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2nd Edition

HUMAN PHYSIOLOGY

for Medical Students

With Case Scenarios & Clinical Applications

Updated MCQs and Review Questions

As per the Competency-based Medical Education Curriculum (NMC)



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PY1.2	Describe and discuss the principles of homeostasis	Y	3	11
PY1.3	Describe intercellular communication	Y	61	554
PY1.4	Describe apoptosis – programmed cell death	Y	4	29
PY1.5	Describe and discuss transport mechanisms across cell membranes	Y	5	34
PY1.6	Describe the fluid compartments of the body, its ionic composition and measurements	Y	2 20	7 183
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PY1.8	Describe and discuss the molecular basis of resting membrane potential and action potential in excitable tissue	Y	6	48
PY2.1	Describe the composition and functions of blood components	Y	11	99
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PY2.7	Describe the formation of platelets, functions, and variations	Y	17	159
PY2.8	Describe the physiological basis of hemostasis, and anticoagulants. Describe bleeding and clotting disorders (Hemophilia, purpura)	Y	18	164
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PY3.1	Describe the structure and functions of a neuron and neuroglia; Discuss nerve growth factor and other growth factors/cytokines	Y	6	44
PY3.2	Describe the types, functions and properties of nerve fibers	Y	6	44
PY3.3	Describe the degeneration and regeneration in peripheral nerves	Y	6	58
PY3.4	Describe the structure of neuro-muscular junction and transmission of impulses	Y	8	79
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PY3.6	Describe the pathophysiology of myasthenia gravis	Y	8	82
PY3.7	Describe the different types of muscle fibers and their structure	Y	7	65
PY3.8	Describe action potential and its properties in different muscle types (skeletal and smooth)	Y	7 10	68 91
PY3.9	Describe the molecular basis of muscle contraction in skeletal and in smooth muscles	Y	7 10	69 92
PY3.10	Describe the mode of muscle contraction (isometric and isotonic)	Y	7	71
PY3.11	Explain energy source and muscle metabolism	Y	7	73
PY3.12	Explain the gradation of muscular activity	Y	7	75

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Number	Competency: The student should be able to	Core(Y/N)	Chapter Number	Page Number
PY3.13	Describe muscular dystrophy: myopathies	Y	7	75
PY3.17	Describe strength-duration curve	Y	6	55
PY4.1	Describe the structure and functions of digestive system	Y	44	405
PY4.2	Describe the composition, mechanism of secretion, functions, and regulation of saliva, gastric, pancreatic, intestinal juices and bile secretion	Y	45 46 47 48 49 50	416 425 438 444 452 455
PY4.3	Describe GIT movements, regulation and functions. Describe defecation reflex. Explain role of dietary fiber	Y	50 51	456 459
PY4.4	Describe the physiology of digestion and absorption of nutrients	Y	52	469
PY4.5	Describe the source of GIT hormones, their regulation and functions	Y	53	477
PY4.6	Describe the Gut-Brain axis	Y	44	409
PY4.7	Describe and discuss the structure and functions of liver and gallbladder	Y	48	443, 447
PY4.8	Describe and discuss gastric function tests, pancreatic exocrine function tests and liver function tests	Y	47 48	441 448
PY4.9	Discuss the physiology aspects of: peptic ulcer, gastroesophageal reflux disease, vomiting, diarrhea, constipation, adynamic ileus, Hirschsprung's disease	Y	46 51	432 463, 466
PY5.1	Describe the functional anatomy of heart including chambers, sounds; and pacemaker tissue and conducting system	Y	22	202
PY5.2	Describe the properties of cardiac muscle including its morphology, electrical, mechanical and metabolic functions	Y	9 22	85 208
PY5.3	Discuss the events occurring during the cardiac cycle	Y	24	224
PY5.4	Describe generation, conduction of cardiac impulse	Y	22	205
PY5.6	Describe abnormal ECG, arrhythmias, heart block and myocardial infarction	Y	23	212 217
PY5.7	Describe and discuss hemodynamics of circulatory system	Y	25	234
PY5.8	Describe and discuss local and systemic cardiovascular regulatory mechanisms	Y	26 28	243 261
PY5.9	Describe the factors affecting heart rate, regulation of cardiac output and blood pressure	Y	26 27 28	243 253 263
PY5.10	Describe and discuss regional circulation including microcirculation, lymphatic circulation, coronary, cerebral, capillary, skin, fetal, pulmonary and splanchnic circulation	Y	19 32 36	179 290 343
PY5.11	Describe the patho-physiology of shock, syncope and heart failure	Y	28	272
PY5.12	Record blood pressure and pulse at rest and in different grades of exercise and postures in a volunteer or simulated environment	Y	29	281
PY5.16	Record arterial pulse tracing using finger plethysmography in a volunteer or simulated environment	N	29	281
PY6.1	Describe the functional anatomy of respiratory tract	Y	33	315
PY6.2	Describe the mechanics of normal respiration, pressure changes during ventilation, lung volume and capacities, alveolar surface tension, compliance, airway resistance, ventilation, V/P ratio, diffusion capacity of lungs	Y	34 35 36 37	322 331 348 351
PY6.3	Describe and discuss the transport of respiratory gases: Oxygen and Carbon dioxide	Y	38	357
PY6.4	Describe and discuss the physiology of high altitude and deep sea diving	Y	40	386
PY6.5	Describe and discuss the principles of artificial respiration, oxygen therapy, acclimatization and decompression sickness	Y	39 40 42	380 389 398
PY6.6	Describe and discuss the pathophysiology of dyspnea, hypoxia, cyanosis asphyxia; drowning, periodic breathing	Y	39	378
PY6.7	Describe and discuss lung function tests and their clinical significance	Y	43	401
PY7.1	Describe structure and function of kidney	Y	54	483

