1
General Physiology

General physiology

The goal of physiology is to explain the physical and chemical factors that are responsible for the origin, development and progression of life. Each type of life, from the very simple virus up to the largest tree or to the complicated human being, has its own functional characteristics.

Therefore, the vast of physiology can be divided into-

i. Viral physiology
ii. Bacterial physiology
iii. Celluar physiology
iv. Plant physiology
v Human physiology and many more subdivision.

(Ref. Guyton & Hall- 11th Edition; Page 3)

Human physiology

In *human physiology*, we attempt to explain the specific characteristics and mechanisms of human body that make it a living being. The very fact that we remain alive is almost beyond our own control, for hunger make us seek for food and fear makes us seek refuge. Sensations of cold make us provide warmth and other forces cause us to seek fellowship and to reproduce. Thus, the human being is actually an automaton, and the fact that we are sensing, feeling, and knowledgeable beings is part of this automatic sequence of life; these special attributes allow us to exit under widely varying conditions.

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In unicellular organisms, all vital processes occur in a single cell. As the evolution of multicellular organisms has progressed, various cell groups have taken over particular functions. In humans and other vertebrate animals, the specialized cell groups include - *a gastrointestinal system to* digest and absorb food, *a respiratory system* to take up O_2 and eliminate CO_2; *a urinary sytem* to remove wastes; *a cardiovascular system* to distribute food, O_2, and the products of metabolism; *a reproductive system* to perpetuate the species; and *nervous and endocrine systems* to coordinate and integrate the functions of the other systems. This book is concerned with the way these systems function and the way each contributes to the functions of the body as a whole.

This chapter presents general concepts and principles that are basic to the function of all the systems. It also includes a short review of fundamental aspects of cell physiology. Additional aspects of cellular and molecular biology are considered in the relevant chapters on the various organs.

Homeostatic mechenisms of the major functional systems

Homeostasis : The term *homeostsis* is used by the physiologist to mean maintenance of nearly constant conditions in the internal environment.

Essentially all organs and tissues of the body perform functions that help to maintain these constant conditions. For instant, the lungs provide oxygen to the extra cellular fluid to replinish the oxygen used by the cells, the kidneys maintain constant ionic concentrations and gastrointestinal system provides nutrients.

(Ref. Guyton & Hall- 11th Edition; Page 4)

The different functional systems of the body

1. ***Extracellular fluid transport and mixing system-*** *The blood circulatory system* : Extracellular fluid transported through all parts of the body in two stages. The first stage is movement of blood through the body in the blood vessels, and the second is movement of fluid between the blood capillaries and the intracellular spaces between the tissue cells.

   All the blood in the circulation traverses the entire circulatory circuit an average of once each minute when the body is at rest and as many as six times each minute when a person is extremely active.

   As blood passes through the blood capillaries continual exchange of extracellular fluid also occurs between the plasma portion of the blood and the interstitial fluid that fills the intercellular spaces. The walls of the capillaries are permeable to most molecules in the plasma of the blood, with the exception of the large plasma protein molecules. Therefore, large amounts of fluid and its dissolved constituents diffuse back and forth between the blood and the tissue spaces. This process of diffusion is caused by kinetic motion of the molecules in both the plasma and the interstitial fluid. That is, the fluid and dissolved molecules are continually moving and bouncing in all directions within the plasma and the fluid in the intercellular spaces, and also through the capillary pores. Few cells are located more than 50 micrometers from a capillary, which ensures diffusion of almost any substance from the capillary to the cell within a few seconds. Thus, the extracellular fluid everywhere in the body-both that of the plasma and that of the interstitial fluid-is continually being mixed, thereby maintaining almost complete homogeneity of the extracellular fluid throughout the body.

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2. ***Origin of nutrients in the extracellular fluid*** :
   a. *Respiratory system* : The blood picks up oxygen in the alveoli, thus acquiring the oxygen needed by he cells.
   b. *Gastrointestinal tract* : Here different dissolved nutrients, including carbohydrates, fatty acids, and amino acids, are absorbed from the ingested food into the extracellular fluid of the blood.
   c. *Liver and other organs* : The liver changes the chemical compositions of many of these substances to more usable forms, and other tissues of the body- fat cells, gastrointestinal mucosa, kidneys, and endocrine glands- help modify the absorbed substances or store them until they are needed.
   d. *Musculoskeletal system* : The musculoskeletal system provide the body to move to the appropriate place at the appropriate time to obtain the foods for nutrition. It also provides motility for protection against adverse surroundings, without which the entire body, along with its homeostatic mechanisms, could be destroyed instantaneously.

   (Ref. Guyton & Hall -11th Edition; Page 5)

3. ***Removal of metabolic end products*** :
   a. Removal of carbon dioxide by the lungs. Carbon dioxide is the most abundant of all the end products of metabolism.
   b. *Kidneys* removes most of the other substances from plasma include different end products of cellular metabolism, such as urea and uric acid; they also include excesses of ions and water from the food that might have accumulated in the extra cellular fluid.

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4. ***Regulation of body function*** :

   Body function is regulated by two major regulatory system.

   A. ***Nervous regulation*** : The nervous system is composed of three major parts - the sensory input portion, the central nervous system (or integrative portion) and the motor portion.
      a. *Sensory receptors :* Detect the state of the body or the state of surroundings such as touches, visual image etc.
      b. *Nervous system :* Composed of brain and spinal cord. The brain can store information, general thoughts, create ambition and determine reactions that the body performs in response to the sensations.
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   A large segment of the nervous system is called the *autonomic system*. It operates at a subconscious level and controls many functions of the internal organs, including-
   i. The level of pumping activity by the heart.
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   iii. Secretion by many of the bodys glands.

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   B. ***Hormonal system of regulation:*** Located in the body are eight major endocrine glands that secrete chemical substances, called *hormones*.

   Hormones are transported in the extracellular fluid to all parts of the body to help regulation of cellular function, such as -
   1. Thyroid hormone : Increases the rate of most chemical reactions in all cells thus helping to set the tempo of bodily activity.
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   Thus, the hormones are a systems of regulation that complements the nervous system.

The nervous system in general, regulates many muscular and secretory activities of the body, where as the hormonal system regulates mainly the metabolic functions.

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   For instance,
   i. The *respiratory system*, operating in association with the nervous system, regulates the concentration of CO_2 in the extracellular fluid (ECF).
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Conversely, a decrease in arterial pressure below normal relaxes the stretch receptors, allowing the vasomotor center to become more active than usual, thereby causing vasoconstriction and increased heart pumping, and raising arterial pressure back toward normal.

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Characteristics of control systems

Hundreds of control systems working for maintenance of homeostasis show two common modes of actions -

1. Negative feedback system
2. Positive feed back system.

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Example : If the concentration of carbon dioxide in the extracellular fluid increases, the pulmonary ventilation also increases. This inturn causes decreased CO_2 concetration. Conversely, if the CO_2 concentration falls to low, this causes a feed back increase in the concentration.

Essentially all control system of the body operate by negative feed back system.

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Positive feedback can sometimes cause vicious cycles and death : Example : The heart of the normal human being pumps about 5 liters of blood per minute. However, if the person suddenly bled 2 liters, the amount of blood in the body is decreased to such a low level that not enough is available for heart to pump effectively. As a result the arterial blood pressure and the flow of blood to the heart muscle diminises. This results in the weakening of the heart, further diminises the pumping and coronary blood flow, and still more weakness of the heart. The cycle repeats itself again and again until death. Note that each cycle in the feedback results in further weakening of the heart. In other words, the initiating stimulous causes more of the same, which is *positive feedback.*

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Positive feedback can sometimes be useful- explain.

In rare instances, the body has learned to use positive feedback to its advantage as follows :

1. *Blood clotting* : When a blood vessel is ruptured a clot begins to form. Multiple enzymes called clotting factors are activated with the clot itself. Some of these factors activates the other inactivated enzyme and causing still more clot.
2. *Child brith* : When uterine contractions become strong enough for the baby's head to begin pushing through the cervix, stretch of the cervix sends signals back to the body of the uterus, causing more powerful contractions and parturition occurs.
3. *Generation of nerve signals* : When the membrane of a nerve fibre is stimulated, this causes slight leakage of sodium ions through sodium channels in the nerve membrane to the interior of the fibre. The sodium ions entering the fibre then change the membrane potential, which in turn causes more opening of the channels, more change of potential, still more opening of channels and so forth. Thus creates the nerve action potential which excites the nerve fibre still further along its length and ultimately signals goes all the way to all ends of the nerve fiber.

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Q. 00. **How does the cell membrane contribute to cell homeo stasis.**

Ans. Role of the cell membrane in cell homeostasis :

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i. The lipid layer in the middle of the membrane is impermeable to the usual water-soluble substances, such as ions, glucose, and urea. Fat-soluble substances, such as oxygen, carbon dioxide, alcohol, can penetrate this portion of the membrane with ease.

ii. The cholesterol in the cell membrane mainly help to determine the degree of permeability of the bilayer to water soluble constituents of the body fluids. The cholesterol also controls much of the fluidity of the membrane as well.

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b. *Role of the cell membrane proteins in cell homeostasis* :

i. *Adhesion molecules* : Some are cell *adhesion molecules* that anchors cells to their neighbors or to basal lamina.

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iii. *Carriers* : Some proteins function as *carriers*, transporting substances down electrochemical gradient by facilitated diffusion.

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i. Many of them are electrically negatively charged, which gives most cells an over all negatively surface charge that repels other negative objects.

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Normal ranges and physical characteristics of important extracellular fluid constituents : *Table-1* lists the more important constituents and physical characteristics of extracellular fluid along with their normal values, normal range and maximum limits without causing death for short periods of time. Note specially the narrowness of the normal range for each one of these values out side these ranges are usually the cause of or the result of illness.

Even for more important are the limits beyond which abnormalities can cause death. For instance-

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iv. Also when the calcium ion concentration falls below about one half normal the person is likely to experience tetanic contraction of muscles throughout the body because of spontaneous generation of nerve impulses in the peripheral nerves.

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Thus, consideration of these example should give one an extreme appreciation of the value and even in necessity of the vast numbers of control systems that keep the body operating in health; in absence of any one of thease controls serious illness or death can result. *(Ref. Guyton & Hall- 11th Edition; Page 7)*

Table -1. ***Some important constituents and physical characteristics of the extracellular fluid, the normal range of control, and the approximate nonlethal limits for short periods.*** *(Ref. Guyton & Hall 11th edition, Page-7)*

Constituents	*Normal value*	*Normal range*	*Approximate Non lethal limits*	*Units*
Oxygen	40	35 - 45	10 - 1000	mm Hg
Carbon dioxide	40	35 - 45	5 - 80	mm Hg
Sodium	142	138 - 146	115 - 175	mmol/L
Potassium	4.2	3.8 - 5.0	1.5 - 9.0	mmol/L
Calcium ion	1.2	1.0 - 1.4	0.5 - 2.0	mmol/L
Chloride ion	108	103 - 112	70 - 130	mmol/L
Bicarbonate ion	28	24 - 32	8 - 45	mmol/L
Glucose	85	75 - 95	20 - 1500	mg/dl
Body temperature	98.4 (37.0)	98 - 98.8(37.0)	65 - 110(18.3-43.3)	°F(°C)
Acid-base	7.4	7.3 - 7.5	6.9 - 8.0	pH

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v. When glucose concenrtration falls below one half normal the person frequently develop extreme mental irritability and some times even convulsions.

Thus, consideration of these example should give one an extreme appreciation of the value and even in necessity of the vast numbers of control systems that keep the body operating in health; in absence of any one of these controls serious illness or death can result. *(Ref. Guyton & Hall- 11th Edition; Page 7)*

Table -1. ***Some important constituents and physical characteristics of the extracellular fluid, the normal range of control, and the approximate nonlethal limits for short periods.*** *(Ref. Guyton & Hall 11th edition, Page-7)*

Constituents	*Normal value*	*Normal range*	*Approximate Non lethal limits*	*Units*
Oxygen	40	35 - 45	10 - 1000	mm Hg
Carbon dioxide	40	35 - 45	5 - 80	mm Hg
Sodium	142	138 - 146	115 - 175	mmol/L
Potassium	4.2	3.8 - 5.0	1.5 - 9.0	mmol/L
Calcium ion	1.2	1.0 - 1.4	0.5 - 2.0	mmol/L
Chloride ion	108	103 - 112	70 - 130	mmol/L
Bicarbonate ion	28	24 - 32	8 - 45	mmol/L
Glucose	85	75 - 95	20 - 1500	mg/dl
Body temperature	98.4 (37.0)	98 - 98.8(37.0)	65 - 110(18.3-43.3)	°F(°C)
Acid-base	7.4	7.3 - 7.5	6.9 - 8.0	pH

Chemical compositions of extracellular and intracellular fluids :

	Extracellular fluid	*Intracellular fluid*
Na^+	142 mEq/L	10 mEq/L
K^+	4 mEq/L	140 mEq/L
Ca^{++}	*2.4 mEq/L*	*0.0001 mEq/L*
Mg^{++}	*1.2 mEq/L*	*58 mEq/L*
Cl^-	103 mEq/L	4 mEq/L
HCO_3^-	28 mEq/L	10 mEq/L
Phosphates	*4 mEq/L*	*75 mEq/L*
SO_4^{--}	*1 mEq/L*	*2 mEq/L*
Glucose	90 mg/dl	0 to 20 mg/dl
Amino acids	30 mg/dl	200 mg/dl?
Cholesterol		
Phospholipids	*0.5 gm/dl*	*2 to 95 gm/dl*
Neutral fat		
PO_2	35 mm of Hg	20 mm of Hg?
PCO_2	*46 mm of Hg*	*50 mm of Hg?*
pH	*7.4*	*7.0*
Proteins	2 gm/dl (5 mEq/L)	16 gm/dl (40 mEq/L)

(Ref. Guyton & Hall- 11th Edition; Page-46)

Osmolar substances in plasma, extracellular fluid (ECF) and intracellular fluid (ICF) *in mosm/liter*

	Plasma (mosm/liter of H_2O)	*Interstitial (mosm/liter of H_2O)*	*Intracellular (mosm/liter of H_2O)*
Na^+	*142*	139	14
K^+	4.2	4	*140*
Ca^{++}	1.3	1.2	**0**
Mg^+	0.8	0.7	20
Cl^-	*108*	108	4
HCO_3	24	28.3	10
HPO_4^- /$H_2PO_4^-$	2	2	*11*
SO_4^-	0. 5	0.5	1
Phosphocreatine	-	-	45
Carnosine	-	-	14
Amino acids	2	2	8
Creatine	0.2	0.2	9
Lactate	1.2	1.2	1.5
Adenosine triphosphate	-	-	5
Hexose monophosphate	-	-	3.7
Glucose	5.6	5.6	-
Protein	1.2	0.2	4
Urea	4	4	4
Others	4.8	3.9	10
Total mOsm/liter	301.8	300.8	301.2
Corrected osmolar activity (mOsm/liter)	282.0	281.0	281.0
Total osmotic pressure at 37°C (mm Hg).	*5443*	*5423*	*5423*

(Ref. Guyton & Hall- 11th Edition; Page 294)

Automaticity of the body

Purpose :

1. The overall organization of the body.
2. The means by which the different parts of the body operate in harmony.

Body is actually a social order of about ***100 trillion cells*** organized into different functional structures, some of which are called organs. Each functional structure provides its share in the maintenance of homeostatic conditions in the extracellular fluid, which is called the internal environment. As long as normal conditions are maintained in the internal environment, the cells of the body continue to live & function properly. Thus each cell benefits from homeostasis, and in turn, each cell contributes its share toward the maintenance of homeostasis. The reciprocal interplay provides continuous automaticity of the body until one or more functional systems lose their ability to contribute their share of function. When this happens, all the cells of the body suffer. Extreme dysfunction leads to death, where as moderate dysfunction leads to sickness.

(Ref. Guyton & Hall -11th Edition; Page 9)

Organization of the body

The cells that make up the bodies of all but the simplest multicellular animals, both aquatic and terrestrial, exist in an " internal sea" of extracellular fluid (***ECF***) enclosed within the integument of the animal. From this fluid, the cells take up O_2 and nutrients; into it, they discharge metabolic waste products. The ECF is more dilute than present day seawater, but its composition closely resembles that of the primordial oceans in which, presumably, all life originated.

In animals with a closed vascular system, the *ECF* is divided into 2 components :

1. *Interstitial fluid*
2. *Circulating blood plasma.*

The plasma and the cellular elements of the blood, principally red blood cells, fill the vascular system, and together they constitute the *total blood volume*. The interstital fluid is that part of the ECF that is outside the vascular system, bathing the cells. About one third of the *total body water (TBW)* is extracellular; the remaining two thirds are intracellular *(intracellular fluid)*.

