Textbook Of Medical Physiology

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Dedication This book is dedicated to the sweet memories of my parents Sri Ananthapura Shankaranarayanayya and Smt. Radhamma **NITTE University** (Declared as Deemed-to-be-University under section 3 of UGC Act, 1956) Deralakatte, **Mangalore-575 018 FOREWORD** I am happy to note that Dr. A.P. Krishna, Professor in the Department of Physiology, K.S. Hegde Medical Academy has brought out this book on the fundamentals of Physiology. This painstaking academic endeavor could not have come at a better time for students just seeking admissions to the first year of the MBBS course. Physiology is a basic science subject forming part of the pre-clinical curriculum. The functioning of the human body is a marvel of nature and its study is an exciting journey to all, more so, the student who has just passed Pre University and entered the portals of undergraduate learning. Dr. Krishna has made this study easy with his presentation which is informative and yet addresses the curriculum. The presence of diagrams, flowcharts and tables adds to the lucid learning to the new initiate. I commend this work and wish that Dr. Krishna adds many more books to make this learning fruitful to the young students. **N. Vinaya Hegde** Chancellor NITTE University **PREFACE TO THE SECOND EDITION** I have written a book “Textbook of Physiology” with the intention of helping the students of BDS, BPT, B.Sc. Nursing, BAMS, BHMS, B. Pharm. courses. The book was well accepted and appreciated by a large group of students and teachers. The eighth edition of the book was published in the year 2013. After the warm response of first edition, it is a great pleasure for me to present the revised updated second edition of *Textbook of Medical Physiology*. I believe that this book may have shortcomings and mistakes. I earnestly request all the students as well as experienced teachers to give your valuable suggestions. Your feedback will be used for the further improvement of the book. I place on record my sincere gratitude to Sri Nitte Vinaya Hegde, President Nitte Education Trust and Chancellor, Nitte University for his constant encouragement. I extend my sincere thanks to Dr. M. Shantharam Shetty, Pro. Chancellor, Nitte University, Dr. S. Ramananda Shetty, Vice-Chancellor and Dr. Satheesh Kumar Bhandary, Dean, K.S. Hegde Medical Academy, Mangalore for their support and blessings. I am grateful to colleagues in my department and many physiology teachers of various other medical colleges. A very special thanks to my beloved students **â€” past, present and future.** A special appreciation to Mrs. Suman Krishna, Dr. Alka, Dr. Nikhil Joshi, Mrs. Ankita, Mr. Santosh and Baby Vihaan for their constant loving support. I conclude with an optimistic note that this book will be of use for the readers. Last but not the least I am thankful to Mr. Rajan Jain, Director of Scientific International Pvt. Ltd. and Mr. Sunil K. Panda, Editor-cum-Coordinator for the tireless effort to bringing out the book in a short span of time with nice get up. 1st Aug. 2014 **A.P. Krishna** Ph. 91-9845213997, 9480227878 E-mail: apsnkrishna@yahoo.co.in **PREFACE TO THE FIRST EDITION** Several senior and junior teachers of physiology of many colleges motivated me to write a textbook for MBBS students. This motivation was strongly supported by a large number of medical students who compelled me to venture into the task of writing a book for Medical students. This culminated in writing a “Textbook of Medical Physiology”. I am happy to present the first edition of the book. I believe that this book may have shortcomings and mistakes. I earnestly request all the students as well as experienced teachers to

give your valuable suggestions. Your feedback will be used for the further improvement of the book. I am extremely happy to bring out this book on the year marked as Centenary Celebration of Founder of Nitte Education Trust, Justice K.S. Hegde and on the happy occasion of getting Deemed University status. I place on record my sincere gratitude to Dr. Nitte Vinaya Hegde, President Nitte Education Trust and Chancellor, Nitte University for his constant encouragement. I extend my sincere thanks to Dr. M. Shantharam Shetty, Vice-Chancellor, Nitte University and Dr. Arunachalam Kumar, Dean, K.S. Hegde Medical Academy, Mangalore for their support and blessings. I am grateful to colleagues in my department and many Physiology teachers of various other Medical colleges. A very special thanks to my beloved **students â€" past, present and future.** This textbook is presented to **Sri N. Vinaya Hegde, Chancellor, Nitte University** on the occasion of Centenary Celebration of founder of Nitte Education Trust, Justice K.S. Hegde. A word of gratitude of Mr. Nagaraja M. of Gayathri Printing Press for his role in printing and Mrs. Suman Krishna of M/s Suman Publications for taking the responsibility of publishing. I conclude with an optimistic note that this book will be of use for the readers. Mangalore 15-06-2009 **Dr. A.P. Krishna** Professor Deptt. of Physiology K.S. Hegde Medical Academy Mangalore-18 **DETAILED CONTENTS**

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Ayurveda **Sushruta** 6th Century B.C. Indian Physician cum Surgeon Famous for Plastic surgery, Cataract surgery, Rhinoplasty **William Francis Ganong** Physiologist, Endocrinologist and Neurobiologist **(2) Luigi Galvani** 9-09-1737–4-12-1798 Italian Physician Known for Bioelectricity **Professor B.K. Anand** 18-9-1917–2-4-2007 Indian Physiologist Known for discovering feeding centre in hypothalamus **Jens Christian Skou** 8-10-1918 Danish Biochemist and Doctor Known for Sodium Potassium ATPase Nobel Prize (1997) **Claude Bernard** 12-07-1813–10-02-1878 French Physiologist Famous for the term 'Homeostasis' **Chapter 1 INTRODUCTION AND GENERAL PHYSIOLOGY PHYSIOLOGY INTRODUCTION** The term **â€œPhysiologyâ€•** was originally derived from a Greek root with Latin equivalent Physiologia which means natural knowledge. Now the term Physiology means a branch of science dealing with the study of functions of living organisms, as a whole or its individual parts. Physiology deals with the study of body functions. It can be attempted at various levels. Cellular level or cell physiology, Organ level, Tissue level, System level, Whole body level, Physiology aims at studying the dynamic relationship among different organs, tissues and systems. The harmonious functions of various organs are the basis of normal life. The aim of physiology is to explore the sum total of functions of these different organs and their individual actions culminating in life. Like in any branch of science, continuous research activities are taking place in physiology throughout the world. Attempts were made to understand various complex mechanisms and their interactions. This leads to the expansion of frontier of knowledge in physiology. This generates the need for specialization and super specialization of subjects. Several newer branches of physiology were already evolved. 1. Animal physiology and comparative animal physiology. 2. Experimental physiology. 3. Clinical physiology. 4. Psychophysiology or Behavioural physiology. 5. Neurophysiology. 6. Environmental physiology. 7. Sports physiology. Physiology in general is the discipline that deals with the bodily functions and their control. It is a mechanistic view of life and it tries to explain life in terms of different physical and chemical processes. In physiology we mostly discuss normal body functions. However, a student who later is likely to become a member of a medical team in life deals with abnormal people – or patients. Therefore it is quite natural to have a doubt about the need of studying normal physiology. It is a must to know what are the normal functions and activities of a body and parts of a body, then only one can detect any deviation from normal. Without knowing what is normal. One cannot say what is abnormal. It is also needed to evaluate the extent of variation, the cause for it, to decide a means of bringing back the situation to the normalcy by a suitable treatment. By the term normal we do not mean a single rigid figure or a fixed line. It always means a range, for example one may say normal body temperature is 98.6°F, but it does not mean that fixed figure. Even in a healthy person, body temperature may vary from 97.6°F – 99.6°F. This type of variation is physiological variation. Body has a built-in mechanism to bring back the deviated condition to the normal state. It is a complex feed back control mechanism which maintains a constant internal environment. Maintenance of a constant internal environment is termed as milieu interieur in French Later Walter Cannon coined by Claude Bernard. Human body is a mass of living cells. These cells are bathed in extracellular fluid ECF and these cells are filled with intracellular fluid ICF. The composition, volume osmolality, pH, and temperature of ICF and ECF are kept constant, inspite of changes in the environmental factors. There are factors which try to destabilize it. As long as body is able to maintain its constant internal environment, there is no disease and there is no need of any treatment. The moment this mechanism fails, external intervention is needed in terms of treatment – physical, chemical or surgical. Hormone Gland Target tissue Inhibition with a mechanism to correct the variable. The elevation in body temperature can be detected by thermoreceptors present in the body, they send this information to hypothalamus. Hypothalamus in turn initiates corrective steps so that the increased body temperature is brought down to normal. Corrective measures may include sweating, vasodilatation etc. As long as this homeostatic control mechanism is functional no disease or disorder. If it fails it will result in dysfunction. Product —Negative feedback mechanism Hormone Internal stimuli Homeostasis Normal state Constant physiological and biochemical state External stimuli Gland Target tissue Disturbance or upset in balance + Product —Positive feedback mechanism Alteration in physiological & biochemical variables **Fig. 1.1 Feedback mechanism**

Homeostasis regulatory mechanisms Homeostasis is the stability of the internal environment. But there are various environmental and physiological parameters that influence the destabilization of the constancy of internal body environment. Imbalance in the constant internal environment may lead to some organ or system dysfunction. Therefore, in our body there are various controlling mechanisms which tend to maintain the homeostatic state of the body. Among that negative and positive feedback mechanisms play prominent role. **Homeostasis** It is very important to know how the homeostasis of various physiological and biochemical variables is achieved. It is also required to understand how the disturbances in these homeostatic regulations may result in various dysfunctions and disorders. Once this fundamental mechanisms are understood it will be easier to interfere and manipulate the variables so that homeostasis is brought back to the normal. That is the guiding principle of treatment of a disease or disorder. Usually homeostatic regulatory mechanism has got two components. First one to detect the deviation in the physiological variables. Secondly to correct the variables, so that normally is restored. For example, when body temperature increases beyond the normal level, normal level is commonly referred as set point, there should be a mechanism to detect the change in the variable followed Change in variables is detected by receptors Response by organ or Organs Altered variable is brought back to normal state If fails Homeostasis reestablished Leads to disease or disorder Needs treatment that is external support to restore normally **Fig. 1.2 Positive feedback:** This feedback mechanism is known to exaggerate the rate of process or reactions. Therefore, this control mechanism does not operate to provide homeostasis. For example, during the process of child birth (delivery), the head of fetus presses the cervix, this stimulus distend the cervix, which in turn send the feedback to the posterior lobe of pituitary gland, after analyzing the signals pituitary gland releases the hormone oxytocin, which increases the force of uterine muscle contraction this helps to further pushing of the fetus towards cervix, this cycle increases the secretion and release of more and more oxytocin till the fetus is delivered. In positive feedback mechanism the stimulus and the response or the cause and the effect are operating in the same direction. In such mechanisms an increase in a particular physiological variable respond which further increases the variable. This type of control mechanism do not operate to provide homeostasis classical example. During irreversible stage of haemorhagic shock. Cardiac output has diminished to a very low level. Coronary blood flow falls— oxygen supply to cardiac muscles decreases. This will further decrease the force of contraction of heart, decrease stoke volume, further decrease cardiac and put—go on and on leading to death. Some other examples for positive feedback mechanism. 1. Luteinizing hormone secretion: During preovulatory phase oestrogen stimulates this secretion of LH from anterior pituitary 2. Action of trypsin: Once a small quantity of trypsin is formed from trypsinogen in the small intestine, all remaining inactive enzymes are activated 3. Activation of blood clotting factors one after the other. **Negative feedback:** This feedback mechanism is known to slow down the rate of process or reactions. Therefore, homeostatic regulation is generally achieved through negative feedback mechanism. *For example:* If particular hormone concentration in blood increased beyond the normal level, this immediately send the negative signals to that specific endocrine gland to cease the further secretion of that hormone so as to maintain the normal hormonal level in the blood. This mechanism also called as corrective mechanism because it initiates the action which directly opposes a variation from normal limits. Another example for negative feedback mechanism is restoration of body fluid volume. Suppose a person plays outdoor game under hot sun. He will be losing water leadsing to dehydration. This will increase the osmotic concentration of blood. Elevation of osmotic concentration will stimulate the osmo receptors of hypothalamus. This will produce the sense of thirst. Thirst leads to water intake. Absorption of water from the intestine to blood restores the fluid. Increase in the osmotic concentration of blood is the stimulus. Drinking of fluid is the response. Response nullifies the stimulus. This is a negative feedback mechanism. The secretion of most of the hormones are controlled by negative feedback mechanism. For example hypothalamus secretes a small peptide— Thyrotropin Releasing Factor, TRF. This will stimulate the anterior pituitary to secrete more of thyroid stimulating hormone TSH. TSH in-turn stimulate and increase the secretion of thyroxin from thyroid gland. Increase in the plasma concentration of thyroxin will in-turn exhibit inhibition at the level of hypothalamus and

anterior pituitary. Because of this secretion of all the hormones in this hypothalamo-hypophyseal-thyroid axis are inhibited. Hypothalamus – TRF Anterior pituitary – TSH + Thyroid gland Thyroxine **Fig. 1.3** The common approach of studying Physiology is system wise. System is a group of organs and structures concerned with a common body functions. 1. Circulatory system or Cardiovascular system 2. Respiratory system 3. Excretory system 4. Digestive system 5. Endocrine system 6. Nervous system 7. Special senses 8. Musculo-skeletal system 9. Reproductive system Each system is composed of a set of inter connected and interdependent organs which act together for a common purpose, which is not possible by any one of them alone. However, it should be remembered that any system can perform their designated duties only with harmonious coexistence with other systems but cannot do anything in isolation. An organ, *e.g.,* heart, is a structural unit of the body. An organ is composed of different tissues and serves a specific function. Tissues are a group of similarly specialized cells which together perform a certain specific function. Basically there are four types of tissues—Muscular, Neural, Epithelial and Connective tissue. Tissues are made of cells and function of tissues is function of cells. **GENERAL PHYSIOLOGY** Body is made of several individual systems. Human physiology is studied by dealing with the study of one system after another. All these systems function on the basis of some fundamental physical and chemical principles and processes which are common to all of them. General physiology includes these fundamental principles which help to understand the activities of individual systems. **Cell Physiology** A typical cell, Cell membrane, Cell organelles. Membrane transports: Diffusion, Osmosis, Active and Passive transport, Endocytosis, Exocytosis, Phagocytosis. Membrane potentials Resting membrane potential, Action potential, properties, Phases, Ionic basis. Osmolarity, Osmolality, Nernst equation, Equilibrium, GibbsDonnan membrane. Apoptosis, dehydration derhydration. **Cell Physiology** Cell is the basic structural and functional unit of the body. This concept was first proposed by Schleiden and Schwann. Living organism is a society of cells. At birth number of cells is about 2 × 1012 and in adult number of cells is about 6 × 1013. Major types of cells are nerve cell, muscle cell, red blood cell, gland cell and immune cell. Cell is composed of cell membrane surrounding the protoplasm cell. Cell = Cell membrane *plus* protoplasm. Protoplasm = Cytoplasm *plus* nucleus. **A typical cell: Cell membrane:** It is a thin, elastic semipermeable membrane, enveloping the cell. It separates extracellular fluid from intracellular fluid. It is also called plasma membrane. It has a thickness of 7.5–10 nm. **Compostion:** - Lipid bilayer. - Protein (intrinsic, and extrinsic and transmembrane). - Carbohydrates [5%]. Smooth endoplasmic reticulum Centrioles Ribosomes Mitochondrion Smooth endoplasmic reticulum Lysosome Rough endoplasmic reticulum Nuclear membrance Nucleus Nucleolus **Fig. 1.4** Normal cell structure Extrinsic Extracellular fluidproteins Carbohydrate Golgi apparatus Microvilli Hydrophilic head Transmembranous Intrinsic protein Cytosol Phospholipid bilayer **Fig. 1.5** Plasma membrane Hydrophobic tail **Lipid Bilayer** The two major lipids are phospholipids and cholesterol. The lipid layer is fluid in nature, floats and substances dissolved in it also floats along with it. **Lipid bilayer is amphipathic layer** Phospholipid molecule is composed of polar hydrophilic head and non-polar, hydrophobic, hydrocarbon tail end. The tail ends of two layers are facing each other at centre. **Functions:** 1. Contributes to semi-permeability and selective permeability nature of cell membrane. It is permeable to fat soluble substances like oxygen, carbon dioxide etc. It is impermeable to water soluble substances like glucose, urea, ion etc. 2. Cholesterol: It gives structural stability to cell membrane. **Carbohydrate layer:** Carbohydrates are found in combination with lipid or protein and hence called glycolipids or glycoproteins respectively. It is called Glycocalyx. Carbohydrates may be also present in the form of proteoglycans. **Functions:** 1. It forms connection for adjacent cells and links adjacent cells together by membrane junctions. 2. This layer is negatively charged. Hence repels negatively charged substances. 3. They form receptors for binding of some hormones. 4. They take part in immunological reactions. 5. Carbohydrate present on RBC membrane help to form blood group antigen. **Protein layer Intrinsic**—attached to inner surface of membrane. **Extrinic**—present at outer surface. **Transmembrane**—extends from outside to inside. **Functions:** 1. They consist of protein channels for the permeability of ions and water soluble substances. 2. Help in transmission of impulses. 3. Provide structural integrity to cell. 4. Some proteins function as enzymes. 5. Some