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Number	Competency: The student should be able to	Core(Y/N)	Chapter Number	Page Number
PY7.2	Describe the structure and functions of juxtaglomerular apparatus and role of renin-angiotensin system	Y	54	487
PY7.3	Describe the mechanism of urine formation involving processes of filtration, tubular reabsorption and secretion; concentration and diluting mechanism	Y	55	494
PY7.4	Describe and discuss the significance and implication of renal clearance	Y	55	496 509
PY7.5	Describe the renal regulation of fluid and electrolytes and acid-base balance	Y	55	498
PY7.6	Describe the innervations of urinary bladder, physiology of micturition and its abnormalities	Y	55 56	509 519
PY7.7	Describe artificial kidney, dialysis and renal transplantation	Y	55	514
PY7.8	Describe and discuss renal function tests	Y	57	524
PY7.9	Describe cystometry and discuss the normal cystometrogram	Y	56	521
PY8.1	Describe the physiology of bone and calcium metabolism	Y	66	608
PY8.2	Describe the synthesis, secretion, transport, physiological actions, regulation and effect of altered (hypo and hyper) secretion of pituitary gland, thyroid gland, parathyroid gland, adrenal gland, pancreas and hypothalamus	Y	62 63 65 66 67 68	565, 579 582 591 610 620 640
PY8.3	Describe the physiology of thymus and pineal gland	Y	64 69	587 654
PY8.4	Describe function tests: Thyroid gland; adrenal cortex, adrenal medulla and pancreas	Y	65 67 68	599 620 640
PY8.5	Describe the metabolic and endocrine consequences of obesity and metabolic syndrome, stress response. Outline the psychiatry component pertaining to metabolic syndrome	Y	68	648
PY8.6	Describe and differentiate the mechanism of action of steroid, protein and amine hormones	Y	61	552 555
PY9.1	Describe and discuss sex determination; sex differentiation and their abnormiities and outline psychiatry and practical implication of sex determination	Y	71	665
PY9.2	Describe and discuss puberty: onset, progression, stages; early and delayed puberty and outline adolescent clinical and psychological association	Y	71	670
PY9.3	Describe male reproductive system: functions of testis and control of spermatogenesis and factors modifying it and outline its association with psychiatric illness	Y	72	673
PY9.4	Describe female reproductive system: (a) functions of ovary and its control; (b) menstrual cycle—hormonal, uterine and ovarian changes	Y	73	684
PY9.5	Describe and discuss the physiological effects of sex hormones	Y	72 73	678 690
PY9.6	Enumerate the contraceptive methods for male and female. Discuss their advantages and disadvantages	Y	77	714
PY9.7	Describe and discuss the effects of removal of gonads on physiological functions	Y	72	680
PY9.8	Describe and discuss the physiology of pregnancy, parturition and lactation and outline the psychology and psychiatry—disorders associated with it	Y	74 76	701, 706 711
PY9.9	Interpret a normal semen analysis report including (a) sperm count, (b) sperm morphology, and (c) sperm motility, as per WHO guidelines and discuss the results	Y	72	678
PY9.10	Discuss the physiological basis of various pregnancy tests	Y	74	705
PY9.11	Discuss the hormonal changes and their effects during perimenopause and menopause	Y	73	696
PY9.12	Discuss the common causes of infertility in a couple and role of IVF in managing a case of infertility	Y	77	717
PY10.1	Describe and discuss the organization of nervous system	Y	78	721
PY10.2	Describe and discuss the functions and properties of synapse, reflex, receptors	Y	79 80 81	731 747 761

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Number	Competency: The student should be able to	Core(Y/N)	Chapter Number	Page Number
PY10.3	Describe and discuss somatic sensations and sensory tracts	Y	80 81 82	747 761 770
PY10.4	Describe and discuss motor tracts, mechanism of maintenance of tone, control of body movements, posture and equilibrium and vestibular apparatus	Y	84 89 90	798 838 845
PY10.5	Describe and discuss structure and functions of reticular activating system, autonomic nervous system (ANS)	Y	88 94	835 863
PY10.6	Describe and discuss spinal cord, its functions, lesion and sensory disturbances	Y	85	810
PY10.7	Describe and discuss functions of cerebral cortex, basal ganglia, thalamus, hypothalamus, cerebellum and limbic system and their abnormalities	Y	83 86 87 91 92 93	794 815 825 849 855 860
PY10.8	Describe and discuss behavioral and EEG characteristics during sleep and mechanism responsible for its production	Y	95	873
PY10.9	Describe and discuss the physiological basis of memory, learning and speech	Y	96	882
PY10.13	Describe and discuss perception of smell and taste sensation	Y	100 101	965 969
PY10.14	Describe and discuss patho-physiology of altered smell and taste sensation	Y	100 101	965, 968 973
PY10.15	Describe and discuss functional anatomy of ear and auditory pathways and physiology of hearing	Y	99	943
PY10.16	Describe and discuss pathophysiology of deafness. Describe hearing tests	Y	99	957
PY10.17	Describe and discuss functional anatomy of eye, physiology of image formation, physiology of vision including color vision, refractive errors, color blindness, physiology of pupil and light reflex	Y	98	901
PY10.18	Describe and discuss the physiological basis of lesion in visual pathway	Y	98	930
PY10.19	Describe and discuss auditory and visual evoke potentials	Y	99	960
PY11.1	Describe and discuss mechanism of temperature regulation	Y	59	534
PY11.2	Describe and discuss adaptation to altered temperature (heat and cold)	Y	59	540
PY11.3	Describe and discuss mechanism of fever, cold injuries and heat stroke	Y	59	540
PY11.4	Describe and discuss cardio-respiratory and metabolic adjustments during exercise; physical training effects	Y	30 41 102	285 395 977
PY11.5	Describe and discuss physiological consequences of sedentary lifestyle	Y	102	977
PY11.6	Describe physiology of infancy	N	102	977
PY11.7	Describe and discuss physiology of aging; free radicals and antioxidants	N	102	977
PY11.8	Discuss and compare cardio-respiratory changes in exercise (isometric and isotonic) with that in the resting state and under different environmental conditions (heat and cold)	Y	102	977
PY11.11	Discuss the concept, criteria for diagnosis of brain death and its implications	Y	102	977
PY11.12	Discuss the physiological effects of meditation	N	95	878
PY11.14	Demonstrate basic life support in a simulated environment	Y	42	399

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Cell Physiology

CHAPTER 4

LEARNING OBJECTIVES

Must know

- Describe the structure and functions of a mammalian cell
- Discuss the functions of the cell organelles and its clinical importance
- Draw the electron microscopic structure of a typical mammalian cell
- Describe the structure of the cell membrane and enumerate the functions of cell membrane proteins
- Explain the functions of proteasomes and its clinical importance
- Explain the steps in apoptosis and its clinical significance
- Briefly mention the different intercellular junctions and their functions

Desirable to know

- Describe mitosis and meiosis with the help of diagrams
- Explain human genome project
- Describe the types of mutations
- Discuss cloning and DNA fingerprinting

INTRODUCTION

PY1.1: Describe the structure and functions of a mammalian cell.

