$$M = \frac{S(mn)}{S(n)} = \frac{m_1n_1 + m_2n_2 + m_3n_3 + \ldots + m_1n_1}{n_1 + n_2 + m_3 + \ldots + n_r}$$

If the size of the samples is same for all the cases (i.e., $n_1 = n_2 = \ldots = n_r$) then

$$M = \frac{n(m_1 + m_2 + m_3 + \ldots + m_r)}{rn} = \frac{S(m)}{r}$$

Averages as Ideal Values

It is already stated that the larger the number of individual values, the more likely that the mean will attain the ideal value as the dispersed values will balance each other. The averages obtained from the small group of estimates may not be very near to the true mean, so they are denoted by the Roman letters as m_1, m_2, etc.; to differentiate from the ideal value which is denoted by the Greek letter μ.

DEVIATIONS OR SCATTERS

Suppose we are measuring the systolic blood pressure of a group of male individuals by means of two methods. With the first method the lowest reading (datum) is 96 mm of Hg and highest of 104 mm of Hg; and with the second process lowest is 45 mm of Hg and highest is 155 mm of Hg. Both the groups are normally distributed with an average 100 mm of Hg. Now what method is to be recommended where only one sample or reading is possible? To answer this question the following statistical analysis may help us. It is seen that the individual readings in case of the first method are more nearer to the true mean than that of the second one. In that case with the second

method, a single reading may give a impression of the situation with a larger error. These differences or distances from the mean are named as deviations or scatters.

Range of Data

The simplest and commonest measure of scatter is the range, which is the interval between the lowest and the highest value of a set of data, e.g. in the above paragraph the range of data is 96–104 with the first method and 45 to 155 in the second one. The end points have got no definite destination the size of the range to some extent depends on the size of the sample, i.e. a larger sample is more likely to contain more extreme values making the range larger than a smaller sample. So, it is not at all a reliable measure of scatter.

Mean Deviation (MD)

It is a better way of measuring the scatter as it takes account of all the numbers of the sample and its value does not depend on the size of the sample, but on the size of the deviations respectively. The difference between any individual reading and the arithmetic mean in a set of data is named as the deviation. The sum of the deviations without considering the sign (of the difference) divided by the number of values is called the mean deviation.

$$MD = \frac{|x \quad \bar{x}|}{n}$$

when $|x - \bar{x}|$ = the difference ignoring the sign
and n = number of values

Variance and Invariance

$$V(\text{variance}) = \frac{\sum(x - \bar{x})^2}{n}$$

It is largest in a population in which the individuals vary a lot.

The invariance is the reciprocal of the variance which is largest in a population where the individual readings vary minimum, i.e.

$$I(\text{invariance}) = \frac{n}{\sum(x - \bar{x})^2}$$

Standard Deviation

The standard deviation is the square root of the variance, i.e. standard deviation (σ) = $\sqrt{(x \quad \bar{x})^2 / n}$. As the ideal or true mean of a population can be obtained only approximately from a sample so the true standard deviation can be estimated also approximately from the available sample. With this appreciation the standard deviation can best be estimated with the following formula:

$$\sigma = \sqrt{(x \quad \bar{x})^2 / (n \quad 1)}$$

The arithmetic labour that is involving in calculating the standard deviation can be minimised with the following systematic tabular form (Table A3.2).

It is the most commonly used expression of deviations. It has the advantages as that of the mean deviation, and some other advantages specially when dealing with samples of a normally distributed population. With such distribution, one standard deviation (σ) at both positive and negative sides of the mean ($\bar{x} \pm \sigma$) will cover about two-thirds or 66% of the total number of values, similarly ($\bar{x} \pm 2\sigma$) will cover 95% and ($\bar{x} \pm 3\sigma$) will cover 99% in approximate of the total number of values (Fig. A3.5).

Gaussian Frequency Distribution

The arithmetic labour that is involving in calculating the standard deviation can be minimised with the following systematic tabular form (Table A3.3).

The above-mentioned method for calculating the standard deviation is suitable for smaller groups of results but not for large-sized samples. For large samples the following table is more appropriate.

Table A3.2: Arithmetic calculation and standard deviation

No. of observations	*Individual observations* ($\bar{x}$)	*Deviation* ($x - \bar{x}$)	*Squared deviations* $(x - \bar{x})^2$	*Calculation of SD* (σ) [σ, *sigma (small)*]
1	18	–2	4	$\Sigma(x - \bar{x})^2 = 60$
2	10	–0	0	$\sigma = \sqrt{\Sigma(x - \bar{x})^2/(n-1)}$
3	9	–1	1	$= \sqrt{(60/9)}$
4	11	–1	1	$= \sqrt{6.66}$
5	12	–2	4	$= \pm 2.58$
6	10	–0	0	
7	7	–3	9	
8	6	–4	16	
9	13	–3	9	
10	14	–4	16	
Total	$\Sigma(x) = 100$	$\Sigma(x - \bar{x}) = 0.0$	$\Sigma(x - \bar{x})^2 = 60$	
	$\bar{x} = \frac{100}{10} = 10$			

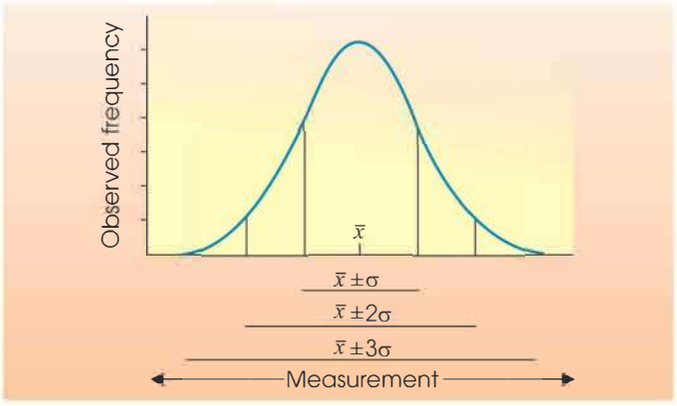


Fig. A3.5: Relationship between the standard deviation and the normal or Gaussian frequency distribution

SAMPLING

A true mean is the mean of a infinitely large number of readings of a parameter. In experiments it is not possible for us to collect an infinite number of readings of a parameter, so we have to try to collect a reasonably small number of readings which are representative of the large population and in this way we are sampling the universe of possible readings. A sample should never be selected but collected randomly. A selected sample is not a representative of the universe and will exhibit higher error of sampling. Errors of sampling are of large consideration in cases where only one or more samples are available as a basis for inductive inference and the total population from which the samples are drawn, is not observable. Obviously we should like that the true mean and the true standard deviation will coincide with the mean and the standard deviation of the sample, which are affected by the following factors.

Size of the Sample

Greater the ratio of the sample number to the population, more nearer will be the sample to the true population. This accuracy increases as the ratio of the square root of those numbers, i.e. if the sample number increases from 10 to 100 then the increase in accuracy will be $= \{\sqrt{100} / \sqrt{10}\}$.

Variability of the Readings

When the range of data is shorter, then there is a possibility that the mean of the sample will vary less from the true mean, but in case of a larger range of data, there is a greater possibility of variation of the sample mean from the true mean. So, sampling should be as much large as possible otherwise it may give a different representation of the true population.

Frequency Distribution of Means

Let μ be the true mean of a normally distributed population and σ the standard deviation. Then m_1, m_2, etc. the means of the n number of samples, will be normally distributed about μ with a standard deviation $(\sigma/\sqrt{n})$. This is also true for the population riot normally distributed but the variations from the normality are not much.

Standard Error of Mean (Standard Error)

This frequency distribution of means is of a great importance for practical purpose as it indicates that how much the sample mean is varying from the true mean. In other words, it gives an estimate of the error of sampling for which this standard deviation of the true mean is also named as standard error of mean or simply as standard error (e). It should be carefully noted that 'standard deviation' represents commonly the standard deviation of the individual values, and 'standard error' stands for the 'standard deviation of the mean'.

So, standard error = $(\sigma/\sqrt{n})$.

Standard error of the sum of two means

$$e_{(m_1+m_2)} = \sqrt{(e_{m_1})^2 + (e_{m_2})^2}$$

Standard error of difference of the two means

$$e_{(m_1+m_2)} = \sqrt{(e_{m_1})^2 + (e_{m_2})^2}$$

Table A3.3: Arithmetic calculation of standard deviation for larger groups

Mean value of the smaller ranges in cm	*Frequencies*	*Deviations*	*Squared deviations*	*Product of respective deviation and frequency*	*Product of squared deviation and frequency*	*Working*
149	4	–5	25	–20	100	Working mean = 154
151	9	–3	9	–27	81	Mean = 154 + 0.12 = 154.12
153	12	–1	1	–12	12	Correction for mean (6^2/50) = 0.72
155	14	1	1	14	14	Corrected sum of squared deviation ... 354 – 0.72 =
157	8	3	9	24	72	353.28 sq cm
159	3	5	25	15	75	$\therefore$ SD = $\sqrt{353.28/49}$
Total	**50**	–	**70**	**–6**	**354**	= ± 2.68 cm

Standard error of product of the two means

$$e_{(m_1 m_2)} = \sqrt{(e_{m_1})^2 + (e_{m_2})^2 + (e_{m_2})^2 + (e_{m_1})^2}$$

Standard error of product of two means

$$e_{(m_1 / m_2)} = \sqrt{\frac{(e_{m_1})^2}{(m_2)^2} + \frac{(e_{m_2})^2}{(m_1)^2}}$$

When the true standard error (e) is known then the range, within which the probability (P) of the true mean, may be given by the expression $\bar{x} \pm ke$, where $\bar{x}$ is the mean, k is a suitable constant.

When, P = 66 out of 100, then k is a approximately equal to 1, P = 95 out of 100, then k is approximately equal to 2.

P = 99 out of 100, then k is approximately equal to 3.

The stated probability can also be applied to the range ($\bar{x} \pm ke_{\bar{x}}$), where faction t has a value which is largest with the smallest sample size and approaches k as the sample size increases, and $e_{\bar{x}}$ is the standard error of the mean.

Now, if the arbitrary range be known then probability can be calculated out and in the reverse way, if the probability is fixed (known), the range can be worked out, with the help of the t table.

Degree of Freedom

Degree of freedom is the number of values of a sample which are freely variable without affecting the mean. For example, say, 3, 5 and 7 are forming a set of sample. So, the mean ($\bar{x}$) is equal to 5 and total number of values (n) is 3. Now any two of them can vary freely (i.e. the value may alter) and then the original mean ($\bar{x}$) 5 can be restored by necessary alteration of the third value. So, normally the degree of freedom (n^*) is equal to ($n-1$) but in more complicated situation n^* may have a lesser value. In the t table, the t value is given at different probability against the degrees of freedom (n^*) for each set of sample (Table A3.4).

Fiducial Limit (Table A3.5)

With the t value we can estimate the accuracy of the mean of a set of sample. If we choose a value of probability of occurrence of the true mean to lie in a range on either side of the sample mean and then we can find out the corresponding t values with the degree of freedom. Now we can have the limits with this t value, sample mean and the standard error with the following formula ($\bar{x} \pm ke_{\bar{x}}$); and this is named as fiducial limits of the mean. For example, suppose we want to find out the limits for 95% probability of

Table A3.4: 't table'

n^*	P = 0.9 (90%)	0.8 (80%)	0.7 (70%)	0.6 (60%)	0.5 (50%)	0.4 (40%)	0.3 (30%)	0.2 (20%)	0.1 (10%)	0.05 (5%)	0.02 (2%)	0.01 (1%)	0.001 (0.1%)
1	0.158	0.325	0.510	0.727	1.000	1.376	1.963	3.078	6.314	12.706	31.821	63.657	636.619
2	0.142	0.289	0.445	0.617	0.816	1.061	1.386	1.886	2.920	4.303	6.965	9.925	31.598
3	0.137	0.277	0.424	0.584	0.765	0.978	1.250	1.638	2.353	3.182	4.541	5.841	12.941
4	0.134	0.271	0.414	0.569	0.741	0.941	1.190	1.533	2.132	2.776	3.747	4.604	8.610
5	0.132	0.267	0.408	0.559	0.727	0.920	1.156	1.476	2.015	2.571	3.365	4.032	6.859
6	0.131	0.265	0.404	0.553	0.718	0.906	1.134	1.440	1.943	2.447	3.143	3.707	5.959
7	0.130	0.263	0.402	0.549	0.711	0.896	1.119	1.415	1.895	2.365	2.998	3.499	5.405
8	0.130	0.262	0.399	0.546	0.706	0.889	1.108	1.397	1.860	2.306	2.896	3.355	5.041
9	0.129	0.261	0.398	0.543	0.703	0.883	1.100	1.383	1.833	2.262	2.821	3.250	4.781
10	0.129	0.260	0.397	0.542	0.700	0.879	1.093	1.372	1.812	2.228	2.764	3.169	4.587
11	0.129	0.260	0.396	0.540	0.697	0.876	1.088	1.363	1.796	2.201	2.718	3.106	4.437
12	0.128	0.259	0.395	0.539	0.695	0.873	1.083	1.356	1.782	2.179	2.681	3.055	4.318
13	0.128	0.259	0.394	0.538	0.694	0.870	1.079	1.350	1.771	2.160	2.650	3.012	4.221
14	0.128	0.258	0.393	0.537	0.692	0.868	1.076	1.345	1.761	2.145	2.624	2.977	4.140
15	0.128	0.258	0.393	0.536	0.691	0.866	1.074	1.341	1.753	2.131	2.602	2.947	4.073
16	0.128	0.258	0.392	0.535	0.690	0.865	1.071	1.337	1.746	2.120	2.583	2.921	4.015
17	0.128	0.257	0.392	0.534	0.689	0.863	1.069	1.333	1.740	2.110	2.567	2.898	3.965
18	0.127	0.257	0.392	0.534	0.688	0.862	1.067	1.330	1.734	2.101	2.552	2.878	3.922
19	0.127	0.257	0.391	0.533	0.688	0.861	1.066	1.328	1.729	2.093	2.539	2.861	3.883
20	0.127	0.257	0.391	0.533	0.687	0.860	1.064	1.325	1.725	2.086	2.528	2.845	3.850
21	0.127	0.257	0.391	0.532	0.686	0.859	1.063	1.323	1.721	2.080	2.518	2.831	3.819
22	0.127	0.256	0.390	0.532	0.686	0.858	1.061	1.321	1.717	2.074	2.508	2.819	3.792
23	0.127	0.256	0.390	0.532	0.685	0.858	1.060	1.319	1.714	2.069	2.500	2.807	3.767
24	0.127	0.256	0.390	0.531	0.685	0.857	1.059	1.318	1.711	2.064	2.492	2.797	3.745
25	0.127	0.256	0.390	0.531	0.684	0.856	1.058	1.316	1.708	2.060	2.485	2.787	3.725
26	0.127	0.256	0.390	0.531	0.684	0.856	1.058	1.315	1.706	2.056	2.479	2.779	3.707
27	0.127	0.256	0.389	0.531	0.684	0.855	1.057	1.314	1.703	2.052	2.473	2.771	3.690
28	0.127	0.256	0.389	0.530	0.683	0.855	1.056	1.313	1.701	2.048	2.467	2.763	3.674
29	0.127	0.256	0.389	0.530	0.683	0.854	1.055	1.311	1.699	2.045	2.462	2.756	3.659
30	0.127	0.256	0.389	0.530	0.683	0.854	1.055	1.310	1.697	2.042	2.457	2.750	3.646
∞	**0.12566**	**0.25335**	**0.38532**	**0.52440**	**0.67449**	**0.84162**	**1.03643**	**1.28155**	**1.64485**	**1.94996**	**2.32634**	**2.57582**	**3.291**

Table A3.5: Fiducial limit of the mean

No. of observations	*Blood pressure at systole of the mean mm of Hg*	*Deviations* $(x-\bar{x})$	*Squared deviations* $(x-\bar{x})^2$	*Working*
1	123	0.1	0.01	No. of observations = 10
2	130	7.1	50.41	Mean ($\bar{x}$) = 122.9
3	116	–6.9	47.61	SD = $\sqrt{\Sigma(x-\bar{x})^2/(n-1)}$
4	118	–4.9	24.01	= ±4.7246 mm of Hg
5	126	3.1	09.61	Standard error = $\sigma/\sqrt{n}$
6	124	1.1	1.21	= ($\pm 4.7246/\sqrt{10}$)
7	120	–2.9	8.41	= ±1.49 mm of Hg
8	128	5.1	26.01	
9	126	3.1	9.61	
10	118	–4.9	24.01	
Total	**1229**	**0**	**200.90**	
Mean	122.9			

occurring of the true mean; it can also be stated in the other way that the limit for 5% chance of non-occurrence of the true mean. So, here the $P = 0.05$ or (5/100). $n^* = 9$ and with reference to the t table, the $t = 2.262$.