proteins form receptors for hormone. 6. Some proteins act as carriers for the transportation of substances from one side to other side. **Overall Functions of Cell Membrane** 1. Forms protective covering of cell. 2. Shows selective permeability and semipermeability. Detect chemical messengers arriving at the cell surface. 3. Determines the shape and size of cell. 4. Helps in generation and maintenance of transmembrane potential. 5. Facilitates in exchange of gases. 6. Also help in transport of macromolecules (pinocytosis and phagocytosis). 7. Absorption of nutrients and excretion of metabolic wastes. 8. Regulate the passage of substances into and out of the cells. The plasma membrane is not **solid but fluid** structure. The proteins embedded in it gives it the mosaic appearance and hence this model of cell membrane is called Fluid mosaic model. (Singer and Nicolson 1972) **Cytoplasm** is the fluid present inside cell. Cytoplasm consists of: 1. Cell organelles 2. Chemical contents (a) Water — 70–85% (b) Protein — 10–20% (c) Carbohydrate 6% (d) Fats — 2–4% (e) Electrolytes — small amounts. *e.g.,* K+, sulphates which help in maintaining membrane potential across the cell. **1. Mitochondria** It is called power house of cell. **Shape :** The mitochondria is rod shaped or oval. **Size :** Size varies from 0.2–0.5 micron. **Number :** It varies. A single cell of liver may have as many as 2,500 mitochondria **Structure :** Double layered membrane. Inner layer has folds called cristae which increase surface area for enzymatic reaction. – The stalked particles attached to mitochondria are called Racker's particles. – Matrix contain RNA and mitochondrial DNA **Functions:** – It plays a very important role in cellular respiration and generation of energy as ATP. – Various metabolic reactions take place in mitochondria, *e.g.,* Krebs cycle, Urea cycle. **2. Endoplasmic reticulum (ER)** It is the extensive network of interconnected sacs or tubes found in cytoplasm of majority of Eukaryotes. It is lined by a single layered unit membrane. Endoplasmic reticulum of muscle cells is called **Sarcoplasmic reticulum.** **Classification:** There are two types based on presence or absence of ribosomes attached to their surface. Outer membrane Inner membrance Cristae Ribosomes Secretary vesicles Cisternae **Mitochondrion** Golgi body DNA Matrix Nucleolus Ribosome Small subunit Nucleo plasm Nucleo pores **Nucleus** Large subunit Ribosome Rough endoplasmic reticulum **Fig. 1.6** Cell organelles **1. Rough endoplasmic reticulum (RER)** Ribosomes are attached to their surface and thus makes the surface rough. – Since ribosomes are present the major function is biosynthesis of protein. **2. Smooth endoplasmic reticulum** Ribosomes are absent—Cholesterol synthesis takes place here. **Functions of endoplasmic reticulum** 1. Biosynthesis of protein (RER). 2. Synthesis of cholesterol and other steroids (SER). 3. The tubular space within the ER functions as a intracellular transport system for ions within the cell. 4. It provides site for storage of product. 5. It functions as cytoskeleton. **3. Golgi body** It consists of a few flattened sacs and tubes placed one over other. Flattened sac is called Cisternae. **Functions:** 1. Processing of protein synthesized by ribosomes and ER. It modifies and packs the protein. 2. It later give rise to acrosome in male germ cells. 3. It give rise to lysosomes. **4. Lysosomes** They are called suicide bags of cell. They are vesicle—like organells present through out the cell. They arises from the Golgi body. They contain digestive enzymes called hydrolases. **Functions:** – Digestion of nutrients intracellularly – Destruction of bacteria and other foreign body. Thus protects the cell. – Digestion and removal of old, worn out and dead cells of the tissue (Auto digestion). **5. Ribosomes** Ribosomes are called protein factory of cells. There are two types: 1. Bound ribosomes (attached to RER) and 2. Free ribosomes. **Ribosomes size:** It is expressed in Svedberg unit. It is 70S for prokaryotes and 80S for eukaryotes. Each 80S ribosome is made up of two subunits of 40S and 60S. **Function:** It plays a very important role in translation process of protein synthesis **6. Centrioles** They are two cylindrical rods which appear during cell division. **Functions:** It helps in the formation of spindle fibres and direct the chromosomes during cell division. **7. Cytoskeleton** Plays a very important role in maintaining the structure and shape of the cell. It is a complex set of rods that act as supporting structure They are of two types 1. Microfilament 2. Microtubules. **Microtubules:** Made up of protein called tubulin. **Functions:** 1. Formation of spindle fibre. 2. Structural stability to cells. 3. Intracellular transport of ions. **Microfilament:** Made up of action and myosin filament. These are contractile proteins and plays a very important role in muscle contraction. **8. Nucleus** It is the master of cell organelles. The nucleus is spherical and situated at the centre of the cell. **Nuclear membranes:** Double layered membrane with pores called nucleopores. Exchange of materials between nucleus and

cytoplasm occur through these pores. **Nucleoplasm** It is the ground substance of nucleus. It is called karyolymph or nuclear sap. It contains enzymes and other substances required for synthesis of RNA and DNA. **DNA:** It is the genetic material which contain stored hereditary information. RNA and DNA are together responsible for protein synthesis. DNA contains information for the protein to be synthesized and hence direct the protein synthesis and RNA regulates the synthesis of protein. **Nucleoli** It is darkly stained structure within the nucleus. It is the site for synthesis of ribosomes. **Cell junctions** In between the adjacent, epithelial cells there is usually an association, this is known as a junction. The junctions between the two adjacent cells can be of several types such as: **Gap junction** The membranes of adjacent cells lie very close to each other, and this gap is filled with densely packed particles through each of which are connected by a sort of channel. It permits movements of molecule from one cell to another cell. Gap junctions mainly found in cardiac and smooth muscles which facilitate rapid propagation of electrical changes from one cell to another cell. Gap junction **Fig. 1.7** Gap junction **Desmosome** In between the two membranes of the adjacent cells, there is small gap; this gap is filled with accumulation of dense proteins and the fibers extending from the each membrane. This type of junctions mainly present in skin, which is regularly subjected for tensile stress (physical stretching). Extra cellular space Cell membrance **Fig. 1.8** Desmosome **Tight junctions** The cell membranes of the adjacent cells are fused together. This type of the junctions acts as a barrier and prevents the movements of ions or molecules from one cell side to the other cell. Tight junctions mainly present at choroid plexus, intestinal mucosal layer and renal tubules. Tight Proteinjunctionridges **Fig. 1.9** Tight junction **Cellular receptors** Cells receive information from outer environment through a class of proteins known as receptors. Notch is a cell surface protein that functions as a receptor. Animals have a small set of genes that code for signaling proteins that interact specifically with Notch receptors and stimulate a response in cells that express Notch on their surface. Molecules that activate or in some cases, inhibit these receptors can be classified as hormones, neurotransmitters, cytokines, growth factors but all of these are called receptor ligands. The details of ligand-receptor interactions are fundamental to cell signaling. Other signaling molecules are unable to permeate the hydrophobic cell membrane due to their hydrophilic nature, so their target receptor is expressed on the membrane. When such signaling molecule activates its receptor, the signal is carried into the cell usually by means of a second messenger such as cAMP. **Cell signaling** Cell signaling is part of a complex system of communication that governs basic cellular activities and coordinates cell actions. The ability of cells to perceive and correctly respond to their microenvironment is the basis of development, tissue repair, and immunity as well as normal tissue homeostasis. Errors in cellular information processing are responsible for diseases such as cancer, autoimmunity, and diabetes. **Intercellular communications** Cells communicate with each other via direct contact known as juxtacrine signaling, over short distances called as paracrine signaling, or over large distances and/or scales termed as endocrine signaling. Some cell-to-cell communication requires direct cellcell contact. Some cells can form gap junctions that connect their cytoplasm to the cytoplasm of adjacent cells. In cardiac muscle, gap junctions between adjacent cells allows for action potential propagation from the cardiac pacemaker region of the heart to spread and coordinately cause contraction of the heart. Many cell signals are carried by molecules that are released by one cell and move to make contact with another cell. Endocrine signals are called hormones. Hormones are produced by endocrine cells and they travel through the blood to reach all parts of the body. Specificity of signaling can be controlled if only some cells can respond to a particular hormone. Paracrine signals target only cells in the vicinity of the emitting cell. Neurotransmitters represent an example. Some signaling molecules can function as both a hormone and a neurotransmitter. **Intracellular communications** Receptor activation caused by ligand binding to a receptor is directly coupled to the cell's response to the ligand. The entire set of cell changes induced by receptor activation is called a signal transduction mechanism or pathway. A more complex signal transduction pathway involves changes of protein-protein interactions inside the cell, induced by an external signal. Many growth factors bind to receptors at the cell surface and stimulate cells to progress through the cell cycle and divide. Several of these receptors are kinases that start to phosphorylate themselves and other proteins when binding to a ligand. This phosphorylation can

generate a binding site for a different protein and thus induce protein-protein interaction. Other signaling molecules are unable to permeate the hydrophobic cell membrane due to their hydrophilic nature, so their target receptor is expressed on the membrane. When such signaling molecule activates its receptor, the signal is carried into the cell usually by means of a second messenger such as cAMP. Signal transduction pathways provide opportunities for feedback, signal amplification, and interactions inside one cell. **TABLE 1.1 Different Transport Mechanism** Passive transport Active transport Transport of macromolecules Diffusion Osmosis Primary Secondary Pinocytosis Phagocytosis Simple Facilitated diffusion diffusion Sodium Sodium counter cotransport transport **Membrane Transport** Membrane The major types of mechanisms for transport across the cell membrane are: 1. Passive transport—which requires no energy. 2. Active transport—requires energy. 3. Macromolecular transport. Passive transport may be in the form of diffusion or osmosis. **Diffusion:** Movement of solute particles from a region of higher solute concentration to a region of lower solute concentration along the concentration gradient due to the Brownian movement of molecules. It is down hill movement and does not require energy. Diffusion is of two types: (a) Simple (b) Facilitated. **Simple diffusion** is without the involvement of any carrier proteins, by random movement of particles through lipid layer or protein channels [membrane pores or gaps]. **Facilitated diffusion:** Substance binds with a carrier protein and conformational changes occur in that protein molecule and then the substance will diffuse. Plasma Cytoplasm Carrier D-glucose Sugar / carrier complex **Fig. 1.10** Facilitated diffusion **Simple diffusion through lipid layer** Fat soluble substances (like O2, CO2) diffuse through the lipid layer. **Factors determining diffusion** 1. **Permeability:** Which inturn, depends on (a) Thickness—more thick membrane less diffusion. (b) Cross sectional area—directly proportional. (c) Presence of protein channels. (d) Molecular weight of substance to be diffused —More the molecular weight more will be the resistance for its movement and hence less permeability. (e) **Diffusion coefficient** (expression for permeability) D = permeability × area of cross section. (f) Temperature—Increase in temperature increases the thermal motion of the molecules and hence increases the permeability. (g) Solubility—Fat soluble substance can be easily diffused. 2. **Concentration gradient** More the concentration, gradient more is the diffusion. Other types of gradient are pressure gradient and electrochemical gradient. 3. **Ionic charge:** Increase in negativity decreases the permeability and hence decreases the rate of diffusion. It is true for positivity too. *dc*Fick's law J = □D*dx* J = rate of diffusion A = area of cross section X = thickness D = diffusion coefficient C = concentration **Diffusion through protein channels** Membrane protein provides aqueous pathways for different ions. They are of two types: 1. Leak channels 2. Gated channels **Leak channels** are always open and diffusion through them cannot be controlled. *e.g.*, K+ leak channels. **Gated channels:** They open and close when required and diffusion through them can be controlled. They are: 1. Voltage gated channels [influenced by change in voltage] 2. Ligand gated channels [influenced by hormones] 3. Mechanically gated channels. **Factors affecting are:** 1. Molecular weight 2. Rate of kinetic movement of substance. **Facilitated diffusion** (for water soluble substances and substances with larger molecular weight), it is also called carrier mediated diffusion. **Example:** Transport of glucose and other monosaccharides and amino acids in proximal convoluted tubules. **Properties:** 1. Carrier proteins with binding sites are specific for transport of a particular substance. 2. Saturation: Rate of diffusion increases with increase in solute concentration upto a certain extent after which it shows saturation. 3. Inhibition (competitively) **Osmosisâ€"Definition:** Movement of water and other solvent molecules from a region of lower solute concentration to a region of higher solute concentration across a semipermeable membrane. **Or,** Movement of water or other solvent molecules from a region of higher solvent concentration to a region of lower solvent concentration across a semipermeable membrane. In the cell plasma membrane act as semipermeable membrane for osmosis. **Osmotic pressure:** It is the hydrostatic pressure required to stop osmosis from one compartment to another. It is directly proportional to number of solute and inversely proportional to volume of solvent. It is also influenced by the temperature. **Solvent drag:** During bulk flow of solvent it carries along with it some solutes (ions) passively and this is called solvent drag. **TABLE 1.2 Comparison between diffusion and osmosis S.No. Diffusion Osmosis** 1. Movement of ions or