Cell theory, proposed by German physiologists **Matthias Schleiden** and **Theodor Schwann**, states that all living things are made up of cells and it is the basic structural, functional and smallest living unit of the body. In 1665, **Robert Hook** coined the word 'cell.' About 200 different types of specialized cells are present in the body. Each type of cell performs a particular function. Size of the different cells varies depending on the function. The cell with the largest diameter is an oocyte with a diameter of about 140 mm. Longest cells are neurons in the pyramidal tract reaching the sacral segments of spinal cord. There are about 100 trillion cells in the human body, the most abundant being red blood corpuscles (25 trillion). Almost all cells of the body have the ability to reproduce, except most of the neurons (bipolar neurons of olfactory mucosa and hippocampal neurons can regenerate).

Cell biology is the study of cellular structure and function.

PARTS OF A CELL

The parts of a cell include:

- Plasma membrane or cell membrane
- Cytoplasm
- Nucleus.

PLASMA MEMBRANE

Each cell is enclosed by a membrane called plasma membrane, which separates intracellular fluid from extracellular fluid. It is a **selectively permeable** membrane, which regulates transport of substances into and out of the cell. It allows some substances to pass through it and excludes others. The permeability can be varied due to the presence of ion channels and other transport proteins. The nucleus and other organelles are also surrounded by a membrane.

CYTOPLASM

Cytoplasm consists of all the contents of cell between the plasma membrane and nucleus. It is divided into **cytosol** and **organelles**. Cytosol is the fluid portion of cytoplasm containing water, solutes, suspended particles, etc. Organelles, also known as **little organs**, have characteristic shape and perform specific functions, e.g., ribosome, endoplasmic reticulum, Golgi complex, lysosome, peroxisomes, mitochondria, etc. **(Fig. 4.1)**.

NUCLEUS

Nucleus contains most of the DNA in the cell. It contains chromosomes and each chromosome contains thousands of hereditary units called genes that control all the functions of the cell.

PLASMA MEMBRANE

Structure of Cell Membrane

Under electron microscopy, cell membrane is a three- layered structure showing an outer electron dense layer, middle electron loosened layer and inner electron dense layer. **Osmium tetroxide** is the fixative used in electron microscopy.

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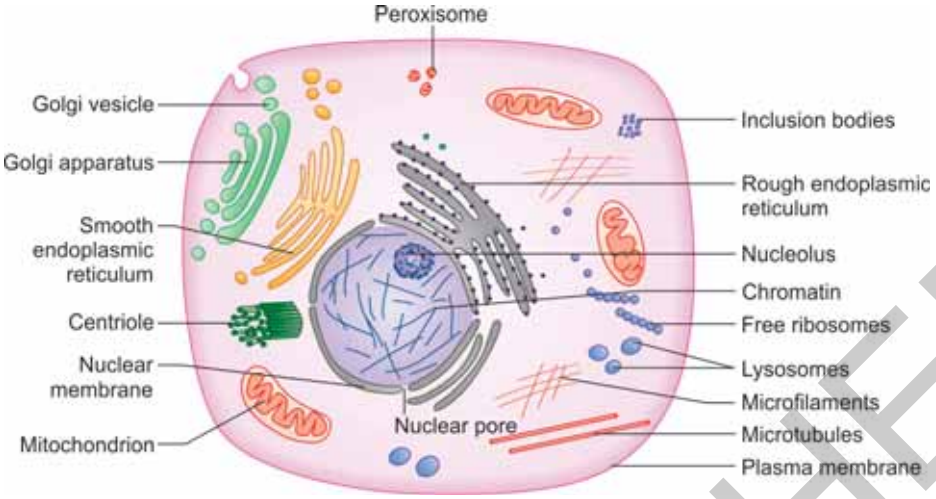

Fig. 4.1: Electron microscopic structure of cell.

Thickness of the cell membrane is about 7.5 nm or 75 angstroms [A^0]. Membrane is primarily **lipoprotein** in nature and sometimes it may be **glycoprotein**. The approximate composition is 55% proteins, 25% phospholipids, 13% cholesterol, 4% other lipids and 3% carbohydrate.

The lipids are **phospholipids, cholesterol** and **sphingomyelin**. Phospholipids are **phosphatidylcholine, phosphatidylserine** and **phosphatidylethanolamine**. The shape of the phospholipid molecule is roughly that of a clothes-pin. The head end of the molecule contains a phosphate portion and is relatively soluble in water and is called **polar or hydrophilic end**. The tail portion is relatively insoluble and is called **nonpolar or hydrophobic end**. The uncharged hydrophobic end resides within the depth of the cell membrane and the charged hydrophilic end is exposed to the ECF and cytoplasm **(Fig. 4.2)**.

There are different proteins embedded in the cell membrane. Proteins may be **integral proteins or peripheral proteins**. Integral proteins exist as separate globular units and pass through the membrane. Peripheral proteins stud the inside and outside of the membrane. The proteins are held to the cell surface by *glycosyl phosphatidylinositol* (GPI) anchors. When the protein extends throughout the thickness of the membrane, it is called **transmembrane protein channel**. The amount of protein varies significantly with the function of the cell but makes up an average 50% of the mass of the membrane.

Plasma membranes are dynamic structures because most of the membrane lipids and membrane proteins rotate easily and move sideways in their own half of the lipid bilayer. They seldom move from one half of the bilayer to the other. Therefore, the halves of the membrane bilayer remain asymmetric. Cholesterol molecules are dissolved in the lipid bilayer and it controls much of the fluidity of the membrane. The structure of cell membrane is referred to as **fluid mosaic model.** This fluidity helps the cell to undergo significant changes in shape (during cell movement, cell division, endocytosis, exocytosis, etc.) without affecting their structural integrity.

In vitro fertilization (IVF) is possible because of the **plasma membrane fluidity**. A sperm cell can be injected into an oocyte through a tiny syringe in IVF. The puncture site seals spontaneously because of the fluid nature of the cell membrane. This property of lipid bilayer also helps in cloning experiments, where the nucleus is removed from a cell and replaced by another.

Functions of Cell Membrane

- Protection of the cell contents: Cell membrane forms a physical barrier between the intracellular and extracellular compartments.
- Maintains the structural integrity of the cell and provide shape to the cell.