(Ref. W. F. Ganong 22th Edition; Page-1)

Content in grams of A 70 kilogram man :

Constituent	Amount (grams)
1. Water	41,400 (41.4 kg)
2. Fat	12,600 (12.6 kg)
3. Protein	12,600 (12.6 kg)
4. Carbohydrate	300
5. Na	63
6. K	150
7. Ca	1,160
8. Mg	21
9. Cl	85
10. P	670
11. S	112
12. Fe	3
13. I	0.014

(Ref. Guyton & Hall- 11th Edition; Page 878)

Body composition

In the average 70 kilogram adult male :

Constituent	% of total body weight
1. Protein & related substances	: 18%
2. Mineral	: 7%
3. Fat	: 15%
4. Water (42 litre or)	: 60%

a. *Intracellular component* of body water (28 litres or) : 40%

b. *Extracellualr component* of body water (14 litres) : 20%

i. 25% of the extracellular component is in the vascular system-(*plasma*-3 litres) : 05%

ii. 75% of the extracellular component is in the outside of blood vessels (*Interstitial fluid*) : 15%

(Total blood volume is about 8% of body weight.)

(Ref. W. F. Ganong 22th Edition; Page 1)

iii. *Transcellular fluid : 1 to 2 litres*

This compartment includies- fluid in the synovial, peritonial, pericardial, and intraoccular spaces, as well as the cerebrospinal fluid.

(Ref. Guyton & Hall- 11th Edition; Page-292)

N.B. In the average 70-kilogram adult human, the total body water is about 60% of the body weight, or about 42 liters. This percentage can change, depending on age, sex, and degree of obesity. As a person grows older, the percentage of total body weight that is fluid gradually decreases. This is due in part to the fact that aging is usually associaed with an increased percentage of the body weight that is fat, which in turn decreases the percentage of water in the body. Because women normally have more body fat than men, they contain slightly less water than men in proportion to their body weight. Therefore when discussing the 'average' body fluid compartments, we should realize that variations exits, depending on age, sex, and percentage of body fat.

(Ref. Guyton & Hall- 11th Edition; Page-292)

Body fluid compartments

The body fluid is mainly distributed between two compartments

1. *Intracellular fluid compartment :* It is the sumtotal of the fluid content of all cells of the body. It is about 28 liters.
2. *Extracellular fluid compartment :* It is the fluid out side of the cell. It is about 14 litres.

   The extracellular fluid in turn is divided into the *interstitial fluid* and blood *plasma.*
3. There is another small compartment of fluid that is referred to as ***transcellular fluid.*** It is usually considered to be a specialized type of extracellular fluid, although in some cases, its composition may differ markedly from that of plasma or interstitial fluid. It constitutes about 1 to 2 liters.This compartments includes fluids-
   i. Synovial fluid
   ii. Peritonial fluid
   iii. Pericardial fluid
   iv. Intraocular fluid
   v. Cerebrospinal fluid.

(Ref. Guyton & Hall- 11th Edition; Page 292, 293)

% of total body fluid compartments :

Total body water (42 litre or) : 60%

a. *Intracellular component* of body water (28 litres or) : 40%

b. *Extracellualr component* of body water (14 litres) : 20%

i. 25% of the extracellular component is in the vascular system-(*plasma*-3 litres) : 05%

ii. 75% of the extracellular component is in the outside of blood vessels (*interstitial fluid*) : 15%

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(Ref. W. F Ganong 22th Edition; Page 1)

iii. *Transcellular fluid : 1 to 2 litres*

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(Ref. Guyton 11th Edition; Page 292)

The cell & its function

Organisation of cells :

The cell is the structural and functional unit of the living organism. Each of the 100 trillion or more cells in a human being is a living structure that can survive indefinitely and, in

most instances, can even reproduce itself provided its surrounding fluids contain appropriate nutrients.

A ***typical cell*** has two major parts- the *nucleus* and the *cytoplasm*. The nucleus is separated from the cytoplasm by a *nuclear membrane*, and the cytoplasm is separated from the surrounding fluid by a *cell membrane*, also called *plasma membrane*.

(Ref. Guyton & Hall- 11th Edition; Page 11, 12)

Physical structure of cell

The cell is not merely a bag of fluid, enzymes, and chemicals; it also contains highly organized physical structures, called *intracellular organelles*. *Structures of cell are followings* :

A. Cell membrane
B. Protoplasm
   a. **Nucleus**
      i. Nuclear membrane
      ii. Nucleolus
      iii. Nucleoplasm or nuclear sap
      iv. Chromatin
         1. Heterochromatin
         2. Euchromatin
   b. **Cytoplasm**
      i. ***Organelles***
         1. *Membranous organelles*
            Mitocondria
            Endoplasmic reticulumn
            Golgi complex
            Lysosomes
            Peroxisomes
         2. *Non membranous organelles*
            Ribosomes
            Centrioles
            Filaments
               Microfilaments
               Intermediate filaments
            Microtubules
      ii. ***Inclusions***
         1. Secretory granules
         2. Pigment granules
         3. Lipid and glycogen
         4. Crystals.

(Ref. Guyton & Hall- 11th Edition; Page12 & others)

The specialization of the cells in the various organs is very great, and no cell can be called 'typical' of all cells in the body. However a number of structures *(organelles)* are common to most cells.

(Ref. W. F. Ganong 22th Edition; Page 8)

Protoplasm

The different substances that make up the cell are collectively called protoplasm. Protoplasm is mainly composed of five basic substances- *water, electrolytes, proteins, lipids and carbohydrates.*

1. ***Water*** : The principal fluid medium of the cell is water, which is present in a concentration of between 70 to 85 percent. Many cellular chemicals are dissolved in water. Others are suspended in the water as solid particulates. Chemical reactions take place among the dissolved chemicals or at the surfaces of the suspended particles or membranes.

(Ref. Guyton & Hall- 11th Edition; Page 11)

2. ***Ions*** : The most

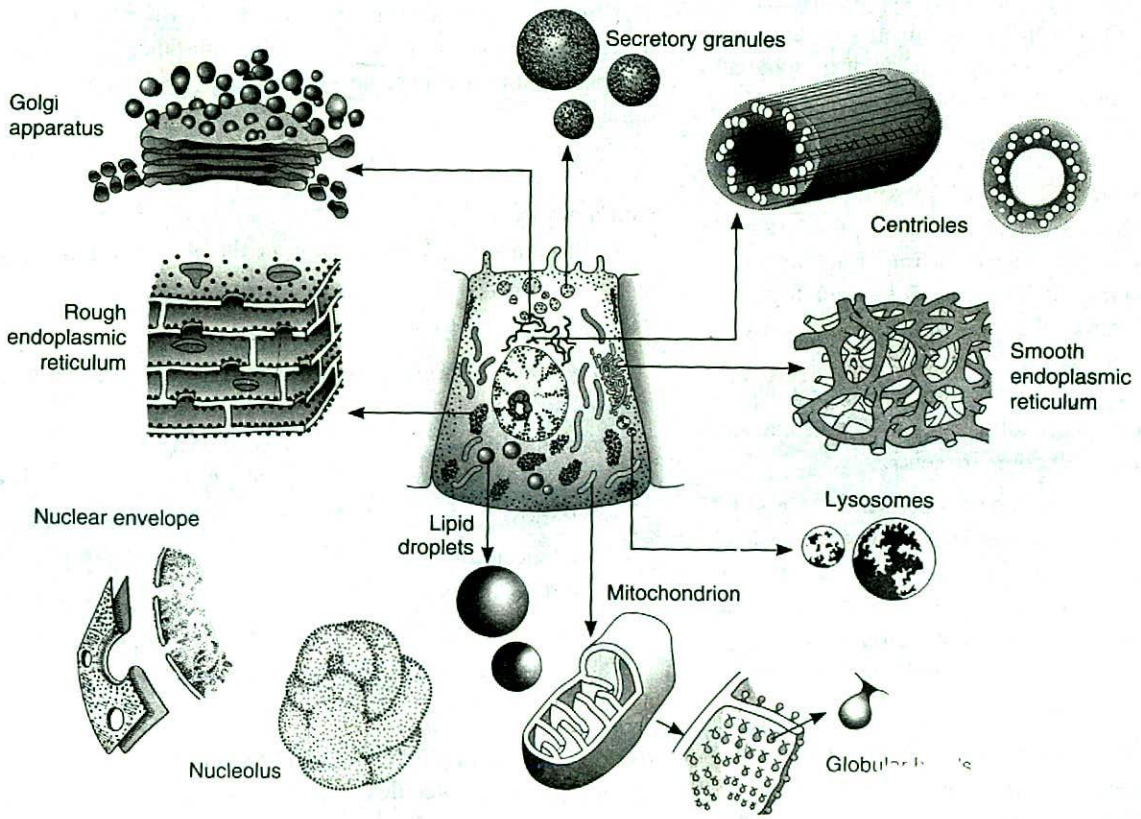


Fig: 1-1. Diagram showing a hypothetical cell in the center as shown with the light microscope. It is surrounded by various organelles.

important electrolytes in the cell are K^+, Mg^{++}, PO_4^{-3}, SO_4^{-2}, HCO_3^- and smaller quantities of Na^+, Ca^{++}, Cl^-.

Function :

i. Electrolytes provide inorganic chemicals for cellular reactions.

ii. They are necessary for operation of some of the cellular control mechenism. For instances, ions acting at the cell membrane are required for transmission of electro-chemical impulses in nerve and muscle fibres.

(Ref. Guyton & Hall- 11th Edition; Page 11)

3. ***Proteins*** : These normally constitute 10 to 20 percent of the cell mass.

These are of two types :

i. Structural proteins

ii. Functional proteins.

Structural proteins : They are polymers of many protein molecules, present in the cell mainly in the form of long thin filaments. The most prominent use of such intracellular filaments is to provide the contractile mechenism of all muscles. Filaments, however are also organised into microtubule that provide the *cyto-skeletons* of such organelles as cillia, nerve axons & the mitotic spindles of mitosing cells. Extracellularly fibrillar proteins are found specially in the collagen and elastin fibres of connective tissue, blood vessels, tendons, ligaments & so forth.

Globular proteins : Composed of individual protein molecules or at most, combination of a few molecules in a globular form rather than a fibrillar form. These are mainly enzymes of the cell & in contrast to the fibrillar proteins are often soluble in the cell fluid or integral parts of or adherent to membranous structures inside the cell.

(Ref. Guyton & Hall- 11th Edition; Page 11)

4. ***Lipids*** : Lipids are several types of substances that are grouped together because of their common properties of being soluble in fat solvents. The most important lipids in most cells are *phospholipids* and *cholesterol*, which together constitute about 2 per cent of the total cell mass. The special importance of phospholipids and cholesterol is that they are mainly insoluble in water and, therefore are used to form cell membrane as well as intra cellular membranous barriers that separate the different cell compartments.

In addition to phospholipids and *cholesterol*, some cells contains large quantities of *triglycerides*, also called *neutral fat*. In the so-called fat cells, triglycerides often account for as much as 95 per cent of the cell mass. The fat stored in this cells represents the body's main storehouse of energy-nutrient that can later be dissoluted and used for energy wherever in the body it is needed.

(Ref. Guyton & Hall- 11th Edition; Page 12)

5. ***Carbohydrates*** : Carbohydrates have little structural function in the cell except as part of glycoprotein molecules but they play a major role in nutrition of the cell. A small amount of carbohydrate is virtually always stored in the cells in the form of *glycogen* and can be used rapidly to supply the cells energy needs. Carbohydrate in the form of dissolved glucose is always present in the surrounding extracellular fluid, so that it is easily available to the cell. It is averaging 1% of total cell mass. As much as 3% in muscles & 6% in liver cells.

(Ref. Guyton & Hall- 11th Edition; Page 12)

Physical structure of the cell

The cell is not merely a bag of fluid, enzymes, and chemicals; it also contains highly organized physical structures, many of which are called *organelles*. The physical nature of each structure is equally as important to the function of the cell as the cell's chemical constituents. For instance, without one of the organelles, the *mitochondria,* more than 95 per cent of the cells energy supply would cease immeditely.

Membranous structures of the cell

Essentially almost all the organelles of the cell are lined by membranes. These membranes include-

1. Cell membrane
2. Nuclear membrane
3. Membrane of the endoplasmic reticulum.
4. Membrane of the mitochondria
5. Membrane of the lysosomes
6. Membrane of the Golgi apparatus.

The lipids of the membranes provide a barrier that prevents movements of water and water soluble substances from one cell compartment to the other because the water is not soluble in the lipids.

(Ref. Guyton & Hall- 11th Edition; Page 12)

Cell membrane

The cell membrane, which envelops the cell, is a thin, pliable, elastic structure.

Thickness : 7.5 to 10 nanometers.

Composition : It is composed almost entirely of proteins and lipids. The approximate composition is-

1. Protein			: 55%
2. Lipid		:	42%
a. Phospholipids	:	25%	
b. Cholesterol	:	13%	
c. Others lipids	:	4%	
5. Carbohydrates			: 3%

(Ref. Guyton & Hall- 11th Edition; Page 12)

Structure of cell membrane :

Its basic structure is a lipid bilayer interposed with large globular protein molecules.

a. *Lipid of the cell membrane* : Composed almost entirely of

phospholipids and cholesterol (lipid in nature). One part of the phospholipid and cholesterol is soluble in water, that is, *hydrophilic*, whereas the other part is soluble only in fat, that is, *hydrophobic*. The phosphate radicle of the phospholipid is hydrophilic and the fatty acid radicles are hydrophobic.

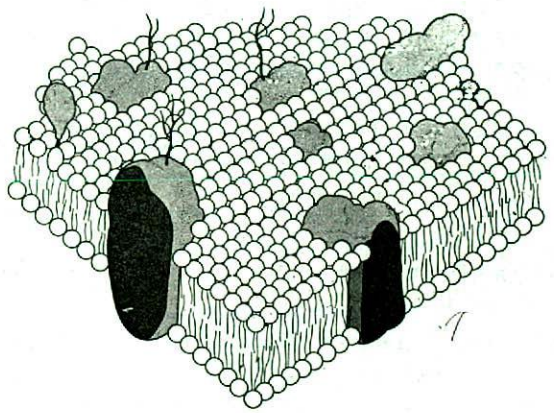


Fig: 1-2. Biological membrane. The phospholipid molecules each have two fatty acid chains (wavy lines) attached to a phosphate head (open circle). Proteins are shown as irregular coloured globules. Many are integral proteins, which extend through the membrane, but peripheral proteins are attached to the inside (not shown) and outside of the membrane, sometimes by glycosylphosphati -dylinositol (GPI) anchor.

The *lipid layer* in the middle of the membrane is impermeable to the usual water-soluble substances, such as ions, glucose, and urea. Conversely, fat-soluble substances, such as oxygen, carbon dioxide, alcohol, can penetrate this portion of the membrane with ease.

A special feature of the *lipid bilayer* is that it is a fluid and not a solid. Therefore, portions of the membrane can literally flow from one point to another along the surface of the membrane. Proteins or other substnces dissolved or floating in the lipid bilayer diffuse to all areas of the cell membrane.

The *cholesterol* in the cell membrane mainly help to determine the degree of permeability of the bilayer to water soluble constituents of the body fluids. The cholesterol also controls much of the fluidity of the membrane as well.

(Ref. Guyton & Hall- 11th Edition; Page 12, 13)

b. *The cell membrane proteins* : These are membrane proteins, most of which are glycoproteins. The cell membrane proteins are of two types :

i. *Integral proteins* : Many of the integral proteins provides structural *channels (or pores)* through which water soluble substances specially ions, can diffuse between the extracellular and intracellular fluid. These *protein channels* also have selective properties that allow preferential diffusion of some substances more than others.

Others of the integral proteins act as carrier proteins for transporting substances that otherwise could not penetrate the lipid bilayer. Some times these even transport substances in the direction opposite to their natural direction of diffusion, which is called *'active transport*. Still others acts as enzymes.

ii. *Peripheral proteins* : The peripherals proteins occur mainly on the inside of the membrane, and they offen are attached to one of the integral proteins. These peripheral proteins function almost entirely as enzymes or as other types of controllers of intracellular function.

(Ref. Guyton & Hall- 11th Edition; Page 13)

Functions of the membrane proteins :

1. Some are cell *adhesion molecules* that anchors cells to their neighbors or to basal lamina.
2. There are proteins that function as *pumps*, actively transporting ions across the membrane.
3. Some proteins function as *carriers*, transporting substances down electrochemical gradient by facilitated diffusion.
4. Still others are *ions chennels*, which, when activated, permit the passage of ions into or out of the cell.
5. Proteins in another group function as *receptors* that bind neurotransmitters and hormones, initiating physiological changes inside the cell.
6. Proteins also function as enzymes, catalyzing reactions at the surfaces of the membrane.
7. Some glycoproteins function in *antibody processing and distinguishing* self from nonself.

(Ref. Ganong 22th Edition; Page-9,10)

C. *Membrane carbohydrate* : Membrane carbohydrate occur almost invariably in combination with proteins or lipids in the form of glycoproteins or glycolipids. In fact most of the integral proteins are glycoproteins and about one tenth of the membrane lipid molecules are glycolipids. The 'glyco' portions of these molecules almost invariably protude to the outside of the cell, dangling outward from the cell surface. Many other carbohydrate compounds, called *proteoglycans*, which are mainly carbohydrate substances bound to small protein cores, often are loosely attached to the outer surface of the cell as well. Thus, the entire outside surface of the cell often has a loose carbohydrate coat called the *glycocalyx*.