The 95% fiducial limits of the mean for the above example are therefore

$$\bar{x} \pm te_{\bar{x}} = 12.9 \pm (2.262 \times 1.49)$$
$$= 122.9 \pm 3.46$$
$$= 119.44 \text{ and } 126.36.$$

In other words,

$$\bar{x} \pm te_{\bar{x}} = 119.44,$$
$$\bar{x} \pm te_{\bar{x}} = 126.36.$$

Fiducial limit of the mean is 119.44 to 126.36.

Probability of a Difference

Just in the reverse way by putting a value of the stated range in the previously calculated fiducial limit's equation of the mean, we can find out the t value. Now with the help of the t table we can have the frequency probability that the value is expected to lie. For example, by putting one person's blood pressure (116 mm of Hg) in the above calculated fiducial limits, we may have the t value,

$\bar{x} - 116 = te_{\bar{x}}$, by putting the values of $\bar{x}$, $te_{\bar{x}}$ we can have

$$122.9 - 116 = 1.49\ t$$
$$\therefore \quad t = (6.9)/(1.49) = 4.63.$$

Now consulting the t table with the t value (94.63) and the 9 degrees of freedom, it can be found out that $0.01 > P > 0.001$. So, by observing the P value in this case, it can be stated that the difference between the expected value and our result (116 mm of Hg) is much for happening which actually carrying this difference.

So, in such cases we have to revise the expected value or look for some modification of this experimental method adopted for that work.

Significance

The difference between the experimental results and the control result may be stated as 'significant' or 'insignificant' by finding the P value. The term 'significance' is used in the sense that it is unlikely to occur due to chance and in the reverse way 'insignificant' means that it is just due to a chance. This significance test is of great importance for the judgement of the scientific investigations. It is customary to regard unlikely to be by chance when $P < 0.5$ (i.e. one trial in twenty) as being significant and $P < 0.01$ (i.e. one trial in hundred as highly significant.

Significance Test of a Difference between Two Groups of Quantitative Measurements (Table A3.6)

When the same parameter (e.g. blood pressure) is studied in two conditions (e.g. normal and drug treated), then this t test can answer whether the change due to the drug treatment is significant or not. We can determine the probability from the t value obtained from the following formula:

$$t = \frac{\text{Difference between means}}{\text{Standard error of difference between means}}$$

i.e. $t = \dfrac{(\bar{a}-\bar{b})}{e(a-\bar{b})}$ when first means = a; second mean = b

Standard error of the difference of two means = $\pm^e (a-b)$

$$\text{or } t = \pm \frac{(\bar{a}-\bar{b})}{\sqrt{(e_{\bar{b}})^2 + (e_{\bar{b}})^2}} \text{ as } {}^e(a-\bar{b}) = \sqrt{(e_{\bar{b}})^2 + (e_{\bar{b}})^2}$$

Table A3.6: Significance test of a difference between two groups of qualitative measurement

No. of expt.	Blood pressure in mm of Hg		$(a-a)^2$	$(b-b)^2$	Working
	Normal (a) (control)	Treated (b) (experimental)			
1	225	210	4	81	$t = \frac{(\bar{a}-\bar{b})}{\sqrt{(e_{\bar{b}})^2+(e_{\bar{b}})^2}}$
2	220	215	49	16	
3	230	205	9	196	$= \frac{8}{\sqrt{7.896+7.617}}$
4	220	220	49	1	
5	240	230	169	121	$= \frac{8}{\sqrt{15.513}}$
6	215	225	144	36	$= \pm 2.397$
7	235	210	64	81	Degrees of freedom
8	220	230	49	121	$= (n_a - 1) + (n_b - 1)$
9	240	225	169	36	$= (10-1) + (10-1)$
10	225	220	4	1	$= 20 - 2$
Total	**2270**	**2190**	**710**	**690**	$= 18$
Mean	$a = 227.0$	$\bar{b} = 219.0$	$^e\bar{a} = \pm 2.81$	$^e\bar{b} = \pm 2.76$	
		$(\bar{a}-\bar{b}) = 8$	$(^e\bar{a})^2 = 7.896$	$(^e\bar{b})^2 = 7.617$	

Now let us have an example, where blood pressure is recorded of ten normal persons and ten drug-treated persons. The records are stated in Table A3.6 from which the significance test done:

Consulting the t table we find that there is a probability $0.05 > P > 0.02$. That means the drug has produced a significant change in blood pressure. If in some other case it appears that the change is no significant but still there is some change then the technique of the experiment may be altered to have a more significant result.

x^2 Test (Table A3.7)

In many occasions we want to compare two or more groups to find out the efficiency or suitability of the methods, or drugs or something else, i.e. qualitative

Table A3.7: Fisher's X^2

n*	P = 0.99	0.98	0.95	0.90	0.80	0.70	0.50	0.30	0.20	0.10	0.05	0.02	0.01
1	0.000157	0.000628	0.00393	0.0158	0.0642	0.148	0.455	1.074	1.642	2.706	3.841	5.412	6.635
2	0.0201	0.0404	0.103	0.211	0.446	0.713	1.386	2.408	3.219	4.605	5.991	7.824	9.210
3	0.115	0.185	0.352	0.584	1.005	1.424	2.366	3.665	4.642	6.251	7.815	9.837	11.345
4	0.297	0.429	0.711	1.064	1.649	2.195	3.357	4.878	5.989	7.779	9.488	11.668	13.277
5	0.554	0.752	1.145	1.610	2.343	3.000	4.351	6.064	7.289	9.236	11.070	13.388	15.086
6	0.872	1.134	1.635	2.204	3.070	3.828	5.348	7.231	8.558	10.645	12.592	15.033	16.812
7	1.239	1.564	2.167	2.833	3.822	4.671	6.346	8.383	9.803	12.017	14.067	16.622	18.475
8	1.646	2.032	2.733	3.490	4.594	5.527	7.344	9.524	11.030	13.362	15.507	18.168	20.090
9	2.088	2.532	3.325	4.168	5.380	6.393	8.343	10.656	12.242	14.684	16.919	19.679	21.666
10	2.558	3.059	3.940	4.865	6.179	7.267	9.342	11.781	13.442	15.987	18.307	21.161	23.209
11	3.053	3.609	4.575	5.578	6.989	8.148	10.341	12.899	14.631	17.275	19.675	22.618	24.725
12	3.571	4.178	5.226	6.304	7.807	9.034	11.340	14.011	15.812	18.549	21.026	24.054	26.217
13	4.107	4.765	5.892	7.042	8.634	9.926	12.340	15.119	16.985	19.812	22.362	25.472	27.688
14	4.660	5.368	6.571	7.790	9.467	10.821	13.339	16.222	18.151	21.064	23.685	26.873	29.141
15	5.229	5.985	7.261	8.547	10.307	11.721	14.339	17.322	19.311	22.307	24.996	28.259	30.578
16	5.812	6.614	7.962	9.312	11.152	12.624	15.338	18.418	20.465	23.542	26.296	29.633	32.000
17	6.408	7.255	8.672	10.085	12.002	13.531	16.338	19.511	21.615	24.769	27.587	30.995	33.409
18	7.015	7.906	9.390	10.865	12.857	14.440	17.338	20.601	22.760	25.989	28.869	32.346	34.805
19	7.633	8.567	10.117	11.651	13.716	15.352	18.338	21.689	23.900	27.204	30.144	33.687	36.191
20	8.260	9.237	10.851	12.443	14.578	16.266	19.337	22.775	25.038	28.412	31.410	35.020	37.566
21	8.897	9.915	11.591	13.240	15.445	17.182	20.337	23.858	26.171	29.615	32.671	36.343	38.932
22	9.542	10.600	12.338	14.041	16.314	18.101	21.337	24.939	27.301	30.813	33.924	37.659	40.289
23	10.196	11.293	13.091	14.848	17.187	19.021	22.337	26.018	28.429	32.007	35.172	38.968	41.638
24	10.856	11.992	13.848	15.659	18.062	19.943	23.337	27.096	29.553	33.196	36.415	40.270	42.980
25	11.524	12.697	14.611	16.473	18.940	20.867	24.337	28.172	30.675	34.382	37.652	41.566	44.314
26	12.198	13.409	15.379	17.292	19.820	21.792	25.336	29.246	31.795	35.563	38.885	42.856	45.642
27	12.879	14.125	16.151	18.114	20.703	22.719	26.336	30.319	32.912	36.741	40.113	44.140	46.963
28	13.565	14.847	16.928	18.939	21.588	23.647	27.336	31.391	34.027	37.916	41.337	45.419	48.278
29	14.256	15.574	17.708	19.768	22.475	24.577	28.336	32.461	35.139	39.087	42.557	46.693	49.588
30	14.953	16.306	18.493	20.599	23.364	25.508	29.336	33.530	36.250	40.256	43.773	47.962	50.892

Table A3.8

	Without vaccine (placebo)	*With low dose vaccine*	*With high dose vaccine*	*Total*
Attacked with the disease	78	62	60	200
Not attacked	60	68	72	200
Total	**138**	**130**	**132**	**400**
Expected attacks 50%	69	65	66	
(obs. –exp.)²	81	9	36	
(obs. –exp.)²/(exp.)	1.17	0.14	0.55	1.86

statistics in which we are not dealing with finer variations but with the quality (attribute) concerned. In such cases the number of individuals in each class is very high but the number of classes is limited or small.

For a single observed value:

$$x^2 = \frac{(\text{observed frequency} - \text{expected frequency})^2}{\text{expected frequency}}$$

and for a number of values

$$x^2 = S\left\{\frac{(\text{observed frequency} - \text{expected frequency})^2}{\text{expected frequency}}\right\}$$

Suppose we want to compare the different doses of a vaccine for a particular disease. Three groups are taken, 1st without vaccine, 2nd with low dose vaccine and 3rd with high dose vaccine. Now the cases of occurrence and non-occurrence of the disease are represented in Table A3.7.

It is assumed that if the vaccine has no effect than the 50% of each group should be the expected case number as it is seen in the table that out of total 400, 200 persons are attacked with the disease.

For the above table the x^2 values for single observation are 1.17, 0.14, 0.55 (Table A3.8). When these three numbers of x^2 values are summated together, then $x^2 = 1.86$, i.e. $(1.17 + 0.14 + 0.55 = x^2$ for a number of values).

We now have to determine n^*, the degrees of freedom in the sample.

It is seen that two of the observed values can alter or vary freely, so that by necessary alteration of the 3rd one, the total 200 may be maintained. So, the degree of freedom (n^*) in this case is $(3 - 1) = 2$. Now by using the x^2 table the P value may be obtained which in this case is lying in between $0.5 > P > 0.3$ which means that the above observed results can occur 3 to 5 times in 10 trails. This indicates that the vaccine has a definite or positive protective action though not significant statistically in the above observations which may be statistically significant when it is trailed with larger number of observations.

REGRESSION (Table A3.9)

When we measure two attributes of each of individuals in a group, e.g. height and weight of a group of human beings; or height of blood pressure and different doses of epinephrine in rats. Now there is possibility of having some correlation between these two attributes. Before considering about the correlation, first of all we have to plot the results graphically by putting controlled variable (epinephrine) as the abscissa and the other as the ordinate. This controlled variable is also known as the independent variable in contrast to the dependent variable. Now, if there is any relation between these two variable observations, there will be more or less some regularity in the arrangement of the points; but if there is no such relation between them, the points will be scattered. Now there will have a probability of fitting a straight or curved line (at least approximately) to the points representing somewhat related observations.

Mathematical Expression of the Best Fitting Lines

Say, the independent variable be x and y be the dependent variable and when these values are plotted graphically, then the shape of the fitting line will depend on nature of the equation.

Thus, the equation $y = a + bx$, when a and b are the intercept on the y axis and slope of the line respectively and x and y are variables. This equation will always represent a straight line. When the value of b is positive the line will slope downwards and to the left and will lie in the upper right and lower left quadrants. If the units for x and y are put to equal lengths then the slope of the line will be give by b = tan, where is the angle enclosed by the line and the abscissa on the side of the positive value of x.

That will be the best fitting line for which the sum of deviations of the observed value y from the predicted value Y is zero and the sum of the square of the deviations is minimum (similar to the best or ideal value). It can be shown that the line passing through the mean values of x and y will have the coefficient b of the following value:

$$b = \frac{S\{(x - \bar{x})(y - \bar{y})\}}{S(x - \bar{x})^2}$$

The value of a can be obtained by putting this value of b and values of x and y at a particular point whose co-ordinates are $\bar{x}$ and $\bar{y}$ (since it is known that the line must pass through the mean values of x and y).

The best fitting line so obtained for the observed value of x and y is known as regression line relating x and y and the coefficient b is known as the regression coefficient. The equation for the best fitting line may also be named the regression equation.

Table A3.9: Calculation of regression coefficient

No. of Observation	Epinephrine	% Change µg blood pressure	Deviations (rise) in	Product of deviations		Squared deviation	Working
	x	y	$(x-\bar{x})$	$(y-\bar{y})$	$(x-\bar{x}) \times (y-\bar{y})$	$(x-\bar{x})^2$	
1	5	20	–22.5	–74	1665.0	506.25	$b = \frac{S[(x-\bar{x})(y-\bar{y})}{S(x-x)^2}$
2	10	35	–17.5	–59	1032.5	306.25	$= \frac{7160.0}{2064.5}$
3	15	45	–12.5	–47	587.5	157.25	= 3.47
4	20	65	–7.5	–29	217.5	56.25	
5	25	82	–2.5	–12	30.0	6.25	
6	30	102	+2.5	+8	20.0	6.25	
7	35	120	+7.5	+26	195.0	56.25	
8	40	142	+12.5	+48	600.0	157.25	
9	45	159	+17.5	+63	1102.5	306.25	
10	50	170	+22.05	+76	1710.0	506.25	
Total	**275**	**940**	**0.0**	**0.0**	**7160.0**	**2064.50**	
	$\bar{x}$ = 27.5	$\bar{y}$ = 94.0			$S(x-\bar{x}) \times (y-\bar{y})$ = 716.0	$S(x-\bar{x})^2$ = 2064.5	

The calculations may be shortened by using method as that used for shortening the calculation of standard deviation by putting, i.e.

$$S(x-\bar{x})^2 = S(x^2) - \frac{S^2(x)}{n} \text{ and}$$

$$S(x-\bar{x})(y-\bar{y}) = S(xy) - \frac{S(x).S(y)}{n}$$

In some cases we may have a priori reason to know that the best fitting line (regression line) passes through the origin; in other words, the equation of the line is such that when $x = 0$ then y is also equal to zero. In such cases the method of determination of the regression equation is still easier as $b = \frac{S^2(x)}{S(x^2)}$ and the equation is $y = bx$

The other formula for regression coefficient is

$$b = r\frac{\text{standard deviation of } y}{\text{standard deviation of } x}$$

when r is the correlation coefficient.