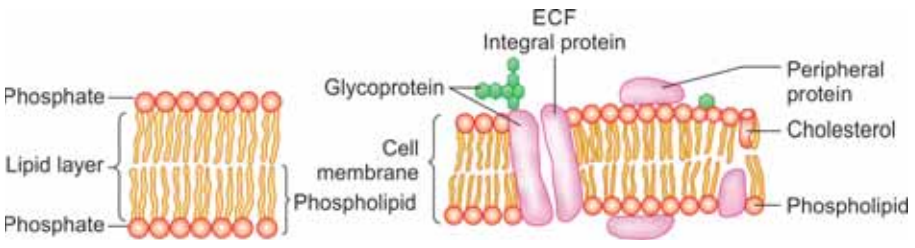

Fig. 4.2: Structure of cell membrane.

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- Cell membrane being a selectively permeable membrane helps in the transport of substances across it and helps to maintain the composition of intracellular fluid and extracellular fluid constant.
- Gases like oxygen, carbon dioxide, nitrogen; lipids, steroid hormones, etc., can move freely across the cell membrane.
- It helps in endocytosis and exocytosis.
- It contributes to intercellular connections.
- The cell membrane proteins serve several functions (details are given below).

Functions of Cell Membrane Proteins

- *Structural proteins or integral proteins* contribute to the structure of cell membrane.
- Some cell membrane proteins are *cell adhesion molecules* that anchor cells to their neighbors or to the basal lamina, e.g., integrin, cadherin, selectin, etc.
- Some proteins function as *pumps* for active transport of substances in the direction opposite to their electrochemical gradients for diffusion, e.g., Na^+–K^+ pump.
- *Some integral proteins act as carrier proteins* for the transport of substances which could not penetrate the lipid bilayer, down their electrochemical gradient, e.g., glucose transporters (GLUT).
- *Proteins act as ion channels* which permit the passage of ions into or out of the cell when activated, e.g., Na^+ channel, Ca^{2+} channel, etc.
- Aquaporins are membrane proteins present in most cells, which act as *water channels* permitting high rate of water flow through the membrane.
- Peripheral proteins act as *enzymes*, catalyzing chemical reactions on the membrane surface. For example, the enzymes located on the side of the intestinal cells that faces the lumen of the intestine, break down small polysaccharides into simple sugars or break down polypeptides to amino acids so that they can be transported into the cells.
- Some membrane proteins act as *receptor sites* for hormones and neurotransmitters, e.g., acetyl choline (ACh) receptor, insulin receptor, etc. Integral proteins act as receptors for water-soluble hormones like peptide hormones which cannot penetrate the cell membrane. They help to relay the signal from the extracellular part of the receptor to the interior of the cell. Thus they provide a means of conveying information about the environment to the interior of the cell.
- Membrane proteins like glycoproteins and glycolipids act as *cell identity markers.* ABO blood group antigens on the RBC membrane, major histocompatibility complex (MHC) protein, etc., are the examples.
- Glycoproteins function as antigens in antibody processing and also help in distinguishing self from non-self.

CYTOPLASM

Cytoplasm consists of **cytosol and cell organelles**.

CYTOSOL

Fluid portion of cytoplasm, which constitutes 55% of total cell volume, is called **cytosol**; 75–90% of cytosol is composed of water and the rest by solids. The solids include ions, glucose, amino acids, fatty acids, proteins, lipids, enzymes, ATP, waste products, etc. It also contains stored foods like glycogen granules, lipid droplets, etc., which are called **cell inclusions**. Most of the chemical reactions in the cell occur in the cytosol.

Cell inclusions are chemical substances produced by the cell and are not bound by membrane, e.g., **melanin** in skin, hair, eye, etc., protect body from harmful ultraviolet rays of sun. **Glycogen** is a polysaccharide stored in liver, skeletal muscle, uterus, vagina, etc., which is broken down to glucose in times of need. **Triglycerides** are stored in adipocytes (fat cells) and are broken down to release energy. It constitutes 95% of the cell mass of adipocyte.

Proteins constitute 10–20% of the cell mass. They are divided into structural and functional proteins. Structural proteins are present in the cell in the form of long filaments which form the cytoskeleton in the cell. Functional proteins are mainly the enzymes of the cell which catalyze intracellular chemical reactions.

Cytoskeleton

Cytoskeleton is a network of different kinds of protein filaments present in the cytosol. It provides a structural framework for the cell. It also helps in the movement of organelles in the cell, movement of chromosomes during cell division and also helps in the phagocytic activity. Three types of filaments contribute to cytoskeleton:

1. Microfilaments
2. Intermediate filaments
3. Microtubules

Microfilaments

Microfilaments are the thinnest elements which are long solid fibers about 5–9 nm in diameter. They are composed of two F-actin strands that are coiled helically. It provides mechanical support and helps in the movement of the cell. Microfilaments are anchored to the plasma membrane by anchoring proteins. They are abundant at the zonula adherens.

The molecular motor of microfilament is myosin. Microfilaments help in muscle contraction, cell division, movement of phagocytes to the sites of inflammation, etc. Microfilaments also support microvilli of epithelial cells of the intestinal mucosa.

Intermediate Filaments

Intermediate filaments are thicker than microfilaments with a diameter of 8–14 nm. They are made up of **cytokeratin** in epithelial cells and **vimentin** is a major intermediate filament in fibroblasts. They serve as the flexible scaffolding for the cell, giving structural strength to it. They help to stabilize the position of organelles like nucleus where they connect the nuclear membrane to the cell membrane. Intermediate filaments are also present in desmosomes. In the absence of

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intermediate filaments, cells rupture more easily, and when they are abnormal, blistering of the skin is seen.

Microtubule

Microtubule is the **largest** cytoskeletal component. They are long, unbranched hollow tubes about 15–20 nm in diameter composed of the protein, **tubulin** (α-tubulin and β-tubulin subunits). Centrosome is the site of formation of microtubules. A third subunit, γ-tubulin, is associated with the production of microtubules in centrosomes. Functions of microtubules are:

- ❖ They help to maintain cell shape and also help in the movement of secretory vesicles and mitochondria from one part of the cell to another. Movement is associated with molecular motors called **kinesins** and **dyneins**. These proteins help to propel substances and organelles along a microtubule. Cargo can be transported in either direction on microtubules.
- ❖ They form mitotic spindle and participate in the movement of chromosomes during cell division.
- ❖ They also help in the movement of cilia and flagella.