The carbohydrate moieties attached to the outer surface of the cell have several important functions :

1. Many of them are electrically negatively charged, which gives most cells an over all negatively surface charge that repels other negative objects.
2. The glycocalyx of some cells attaches to the glycocalyx of other cells, thus attaching cell one to another.
3. Many of the carbohydrates act as receptor substances for binding hormones such as insulin, and when bound, this

combination activates attached internal proteins that in turn activate a cascade of intercellular enzymes.

4. Some carbohydrate moieties enter into immune reactions.

(Ref. Guyton & Hall- 11th Edition; Pages 14)

Membrane transport proteins

Membrane permeability & membrane transport proteins : Small, nonpolar molecules- including O_2 and N_2 and small uncharged polar molecules such as CO_2 diffuse across the lipid membranes of cells. However, the membranes have very limited permeability to other substances. Instead, they cross the membranes by endocytosis and exocytosis and by passage through highly specific ***transport proteins***, transmembrane proteins that form channels for ions or transport substances such as glucose, urea, and amino acids.

i. *Aquaporins* : The limited permeability applies even to water, with simple diffusion being supplemented throughout the body with various water channels (*aquaporins*).

ii. *Simple aqueous ion channels* : Some transport proteins are simple aqueous ion channels, though many of these have special features that make them effective for a given substance such as Ca^{++} or, in the case of aquaporins, for water.

iii. *Gated and continuously open channels* : Some of the transport proteins are continuously open and some are gated; ie, they have gates that open or close.

   a. *Voltage-gated* : Are gated by alterations in membrane potential. A typical voltage-gated channel is the Na^+ channel.

   b. *Ligand-gated* : Are opened or closed when they bind a ligand. A typical ligand-gated channel is the acetylcholine receptor.

   The ligand is often external, eg, a neurotransmitter or a hormone. However, it can also be internal; intracellular Ca^{++}, cAMP, lipids, or one of the G proteins produced in cells can bind directly to channels and activate them.

iv. *Mechanosensitive channels* : Some channels are also opened by mechanical stretch, and these mechanosensitive channels play an important role in cell movement.

v. *Carriers* : This transport proteins bind ions and other molecules and then change their configuration, moving the bound molecule from one side of the cell membrane to the other. Molecules move from areas of high concentration to areas of low concentration (down their *chemical gradient*), and cations move to negatively charged areas whereas anions move to positively charged areas (down their *electrical gradient*).

   Facilitated diffusion : When carrier proteins move substances in the direction of their chemical or electrical gradients, no energy input is required and the process is called facilitated diffusion. A typical example is glucose transport by the glucose transporter, which moves glucose down its concentration gradient from the ECF to the cytoplasm of cell.

   Active transport : This carriers transport substances against their electrical and chemical gradients. This form of transport requires energy and is called active transport. In animal cells, the energy is provided almost exclusively by hydrolysis of ATP. Not surprisingly, therefore, the carrier molecules are ATPases, enzymes that catalyze the hydrolysis of ATP. One of these ATPases is *sodium potassium-activated adenosine triphosphatase* (Na^+-K^+ ATPase), which is also known as the Na^+-K^+ pump. There are also H^+-K^+ ATPases in the gastric mucosa and the renal tubules. Ca^{++} ATPase pumps Ca^{++} out of cells. Proton ATPases acidify many intracellular organelles, including parts of the Golgi complex and lysosomes. F-ATPases are present in mitochondria and synthesize ATP. Some cell membranes contain ATPases that transport Ca^{++}.

vi. *Uniports* : Some of the transport proteins are called uniports, because they transport only one substance.

vii. *Symports* : Transport requires the binding of more than one substance to the transport protein and the substances are transported across the membrane together. An example is the symport in the intestinal mucosa that is responsible for the cotransport by facilitated diffusion of Na^+ and glucose from the intestinal lumen into mucosal cells.

viii. *Antiports* : They exchange one substance for another. The Na^+-K^+ ATPase is a typical antiport; it moves three Na^+ out of the cell in exchange for each two K^+ that it moves into the cell.

(Ref. Ganong 22th edition, Page 30, 31, 32)

Cytoplasm & its organelles

Cytoplsm

The cytoplasm is filled with both minute and large dispersed particles and organelles, ranging in size from a few nanometers to many micrometers. Clear fluid portion of cytoplasm in which the particles are dispersed is called *cytosol*; this contains mainly dissolved proteins, electrolytes and glucose.

Dispersed in the cytoplasm are nutral fat globules, glycogen granules, ribosomes, secretory vesicles & five specially important organelles- the *endoplasmic reticulum, the Golgi apparatus, mitochondria, lysosomes and peroxisomes.*

(Ref. Guyton & Hall- 11th Edition; page 14, 15)

Functions of cytoplasm

1. *Metabolic function:* Resulting in the synthesis of essential compounds for body growth and liberation of energy.
2. *Special functions :*
   i. *Irritability* : Ability to respond stimuli.
   ii. *Conductivity* : conducting an electrical disturbance in the form of impulse.
   iii. *Contractility* : Shortening or increasing the tension in response to stimulus.

Cell Organelles

The cell is not merely a bag of fluid, enzyms, and chemicals; it

also contains highly organized physical structures, many of which are called cell organelles.

The physical nature of each of these is equally as important to the function of the cell as the cell's chemical constituents. For instance, without one of the organelles, the mitochon-dria, more than 95 percent of the energy supply of the cell would cease immediately.

Five important cell organelles are :

1. Endoplasmic reticulum
2. Golgi apparatus
3. Mitochondria
4. Lysosomes
5. Peroxisomes.

(Ref. Guyton & Hall- 11th edition;Page-14 & 15 & others)

Endoplasmic Reticulum

These are the network of tubular and flat vesicular structures present in the cytoplasm. The tubules and vesicles inter-connect with one another.

Structure : The walls of the *endoplasmic reticulumn* are constructed of lipid bilayer membranes that contains large amounts of proteins, similar to the cell membrane. The total surface area of this structure in some cells- the liver cells, for instance- can be as much as 30 to 40 times as great as the cell membrane area.

The space inside the tubules and vesicles is filled with *endoplasmic matrix*, a watery fluid medium that is different from the fluid in the cytosal outside the endoplasmic reticulumn.

Types :

i. *Granular endoplasmic reticulum :* Outersurface is covered with ribosomes.
   Function : Synthesis of protein in the cell.

ii. *Agranular endoplasmic reticulum :* Outer surface is devoid of ribosome.
   Function : Synthesis of lipid substances and in many other enzymatic processes of the cell.

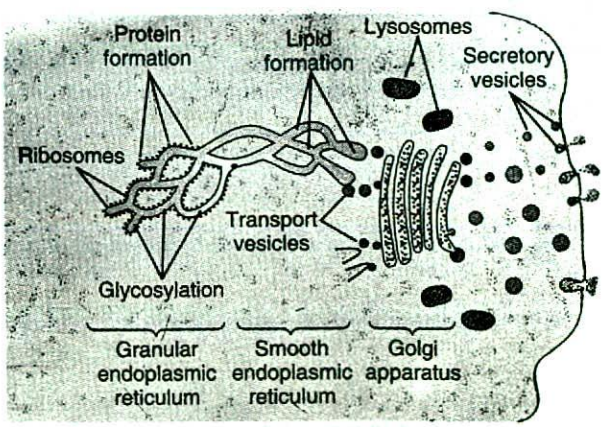


Fig: 1-3. Formation of proteins, lipids, and cellular vesicles by the endoplasmic reticulum and Golgi apparatus.

Functions of endoplasmic reticulum :

i. Synthesis of protein in the cell- by granular endoplasmic reticulum.

ii. *Agranular endoplasmic reticulum :* Synthesis of lipid substances and in many other enzymatic processes of the cell.

Other significant function of the endoplasmic reticulumn, especially the smooth reticulumn, incluide the following :

iii. It provides the enzymes that control glycogen breakdown when glycogen is to be used for energy.

iv. It provides a vast number of enzymes that are capable of detoxifying substances such as drugs that might damage the cell. It achives detoxification by coagulation, oxidation, hydrolysis, conjugation with glucuronic acid, or in other ways.

(Ref. Guyton & Hall- 11th page-15 & 20)

Ribosome

Ribosomes are minute granular particles measure approximately 22 by 32 nm.

Structure : The ribosomes are complex structures, containing many different proteins and at least three ribosomal RNAs.

Type :

1. Free ribosomes
2. Ribosomes attached with endoplasmic reticulum.

Function :

a. *Free ribosomes* :
   i. Synthesize cytoplasm proteins such as hemoglobin.
   ii. Synthesize proteins found in peroxisomes and mitochondria.

b. *Ribosomes attached with endoplasmic reticulumn* :
   i. Synthesize all transmembrane proteins.
   ii. Synthesize most secreted proteins.
   iii. Synthesize most proteins that are stored in the Golgi apparatus, lysosomes, and endosomes.

(Ref. Guyton & Hall- 11th Edi, P-15; Ganong 22th Edi, P-18)

Golgi Apparatus

It usually is composed of four or more stacked layers of thin, flat enclosed vesicles lying near one side of the nucleus .It is closely related to the endoplasmic reticulumn. The walls are constructed of lipid bilayer membranes that contains large amounts of proteins.

This apparatus is prominent in secretory cells; where it is located on the side of the cell from which the secretory substances are extruded.

(Ref. Guyton & Hall- 11th Edition; Page-15)

Function :

The Galgi apparatus functions in association with the endoplasmic reticulum.

i. Substances transported from the endoplasmic reticulum to the Galgi apparatus are then processed in the Golgi

apparatus to form lysosomes, secretory vesicles, or other cytoplasmic components.

ii. It is associated with transmission of secretory products.

iii. Intracellular vesicles formed by the Galgi apparatus replenishes the membranes.

iv. It has the capability of synthesizing certain carbhydrates that can not be formed in the endoplasmic reticulum i.e *hyaluronic acid* and *chondroitin sulfate.*

(Ref. Guyton & Hall- 11th Edition; Page-15 & 21)

Functions of the hyaluronic acid and *chondroitin sulfate :*

a. They are the major components of proteoglycans secreted in mucus and other glandular serretions.

b. They are the major components of the *ground substance* in the interstitial spaces, acting as filter between collagen fibers and cells.

c. They are principle components of the organic matrix in both cartilage and bone.

Types of vesicles formed by the Golgi apparatus :

i. Secretory vesicles

ii. Lysosomes.

Mechanism of transmission of secretory products : As substances are formed in the endoplasmic reticulum, especially the proteins, they are transported through the tubules towards the portions of smooth endoplamic reticulum that lie nearst the Golgi apparatus. At this point, small *transport vesicles* composed of small envelopes of smooth endoplasmic reticulum continually breaks away and diffuse to the *deepest layer* of Golgi apparatus. Inside the vesicles are the synthesized proteins and other products from the endoplasmic reticulum.

The transport vesicles instantly fuse with the Galgi apparatus and empty their contained substances into the vesicular spaces of Golgi apparatus. Here, additional carbohydrate moiety are added to the secretions. Also, a most important function of the Galgi apparatus is to compact the endoplasmic reticulum secretions into highly concentrated packets. As the secretion pass towards the outermost layers of the Golgi apparatus, the compaction and processing proceed. Finally both small and large vesicles continually break away from the Golgi apparatus, carrying with them the compacted secretory substances, and the vesicles diffuse throughout the cell.

(Ref. Guyton & Hall- 11th Edition; Page-21,22)

Lysosome

Lysosomes are vesicular organelles that form by breaking off from the Golgi apparatus and then dispersing throughout the cytoplasom.

a. *Diameter* : The lysosome is quite different in different types of cells, but it usually is 250 to 750 nanometers in diameter.

b. *Structure* : It is surrounded by a typical lipid bilayer membrane and is filled with large numbers of small granules 5 to 8 nanometers in diameter, which are protein aggregates of as many as 40 different hydrolase (digestive) enzymes. Ahydrolytic enzyme is capable of splitting an organic compound.

Ordinarily, the membrane surrounding the lysosome prevents the enclosed hydrolytic enzymes from coming in contact with other substances in the cell and, therefore, prevents their digestive actions.

Some of the enzymes found in lysosomes and the cell components that are their substrate :

Enzyme	*Substrate*
Ribonuclease	RNA
Deoxiribonuclease	DNA
Phosphatase	Phosphate esters
Glycosidases	Complex carbohydrates; glycosides polysaccharides
Arylsulfatases	Sulfate esters
Collagenase	Proteins
Cathepsins	Proteins

In certain genetic disorders of the body, some of the usual digestive enzymes are missing from the lysosomes, especially enzymes that are required to digest lipid aggregates or glycogen granules. In such instances, extreme quantities of lipids or glycogen often accumulate in the cells of many organs, especially in the liver, and lead to early death of the person.

Function of lysosome :

1. Lysosomes provide an *intracellular digestive system* that allows the cell to digest within itself-
   a. Damaged cellular structures.
   b. Food particles that have been ingested by the cell.
   c. Unwanted matter such as bacteria.
2. *Regression of tissues* : Tissues of the body often regress to smaller size. For instance, this occurs in the uterus after pregnancy, in muscles during long periods of inactivity, and in mammary glands at the end of lactation. Lysosomes are responsible for much of this regrssion. The mechenism by which lack of activity in a tissue causes the lysosomes to increase their activity is unknown.
3. *Removal of damaged cells or damaged portions of cells from tissues-* ***Autolysis of cells*** : Removal of damaged cells or damaged portions of cells from tissues- cells damaged by heat, cold, trauma, chemicals, or any other factor is another special role of the lysosomes.

   Damage to the cell causes lysosomes to rupture. The hydrolases begin immediately to digest the surrounding organic substances.

   i. *If the damage is slight*, only a portion of the cell is removed, followed by repair of the cell.

   ii. *If the damage is severe*, the enter cell is digested, a process called ***autolysis***. In this way, the cell is completely removed, and a new cell of the same type ordinarily is formed by mitotic reproduction of an adjacent cell to take the place of the old one.

4. The lysosomes also contain bactericidal agents that can kill phagocytized bacteria before they can cause cellular damage. These agents include *lysozyme* that dissolves the bacterial cell membrane, *lysoferrin* that binds iron and other metals that are essential for bacterial growth, and acid at a pH of about 5.0 that activates the hydrolases and inactivates some of the bacterial metabolic systems.

(Ref. Guyton 11th ed; P-16, 20; Ganong 22th ed, Page-11, 12)

Peroxisomess

Peroxisomes are similar physically to lysosomes. They are believed to be formed by self-replication (perhaps by budding off from the smooth endoplasmic reticulum). They contain oxidases.

Function : Several of the oxidases are capable of combining oxygen with hydrogen ions from different intracellular chemicals to form hydrogen peroxide (H_2O_2) . The hydrogen peroxide in turn is itself a highly oxidizing substance, and this is used in association with *catalase*, another oxidase enzyme present in large quantities in peroxisomes, to oxidize many substances that might otherwise be poisonous to the cell. For instance, about half the alcohol a person drinks is detoxified by the peroxisomes of the liver cells in this manner.

(Ref. Guyton Hall- 11th Edition; Page-16)

Difference between lysosomes and peroxisomes

Lysosomes	*Peroxisomes*
1 They are formed by breaking off from the Galgi apparatus.	1.They are formed by budding off from the smooth endoplasmic reticulum.
2. They contain hydrolases.	2.They contain oxidases.

(Ref. Guyton & Hall- 11th Edition; Page-16)

Secretory Vesicles

One of the important functions of many cells is secretion of special substances. Almost all such secretory substances are formed by the endoplasmic reticulum-Golgi apparatus system and are then released from the Golgi apparatus into the cytoplasm in the form of storage vesicles called secretory vesicles or ***secretory granules***.

Example : In pancreatic acinar cells, secretory vesicles store protein pro-enzymes (enzymes that are not activated). The pro-enzymes are secreted latter through the outer cell membrane into the pancreatic duct and thence into the duodenum, where they become activated and perform digestive functions on the food in the intestinal tract.

(Ref. Guyton & Hall- 11th Edition; Page-16)

Mitochondria

The mitochondria are the powerhouse of the cell. Total number per cell varies from less than one hundred upto several thousand. It is variable in size and shape, some are only a few hundred nanometers in diameter and globular in shape, where as others are as large as 1 micrometer in diameter, as long as 7 micrometers and branching or filamentous in shape.

The basic structure of the mitochondrion is composed mainly of two *lipid bilayer - protein membranes* : an outer membrane and an inner membrane. Many infolding of the inner membrane form shelves called cristae on to which oxidative enzymes are attached. In addition, the inner cavity of the mitochondrion is filled with a matrix containing large quantities of dissolved enzymes.

Mitochondria are self replicative, that means one mitochondrion can form a second one, a third one and so on, whenever there is need in the cell for increased amounts of ATP.