The regression coefficient may be calculated with less complication (Table A3.9).

Now putting the values of b, $\bar{x}$ and $\bar{y}$ (as the line must pass through $\bar{x}$ and $\bar{y}$) in the regression equation $y = a + bx$

$94.0 = a + 3.47 \times 27.5 = a + 95.42$

$\therefore\ a = 94.0 - 95.42 = -1.42$

So, the desired equation for the best fitting line is $y = -1.42 + 3.47x$ (Fig. A3.6).

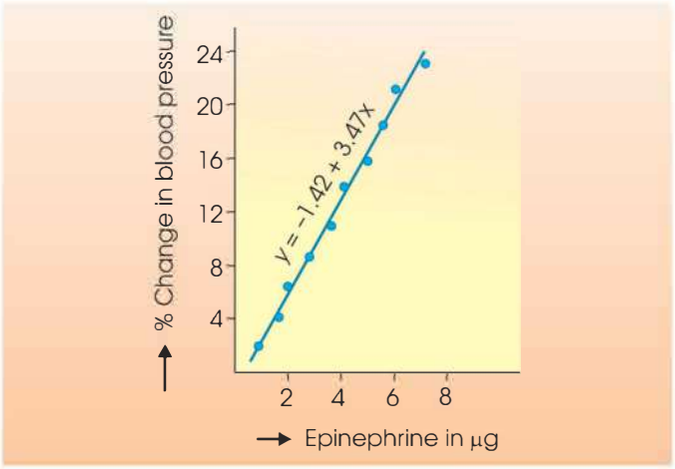


Fig. A3.6: Graphical representation of the regression equation (best fitting line) with the help of previous table

Goodness of Fitting of a Regression Line

The goodness of fitting of a regression line can be tested by calculating the squares of the deviations of the observed values (x) from the expected values (X) and then dividing by the expected values (X), i.e. $x - X/X$. Thus, values are obtained and are distributed as x^2. The probability of their occurrence by chance can be obtained by summating them and seeking the value so obtained in a table x^2, with, in the case of a straight line, two less degrees of freedom than there are points on the line.

Variance and Standard Deviation from Regression

When the deviations of x are measured from the expected values of X, which is calculated from the

corresponding values of y and the regression equation but not from their own mean. Then the sum of squared deviations of a from X divided by the degree of freedom (n^*) will give the variance of x from regression. The number of degrees of freedom is determined with the usual method.

Variance of x from regression

$$S_{x.y} = \frac{S(x-x)^2}{(n-2)^2}$$

Similarly, standard deviation from regression

$$S_{x.y} = \sqrt{\frac{S(x-x)^2}{(n-2)^2}}$$

Standard error of the mean of one dependent variable say, e.g. $\bar{x}$ can be obtained with the following formula: $e_{\bar{x}} = \frac{S_{x.y}}{\sqrt{n}}$; and then the significance test of the regression line may be performed.

CORRELATION

In the situations where one variable is independent, i.e., in our control and the other is dependent on the former, then we have to consider the relationship with the regression equation. But there are also situations where both the variables are beyond our control and one is dependent or independent on the other. Now to consider whether they have any real or only apparent relationship, we have to go through the term correlation (a modification of regression).

The correlation coefficient (r) is that coefficient which relates x and y when these are measured in standard measure and it also measures the association or correlation between the variables, e.g. children who are above average body weight to be more resistant to a certain disease.

In such cases we can assess the relationship by calculating the r with the following formula:

$$r = \frac{S(x-\bar{x})(y-\bar{y})}{\sqrt{S(x-\bar{x})^2(y-\bar{y})^2}}$$

The alteration formula for correlation coefficient is:

$$r = b\frac{\text{standard deviation of } x}{\text{standard deviation of } y}$$

where b is the regression coefficient.

The value of correlation coefficient be treated as similar to probability. When r = 1.0 there is a rigid (definite) connection between the two variables and when $r = 0$ there is absolutely no connection or relation.

ANALYSIS OF VARIANCE (Table A3.10)

The significance of test—t test is convenient for quantitative measurements when the data are divisible into two groups. But if the data are of more extensive or of subsidiary divisions then the method known as analysis of variance is more convenient, where the t test is not directly applicable. For example, suppose we want to study the effect of three different ergogenic aids on human subjects of both sexes, five males and five females, in each group. So, with the control or dummy (placebo) groups, there are four (three experimental and one control) male and four female human subject groups from which we can calculate the number of mean values. First, the grand mean of whole set of measurements which may be named as $\bar{x}$, secondly, the two mean values of male and female subjects as $\bar{x}_M$ and $\bar{x}_F$ thirdly, mean values of the four groups comprising of both male and female subjects—$\bar{x}_A$, $\bar{x}_B$, $\bar{x}_C$, and $\bar{x}_D$. The last set of mean values can be obtained from the four male and four female groups separately as $\bar{x}_{AM}$, $\bar{x}_{BM}$, $\bar{x}_{CM}$, $\bar{x}_{DM}$ and $\bar{x}_{AF}$, $\bar{x}_{BF}$, $\bar{x}_{CF}$, $\bar{x}_{DF}$ respectively.

Now, if we put the working hypothesis as that the subjects are devoid of any effect due to the ergogenic aid or sex. Then all the means calculated are the estimates of true mean of the population from where the sample is collected, with variance ($\sigma/\sqrt{n}$), when σ = true standard deviation of the population and n = number or subjects in a particular estimate of the mean. So, all the calculated variances are the estimates of the true variance and the difference in these two will be the effect of random sampling. The ratio of two estimates of variance of a normally distributed population is denoted as the statistic F or e^{2z} (here e is the base of natural logarithms and not the standard error). Similarly, the distribution is known as the statistic z, which is half the difference between two natural logarithms of two estimates of the variance. The values of e^{2z} and z for common values of n (size of the samples) and the corresponding value of P (probability can be obtained from the table of e^{2z}. Similarly, the probability of ratio of the variances of grand mean ($\bar{x}$) and this group of males can be determined from the table e^{2z}. The value of P will indicate whether the results are drawn from a single normally distributed population or not.

Example: If m = number of groups, n = number of individuals in each group, $\bar{x}$ = grand mean, $\bar{x}_L$ = general term for group mean, $\bar{x}_S$ = general term for sex mean and x_1, x_2, x_3, etc., i.e. x are the individual values. Table A3.10 shows the method of calculation of variance for the above mentioned set of data.

EXPERIMENTAL DESIGN

Under the previous headings we have considered how to analyse or interpret the experimental results when they have been obtained. But this analysis or interpretation of the results or observations depends mostly on the method or way by which they are

Table A3.10: Calculating variance

Item Numbers	*Items (included in the calculation of variance)*	*Degree of freedom*	*Sum of the squared deviations*	*Variance* $\frac{S(d)^2}{(n-1)}$
1	Between groups	$m-1$ $4-1=3$	$S(\bar{x}-\bar{x}_L)^2$ (between grand mean and treatment means)	$\frac{S(\bar{x}-\bar{x}_L)^2}{(m-1)}$
2	Between sexes	$2-1=1$	$S(\bar{x}-\bar{x}_s)^2$ (between grand mean and sex means)	$\frac{S(\bar{x}-\bar{x}_s)^2}{1}$
3	As a whole	$mn-1$ $4\times10-1=39$	$S(x-\bar{x})^2$ (between grand mean and individual values)	$\frac{S(x-\bar{x})^2}{mn-1}$
4	Within groups	$m(n-1)$ $4(10-1)=36$	$S(\bar{x}_L-x)^2$ (between treatment means and individual values)	$\frac{S(\bar{x}_L-x)^2}{m(n-1)}$
5	Residual (within groups)	$(mn-m-1)$ $40-4-1=35$	$S(x-\bar{x})^2-\{S(\bar{x}-\bar{x}_L)^2+S(\bar{x}-\bar{x}_s)^2\}$ $=S(x-\bar{x}_L)^2-S(\bar{x}-\bar{x}_s)^2$ *(by difference, item 3–1–2)*	$\frac{S(x-\bar{x})^2-S(\bar{x}-\bar{x}_L)^2}{mn-m-1}$

obtained. Because it is quite possible that the observations, obtained out of a long laborious experiment, may not have any useful information. So it is preferred that the question of design of experiment and analysis of observations should be considered at the same time. The analysis of observations has already been considered in the previous pages; here we have to consider the experimental design only. During consideration of the experimental design the following factors are to be kept in mind.

Range of Reliable Induction

The design of the experiment depends upon the type of problem we want to study and the type of inference we wish to make. To have a more general inference the sample (observation) should be taken from a hypothetical infinite population and the method of sampling would have to afford a random sample and not one biased to suit the convenience of the experiments. Say for example, it is observed that the administration of epinephrine causes rise of blood pressure in cats, dogs and rabbits; from this the inference may be drawn that the epinephrine causes rise of blood pressure in all mammals. This is inference may be correct but to justify the inference, the observations should be performed on more number of mammalian group of animals which will make the inference more reliable.

Null Hypothesis

When some inferences are draw on some common features present in the observed facts—then the inference drawn is named as hypothesis. During setting up of the experimental design, one control and other experimental groups always be set up, i.e. one group without the factor X (control) and other group with the factor X (experimental). Now during analysis the statistical tests are always concerned with the difference between the observations (control and experimental) and not with the isolated observation. So, the control observation is equally important along with the experimental one. By considering the difference in observations, all other factors except the factor X are eliminated. So, the result obtained is expected to be due to the factor X only. There is one hypothesis that two or more sets of measurements are likely to have drawn by chance from the same population. This can well be tested with the statistical methods. So, according to this hypothesis the observed differences are likely to be due to errors of sampling and there is not necessarily any confirmable difference between the groups. This hypothesis is named as the null hypothesis. This is especially suitable for rigid deductions and practical use.

Segregation of Causes of Variation

During consideration of the experimental design we should be justified that the results or differences obtained in the group-containing factor X, is due to the presence of the factor X only and in that case only. We can attribute the function (effect) to X. But it is inevitable that a large number of other factors (known or unknown) will affect the experimental subjects, e.g. age, height, weight, physical condition, etc. and we cannot say that these small or minor differences will not affect the observed results. So we should have an eye that any small variation in-between the subjects is to be avoided as far as practicable. The experiment must be

so performed that the non-specific factors may affect the result contributing to the residual variance but not to the variance related to the factor X. This may be achieved by random allocation.

Random Allocation

The selection of the experimental animals (or human subjects) should be made at random, i.e. all the weaker or stronger animals should not be placed in the same group but the groups should contain the animals of both weak and strong groups equally. This may be done by numbering the individual animal and the numbered cards were shuffled well. Then by pulling one card at a time at random and putting that numbered animal to one group, the purpose of random allocation may be served.

Reduction of Experimental Error

When all the above factors are considered in an experimental design, the significance of the results will depend directly on the magnitude difference produced by the factor X (i.e. difference between the experimental and the control), on the number of observations and inversely on the standard deviation or error. The first factor, i.e. the difference produced by the factor X is beyond our control yet in medical experiments this may be affected by the alteration of the dosage and during of the drug. For a more reliable inference, the number of observation should be as high as possible. The experimental material should be made as homogeneous as possible and experimental conditions should be rigidly controlled and statistical analysis should be performed to estimate the cause of variation not attributable to the experimental factors. This may be summarised in the following headings:

- ***Replication:*** The experiment should be conducted repeatedly in identical condition. This will reduce the experimental error and give precise to the observation.
- ***Error control:*** Any factor, e.g. age, sex, temperature, etc. which may affect the experimental observation should be considered strictly. The experimental and the control experiment should be performed on the same condition from every aspect.
- ***Randomisation:*** By selecting the subject, the validity to the data may be increased.

NOMOGRAM

It is the graphical representation of mathematical laws which are expressed analytically by means of equations.

The term is sometimes restricted to a special type of chart which is used by bringing the points of these scales into alignments. The theory or nomogram is based mostly on analytical geometry. If the nomogram is once prepared with some labour, complicated problems of that system can be solved with speed and with slight labour, though the solutions are not of high accuracy. This is particularly helpful when many similar numerical problems are to be solved. Say for a simple example, it is well known that the height, weight and body surface of a person have got some definite relationship, so when the nomogram is prepared with that definite relationship, the value of anyone of these three parameters can be solved out from the remaining two (Figs A3.8 and A3.9).

The nomograms of equations of many variables are prepared by using a sequence of scale alignments or by employing networks of scales. They can be used by a person of ordinary knowledge or experience. These