APPLIED ASPECT

Anti-cancerous drugs like **vincristine** destroy microtubules in the highly mitotic tumor cells and thus prevent cell division and further growth of the tumor. Colchicine and vinblastine prevent microtubule assembly. Paclitaxel (Taxol), the anticancer drug, binds to microtubules and make them so stable that organelles cannot move. Mitotic spindle cannot be formed and the cells die.

Molecular Motors

Molecular motors are 100–500-kDa ATPases that move proteins, organelles and other cell parts (collectively referred to as cargo) to all parts of the cell. Each consists of two domains. First domain attach to the cargo at one end and at the other end, the second domain, i.e., the head binds to microtubules or actin polymers. Head part has ATPase activity. Hydrolysis of ATP in their heads causes the molecules to move. There are three super families of molecular motors; kinesins (associated with mitosis and meiosis), dyneins (in cilia and flagella) and myosin (in muscle contraction).

Diseases associated with molecular motor dysfunction include Charcot Marie tooth type 2A, polycystic kidney disease, retinitis pigmentosa, lissencephaly, primary ciliary dyskinesia or Kartagener's syndrome and myosin storage myopathy.

Functions of Molecular Motors

- ❖ Transport of vesicles in the cytoplasm
- ❖ Ciliary movement and movement of mucus on epithelium
- ❖ Movement of chromosomes during cell division
- ❖ Movement of myofilament during muscle contraction.

Molecular motors are also classified as:

- ❖ **Microtubule-based molecular motors** produce motion along microtubules, e.g., conventional kinesin and dyneins.
- ❖ **Actin-based molecular motors** produce motion along, actin, e.g., myosin I to V involved in muscle contraction and cell migration.

Kinesin

Conventional form of kinesin is double headed and tends to move its cargo towards the positive ends of microtubules (orthograde). In neurons, kinesin bound vesicles move from microtubular (negative) ends originating at the centromere in the cell body towards the positive end in axons. This is known as anterograde fast axonal transport. Some kinesins are associated with mitosis and meiosis.

Dynein

Dyneins are the fastest molecular motors which move at a speed of 14 μm/sec as compared to kinesin which move cargo at a rate of 2 μm/sec. Dyneins are of two types: **Cytoplasmic form and axonemal form.** Cytoplasmic dynein move particles and membranes to the negative end of the microtubules, i.e., retrograde motion from periphery to center of cell. It helps in positioning Golgi complexes and other organelles in the cell. It is also involved in movement of chromosomes and positioning mitotic spindle for cell division. Axonemal dynein oscillates and is responsible for the beating of flagella and cilia. They have microtubular "9+2" arrangement.

Myosin

The multiple forms of myosin are divided into 18 classes. It is an actin-based molecular motor. Myosin I to V are the main actin-based molecular motors. Myosin molecules are tadpole shaped with head and tail and a total length of 150 nm. Head is 15–25 nm long and 4 nm thick. Tail is 1.5–2 nm thick. Both muscle myosin and non-muscle myosin show binding to actin to form actomyosin. It contains Ca^{2+} activated ATPase. Myosin constitutes 54% of myofibril with molecular weight 450,000. The heads of myosin molecule binds to actin and produce motion by bending their neck regions around pivot point called hinge region. Thus they perform functions like

- ❖ Muscle contraction
- ❖ Contraction of intestinal villi
- ❖ Cell migration.

Cilia and Flagella

Cilia and flagella are motile processes of cells. Both have the same diameter, but flagella are about 10 times longer. Cilia usually occur in large numbers on cell surface, while flagella are usually limited to one or two per cell. Mucociliary transport seen in the respiratory tract is a function of cilia. Movement of sperm is due to flagellar action.

Dynein is the molecular motor responsible for the beating of cilia and flagella.

Primary ciliary dyskinesia refers to a group of inherited disorders that limit ciliary structure and function. In Kartagener's syndrome, the molecular motor protein dynein responsible for ciliary beating and flagellar movement is absent congenitally. These patients suffer from airway obstruction and infection (bronchiectasis), infertility due to lack of sperm motility, etc.

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CELL ORGANELLES

An **organelle** is a membrane-bound structure present in the cytoplasm, which can be isolated by ultracentrifugation. It includes the mitochondria, endoplasmic reticulum, Golgi apparatus, peroxisome, and lysosome. *The nucleolus, ribosomes, and cytoskeleton proteins are not considered as organelles because they are not membrane bound.* Different types of reactions occur in different organelles. Each organelle has its own enzymes, which carry on specific cell reactions. The number and type of organelles depend on the functional state of the cell. Some consider nucleus as a large organelle **(Fig. 4.1)**.

Centrosome

Centrosome consists of a pair of **centrioles** and **pericentriolar material**. The centrioles are cylindrical structures, and each is composed of nine clusters of 3 microtubules arranged in a circular pattern. Pericentriolar material contains hundreds of ring-shaped complexes composed of protein **tubulin**. These proteins play a critical role in cell division. The centrosome is also called microtubule-organizing center. When a cell divides, the centrosomes duplicate themselves and the pairs move apart to form the poles of the mitotic spindles, which are made of microtubules. *Neurons lack centrosome and hence, cannot divide.*

Ribosomes

Ribosomes are small granules, which contain ribosomal RNA (rRNA) and many proteins. The rRNA is synthesized by DNA in the nucleolus. Ribosomes are the site of protein synthesis in the cell. Ribosomes are of two types: **free ribosomes** present in the cytoplasm and **bound ribosomes** located in the rough endoplasmic reticulum. Free ribosomes synthesize cytoskeletal proteins and other cytoplasmic proteins such as hemoglobin. Bound ribosomes synthesize all membrane proteins and most of the proteins that are secreted by the cell.

The ribosomes of eukaryotes and prokaryotes are different. Hence, in bacterial infections, antibiotics are able to selectively inhibit the prokaryotic ribosomes of the bacteria but not of the human cells. Thus, only the bacteria are destroyed following antibiotic therapy.