particles from a region of higher Movement of solvent particles from its region of higher concentration to a region of lower concentration. concentration to the region of lower concentration through a semipermeable membrane. It is diffusion through semipermeable membrane. 2. It can be facilitated by using a carrier (Carrier– mediated). It cannot be facilitated. 3. It can be stopped only by separating the two media when It can be stopped by applying a suitable pressure (osmotic the gradient is present. pressure). 4. Concentration difference, or electric potential difference Concentration difference for solvent across a membrane or pressure difference are mainly responsible for impermeable to solute is responsible for osmosis. diffusion. **Active transport** Movement of solute particles from a region of higher concentration to a region of lower concentration is called active transport. It requires energy expenditure. Energy is supplied by break down of ATP. It occurs against concentration gradient and hence called uphill movement. It requires carrier protein. **Two types:** 1. Primary active transport 2. Secondary active transport **Primary active transport** In primary active transport the transport occurs by the direct utilisation of energy (hydrolysis of ATP and other high energy bonds). *Example:* Sodium Potassium ATPase pump. The carrier protein of Sodium Potassium ATPase pump has six binding sites, three for sodium, two for potassium and one for ATPase which breaks down the ATP. Transfer of three sodium ions occur in exchange for two potassium ions with expenditure of energy. Sodium moves from inside of the cell to outside and potassium moves in. This is responsible for generation and maintenance of membrane potential and hence this pump is called **Electrogenic pump. Mechanism of transport** The substance (molecule or ion) to be transported first attaches itself or binds to the carrier protein which activates ATPase and ATP is hydrolysed. This causes conformational changes in the protein molecule and outer surface of the protein faces inside and inner surface faces outside and the substance is liberated. **Secondary active transport:** Also called exchange transport. Transport of molecules or ions in opposite direction with the help of carrier protein with the utilisation of energy. *Example:* 1. HCO and Cl counter transport3 2. Na+ and H+ counter transport Co-transport of ions can also exist in similar manner *e.g.*, Na+ and glucose co-transport. Transport protein ADP ATP Extracellular Pifluid Pi Membrane Intracellular fluid Transported solute **Fig. 1.11** Primary active transport Extracellular fluid High Na+ Low glucose Intercellular fluid Low Na+ High glucose Extracellular fluid High Na+ Low glucose Intercellular fluid Low Na+ Low H+ **Co-transport Counter transport Fig. 1.12** Carrier mediated transport **TABLE 1.3 Comparison between active and passive transport S.No. Active transport Passive transport** 1. Transport is against concentration gradient. Transport is along the concentration gradient. 2. Incurs expenditure of energy. Energy is not required. 3. Shows saturation. 4. Specificity: Specific for particular molecules. 5. Shows competitive inhibition. Related molecules can inhibit transport of another molecule by this process. No saturation. The process continues till an equilibrium is obtained except in facilitated diffusion. No such specificity. No such competitive inhibition is seen. **Transport of macromolecules** Endocytosis and exocytosis are two types of mechanism for transport of macromolecules. Extracellular fluid Solid material Plasma membrane Phagosome Liquid material Plasma membrane Pinosome Plasma membrane Cytoplasm Cytoplasm Cytoplasm A. Phagocytosis **Fig. 1.13** Transport of macromolecules B. Pinocytosis **Endocytosis (into the cell) is of two types:** 1. Pinocytosis—Cell drinking 2. Phagocytosis**â€"**Cell eating **Pinocytosis:** The macromolecule to be transported binds to receptors on the cell membrane. The membrane then dips or invaginates. The membrane finally covers it. The substance is now enclosed by a part of membrane as a bubble. It is called pinocytic vesicle which breaks off from cell membrane and later acted upon by lysosomes. **Phagocytosis:** It occurs in the same way as pinocytosis. The bubble is called phagocytic vesicle. The process is seen in protozoans (*e.g.,* amoeba) and lower metazoans (*e.g.*, sponges). In man such a process is used by white blood cells (WBCs) and connective tissue called phagocytes. **Exocytosis:** By this process the intracellular substances are released into the surrounding tissue. *Example*—is the release of neurotransmitters (which is stored as secretory granules in vesicles) from nerve endings. The molecule binds to the inner surface of plasma membrane. At this place the cell membrane evaginates forming vesicle which is later pinched off. +30 Spike potential +20 Overshoot +10 0 –10 –20 –30 –40 –50 Firing –55 level –60 Point of stimulus –70 After deporisation Latent After period hyperpolarisation Time (ms)

Absolute refractory Reflectiveperiod refractory period **Fig. 1.14** Action potential It is a property shown by nerves and muscles. Excitability is defined as ability to respond to a stimulus by way of generating an action potential. Stimulus means a change in the energy level. Resting membrane potential (RMP) is defined as the potential difference or voltage difference existing between inside and outside of a nerve membrane when it is at rest. Normal RMP is –70 mv to –90 mv. RMP is due to unequal distribution of ions between inside and outside nerve membrane. There is more sodium ions and chloride ions outside the nerve membrane whereas K**+** and negatively charged protein ions are more inside the membrane. This unequal distribution of ions are due to the following reasons: 1. Operation of sodium potassium pump—It is an active transport mechanism. It involves carrier proteins and requires energy expenditure. 2. Permeability of membrane to potassium ions is greater than sodium ions. 3. Presence of net negatively charged non-diffusable protein ions inside the membrane. When the nerve is stimulated the permeability of membrane changes. It becomes more permeable to sodium ions. Na+ rush from outside to inside of membrane. This is known as sodium influx. Entry of positively charged ions make the inside of the membrane more and more positive, less and less negative. The polarity is lost. This phase is depolarisation. For a fraction of a second the inner side of the membrane becomes positive (+30 mv.) But once again polarity is reestablished. This phase is known as repolarisation. Action potential is defined as a changing potential taking place across the membrane with depolarisation followed with repolarisation spreading along the length of nerve membrane. One osmol is the osmotic pressure exerted by one molar solution. Osmolarity—Number of osmoles per liter of solution. Osmolality—Number of osmoles per kilogram of solvent. Osmolarity is important for regulation of cell volume. If a cell is surrounded by a solution the osmolarity of which is lower than that of the intracellular fluid (hypotonic solution) water enters the cell. Swelling it up and sometimes rupturing it. On the other hand, if the cell is surrounded by a hypertonic solution. Water leaves the cell making it shrunken. Therefore the cell should always be surrounded by an interstitial fluid the osmolarity of which is the same as that of the intracellular fluid (isotonic solution). The homeostatic mechanisms for regulation of body fluid volume and osmolarity are coupled. Relationship between osmolarity and osmotic pressure. At 37°C, 1 milliosmole/L. Hence their osmotic pressure = 300 × 19.3 = 5790 mmHg. However, the actual osmotic pressure is about 6% less. *i.e.,* about 5500 mmHg. The reason for the discrepancy is that many oppositely charged ions, *e.g.,* sodium and chloride ions, attract each other. Therefore a sodium chloride molecule actually exerts slightly less than double the osmotic pressure exerted by one molecule of an unionised molecule. **Nernst equation** One useful application of the Nernst equation is determining ion concentration. If you know the concentrations of all but one species and the voltage, you can get the concentration of the final species. This is how pH meters work: the unknown concentration is (H+), and they simply measure the voltage in the cell. The Nernst equation isIF $E = E0 - RT$] ln (Q)HnFK The reaction quotient Q has the form and value PH2*Fe+2 Q =+ 2H Q = 10500 H+ 2 Where, if the temperature of the reaction at 25oC, the term RT/F is 0.0257 V.F I bgGRT] ln$E = E0$ ⊞H F nFK I F05 I 0.389 = 0.409 – G0 0257J*lnG[H+]2J FH2 05I K H K 1.556 = lnG[H]+ 2J H K 054.74 =[H+]2 [H+] = 0.325 M **Gibbs-Donnan Equilibrium** The Gibbs–Donnan equilibrium is a phenomenon of solutions that contributes to the formation of an electrical potential across a cell membrane. The Gibbs-Donnan equilibrium (Donnan effect) is a name for the behavior of charged particles near a semi-permeable membrane to sometimes fail to distribute evenly across the two sides of the membrane. The usual cause is the presence of a different charged substance that is unable to pass through the membrane and thus creates an uneven electrical charge. For example, the large anionic proteins in blood plasma are not permeable to capillary walls. Because small cations are attracted, but are not bound to the proteins, small anions will cross capillary walls more readily than small cations. **Dehydration** Dehydration occurs when the amount of water leaving the body is greater than the amount being taken in. The body is very dynamic and always changing. This is especially true with water in the body. The body is able to monitor the amount of fluid it needs to function. The thirst mechanism signals the body to drink water when the body is dry. As well, hormones like anti-diuretic hormone (ADH) work with the kidney to limit the amount of water lost in the urine when the body needs to conserve water. Effects may include headaches

similar to what is experienced during a hangover, muscle cramps, a sudden episode of visual snow, decreased blood pressure (hypotension), and dizziness or fainting when standing up due to orthostatic hypotension. Untreated dehydration generally results in delirium, unconsciousness, swelling of the tongue and in extreme cases death. Dehydration symptoms generally become noticeable after 2% of one's normal water volume has been lost. Initially, one experiences thirst and discomfort, possibly along with loss of appetite and dry skin. This can be followed by constipation. Athletes may suffer a loss of performance of up to 30% and experience flushing, low endurance, rapid heart rates, elevated body temperatures, and rapid onset of fatigue. Symptoms of mild dehydration include thirst, decreased urine volume, abnormally dark urine, unexplained tiredness, irritability, lack of tears when crying, headache, dry mouth, dizziness when standing due to orthostatic hypotension, and in some cases can cause insomnia. In moderate to severe dehydration, there may be no urine output at all. Other symptoms in these states include lethargy or extreme sleepiness, seizures, sunken fontanel (soft spot) in infants, fainting, and sunken eyes. **Overhydration** Overhydration occurs when the body takes in more water than it loses. Overhydration can occur, for example, when athletes drink excessive amounts of water or sports drinks to avoid dehydration, or when people drink much more water than their body needs because of a psychiatric disorder called psychogenic polydipsia. The result is too much water and not enough sodium. **Apoptosis** Apoptosis is a process of programmed cell death in which body cells die and get absorbed. Sometimes it is called as cell suicide. Apoptosis, or programmed cell death, is a normal component of the development and health of multicellular organisms. Cells die in response to a variety of stimuli and during apoptosis they do so in a controlled, regulated fashion. This makes apoptosis distinct from another form of cell death called necrosis in which uncontrolled cell death leads to lysis of cells, inflammatory responses and, potentially, to serious health problems. Apoptosis, by contrast, is a process in which cells play an active role in their own death that's why apoptosis is often referred to as cell suicide. Upon receiving specific signals instructing the cells to undergo apoptosis a number of distinctive changes occur in the cell. A family of proteins known as caspases is typically activated in the early stages of apoptosis. These proteins breakdown or cleave key cellular components that are required for normal cellular function including structural proteins in the cytoskeleton and nuclear proteins such as DNA repair enzymes. The caspases can also activate other degradative enzymes such as DNases, which begin to cleave the DNA in the nucleus. Apoptosis is a natural phenomenon which plays an important role during embryonal development such as degeneration of many tissues like web in the fingers, death of neurons during brain development. Also in adulthood, apoptosis responsible for shedding of villi of small intestine and in female it helps in cyclical shedding of endometrium during the time of menstruation. Uncontrolled apoptosis may lead to number of degenerative diseases and cancers. ***Blood*** **Karl Landsteiner** 14-06-1868–26-6-1943 Austrian Biologist & Physician Discovered ABO and Rh Blood group Nobel Prize (1930) **Erik Adolf Von Willebrand** 01-02-1870–12-09-1949 Finland Medical Doctor Famous for his study of blood clotting disorders Von Willebrand disease **Metnikoff** 16-5-1845–15-7-1916 Russian microbiologist Famous for immune system-phagocytosis Noble Prize (1908) **(18) Paul Oskar Morawitz** 03-04-1879–01-07-1936 Famous for Study of blood coagulation, clotting factors, blood transfusion without the benefit of blood typing **Robert Gwyn Macfarlane** 26-06-1909–26-3-1987 British Physician Famous for the study of Blood Clotting cascade and haemophilia **Paul Ehrlich** 14-03-1854–20-08-1915 German Immunologist Famous for Autoimmunity Nobel Prize (1908) **Chapter 2BLOOD AND BODY FLUIDS** Introduction—Properties, composition and functions of blood. Plasma Proteins—Types, plasma level, functions. **Red Blood Cells:** Morphology, normal count, physiological variation, and functions. **Erythropoiesis:** Definition, sites, hemopoietic stem cells, stages of erythropoiesis. Factors influencing erythropoiesis. Regulation of erythropoiesis—erythropoietin and other hemopoietic factors **Hemoglobin:** Normal level. Physiological variations, Structure, Types, compounds of hemoglobin, Fate of Hb. **White Blood Cells:** Classification of WBC, normal values morphology, functions, variations, Leukopoiesis, Leukaemia. **Platelet:** Platelet structure, normal value, production, functions. Purpura and Bleeding Time. Hemostasis: Major steps—Primary and Secondary, Coagulation factors. Extrinsic

and intrinsic mechanisms of coagulation. Physiological mechanisms preventing intravascular coagulation—Endogenous anticoagulant systems. Endogenous fibrinolytic systems, Intravascular blood coagulation, Disseminated Intravascular coagulation. Anticoagulants—Types, Mechanism of action and uses. Bleeding and Clotting Disorders—von Willebrand disease, Hemophilia, Vitamin K deficiency. Clotting time, Bleeding time, Prothrombin time. **Blood Group:** Physiological basis for blood groups The ABO system. The Rh system—Hemolytic Disease of Newborn (HDN). Other minor blood group systems. **Blood transfusion:** Indications, Collection, Precautions to be taken—cross matching, screening for infections, Consequences of mismatched transfusion, Hazards of blood transfusion. Blood bank. Significance of blood grouping. **Anemia:** Definition, etiological and morphological classification. Effects of anemia on physiological systems. Signs and symptoms. Common types of anemia—Iron deficiency anemia, pernicious anemia, sickle cell anemia, and thalassemia—their causes and salient features. Polycythemia—Primary and secondary, Physiological effects. ESR, PCV, Blood Indices, Osmotic fragility. Blood volume: Normal value, Physiological variation, Principles of measurement, regulation. Body Fluids and compartments. Distribution of total body water (TBW). Principles of measurement of body fluids. Effect of dehydration and overhydration. Reticulo endothelial system. Odema. **Immunity:** Definition and types of immunity. Mechanisms (i) Cell mediated immunity (ii) Humoral immunity. Physiological basis of immunisation. Autoimmune disease, AIDS, Graft rejection. **BLOOD** Cardio vascular system comprises of heart, blood and blood vessels. The branch of physiology dealing with blood is called **hematology.** "Blood is a fluid connective tissue of the body". Blood connects different parts of the body. It connects different parts by virtue of circulation. **Sir William Harvey** was the scientist who discovered the circulation of blood. Hematology includes the study of blood and blood disorders. The proper analysis of blood may help in the diagnosis and management of blood disorders as well as many other diseases. Hematological investigation is very routine and important in medical practice. Many bodily dysfunctions can be detected by noting the alternations in blood even in their early stage. These laboratory findings of blood parameter are fairly reliable in the diagnosis and prognosis of diseases collection of blood samples and investigation is very easy. Therefore hematological investigation has become an integrated part of medical practice. **Properties of Blood** 1. Volume of blood present in the body is 5-6 litres 2. The colour of blood is red. This is due to the presence of oxyhaemoglobin. 3. The pH of blood is 7.4. Slightly alkaline. 4. Specific gravity is the relative density of blood compared to water = 1.060 5. Viscosity means thickness of any fluid compared to water. Viscosity of blood is 5 times greater than water. Blood is thicker than water. **Composition of Blood** Blood is divided into two major components—Plasma and formed elements or cells. **COMPOSITION Blood** Blood cells - 45% formed elements **Plasma 55%** Erythrocytes or RBC 5 million/c.mm Leukocytes or WBC 4000-11000/c.mm Platelets or Thrombocytes 2-4 lacs/c.mm Water Solids 91% 9% Granulocytes Agranulocytes Organic 8% Inorganic 1% Neutrophils Basophils 40-70% 0-1% Eosinophils Lymphocyte Monocyte 1-5% 25-40% 2-8% 1. Plasma proteins (a) Albumin (b) Globulin (c) Fibrinogen (d) Prothrombin 2. Amino acids 3. Glucose 4. Fats and lipids (a) Free fatty acids Cations Anions ++ –Na K Cl, HCO3 Ca ++Mg++PO––, SO–– 44 Mn++, Fe++ (b) Mono/Di/Tri glycerides (c) Cholesterol (d) Phospholipids 5. Vitamins 6. Hormones 7. Nitrogenous waste products (a) urea (b) uric acid (c) creatinine, Bile pigments, xanthine. **Fig. 2.1** Composition of blood **1. Plasma** It is the liquid portion of blood in which various types of blood cells are suspended. By volume plasma is 55% of blood and the portion of blood cells is 45%. **Blood cells** or **formed elements of blood** are mainly of three types: **They are:** 1. Red Blood Corpuscles (RBCs) or Erythrocytes 2. White Blood Corpuscles (WBCs) or Leukocytes 3. Platelets or Thrombocytes **WBC are broadly classified into two types:** 1. Granulocytes 2. Agranulocytes **Granulocytes are of three types:** 1. Neutrophils 2. Eosinophils and 3. Basophils **Agranulocytes are of two types:** 1. Lymphocytes and 2. Monocytes **Plasma Difference between plasma and serum** Serum = Plasma without some clotting factors like fibrinogen, prothrombin, V, VIII and XIII. Serum is the fluid oozing out of a blood clot. Plasma = Blood without blood cells **Composition of plasma** Plasma is made of water, solids and gases. Water = 90 – 92%, Solids = 8 – 10%. The solids are classified into two: 1. Organic constituents and 2. Inorganic constituents 1. **Plasma proteins** (a) Albumin Alpha (b) Globulins Beta Gama (c) Fibrinogen (d)