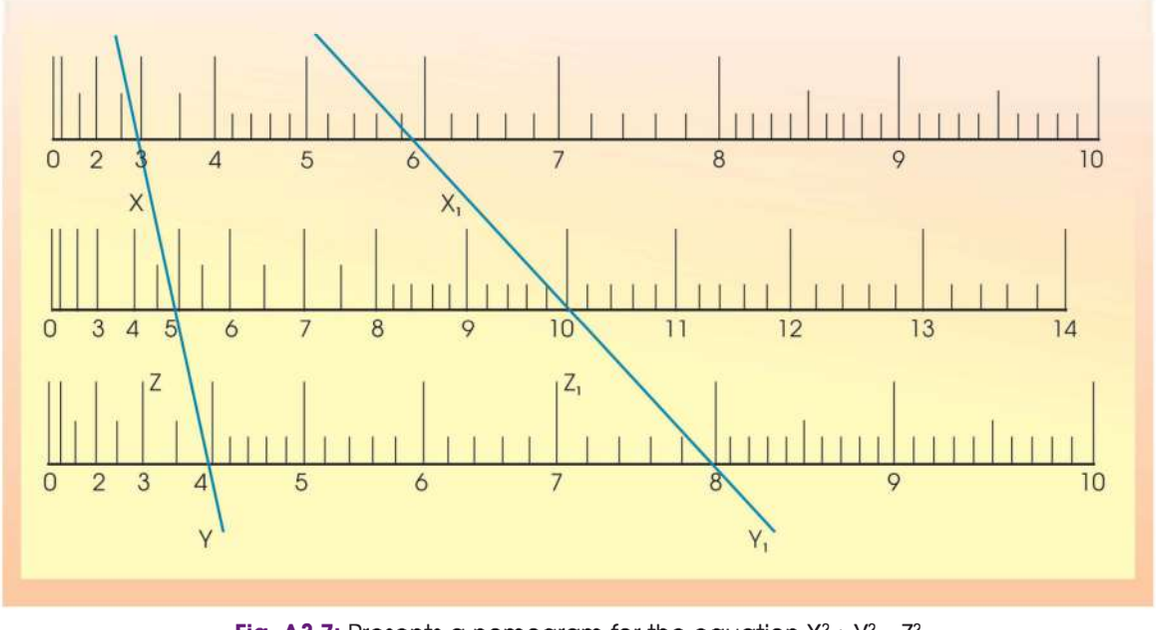


Fig. A3.7: Presents a nomogram for the equation $X^2 + Y^2 = Z^2$

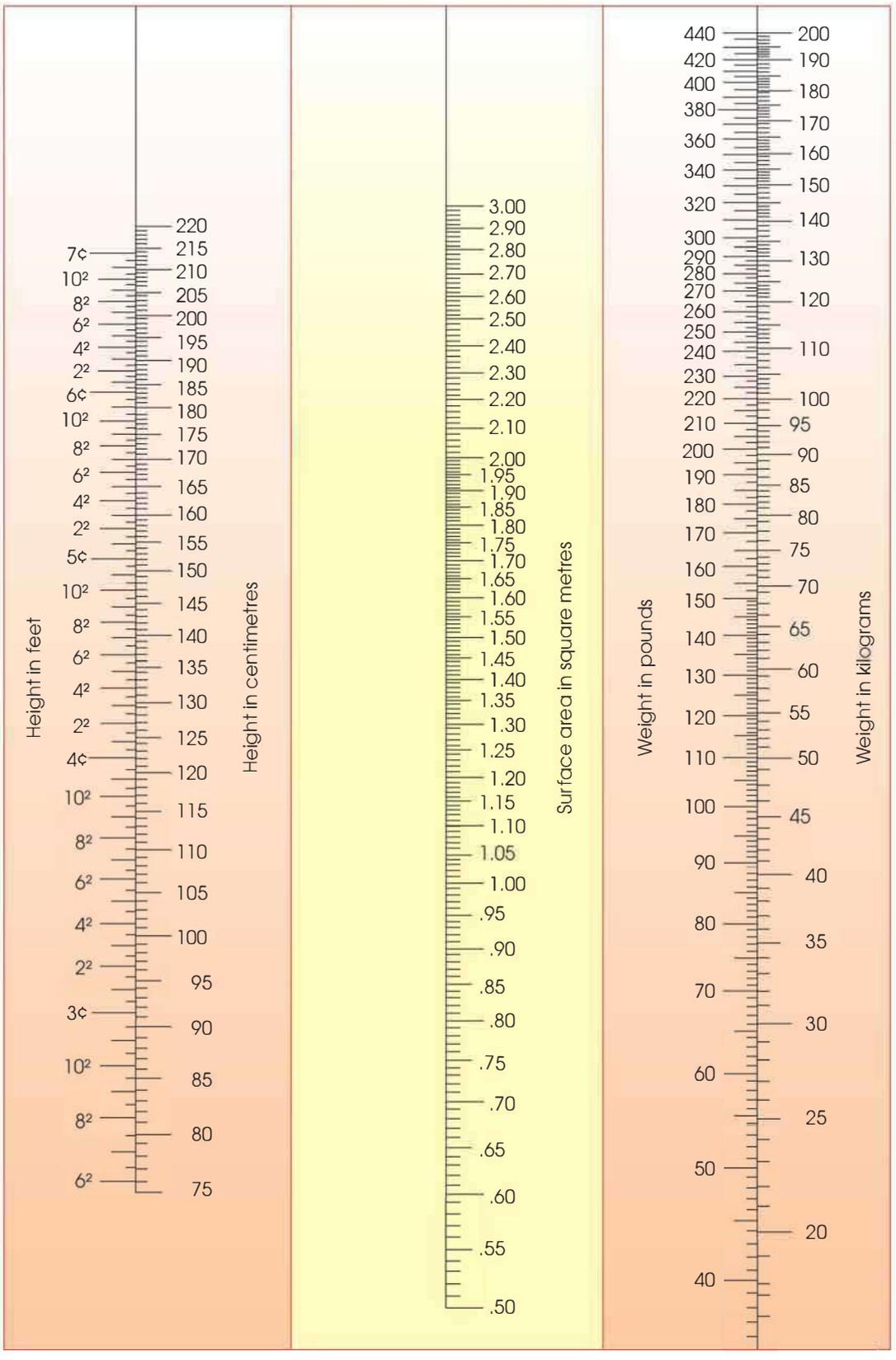


Fig. A3.8: Nomogram for estimating surface area of older children and adults

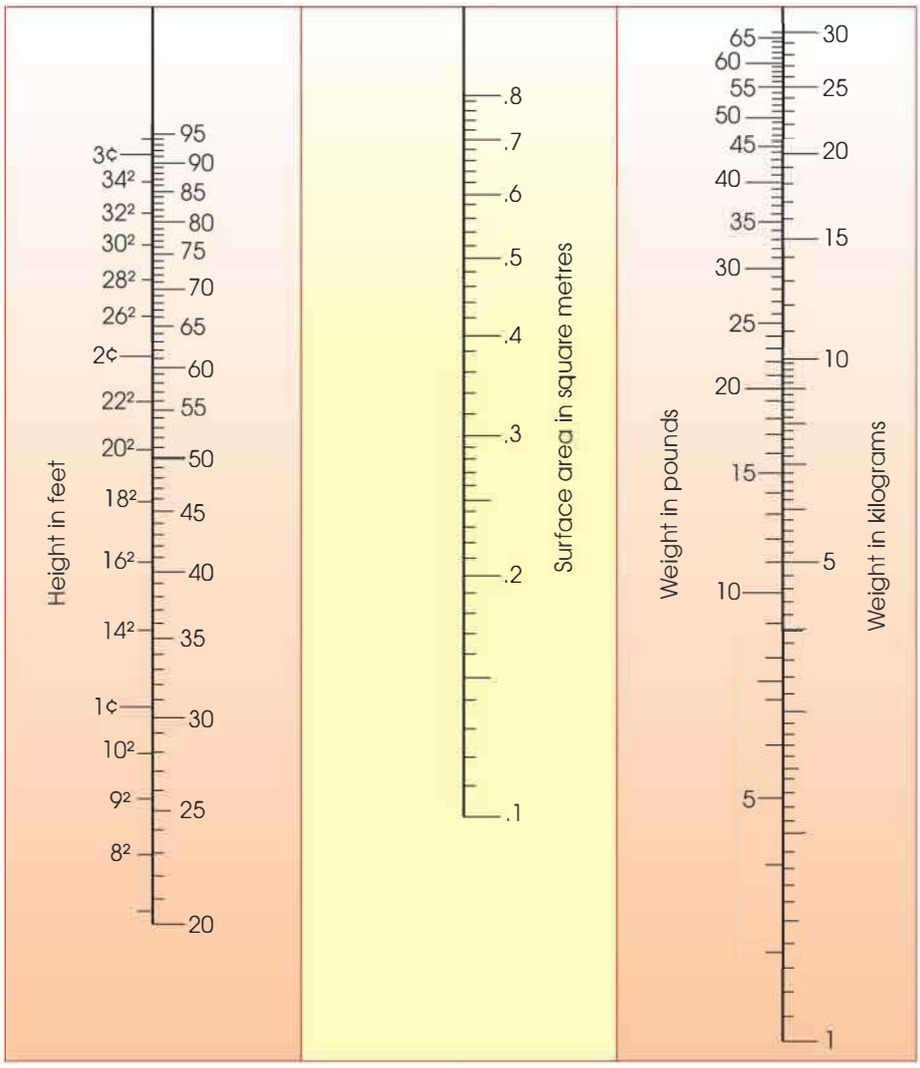


Fig. A3.9: Nomogram for estimating surface area of infants and young children. To determine the surface area of the individual it can be drawn a straight line between the point representing his height on the left-hand vertical scale to the point representing his weight on the right-hand vertical scale. The point at which this line intersects the middle vertical scale represents the individual's surface area in square metres

graphic representations are used widely in the problems of engineering, industry, natural and physical sciences.

In the more general forms of nomogram, the alignment chart for the solutions ranged in various ways, and one or more of the scales may be curved. The nature of the resulting scale-curved or straight depends upon the parametric equations. Only three scales need be drawn and they can be used by interpolating a straight line over these scales, i.e. interpolating the straight line drawn through the two known points ($X_1 = 6, Y_1 = 8$ as Fig. A3.7), corresponding third (unknown) value ($Z_1 = 10$, Fig. A3.7)—point of intersection can be obtained. Now in actual practice if these lines are really drawn, a few lines will mark the graph. This can be avoided by stretching a fine thread or by placing a straight line of a transparent scale in position across the chart (Fig. A3.7).

Appendix

4 Unit and Measurement and Tables of Normal Homeostatic Values in Human

UNITS AND MEASURES

1. **Some prefixes that are used for various units, but not used alone:**

mega = M = 10^6	kilo = k = 10^3
centi = c = 10^{-2}	milli = m = 10^{-3}
micro = µ = 10^{-6}	nano = n = 10^{-9}
pico = p = 10^{-12}	

2. **Mass**

gram = g, *or* gm
kilogram = kg, *or* kgm
milligram = mg, *or* mgm
microgram = µg
millimicrogram, *or* nanogram = mµg, *or* ng
micromicrogram, *or* picogram = µµg, *or* pg
1 kg = 1000 g
1 g = 1000 mg = 1,000,000 µg
1 kilogram = 15,432 grains, *or* 35.274 ounces (avoir), *or* 2.20462 pounds
1 gram = 15.432.36 grains, *or* 0.03527 ounce (avoir), or 0.00220 pound
1 milligram = 0.015432 grain
1 ounce = 28.350 g
1 lb = 453.59 g = 0.4536 kg
1 grain = 64.799 mg = 0.0648 g
1 ton = 1016 kg
1 tonne = t = 1000 kg = 0.984 ton

3. **Capacity or volume**

1 cubic millimetre = 1 mm^3 millilitre = ml litre 1
1 **litre** is the volume of 1 kilogram of water at its maximum density (3.98°C) and at 760 mm of Hg at atmospheric pressure.
1 millilitre (ml) = 16.894 minims
1 litre = 1000 ml
1 = 35.196 fluid ounces
1 litre = 61.0239 $inches^2$ = 1.7598 pints (O) = 0.22 gallon (C).
1 pint = 20 fluid ounces (avoir) = 568 ml
1 cc = 0.061 $inch^3$
1 litre = 1.000027 cubic decimetres
Thus, 1 ml = 1.000027 cubic centimetres (cc)
The **cubic centimetre** is based on the standard of length, i.e. the metre, and is very nearly but not quite the same as the ml. However, ml and cc are usually treated as identical.
1 ml = 1000 µl
1 µ1 = 1.000028 mm^3
1 gallon = 4.551 l
1 gallon = 8 pints = 0.00455 m^3
1 cu in = 16.387 cm^3
1 cu ft = 0.028 m^3 = 28.32 l
1 cu ft water = 62.39 lb = 28.32 kg
1 fluid ounce = 8 fluid drachms (avoir) = 28.412 ml
1 fluid drachm or fl dr = 60 minims (avoir) = 3.5515 ml
1 minim = 0.059152 ml
1 pint (UK) = 0.568 litre
1 pint (USA) = 0.4544 litre
1 gallon (UK) = 4.546 litres
1 gallon (USA) = 3.651 litres

4. **Length**

metre = m	centimetre = cm
millimetre = mm	micron = µm
millimicron = nm	Angstrom unit = Å

1 m = 100 cm = 1000 mm = 10^6µm = 10^9 mµ = 10^{10}Å
A = 10^{-10} m = 0.1 nm
1 µm = 10^{-6} m = 1000 nm = 10000 Å
1 nm = 10^{-9} m = 10 Å
1 in = 2.5400 cm = 0.02540 m
1 cm = 0.394 inch
1 foot = 30.4800 cm
1 m = 39.370113 inches = 3.2808 feet
1 yd = 0.9144 m
= 1.0936 yards
1 mile = 1760 yd = 1.6093 km

1 km = 3281 feet = 0.6214 mile
1000 ft = 0.3048 km
1 nautical mile = 1.852 km

5. Area

1 sq in = 645.16 mm^2 = 6.4516 cm^2
1 sq ft = 0.093 m^2
1 m^2 = 1.196 sq yd = 10.764 sq ft
1 sq yd = 0.836 m^2
1 hectare = 2.471 acres
1 acre = 4840 sq yd = 4047 m^2 = 0.4047 hectare
1 sq mile = 640 acres = 2.59 km^2 = 259 kectacres

6. Conversion

To convert cm H_2O to mm of Hg, multiply by 0.736.

To convert grammes per ml into grains per fluid ounce, multiply by 4.375.

To convert grammes into ounces (avoirdupois), multiply by 10 and divide by 283.

To convert litres into pints, multiply by 88 and divide by 50.

To convert kilos into pounds, multiply by 1000 and divide by 454.

To convert Fahrenheit into degree Celsius (Centigrade), subtract 32, multiply the remainder by 5, and divide the result by 9.

To convert degree Celsius (Centigrade) into Fahrenheit, multiply by 9, divide by 5, and add 32.

The following table shows the relation of degrees Fahrenheit to degree Celsius (Centigrade) as far as is likely to be required in clinical work.

Celsius (Centigrade)	*Fahrenheit*	*Celsius (Centigrade)*	*Fahrenheit*
110°	230°	36.5°	97.7°
100	212	36	96.8
95	203	35.5	95.9
90	194	35	95.0
85	185	34	93.2
80	176	33	91.4
75	167	32	89.6
70	158	31	87.8
65	149	30	86
60	140	25	77
55	131	20	68
50	122	15	59
45	113	10	50
44	111.2	+5	41
43	109.4	0	32
42	107.6	–5	23
41	105.8	–10	14
40.5	104.9	–15	+5
40	104.0	–20	–4
39.5	103.1	0.54°	1°
39	102.2	1	1.8
38.5	101.3	2	3.6
38	100.4	2.5	4.5
37.5	99.5		
37°	98.6°		

To change	*To*	*Multiply by*
millimetres	inches	0.03937
metres	inches	39.37
cubic metres	cubic yards	1.3079
litres	cubic inches	61.02
litres	ounces of water	35.275
inches	millimetres	25.4
feet	metres	0.3048
ounces	grams	28.35
centimetres	inches	0.3937
square centimetres	sqaure inches	0.155
cubic centimetres	millilitres	1.0
cubic centimetres	cubic inches	0.061
cubic centimetres	grams of water	1.0
cubic centimetres	drops	12.0
feet	centimetres	30.48
square feet	square centimetres	929.0
cubic feet	ounces of water	999.0
gallons	litres	3.785
grams	ounces	0.035274
square inches	square centimetres	6.4516
cubic inches	cubic centimetres	16.387
cubic inches	pints	0.0346
cubic inches	grams of water	16.39
square metres	square centimetres	10, 000.0
cubic metres	litres	1000.0
miles	kilometres	1.6094
sqaure miles	square kilometres	2.59
pints	cubic centimetres	+73.18
pints	ounces of water	16.69
pints	cups	2.0
pints	tablespoons	32.0
pints	teaspoons	96.0
quarts	tablespoons	64.0
quarts	teaspoons	192.0
quarts	kilograms of water	0.946
tablespoons	cups	0.0625
tablespoons	cubic centimetres	15.0
tablespoons	dessertspoons	1.5
tablespoons	teaspoons	3.0
tablespoons	drops	180.0
teaspoons	cubic centimetres	5.0
teaspoons	cups	0.02
teaspoons	drops	60.0

7. Density

The systeme internationale (S1) unit of density is the kilogram per cubic metre, kg per m^3
1 lb per in^3 = 2.768 × 10^4 kg/m^3
1 lb per ft^8 = 16.02 kg/m^3

8. Pressure

1 atmosphere of pressure
= 760 mm of Hg = 760 torr
= 29.92 in Hg = 29.92 in Hg
= 1033 g wt per cm^2 = 10.33 metres water
= 14.70 lb/in^2 = 33.9 ft water

= 1013 millibars = 1033.3 g/sq in
= 1013250 dynes/cm^2 = 14.7 lb/sq in
= 101.33 Nm^{-2} = 2116.3 lb/sq in
1 mm H_2O = 98.06 dynes per cm^2 = 0.0736 mm of Hg
1 mm of Hg = 1333 dynes per cm^2
= 1 atmosphere ÷ 760
= 1 torr = 133.3 Nm^{-2}
1 Nm^{-2} = 1.019 × 10^{-2} g per cm^2 1 bar = 750.062 mm of Hg
Pressure of 1 mm column of water = 7.3554 × 10^{-2} mm of Hg
1 mm column of Hg = 1.3595 × 10 mm H_2O
1 lb per $inch^2$ = 7.031 × 10^2 kilopounds per m^2 = 6894 Nm^{-2}
1000 lb per $inch^2$ = 0.703 kg per mm^2
1 millibar (1 mb) = 1000 dynes per cm^2
One **dyne** is the force which would produce an acceleration of 1 cm per sec per sec (i.e. 1 cm sec^{-2}) if acting on 1 g.
1 dyne = 10^{-5} N.