Endoplasmic Reticulum

Endoplasmic reticulum is a system of membrane-enclosed channels of varying shapes, called *cisterns*. Endoplasmic reticulum is continuous with the nuclear membrane. Two types of endoplasmic reticulum are **rough endoplasmic reticulum (RER)** studded with ribosomes and **smooth endoplasmic reticulum (SER)**, which has no ribosomes attached to it. RER synthesizes proteins and helps in the storage of proteins as glycoproteins.

SER is the site of synthesis of fatty acids, phospholipids, steroids, etc. Steroid secreting cells are rich in SER. In skeletal and cardiac muscle cells, SER is called sarcoplasmic reticulum, from which Ca^{2+} is released during muscle contraction. SER is also the site of detoxification of drugs and poisons, especially in liver cells. *Glucose 6-phosphatase is the marker enzyme for SER.*

Golgi Apparatus

Golgi apparatus is an organelle with **secretory activity**. In secretory cells, Golgi complex is extensive. It consists of flattened sacs called **cisterns**, which are arranged in the form of a pile of plates. Associated with cisterns are **Golgi vesicles**. The Golgi complex processes and delivers proteins and lipids to plasma membrane and also forms lysosome and secretory vesicles. The secretory vesicles bud off from the cistern into the cytoplasm and are finally exocytosed to the cell exterior.

Most of the substances synthesized in the smooth endoplasmic reticulum enter the Golgi apparatus. The substances are modified and encased in vesicles for secretion. Raw proteins are modified and carbohydrates are added to them. The substances include hormones, enzymes, etc. In addition to processing the substances already formed in the endoplasmic reticulum, Golgi apparatus also synthesize substances that cannot be formed in the endoplasmic reticulum like hyaluronic acid and chondroitin sulphate.

Lysosomes

Lysosomes discovered by Belgian biologist, Christian de Duve (Nobel prize in physiology in 1974) are membrane- enclosed vesicles, which are budded off from the Golgi complex. It is present in nearly all animal cells and forms the **digestive apparatus** of the cell. Lysosomal enzymes are synthesized in the RER and then processed by the Golgi apparatus. There are about 40 different types of hydrolytic enzymes inside the lysosomes contained in small granules 5–8 μm in diameter. Lysosomal enzymes are utilized for digesting large molecules of proteins, polysaccharides, fats and nucleic acids. *The marker enzyme for lysosome is acid phosphatase.*

The interior of lysosome is acidic due to the presence of active H^+ pumps in the membrane, which pump H^+ into the lysosomes from the cytosol. The lysosomal pH is 5, which is the optimum pH for the activity of lysosomal enzymes.

Functions of Lysosomes

- Lysosomes remove old and worn out organelles by **autophagy**. Sometimes, lysosomal enzymes destroy the host cell by a process called **autolysis** when damaged cells cannot be repaired. Lysosomal enzymes released at the site of inflammation help to digest cellular debris, bacteria, etc., and prepare the area for repair.
- The granules of neutrophils, eosinophils and basophils are actually lysosomes. Bacteria, worn out cells, viruses, etc., engulfed by phagocytosis by neutrophils, macrophages, etc., form phagosome and it fuses with the lysosomal membrane. The lysosomal enzymes digest the ingested material and the residue is excreted out by exocytosis. Sometimes in some cells the residual body remains as **lipofuscin granules** and it contributes to cell aging. By determining the amount of lipofuscin in a cell, the age of the cell can be determined.

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- Apoptosis by lysosomal enzymes is often important in the process of development. For example, in the embryonic stage, the hands are webbed till lysosomes digest the tissues between the fingers. Lysosomes also help in the regression of tissues like uterus after delivery, muscles after long period of inactivity, etc.

Lysosomal storage disorders: There are many diseases due to faulty lysosomes. When a lysosomal enzyme is congenitally absent, it results in one of a group of disorders called **lysosomal storage disorders**. In this condition, lysosomes become engorged with indigestible substrates. There are over 50 such diseases. For example, **Tay-Sachs disease** is due to congenital absence of a lysosomal enzyme, hexosaminidase-A, which breaks down a membrane glycolipid, ganglioside (GM2) present in nerve cells. GM2 accumulates in Tay-Sachs disease, which leads to impaired nerve function like mental retardation and blindness due to the engorgement of brain cells with the lipid. Others include **Fabry disease** caused by deficiency of α-galactosidase and **Gaucher's disease** caused deficiency of β-galactocerebrosidase. In **Niemann-Pick disease**, there is deficiency of acid sphingomyelinase and sphingomyelin accumulates in lysosomes. The symptoms are related to the organ in which sphingomyelin accumulates. Main features are hepatosplenomegaly, thrombocytopenia, ataxia, dysarthria, dementia and seizures.

Peroxisomes

Peroxisomes or microbodies are single membrane bound organelles present in all eukaryotic cells except RBCs. They are named peroxisomes because they perform hydrogen peroxide based respiration. Due to their small size, they are called microbodies. They are similar to lysosomes, but smaller in size (0.5 μm in diameter). They are rich in enzymes like peroxidase, catalase, D-amino acid oxidase and to a lesser extent urate oxidase **(Table 4.1)**. They contain nearly 50 metabolic enzymes that oxidize various organic substances producing H_2O_2. *Marker enzymes for peroxisomes are catalase and urate oxidase.*

Peroxisomes are formed from endoplasmic reticulum and after 4–5 days they are destroyed by autophagy. The enzymes of peroxisomes are synthesized from ribosomes of endoplasmic reticulum. Proteins are also directed into peroxisomes by the help of protein chaperons called peroxins which are coded by PEX genes. There are about 32 **peroxins** which carry about peroxisomal function inside the organelle.

Peroxisomes are present in plenty in the liver and tubular epithelial cells of kidney. In the liver peroxisomes detoxify alcohol and other harmful compounds. For example, catalase is an enzyme, which uses H_2O_2 to oxidize toxic substances present in blood like phenol, formic acid, formaldehyde, etc., especially in the liver and kidney. Drugs used for lowering blood lipids like clofibrate, causes an increase in the number of peroxisomes and these drugs are referred to as peroxisome proliferators.

Table 4.1: Differences between lysosomes and peroxisomes.