Function :

i. The enzymes of the mitochondria cause oxidation of the nutrients (carbohydrate, protein, and fat), thereby forming carbon dioxide & water and liberate energy. The liberated energy is used to synthesize a high energy substance called adenosine triphosphate (ATP).

   ATP is then transported out of the mitochondrion and it diffuses throughout the cell to release its energy wherever it is needed for performing cellular function.

ii. Mitochondria contain deoxyribonucleic acid (DNA) that controls replication of the cell.

(Ref. Guyton & Hall- 11th Edition; Page-16,17)

N.B. Sperms contribute few, if any, mitochondria to the zygote; so the mitochondria come almost entirely from the ovum and their inheritance is almost exclusively maternal.

(Ref. Ganong 22th Edition; Page-11)

Nucleus

The nucleus is the control center of the cell. It is concerned with the control of constructive and functional activities of the cell. The shape, size and number of nucleus vary with different types of cells.

During interphase a nucleus consists of -

i. *Nuclear membrane :* Under electron microscope, the nuclear membrane, a nuclear envelope is seen to consist of two layers and separates it from the surrounding cytoplasm. Each membrane layer is 70-80 Å thick. The nuclear evnelope is penetrated by several thousand nuclear pores. The pore is about 9 nanometers in diameter.

ii. *Nucleoplasm :* Also called nuclear sap or karyolymph. It is a viscid material more viscid than the cytoplasm which fills the space bound by the nuclear membrane.

iii. *Nucleoli (plasmosomes) :* The nuclei of most cells contain one or more lightly staining structures called nucleoli. It is not bound by membrane.

iv. *Chromatin granules :* These are the small granular element found within the nucleoplasm, which show intense staining reaction with basic coal tar dyes.

(Ref. Guyton & Hall- 11th Edition; Page-17, 18 & others)

Function of nucleus :

i. It is the dynamic centre of life as it controls nutritive and respiratory activites of the cells.
ii. It influences growth and initiates divisions or reproduction of cell.
iii. The DNA molecules of Nucleus act as regulator of synthesis of enzyme protein or proteins in the cytoplasm.
iv. The DNA also inherit the character to the offspring through genes.

N.B. Nucleus contains chromatin (DNA molecules); chromatin becomes chromosome during cell division; chromatin contains genes.

No centriole no mitosis. Vincristin (anticancer drug) acts by poisoning spindles and stoping mitosis; no mitosis possible in neurons.

DNA synthesizes RNA and RNA molecules stay in the cytoplasm, hanging from the endoplasmic reticulam as ribosomes or free in cytosol (free ribosomes).

There may be nucleolie in the nucleus where there is plenty of RNA molecules, otherwise RNA molecules found mainly in the cytoplasm.

Cytoskeleton

Definition : Cytoskeleton is a system of fibers that not only maintains the structure of the cell but also permits it to change shape and move.

All cell have cytoskeleton. The cytoskeleton is made up primarily of microtubules, intermediate filaments, and microfilaments, along with proteins that anchor them, tie them together, and in the case of microtubules and microfilaments move along them.

a. ***Microtubules*** : Microtubules are long, hollow structures with 5 nm walls surrounding a cavity 15 nm in diameter. They are made up of two globular protein subunits, alpha and beta tubulin. A third subunit, delta tubulin, is associated with the production of microtubules by the centrosomes.

Microtubules are a dynamic portion of the cell skeleton, because of their constant assembly and diassembly.

Function of microtubules :

i. They provide the tracks for transport of vesicles, organelles such as secretory granules, and mitochondria from one part of the cell to another.

Microtubules can transport in both directions, and indeed, the same microtubule has been transporting two particles in opposite directions.

ii. They form the spindle, which moves the chromosomes in mitosis.

Applied : Microtubules assemly is prevented by colchicine and vinblastine. The anticancer drug paclitaxel (*Taxol*) binds to microtubules and makes them so stable that organelles cannot move and mitotic spindles cannot form, leading to cell death.

b. ***Intermediate filaments*** : Intermediate filaments are 8-14 nm in diameter and are made up of various sub-units.

Some of these filaments connect the nuclear membrane to the cell membrane. They appear to be part of the cytoskeleton, but their exact function is not known.

c. ***Microfilaments*** : Microfilaments are long solid fibers 4-6 nm in diameter. They are made up of actin. Actin and its mRNA are present in all types of cells. It is the most abudant protein in mammalian cells, sometimes accounting for as much as 15% of the total protein in the cell. Actin by its interaction with myosin brings about contraction of muscle.

(Ref. Guyton & Hall-11th Edition & others)

Centrosomes

Near the nucleus in the cytoplasm of eukaryotic animal cells is a centrosome. The centrosome is made up of two centrioles and surrounding amorphous pericentriolar material.The centrioles are short cylinders located near the nucleus, and they are arranged so that they are at right angles to each other. Microtubules in groups of three run longitudinally in the walls of each centriole. There are nine of these triplets spaced at regular intervals around the circumference.

The centrosomes are microtubule-organizing centers (MTOCs) that contain gama tubulin. The microtubules grow out of this gama tubulin in the pericentriolar material. When a cell divides, the cetrosomes duplicate themselves, and the pairs move apart to form the poles of the mitotic spindle, which is made up of microtubules. In multinucleate cells, there is a centrosome near each nucleus.

Cell adhesion molecules

Cells are attached to the basal lamina and to each other by *cell adhesion molecules (CAMs)* that are prominent parts of the intercellular connections.

These adhesion proteins have attracted great attention in recent years because they are important in embryonic development and formation the nervous system and other tissues, in holding tissues together in adults, in inflammation and wound healing, and in the metastasis of tumours.

Many pass through the cell membrane and are anchored to the cyto- skeleton inside the cell. Some bind to like molecules on the other cells (homophilic binding) , where as others bind to other molecules (hetero philic binding). Many binds to laminas, a family of large cross-shape molecules with multiple receptor domains in the extracellular matrix.

Types of cell adhesion molecules :

1. *Integrins,* heterodimers that bind to various receptors.
2. Adhesion molecules of the *IgG superfamily of immunoglobulins*, some of which bind to other molecules and some of which bind homophilically.
3. *Cadherins*, Ca^{++} dependent molecules that mediate cell-to-cell adhesion by homophilic reactions.
4. *Selectins*, which have lectin like domains that bind carbohydrates.

The cell adhesion molecule not only fasten cells to their neighbour- they also transmit signals into and out of the cell.

(Ref. Ganong 22th edition; Page-15,16)

Intercellular Connections

Two types of Junctions:

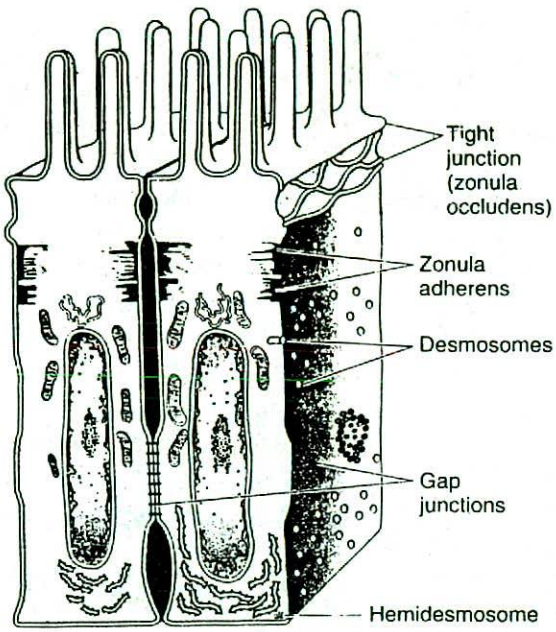
i. *Tight junction* or *Zonula occludens*: Junction that fasten the cells to one another and surrounding tissues.

ii. *Desmosome and zonula adherens* : Holds cells together.

iii. *Hemidesmosome and focal* : Attach cells to their basal lamina.

iv. *Gap junction* : Junctions that permit transfer of ions and other molecules from one cell to another.

Tight junction : It sorrounds the apical margins of the cells in epithelia such as the intestinal mucosa, the walls of the renal tubules, and the choroid plexus. They are made up of ridges half from one cell and half from the other which adhere so strongly at cell junctions that they almost obliterate the space between the cells. The ridges are made up of proteins.



Gap Junction : At gap junctions, the intercellular space narrows from 25 nm to 3 nm. Each cells are lined up with one another. When lined up with the channel in the corresponding connexon in the adjacent cell, permits substances to pass between the cells without entering the ECF. The diameter of the channel is normally about 2 nm, which permits the passage of ions, sugars, amino acids, and other solutes with the molecular weight upto 1000. Gap junctions thus permit the rapid propagation of electrical activity from cell to cell and the exchange of various chemical messengers.

(Ref. Ganong 22th Edition; Page-17)

Q. 01. **What do you mean by intercellular communications?**

Ans. *Intercellular communication* : Cells communicate with each other via chemical messengers. Within a given tissue, some messengers move from cell to cell via *gap junctions* without entering the ECF.

The chemical messengers include amines, amino acids, steroids, polypeptides, and in some instances lipids, purine nucleotides, and pyrimidine nucleotides. It is worth noting that in various parts of the body, the same chemical messenger can function as a neurotransmitter, a paracrine mediator, a hormone secreted by neurons into the blood (neural hormone), and a hormone secreted by gland cells into the blood.

Types : There are three general types of intercellular communication mediated by messengers in the ECF :

i. *Neural communication* : In which neurotrans-mitters are released at synaptic junctions from nerve cells and act across a narrow synaptic cleft on a postsynaptic cell.

ii. *Endocrine communication* : In which hormones and growth factors reach cells via the circulating blood.

iii. *Paracrine communication* : In which the products of cells diffuse in the ECF to affect neighboring cells that may be some distance away.

Autocrine communication : In addition, cells secrete chemical messengers that in some situations bind to receptors on the same cell, ie, the cell that secreted the messenger (autocrine communication).

Juxtacrine communication : An additional form of intercellular communication is called juxtacrine communication.

(Ganong 22th Edition, page-36,37)

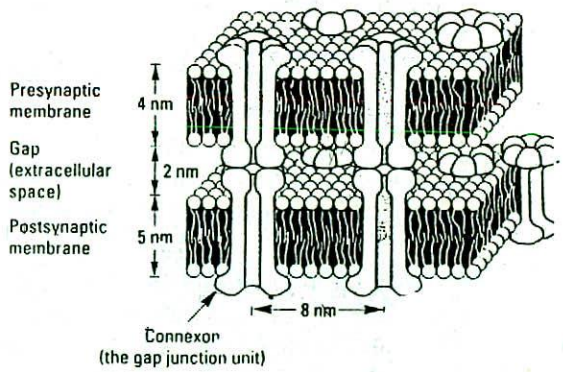


Fig : 1-4. *Intercellular Connections*

Functional systems of the cell

A. **Ingestion by the cell- Endocytosis** : If a cell is to live and grow and reproduce, it must obtain nutrients and other substances from the surrounding fluids. Most substances pass through the cell membrane by *diffusion* and *active transport.*

Diffusion means simple movement through the membrane caused by random motion of the molecules of the substances, moving either through cell membrane pores or, in the case of lipid soluble substances, through the lipid matrix of the membrane.

Active transport means actual carrying of a substance through the membrane by a physical protein structure that penetrates all the way through the membrane.

Very large particles enter the cell by a specialized function of the cell membrane called *endocytosis*. The principle forms of endocytosis are *pinocytosis* and *phagocytosis*.

(Ref. Guyton & Hall- 11th Edition; Page-19)

a. ***Pinocytosis*** : Pinocytosis means the ingestion of extremely small globules of extracellular fluid, forming minute vesicles in the cell cytoplasm.

Pinocytosis occurs continually at the cell membranes of most cells but specially rapidly in some cells. For instance, it occurs so rapidly in macrophages that about 3 per cent of the total macrophage membrane is engulfed in the form of vesicles each minute. Even so, the pinocytic vesicles are so small- usually only 100 to 200 nanometer in diameter- that most of them can be seen with the electron microscope.

Pinocytosis is the only means by which most large macromolecules, such as most protein molecule, can enter cells. In fact the rate at which pinocytic vesicles form usually is enhanced when such macromolecules attach to the cell membrane.

Mechenism :

1. Small globules of extracellular fluid such as protein molecules attaching to the cell membrane.
2. These molecules usually attach to specialized protein *receptors* on the surface of the membrane that are specific for the type of protein that is to be absorbed .
3. The receptors generally are concentrated in small pits on the outer surface of the cell membrane, called *coated pits*.
4. On the inside of the cell membrane beneath this pits is a laticework of fibrillar protein called *clathrin* as well as other proteins, perhaps including contractile filaments of actin and myosin.
5. Once the protein molecules have bound with the receptors, the surface properties of the cell membrane change in such a way that the enter pit invaginates inward and fibrillar proteins surrounding pit cause its borders to close over the attached proteins as well as over a small amount of extracellular fluid.
6. Immediately thereafter, the invaginaed portion of the membrane breaks away from the surface of the cell, forming a *pinocytic vesicles* inside the cytoplasm of the cell.

Requirements :

1. This process requires energy from within the cell; this is supplied by ATP.
2. It also requries the presence of calcium ions in the extracellular fluid, wich probably react with contractile protein filaments beneath the coated pits to provide the force for pinching the vesicles away from the cell membrane.

(Ref. Guyton & Hall- 11th Edition; Page-19)

b. ***Phagocytosis*** : Phagocytosis means ingestion of large particles, such as bacteria, cells, and portions of degerating tissue.

Only certain cells have the capability of phagocytosis, most notably the tissue macrophages and some of the white blood cells.

Mechenism : Phagocytosis is initiated when a particle such as a bacterium, a dead cell, or tissue debries binds with receptors on the suface of the phagocyte. In the case of bacteria, each bacterium is usually is already attached to a specific antibody, and it is the antibody that attaches to the phagocyte receptors, dragging the bacterium along with it.

1. The cell membrane receptors attach to the surface ligands of the particle.
2. The edges of the membrane arround the points of attachment evaginate outward within a fraction of a second to surround the entire particle ; Then, progressively more and more membrane receptors attach to the particle ligands, all this occuring suddenly in a zipperlike manner to form a closed *phagocytic vesicle*.
3. Actin and other contractile fibrils in the cytoplasm surround the phagocytic vesicle and contract arround its outer edge, pushing the vesicle to the interior.
4. The contractile proteins then pinch the vesicle off, leaving it in the cell interior.
5. Immediately thereafter, the invaginaed portion of the membrane breaks away from the surface of the cell, forming a *phagocytic vesicles* inside the cytoplasm of the cell.

(Ref. Guyton & Hall- 11th Edition; Page-19, 20)

B. **Digestion of pinocytic and phagocytic foreign substances in the cell-*function of the lysosomes*** :

Almost immediately after a pinocytic or phagocytic vesicle appears inside a cell, one or more lysosomes become attached to the vesicle and empty their acid hydrolases to the inside of the vesicle.

Thus, a *digestive vesicle* is formed in which the hydrolases begin hydrolyzing the proteins, carbohydrates, lipids, and other substances in the vesicle. The products of digestion are small molecules of amino acids, glucose, phosphates, and so forth that can diffuse through the membrane of the vesicle into the cytoplasm. What is left of the digestive vesicle, called the *residual body,* represents the undigestible substances. In most instances, this is finally excreted through the cell membrane by a process called *exocytosis,* which is essentially the opposite the endocytosis. Thus the pinocytic and phagocytic vesicle-lysosomes may be called the *digestive organs* of the cells.

1. *Regression of tissues* : Tissues of the body often regress to smaller size. For instance, this occurs in the uterus after pregnancy, in muscles during long periods of inactivity, and in mammary glands at the end of lactation. Lysosomes are responsible for much of this regrssion. The mechenism by which lack of activity in a tissue causes the lysosomes to increase their activity is unknown.

2. *Removal of damaged cells or damaged portions of cells from tissues- Autolysis of cells* : Removal of damaged cells or damaged portions of cells from tissues- cells damaged by heat, cold, trauma, chemicals, or any other factor is another special role of the lysosomes.
   Damage to the cell causes lysosomes to rupture. The hydrolases begin immediately to digest the surrounding organic substances.
   i. *If the damage is slight*, only a portion of the cell is removed, followed by repair of the cell.
   ii. *If the damage is severe*, the enter cell is digested, a process called *autolysis*. In this way, the cell is completely removed, and a new cell of the same type ordinarily is formed by mitotic reproduction of an adjacent cell to take the place of the old one.
3. The lysosomes also contain bactericidal agents that can kill phagocytized bacteria before they can cause cellular damage. These agents include *lysozyme* that dissolves the bacterial cell membrane, *lysoferrin* that binds iron and other metals that are essential for bacterial growth, and acid at a pH of about 5.0 that activates the hydrolases and inactivates some of the bacterial metabolic systems.