Prothrombin (e) Enzymes — Biological catalysts 2. Carbohydrates are mostly present in the form of glucose. 3. Amino acids 4. The fats and lipids present in the blood are free fatty acids, monoglycerides, diglycerides, triglycerides, phospholipids and cholesterol. 5. Hormones—They are organic chemical substances secreted by the duct-less glands. 6. Nitrogenous waste products like, urea, uric acid, creatinine, xanthine, bilirubin etc. 7. Vitamins. **Inorganic constituents** This comprises of various salts. This includes: 1. Sodium salts 3. Calcium salts 5. Manganese salts 2. Potassium salts 4. Magnesium salts These salts get ionised as cations like Na+, K+, Mg++, Ca++, Mn ++ and anions like Cl–, SO4– –, PO4– –, HCO– 3 **Functions of blood** One of the important function of blood is transportation. Blood acts as the transporting agent of the body. 1. **Transportation of respiratory gases** *i.e.,* O2 and CO2. Oxygen is needed to produce energy by metabolism. O2 is transported from the lungs to the tissues by blood. CO2 is transported from the tissues to the lungs by the blood. CO2 is formed by oxidation, as the end product of metabolism. Example if glucose is oxidised we get CO2 C6H12O6 + 6O2 □□ 6CO2 + 6H2O 2. **Transportation of nutrients** (food like vitamins, minerals, water, fats and lipids, carbohydrates) from the gastro intestinal tract (G.I.T) to various parts of the body. 3. **Transportation of waste productsâ€"** Excretory function. Blood picks up the waste products from the site of production and carries them to the site of excretion, excretory organs like kidneys, lungs, G.I.T. and skin. 4. **Transportation of hormones** Hormones are organic chemical substances secreted by ductless glands or endocrine glands and manifest their functions away from the site of secretion. Blood carries the hormones from the site of secretion to the site of action. 5. **Defence** Blood helps in the defence of the body. Blood takes part in three types of defence. (a) **Phagocytosis** WBC or leucocytes engulf foreign organisms, bacteria, fungus etc. and kill the microorganisms. So the microorganisms thereby do not get the chance of multiplication. The body is protected from the harmful effects of microorganisms. (b) **Producing antibodies** (formed from gama globulin). When a group of micro organisms enter the body for the first time they act as antigens. Against these antigens, antibodies are developed from gama globulins. When same group of microorganisms enter the body at a later date, they will be destroyed or killed by the antibody molecules already present in the body. This gives a long term protection to the body. This mechanism is known as immunity. (c) Blood shows the property of coagulation or clotting. This mechanism converts liquid blood into semisolid. This minimises the loss of blood from a cut blood vessel. 6. **Regulative functions** (a) Regulation of pH or regulation of acid-base balance *i.e.,* maintaining a constant pH. pH of blood is maintained by the action of chemical buffers of the blood. There are three important groups of buffers in the blood. **They are:** 1. NaHCO3 and carbonic acid buffer (H2CO3). 2. Phosphate buffer, NaH2PO4, Na2HPO4. 3. Protein buffers. **Buffer:** Prevents wide fluctuation in pH. (b) Blood takes part in the regulation of body temperature. Blood takes part in the distribution of thermal energy between different parts of the body. When the body temperature increases, blood vessels of the skin undergo dilatation. Because of this more blood may flow to the skin. Along with the blood more thermal energy flows to the skin and higher thermal energy is lost from the skin. This helps in the cooling of the body. When the body temperature is low, vasoconstriction of pheripheral blood vessels takes place. Because of this, less blood and less thermal energy will reach the skin. Less thermal energy is lost from the skin. This helps in the conservation of thermal energy. (c) Blood takes part in the regulation of water balance. Blood acts as a buffer for water. It takes part in the distribution of water among the different compartments of the body (intra cellular, extra cellular etc.). **PLASMA PROTEINS** Plasma proteins are a group of proteins present in the plasma. Plasma protein concentration is about 7.3 gms/ 100 ml (deci litre) of blood. The important plasma proteins are serum albumin, serum globulin, fibrinogen and prothrombin. Albumin is about 4.8 gm/100 ml of blood. Globulin is about 2.3 g/100 ml Fibrinogen – 0.3 gm/100 ml of blood. Prothrombin is only in 'trace'. 40 mg/100 ml. **Molecular weight** Albumin – 69,000 Globulin – 9000–150000 Fibrinogen – 340000 Normal albumin globulin ratio is 2 : 1. **Site of synthesis:** All the proteins of plasma are synthesised in the liver except gama globulins. They are produced by lymphocytes. The plasma proteins are separated using a technique called as electrophoresis. **Functions of Plasma Proteins** 1. When a blood vessel is injured, it produces prothrombin activator. This converts prothrombin to "thrombin". Thrombin is a proteolytic enzyme. It converts fibrinogen to fibrin. Fibrin gets

polymerised and give rise to fibrin threads. The fibrin threads give rise to a net work or mesh work. This net work of fibrin thread traps various type of blood cells. This will prevent excess loss of blood from a cut blood vessel. ProthrombinProthrombin activator Thrombin Fibrinogen Fibrin Fibrin threads clot 2. Plasma proteins contribute to the colloidal osmotic pressure of blood. About 80% of osmotic pressure is exerted by albumin because its concentration is highest. It controls the distribution of water among the different compartments of the body. This force also controls glomerular filtration rate (G.F.R). 3. Plasma proteins, albumin and fibrinogen contribute to about 50% the viscosity of blood. When the viscosity increase the resistance for the flow of blood will increase. It is one of the factor controlling blood pressure. The viscosity depends on the molecular shape of plasma protein. Fibrinogen contributes maximum viscosity because of its elongated and fibrillar shape. 4. **Transportation function** (a) Transportation of small amounts of CO2 as carbamino proteins. (b) Transportation of hormones. Hormones usually get attached to plasma proteins and carried from place to place. (c) Transportation of minerals and vitamins. 5. **Defensive function** Help in the protection of the body. The gamaglobulins develop as antibodies. This helps in the long term defence of the body against microorganisms. 6. Plasma proteins help in the regulation of acid base balance or pH by acting as chemical buffers. 7. Plasma proteins act as a nutrient reserve. During nutritional crisis, plasma proteins may be broken down for energy production. The nutritional crisis includes malabsorption, malnutrition, fasting, dieting and starvation. **Variations in Plasma Proteins Decreases in** Decrease in Albumin: (a) Physiological 1. Infancy 2. Pregnancy (b) Pathological–Impaired protein synthesis 1. Hepatitis 2. Cirrhosis of liver 3. Severe malnutrition 4. Malabsorption 5. Burns **Decreases in** 1. Emphysema 2. Acute hemolytic anemia 3. Glomerulo nephritis **Decreases in** 1. Carcinoma prostrate 2. Intravascular coagulation 3. Use of anabolic steroids **II. Albumin Increases in** 1. Dehydration 2. Exess glucocorticoids 3. Congestive cardiac failure **III. Globulin Increases in** 1. Multiple myeloma 2. Tuberculosis 3. Lymphatic leukemia 4. Cirrhosis of liver 5. Nephritis 6. Rheuatic arthritis **IV. Fibrinogen Increases in** 1. Pregnancy 2. Malaria 3. Tissue injury 4. Acute or chronic infections 5. Myocardial infarction 6. Stroke **I. Total Plasma Protein Increases in Hyperproteinemia** 1. Dehydration 2. Hemolysis 3. Acute infections like hepatitis 4. Pheumatid Arthritis 5. Exess glucocorticoides **V. Albumin Globulin Ratio A : G ratio Decreases in Hypoproteinemia** 1. Haemorrahage 2. Nutritional deficiency and malabsorption 3. Malabsorption 4. Pregnancy due to hemodilution 5. Chronic liver disease 6. Renal disease like nephrotic syndrome **Increases in** 1. Hypothyroidism 2. Exess glucocorticoides **Decreases in** 1. Liver dysfunction 2. Nephrosis **ERYTHROCYTE OR RED BLOOD CORPUSCLE (RBC)** These are non nucleated type of cells present in plenty in blood. **Shape:** Biconcave disc or dumbbell shape. Below the erythrocyte cell membrane there are two contractile proteins actin and spectrin. The positioning of spectrin gives bicon cave shape to the RBC. **Advantages of shape:** 1. It provides more surface area for gaseous exchange. 2. It helps to easily squeeze through narrow blood vessels. 2 m 1 m7.2 m 2 m 7.2 m Surface view Sideview **Fig. 2.2** Red blood corpuscles A matered RBC has no nucleus, no mitochondria, no ribosome and no endoplasmic reticulum. Advantage of having no nucleus. It gets more space for the accommodation of more haemoglobin. **Size:** Diameter 7.2 µ. Thickness at sides 2 µ, at centre 1 µ. Surface area 120 sq micron, volume: mean corpuscular volume—90 cubic micron. Variations in the size of the RBC is known as **anisocytosis.** *e.g.*, In pernicious anemia RBC size will be large and it is called as macrocyte, in iron depicient anemia size of RBC is small known as microcyte. Variation in the shape of RBC is known as **poikilocytosis.** *e.g.,* Sickle cell anemia—RBC shape in sickle shape. **RBC count:** 5 million/c.mm of blood. **Physiological variation in RBC count** 1. **Age:** RBC count is more in infants and children, less in adult, still decreases in old age. RBC count in a new born infant may be as high as 7–8 million/c.mm. 2. **Sex:** RBC count is more in male than female. In adult male RBC count is 4.5–5.5 milliion/c.mm, average is 5 million/c.mm of blood, in adult female RBC count is 4–5 million/c.mm, average is 4.5 million/c.mm of blood. 3. **Altitude:** Altitude is the height of place of living. RBC count is more in people living at high altitude than those living at sea level. At high altitude places oxygen content in atmospheric air is less (hypoxia). To take up whatever oxygen is available, the number of RBC increases. This type of physiological adjustments with environmental factors is known as **acclimatisation.** 4. **Pregnancy:** Total number of RBC in the

blood increases during pregnancy, but RBC count per c.mm of blood decreases. This is because more increase in blood volume rather than increase in RBC count. This is known as haemodilution 5. **Exercise:** RBC count increases during exercise. 6. **Athlete:** RBC count is more in athletes. 7. **Emotion:** RBC count increases during emotional states. **Pathological variation** Pathological increase — Polycythemia Pathological decrease — Anemia **Production of RBC â€" Erythropoiesis** Erythropoiesis or haemopoiesis is the physiological process of production of RBC. Erythropoiesis mostly takes place in the bone marrow, but it depends upon the stage of life. **TABLE 2.1 Stages, sites and phases of erythropoiesis Sl. Stage of Life No.** 1. Embryo 1–3 months 2. Foetus 3–6 months 3. After Birth 4. After 20 years Bone marrow of all the bones Bone marrow of small and flat bones. Proerythroblast Basophilic cytoplasm Basophilic erythroblast Early normoblast Polychromatophilic erythroblast Intermediate normoblast Orthochromatic erythroblast Late normoblst Cart wheel appearance Reticulocyte Pyknosis Erythrocytes **Site of Erythropoiesis** Yolk sac Liver and spleen **Phase** Mesoblastic phase Hepatic phase Myeloid phase Myeloid phase **Fig. 2.3** Stages of erythropoiesis **Stages of Erythropoiesis** RBC production starts from large nucleated type of cells known as pluripotent stem cells. These cells undergo repeated mitotic cell division and gives rise to committed stem cell or Progenitor cells. Committed stem cells of myeloid series ultimately can produce RBC, neutrophil, monocyte, eosinophil or platelet. Again mitotic cell division takes place and lead to colony forming cell unit—erythrocyte. This colony forming cells give rise to proerythroblast or pronormoblast. This is a nucleated type of cell with a diameter more than 22 µ. Pronormoblast gives rise to the next stage of cells—early normoblast. The next stage is intermediate normoblast or polychromatophilic normoblast. Intermediate normoblast further gives rise to late normoblast. Late normoblast further give rise to reticulocyte. Reticulocytes mature into erythrocytes or RBC. 1 million RBCs are produced per second. Blood may contain about 1% of RBC in reticulocyte stage. Increase in the percentage of reticulocyte in blood is known as **reticulocytosis. Normal reticulocyte count** (a) Foetus — 30–50% (b) At birth — 2–6% (c) Adult — 0.5–1% Important changes taking place during erythropoiesis. 1. Change in the size of the cells. There is a gradual reduction of size of the cells 2. **Disappearance of nucleus:** This is also a gradual process. It starts from intermediate normoblast stage. At this stage nucleus shows shrinkage. In the next stage nucleus disintegrates or breaks down into fragments. By reticulocyte stage, DNA strands/ nucleus disappears. Only RNA strands may be seen. 3. Synthesis of haemoglobin starts from intermediate normoblast stage. This process continues during subsequent stages. Matured RBC is saturated with haemoglobin upto 33%. **TABLE 2.2 Stages of erythropoiesis S. No. Name of the cell Diameter (in microns) Nucleus Characteristics Cytoplasm Appearance Characteristics** 1. Haemocytoblast 18–23 Large Small amount, thin rim of deep basophilic cytoplasm 2. Proerythroblast 14–19 Large with distinct nucleoli and reticulum of fine chromatin threads Basophilic and less in quantity No haemoglobin 3. Early normoblast Basophilic and less in quantity No haemoglobin 11–17 Nucleus and chromatin becomes more dence, nucleoli are absent or rudimentary 4. Intermediate normoblast (polychromatophil) 10-14 More condensed often eccentric. No nucleoli Becomes polychromatic because of appearance of haemoglobin 5. Late Normoblast (orthochromatic erythroblast) 7-10 Nucleus is very dense and takes a deep stain (pyknotic) Polychromatic Quantity cytoplasm increases 6. Reticulocyte 7-7.5 Round Disappears Net like structure (reticulum) in cytoplasm Some RNA is still present 7. Erythrocyte Mature RBC 7.2 Biconcave disc No nucleus Plenty of haemoglobin 4. Changes in the shape. Upto reticulocyte stage, all the cells are spherical in shape. When reticulocyte matures the shape change into a biconcave disc. 5. Changes in the staining property of cells. Haemoglobin synthesis starts at the intermediate normoblast stage and mitotic cell division stops at late normoblast stage. It takes about 8 days from pronormoblast to reticulocyte. **Factors Essential for Erythropoiesis or Factors Influencing Erythropoiesis 1. Proteins** Proteins are essential for supplying amino acids required in the synthesis of haemoglobin. Deficiency of protein in the diet (food) will lead to nutritional deficiency anaemia. **2. Iron** Iron is essential for the synthesis of haemoglobin. Green leafy vegetables are good sources of iron. Deficiency of iron in the diet leads to improper haemoglobin synthesis. This results in a type of anaemia iron deficient anaemia. Which is characterised by **Microcytic Hypochromic. 3. Vitamins: Maturation factors** Vitamin