9. Heat

The calorie (small calorie, or gram calorie) is the amount of heat required to raise the temperature of 1 gram of water from 14.5°C to 15.5°C. (This unit is deprecated.)

Thermodynamic temperature is traditionally expressed in °C, degrees Celsius (degrees Centigrade) denoted by *t*.

Degrees Kelvin (K) is reckoned from absolute zero so that

$t = T - 275.15$ where T = absolute temperature

The **large calorie** (kcal, or kilogram calorie, or **kilocalorie**) is the amount of heat required to raise the temperature of 1 kg of water from 14.5°C to 15.5°C.

Heat equivalent of one litre of oxygen

5.14 calories for glycogen
4.6 calories for protein
4.4 calories for oils
5.06 calories for starch
4.6 calories for fat
5.08 calories for sucrose
22.4 litres of O_2 = 30 grams of glycogen
1 litre of O_2 = appox 5 calories = approx
15,000 foot-pounds = 2134 kilogram metres
1 gram of O_2 = approx. 3.5 calories
A 10°C, 760 mm pressure, 1 litre CO_2 = 19652 grams; 1 litre O_2 = 1.4292 grams; 1 litre air = 1.2928 grams; 1 litre water vapour = 0.8038 gram
1 gram water vapour = 1.2440 litres
1 calorie = 1 kilogram calorie (kcal) = 1000 gram calories
= 3.968 BTU at 60°F = 4185 joules
= 3086 foot-pounds = 426.7 kilogram metres
= 69.7 watt-minutes
1 watt-minute = 6.12 kilogram metres per second
= 0.01435 calorie
1 BTU = 0.252 calorie at 15°C = 778 foot-pounds

10. Miscellaneous

π = 3.1415927 cycles per second, CPS, c/s Hz
$\simeq$ 22/7 e = 2.7183 acceleration due to gravity = g
Standard g = 980.7 cm per sec per sec (approx. 981 cm sec^{-2})
= 32.174 feet per sec per sec (approx. 32.2 ft sec^{-2})
1 erg = 7.371 × 10^{-8} foot-pound (ft-lb)
1 dyne = 2.247 × 10^{-6} pound-weight (lb-wt)
1 kilogram-metre (kg-m) = 7.233 ft-lb = 0.002344 calorie = 0.009298 BTU
1 ft-lb = 0.1383 kg-m = 1.356 × 10^7 ergs = 1.356 J = 0.000324 calorie
1 ft-wt = 4.45 × 10^5 dynes

The SI unit of force is the **newton**, N. This kind of force produces an acceleration of 1 m per sec per sec acting on 1 kg.

1 N = 10^5 dynes 1 pound-force = 4.448 N 1 poundal = 0.138 N
1 kilogram-force = 9.806 N (deprecated)

One **erg** is the work done when a force of 1 dyne acts through 1 cm in the direction of force. 1 erg = 10^{-7} J

The SI unit of work in the **joule** (J), the work done when a force of 1 N acts through 1 m in the direction of force.

1 J = 0.2423 calorie = 10^7 ergs = 10,198 gram centimetres
= 0.00987 litre centimetre
1 kilogram force, 1 kilopound = weight of 1 kg at standard g = 9.806 N
Power is the rate of doing **work**. The unit of power is watt (W) at the rate of about one-fourth calorie per second = 0.01435 calorie
1 watt = 1 joule/sec
1 kilowatt hour = 3412 BTU
1 watt-minute = 6.12 kg metres per second = 0.01435 calorie
1 kg metre per sec = 9.81 watts
1 watt hour = 0.85968 calorie
1 horse-power (hp) = 33,000 ft-lb per min = 746 W = 0.746 kilowatt
= 2.1 litres of O_2 per min = 10.7 calories per min = 642 calories per hour
1 kcal = 427 kg m
1 mile per gallon = 2.83 litres per km
1 mile per hour = 88 ft per minute = 1.447 m per sec = 26.82 m per minute
Osmolarity is expressed in osmoles per litre of solution.

Osmolality is expressed osmoles per kg of water
millisecond msec (sometimes written σ)
1 sec = 1000 msec = 1000000 μsec

11. Table of normal values

Blood Count
Red cells: Males 4.5 to 6.5 (5) million per cu mm
Females 3.9 to 5.6 (4.5) million per cu mm
White cells: 4,000 to 11,000 per cu mm
Neutrophils: 3,000 to 6,000 per cu mm (60 to 70%)
Eosinophils: 150 to 400 per cu mm (1.0 to 4.0%)
Basophils: 0 to 100 per cu mm (0 to 1%)
Lymphocytes: 1500 to 2700 per cu mm (25 to 30%)
Monocytes: 350 to 800 per cu mm (5 to10%)
Platelets: 250,000 to 450,000 per cu mm
Reticulocytes: 0.5 to 1.5% of red blood cells
Haemoglobin (100% = 14.5 gm per 100 ml):
Males 14 to 17 gm per 100 ml (95 to 115%, Haldane)
Females 12 to 15.5 gm per 100 ml (82 to 105%, Haldane)
Packed cell volume (PCV) per cent:
Males 42 to 50 (45)
Females 38 to 45 (40)
Mean corpuscular volume (MCV) in cu micron 78 to 94 (87)
Mean corpuscular haemoglobin (MCH) in pg 27 to 32 (29.5)
Mean corpuscular haemoglobin concentration (MCHC) per cent.
32 to 38 (35)
Mean corpuscular diameter (MCD) in micron 6.7 to 7.7 (7.2)
Osmotic fragility of red cells: Haemolysis begins at 0.48 per cent saline and is complete at 0.33 per cent saline.
Bleeding time: 2 to 5, sometimes up to 7, (3.25) minutes.
Coagulation time (normal): 6 to 17 minutes in glass-tube
19 to 60 minutes in siliconsied tube (Lee and White)
5 to 11 minutes (Date and Laidlaw)
Prothrombin time: 11 to 16 seconds

ESR:	(Westergren)	Men 3 to 5 mm in 1 hour
	(Westergren)	Women 4 to 7 mm in 1 hour
	(Wintrobe)	Men 0 to 6.5 (3.7) mm in 1 hour
	(Wintrobe)	Women 0 to 15 (3.7) mm in 1 hour

Total blood volume (normal): 78 to 97 ml per kg body weight

Normal Values in Human Whole Blood*

Aceto-acetate + acetone	0.3 to 2.0 mg *per* 100 ml
Aldosterone	3.0 to 10 mμg *per* 100 ml
α-amino acid nitrogen	3.0 to 5.4 mg *per* 100 ml
Amylase	4.0 to 25.0 units *per* ml
Ascorbic acid	0.4 to 1.5 mg *per* 100 ml in *fasting period*
Bilirubin	0.1 to 0.3 mg *per* 100 ml (*directly*); 0.2 to 1.3 mg *per* 100 ml (*indirectly*)
Calcium	4.2 to 5.2 mEq *per* litre; 8.5 to 10.5 mg *per* 100 ml
CO_2 content	25 to 30 mEq *per* litre
Carotenoid	8 to 40 μg *per* 100 ml
Ceruloplasmin	26 to 38 mg *per* 100 ml
Chloride	340 to 380 mg *per* 100 ml
Cholesterol	150 to 280 mg *per* 100 ml
Cholesterol ester	60 to 75% of cholesterol (*total*)
Copper (*total*)	1.0 to 2.0 μg *per* ml
Cortisol (17-hydro-xycorticoids)	0.05 to 0.2 μg *per* ml
Creatinine	0.6 to 1.5 mg *per* 100 ml
Glucose (*folin*)	0.8 to 1.2 mg *per* ml in *fasting period*
Glucose (*true*)	0.7 to 1.0 mg *per* ml
PBI	3.4 to 8.0 μg *per* 100 ml
Iron	0.5 to 1.5 μg *per* ml
Lactic acid	0.6 to 1.8 mEq *per* litre
Lipase	Less than 2 units *per* ml
Lipoid (*total*)	4.5 to 10.0 mg *per* ml
Mg	1.0 to 2.0 mg *per* 100 ml; 1.5 to 2.5 mEq *per* litre
NPN	0.15 to 0.35 mg *per* ml
Osmolality	285 to 295 mOsm *per* litre
pCO_2 (*arterial*)	35 to 45 mm of Hg
Pepsinogen	200 to 430 units per ml
pH	7.36 to 7.45
Phenylalanine	0.0 to 2.0 mg per 100 ml
Phospholipid	1.5 to 2.3 mg per ml
Phosphorus (*inorganic*)	3.0 to 4.5 mg per 100 ml (up to 6.0 mg per 100 ml—infants in first year)
pO_2 (*arterial*)	75 to 100 mm of Hg
Protein (*total*)	6.0 to 8.0g per 100 ml
Albumin	4.0 to 5.0 g per 100 ml
Globulin	2.0 to 3.0 g per 100 ml
Pyruvic acid	0.0 to 0.12 mEq per litre
Sodium	3.0 to 3.5 mg per ml; 135 to 145 mEq per litre
Sulphate	0.5 to 1.5 mEq per litre
Transaminase	10 to 40 units per ml
Urea nitrogen	8 to 24 mg per 100 ml
Uric acid	3.0 to 7.0 mg per 100 ml
Vitamin A	15 to 60 μg per 100 ml

*Modified by Ganong

Appendix 5 Daily Dietary Allowance Chart*

Age (yr)	Wt (kg)	Ht (cm)	Cal	Protein (g)	Fat-soluble vitamins					Water-soluble vitamins					Minerals				
					A activity (IU)	E activity (IU)	Ascorbic acid (mg)	Folic acid (mg)	Niacin equiv (mg)	Riboflavin (mg)	Thiamine (mg)	B_6 (mg)	B_{12} (mg)	Ca (g)	Phos (g)	I (µg)	Fe (mg)	Mg (mg)
Infants																		
0–1/6	4	55	kg × 120	kg × 2.2	1500	5	35	0.05	5	0.4	0.2	0.2	1.0	0.4	0.2	25	6	40
1/6–1/2	7	63	kg × 110	kg × 2.0	1500	5	35	0.05	7	0.5	0.4	0.3	1.5	0.5	0.4	40	10	60
1/2–1	9	72	kg × 100	kg × 1.8	1500	5	35	0.1	8	0.6	0.5	0.4	2.0	0.6	0.5	45	15	70
Children																		
1–2	12	81	1100	25	2000	10	40	0.1	8	0.6	0.6	0.5	2.0	0.7	0.7	55	15	100
2–3	14	91	1250	25	2000	10	40	0.2	8	0.7	0.6	0.6	2.5	0.8	0.8	60	15	150
3–4	16	100	1400	30	2500	10	40	0.2	9	0.8	0.7	0.7	3	0.8	0.8	70	10	200
4–6	19	110	1600	30	2500	10	40	0.2	11	0.9	0.8	0.9	4	0.8	0.8	80	10	200
6–8	23	121	2000	35	3500	15	40	0.2	13	1.1	1.0	1.0	4	0.9	0.9	100	10	250
8–10	28	131	2200	40	3500	15	40	0.3	15	1.2	1.1	1.2	5	1.0	1.0	110	10	250
Males																		
10–12	35	140	2500	45	4500	20	40	0.4	17	1.3	1.3	1.4	5	1.2	1.2	125	10	300
12–14	43	151	2700	50	5000	20	45	0.4	18	1.4	1.4	1.6	5	1.4	1.4	135	18	350
14–18	59	170	3000	60	5000	25	55	0.4	20	1.5	1.5	1.8	5	1.4	1.4	150	18	400
18–22	67	175	2800	60	5000	30	60	0.4	18	1.6	1.4	2.0	5	0.8	0.8	140	10	400
22–35	70	175	2800	65	5000	30	60	0.4	18	1.7	1.4	2.0	5	0.8	0.8	140	10	350
35–55	70	173	2600	65	5000	30	60	0.4	17	1.7	1.3	2.0	5	0.8	0.8	125	10	350
55–75+	70	171	2400	65	5000	30	60	0.4	14	1.7	1.2	2.0	6	0.8	0.8	110	10	350
Females																		
10–12	35	142	2250	50	4500	20	40	0.4	15	1.3	1.1	1.4	5	1.2	1.2	110	18	300
12–14	44	154	2300	50	5000	20	45	0.4	15	1.4	1.2	1.6	5	1.3	1.3	115	18	350
14–16	52	157	2400	55	5000	25	50	0.4	16	1.4	1.2	1.8	5	1.3	1.3	120	18	350
16–18	54	160	2300	55	5000	25	50	0.4	15	1.5	1.2	2.0	5	1.3	1.3	115	18	350
18–22	58	163	2000	55	5000	25	55	0.4	13	1.5	1.0	2.0	5	0.8	0.8	100	18	350
22–35	58	163	2000	55	5000	25	55	0.4	13	1.5	1.0	2.0	5	0.8	0.8	100	18	300
35–55	58	160	1850	55	5000	25	55	0.4	12	1.5	0.9	2.0	5	0.8	0.8	90	18	300
55–75+	58	157	1700	55	5000	25	55	0.4	10	1.5	0.9	2.0	6	0.8	0.8	80	10	300
Pregnancy	...	...	+200	65	6000	30	60	0.8	15	1.8	+0.1	2.5	8	+0.4	+0.4	125	18	450
Lactation	...	...	+1000	75	8000	30	60	0.5	20	2.0	+0.5	2.5	6	+0.5	+0.5	150	18	450

*Adapted from the Food and Nutrition Board, National Academy of Science, National Research Council (1968), USA.