(Ref. Guyton 11th ed; P-16, 20; Ganong 22th ed; P-11,12)

C. **Synthesis and formation of cellular structures by the endoplasmic reticulum and the Golgi apparutus** :

1. ***Specific functions of the endoplasmic reticulum*** :
   Most of the synthesis begins in the endoplasmic reticulum. The products that are formed then passed on to the Golgi apparatus, where they are further processed before release into the cytoplasm.
   i. *Proteins are formed by the granular endoplasmic reticulum* : Protein molecules are synthesized within the structures of the ribosomes. The ribosomes extrude some of the synthesized protein molecules directly into the cytosal, but they are also extrude many more through the wall of the endoplasmic reticulum to the interior of the endoplasmic vesicles, tubules, that is, into the *endoplasmic matrix*.
   ii. *Synthesis of lipids by the endoplasmic reticulum, especially by the smooth endoplasmic reticulum* : The endoplasmic reticulum also synthesizes lipids, espicially phospholipids and cholesterol. These are rapidly incorporated into the lipid bilayer of the endoplasmic reticulum itself, thus causing the endoplasmic reticulum to grow more extensive. This occurs mainly in the smooth portion of the endoplasmic reticulum.
   To keep the endoplasmic reticulum from growing beyond the needs of the cell, small vesicles called *endoplasmic reticulum vesicles* (ER vesicles) or *transport vesicles* continually break away from the smooth reticulum; most of these vesicles then migrate rapidly to the Golgi apparatus.

   Other significant function of the endoplasmic reticulumn, especially the smooth reticulumn, incluide the following :
   iii. It provides the enzymes that control glycogen breakdown when glycogen is to be used for energy.
   iv. It provides a vast number of enzymes that are capable of detoxifying substances such as drugs that might damage the cell. It achives detoxification by coagulation, oxidation, hydrolysis, conjugation with glycuronic acid, or in other ways.

   (Ref. Guyton & Hall- 11thEdition; Page-20, 21)

2. ***Specific functions of the Golgi apparatus*** :
   i. *Synthetic function of the Golgi apparatus* : It has the capability of synthesizing certain carbohydrates that can not be formed in the endoplasmic reticulum i.e *hyaluronic acid* and *chondroitin sulfate*.
   Functions of the hyaluronic acid and chondroitin sulfate are as follows :
   a. They are the major components of proteoglycans secreted in mucus and other glandular secretions.
   b. They are the major components of the *ground substance* in the interstitial spaces, acting as filter between collagen fibers and cells.
   c. They are principle components of the organic matrix in both cartilage and bone.
   ii. *Processing of endoplasmic secretions by the Galgi appatus- Formation of Vesicles* : As substances are formed in the endoplasmic reticulum, especially the proteins, they are transported through the tubules towards the portions of smooth endoplamic reticulum that lie nearst the Golgi apparatus. At this point, small *transport vesicles* composed of small envelopes of smooth endoplasmic reticulum continually breaks away and diffuse to the *deepest layer* of Golgi apparatus. Inside the vesicles are the synthesized proteins and other products from the endoplasmic reticulum.
   The transport vesicles instantly fuse with the Galgi apparatus and empty their contained substances into the vesicular spaces of Golgi apparatus. Here, additional carbohydrate moiety are added to the secretions. Also, a most important function of the Galgi apparatus is to compact the endoplasmic reticulum secretions into highly concentrated packets. As the secretion pass towards the outermost layers of the Golgi apparatus, the compaction and processing proceed. Finally both small and large vesicles continually break away from the Golgi apparatus, carrying with them the compacted secretory substances, and the vesicles diffuse throughout the cell.

To give an idea of the timing of these processes : When a glandular cell is bathed in radioactive amino acids, newly formed radioactive protein molecules can be detected in the granular endoplasmic reticulum within 3 to 5 minutes. Within 20 minutes, newly formed proteins are already present in the Golgi apparatus, and within 1 to 2 hours, radioactive proteins are secreted from the surface of the cell.

(Ref. Guyton & Hall- 11th Edition; Page-21)

Types of vesicles formed by the Golgi Apparatus- *Secretory Vesicles and Lysosome* : In a highly secretory cell, the vesicles formed by the Golgi apparatus are mainly *secretory vesicles* containing protein substances that are to be secreted through the surface of the cell membrane. These secretory vesieles first diffuse to the cell membrane, then fuse with it and empty their substances to the exterior by the mechanism called *exocytosis*. Exocytosis, in most cases, is stimulated by the entry of calcium ions into the cell; calcium ions interact with the vesicular membrane in some way that is not understood and cause its fusion with the cell membrane, followed by exocytosis- that is, opening of the membrane's outer surface and extrusion of its contents outside the cell.

Some vesicles, however, are destined for intracellular use.

(Ref. Guyton & Hall- 10th Edition; Page-18,19)

Use of intracellular vesicles to replenish cellular membrane : Others of the intracellular vesicles formed by the Golgi apparatus fuse with the cell membrane or with the membranes of intracellular structures such as the mitochondria and even the endoplasmic reticulum. This increases the expanse of these membranes and there by replinishes the membranes as they are used up. For instance, the cell membrane loses much of its substance every time it forms a *phagocytic* and *pinocytic vesicle*, and it is vesicles from the Golgi apparatus that continually replenish the cell membrane.

In summary, *the membranous system of the endoplasmic reticulum and Golgi appatatus represents a highly metabolic organ capable of forming new intracellular structures as well as secretory substances to be extruded from the cell.*

(Ref. Guyton & Hall- 11th Edition; Page-21)

D. **Extraction of energy from nutrients-** ***Functions of the mitochondria*** : The principal substances from which cells extract energy are the foodstuffs that react with oxygen- carbohydrates, fats, and proteins. In the human body, essentially all carbohydrates are converted into glucose by the digestive tract and liver before they reach the cell. Similarly, the proteins are converted into amino acids and the fats into fatty acids. Inside the cell, foodstuffs react chemically with the oxygen under the influence of various enzymes that control the rates of the reactions and channel the energy that is released in the proper direction.

Briefly, almost all these oxidative reactions occur inside the mitochondria, and the energy that is released is used to form the high energy compound adenosine triphosphate (ATP). Then, the ATP, not the original foodstuffs themselves, is used throughout the cell to energize almost all the subsequent intracellular metabolic reactions.

(Ref. Guyton & Hall- 11th Edition; Page-22)

Transport Across Cell Membranes

Transport across cell membranes is accomplished primarily by *exocytosis, endocytosis, movement through ion channels, primary and secondary active transport.*

Exocytosis

Difinition : Extrusion of proteins from cell to the surrouding fluid is called exocytosis. It requires ca^{++} and energy, along with proteins.

Process : Proteins that are secreted by cells move from the endoplasmic reticulum to the Golgi apparatus, and from the trans golgi, they are extruded into secretory granules or vesicles. The graules and vesicles move to the cell membrane. Their membrane then fuses to the cell membrane and the area of fusion breaks down. This leaves the contents of the granules or vesicles outside the cell and the cell membrane becomes intact.

Pathways :

1. Nonconstitutive pathway : Proteins from the Golgi apparatus initially enters secretory granules, where processing of prohormones to mature hormones occurs before exocytosis.
2. Constitutive pathway : Involves the prompt transport of proteins to the cell membrane in vesicles, with little or no processing or storage.

Endocytosis

Ingestion of nutrients and other substances from the surrounding fluid by the cell is called endocytosis.

Two principal forms of endocytosis are- *pinocytosis & phagocytosis.*

Phagocytosis : It is the process by which bacteria, dead tissues, or other bits of material visible under the microscope are engulfed by cells such as the polymorpho nuclear leucocytes of the blood.

Process : The material makes contact with the cell membrane, which then invaginates. The invagination is pinched off, leaving the engulfed material in the membrane enclosed vacuole and the cell membrane intact.

Pinocytosis *(cell drinking)* : It means the ingestion of extremely small substances that are in solution and hence not visible under the microscope.

Each types of endocytosis can be-

1. *Constitutive* : It is a continues process that is not induced.
2. *Receptor mediated* : It is produced for the most part via specialized clathrin coated pits on the cell membrane. It is triggered by various ligands binding to their receptors on

the cell membrane. Receptor mediated endocytosis occur more rapidly than constitutive endocytosis.

Types of endocytosis :

Types of endocytosis	*Size of vesicle or vacuole*	*Intermediate organelle*
Phagocytosis		
Receptor mediated	0.1-10 mm	Phagosome
Non-receptor mediated	0.1-10 mm	Vacuole
Pinocytosis		
Clathrin dependent		
Receptor mediated	100 nm	Endosome
Synaptic vesicle retrieval	50 nm	Endosome
Clathrin-independent		
Potocytosis	60 nm	Caveolae
Micropinocytosis	100 nm	Micropinosome
Maeropinocytosis	0.5-6 mm	Macropinosome

Osmosis

Definition : Migration of solvent from the solution of lower concentration to the higher concentration, when they are seperated by a semipermeable membrane is called Osmosis.

Rate of osmosis depends upon :

i. Difference in osmotic pressure of the solution.
ii. Permeability of the membrane.
iii. Electrical potential across the membarane and charge upon the wall and pore of the membrane.

Osmotic pressure : The force (pressure) by which the osmosis occurs is called osmotic pressure.

Physiological importance :

i. Absorption from the intestine.
ii. Exchange in the capillary bed.
iii. Regulation of urine formation.
iv. Continuous osmotic exchange between plasma and red cells.
v. *Clinical use*- injection of saline are given by way of treatment.

Q. ***On which factors osmotic pressure depends and why?***

Ans. Osmotic pressure depends upon the total number of the particles per unit volume but not upon the size of the molecules.

Because each particle in a solution exerts, on the average, the same amount of pressure against the membrane.

Q. ***Do you think crystaloid particles exert more osmotic pressure than colloid particles, why?***

Ans. Yes, crystaloid particles exert more osmotic pressure. Because, ionisable particle exert more osmotic pressure than non-ionised particles.

Q. ***Why ionise particle exert more osmotic pressure than non-ionised particles?***

Ans. A substance, which ionises has more number of osmotic particle, so osmotic pressure of ionised substance is more than of non-ionised substance.

Relation between osmolality to osmotic pressure :

At nomal body temperature, 1 milliosmole per liter concentration is equivalent to 19.3 mm Hg of osmotic pressure.

So, Osmotic pressure (mm Hg) = 19.3 x Osmolality (milli osmole /L)

Diffusion

Definition : The continual movement of molecules in a solution from a higher concentration to lower concentration is called diffusion.

Diffusion depends upon the weight and size of the molecules.

Physiological importance of diffusion :

i. Admixture of food stuffs with digestive juice.
ii. Absorption from the intestine.
iii. Exchange between plasma and red cells.
iv. Exchange in the capillary bed.
v. Admixture of gases in the lungs.

Factors affect the rate of diffusion :

1. *Concentration gradient :* The greater the concentration difference, the greater is the rate of diffusion.
2. *Molecular diameter :* The less the diameter of the molecule, the greater is the rate of diffusion.
3. *Distance between the area :* The shorter is the distance, the greater is the rate of diffusion.
4. *Cross section :* The greater the cross section of the chamber in which the diffusion is taking place, the greater is the rate of diffusion.
5. *Temperature :* The greater the temperature, the greater is the rate of diffusion.

Diffusion rate =

$$\frac{\text{Concentration difference x cross sectional area x temperature}}{\sqrt{\text{Molecular weight x distance}}}$$

Types of diffusion

i. *Simple diffusion :* Some lipid soluble substances (O_2, CO_2, alcohol, and fatty acids. can easily diffuse through the cell membrane, called simple diffusion. Here carrier is not required.
ii. *Facilitated diffusion :* Some lipid insoluble subs tance (glucose etc) can diffuse through the lipid matrix of cell membrane with the help of carrier mechanism called facilated diffusion. Here carrier is required.

Factors essential for facilitated diffusion

i. Concentration gradient
ii. Amount of carrier
iii. Enzyme.
iv. The rapidity with which the chemical reaction involved in the mechanism takes place.

Difference between the simple and facilitated diffusion

Simple diffusion	*Facilitated diffusion*
i. Carrier is not needed.	i. Carrier must be present.
ii. Rate of diffusion is almost exactly proportional to the difference of the concentration of particle on the two side of the membrane.	ii. For a carrier transported substance, rate of diffusion approches a maximum, as the concentration of the substance increase.

Passive transport

The movement of substance across the cell membrane along the concentration gradient is called passive transport.

The gradients are -

i. Osmotic pressure
ii. Hydrostatic pressre
iii. Gradient of concentration and potential.

Tyses :

i. Diffusion.
ii. Osmosis.
iii Filtration.
iv. Flow due to gravity.

Filtration

a. *Definition* : It is the process by which undissolved particles are separated from a liquid through a membrane as a result of mechanical force (filtering force).
b. *Filtering force* :
   i. Gravity.
   ii. Hydrostatic pressure.
c. *Filtering membrane* :
   i. Cloth
   ii. Filter paper
   iii. Membrane.
d. *Filtration depends on* :
   i. Pressure difference across the filtering membrane.
   ii. Pore size of the membrane
   iii. Osmotic pressure of the fluid to be filtered
e. *Improtance* :
   i. Absorption from the small intestine.
   ii. Passage of water, salts, food stuff etc. from the blood stream to the tissue fluid.
   iii. Formation of urine
   iv. Formation of CSF.

Movement through ion channels

Most ion channels probably evolved by gene duplication and divergence from an ancestral molecule with six membrane spanning segments. The wide diversity in ion channel properties permits ion transport.

1. *Na^+ channels :* They are tetramers, with each subunit crossing the membrane six times.
2. *K^+ channels :* They are tetrameric. Their subunits are encoded by a number of different genes, and many of the genes are able to generate different domain structures by alternate splicing.
3. *Cl^- channels :* They are involved for the most part in volume regulation of cells, in transepithelial ion transport and apparently in regulation of muscle and kidney function. For example GABA receptor and the glycine receptor are Cl channels.
4. *Ca^{++} channel* etc.

Cardiac ion channels :

i. *Voltage-gated channels*
   Na^+
   T Ca^{2+}
   L Ca^{2+}
   K^+
   Inward rectifying
   Delayed rectifying
   Transient outward
ii. *Ligand-gated K^+ channels* :
   Ca^+ activated
   Na^+ activated
   ATP-sensitive
   Acetylcholine-activated
   Arachidonic acid-activated.

(Ref. Ganong 21th edition, Page 80)

Potassium (K^+) channel

Most K^+ channels are tetramers, with each of the four sub-units forming part of the pore through which K^+ ions pass. Their subunits are encoded by a number of different genes, and many of the genes are able to generate different domain structures by alternate splicing. Fast-inactivating voltage-gated K^+ channels have a unique feature. Each of the tetramers has a polypeptide ball structure on the end of a polypeptide chain, and the ball moves into the channel, producing inactivation *(Fig. 1-31 Ganong)*. There are ball-and-chain structures on all four tetramers even though there is only one K^+ pore. In the acetylecholine ion channel and other ligand-gated cation or anion channels, five subunits make up the pore.

(Ref. Ganong 22th edition, Page 32)

Function and mechenism : The repolarization (phase 3) to the resting membrane potential (phase 4) is due to closure of the Ca^{++} channels and K^+ efflux through various types of K^+ channels. There are *three types of K^+ channels that produce repolarization* :

i. The first produces a *transient, early outward current* (I_{TO}) that produces an early incomplete repolarization.
ii. The second is *inwardly rectifying*, ie, at plateau potentials it allows K^+ influx but resists K^+ efflux and only at lower membrane potentials does it permit K^+ efflux. The current it produces is called I_{kr}.

iii. The third type is a *slowly activating (delayed rectifying)* type that produces a current called I_{ks}.

The sum of I_{kr} and I_{ks} is a small net outward current that increases with time and produces repolarization.

The subunits that make up the K^+ channels responsible for I_{kr} cross the membrane six times and are the product of HERG (for *human ether-a-go-go-related gene*). The channel responsible for I_{ks} is made up of a protein that crosses the membrane six times combined with a small protein called **minK** (because of its size) that has only a single membrane-spanning domain.

(Ref. Ganong 21th edition, Page 80)

a. ***In the heart***, repolarization is due to net K^+ efflux through three types of K^+ channels. Rhythmically discharging cells have a membrane potential that, after each impulse, declines to the firing level. Thus, this prepotential or pacemaker potential triggers the next impulse. At the peak of each impulse, Ik begins and brings about repolarization. Ik then declines, and as K^+ efflux decreases, the membrane begins to depolarize, forming the first part of the prepotential.

Applied : When the cholinergic vagal fibers to nodal tissue are stimulated, the membrane becomes hyperpolarized and the slope of the prepotentials is decreased because the acetylcholine released at the nerve endings increases the K^+ conductance of nodal tissue. This action is mediated by M_2 muscarinic receptors, which, via the $\beta\gamma$ subunit of a G protein, open a special set of K^+ channels. The resulting I_{KAch} counters the decay of I_k.