B12 or cyanocobalamine and folic acid. These two vitamins are the members of vitamin B-complex. These two vitamins together are called as extrinsic factors. These vitamins are essential for DNA synthesis. Therefore they are required for cell multiplication and also for the maturation of RBC. The deficiency of these vitamins will lead to maturation failure. This will result in megaloblastic anaemia or maturation failure anaemia. **4. Intrinsic factor of Castle** It is a glyco protein secreted from the wall of the stomach or gastric mucosa. So, it is one of the component of gastric juice. This intrinsic factor gives a protective covering to the extrinsic factor—vitamin B12 and folic acid. Because of this it prevents the destruction of the vitamins by the actions of enzymes and acids of gastro intestinal tract (G.I.T.). Deficiency of intrinsic factors will expose the extrinsic factors to the actions of enzymes and acids. This will destroy the vitamins, ultimately leading to **pernicious anaemia.** Deficiency of intrinsic factor is seen during severe peptic or gastric ulcers. **5. Other vitamins** B1 Thiamine, B2 Riboflavine, B6 Pyridoxine and vitamin C are also essential for erythropoiesis. **6. Other minerals** Like Copper, Cobalt, Nickel, Bismuth etc. are trace elements that are also essential for RBC production. **7. Burst Promoting Action (BPA)** It is a group of proteins secreted by agranulocytes like monocytes and lymphocytes. B.P.A. stimulates the bone marrow and increases the proliferation of cells. **8. Hypoxia** It means low oxygen content in the blood. Hypoxia increases R.B.C. production by stimulating the kidneys to produce erythropoietin. This stimulates committed stem cells to multiply. **9. Hormones** Like androgens, thyroxine, corticoids, oestrogen, growth hormone and prolactin. Androgens, corticoids, thyroxine, growth hormone and prolactin increases the formation of erythropoietin, thereby stimulate bone marrow and increases the rate of cryotherapies. Oestrogen decreases erythropoiesis. **Regulation of Erythropoiesis** Regulation of erythropiesis means controlling the rate of R.B.C. production or the rate of erythropoiesis. Body has to maintain a constant R.B.C. count of around 5 million per cubic mm of blood. This provides an optimum cardio vascular efficiency to the body. If the R.B.C. count increases, that condition is known as polycythemia. This condition is harmful for the body. Decrease in R.B.C. count is known as anaemia. This is also harmful to the body as R.B.Cs once produced are not permanent. They are subjected to the process of aging. The R.B.Cs have a life span of 120 days. The older R.B.C. cell wall becomes less and less elastic and more and more (brittle) fragile. This senile (old) R.B.Cs are easily destroyed by the Reticulo Endothelial system. This process is known as haemolysis. At one hand there is erythropoiesis on the other hand there is haemolysis. A constant R.B.C. count can be maintained by establishing an equilibrium between the rate of erythropoiesis and haemolysis. But, body cannot adjust the rate of haemolysis. Therefore the only way to maintain a constant RBC count is by regulating erythropoiesis. **Mechanism** Suppose, if the O2 content in the blood decreases that condition is called as hypoxia. Hypoxia stimulates kidneys. In response to hypoxia kidneys secrete renal erythropoietin. Liver secrtes about 10% of erythropoietin. The erythropoietin acts as a hormone. This hormone acts on the bone marrow, Kidneys Liver 2O /Hypoxia –ve Erythropoietin or HaemopoietinRBC count Rate of erythropoiesis Bone marrow **Fig. 2.4** Regulation of erythropoiesis *i.e.,* it stimulates the bone marrows, to increase the rate of erythropoiesis. So the RBC count increases. This will increase the O2 content in the blood. So hypoxia is removed. It is an example for negative feed back mechanism. **Polycythemia** It is a clinical condition in which there is a significant increase in erythrocyte count and haemoglobin concentration. **HAEMOGLOBIN** It is a metallo protein present inside the RBC. It is an iron containing protein, a red colored pigment present inside the RBC. It is a conjugated protein. It has got two parts. 1. Protein part — Globin 2. Non-protein part prosthetic group — Haem. Globin is made up of 4 polypeptide chains, 2 α chains, 2 β chains, α chains contain 141 amino acids and β chain contains 146 amino acids. Haemoglobin is a protein with 574 amino acids and a molecular weight of 68,000. Haem consists of protoporphyrin ring with iron in the ferrous state. Protoporphyrin is made up of 4 pyrole rings. Haem contributes to 4% of weight of Hb, remaining 96% is by the globin part. **Functions of Haemoglobin** 1. Transportation of oxygen. 2. Transportation of small quantity of CO2 . 3. It acts as a chemical buffer, helps in the regulation of pH or acid base balance. 4. Oxygenated haemoglobin gives red color to blood. **Haemoglobin concentration** 15 gm/dl or 100 ml 15 gm % **Physiological variations** 1. **Age:** Haemoglobin concentration is more in new born and infants than adults. In new born infants Hb concentration is

about 17 gm %. 2. **Sex:** Haemoglobin concentration is more in male than female Adult male 14–17 gm % Adult female 12–15 gm % 3. **Altitude:** Hb concentration is more in people living at high altitudes. 4. **Emotion:** Hb concentration increases during emotional states. 5. **Exercise:** Hb concentration increases. 6. **Pregnancy:** Total quantity of haemoglobin increases during pregnancy but haemoglobin concentration decreases due to haemodilution. 1. Succinyl CoA + 2 Glycine abamino keto adipic acid 2. -amino ab-Keto adipic acid d -amino levulinic acid d3. 2 -amino levulinic acidCondensation Porphobilinogen IIIALA dehydratase 4. 4 molecules of porphobilinogen Porphobilinogen IX 5. Protoporphyrin IX Fe ++ Haem 6. Haem + Globin Haemoglobin **Fig. 2.5** Biosynthesis of haemoglobin **TABLE 2.3 Fate of RBC and haemoglobin Bone marrow R.B.C. Production** R.B.C. in blood life span 120 days R.E. system (Liver, spleen lymph nodes and bone marrow Haemolysis of R.B.C. Haemoglobin Haem Globin IronProtoporphyrin Amino acid pool Transferritin in blood Microsomal oxygenase Reused in the synthesis of proteins including Hb Bileverdin (green) Bileverdin reductase Ferritin stored in liver Bilirubin conjugated with a-albumin of plasma LIVER Conjugated with glucuronic acid Bilirubin glucuronic acid Bile Intestine bacterial degradation (Brown) Stercobilinogen Urobilinogen (Yellow) Stercobilin Reabsorbed to blood Excreted through faeces Kidneys Urobilin Filtered and excreted through urine **Fate of Hemoglobin** RBC has a life span of about 120 days. The cell membrane of senile RBCs become fragile and brittle such old RBCs are destroyed by the reticulo endothelial cells of bone marrow, liver, spleen and lymple node. Hemoglobin is liberated from ruptured RBC. The tetrapyrrole ring of home is opened up and four pyrrole rings lie side by side. Globin and iron are removed. Iron is stored in the liver as ferittin. Globin will be metabolised like any other proteins. The tetrapyrrole straight chain compound is called as biliverdin. Biliverdin oxidised to bilirubin. All these reactions take place with in the phagocytic cells. Bilirubin come out of phagocytic cells. Bilirubin come out of phagocytic cells. It combines with albumin—albumin complex. This portion of bilirubin is called as free bilirubin or unconjugated bilirubin. Through the circulation free bilirubin reaches the liver. Here bilirubin get conjugated with glucaronyl transferage. The conjugated bilirubin is water soluble and released into bile and reaches small intestine. Conjugated billirubin gives color to bile. Along with bile bilirubin glucuronide reaches the lower part of small intestine. Here bacterial enzymes split the conjugated bilirubin. Bilirubin immediately get oxidised. Two types of compounds are formed brown colored stereobilinogen. Yellow colored urobilinogen. Stercobilinogen is excereted through stool as stercobilin. Urobilinogen is absorbed by the blood from the intestine, carried to kidney, get filtered as lost through urine as urobilin. **TABLE 2.4 Types of haemoglobin** Hb A – Hb α2 β2 Hb A2 – Hb α2 δ2 Hb F – Hb α2 γ2 Hb S – Hb α2 β2 **TABLE 2.5 Haemoglobin variants causing haemoglobinopathy Haemoglobin Point mutation Amino Acid position substitution** Hb S Hb C Hb E Hb D (Punjab) Hb O (Arab) Hb sM Beta 6 Glu - Val Beta 6 Glu - Lys Beta 26 Glu - Lys Beta 121 Glu - Gln Beta 121 Gu - Lys Proximal or His - Tyr distal Histidine in α or β chain **TABLE 2.6 Compounds of haemoglobin HAEMOGLOBIN I. Addition Compounds Haemoglobin ligands II. Derived or Decomposition Compounds** 1. Oxyhaemoglobin 2. Methaemoglobin 3. Carboxyhaemoglobin or Co-haemoglobin 24. CO -haemoglobin or Carbohaemoglobin or Carbamino compound 5. NO-haemoglobin or Nitric oxide haemoglobin 6. Sulphahaemoglobin or H S-haemoglobin 2 **A. Iron containing compounds B. Iron free compounds** 1. Haematin 2. Haemin 3. Haemochromogen 4. Cathaemoglobin 5. Haem 6. Cytochromogen 7. Methemoglobin—Iron is oxidised from ferrous to ferric state 8. Glycosylated or glycated hemoglobin. Glucose attached to hemoglobin. 1. Haematoporphyrin 2. Haemopyrrole 3. Haematodin 4. Bilirubin 5. Biliverdin 6. Stercobilin 7. Urobilin **Haemoglobinopathies** Haemoglobinopathies (Hereditary disorders of haemoglobin; disorders of haemoglobin structure and synthesis). Haemoglobinopathies are disorders that affect the structure, function or production of haemoglobin due to abnormalities in the formation of globin two types. 1. Qualitative abnormality of haemoglobin results from alterations in the amino acid sequence of the polypeptide chains which produces structurally defective haemoglobins. 2. Quantitative abnormality of haemoglobin results from impaired or absent polypeptide chain formation but amino acid sequence is normal. **TABLE 2.7 Types of haemoglobinopathies Qualitative haemoglobinopathies Quantitative haemoglobinopathies** Haemoglobin S thalassaemia)

Thalassaemias (α, β- Haemoglobin C **Combined qualitative and quantitative haemoglobinopathies** Heaemoglobin E Sickle cell β-thalassaemia Haemoglobin D Punjab Altered oxygen affinity High affinity haemoglobin Low affinity haemoglobin Haemoglobin that oxidise easily Unstable haemoglobin M haemoglobin Defect in the synthesis of heme-prophyrias. It may be inherited or acquired. Over production of prophyrins due to over activity of enzyme delta amino levunic acid. Symptoms-Photosensitivity and Psychosis. **Acquired haemoglobinopathies** Methaemoglobinaemia Carboxyhaemo globinaemia **WHITE BLOOD CORPUSCLES (WBCs) OR LEUKOCYTES** These are the nucleated type of blood cells. Total leucocyte count is 4000–11000/c.mm of blood. **1. Leukocytopenia or Leukopenia** It is a clinical condition in which W.B.C. count is significantly below normal, *i.e.,* 2000 or 3000/c.mm **Cause** (a) Bone marrow aplasia (b) Anaphylactic shock (c) Typhoid (d) Cirrosis of liver (e) Excess of ACTH (f) Drug induced bone marrow aplasia. If the W.B.C. count is less, the power of defence will be very weak, *i.e.,* the body cannot defend against the microorganisms. As a result the body gets infected easily. **2. Leukocytosis** It is a clinical condition in which there is a significant increase in W.B.C. count It is seen in pathological conditions like allergy, tuberculosis, cold etc. **3. Leukemia** It is a clinical condition in which there is a significant increase in immature nonfunctional W.B.C. due to carcinogenic reasons. The body is easily infected, more prone for infection, pains in joints. **Differential Leukocyte count, DLC or DC Classification of W.B.C.** Granulocytes Agranulocytes The criteria for the classification is the presence or absence of granules in the cytoplasm. If granules are present they are called as granulocytes. If the granules are absent they are called as agranulocytes. **TABLE 2.8 Differential leukocyte count and absolute count Sl. Types of No. leukocytes Granulocytes Percentage Absolute count** 1. Neutrophils 40–70% 3000–6000/ cmm methylene blue colour. The number of lobes of nucleus ranges from 1 to 5. D.L.C. of neutrophils is 40–70%. **Classification of neutrophils** Neutrophils are further classified based upon number of lobes present in the nucleus. They are classified into five types. 2. Eosinophils 1–5% 150–300/cmm 3. Basophils **Agranulocytes** 1. Lymphocytes 2. Monocytes 0–1% 10–100/cmm 25–40% 1500–2700/cmm 2–8% 300–600/cmm Type I Type II Type III Type IV Type V Number of lobes indicate the age of the cells. As the age advances number of lobes increase. **Arneth count** The percentage of different types of neutrophils is known as Arneth count. **Granulocytes** Neutrophils Basophils Eosinophils Type I 5% Type II 30% Type III 45% Type IV 18% Type V 2% **Fig. 2.8** Normal arneth count Neutrophil 40-70% Eosinophil 1-5% Basophil 0-1% **Fig. 2.6** Granulocytes Agranulocytes LymphocyteMonocyte LymphocyteMonocyte25-40% 2-8% **Fig. 2.7** Agranulocytes **Criteria of classification** Size of the cells, shape of the nucleus and mainly the staining behaviour or staining property. **Neutrophil** It is a type of granulocyte. Cell is round in shape. Size is 10–12 micron in diameter. **Nucleus:** Nucleus is multilobed. The nucleus is blue in colour. The cytoplasm is granulated. It consists of numerous fine granules. The granule will take up both eosin and **Functions of Neutrophils** 1. It acts as a mobile defence unit of the body. When micro organisms enter the body, neutrophils are attracted to the site of infection. This process is known as **chemotaxis.** At the site of infection the neutrophils squeeze out of the pores of the blood capillary. This process is known as **diapedesis.** The neutrophils engulf the micro organisms. This process is known as **phagocytosis.** By this way it kills the micro organisms and protects the body. **Basophils** It is a type of granulocyte. Shape is round or spherical. **Size:** It is smaller than the neutrophil. It is about 8–10 micron in diameter. **Nucleus:** Nucleus is usually bilobed, 'S' shaped, blue in colour. **Granules:** Granules are big in size and appear in dull blue colour. Basophils take methylene blue. **D.L.C. of Basophils:** Percentage of basophil is 0–1%. **Functions of Basophils** 1. It secretes a natural anticoagulant heparin. It prevents intra vascular blood clotting. 2. It shows mild phagocytic action. **Eosinophils:** It is a type of granulocyte. **Shapeâ€"Spherical Size:** Size is same as neutrophil *i.e.,* 10–12 micron in diameter. Nucleus is bilobed and telephone receiver like. **Granules:** Granules are plenty in number and coarse. Granules appear in shining pink or eosin colour. Sometimes the density of the granules cover the nucleus. *i.e.,* nucleus is submerged. The cell wall of the eosinophil is weak and during staining procedure it may be broken. **D.L.C:** The percentage of eosinophils is 1–5%. **Function:** It helps in fighting against allergic responses. Allergic responses are mediated through a local hormone histamine. Eosinophil contains an