Lysosomes	*Peroxisomes*
Larger	Smaller
Formed from Golgi apparatus	Formed by self-replication or budding from smooth ER
Digestive organ of cell	Detoxifying organ of the cell
Contain hydrolases	Contain oxidases and catalase and form H_2O_2
Help in intracellular digestion of food, bacteria, damaged cell structures, etc.	Along with catalase, help in the detoxification of injurioussubstances

Functions of Peroxisomes

It include both catabolic and anabolic functions:

- Oxidation of very long chain fatty acids (more than 22 carbon atoms) like phytanic acid which cannot be directly performed in the mitochondria occurs in the peroxisomes. They are converted to medium and short chain fatty acids.
- Oxidation of ceruloplasmin and release of copper
- Oxidation of purine and release of uric acid
- D-amino acids like D-aspartate are oxidized in peroxisomes by D-amino oxidase (most of the human amino acids are L amino acids)
- Polyamine oxidation
- Reduction of H_2O_2 by catalase present in peroxisomes to reduce oxidative stress. 40% of protein in peroxisome is catalase which converts excess H_2O_2 to water and oxygen.
- It plays a key role in the production and scavenging of reactive oxygen species.
- About half of the alcohol ingested is detoxified by the peroxisomes of liver cells.
- Peroxisomes also have **anabolic functions** like synthesis of plasmalogens (a class of glycerophospholipids required for the proper function of integral membrane proteins and for the generation of lipid second messengers), bile acids, etc. Myelin sheath contains higher concentration of plasmalogens (80–90%) and hence peroxisomal disorders present with neurological abnormalities.

APPLIED ASPECT

Mutations in the gene coding peroxisomal enzymes result in peroxisome biogenesis disorders (PBD) collectively called **Zellweger spectrum disorders.** It includes Zellweger syndrome (most severe form), neonatal adrenoleukodystrophy (intermediate form) and infantile Refsum disease (the mildest form). Zellweger spectrum disorders are caused by defects in any one of the 13 genes, termed PEX genes, required for the normal formation and functions of peroxisomes. The disease can affect most organs of the body.

Zellweger syndrome or cerebrohepatorenal syndrome: Average lifespan is 5–7 months. It is characterized by craniofacialdysmorphia and neurological abnormalities. Biochemical abnormalities include increased conjugated bilirubin, increased serum iron, hypoprothrombinemia and increased serum transaminase.

Neonatal adrenoleukodystrophy (NALD) is characterized by demyelination of white matter, atrophy of adrenal cortex, etc. There will be hypotonia, convulsions, absent grasp reflex, bronzing of skin, etc.

Infantile Refsum disease (IRD) is the mildest variant of the peroxisome biogenesis disorder characterized by hypotonia, retinitis pigmentosa, developmental delay, sensorineural hearing loss and liver dysfunction. It is due to accumulation of phytanic acid. Recent studies show that altered function of peroxisomes also plays a role in the development of **Alzheimer's disease, Parkinson's disease and multiple sclerosis.**

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Mitochondria

Mitochondria are filamentous or sausage-shaped organelle present in the cytoplasm of cells. The size, shape and the number of mitochondria in a cell depend on the type of the tissue and the activity of the cell. They are ovoid bodies having a diameter of 0.5 to 1 μm and a length between 2 to 7 μm. The number of mitochondria per cell varies from one to 10,000 depending on the cell functions; average per cell is around 200. It is a double-layered organelle; the outer layer is smooth and the inner membrane is arranged in a series of folds called **cristae**. The cavity of mitochondrion is filled with matrix.

The smooth outer membrane contains 50% lipids, cholesterol and phosphatidyl inositol. It has an integral protein called **porin** through which molecules with molecular weight less than 10,000 can diffuse freely. Outer membrane also contains enzymes involved in oxidation of epinephrine, degradation of tryptophan, elongation of fatty acids, etc. The inner membrane is not smooth, but folded inwards to form cristae. It contains more than 100 different polypeptides and a high protein/lipid ratio. It is devoid of cholesterol, but contains an unusual phospholipid **cardiolipin**. Inner membrane is impermeable and molecules and ions require special membrane transporters to gain entrance to the matrix. Inner membrane cristae are covered by particles of 8.5 nm size called elementary or F1 particles which are regularly spaced on the inner surface of the membrane. There are about 10^4 to 10^5 elementary particles per mitochondrion. These represent a special ATPase involved in coupling of oxidation and phosphorylation. The enzymes on the inner mitochondrial membrane are present in a highly organized, repetitive pattern of subunits, which facilitate sequential catalytic reactions.

Matrix has gel-like consistency owing to the presence of high concentration of water-soluble proteins. The enzymes in the matrix are involved in citric acid cycle and protein and lipid synthesis.

The matrix also contains ribosomes, RNA and DNA. Mitochondrial DNA is of maternal origin and this DNA can undergo self-replication and when required can form a second or third mitochondria. The enzymes needed for oxidative phosphorylation are coded by the mitochondrial DNA which is a double-stranded circular molecule containing approximately 16,500 base pairs. Other mitochondrial enzymes are synthesized in ribosomes in the cytoplasm and transported into the mitochondria. The mitochondria have machinery to synthesize protein necessary for proliferation of mitochondria and RNA. Human mitochondrial DNA encodes 2 ribosomal RNAs and 22 t-RNA that are used in protein synthesis. 5–10% of protein synthesis in the organelle is carried out by its own machinery.

Functions of Mitochondria

- Mitochondria are called the **powerhouses** of the cell since 95% of ATP is formed in them by **oxidative phosphorylation.** Main function of mitochondria is energy production by phosphorylation of ADP and generation of ATP (via TCA cycle), which forms the energy currency of the cell. Thus it helps in regulating cellular metabolism.
- Metabolic functions other than TCA cycle include beta oxidation of fatty acids, ketone body formation, urea synthesis, pyrimidine synthesis and gluconeogenesis.
- The inner membrane of mitochondria contains certain proteins involved in uptake and release of calcium ions and thus they play an important role in regulating the concentration of calcium in the cytosol. It acts as a reservoir of Ca^{2+} particularly in osteoblasts and calcifying tissue (the endoplasmic reticulum is the main site of cellular storage of calcium).
- Has a role in apoptosis. Cytochrome C released from mitochondria activates caspases and trigger apoptosis when cells are deprived of growth factors and other surviving signals.
- It helps in the production of heat (non-shivering thermogenesis which occurs in brown fat). The process is controlled by a protein called **thermogenin (UCP1)** present in brown fat.
- Recent studies show that it has a role in systemic inflammatory response. At the site of tissue damage, release of mitochondrial particles activates the immune system.