(Ref. Ganong 22th edition, Page 548, 549)

b. ***In the nerve***, a *third factor producing repolarization* is the opening of *voltage-gated* K^+ channels. This opening is slower and more prolonged than the opening of the Na^+ channels, and consequently, much of the increase in K^+ conductance comes after the increase in Na^+ conductance. The slower opening and delayed closing of the voltage-gated K^+ channels also explain accommodation. If depolarization occurs rapidly, the opening of the Na^+ channels overwhelms the repolarizing forces, but if the induced depolarization is produced slowly, the opening of K^+ channels balances the gradual opening of Na^+ channels, and an action potential does not occur.

(Ref. Ganong 22th edition, Page 59)

c. ***Slow postsynaptic potentials*** : Slow EPSPs and IPSPs have been described in autonomic ganglia, cardiac and smooth muscle, and cortical neurons. These postsynaptic potentials have a latency of 100-500 ms and last several seconds. The slow EPSPs are generally due to decreases in K^+ conductance, and the slow IPSPs are due to increases in K^+ conductance. In sympathetic ganglia, there is also a late slow EPSP that has a latency of 1-5 seconds and lasts 10-30 minutes. This potential is also due, at least in part, to decreased K^+ conductance, and the transmitter responsible for the potential is a peptide very closely related to GnRH, the hormone secreted by neurons in the hypothalamus that stimulates LH secretion.

(Ref. Ganong 22th edition, Page 90)

d. ***In vascular smooth muscle*** : Vascular smooth muscle cells provide an interesting example of the way high and low cytosolic Ca^{++} can have different and even opposite effects. In these cells, influx of Ca^{++} via voltage-gated Ca^{++} channels produces a diffuse increase in cytosolic Ca^{++} that initiates contraction. However, the Ca^{++} influx also initiates Ca^{++} release from the sarcoplasmic reticulum via ryanodine receptors and the high local Ca^{++} concentration produced by these Ca^{++} sparks increases the activity of ***Ca^{++}-activated K^+ channels*** in the cell membrane. These are also known as big K or ***BK channels*** because K^+ flows through them at a high rate. The increased K^+ efflux increases the membrane potential, shutting off voltage-gated Ca^{++} channels and producing relaxation. The site of action of the Ca^{++} sparks is the β_1-subunit of the *BK channel*, and mice in which this subunit is knocked out develop ***increased vascular tone*** and ***blood pressure***. Obviously, therefore, the sensitivity of the β_1-subunit to Ca^{++} sparks plays an important role in the control of vascular tone.

(Ref. Ganong 22th edition, Page 580)

Active Transport

a. *Definition* : The movement of substance across the cell membrane against the concentration gradient with active expenditure of energy by the help of carrier called active transport.

The energey is derived from ATP and the carriers are present in the cell membrane.

Each type of carrier transports only a specific substance.

b. *The gradient may be :*
   i. Electrical.
   ii. Pressure.
   iii. Concentration
   iv. Speed of flow.

c. *Active transport generally requires :*

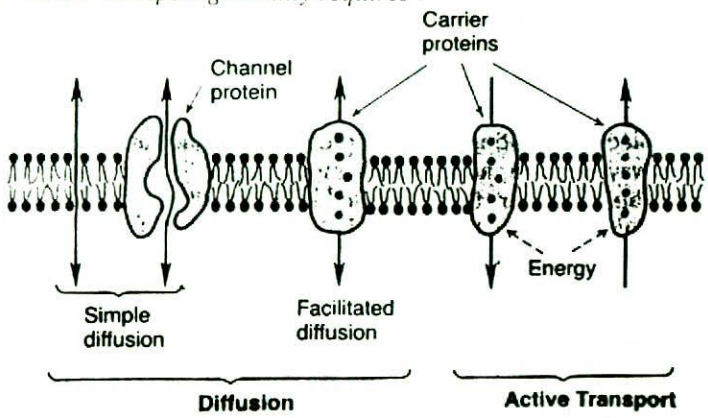


Fig. 1-5. *Transport pathways through the cell membrane and the basic mechanisms of transport.*

i. Active expenditure of energy
ii. Special carrier system
iii. Difference of concentration gradient
iv. Enzymes.

d. *Types of active transport* -
   i. Primary active transport.
   ii. Secondary active transport.
      1. Co-transport
      2. Counter transport.

   Active transport is divided into two types according to the source of the energy used to cause the transport. They are called primary active transport and secondary active transport.

(Ref. Guyton & Hall- 11th Edition; Page-52)

Primary active transport

In primary active transport, the energy is derived directly from the breakdown of adenosine triphosphate (ATP) or some other high energy phosphate compound. Transport depends on carrier proteins that penetrate through the membrane ie *Na^+-K^+ pump.*

(Ref. Guyton & Hall-11th Edition; Page-53)

Na^+-K^+ pump : Sodium-potassium pump refers to the mechanism that transports sodium ions out of the cells to the exterior and at the same time pumps potassium ions from the outside to the inside. Here two K^+ ions are transferred for each three Na^+ ions.

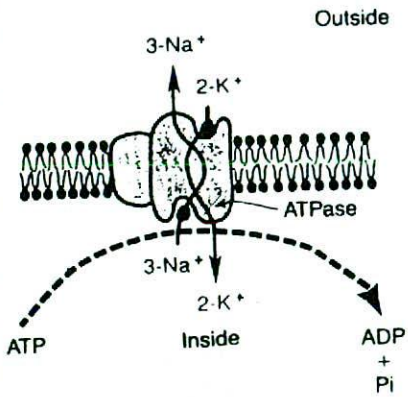


Fig : 1-6. *Sodium-potassium pump*

a. *Structure* : The carrier protein of the N^+-K^+ pump is a complex of two separate globular proteins, a larger one (molecular weight 100,000) and a smaller one (molecular weight 45,000). The function of the smaller protein is not known. *The larger protein has three specific features that are important for function of the pump* :
   i. It has three *receptor sites for binding sodium ions* on the portion of the protein that protrudes to the interior of the cell.
   ii. It has two *receptor sites for potassium ions* on the outside.
   iii. The inside portion of this protein adjacent to or near to the sodium binding sites has ATPase activity.

b. *Mechanism* : When 3 Na^+ ions bind on the inside of the carrier protein and 2 K^+ ions on the outside, the ATPase function becomes activated. This then leaves 1 molecule of ATP, splitting it to ADP and liberating a high energy phosphate bond of energy. This energy is then believed to cause a conformational change in the protein carrier molecule, extruding the sodium ions to the outside and potassium ions to the inside.

c. *Importance of Na^+-K^+ pump* : This pump is responsidble for-
   i. Maintaining the sodium and potassium concentration difference across the cell membrane
   ii. Establishing a negative electrical potential inside the cells.
   iii. The pump is so important to many different functioning systems of the body such as to nerve & muscle fibres for transmission of impulses, various glands for the secretion of different substances, and all the cells of the body to prevent cellular swelling.
   iv. ***Importance of the Na^+-K^+ pump in controlling cell volume*** : *The mechanism for controlling the volume is as follows* :
      1. Inside the cell are large numbers of proteins and other organic compounds that cannot escape from the cell. Most of these are negatively charged and therefore collect around them large numbers of positive ions as well. All these substances then tend to cause *osmosis of water* to the interior of the cell. Unless this is checked, the cell will swell indefinitely until it bursts. The normal mechanism for preventing this is the Na^+-K^+ pump.
      2. *Na^+-K^+ pump* pumps three Na^+ ions to the outside of the cell for every two K^+ ions pumped to the interior. Also, the membrane is far less permeable to sodium ions than to potassium ions, so that once the sodium ions are on the outside, they have a strong tendency to stay there. Thus, this represents a continual net loss of ions out of the cell, which initiates osmosis of water out of the cell as well.
      3. If a cell begins to swell for any reason, this automatically activates the Na^+-K^+ pump, moving still more ions to the exterior and carrying water with them.

   Therefore, the Na^+-K^+ pump performs a continual surveillance role in maintaining normal cell volume.

(Ref. Guyton & Hall- 11th Edition; Page-53, 54)

Electrogenic pump

i. *Definition* : Na^+-K^+ pump creates an electrical potential across the cell membrane because in every pump cell loses one positive charge; so Na^+-K^+ pump is called electrogenic pump.

ii. *Stimulatory factors* :
   a. Aldosterone, thyroid hormones increase the formation of

Na^+-K^+ATPase molecule, and thus increase Na^+-K^+ pump.

b. Insulin increases Na^+-K^+ pumps activity probably by a variety of different mechanisms.

iii. *Inhibitory factors* :

a. The activity of the Na^+-K^+ pump is inhibited by cardiac glycosides (digitalis) - due to inhibition of Na^+-K^+ ATPase.

b. Dopamine in the kidney inhibits the Na^+-K^+ pump by phosphorylating Na^+-K^+ ATPase.

(Ref. Guyton & Hall- 11th Edition; Page-53, 54)

Primary active transport of calcium : Calcium ions are normaly maintained at extremely low concentration in the intracellular cytosol of virtually all cells in the body, at concentration about 10,000 times less than that in the extracellular fluid. This is achieved mainly by two primary active transport calcium pumps. *One* is in the cell membrane and pumps calcium to the outside of the cell. The *other* pumps calcium ions into one or more of the internal vesicular organelles of the cell such as into the sarcoplasmic reticulum of muscle cell and into the mitochondria in all cells. In each of these instances, the carrier protein penetrates the membrane from side to side and also serves as an ATPase, having the same capability to cleave ATP as the ATPase sodium carrier protein. The difference is that this protein has a highly specific binding site for calcium instead of sodium.

(Ref. Guyton & Hall- 11th Edition; Page-54)

Primary active ransport of hydrogen ions : At two places in the body are important primary active transport systems for hydrogen ions. They are-

i. In the gastric glands of the stomach .

ii. In the late distal tubules and cortical collecting ducts of the kidneys.

In the gastric glands, the deep-lying *parietal cells* have the most potent primary active mechanism for transporting hydrogen ions of any part of the body. This is the basis for secreting hydrochloric acid in the stomach digestive secretions. At the secretory side of the parietal cells, the hydrogen ion concentration can be increased as much as a million fold and then released in association with chloride ions in the form of hydrochloric acid.

In the renal tubules there are special intercalated cells in the late distal tubules and cortical collecting ducts that also transport hydrogen ions by primary active transport. In this case, large amounts of hydrogen ions are secreted into the tubules to eliminate them from the body for the purpose of controlling the blood hydrogen ion concentration. The hydrogen ions can be secreted against a concentration gradient of about 900 fold.

At many other points in the body, hydrogen ions are transported by secondary active transport, but in these instances, they usually are transported against far less concentration gradients, such as 4 to 1 up to 10 to 1.

(Ref. Guyton & Hall- 11th Edition; Page-54)

N.B. Energetics of promary active transport : Pl. follow Guyton 11th Edition, Page 54.

Secondary active transport

In secondary active transport, the energy is derived secondarily from energy that has been stored in the form of ionic concentration differences between the two sides of a membrane, created in the first place by primary active transport.

Depends on : Transport depends on carrier proteins that penetrate through the membrane.

Types :

i. Co-transport

ii. Counter transport.

(Ref. Guyton & Hall- 11th Edition; Page-54)

i. **Co-transport** : When sodium ions are transported out of cells by primary active transport, a large concentration gradient of sodium usually develops very high concentration outside the cell and very low concentration inside. This gradient represents a storehouse of energy because the excess sodium outside the cell membrane is always attempting to diffuse to the interior. Under the appropriate conditions, this diffusion energy of sodium can literally pull other substances along with the sodium through the cell membrane. This phenomenon is called co-transport; it is one form of secondary active transport.

For sodium to pull another substance along with it, a coupling mechanism is required. This is achieved by means of still another carrier protein in the cell membrane. The carrier in this instance serves as an attachment point for both the sodium ion and the substance to be co-transported. Once they both are attached, a conformational change occurs in the carrier protein, and the energy gradient of the sodium ion causes both the sodium ion and the other substance to be transported together to the interior of the cell.

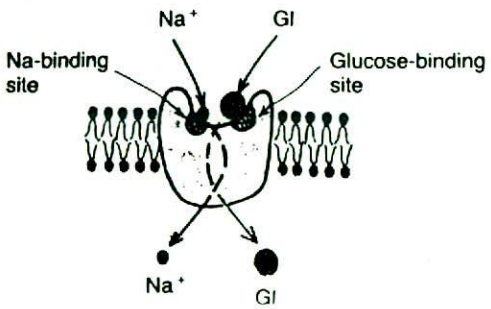


Fig. 1-7. *Postulated mechanism for sodium co-Transport of glucose.*

Co-transport of glucose and amino acids along with sodium ions : *Glucose and many amino acids* are transported into most cells against large concentration gradients; the mechanism of this is entirely by

the co-transport mechanism. The transport carrier protein has two binding sites on its exterior side, one for sodium and one for glucose. Also, the concentration of sodium ions is very high on the outside and very low inside, which provides the energy for the transport. A special property of the transport protein is that the conformational change to allow sodium movement to the interior will not occur until a glucose molecule also attaches. But when they are both attached, the conformational change takes place automatically, and both the sodium and the glucose are transported to the inside of the cell at the same time. Hence, this is a sodium-glucose co-transport mechanism.

Sodium co-transport of the amino acids occurs in the same manner as for glucose, except that it uses a different set of transport proteins. Five amino acid transport proteins have been identified, each of which is responsible for transporting one subset of amino acids with specific molecular characteristics.

Sodium co-transport of glucose and amino acids occurs especially in the epithelial cells of the intestinal tract and renal tubules to aid in the absorption of these substances into the blood.

(Ref. Guyton & Hall- 11th Edition; Page-54)

Other important co-transport mechanisms in at least some cells include co-transport of chloride ions, iodine ions, iron ions, and urate ions.

(Ref. Guyton & Hall- 11th Edition; Page-54)

ii. **Counter transport** : In counter-transport, sodium ions again attempt to diffuse to the interior of the cell because of their large concentration gradient. However, this time, the substance to be transported is on the inside of the cell and must be transported to the outside. Therefore, the sodium ion binds to the carrier protein where it projects through the exterior surface of the membrane, whereas the substance to be counter-transported binds to the interior projection of the carrier protein. Once both have bound, a conformational change occurs again, with the energy of the sodium ion moving to the interior causing the other substance to move to the exterior.

(Ref. Guyton & Hall-11th Edition; Page-54)

Sodium counter-transport of calcium and hydrogen ions : Two especially important counter-transport mechanisms are *sodium-calcium counter-transport* and *sodium-hydrogen counter-transport*.

a. *Sodium-calcium counter-transport* occurs through all or almost all cell membranes, with sodium ions moving the interior and calcium ions, to the exterior, both bound to the same transport protein in a counter-transport mode. This is in addition to primary active transport of calcium that occurs in some cells.

b. *Sodium-hydrogen counter-transport* occurs in several tissues. An especially important example is in the proximal tubules of the kidneys, where sodium ions move from the lumen of the tubule to the interior of the tubular cells, whereas hydrogen ions are counter transported into the lumen. This mechanism is not nearly so powerful for concentrating hydrogen ions as is the primary active transport of hydrogen that occurs in some of the more distal renal tubules, but it can transport such large numbers of hydrogen ions that it is nevertheless a key to hydrogen ion control in the body fluids.

(Ref. Guyton & Hall- 11th Edition; Page-55)

Membrane Potential

Membrane Potential

Definition : The electrical potential difference across the membrane is called *membrane potential.*

Membrance potentials (potential difference between the outside and inside of the cell memrane) are of 2 types-

a. Resting membrane potential (RMP)
b. Action potential.

Resting membrane potential

Definition : The electrical potential difference across the membrane at resting condition is called resting membrane potential.

The membrane potential of a nerve fiber is -90 mV. It is always expressd in negative because the inside of the cell membrane is always negatively charged in relation to the exterior as the cell membrane are impermeable to intracellular protein and other anions.

Causes : Two basic means by which membrane potentials can develop are :

i. Diffusion of ions through the membrane as a result of ion concentration differences between the two sides of the membrane i.e diffusion of potassium and sodium ions. The emphasis is on potassium leakage because, on average, the *potassium-sodium 'leak' channels* are far more permeable to potassium than to sodium, normally about 100 times as permeable. Which gives an internal potential of -86 millivolts.

ii. Active transport of ions through the membrane i.e sodium-potassium pump. Which gives an internal potential of -4 millivolts.

So the net membrane potential of a nerve membrane is -90 millivolts.

(Ref. Guyton & Hall-11th Edition; Page 59, 60)

Origin of normal resting membrane potential *(In a nerve membrane)* :

1. *Contribution of the potassium diffusion potential* : Because of high ratio of potassium ions inside to outside of the cell

membrane, 35 to 1, the Nernst potential corresponding to this ratio is -94 millivolts. Therefore, if potassium ions were the only factor causing the resting potential, this resting potential inside the fiber also would be equal to -94 millivolts.

2. *Contribution of sodium diffusion through the membrane* : Slight permeability of the nerve membrane to sodium ions, caused by the minute diffusion of sodium ions through the K^+-Na^+ *leak channels*. The ratio of sodium ions from inside to outside the membrane is 0.1, and this gives a calculated Nernst potential for the inside of the membrane of +61 millivolts.