Multiple Choice Questions

- Endocrine and Reproduction
- Central Nervous System and Special Senses

Multiple Choice Questions

ENDOCRINE AND REPRODUCTION

1. **Average weight of the pituitary gland is:**
   a. 0.1 gm b. 0.5 gm
   c. 1 gm d. 5 gm
   e. 10 gm
2. **Anterior lobe of pituitary gland consists of:**
   a. Pars distalis and pars tuberalis
   b. Pars distalis and pars nervosa
   c. Processus infundibuli and median eminence
   d. Pars nervosa and tuber cinereum
   e. None of these
3. **Pars distalis forms about:**
   a. 15% of the hypophysis b. 25% of the hypophysis
   c. 45% of the hypophysis d. 55% of the hypophysis
   e. 75% of the hypophysis
4. **Hypothalamic releasing factors (RF) which control the secretory function of the anterior pituitary reach the anterior pituitary via:**
   a. CSF
   b. Internal carotid artery
   c. Hypothalamico-hypophyseal portal system
   d. Circle of Willis
   e. Cavernous sinus
5. **Atrophy of the anterior pituitary in infants and children produces:**
   a. Dwarfism b. Gigantism
   c. Acromegaly d. Mongolism
   e. All of the above
6. **Which of the following inhibits growth hormone secretion from the anterior pituitary:**
   a. Insulin b. ACTH
   c. Thyroxine d. Oestrogen
   e. None of the above
7. **Of the following which has got both activating and inhibiting effects on ACTH secretion:**
   a. Hippocampus
   b. Amygdala
   c. Midbrain
   d. Peripheral nerves and spinal cord
   e. Cerebral cortex
8. **Of the following which is secreted by the acidophil cells of the anterior pituitary:**
   a. HGH b. TSH
   c. ACTH d. FSH
   e. ICSH
9. **Vasopressin is synthesised in:**
   a. Posterior pituitary b. Anterior pituitary
   c. Hypothalamic nuclei d. Cerebral cortex
   e. Medulla oblongata
10. **ADH stimulates reabsorption of water by:**
    a. Bowman's capsule
    b. Proximal convoluted tubule
    c. Loop of Henle
    d. Distal convoluted tubule
    e. None of these
11. **In an extreme case of diabetes insipidus, maximum output of urine may be as high as:**
    a. 20 litres b. 40 litres
    c. 60 litres d. 120 litres
    e. 170 litres
12. **Human thyroid gland stores:**
    a. 0.5 mgm of iodine per gram of the dry gland
    b. 2 mgm of iodine per gram of the dry gland
    c. 5–8 mgm of iodine per gram of the dry gland
    d. 10 mgm of iodine per gram of the dry gland
    e. No iodine at all
13. **The thyroid gland contains about:**
    a. 1% of the total iodine content of the body
    b. 5% of the total iodine content of the body
    c. 10% of the total iodine content of the body
    d. 20% of the total iodine content of the body
    e. 95% of the total iodine content of the body
14. **Propylthiouracil is an antithyroid compound and its mechanism of action:**
    a. Interferes in iodination of tyrosine
    b. Inhibits concentration of iodide within the gland
    c. Prevents absorption of iodine from intestine
    d. Forms of progoitrin and goitrin
    e. Decreases vascularity of the gland
15. **Secretion of parathormone is controlled by:**
    a. Anterior pituitary b. Posterior pituitary
    c. Hypothalamus d. Blood calcium level
    e. All of them
16. **Which of the following stimulates insulin secretion?**
    a. GH (STH) b. Vagal stimulation
    c. Cyclic 3′, 5′-AMP d. All of them
    e. None of them
17. **Which of the following inhibits insulin secretion?**
    a. Epinephrine b. Vasopressin
    c. Glucagon d. Glucocorticoids
    e. All of them
18. **Glucagon secretion is inhibited by:**
    a. Hypoglycaemia b. Hyperglycaemia
    c. Muscular exercise d. Pancreozymin
    e. Protein meals
19. **Which of the following diminishes blood sugar level?**
    a. Glucocorticoids
    b. ACTH
    c. Thyroxine
    d. Stimulation of right vagus
    e. Sympathetic stimulation
20. **Features of hypoglycaemia include:**
    a. Tremors
    b. Flushing, palor and perspiration
    c. Delirium, coma and convulsion
    d. Loss of deep reflexes
    e. All of them

From the following direction given below, select answers for questions 21–39:

a. If statements (i), (ii) and (iii) are correct
b. If statements (i) and (iii) are correct
c. If statements (ii) and (iv) are correct
d. If the statement (iv) is only correct

21. Developmentally the pituitary gland has two parts—adenohypophysis and neurohypophysis:
i. Adenohypophysis consists of pars distalis, pars intermedia and pars tuberalis
ii. Adenohypophysis develops from primitive buccal cavity
iii. Neurohypophysis develops from the floor of the III ventricle
iv. The stalk of the Rathke's pouch persists in adult life and forms the pituitary stalk

22. Administration of growth hormone:
i. Increases protein synthesis
ii. Increases amino acid content of plasma
iii. Increases plasma level of NEFA (non-esterified fatty acids)
iv. Produces hypoglycaemia

23. After hypophysectomy:
i. Thyroid takes up more inorganic iodide from the plasma
ii. Increases the vascularity of the thyroid gland
iii. Increases the thyroid acinar cell height
iv. Acini contain larger amount of colloid

24. ACTH is secreted by the basophil cells of the anterior pituitary:
i. It is glycoprotein in nature
ii. It has been isolated in α- and β-forms
iii. It is destroyed at a temperature of 60°C
iv. It controls the growth of adrenal cortex

25. Administration of ACTH produces:
i. Increased excretion of potassium
ii. Retention of sodium
iii. Elevation of blood sugar
iv. Increase in circulatory eosinophils

26. Degeneration of anterior pituitary is characterized by:
i. Sterility
ii. Extreme weakness
iii. Hypoglycaemia
iv. Increased urinary excretion of 17-ketosteroids

27. Melanocyte-stimulating hormone:
i. It is same as melatonin
ii. It is secreted by pars tuberalis of anterior pituitary
iii. Hydrocortisone (cortisol F) stimulates secretion of MSH
iv. Epinephrine and norepinephrine inhibit the action of MSH

28. Oxytocin shares some of the activities of ADH and thus it is:
i. Minimally antidiuretic
ii. Causes contraction of uterus
iii. Causes contraction of smooth muscles of mammary glands
iv. Increases vasoconstriction and peripheral resistance

29. Iodine remains in blood in two forms—inorganic iodine and protein-bound iodine:
i. Normal level of inorganic iodide in blood varies between 0.5 mg and 1 mg/100 ml
ii. Normal level of PBI is 5 to 8 µg/100 ml
iii. In hyperthyroidism PBI level diminishes and may become as low as 0.5 µg/100 ml
iv. This iodine (PBI) may be precipitated out

30. Normal adult thyroid gland secretes about 1 mg of thyroxine per day:
i. Each mg of thyroxine raises the BMR to about 1000 calories
ii. Thyroxine increases oxygen consumption of the brain tissue
iii. Thyroxine promotes gluconeogenesis
iv. Thyroxine cannot accelerate the rate of a denervated heart

31. Thyroid gland concentrates iodide:
i. This is an active process
ii. Uptake of iodide by the gland is inhibited by TSH
iii. Uptake of iodide is also inhibited by cyanide
iv. The iodide directly combines with tyrosine without being oxidized

32. Thyroclacitonin lowers plasma calcium and phosphate:
i. It is secreted by the parathyroid glands
ii. It is detected in blood when blood calcium level is above normal
iii. Secretion of thyrocalcitonin is under control of pituitary hormones
iv. Hypocalcaemic action of the hormone is due to inhibition of bone resorption and calcium release

33. In a case of manifest tetany in man:
i. There is an increased neuromuscular irritability
ii. Urinary excretion of calcium and phosphorus is reduced
iii. Carpopedal spasm, Chvostek's signs and Erb's sign may be elicited
iv. Lowering of total calcium is more important than lowered ionic calcium in its causation

34. Active principal of parathyroid is parathormone:
i. Parathormone remains stored in the parathyroid gland
ii. It increases rate of bone resorption with consequent mobilization of calcium and phosphate
iii. It increases reabsorption of phosphate and inhibits reabsorption of calcium by renal tubules
iv. The action of PTH on bone and kidneys is stimulated by adenyl cyclase

35. Calcium constitutes about 2% of total body weight:
i. Absorption of calcium mainly takes place in the terminal part of ileum and caecum
ii. Organic calcium is better absorbed than inorganic calcium
iii. High phosphorus-containing foods help calcium absorption
iv. Vitamin D is essential for calcium absorption in man

36. Phosphorus is present in all tissues of the body:
i. Calcium/inorganic phosphorus ratio in blood on the average 2 : 1

ii. Anything that raises serum calcium level also raises phosphate level proportionally
iii. Acidity and bile salts favour phosphate absorption
iv. Vitamin D stimulates phosphate transport and fatty acids in food diminish phosphate absorption

37. The chemical structure of insulin:
i. Is such that it is effective when taken by mouth
ii. Is three chains of amino acids linked by disulphide bonds
iii. Is same as proinsulin
iv. Is rich in cysteine, leucine and glutamic acid

38. Insulin is synthesized by the ribosomes of β-cells of the islets of Langerhans as β-granules:
i. These β-granules remain enclosed within a membranous sac
ii. These β-granules are liberated into the extracellular space of the islets of Langerhans by a process known as emiocytosis
iii. This process requires the help of calcium ion
iv. The insulin thus released from the β-cells reached the blood flow and tissues as zinc-insulin

39. Glucagon is secreted by α-cells of the islets of Langerhans:
i. It is polypeptide in nature
ii. It has been synthesized in laboratory
iii. It is also present in the mucosa of stomach and duodenum
iv. Its mode of action is unknown

For the numbered items on the left-hand column, choose a correct lettered item from the right-hand column that best applies:

40. Steroid feedback mechanism
a. Blood level of ACTH contents the endogenous secretion of ACTH

41. Short feedback mechanism
b. Responsible for lactation in the post-partum women

42. LH
c. Controls the activity and growth of gonads

43. LTH
d. Blood level of steroid corticoids controls the secretion of ACTH

44. Chvostek's sign
e. Tapping of the facial nerve near the styloid process causes facial spasm

45. Erb's sign
f. Increased excitability of motor nerves to galvanic current

46. α-cells of pancreas
g. Secrete somatostatin

47. β-cells of pancreas
h. Secrete glucagon

48. δ-cells of pancreas
i. Secrete insulin

From the following directions given below, select answers for questions 49–57:
a. If the statement is correct and the reason is also correct
b. If the statement is correct but the reason is wrong
c. If the statement is wrong but the reason is correct
d. If both the statement and the reason are incorrect

49. Hypophysectomy accelerates the growth of the gonads, because hypophysectomy controls gonads

50. Lactation does not occur during pregnancy, because placental gonadotrophins inhibit prolactin secretion

51. ADH reduces chloride loss in urine, because it increases chloride absorption.

52. In man, oxytocin acts on uterus in late pregnancy, because high proportion of oestrogen during this period makes the uterine muscles more sensitive to oxytocin.

53. A high acidity favours calcium absorption, *because* the calcium salts become soluble in acid medium.

54. Alkalaemia may produce symptoms of hypocalcaemia, because alkalaemia decreases total serum calcium.

55. Normal pancreatic tissue is rich in Zn, because insulin remains stored in it as a Zn salt.

56. In advanced diabetes RQ is about 0.7, because in absence of insulin in this condition mostly fats are burnt.

57. Hypoglycaemia affects the nerve cells last, because nerve cells do not use sugar as the source of energy.

For the following questions 58 to 75 a statement is followed by four possible answers. Answers by using the key outlined below:
a. If only (i), (ii) and (iii) are correct
b. If only (i) and (iii) are correct
c. If only (ii) and (iv) are correct
d. If only (iv) is correct
e. If all (i), (ii), (iii) and (iv) are correct

58. Adrenal gland:
i. Adrenal gland in foetus and in neonates are proportionally larger than in the adult
ii. Foetal adrenal cortex consists of provisional and permanent cortex which are functionally and structurally the same
iii. One of the major functions of foetal adrenal is to secrete sulphate conjugates of androgens, which become converted into active androgens and oestrogens in the placenta
iv. Adrenal cortex is ectodermal in origin

59. Adrenal gland:
i. Accessory adrenal cortical tissues are more abundant than accessory medullary tissues in man
ii. The blood vessels of adrenal gland enters it though the surface
iii. The nerve fibres enter the gland through the hilus and control both the medulla and the cortex
iv. The nerve fibres of the adrenal glands are medullated and are entirely preganglionic

60. Adrenal cortex:
i. Histologically adrenal cortex consists of three well-defined layers—zona fasciculata, zona glomerulosa and zona reticularis from inside outwards
ii. Zona glomerulosa secretes mainly aldosterone, and small amount of glucocorticoids and sex hormones
iii. Zona reticularis secretes mainly sex hormones and a small amount of aldosterone but no glucocorticoids
iv. Zona fasciculata is the widest layer, rich in ascorbic acid and cholesterol, and secretes glucocorticoids

61. Adrenal steroid:
i. Biosynthesis of adrenal steroids takes place in the mitochondria
ii. Cyclic AMP is necessary for biosynthesis of steroid hormones
iii. ACTH is involved in steroidogenesis
iv. NADPH acts as coenzyme for hydroxylation reaction in different steps

62. Adrenal steroid:
i. Normally adrenal steroid hormones circulate in free and bound forms
ii. Major parts of the steroid hormones remain free in circulation
iii. α-globulins bind glucocorticoids and β-globulins bind sex hormones
iv. The bound hormone is essentially the active form

63. Cortisol has many functions in the body:
i. It favours protein synthesis
ii. It helps absorption of calcium from the gut
iii. It enhances formation of antibodies
iv. It reduces blood without affecting the marrow eosinophil count

64. Hormones of the adrenal medulla are called catecholamines:
i. Catecholamines are formed from the amino acid phenylalanine
ii. Catecholamines are released from the adrenal medulla by a process known as exocytosis
iii. Catecholamine responses are mentioned by intracellular level of cyclic AMP
iv. Catecholamines are metabolised by enzyme mono-amino-oxidase (MAO) and catechol-O-methyl transferase (COMT)

65. Epinephrine differs from norepinephrine in that it:
i. Causes tachycardia
ii. Dilates some vessels, e.g. coronary vessel and skeletal muscle
iii. Inhibits movement of uterus in advanced pregnancy
iv. Respiration is inhibited

66. A patient with a secreting tumour of the adrenal medulla (pheochromocytoma) may have:
i. Paroxysmal or permanent hypertension
ii. Hypoglycaemia
iii. Dyspnoea, sweating, tremors
iv. Decreased BMR and oxygen consumption

67. Adrenal insufficiency causes:
i. Increased blood volume
ii. Decreased plasma K level
iii. Hyperglycaemia
iv. Excretion of 17-ketosteroids is much diminished

68. Almost each tissue contains small amount of prostaglandins. They are:
i. A class of C_{20}fatty acids
ii. Regarded as local tissue hormones and regulate action of neurohormones
iii. Inhibitors of lipolysis
iv. Potent vasodilators

69. Males differ from females in that their:
i. Two sex chromosomes are different (XY)
ii. Urine contains only male hormone
iii. Limit of sex life is not sharp
iv. Public hairs are concave forwards

70. Human spermatozoa:
i. Require temperature lower than that of the interior of body for their genesis
ii. They are motile even when in the seminiferous tubules
iii. Take about 45 minutes to pass from the opening of the cervix to the ovarian end of the fallopian tube
iv. In absence of fertilisation they die within 24 hours in the fallopian tube

71. Fertilisation of human ovum
i. Penetration of the ovum by the sperm is brought about by a lysosomal enzyme present in the tail of the sperm
ii. Only one sperm is allowed to penetrate the ovum
iii. May occur one week after ovulation
iv. Usually occurs at the ampullary-isthmic junction of the fallopian tube

72. In normal menstrual cycle:
i. Ovulation is associated with rise in blood LH level
ii. LH and LTH are directly responsible for premenstrual changes of the endometrium
iii. In absence of fertilisation high level of progesterone inhibits LH and LTH secretion which in turn causes involution of the corpus luteum
iv. High level of progesterone is also the direct cause of menstrual bleeding

73. During pregnancy:
i. Uterine muscle tissue increases mainly due to hyperplasia of uterine muscle fibres
ii. Blood volume increases
iii. Vital capacity, tidal volume and pulmonary ventilation decrease due to raised diaphragm
iv. Cardiac output increases

74. In the placenta:
i. There is free mixing of maternal and foetal blood
ii. The pO_2 of umbilical vein blood is same as the pO_2 in the maternal sinusoid
iii. pO_2 of blood in the maternal sinusoid is same as alveolar air O_2 tension
iv. Adequate oxygenation takes place *because* foetal haemoglobin has the property of taking up oxygen at relatively low oxygen pressure

75. Foetal circulation differs from an adult in that blood in:
i. Brachial artery has a higher oxygen saturation than the femoral artery
ii. Inferior vena cava has higher oxygen saturation than superior vena cava
iii. Major part of the blood from right ventricle passes via ductus arteriosus in the descending aorta
iv. In the left atrium oxygen saturation is higher than the right atrium