APPLIED ASPECT

Mitochondria contain mitochondrial DNA and so **can replicate** and increase their number. *Mitochondrial genes are inherited from the mother in contrast to nuclear genes, which are inherited from both parents*. The head of the sperm that penetrates the ovum lacks mitochondria. Mitochondria have an ineffective DNA repair system, and the mutation rate for mitochondrial DNA is over 10 times the rate for nuclear DNA. It leads to many diseases affecting organs with high metabolic requirement like heart and muscle. Here there will be abnormality in the production of ATP. Depending on the tissue affected, symptoms include altered motor control, gastrointestinal dysfunction, altered growth, visual or hearing problems, susceptibility to infections, cardiac, liver and respiratory diseases. Mitochondrial DNA abnormalities lead to diseases like Leber's hereditary optic neuropathy, cardiomyopathy; mitochondrial encephalopathy, lactic acidosis and stroke (MELAS); Pearson's syndrome characterized by pancreatic insufficiency, lactic acidosis and pancytopenia; metabolic syndrome (type II diabetes mellitus), etc.

Mitochondrial theory of aging: Since mitochondrial DNA is not protected by histones unlike nuclear DNA, they are most likely to get damaged by aging. Also since they are the major sources of reactive oxygen species, they are likely to be a major site of oxidative damage. This also contributes to aging.

Proteasomes

Lysosomes degrade proteins delivered to them in vesicles, which are phagocytosed from outside. Sometimes, the proteins formed in the cytoplasm also need to be removed from the cell. **Proteasomes** are tiny structures in the cell that cause continuous destruction of abnormal proteins and those proteins that are not needed, produced inside the cell. Up to 30% of newly produced proteins in the body are abnormal. Mutant or viral proteins formed in the cells are recognized by T lymphocytes and digested in the proteasomes.

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Desmosomes

Desmosomes are apposed thickenings of membranes of two adjacent cells. At the thickened part, the intercellular space contains **cadherins (Fig. 4.6)**. They attach cells to one another and are mainly seen between cells of epidermis and cardiac muscle cells. Desmosomes prevent cells from pulling apart during contraction, especially in cardiac muscle cells.

Hemidesmosomes

Hemidesmosomes appear like half desmosomes and they anchor cells to the basement membrane and not to each other. The cell adhesion molecules involved are **integrins** and not cadherins **(Fig. 4.6)**. On one side, the integrins are connected to the intermediate filament made up of the protein, **keratin**. On the other side, integrins are attached to the protein **laminins** present in the basal lamina.

Focal Adhesions

Focal adhesions attach cells to the basal lamina. They are associated with actin filaments inside the cell and they play an important role in cell movement.

Gap Junctions

Gap junctions form tunnels that join the cytoplasm of two cells. They also fuse the plasma membranes into a single structure. Normally, the width of the intercellular space is 25 nm. But at gap junctions, the intercellular space narrows to 3 nm.

Units called **connexons** line up in the cell membrane of each cell that contributes to the gap junction. Each connexon is made up of 6 protein subunits called **connexins (Fig. 4.6)**. The subunits surround a channel of diameter 2 nm and the channel of the connexon of one cell is continuous with the channel in the connexon of the adjacent cell at the gap junction. This permits substances to pass from one cell into the adjacent one without entering the ECF. For example, ions, sugars, amino acids, other solutes with molecular weight up to 1000 Da and certain chemical messengers pass from one cell to another through the gap junctions. As it allows ions to pass from one cell to the next cell, it helps in rapid propagation of electrical activity from cell to cell in certain tissues like cardiac muscle.

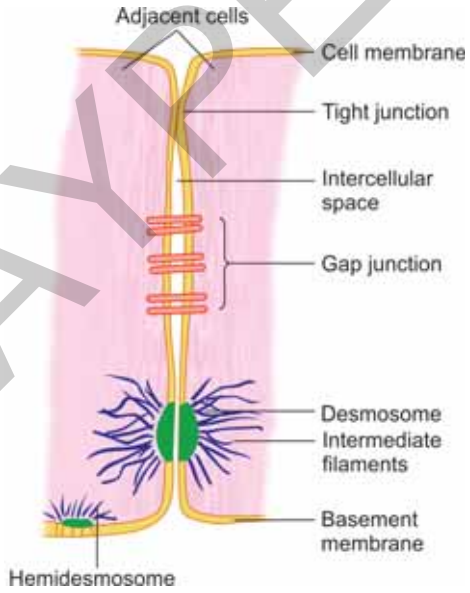

Fig. 4.6: Intercellular connections.

Mutation in the genes coding for the connexins leads to almost 20 different diseases. For example, X-linked **Charcot-Marie-Tooth disease** is a peripheral neuropathy associated with mutation of one particular connexin gene. Other diseasesinclude erythrokeratoderma (a skin disorder), inherited deafness, cataract, idiopathic atrial fibrillation, etc.

MULTIPLE CHOICE QUESTIONS

1. **The structure in the cell that is concerned with synthesis of ribosomes is:**
   a. Nucleolus
   b. Endoplasmic reticulum
   c. Golgi apparatus
   d. Centriole

2. **The correct sequence of cell cycle is:**
   a. G_0-G_1-S-G_2-M b. G_0-G_1-G_2-S-M
   c. G_0-M-G_2-S-G_1 d. G_0-G_1-S-M-G_2

3. **Hemoglobin is synthesized by:**
   a. Rough endoplasmic reticulum
   b. Free ribosomes
   c. Mitochondria
   d. Golgi apparatus

4. **Storage site of Ca^{2+} inside the cell:**
   a. Rough endoplasmic reticulum
   b. Smooth endoplasmic reticulum
   c. Golgi apparatus
   d. Secretory vesicles

5. **The organelle in the cell that contains DNA is:**
   a. Peroxisome b. Proteasome
   c. Mitochondrion d. Ribosome

6. **The organelle that removes toxic hydrogen peroxide formed in the cell:**
   a. Peroxisome b. Lysosome
   c. Proteasome d. Golgi apparatus

7. **The cell organelle which contains enzymes concerned with citric acid cycle and respiratory chain oxidation is:**
   a. Rough endoplasmic reticulum
   b. Smooth endoplasmic reticulum
   c. Golgi apparatus
   d. Mitochondrion

8. **The cell organelle that is referred to as the digestive system of the cell is:**
   a. Peroxisome b. Lysosome
   c. Proteasome d. Golgi apparatus

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