enzyme histaminase. This enzyme destroys histamine. 2. Shows mild phagocytosis. **Eosinophilia:** It is a clinical condition in which the percentage of eosinophils increases *i.e.,* the percentage increases to 10 to 15%. **AGRANULOCYTES** Lymphocytes Monocytes **Lymphocytes:** It is a type of agranulocyte. **Size:** There are two types of lymphocytes, small and large lymphocytes. **Small lymphocytes:** 7-9 µ diameters, Large lymphocytes – 14-16 µ diameters Shape of the cell is round. **Nucleus:** Nucleus is large, round and filling almost entire size of the cell, leaving behind a thin rim of clear cytoplasm. Size of the lymphocytes indicates the age. Small lymphocytes are older. Large lymphocytes are younger. **Function** (a) Lymphocytes are functionally of two types: 1. T-Lymphocytes 2. B-Lymphocytes. They take part in the production of antibodies and it gives a long term protection to the body. The lymphocytes take part in the development of immunity. **TABLE 2.9 Comparison between B-lymphocytes and T-lymphocytes B-lymphocytes T-lymphocytes** 1. Form 20 % of the total lymphocytes. Form 80 % of the total lymphocytes. 2. Produce antibodies. Produce chemicals called cytokines. 3. Processed by bone marrow. Processed by the thymus. 4. Responsible for humoral mediated immunity *i.e.,*act through antibodies. Responsible for cell mediated immunity *i.e.,*they either directly attack or act through cytokines. 5. Protect the body from bacterial infections. 6. Shorter life span. 7. Class 2 MHC present on the membrane. 8. These have membrane bound immunoglobulins on their surface. Protect the body from viral infections tumors and auto immune diseases. Longer life span. Absent. Immunoglobulins are absent on the cell surface. **MONOCYTES** Monocytes are the largest of blood cells. Size is 18 micron in diameter. Nucleus is big, usually kidney shaped and placed at one side of the cell. *i.e.,* excentrically placed. D.L.C. is about 2 – 6%. **Functions** They show phagocytic action. Because of this, they help in the defence of the body by killing the microorganisms. **Summary of functions of Leucocytes â€" WBC Neutrophils Properties and functions of leukocytes** Leukocytes are the mobile defence units of the body. The primary function of leukocytes is phagocytosis. Neutrophils and monocytes are spceiatist type of leukocytes in phagocytosis. It is the ultimate process by which a living cell engulf and destroys a microbe. The major changes in the appearance of neutrophiles when they are active against bacterial infection include toxic granulation, vacuolisation of cytoplasm. Arneth count shifts to the left *i.e.,* percentage of young neutrophils increases in circulation. **Steps of Phagocytosis** (a) Margination (c) Ameboid movement (e) Opsonisation (b) Diapedesis (d) Chemotaxis (f) Phagocytosis. **Margination:** Leukocytes are attracted to the endothelial surface by membrane bound proteins like selectins. Leukocytes roll along the wall of blood vessel and it is called as margination. **Diapedesis:** It is the process by which the neutrophils squeeze out through the narrow pores of blood capillaries and reach the interstitial space. **Ameboid movement:** Leukocytes move through the tissues, in between the cell space by ameboid movement by extending out pseudopodia. **Chemotaxis:** The infected microorganism interacts with plasma proteins and produces certain chemicals called **chemokines**. For example, leukotrienes and cytotokines. These chemicals attract neutrophils to the site of infection. This process is called as chemotaxis. **Opsonisation:** (Greek-prepare for dining). Neutrophils cannot efficiently recognise and attach to most microbes. By opsonisation some plasma factors like opsonones coat the bacteria and there by mark the microbes for ingestion and make them tasty for leukocytes. Opsorins include antibodies and compliment systems. Foreign Pseudopodium particles Phagosome **Fig. 2.9** Steps of phagocytosis **Phagocytosis** Neutrophil membrane pseudopods envelop the microbe forming a vacuole called a phagosome within the cytoplasm. The phagosome fuses with lysosomal granules from the neutrophils cytoplasm. The granules release lytic enzymes into the phagosome. The lytic enzymes lead to eventual killing and digestion of the foreign agent. All these processes require energy that is derived by anaerobic glycolysis (glucose breakdown). One of the products formed in the digestion of the foreign particle is hydrogen peroxide, which is capable of killing microorganisms. Myeloperoxidase one of the enzymes in the primary granules, catalyses a reaction involving H2O2 resulting in a more toxic product. Myeloperoxidase deficiency is reported to be the most common congenital neutrophil disorders. One neutrophil can engulf 15–20 microbes at a time. Neutrophils form the first line of defence against invading microorganisms. **Basophils** 1. Mild phagocytosis – 2. Secrete histamine – responsible for immediate hypersensitivity and acute allergic reactions. 3. Secrete heparin – an anticoagulant –

prevent intravascular blood coagulation. Basophils play a role in acute allergic reactions. Their granules contain histamine, heparin and other substances that are released in response to the presence of allergens. These substances cause increased vascular permeability, smooth muscle spasm, vasodilation, and the clinical symptoms of an allergic reaction: watery eyes, runny nose, and difficult breathing. Histamine is a vasodilator that makes blood vessels more permeable. This effect is usually seen at inflammatory sites and allows increased cellular movement through the vessel walls. Heparin prevents blood clotting. Both histamine and heparin enhance the migration of leukocytes to the inflamed site. **Eosinophils** 1. Mild phagocytosis 2. Produce Major Basic Protein – Kill larvae of parasites – protection against parasitic infection. 3. It secretes Aryl Sulphate B, which inactivates slow reacting substance (SRB) released from mast cells – so prevents anaphylaxis (Exaggerated response to an antigen to which body was sensitised previously). Eosinophil glanular contents react with products from basophil, lymphocytes and mast cells. 4. It secretes enzyme – histaminase – destroys local hormone histamine, which is the chemical mediator of allergy, thereby shows anti allergic response. 5. The factors released from eosinophils decrease the inflamatory response and reduce granulocyte migration into the site of invasion. **Monocytes** Monocytes are found in peripheral blood; macrophages are found in tissue. There is not a large reserve pool of monocytes in the bone marrow. Monocytes are found both in the circulating and the marginal peripheral blood pools. Stimulated by growth factors, monocytes migrate into tissues and are generally called macrophages; some fixed in connective tissue fibres and other sites and some wandering freely through the connective tissue. Macrophages are most numerous in “filter” organs like the spleen, liver, lungs, lymph nodes collectively known as the mononuclear phagocyte system, (formerly the reticuloendothelial system) a system that serves as an important body defence mechanism composed of phagocytic cells. 1. Phagocytic action – Macrophage, protection against micro organisms. 2. Secretion of colony stimulating factors, thereby regulate leucopoiesis. 3. Secrete Interleukin I or monokinin which stimulate T-Lymphocyte-cell mediated immunity. 4. Take part in inflammation. 5. Phagocytosis of dead cells and abnormal erythrocytes. 6. Secrete BPA—which stimulate bone marrow and increases the rate of erythropoiesis. 7. Secrete Trephones—helps in the repair of damaged tissue or wound. 8. Monocytes act as antigen presentors in that they process ingested material and present the antigen on its surface to a T-helper lymphocyte. **Lymphocytes** 1. Produce antibodies and thereby give long term protection to the body against same group of micro organisms. 2. Concerned with development of immunity or resistance: T-Lymphocyte—cell mediated immunity B-Lymphocyte—humoral immunity. **Leukopoiesis** It is the process of production of leukocytes. All the types of leukocytes are produced in the bone marrow except lymphocytes. Lymphocytes are produced in the lymphnode. Pluripotent stem cell or Primitive stem cell Committed stem cell Myeloid stem cells Lymphoid stem cells Erythroid series Megakaryoid Colony forming cells series Unit-G.M. Lymphoblast Prolymphocyte Erythrocyte Thrombocytes Colony forming Colony forming cells granulocytes cells monocyte Large lymphocyte Neutrophil Myeloblast Eosinophil myeloblast Basophil myeloblast Monoblast Intermediate lymphocyte Neutrophil promylocyte Small lymphocyte Eosinophil promyelocyte Basophil Promyelocyte Monocyte Neutrophil myelocyte Eosinophil myelocyte Basophil myelocyte Macrophage Histiocyte Plasma cell Mast cell Neutrophil metamyelocyte Basophil metamyelocyte Basophil metamyelocyte Neutrophil Eosinophil Basophil **Fig. 2.10** Leukopoiesis The pluripotent stem cells give rise to committed stem cells. The committed stem cells of leukopoiesis are of two types: 1. Myeloid stem cells. 2. Lymphoid stem cells. The myeloid stem cells can give rise to three series: (a) Erythroid series ultimately forming RBCs. (b) Megakaryoid series—forming platelets. (c) Stem cells for granulocyte-monocyte series. The stem cells of granulocyte -monocyte series further produce colony forming units or progenitor cells for neutrophil, eosinophil, basophil and monocyte. These colony forming cells ultimately end up with respective cells. Leukopoiesis takes about 10 days, about 5 days for cell division and 5 days for maturation from metamyclocyte stage. **Changes in counts of various types of leukocytes Neutrophiliaâ€”increase in neutrophils more than 10,000/ c.mm of blood Causes: (a) Physiologic** 1. Exercise 2. After injection of adrenaline 3. Pregnancy, lactation 4. Strong emotional stimuli **(b) Pathologic** 1. Acute pyogenic infections. 2. Poisoning by heavy metals like lead,

mercury. 3. Insect venom. 4. Tissue destructions like (i) Burns (ii) Acute Haemorrhage (iii) Myocardial infarction. 5. Appendicitis 6. Emphysema 7. Cushing syndrome 8. Steroid drugs **Neutropenia:** Decrease in neutrophils Causes: 1. Infancy 2. Typhoid/Para typhoid fever 3. Viral infection like measles, Parasitic infection malaria. 4. Bone marrow depression, aplastic anemia 5. Drug toxicity like chloromphenicol. 6. Hypor splunism. **Eosinophilia:** Increase in eosinophils, increase in absolute eosinophil above 500 /c.mm of blood. **Causes:** 1. Allergy – like asthma, hayfever 2. Parasitic infections of blood like malaria, filaria 3. Skin diseases. 4. Intestinal parasitic infection like worms. 5. Rheumatoid arthritis. **Eosinopenia:** Decrease in eosinophil. **Causes:** 1. After injection of ACTH or corticosteroids. 2. Cushing's syndrome. 3. Aplastic anemia. **Agranulocytosisâ€"Decreased or absence of granulocytes.** This is mainly due to bone marrow depression. Due to bone marrow depression the production of granulocytes is reduced, but not much reduction in the production of lymphocytes because they are produced in the lymph node. So **Granulocytopenia** or **agranulocytosis. Basophilia â€" Increase in basophils Causes:** 1. Chickenpox 2. Small pox 3. Tuberculosis 4. Influenza 5. Polycythemia vera 6. Chronic sinusitis. 7. Allergic and inflammatory condition 8. Hypothyroidism, Diabetes mellitus **Basopenia:** Decrease in basophils **Causes:** 1. After administration of glucocorticoids 2. Drug induced reactions. 3. Hyper thyroidism 4. Cushings syndrome **Lymphocytosis:** Increase in lymphocytes **Causes:** 1. Infancy – Relative lymphocytosis L-60 %, N-40 % 2. Chronic infections – Tuberculosis, Syphilis, Diphtheria 3. Lymphatic leukemia 4. Viral infections like mumps. 5. Infective hepatitis. **Lymphocytopenia:** Decrease in lymphocytes **Causes:** 1. Hypoplastic bone marrow 2. AIDS 3. Corticosteroid therapy **Monocytosis:** Increase in monocytes. **Causes:** 1. Tuberculosis 2. Malaria 3. Syphillis 4. Kalaazar 5. Polythenia vera 6. Hodykin's disease 7. Gluco corticoid therapy **Monocytopenia:** Decrease in monocytes. **Causes:** Hypoplastic bone marrow Septicemia. **Life and fate of leukocyte** Compared to erythrocytes the life span of leukocytes is very short. Average life span of neutrophil is 2-4 days, eosinophil 8-12 days basophil 12-15 days, lymphocyte and monocyte 2-3 days. The senile leukocytes get fragmented either in the blood stream or in the reticulo endothilial cells of liver, spleen and lymphnode. **Regulation of leukopoiesis** It is interesting to note that the count of different types of leukocytes are maintained at a constant rate. This is possible by establishing an equillibrium between rate of their production and rate of their destruction. The nuclic acids formed by dead leukocytes inturn stimulate the formation of fresh leukocytes. Certain proteins likegranulopoietic stimulating factor stimulate the proliferation of cells. Dead WBCs are replaced by new formation and a balance is kept up between production and loss. **LEUKEMIA** It is a clinical condition in which there is an abnormal increase in nonfunctional immature leukocytes due to a carcinogenic reason. It is not a common disease but it is a popular disease because of Indian cinema. **Classification** There are two major types of classification. First one is based on the basis of cell types which are predominantly involved**Myeloid leukemia** and **Lymphoid leukemia**. Second classification is on the basis of history of the disease—**acute leukemia** and **chronic leukemia**. Usually two classfications are clubed together as acute myeloblastic leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia and chronic lymphocytic leukemia. Leukemia is about 4% of total cancer. **Major causes:** 1. Some unknown genetic factors. 2. Environmental factors like, (a) Exposure to ionising radiations. (b) Exposure to chemical carcinogens like benzene. (c) Drug induced leukemias. 3. Infection by RNA viruses (Retroviruses). **Clinical signs and symptoms:** 1. As the leukemic cells accumulate in the bone marrow, they suppress normal haemopoietic stem cells. 2. Anaemia is commonly seen. 3. This produces pallor, lethargy and dyspnoea. 4. Bleeding manifestations due to thrombocytopenia. 5. Infections of mouth, throat, skin and respiratory tracts. 6. Pain and tenderness of bones. 7. Splenomegaly or enlargement of spleen. 8. Hepatomegaly due to infiltration of liver by leukocytes. 9. Gum hypertrophy. **Treatment:** 1. Bone marrow transplant. 2. Periodic blood transfusion. 3. Use of anticancer drugs. **PLATELETS OR THROMBOCYTE Platelets:** These are the smallest non nucleated type of blood cells. **Shape:** Round or oval. Lifespan 8–10 days Size of the cell is 2–5 μ diameter. Volume 6–8 cu.micron. Platelets count: 2-4 lakhs/cu.mm of blood. **Variation in platelet count:** Increase in platelet count is known as thrombocytosis. Physiological increase in platelet is seen in (a) violent exercise (b) high attitude. Pathologic increase is seen in – trauma and hamorrage. Pathologic