   What will be the summated calculation of no. 1 and no. 2 : The membrane is highly permeable to potassium but only slightly permeable to sodium, it is logical that the diffusion of potassium contributes far more to the membrane potential than does the diffusion of sodium. In the normal nerve fiber, the permeability of the membrane to potassium is about 100 times as great as to sodium. Using this value in the Goldman equation gives an internal membrane potential of -86 millivolts, which is near to the potassium potential.

3. *Contribution of the Na^+-K^+ pump* : This provide still an additional contribution to the resting potential. Continuous pumping of three sodium ions to the outside for each two potassium ions pumped to the inside of the membrane.The fact that more sodium ions are being pumped to the outside than potassium to the inside causes a continual loss of positive charges from inside the membrane; this creates an additional degree of negativity (about -4 milivolts additional) on the inside beyond that which can be accounted for by diffusion alone. The net membrane potential with all these factors operative at the same time is about -90 milivolts.

In summary, the diffusion potentials alone caused by potassium and sodium diffusion would give a membrane potential of about -86 milivolts, almost all of this being determined by potassium diffusion. Then, an additional -4 milivolts is contributed to the membrane potential by the continuously acting electrogenic Na^+-K^+ pump, giving a net membrane potential of -90 milivolts.

(Ref. Guyton & Hall-11th Edition; Page-60, 61)

Resting membrane potential in different cell

Resting membrane potential in different cell are as follows :

1. Nerve fibers	:	-90 millivolts
2. Neurons	:	-70 millivolts
3. Nodal fibers of cardiac muscles	:	-55 to -60 millivolts
4. Cardiac muscles (Venticular muscle fibers)	:	-85 to -90 millivolts
5. Visceral smooth muscles	:	-50 millivolts
6. Skeletal muscles	:	-85 to -90 millivolts.

Action Potential

Definition : An action potential is a rapid change in the membrane potential followed by a return to the resting membrane potential.

Stages of action potential :

a. Resting stage
b. Depolarization stage
c. Repolarization stage
d. Spike potential
e. Negative after potential
f. Positive after potential or hyperpolarization.

The successive stages of action potential are :

1. *Resting stage :* This is the resting membrane potential before the action potential begins. The membrane is said to be 'polarized' during this stage because of the very large negative membrane potential that is present.
2. *Depolarization stage :* When the negetivity of the membrane potential rises rapidly in positive direction due to influx (enter) of sodium ions is called dedpolarization.
3. *Repolarization stage :* Immediately after depolarization (within a few 10,000ths of a seccond) the negetivity of the membrane potential re-establishes towards the normal negative resting membrane potential due to efflux of K^+. This is called the *repolarization* of the membrane.
4. *Spike potential* : Initially, the depolarization wave over shoots the zero line and then sharply falls. This sharp rise of the depolarization wave and the rapid fall of repolarization wave is called spike potential.

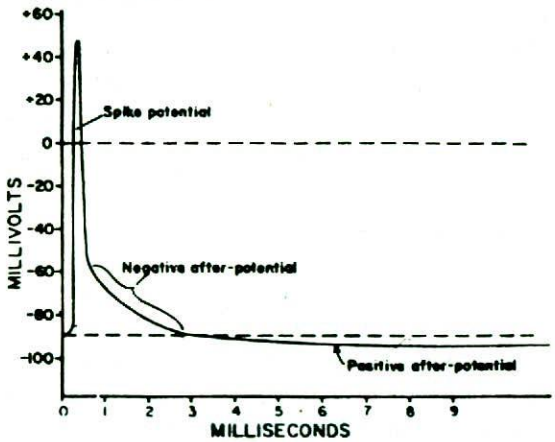


Fig 1-8 . *An ideal action potential*

5. *Negative after Potential :* At the termination of spike potential, the membrane potential sometimes fails to reach the normal resting stage. This is called negative after potential.

   It is believed that sometimes, the concentration of K^+ outside the membrane increases which prevents flow of K^+ from inside to outside. This then prevents the return of membrane potential towards normal.

6. *Positive after potential or hyperpolarization :* Sometimes the negativity of membrane potential become more than its normal level. This is called positive after potential. It is due to excess permeability of membrane to the K^+ at the end of spike potential.

(Ref. Guyton & Hall-11th Edition; page-61 & others)

Refractory period

i. *Definition* : It is the period of action potential during which no action potential is generated in same fiber for another stimulus. It has two parts :

ii. *Parts of refractory peroid* :

   a. *Absolute refractory period (ARP)* : It is the period during which no action potential is developed in previously activated fiber by any strong stimulus.

   b. *Relative refractory period (RRP)* : In this period an action potential may develop by a strong stimulus.

Saltatory conduction

Conduction in myelinated axons depends upon a similar pattern of circular current flow. However, myelin is an effective insulator, and current flow through it is negligible. Instead, depolarization in myelinated axons jumps from one node of Ranvier to the next, with the current sink at the active node serving to electrotonically depolarize to the firing level the node ahead of the action potential. This jumping of depolarization from node to node is called *saltatory conduction*.

It is a rapid process, and myelinated axons conduct up to 50 times faster than the fastest unmyelinated fibers.

(Ref. Ganong 22th edition; page-57)

Orthodromic & Antidromic conduction

An axon can conduct in either direction. When an action potential is initiated in the middle of it, two impulses traveling in opposite directions are set up by electrotonic depolarization on either side of the initial current sink.

In a living animal, impulses normally pass in one direction only, ie, from synaptic junctions or receptors along axons to their termination. Such conduction is called ***orthodromic***. Conduction in the opposite direction is called ***antidromic***. Since synapses, unlike axons, permit conduction in one direction only, any antidromic impulses that are set up fail to pass the first synapse they encounter and die out at that point.

(Ref. Ganong 22th edition; Page-57)

Propagation of action potential

Normally, a resting nerve fibre remains in polarized state, with positive charges lined up along the membrane and negative charges along the inside.

As soon as the fibre is excited, at the point of excitation the polarity is reversed due to increases permeability of Na^+ to the membrane and causes depolarization of the membrane. A local circuit of current flows between the depolarized area and resting area of the membrane; positive current flows inward through the depolarized membrane and outward through. This local depolarization current then excites the adjacent portions of the membrane producing progressively more and more depolarization. The depolarization wave travels in all direction along the entire length of the nerve fibre.

(Ref. Guyton & Hall-11th edition; Page-65,66)

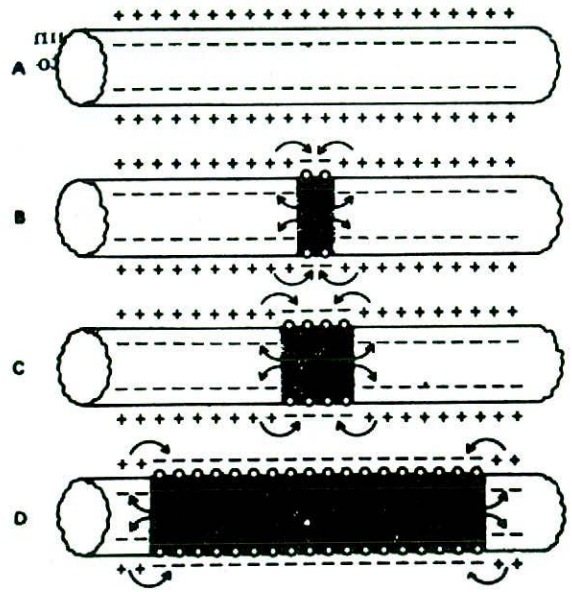


Fig. 1-9. *Propagation of action potential.*

Direction of propagation : An excitable membrane has no single direction of propagation, but the action potential travels in all directions away from the stimulus-even along all branches of a nerve fiber-until the entire membrane has become depolarized.

(Ref. Guyton 11th edition; Page-66)

All-or-nothing principle : Once an action potential has been elicited at any point on the membrane of a normal fiber, the depolarization process travels over the entire membrane if conditions are right, or it does not travel at all if conditions are not right. This is called the *all-or-nothing principle*, and it applies to all normal excitable tissues. Occasionally, the action potential reaches a point on the membrane at which it does not generate sufficient voltage to stimulate the next area of the membrane. When this occurs, the spread of depolarization stops. Therefore, for continued propagation of an impulse to occur, the ratio of action potential to threshold for excitation must at all times be greater than 1. This 'greater than 1' requirement called the ***safety factor for propagation***.

(Ref. Guyton & Hall-11th edition; Page-66)

Nerve Impulse : The process of transmission of depolarization wave along a nerve fibre is called nerve impulse.

Action Potential of Nerve cell

Resting membrane potential of a neuron is usually about -70 mV. A slight decrease in resting membrane potential leads to increased K^+ efflux and Cl^- influx restoring the resting membrane potential. However, when depolarization exceeds 7 mV, the voltage-gated Na^+ channels start to open at an increased rate (Na^+ channel activation), and when the firing level is reached, the influx of Na^+ along its inwardly directed concentration and electrical gradients is so great that it temporarily swamps the repolarizing forces.

The increase in Na^+ conductance is short-lived. The Na^+ channels rapidly enter a closed state called the inactivated state and remain in this state for a few milliseconds before returning to the resting state. In addition, the direction of the electrical gradient for Na^+ is reversed during the over shoot because the membrane potential is reversed, and this limits Na^+ influx. A third factor producing repolarization is the opening of voltage-gated K^+ channels. This opening is slower and more prolonged than the opening of the Na^+ conductance. The net movement of positive charge out of the cell due to K^+ efflux at this time helps complete the process of repolarization. The slow return of the K^+ channels to the closed state also explains the after-hyperpolarization.

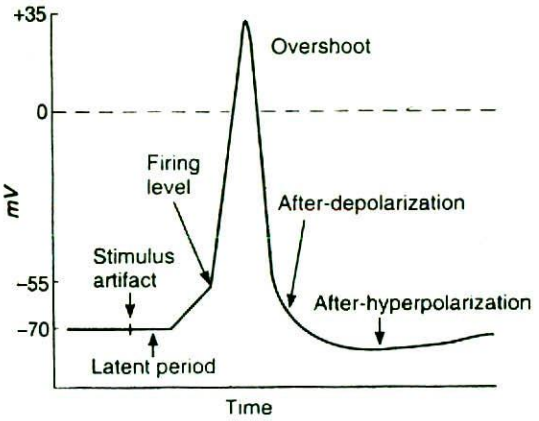


Fig. 1-10. *Action potential in neuron.*

Althogh Na^+ enters the nerve cell and K^+ leaves it during the action potential, the number of ions involved is minute relative to the total numbers present. The fact that the nerve gains Na^+ and loses K^+ during activity has been demonstrated experimentally, but significant differences in ion concentrations can be measured only after prolonged, repeated stimulation.

The slower opening and delayed closing of the voltage-gated K^+ channels also explain accommodation. If depolarization occurs rapidly, the opening of the Na^+ channels overwhelms the repolarizing forces, but if the induced depolarization is produced slowly, the opening of K^+ channels balances the gradual opening of Na^+ channels, and an action potential does not occur.

A decrease in extracellular Ca^{++} concentration increases the excitability of nerve and muscle cells by decreasing the amount of depolarization necessary to initiate the changes in the Na^+ and K^+ conductance that produce the action potential. Conversely an increase in extracellular Ca^{++} concentration stabilizes the membrane by decreasing excitability.

(Ref. Ganong 22th Edition)

Action potential in nerve fibre :

1. *Resting stage :* This is the resting membrane potential before the action potential begins. The membrane is said to be 'polarized' during this stage because of the -90 millivolts negative membrane potential that is present.
2. *Depolarization stage :* At this time, the membrane suddenly becomes very permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to flow to the interior of the axon. The normal polarized state of -90 millivolts is immediately neutralized by the inflowing sodium ions, with the potential rising rapidly in the positive direction. This is called depolarization.

   In large nerve fibres, the membrane potential actully 'overshoots' beyond the zero level and becomes somewhat positive, but *in some smaller fibers* as well as many central system neurons, the potential merely approaches the zero level and does not overshoot to the positive state.
3. *Repolarization Stage :* Within a few 10,000ths of a seccond after the membrane becomes highly permeable to sodium ions, the sodium channels begin to close and the potassium channels open more than they normally do. Then, rapid diffusion of potassium ions to the exterior re-establishes the normal negative resting membrane potential. This is called the *repolarization* of the membrane.

(Ref. Guyton 10th page-56)

Skeletal Muscle Action Potential

Almost everything regarding initiation and conduction of action potentials in nerve fibers applies equally well to skeletal muscle fibers except for quantitative differences. Some of the quantitative aspects of muscle potentials are the following :

1. Resting membrane potential : about -85 to -90 millivolts in skeletal fibers, the same as in large myelinated nerve fibers.
2. Duration of action potential : 1 to 5 milliseconds in skeletal muscle, about five times as long as large myelinated nerves.
3. Velocity of conduction : 3 to 5 m/sec, about 1/18 the velocity of conduction in the large myelinated nerve fibers that excite skeletal muscle.

Spread of the action potential to the interior of the muscle fiber by way of the transvers tubule system : The skeletal muscle fiber is so large that action potentials spreading along its surface membrane cause almost no current flow deep within the fiber. To cause contraction, these electrical currents must penetrate to

the vicinity of all the separate myofibrils. This is achieved by transmission of the action potentials along transverse tubules (T tubules) that penetrate all the way through the muscle fiber from one side to the other. The T tubule action potentials in turn cause the sarcoplasmic reticulum to release calcium ions in the immediate vicinity of all the myofibrils, and these calcium ions

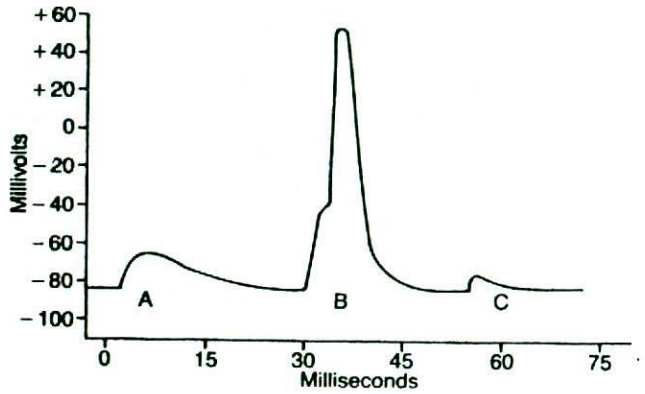


Fig : 1-11. End plate potentials. A, Weakened end plate potential recorded in a curarized muscle, too weak to elicit an action potential; B, normal end plate potential eliciting a muscle action potential. and C, weakened end plate potential.

then cause contraction. This over all process is called excitation-contraction coupling.

Visceral Smooth Muscle Action Potential

Electrical & mechanical activity : Visceral smooth muscle is characterized by the instability of its membrane potential and by the fact that it shows continuous, irregular contractions that are independent of its nerve supply. This maintained state of partial contraction is called tonus or tone. The membrane potential has no true "resting" value, being relatively low when the tissue is active and higher when it is inhibited, but in periods of relative quiescence it averages about -50 mV. Superimposed on the membrane potential are waves of various types . There are slow sine wave-like fluctuations a few millivolts in magnitude and spikes that somethimes overshoot the zero potential line and sometimes do not. In many tissues, the spikes have a duration of

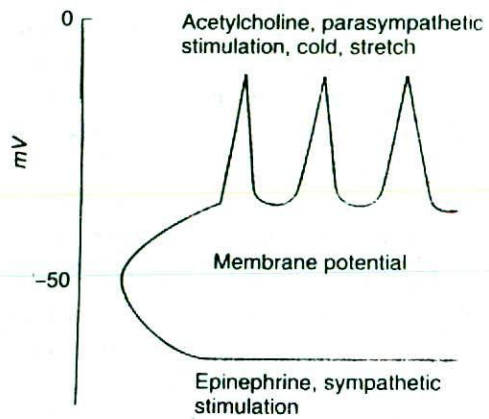


Fig 1-12. Effects of various agents on the membrane potential of intestinal smooth muscle.

about 50 ms. However, in some tissues the action potentials have a prolonged plateau during repolarization, like the action potentials in cardiac muscle. The spikes may occur on the rising or falling phases of the sine wave oscillations. There are, in addition, pacemaker potentials similar to those found in the cardiac pacemakers. However, in visceral smooth muscle, these potentials are generated in multiple foci that shift from place to place. Spikes generated in the pacemaker foci are conducted for some distance in the muscle. Becasue of the continuous activity, it is difficult to study the relation between the electrical and mechanical events in visceral smooth muscle, but in some relatively inactive preparations, a single spike can be generated. The muscle starts to contract about 200 ms after the start of the spike and 150 ms after the spike is over. The peak contraction is reached as long as 500 ms after the spike. Thus, the excitation-contraction coupling in visceral smooth muscle is a very slow process compared with that in skeletal and cardiac muscle, in which the time from initial depolarization to initiation of contraction is less than 10 ms.