76. Glucocorticoids contain:
a. 17 carbon atoms
b. 18 carbon atoms
c. 19 carbon atoms
d. 20 carbon atoms
e. 21 carbon atoms

77. Sex steroids contain:
a. 17 carbon atoms
b. 19 carbon atoms
c. 21 carbon atoms
d. 23 carbon atoms
e. None of these

78. Cortisol level in plasma is 3–15 ng/100 ml. It is:
a. Higher in early morning
b. Very low in early morning
c. Higher near midnight
d. Almost the same in early morning and midnight
e. None of the statements is correct

79. Aldosterone controls mineral metabolism, it increases the reabsorption of:
a. NaCl
b. Bicarbonate
c. Potassium
d. Phosphate
e. (a) and (b)

80. Action of glucocorticoids on carbohydrate metabolism is partly similar and partly antagonistic to insulin: Which of the actions are antagonistic to insulin?
a. Increases gluconeogenesis in the liver
b. Depresses glucose uptake and oxidation by tissues
c. Stimulates formation of glycogen in the liver
d. (a) and (b)
e. (c) and (d)

81. Conn's syndrome (primary hyperaldosteronism) is associated with adrenal tumour and is characterised by:
a. Muscular weakness
b. Hypertension
c. Retention of sodium
d. Alkalosis
e. All of them

82. Normal urinary excretion of neutral 17-ketosteroids in 24 hours in adult male is approximately:
a. 1 to 5 mg
b. 5 to 15 mg
c. 10 to 20 mg
d. 15 to 25 mg
e. 20 to 30 mg

83. Secretion of aldosterone is controlled by a chemical mediator known as glomerulotrophin. It is liberated from:
a. Hypothalamus
b. Anterior pituitary
c. Posterior pituitary
d. Juxtaglomerular cells
e. None of these

84. Melatonin is a hormone secreted by:
a. Anterior pituitary
b. Posterior pituitary
c. Hypothalamus
d. Pineal body
e. Sympathetic nerve endings

For the chemical compounds, for questions 85–90, choose the appropriate structural formulae given in the diagram below:

85. 11-dehydrocoticosterone
86. Cortisol F (hydrocortisone)
87. Aldosterone (aldehyde form)
88. Nonepinephrine
89. Epincphrine
90. DOPA

For the questions 91–93, which of the following statements is correct:

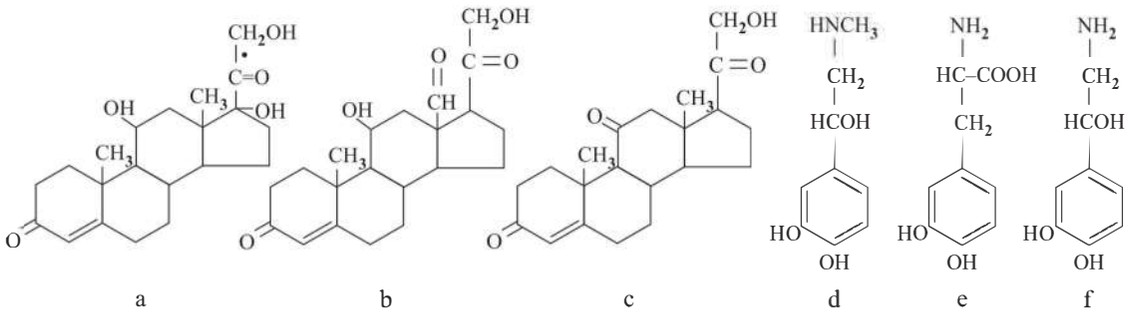
91. Intrauterine contraceptive device (IUCD):
a. Prevents menstruation
b. Inhibits ovulation
c. Prevents fertilisation of the ovum
d. Makes the intrauterine environment hostile to the nidation of the fertilised ovum
e. The method is 100% successful

92. Ligation of the vas deferens (vasectomy) causes:
a. Virilisation
b. Stoppage of spermatogenesis
c. Deficiency of male hormones
d. Loss of the erectile power of the penis
e. None of the above

93. Probable modes of action of a classical contraceptive are:
a. Inhibition of ovulation
b. Modifying tubal transport of the ovum
c. Makes nidation of fertilised ovum difficult
d. Render cervical mucous hostile to serum penetration
e. All of the above

94. Paracrines are chemical messengers
a. Secreted by cells into the extracellular fluid and affect neighbouring target cells of different type
b. Secreted by cells into the extracellular fluid and affect the functions of same cell that produced them
c. Secreted by cells but remain inside the cell
d. None of the above

95. The prostaglandins responsible for cervical dilatation at time of child birth is:
a. PGF_2
b. PGI_2
c. PGE_2
d. None of the above



96. Somatotropes are
a. Single chain of 9 amino acids
b. Single chain of 119 amino acids
c. Single chain of 191 amino acids
d. Single chain of 250 amino acids

97. Somatostatin
a. Inhibit secretion of growth hormone by somatotropes
b. Inhibits secretion of prolactin by lactotropes
c. Stimulates secretion of TSH by thyrotropes
d. Stimulates ACTH by corticotropes

98. Somatomedin C is also known as:
a. Thyrotropin releasing hormone
b. Growth hormone releasing hormone
c. Inulin like growth factor-I
d. Prolactin inhibitory factor

99. Craniopharyngiomas are:
a. Tumours of pharynx
b. Tumours of larynx
c. Tumours of bronchus
d. Tumorous condition involving the pituitary gland

100. Oxytocin is formed primarily in:
a. Supraoptic nuclei b. Intralaminar nuclei
c. Pulvinar nuclei d. Paraventricular nuclei

101. ADH is formed primarily in:
a. Supraoptic nuclei
b. Medial nuclei of hypothalamus
c. Paraventricular nuclei
d. Intralaminar nuclei

102. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is diagnosed on certain essential features such as
a. Plasma osmolality (<275 mOsm/kg), urine osmolality (>100 mOsm/kg) and urinary sodium (>40 mmo/L)
b. Plasma osmolality (<325 mOsm/kg), urine osmolality (<90 mOsm/kg) and urinary sodium (<40 mmo/L)
c. Plasma osmolality (<380 mOsm/kg, urine osmolality (<50 mOsm/kg) and urinary sodium (< 10 mOsm/kg)
d. None of the above

103. The daily rate of secretion of thyroxine and triiodothyronine are:
a. 93% thyroxine and approx 7% triiodothyronine
b. 70% thyroxine and 30% triiodothyronine
c. 60% thyroxine and 40% triiodothyronine
d. 50% thyroxine and 50% triiodothyronine

104. The molecular weight of thyrotropin is:
a. 280 b. 2800
c. 28000 d. 280000

105. The approximate percent of ingested calcium exreted in urine is:
a. 30% (300 mg/day) b. 10% (100 mg/day)
c. 40% (400 mg/day) d. 25% (250 mg/day)

106. The changes in calcium and phosphate levels after sudden removal of parathyroid glands in blood are:
a. 10 mg/dL of calcium and phosphate concentration is halted
b. 9.1 mg/dL of calcium and no change in phosphate concentration
c. 6–7 mg/dL of calcium and phosphate concentration is double
d. None of the above

107. The cystic bone disease of hyperparathyroidism is called:
a. Osteomalacia b. Osteomyelitis
c. Osteogenic sarcoma d. Osteitis fibrosa cystica

108. In case of total lack of aldosterone the total transient loss of sodium in urine in a day will be:
a. 1–2 gm of sodium
b. 3–6 gm of sodium
c. 6–8 gm of sodium
d. 10–20 gm of sodium

109. The hypersecretion of adrenal cortex cause a complete cascade of hormone effect called:
a. Addissons disease b. Simmons disease
c. Cushing syndrome d. Cretinism

110. The tumor of zona glomerulosa cells causes:
a. Fanconis anaemia b. Conn syndrome
c. Addisonia anaemia d. Myasthenia gravis

111. The chromaffin cell tumors causes
a. Albinism b. Hyperprolactinemia
c. Pheochromocytoma d. Gaucher's disease

112. Incretins are gastrointestinal hormones causing:
a. Enhancement in rate of thyroid hormone secretion in response to increase blood glucose
b. Enhancement in rate of oxytocin secretion in response to increase blood glucose
c. Enhancement in rate of insulin release from pancreas is response to increase blood glucose
d. Enhancement in rate of glucagon release from pancreas in response to increase blood glucose

113. The drug metformin used in treatment of diabetes:
a. Suppress liver glucose production
b. Enhance liver glucose production
c. Stimulates gluconeogenesis
d. None of the above

114. The maximum composition in semen formation is by:
a. Prostate b. Bulbourethral glands
c. Seminal vesicle d. Vas deferens

115. Frohlich syndrome is also known as:
a. Cushing syndrome
b. Adiposogenital syndrome
c. SIADH
d. Fanconis anaemia

116. The deficiency of the hormone which causes osteoporosis of bone in old age is:
a. Progesterone
b. Oestrogen
c. Follicle stimulating hormone
d. Luteinizing hormone

117. The ovum remains viable and is capable of being fertilized after being expelled from ovary for period of:
a. 48 hours b. 24 hours
c. 64 hours d. 8 hours

118. The most commonly used synthetic estrogens are:
a. Ethinyl estradiol
b. Norgestrel
c. Ethynodiol
d. Norethindrone

119. The drug sildenafil(Viagra) used for treatment of erectile dysfunction is:
a. Phosphodiesterase-5 (PDE5) inhibitors
b. Phospholipase inhibitor
c. Glucokinase
d. Hexokinase

120. The non haemoglobin iron store in mother at the outset of pregnancy ranges from:
a. 0.1 –0.7 mg
b. 1 –7 mg
c. 10 –70 mg
d. 100 –700 mg

121. The amount of blood flowing through maternal circulation during last month in pregnant lady is approximated:
a. 62 ml
b. 165 ml
c. 625 ml
d. 5000 ml

122. The amount of fat in human milk is:
a. 30%
b. 25%
c. 3.3%
d. 23%

123. The amount of lactalbumin and other protein in human milk is:
a. 0.4%
b. 0.9%
c. 1.2%
d. 1.8%

124. The amount of casein in human and cows milk is:
a. Human milk 0.9%, cows milk 2.7%
b. Human milk 2.1%, cows milk 1%
c. Human milk 0.1%, cows milk 0%
d. None of the above

ANSWERS

1. (b)	2. (a)	3. (e)	4. (c)	5. (a)	6. (e)	7. (e)	8. (a)	9. (c)	10. (d)
11. (a)	12. (c)	13. (e)	14. (a)	15. (d)	16. (d)	17. (c)	18. (b)	19. (d)	20. (c)
21. (b)	22. (a)	23. (d)	24. (d)	25. (a)	26. (a)	27. (d)	28. (a)	29. (c)	30. (b)
31. (b)	32. (c)	33. (a)	34. (c)	35. (d)	36. (b)	37. (d)	38. (a)	39. (a)	40. (d)
41. (a)	42. (c)	43. (b)	44. (e)	45. (f)	46. (h)	47. (i)	48. (g)	49. (d)	50. (a)
51. (d)	52. (c)	53. (d)	54. (b)	55. (a)	56. (a)	57. (d)	58. (b)	59. (e)	60. (b)
61. (b)	62. (b)	63. (d)	64. (c)	65. (a)	66. (b)	67. (d)	68. (d)	69. (a)	70. (b)
71. (c)	72. (b)	73. (d)	74. (d)	75. (d)	76. (e)	77. (c)	78. (a)	79. (a)	80. (d)
81. (e)	82. (b)	83. (d)	84. (d)	85. (c)	86. (a)	87. (b)	88. (f)	89. (d)	90. (e)
91. (d)	92. (a)	93. (e)	94. (a)	95. (c)	96. (c)	97. (a)	98. (c)	99. (d)	100. (d)
101. (a)	102. (a)	103. (a)	104. (c)	105. (b)	106. (c)	107. (d)	108. (d)	109. (c)	110. (b)
111. (c)	112. (c)	113. (a)	114. (c)	115. (b)	116. (b)	117. (b)	118. (a)	119. (a)	120. (d)
121. (c)	122. (c)	123. (a)	124. (a)						

CENTRAL NERVOUS SYSTEM AND SPECIAL SENSES

For the following questions 1–21 a statement is followed by four possible answers. Answer by using the key outlined below:

a. If only (i), ii and (iii) are correct
b. If only (i) and (iii) are correct
c. If only (ii) and (iv) are correct
d. If only (iv) is correct
e. If all (i), (ii), (iii) and (iv) are correct

1. The spinal cord:
i. Consists of 29 segments
ii. Its length is equal to that of the vertebral column
iii. The cord ends at the level of the fifth sacral vertebra
iv. Dura and arachnoid proceed up to the second sacral vertebra

2. CSF:
i. Is contained in subdural space
ii. Surrounds the whole central nervous system being both inside and outside it
iii. Comes out of the ventricles into the subarachnoid space by the aqueduct of Sylvius
iv. The circulation of CSF is helped by the movement of the cilia lining the ventricles

3. Neurone:
i. Is the structural and functional unit of the nervous system
ii. Consists of nerve cell body, axon and dendrite
iii. Axon carries impulses away from the nerve cell
iv. Dendrite carries impulses towards the central nervous system and is devoid of any Nissl granules

4. A nerve fibre:
i. Propagates impulse in one direction only
ii. Will always give maximum response if the stimulus be adequate
iii. Has high Na^+ concentration inside and high K^+ concentration outside in resting phase
iv. Cannot be fatigued

5. **The physiological properties of the nerve fibre vary with their diameter and medullation. thicker the nerve fibres:**
   i. Higher will be the impulse velocity
   ii. Lower will be the spike potential
   iii. Lower will be the refractory period
   iv. Higher will be the stimulus threshold (chronaxie)
6. **Metabolic changes are constantly going on in a nerve fibre:**
   i. Metabolic activity is very high even at resting phase
   ii. During activity ATP and creatine phosphate break down and supply energy for propagation of the nerve impulse
   iii. During activity heat production by nerve fibres is even greater than skeletal muscle tissues
   iv. Increase in the strength of stimulus does not raise the heat production
7. **In the region of myoneural junction:**
   i. Axon terminal (sole foot) is devoid of any myelin sheath
   ii. There are many tiny vesicles and mitochondria
   iii. The acetylcholine is synthesized by the mitochondria and stored in the vesicles
   iv. For liberation of acetylcholine from the vesicle participation of Ca^{++} is required
8. **After complete transaction of a nerve the following changes take place in the nerve cell:**
   i. Nissl granules increase
   ii. Golgi apparatus, mitochondria and neurofibrils break up and disappear
   iii. The cell becomes dehydrated
   iv. The nucleus is pushed to the periphery
9. **After complete transection of a nerve the following changes take place in the distal end:**
   i. The myelin sheath disintegrates into droplets of fat
   ii. Schwann cells multiply and fill up the gap between the two cut end (up to 3 cm)
   iii. Regeneration of nerve fibre within central nervous system is not possible
   iv. A regenerated nerve is devoid of myelin sheath
10. **Acetylcholine is produced at the motor end-plates:**
    i. Intravenous injection of very small doses of acetylcholine causes paralysis of muscle
    ii. Action of acetylcholine is potentiated by choline esterase
    iii. Prostigmine potentiates the action of choline esterase
    iv. Curate prevents the action of acetylcholine
11. **Knee jerk:**
    i. It is a monosynaptic reflex
    ii. Centre is situated in L5–S2
    iii. It is exaggerated in upper motor neurone lesions
    iv. Becomes pendular in lower motor neurone lesions
12. **Sensory tracts in the posterior columns are:**
    i. Tract of Gall
    ii. Tract of Burdach
    iii. Comma tract of Schultze
    iv. Gowers' tract
13. **Second-order neurons of the following sensory tract do not cross:**
    i. Dorsal spinothalamic ii. Ventral spinothalamic
    iii. Spinotectal iv. Spinocerebellar
14. **Pain sensation:**
    i. Nerve endings for pain sensations are organs of Ruffini and Golfi-Mazzoni bodies
    ii. Pain is carried by fine non-medullated nerve fibres
    iii. Pain sensations are carried by the tract of Flechsig and Gowers
    iv. The tracts carrying pain sensation end in thalamus
15. **Pyramidal tracts:**
    i. The tracts are constituted by the fibres originating from the cells of the cerebellum
    ii. 60% fibres of the tracts are myelinated
    iii. Of all pyramidal fibres 20% only end in the cervical region
    iv. Pyramidal cells and their axons are known as upper motoneurone
16. **Extrapyramidal tracts:**
    i. When pyramidal tracts are damaged, extrapyramidal tracts may carry some of their functions
    ii. They are collectively responsible for tone, posture and equilibrium
    iii. The cortex exerts tonic inhibitory control over the lower centres through these tracts
    iv. They control complex movements of the body and limbs
17. **Basal ganglia:**
    i. Are the primitive motor cortex for voluntary muscular activity
    ii. Disease of basal ganglia produces muscular rigidity
    iii. Check abnormal involuntary movements
    iv. Control automatic and associated movements such as swinging of the arms during walking
18. **The ascending reticular activating system:**
    i. Is situated in the cerebral hemisphere
    ii. Stimulation of the system leads to sleep
    iii. It is depressed by epinephrine
    iv. Cerebral cortex stimulates this system
19. **Muscle tone is:**
    i. Purely reflex process
    ii. Lost when posterior nerve root is destroyed
    iii. Lost when motor nuclei in the anterior horn cells are destroyed
    iv. Preserved even when the nerve to the muscle is sectioned
20. **Macula lutea (fovea) is:**
    i. Situated at the posterior pole of the eye
    ii. Devoid of stratum opticum, inner and outer plexiform layers, ganglion cell layer
    iii. Packed with highly developed long thin cones
    iv. Devoid of any rod and crossed by neumerous blood vessels
21. **The cones in the eye:**
    i. Are concerned with colour vision
    ii. Are not concerned with visual acuity

iii. They contain iodopsin
iv. Are numerous at the periphery of the retina

From the numbered items, for questions 22–28, on the left-hand column choose the most appropriate lettered item from the right-hand column:

22. Sensory unit
a. Crude parts of various cutaneous sensations

23. Dermatome
b. Ability to recognise the position and movement of limbs

24. Protopathic sensation
c. Finer aspect of cutaneous sensations

25. Epicritic sensation
d. Area supplied by one sensory fibre

26. Kinaesthetic sensation
e. Area of skin supplied by one posterior root

27. Meissner's corpuscle
f. Pressure receptor

28. Pacinian corpuscle
g. Touch receptor

29. Pituitary peptide is:
a. β endorphin b. Substance P
c. Carnosine d. Adenosine

30. The content in tea and coffee which causes neuronal excitability is:
a. Theophylline b. Theobromine
c. Caffeine d. All of the above

31. The phenomenon of stabiling type of pain in one side of face in sensory area of fifth and ninth nerve is called:
a. Tic douloureux
b. Trigeminal neuralgia
c. Glossopharyngeal neuralgia
d. All of the above

32. Amorphosynthesis is:
a. Lack of awareness of somatic sensation from the opposite side of body
b. Lack of awareness of somatic sensation from same side of body
c. Lack of awareness of visceral sensation from same side of body
d. All of the above

33. The percentage of people noted as taste blind for phenylthiocarbamide
a. About 30–50% b. About 50–60%
c. About 15–30% d. About 60–70%

34. The frequencies of sound that a young person can hear are:
a. between 20 and 20,000 cycles/sec
b. between 10 and 10,000 cycles/sec
c. between 30 and 30,000 cycles/sec
d. between 40 and 40,000 cycles/sec

35. The instrument used to determine the nature of hearing disability are:
a. Audiometer b. Olfactometer
c. Infantometer d. Aesthesiometer

36. The fibrosis in middle ear leads to:
a. Tympanitis b. Otosclerosis
c. Frunculosis d. Non of the above

37. The disorder of eye in which intraoccular pressure is increased in:
a. Neurofibroma b. Astigmatism
c. Myopia d. Glaucoma

38. The pupil of eye can alter size to:
a. As small as 0.5 mm and large as 4 mm in diameter
b. As small as 0.1 mm and large as 2 mm in diameter
c. As small as 1.5 mm and large as 8 mm in diameter
d. As small as 2.5 mm and large as 20 mm in diameter

39. Nyctalopia is:
a. Colour blindness due to vitamin A deficiency
b. Night blindness due to vitamin A deficiency
c. Astigmatism due to vitamin A deficiency
d. None of the above

40. The pigment layer of retina in albinos lack
a. Melanin pigment b. Rhodopsin
c. Lumi rhodopsin d. Scotopsin

41. The test used to charting field of vision is:
a. Visual acuity b. Ophthalmoscopy
c. Perimetry d. Retinoscopy

42. The synaptic delay in chemical synapse is:
a. 1 sec b. Less than 0.5 sec
c. 2 sec d. 1.5 sec

43. The complete transection of nerve leads to degenerative changes in the peripheral part of axons and this process is known as:
a. Walters degeneration b. Williams degeneration
c. Wallerian degeneration d. Wallace degeneration

44. The receptors for pressure, stretch and kinaesthetic impulse are:
a. Organ of Golgi b. End bulb of Krause
c. Meissener's corpuscles d. Pacinian corpuscles

45. The spinovisual reflexes are function of:
a. Spinotectal tract
b. Dorsal spinocerebellar tract
c. Ventral spinocerebellar tract
d. Spino-olivary tract

46. The rubrospinal tract influence:
a. Extensor muscle tone
b. Flexor muscle tone
c. Cross extensor muscle tone
d. None of the above

47. Tract of Helweg is known as:
a. Olivospinal tract b. Reticulospinal tract
c. Vestibulospinal tract d. Cerebrospinal tract

48. The proprioceptive impulses to cerebellum via inferior olivary nucleus is carried by:
a. Spinovestibular tract
b. Spinoreticular tract
c. Spino-olivary tract
d. None of the above

49. Automatic and associated movement is controlled by
a. Thalamus b. Basal Ganglia
c. Hypothalamus d. Pineal gland

50. Progressive hepatolenticular degeneration leads to:
a. Wilson disease b. Athetosis
c. Torsion chorea d. None of the above

51. The vascular lesion in subthalamic nucleus of Luys leads to:
a. Muscular rigidity b. Athetosis
c. Hemibalasmus d. Torsion spasm

52. The function of trochlear nerve is:
a. Contraction of the superior oblique muscle
b. Contraction of the inferior oblique
c. Contraction of lateral rectus
d. Contraction of medial rectus

53. The function of abducent nerve is:
a. Contraction of lateral rectus
b. Contraction of medial rectus
c. Contraction of inferior oblique
d. Contraction of superior oblique

54. The associated nuclei involved in contraction of stylopharyngeus muscle by glossopharyngeal nerve is:
a. Nucleus of tractus solitarius
b. Spinal nucleus of trigeminal
c. Interior salivatory nucleus
d. Nucleus ambiguus

55. The function of hypoglossal muscle is:
a. Constriction of pupil
b. Contraction of gall bladder
c. Contraction of tongue
d. Contraction of spleen

56. The nerve which is responsible for contraction of sternocleidomastoid and trapezoid muscle is:
a. Vagus nerve b. Spinal accessory nerve
c. Abducent d. Olfactory

57. Spinocerebellar dysfunction produces:
a. Hypotonia and ataxia b. Resting tremor
c. Ridgidity d. None of the above

58. The delay in initiation of termination of movement is due to:
a. Vestibulocerebellar dysfunction
b. Cerebro-cerebellar dysfunction
c. Spinocerebellar dysfunction
d. None of the above

59. The thalamic nuclei involved in visual attention and visually guided movement is:
a. Midline nuclei b. Anterior group of nuclei
c. Pulvinar nucleus d. Ventromedial nuclei

60. The drug used in treatment of Parkinsonism is:
a. Penicillin b. Propanolol
c. L'dopa d. Neomercazole

61. The pesion of amygdala may produce:
a. Hyper-reflexia b. Hypotonia
c. Aphasia d. Psychic blindness

62. Bilateral temporal lobectomy may lead to:
a. Kluver-Bucy syndrome
b. Plummer-Vinson syndrome
c. Cushing syndrome
d. Lambert-Eaton syndrome

63. Bilateral ablation of parahippocampal gyrus and hipocampus may lead to:
a. Hyperphagia b. Korsakoff psychosis
c. Schizophrenia d. Kluver-Bucy syndrome

64. Horner syndrome may cause:
a. Ptosis b. Miosis
c. Hypohydrosis d. All of the above

65. The degeneration of dorsal columns in tabes dorsalis occur in:
a. Syphilis b. Tuberculosis
c. Tetany d. Cerebral malaria

66. The area of cerebral cortex involved in learning and performance of memorized sequence of movement without any visual clue:
a. Supplementary motor area
b. Medial premotor area
c. Pre supplementary motor area
d. None of the above

67. Lower motor neurons paralysis may lead to:
a. Atrophy of muscle
b. Individual muscle can be affected
c. Flacid muscle and deep tendon reflex abscent
d. All of the above

68. The upper motor neuron paralysis may lead to:
a. Muscle spastic
b. Deep tendon reflex exaggerated
c. Babinski sign present
d. All of the above

69. The sign and symptoms in melancholic depression may include:
a. Paucity of movements
b. Slowed thinking and sleep disturbances
c. Sucidal thought
d. All of the above

70. Hallucination and memory disturbances with dèjá vu phenomenon is observed in:
a. Petil mal epilepsy b. Temporal lobe epilepsy
c. Grand mal epilepsy d. None of the above

71. The common sleep disorders are:
a. Somnambulism b. Bruxism
c. Nocturnal enuresis d. All of the above

72. Narcolepsy is:
a. Sleep walking
b. Tooth grinding during sleep
c. Bed wetting during sleep
d. Irresistible urge to sleep during day time

73. The neuropeptides which increases apetile and food intake are
a. Galanin b. Orexin
c. Ghrelin d. All of the above

74. The angular acceleration that causes major motion sickness in space craft is also called:
a. Baranys effect
b. Wolf-Chaikoff's effect
c. Coriolis effect
d. None of the above

75. Removal of frontal lobe may lead to:
a. Lack of self control, distractibility and loss of memory
b. Lack of initiative
c. Disturbed orientation of time and space
d. All of the above

76. The inability to understand spoken words but able to read and write although reading is incohrent in:
a. Nominal aphasia b. Syntactial aphasia
c. Semantic aphasia d. Verbal aphasia

77. The drugs that facilitates memory are:
a. Physostigmine b. Nicotine
c. Amphetamine d. All of the above

78. Cerebrospinal fluid can be obtained by:
a. Synovial fluid aspiration
b. Peritoneal aspiration
c. Lumbar puncture
d. Amniocentesis

79. Regulation of body temperature is function of:
a. Thalamus b. Basal ganglia
c. Hypothalamus d. Cerebellum

80. Familial disorder associated with loss of taste sensation is known as:
a. Tonsillitis
b. Familial dysautonomia
c. Taste blindness
d. None of the above

81. Olfactometer of Zwaardemaker is instrument used to test:
a. Optic sensation b. Olfactory sensation
c. Taste sensation d. Pouch sensation

82. The loss of sense of smell is known as:
a. Anosmia b. Parosmia
c. Hyperosmia d. Hyposmia

83. Sectioning of occulomotor nerve may lead to:
a. Ptosis b. Crossed diplopia
c. Loss of light reflex d. All of the above

84. Sectioning of VI cranial nerve leads to:
a. Internal strabismus
b. Homonymous deplopia
c. Inability to move the eyeball outward
d. All of the above

85. Astigmatism may be corrected by use of:
a. Concare lens b. Bifocal lens
c. Cylindrical lens d. Correx lens

86. The process by which refractive error of an eye is detected?
a. Ophthalmoscopy b. Retinoscopy
c. Phacoscopy d. None of the above

87. The trichomatic theory of colour vision was proposed by:
a. Young in 1801 b. Philips in 1901
c. John in 1851 d. Vanslyke in 1801

88. The gustatory papillae of the tongue include:
a. Fungiform b. Circumvallate
c. Foliate d. All of the above

89. The excitatory neurotransmitters are all *except*:
a. Dopamine b. Glutamic acid
c. Serotonin d. Glycine

90. The inhibitory neurotransmitters are all *except*:
a. GABA b. Glycine
c. Nitric oxide d. Dopamine

91. Reward systems are in the brain are located in:
a. Midbrain b. Prefrontal cortex
c. Nucleus accumbens d. All of the above

92. Extensive growth of neuroglial tissue round the central canal of spinal cord with cavity formation occurs in:
a. Syringomyelia
b. Spina bifid
c. Tobes dorsalis
d. Disseminated (multiple) sclerosis

93. Injury at internal capsule level causes:
a. Hemiplegia b. Quadriplegia
c. Paraplegia d. Monoplegia

94. Hypotonia confered to one group of muscle (either flexors or extensors) is called:
a. Spasticity b. Plasticity
c. Ridgidity d. None of the above

95. Monosynaptic reflex is:
a. Tricep reflex b. Abdominal
c. Plantal d. Cremasteric

96. Polysynaptic reflex is:
a. Knee jerk b. Ankle jerk
c. Tricep reflex d. Withdrawl reflex

97. The receptors involved in proprioception and kinaesthesia are:
a. Muscle spindle
b. Golgi tendon organ
c. Joint receptors
d. All of the above

98. Planning and programming of movement is function of:
a. Thalamus b. Hypothalamus
c. Cerebellum d. Basal ganglia

99. The test for hearing is:
a. Yarn matching test
b. Ishihara chart
c. Rinnes test
d. Edridge-Green Lantern test

100. The test for colour vision is:
a. Rinnes test
b. Watch test
c. Edridge-Green-Lantern test
d. Weber's test

ANSWERS

1. (c)	2. (e)	3. (a)	4. (c)	5. (b)	6. (c)	7. (e)	8. (c)	9. (a)	10. (d)
11. (b)	12. (a)	13. (d)	14. (c)	15. (c)	16. (e)	17. (e)	18. (d)	19. (a)	20. (e)
21. (b)	22. (d)	23. (e)	24. (a)	25. (c)	26. (b)	27. (g)	28. (f)	29. (a)	30. (d)
31. (d)	32. (a)	33. (c)	34. (a)	35. (a)	36. (b)	37. (d)	38. (c)	39. (b)	40. (a)
41. (c)	42. (b)	43. (c)	44. (d)	45. (b)	46. (b)	47. (a)	48. (c)	49. (b)	50. (a)
51. (c)	52. (a)	53. (a)	54. (d)	55. (c)	56. (b)	57. (a)	58. (b)	59. (c)	60. (c)
61. (d)	62. (a)	63. (b)	64. (d)	65. (a)	66. (b)	67. (d)	68. (d)	69. (d)	70. (d)
71. (d)	72. (d)	73. (d)	74. (c)	75. (d)	76. (b)	77. (d)	78. (c)	79. (c)	80. (b)
81. (b)	82. (a)	83. (d)	84. (d)	85. (c)	86. (b)	87. (a)	88. (d)	89. (d)	90. (d)
91. (d)	92. (a)	93. (a)	94. (a)	95. (a)	96. (d)	97. (d)	98. (d)	99. (c)	100. (c)

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He has revised and edited of both the volumes of Chatterjee's *Human Physiology* with great amount of dedication, commitment and sincerity.

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