decrease in the count rombocytopenia where platelet count thrombocytopenia is less than 1 lac / c.mm. (a) purpura, (b) aplastic anemia (c) viral infection like dengue fever, rat fever and chicken pox. Platelet count below 50,000/ c.mm is called **critical count.** Mithochondrion Cell membrane Microtubule Thrombopoiesis is controlled by two major factors: 1. Colony stimulating factors 2. Thrombopoietin. (Hemocytoblast) Megakaryoblast Promegakaryocyte Dense granule Glycogen Light granules Canalicular system Megakaryocyte **Fig. 2.11** Platelet **Structure of platelet:** Platelet cell membrane gives rise to invaginations and this forms a network called Canaliculor system. The membrane contains glycoprotein receptors. These receptors are specific for binding with collagen, ADP, fibrinogen, von Willebrard factor. These membrane reacptors help the platelets to adhere on to injured blood vessel. Cytoplasm of platelets contain microtubules, microfilaments, endoplasmic reticulum, mitochondria and granules. Granules are of two types – light granules and dense granules. Light granules or α granules contain platelet derived growth factor, von Willebrand factor, thrombospondin. Dense granules or Σ granules contain nonprotein substances like ATP, ADP, serotonin. Phospholipids from platelet cell membranes forms factors like thromboxane A2. Calcium is stored inside microtubules and endoplasmic reticulum. Microfilaments are made up of protein called actomyocin and thrombosthenin. This gives integrity to cell and helps in the movements. **Production of Platelets - Thrmbopoiesis** Platelets are produced in the bone marrow. Platelets are produced in a precursor cell known as megakaryocyte. The megakaryocytes are large nucleated cells and have a diameter of 22 micron. The megakaryocyte undergoes fragmentation and the broken bits of cell wall develop as platelets. These cell have cellular inclusions like mitochondria, ribosomes, cytoplasm. Platelets can also be formed by budding off from megakaryocytes. Around "1×10" platlets are produced per day. Each megakaryocyte produce 5000-10,000 platelets. Production of platelet is controlled by a hormone thrombopoietin produced by liver and kidneys. Old platelets are destroyed by phagocytosis mostly in the liver and spleen. Metamegakaryocyte Thrombocytes Peripheral blood **Fig. 2.12** Production of platelets **Properties and functions of platelets 1. Platelet plug formation:** Platelets aggregate, or clump together, using fibrinogen and vWF as a connecting agent. The most abundant platelet aggregation receptor is glycoprotein (GP) IIb/IIIa; this is a calcium-dependent receptor for fibrinogen, fibronectin, vitronectin, thrombospondin, and von Willebrand factor (vWF). Activated platelets will adhere, via glycoprotein (GP) Ia, to the collagen that is exposed by endothelial damage. Aggregation and adhesion act together to form the platelet plug. Myosin and actin filaments in platelets are stimulated to contract during aggregation, further reinforcing the plug. Platelet aggregation is stimulated by ADP, thromboxane, and α2 receptoractivator, but inhibited by other inflammatory products like PGI2 and PGD2, platelet aggregation at the site of injury act as a plug and block the flow of blood out of cut blood vessel. Platelet aggregation is enhanced by exogenous administration of anabolic steroids. 2. The aggregation of platelets release vasoactive substances which assist in the vasospasm. Serotonin and thromboxane A2 are released at the site of the inury by the damaged platelets. These two local hormones produce vasoconstriction of damaged blood vessel. The narrowing down the flow of blood to the site of the injury and there by minimising the loss of blood out of blood vessel. The vasospasm lasts for about 30 minutes and is an important factor in the initial process in the arrest of hemorrhage. Vasoconstriction and plug formation are very important in rapid arrest of bleeding and together they form temporary or primary haemostasis. 3. The platelets, release platelet factor III and help in blood coagulation. Due to their thrombosthenin content, the platelets can retract and cause clot retraction, which is necessary for making the clot firm. 4. Platelets help in the coagulation of exudate which follows an acute invasion by bacteria. This coagulation helps to cordon off the bacteria and thus localise the infection. 5. Platelets also responsible in maintaining the integrity and health of vascular endothelium. 6. Platelets help in the repair of damaged endothelium by being deposited on the damaged site and thus making a smooth layer on the intima. 7. In addition to being the chief cellular effector of hemostasis, platelets are rapidly deployed to sites of injury or infection, and potentially modulate inflammatory processes by interacting with leukocytes and by secreting cytokines, chemokines, and other inflammatory mediators. 8. Platelet also secrete platelet-derived growth factor (PDGF).This causes proliferation of endothelium and vascular smooth muscles. This

helps in wound healing. **TABLE 2.10: The substances produced by the platelets and their functions Substance Function** Serotonin(5-HT) Vasoconstriction Adenosine diphosphate (ADP) Promotes platelet aggregation Thromboxane platelet aggregation Vasoconstriction and Clotting factors Promotes coagulation Platelet derived growth factor Stimulates wound healing **Thrombocytopenia:** It is a clinical condition in which there is a significant reduction in the platelet count. **Thrombocytopenic purpura:** It is a clinical condition resulting from low platelet count. **Cause:** 1. Aplasia (Non functioning) of the bone marrow. It is due to (a) repeated x-ray exposure (b) exposure to nuclear radiations (c) drug induced bone marrow depression (d) Bone marrow fibrosis (e) Deficiency of Vit B12 and folic acid. 2. Increased destruction of platelets due to (a) drugs (b) Infection like dengue (c) hypersplenism (d) Cytotoxic chemotherapy (e) HIV infection **Signs and symptoms or clinical features:** 1. The efficiency of platelet plug formation decreases. This leads to prolongation of bleeding time. Bleeding time is the time elapsed from the onset of bleeding till the stoppage of bleeding. Normal bleeding time is 2–5 minutes. Clotting time may be normal. Clotting time is defined as the time elapsed from the onset of bleeding till the formation of clot or fibrin threads. Normal clotting time is 5–8 minutes. Subdermal blood patches is known as **purpura.** These patches initially appear in red colour but later change into brown and black. **Treatment:** Platelet transfusion. **Thrombosthenic purpura:** Qualitative platelet defectsplatelet count may be normal but function is impaired. It is mostly due to (a) drug actions like aspirin, antibiotics, heparin, (b) uremia (c) congenital disorders - defects in membrane glycoproteinsn defect in secretion of ADP/ thromboxene A2. **Idiiopathic thromobocytopenic purpura** It is an auto immune disorder seen more commonly in children and rarely seen in adults. A self antibody is formed against platelets there by destroy the platelets and bring down their number. The common clinical features include spontaneous bleeding mostly from skin, nose and gums. It can be managed by steroid administration and spheenectomy. **Injury to blood vessel** Vesoconstriction Exposure of collagen Surrounding tissue injury 1. Stimulation of pain receptors and nerve plexus leads to neurogenic reflex, results in smooth muscle contraction of bloodvessels Blood comes in contact with wettable surface Liberation of tissue thromboplastin or tissue factor Factor III Activation of platelets adhesion 2. Chemically thromboxane A2 and serotonin released by damaged platelet produce contraction of smooth muscles of blood vessels. Liberation of thromboplastin factor III Platelet plug formation Intrinsic Extrinsic Temporary haemostasis Initiation of blood coagulation by cascade mechanism Arrest of bleeding Fibrin thread formation network of fibrin threads with trapped blood cells = clot Permanent haemostasis Permanent stoppage of bleeding **Haemostasis** Haemostasis is defined as stagnation for the flow of blood out of a cut blood vessel by natural mechanism. There are four major mechanisms. They are 1. Vasoconstriction 2. Platelet plug formation 3. Blood coagulation or clotting and 4. Clot retraction. **Vasoconstriction** When a blood vessel is injured, the injured blood vessel become narrowed. This process is known as vasospasm or vasoconstriction. There are two mechanisms producing vasoconstriction. 1. **Nervous reflex mechanism** When a blood vessels is injured it will stimulate pain receptors. This will in turn stimulate local nerve fibres. This produces contraction of smooth muscles of blood vessels leading to vasoconstriction. 2. **Chemical mechanism** When a blood vessel is injured the damaged platelets secrete a local hormone called serotonin. Serotonin produces vasoconstriction. Vasoconstriction takes place immediately after injury. This helps to minimise the loss of blood from a cut blood vessel. **Platelet plug formation** When a blood vessel is injured the properties of platelets change. The cell membrane become more permeable to water. The cell becomes swollen and sticky. Numerous platelets adhere to each other. This forms a cluster of platelets at the site of injury. This is known as platelet plug. This will physically block the free flow of blood out of a cut blood vessel. **Blood Coagulation or Clotting** Blood coagulation is defined as a complex physiological process by which blood looses its fluidity and become jelly like or semi solid, there by minimising the loss of blood from a cut blood vessel. A number of chemical substances take part in blood coagulation or clotting. These substances are known as blood coagulation factors or clotting factors. They are: Factor I Factor II Factor III Factor IV Factor V Factor VII Factor VIII Factor IX Factor X Factor XI Factor XII Factor XIII – Fibrinogen – Prothrombin – Thromboplastin – Calcium ion – Labile factor – Stable factor – Anti haemophilic factor – Christmas factor – Prower – Stuart factor –

PTA (Plasma thromboplastin anticedent) – Hageman's factor – Fibrin stabilising factor Some new substances are added to the list of clotting factors. This include—high molecular weight kininogen HMW-K or Fitzgeral factor, Prekallikrinin—Prek. Fletecher factor, kallikrinin- ka, PL—platelet phospholipid. All the substances required for blood coagulation are present in the blood itself. In spite of this, blood does not clot as long as blood is inside the blood vessel. Blood will not clot unless and until it is exposed to outside. It is because of the following reasons: 1. Most of the clotting factors are in the inactive form, they require activation. 2. Presence of natural anticoagulants like heparin, Antithrombin I, II, III, alpha 2 macroglobulin. Presence of these anticoagulants oppose blood coagulation. 3. Inner surface of blood vessel is very smooth, which does not allow the factors to stick. 4. The velocity of blood will not allow the factors to react with each other. **Mechanism of blood clotting** There are two major mechanisms: 1. Intrinsic mechanism and 2. Extrinsic mechanism. **Intrinsic mechanism** In this mechanism everything required for blood coagulation comes from blood itself. When a blood vessel is injured blood is exposed to wettable surface. This triggers blood coagulation process. This takes place in three major steps. **Step I** Blood vessel is injured and blood is exposed to outside. Inactive factor XII is converted into active factor XII by the action of substance Kallikrein. Active factor XII convert inactive factor XI into active factor XI. Active factor XI convert inactive factor IX into active factor IX. Thrombin convert inactive factor VIII into active factor VIII. Active factor IX, active factor VIII and Ca++ together convert inactive factor X into active factor X. All these reactions upto the formation of active factor X is known as step I of blood coagulation. Thrombin converts inactive factor V into active factor V. **Step II** Conversion of prothrombin into thrombin. The active factor X, V, thromboplastin (Phospholipid) and calcium ions together act as a prothrombin activator. This will convert plasma protein-prothrombin into thrombin. **Step III** Thrombin is a powerful proteolytic enzyme. Thrombin acts on fibrinogen and converts it into fibrin. Fibrin is insoluble in water. Thrombin also converts inactive factor XIII into active factor XIII. Fibrin get polymerised to give rise to fibrin threads. These fibrin threads are stabilised by active factor XIII. The fibrin threads give rise to a network or meshwork. This network of threads trap all the types of blood cells. This complex is known as clot. Blood has become jelly like and stops flowing out. Blood coagulation involves multiple chain of enzymatic reactions. Therefore it takes time for coagulation. Therefore this mechanism is known as cascade mechanism or water fall mechanism. Kallikrein Factor XII Factor XII* b XII* a XII* Preakallikrein HMW kininogen Factor XI Factor XI* Factor IX Ca ++ Factor XI* Step I Factor VIII Thrombin Factor VIII* Ca++ Factor X Factor X* Step II Prothrombin activator Factor V Thrombin Factor V* Prothrombin Ca++ *Phospholipids* Factor XIII Step III Fibrinogen Fibrin Factor XIII* Fibrin thread clot **Fig. 2.13** Intrinsic mechanism of blood coagulation **Extrinsic mechanism** In this mechanism one of the factor comes from the surrounding damaged tissue – outside the blood. This factor is known as tissue factor or tissue thromboplastin. When a blood vessel is injured the surrounding tissues get damaged. This damaged tissue produce tissue factor. The produced tissue factors diffuse into the blood at the site of injury. The tissue factor acts upon inactive factor VII and convert it into active factor VII. Active factor VII convert inactive factor X into active factor X. The reactions upto the formation of active factor X is known as step I of blood coagulation. Active factor X converts inactive factor V into active factor V. **Step II:** Conversion of prothrombin into thrombin. Active factor X, active factor V, calcium ions and thromboplastin (Phospholipid) together act as prothrombin activator. **Step III:** Thrombin is a proteolytic enzyme. It acts upon fibrinogen and converts it into fibrin. Thrombin also converts inactive factor XIII into active factor XIII. Fibrin gets polymerised into fibrin thread. These threads give rise to a network or meshwork. This network of fibrin threads will trap all the type of blood cells This complex is known as clot. The clot will physically block the free flow of blood out of the cut blood vessel. Tissue trauma Tissue factor Factor VII Factor VIII* Ca++ Prothrombin activator Factor X Factor X* Step I Factor V* Factor V *Ca*++ *Phospho lipids* XIII Step II Prothrombin Thrombin Step III Fibrinogen Fibrin XIII* Fibrin threads cloth **Fig. 2.14** Extrinsic mechanism of blood coagulation Fibrinogen Fibrinapoptides Fibrin monomers Fibrinapoptides Fibrin thread **Fig. 2.15** Scheme of formation of fibrin thread **Fig. 2.16** Blood clot, RBCs entangled in fibrin meshwork **TABLE 2.11 Comparison between intrinsic and extrinsic mechanism of blood clotting Sl. No. Features Intrinsic mechanism Extrinsic**

mechanism 1. Source of thromboplastin 2. Role of factor VII 3. Number of reactions 4. Speed 5. Starts from Damaged platelets, comes from within the blood. Intrinsic source Factor VII is not required More Slow, takes few minutes Activation of factor XII Damaged surrounding tissue, comes from outside the blood. Extrinsic source Factor VII is required Less Fast, takes few seconds Activation of factor VII **Common causes of bleeding disorders** Defective blood clotting Defective capillary contractibility Combined defects Purpura Primary (Idiopathic) Secondary (Idiopathic) Deficiency of clotting factors I, II, V, VIII, IX, X, XI Vitamin K deficiency dueAnticoagulant to overdose Obstructive jaundice Chronic diarrhoea Liver disease Haemorrhagic states in infants **Fig. 2.17** Common causes of bleeding disorders **TABLE 2.12 Haemorrhagic (Bleeding) disorders deficiency of clotting factors Deficiency of Factor Clinical syndrome Cause** I Afibrinogenemia or fibrinogenopenia Congenital, use of anticoagulant like Arvin II Hypoprothrombinemia Decreased Hepatic synthesis of factor II V Parahaemophilia Congenital VIII Haemophilia A (Classical Haemophilia) Congenital IX Haemophilia B (Christmas disease) Genetic disorder X Staurt-Prower factor deficiency Congenital XI Plasma thromboplastin antecedent Congenital vWF Von Willebrands disease, Decreased platelet Acquired, Liver disorder Congenital adherence, Decreased factor VIII **Clotting disorders:** The common clotting disorders are: 1. Von Willebrand's disease 2. Haemophilia 3. Thrombocytopenic purpura 4. Vitamin K deficiency bleeding Von Willebrand's disease. Von Willebrand factor is a protein secreted by platelet. Factor VIII is transported in combination with vWF. During the activation of factor VIII it get separated from vWF. Inherited deficiency of vWF leads to inhibition of platelet adhesion. This leads to severe bleeding. **Haemophilia** Haemophilia is a clotting disorder. It is a sex linked genetic disorder. It is more common in male than in female. Haemophilia is common among British population. – Males 8% – Females 0.5% This disease is inherited through a recessive gene 'h'. This gene is situated in X chromosome. Because of this males are suffers of haemophilia, while females are carriers. Females can be hemophilic if her father is hemophilic and mother is a carrier. Normal male Carrier female(Father) (Mother) Carrier Normaldaughterdaughter HaemophilicNormalson son **Fig. 2.18** Inheritance of haemophilia **Types of Haemophilia** There are three common types of haemophilia. Haemophilia A or classical haemophilia. Factor VIII is deficient. Haemophilia B — Christmas disease Factor IX is deficient. Haemophilia C — Deficiency of factor XI — Autosomal recessive trait. **Signs and symptoms** 1. Prolongation of clotting time to several hours with normal bleeding time. 2. Excessive bleeding even from minor injuries. 3. Excessive bleeding from internal injuries. 4. Soft tissue hematomas and bleeding into joints. **Complications** 1. Haemophilic patients cannot face any surgery. 2. Cannot face tooth extraction. 3. Cannot face menstrual bleeding. 4. There will be excessive bleeding even from minor injuries which may be fatal. **Test for haemophilia â€" Determination of clotting time. Bleeding time time and Prothrombin time may be normal. Management or Treatment** 1. Find out which factor is deficient and inject that factor periodically. 2. Periodic, regular blood transfusion of fresh blood. **Thrombocytopenic purpuraâ€"Due to the decrease in platelet count. Vitamin K deficiency** Vitamin K is a fat soluble vitamin. It is required for the synthesis of clotting factors in the liver. Vit. K is needed for the post translational Carboxylation of some coagulation factors, like prothrombin. Synthesis of following clotting factors like prothrombin, VII, IX and X requires vitamin K. If vitamin K is deficient clotting factors like prothrombin cannot be synthesised. Without sufficient prothrombin, blood cannot clot. This leads to prolongation of clotting time, excessive bleeding from minor injuries. Dietany deficiency of Vit. K is rare because it can be synthesised by colonic bacteria. Vit. K deficiency mostly occurs due to (a) diseases which disturb fat absorption like obstructive jaundice (b) long term antibiotic therapy which dislodge colon bacteria. (c) long term usage of drugs like warfarin which is a competitor of Vit. K. **Anticoagulants** Anticoagulants are chemical substances which prevent blood clotting. Anticoagulants are broadly divided into two groups, natural anticoagulants and lab. anticoagulants. **Natural anticoagulants:** *e.g.,* Heparin, Hirudin Laboratory anticoagulants: Sodium or potassium citrate, ammonium/sodium/potassium oxalate, EDTA (ethylene diamino tetra acetate) Dicoumarol and Warfarin. Double oxalate—mixture of ammonium oxalate and potassium oxalate – 3 : 2, Aspirin. **Mechanism of action of anticoagulants Heparin inhibit** the conversion of prothrombin into thrombin. It also inhibits the

action of thrombin. Hirudin also inhibits the action of thrombin. Heparin activates antithrombin III and prevents coagulation by inhibiting factors IX, X, XI and XII. **Citrates** act as chelating agents. When citrates are added to blood the calcium ions of the blood will adhere to citrate molecules, so free calcium ions are not available. So the blood fails to clot. **Ethylene Diamino Tetra Acetate (EDTA)** It also acts as a chelating agent. It removes free calcium ions from the blood and thereby prevents blood coagulation. **Oxalates** When oxalate is added to blood, it will react with calcium ions and forms calcium oxalate, which gets precipitated. Free calcium ions are not available so the blood fails to clot. **Dicoumarol and Warfarin** It is an organic chemical. It acts as antagonistic of vitamin K. This prevents the synthesis of prothrombin and other clotting factors in the liver. Without prothrombin, blood fails to clot. Dicoumarol can be used as an anticoagulant only inside the body *i.e.,* in vivo. It cannot act as anticoagulant outside the body *i.e.,* in vitro. **Aspirin:** It inhibits the formation of thromboxane A2 and prevents platelet activation. **Uses of Anticoagulants** 1. To preserve blood in the blood bank. 2. To preserve blood samples required for the determination of ESR, PCV (erythrocyte sedimentation rate and packed cell volume). 3. To prevent intra vascular blood clotting. 4. Used during dialysis. 5. In the treatment of pulmonary embolism and cerebral thrombosis. **Fibrinolytic system** A fibrin clot is not designed to last forever. It is a transitory device until permanent repair of the vessel occurs. The fibrinolytic (or thrombolytic) system is the principal effector of clot removal. This system is very much important and keeps the lumen of the blood vessels patent by dissolving the clot. Fibrinolytic system constitutes a plasma proenzyme, plasminogen, which can be activated to the active enzyme plasmin by protein plasminogen activators. Once formed, plasmin digests fibrin, thereby dissolving the clot. This is achieved as follows: Thrombin-thronmbodulin complex on endothelium **Endogenous mechanism** The principal fibrinolytic factor is plasmin which is formed from a circulating glycoprotein called plasminogen. Plasmin is formed from its inactive precursor, plasminogen through intrinsic and extrinsic pathways. **The intrinsic activator system:** Plasminogen is converted to plasmin by both kallekrein and factor XIIa. This pathway contributes only about 15% of the total fibrinolytic activity. **The extrinsic activator system:** There are two extrinsic activator systems in the body *i.e., t*-PA and *u*-PA. Tissue plasminogen activator Plasminogen Plasmin Urokinase plasminogen activator Tissue plasminogen activator (*t*-PA), which is secreted by endothelial cells. During clotting, both plasminogen and t-PA bind to fibrin and become incorporated throughout the clot. The binding of t-PA to fibrin is crucial because t-PA is a very weak enzyme in the absence of fibrin. The presence of fibrin profoundly increases the ability of t-PA to catalyse the generation of plasmin from plasminogen. Thus, fibrin is an important initiator of the fibrinolytic process that leads to its own dissolution. **Significance in clinical practice:** The naturally occurring fibrinolytic system can be activated in certain clinical conditions like: 1. Coronary thrombosis 2. Massive pulmonary embolism 3. Cerebral stroke 4. Acute myocardial infraction. Tissue plasminogen activator, streptokinase, urokinase can be injected. These drugs dissolve the intravascular clot and help to repurfuse the affected vital organs. Plasminogen activators Plasminogen Plasmin Fibrin Soluble fibrin fragments **Fig. 2.19** Fibrinolytic system **INTRA VASCULAR BLOOD COAGULATIONâ€" THROMBOTIC DISORDERS** Normally blood may not clot inside the blood vessels. It is because of the following reasons. 1. Most of the coagulation factors are in the inactive form. They require activation. 2. Presence of anticoagulants—like heparin, antithrombin, I, II, III, α2 macroglobulin etc. These chemicals prevent blood clotting. 3. Inner surface of blood vessel wall is very smooth so the clotting factors may not stick. 4. Blood is under circulation. 5. Even if fibrin is formed inside the blood vessel it will be immediately distroyed by fibrinolytic system by the enzyme plasmin. However, sometimes blood may clot inside the blood vessels. There are two common types of intravascular blood clotting 1. **Thrombosisâ€"Thrombus** Formation of intra vascular stationary blood clot, *e.g.,* Cerebral thrombosis. 2. **Embolismâ€"emboli** Formation of intra vascular freely moving blood clot, *e.g.,* Pulmonory embolism. **Problems and complications** Intra vascular blood clot may block narrow blood vessels. It will block the supply of nutrients and oxygen to the tissues. If it happens in vital tissues like heart and brain, it may cause a permanent irrepairable damage to these vital tissues. This may even lead to death. **Causes of intra vascular blood clotting** 1. Inner surface of blood vessel becomes rough due to deposition of minerals or fat. 2. Inner surface of

blood vessel becomes rough due to infection. 3. Sluggish flow of blood especially after a surgical operation. 4. Increased activity of procoagulants such as fibrinogen, prothrombin. **Prevention and management** Periodic injections of anticoagulants. **Disseminated intravascular coagulation (Defibrination syndrome)** Disseminated intravascular coagulation (DIC) is a complex systemic thrombohemorrhagic disorder involving the generation of intravascular fibrin and the consumption of procoagulants and platelets. The resultant clinical condition is characterised by intravascular coagulation and hemorrhage. Disseminated intravascular coagulation is caused by widespread and ongoing activation of coagulation, leading to vascular or microvascular fibrin deposition, thereby compromising an adequate blood supply to various organs. Four different mechanisms are primarily responsible for the hematologic derangements seen in disseminated intravascular coagulation: 1. Increased thrombin generation, 2. A suppression of anticoagulant pathways, 3. Impaired fibrinolysis, and 4. Inflammatory activation. Activation of intravascular coagulation is mediated almost entirely by the intrinsic clotting pathway. This is characterised by systemic activation of coagulation with the formation of fibrin–platelet thrombin throughout the vascular tree. This is triggered by increased tissue factor activity in the circulation, which can be produced by a variety of stimuli including bacterial endotoxin and lipopolysaccharide. Thrombotic occlusion of small to medium sized vessels by fibrin clot can lead to multiple organ failure. Continual depletion of platelets and coagulation factors creates a consumption coagulopathy. Secondary activation of the fibrinolytic system ensues. The clinical manifestations represent a combination of those due to thrombosis and those due to bleeding, either of which may predominate. Cause of disseminated intravascular coagulation is septicemia, bacteremia including both gram-positive and gram-negative organisms, fungal infections, malaria, chronic malignancies, abortions, snake bite, heat stroke pathogenesesis may cause disseminated intravascular coagulation. **Features of disseminated intravascular coagulation:** 1. Low erythrocyte sedimentation rate (ESR) 2. Thrombocytopenia 3. Prolongation of prothrombin time and activated partial thromboplastin time (aPTT). 4. Reduced plasma fibrinogen level which correlates most closely with bleeding 5. Elevated levels of fibrin degradation products (FDPs) 6. Schistocytes on peripheral smear. **Tests for coagulation** 1. Bleeding time — 2–5 minutes 2. Clotting time — 5–8 minutes 3. Prothrombin time — 11–16 seconds 4. Platelet count — 2–4 lack/c.mm of blood 5. Clot retraction time — 30–60 minutes 6. Partial thromboplastin time — 60–80 sec. **Bleeding time** It is defined as the time elapsed from the onset of bleeding till the stoppage of bleeding. It is the time by which bleeding stops from an injury caused by the puncture of a sharp needle. It measures the time between the injury and the temporary haemostasis. It indicates the efficiency of vasoconstriction and platelet plug formation. Normal value: 2-5 minutes. **Significance:** Bleeding time is prolonged in thrombocytopenic purpura but it remains normal in haemophilia. **Clotting time or Coagulation time** It is defined as the time elapsed from the onset of bleeding till the formation of fibrin threads or clot. It is the time taken by the blood to coagulate outside the body. Capillary tube method is commonly used for the determination of clotting time. Normal value is 5 to 8 minutes. **Significance:** Clotting time is prolonged in haemophilia and vitamin K deficiency, but it is normal in purpura. Bleeding time and clotting time tests are routinely performed before any surgery and tooth extraction. **Prothrombin time (PT)** It is the time required for the activation of prothrombin to thrombin. It is defined as the time taken for coagulation of a sample of recalcified plasma mixed with tissue thromboplastin. **Normal time:** 11-16 seconds. **Procedure:** Blood is collected from the veins without tissue injury, mixed with sodium citrate. Plasma is taken from this blood. The citrated plasma is mixed with tissue thromboplastin (Brain extract) at 370C. Time is noted when gel develops in plasma. **Significance** 1. This test measures the concentration of prothrombin, factor V, VII, and X and reflects the efficiency of extrinsic mechanism of blood coagulation. 2. In haemophilia and Christmas disease PT will be normal because tissue factor does not require factor VIII and IX for activation of prothrombin. 3. PT increases in vitamin K deficiency which produces deficiency of prothrombin, V, VII and X. 4. Anticoagulant therapy with vitamin K antagonist is controlled by measurement of PT, which should be prolonged to about 25-30 seconds, to help prevent intravascular thrombosis. **Clot retraction time:** 30-60 mins. **BLOOD GROUP** Human beings can be classified into different

groups based upon the nature of the blood. Classification of human blood into different types is known as blood grouping. There are thirty different systems of blood grouping. Blood group was first discovered by Landsteiner in 1901. The basis of blood grouping is the presence or absence of antigens and antibodies. Two types of blood grouping are clinically important. They are ABO system of grouping and Rh blood grouping. **Blood Group Systems recognised by the International Society for Blood Transfusion ABO MNS P Rh Lutheran Kell Lewis Duffy Kid Diego Yt Xg ABO system of classification DOMBrod Colton LW Chi do H Kx Gerbich Cromer Knops Indian Ok MER2** According to this classification human blood is classified into four types. A, B, AB and O. The criteria for the classification is presence or absence of antigens and antibodies or agglutinogen and agglutinins. The antigens are mucopolysaccharides present in the cell wall of the R.B.C. Antibodies are gammaglobulins present in the plasma. In the blood group A, antigen A is present in the cell wall of the R.B.C. and beta antibody in the plasma. In the blood group B, antigen B is present in the cell wall of the R.B.C. and alpha antibody is present in the plasma. In AB blood group both antigen A and antigen B are present in the cell wall of the R.B.C. and no antibody in the plasma. In the blood group O, no antigen is present in the cell wall of R.B.C. but both alpha and beta antibodies are present in the plasma. The α β antibodies belong to IgM category.

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