(Ref. Ganong 22th Edition; Page-82)

Cardiac ion channels :

i. *Voltage-gated channels*
   - Na^+
   - TCa^{++}
   - LCa^{++}
   - K^+
   - Inward rectifying
   - Delayed rectifying
   - Transient outward

ii. *Ligand-gated K^+ channels :*
   - Ca^+ activated
   - Na^+ activated
   - ATP-sensitive
   - Acetylcholine-activated
   - Arachidonic acid-activated.

(Ref. Ganong 21th edition, Page 80)

Cardiac Muscle Action potential

Resting membrane & action potentials : The resting membrane potential of individual mammalian cardiac muscle cells is about -90 mV (interior negative to exterior). Stimulation produces a propagated action potential that is responsible for initiating contraction.

Depolarization proceeds rapidly, and an overshoot is present, as in skeletal muscle and nerve. But this is followed by a *plateau* before the membrane potential returns to the baseline. In mammalian hearts, depolarization lasts about 2 ms, but the plateau phase and repolarization last 200 ms or more. Repolarization is therefore not complete until the contraction is half over. With extracellular recording, the electrical events include a spike and a later wave that resemble the QRS complex and T wave of the ECG.

As in other excitable tissues, changes in the external K^+ concentration affect the resting membrane potential of cardiac muscle, whereas changes in the external Na^+ concentration affect the magnitude of the action potential.

i. The initial rapid *depolarization* and the overshoot *(phase 0)* are due to opening of voltage-gated Na^+ channels similar to that occurring in nerve and skeletal muscle.

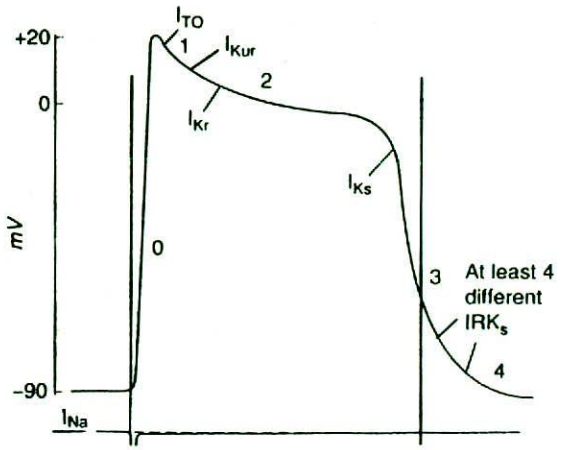


Fig: 1-13. Phases of the action potential of a cardiac muscle fiber. 0, depolarization due to rapid influx of Na+ ions; 1, initial rapid repolarization due to closure of Na channels; 2, plateauphase due to slow influx of Na+ and Ca++ through the slow Na+-Ca++ channels; 3, late rapid repolarizaion due to eflux of K+ ions; 4, base line.

ii. The initial rapid *repolarization (phase 1)* is due to closure of Na^+ channels.

iii. The *subsequent prolonged plateau (phase 2)* is due to a slower but prolonged opening of voltage-gated Ca^{2+} channels.

iv. Final repolarization *(phase 3)* to the resting membrane potential *(phase 4)* is due to closure of the Ca^{2+} channels and K^+ efflux through various types of K^+ channels.

The voltage-gated Na^+ channel in cardiac muscle has two gates an outer gate that opens at the start of depolarization, at a membrane potential of -70 to -80 mV; and an inner gate that then closes and precludes further influx until the action potential is over (Na^+ channel inactivation).

The slow Ca^{2+} channel is activated at a membrane potential of -30 to -40 mV.

There are three types of K^+ channels that produce repolarization. The *first* produces a transient, early outward current (I_{TO}) that produces an early incomplete repolarization. The *second* is inwardly rectifying ie, at plateau potentials it allows K^+ influx but resists K^+ efflux, and only at lower membrane potentials does it permit K^+ efflux. The current it produces is called I_{Kr}. The *third* type is a slowly activating (delayed rectifying) type that produces a current called I_{Ks}. The sum of I_{Kr} and I_{Ks} is a small net outward current that increases with time and *produces repolarization.*

N.B. In cardiac muscle, the repolarization time decreases as the cardiac rate increases.

(Ref. Ganong 22th Edition; Page-78,80)

Nodal fibers of cardiac muscle action potential

Mechanism of Sinus Nodal Rhythmicity : The potential of the sinus nodal fiber between discharges has a negativity of only -55 to -60 millivolts in comparison with -85 to -90 millivolts for the ventricular muscle fiber. The cause of this reduced negativity is that the cell membranes of the sinus fibers are naturally leaky to sodium ions. At this level of negativity, the fast sodium channels have mainly become "inactivated," which means that they have become blocked.

Self-Excitation of Sinus Nodal Fibers : Because of the high sodium ion concentration in the extracellular fluid as well as the negative electrical charge inside the resting sinus nodal fibers, the positive sodium ions outside the fibers even normally tend to leak to the inside. Furthermore, the resting nodal fibers have a moderate number of channels that are already open to the sodium ions. Therefore, influx of positively charged sodium ions causes a rising membrane potential. When it reaches a threshold voltage of about -40 millivolts, the calcium-sodium channels become activated, leading to rapid entry of both calcium and sodium ions, thus causing the action potential.

Then the calcium-sodium channels become inactivated (that is, they close) within about 100 to 150 milliseconds after opening, and at about the same time, greatly increased numbers of potassium channels open. Therefore, the influx of calcium and sodium ions through the calcium-sodium channels ceases, while at the same time large quantities of positive potassium ions diffuse out of the fiber, thus terminating the action potential. Furthermore, the potassium channels remain open for another few tenths of a second, carrying a great excess of positive potassium charges out of the cell, which temporarily causes considerable excess negativity inside the fiber; this is called hyperpolarization. This hyperpolarization initially carries the

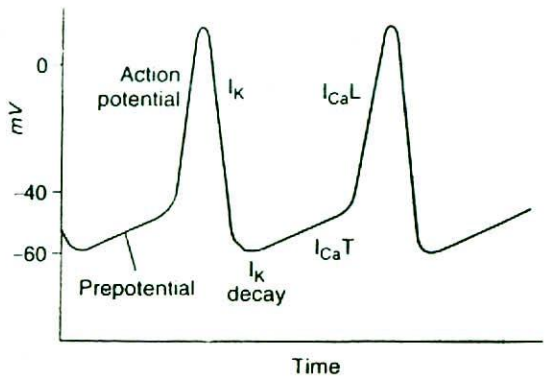


Fig: 1-14. Rhythmical discharge of a sinus nodal fiber. Also, the sinus nodal action potential is compared with that of a ventricular muscle fiber.

"resting" membrane potential down to about -55 to -60 millivolts at the termination of the action potential.

During the next few tenths of a second after the action potential is over, progressively more and more of the potassium channels begin to close. Now the inward-leaking sodium ions once again over balance the outward flux of potassium ions, which causes the "resting" potential to drift upward once more, finally reaching the threshold level for discharge at a potential of about -40 millivolts. Then the entire process begins again: self-excitation, recovery from the action potential, hyperpolarization after the action potentials is over, drift of the "resting" potential again to threshold, then re-excitation again to elicit another cycle. This process continues indefinitely throughout a person's life.

(Ref. Guyton 11th Edition; Page-117, 118)

Skeletal Muscle

All skeletal muscles are composed of numerous fibers ranging from 10 to 80 micrometers in diameter.

Skeletal Muscle Fibre : Each muscle fibre is a single cell, multinucleated; long and cylindrical in shape, and no syncytial bridges between cells. Each fibre is made up of the following successively smaller sub unit-

1. *Sarcolemma :* It is the cell membrane of the muscle fibre. The sarcolemma consist of a true cell membrane, called the *plasma membrane*, and an outer coat consisting of a thin layer of polysaccharide material containing numerous thin collagen fibrillae.
2. *Myofibrils :* Each muscle fibre contains several hundred to several thousand myofibrils. Each fibrils is made by myosin filament and actin filaments, which are large polymarized protein molecule that are responsible for muscle contraction. The myosin and actin filaments partially interdigitate and thus cause the myofibrils to have alternate light and dark band. The light band which contain only actin filaments, are called ***I band*** because they are isotropic to polarized light. The dark band, which contain the myosin filament as well as the end of the actin filament where they overlap the myosin, are called ***A band*** because they are anisotropic to polarized light. The actin filament are attached to ***Z disc.*** The portion of myofibrils that lies between two successive Z discs is called a ***sarcomere*** which is capable of generating its greatest force of contraction.
3. *Sarcoplasm :* The myofibrils are suspended inside the muscle fibre in a matrix called sarcoplasm. The fluid of the sarcoplasm contains large quantities of K, Mg, PO_4, proteins, enzymes and tremendous numbers of mitochondria that lie between and parallel to the myofibrils.

(Ref. Guyton & Hall-11th Edition; Page-72)

Myosin Filament

The myosin filament is composed of multiple myosin molecules, each having a molecular weight of about 480,000. The myosin molecule is composed of six polypeptide chains, two heavy chains and four light chains.

The two heavy chains coil around each other to form a double helix. One end of the each of these chains is folded into a globular protein mass called the myosin head. Thus there are two free heads lying side by side at one end of the double helix myosin molecule; the other end of the coiled helix is called the tail. The four light chains are also parts of the myosin heads, two to each head. The four light chains help control the function of the head during the process of muscle contraction.

(Ref. Guyton & Hall-11th Edition; Page-72)

Actin Filament

The actin filament is composed of three different component-actin, tropomyosin, and troponin.

The actin filament is a double stranded F-actin protein

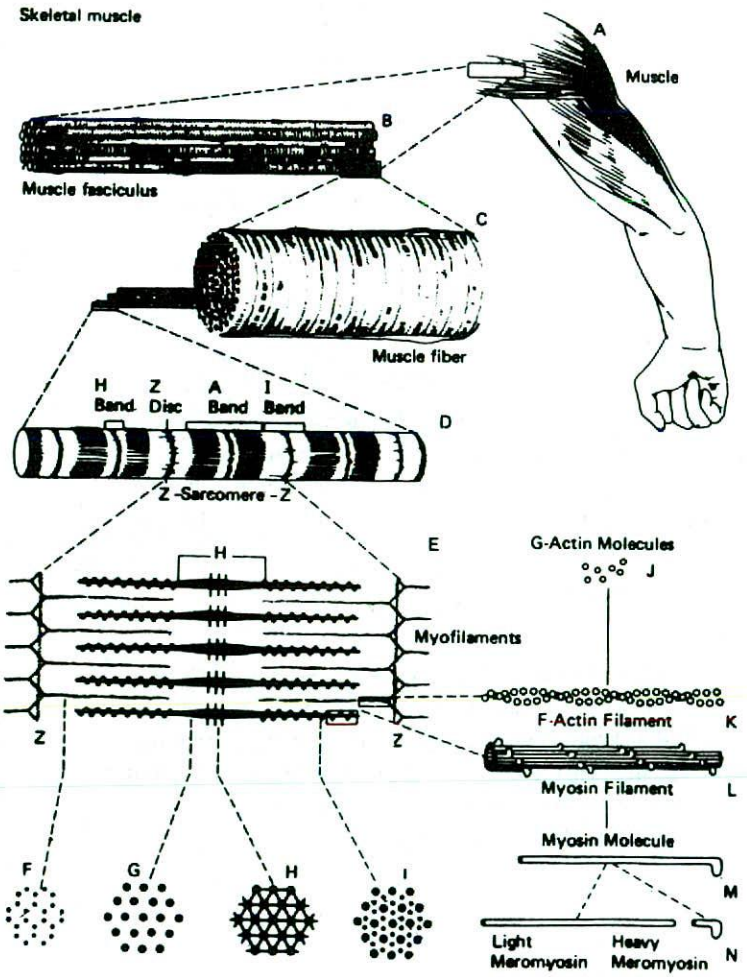


Fig.1-15. Organization of skeletal muscle from gross to the molecular level

molecule. Each strand of the double F-actin helix is composed of polymerized G-actin molecule.

The tropomyosin strand is loosely attached to an F-actin strand and that in a resting state it physically covers the active sites of the actin strands so that interaction can not occur between the actin and myosin to cause contraction.

The ***troponin*** is a complex of three globular protein molecule attached approximately two thirds the distance along each tropomyosin molecule. One of the globular protein (*troponin I*) has a strong affinity for actin, another (*troponin T*) for tropomyosin and a third (*troponin C*) for calcium ions.

(Ref. Guyton 11th Edition)

Mechenism of contraction of skeletal Muscle

Steps in skeletal muscle contraction :

1. Discharge of motor neuron.
2. Release of transmitter (acetylcholine) at motor end plate.
3. Binding of acetylcholine to acetylcholine receptor.
4. Increased Na^+ and K^+ conductance in end plate membrane.
5. Generation of end plate potential.
6. Generation of action potential in muscle fibers.
7. Inward spread of depolarization along T tubules.
8. Release of Ca^{++} from terminal cisterns of sarcoplasmic reticulum and diffusion to thick and thin filaments.
9. Binding of Ca^{++} to troponin C, uncovering myosin binding sites on actin.
10. Formation of cross linkages between actin and myosin and sliding of thin on thick filaments, producing shortening.

(Ref. Ganong 22th Edition; page-70)

Mechenism of relaxation of skeletal Muscle

1. Ca^{++} pumped back into sarcoplasmic reticulum.
2. Release of Ca^{++} from troponin.
3. Cessation of interaction between actin and myosin.

(Ref. Ganong 22th Edition; page-70)

Sliding filament theory of muscle contraction

Mechenism :

a. There is no shortening, thickening, or folding of the individual filaments.
   i. A band remains constant in size
   ii. H zone becomes denser
   iii. I band varies in length becoming shorter.
b. *As a muscle contracts* :
   i. Z lines come closer together
   ii. The width of the I bands decreases
   iii. The width of the H zones decreases
   iv. But, there is no change in the width of the A band.
c. Conversely, *as a muscle is stretched*, the width of the I bands and H zones increases, but there is still no change in the width of the A band.

Excitation & contraction coupling

i. *Excitation & contraction coupling involves four steps* :
   a. The propagation of action potential into the T-tubule and release of Ca^+ from the terminal cisternae
   b. The activation of muscle by Ca^{++}
   c. The generation of tension by the muscle proteins
   d. The relaxation of the muscle.

ii. *Mechanism* : Calcium ions (Ca^{++}) link action potentials in a muscle fibre to contraction.
   a. In resting muscle fibres, Ca^{++} is stored in the endoplasmic (sarcoplasmic) reticulum.
   b. The tubules of the T system terminate near the calcium-filled sacs of the sarcoplasmic reticulum.
   c. Each action potential created at the neuromuscular junction sweeps quickly along the sarcolema and is carried into the T system.
   d. The arrival of the action potential at the ends of the T system triggers the release of Ca^{++}.
   e. The Ca^{++} diffuses among the thick and thin filaments where it binds to troponin on the thin filaments.
   f. This turns on the interaction between actin and myosin and the sarcomere contracts.
   g. Because of the speed of the action potential (milliseconds) the action potential arrives virtually simultaneously at the ends of all the tubules of the T system, ensuring that all sarcomeres contract in unison.

When the process is over, the calcium is pumped back into the sarcoplasmic reticulum using a Ca^{++} ATPase.

Role of calcium in muscle contraction

Action potential along T-tubules
↓
Ca^{++} released fromterminal cisternae of sarcoplasmic reticulum
↓
Ca^{++} ions binds with troponin C
↓
Inhibition of troponin-tropomyosin complex
↓
Uncovers the active sites of the actin
↓
Interaction of actin and myosin
↓
Muscle contraction.

Muscle twitch

i. *Definition* : A single action potential causing a brief contraction followed by relaxation is called muscle twitch.
ii. *Duration* :
   a. Fast muscle fibre : 7.5 milli seconds
   b. Slow muscle fibre : 100 milli seconds.

Rigor mortis

i. *Definition* : The stiffness of muscle after death is called rigor mortis. It usually starts 2-3 hours after death.

ii. *Duration* : It remains up to 36 hours after death.

iii. *Mechenism* : It is due to destruction of all ATP and phosphorylcreatine after death. ATP is required to cause separation of cross bridges from actin filaments. If no ATP is available the actin-myosin complex become stable; this accounts for the extreme muscular rigidity (rigor mortis).

Muscle tetanization

i. *Definition* : It is a condition in which the successive contractions fuse together and cannot be distinguished one from the other.

ii. *Mechenism* : The process of contracting takes some 50 millisecond and relaxation of the fiber takes another 50-100 millisecond. Because the refractory period is so much shorter than the time needed for contraction and relaxation, the fibre can be maintained in the contracted state so long as it is stimulated frequently enough i.e 50 stimuli per second. Such sustained contraction is called *tetanus*.

Sequence of events in contraction and relaxation of visceral smooth muscle :

1. Binding of acetylcholine to muscarinic receptors.
2. Increased influx of Ca^{++} into the cell.
3. Activation of calmodulin dependent myosin light chain kinase.
4. Phosphorylation of myosin
5. Increased myosin ATPase activity and binding of myosin to actin.
6. Contraction.
7. Dephosphorylation of myosin by various phosphatases.
8. *Relaxation*, or sustained contaction due to the latch bridge mechanisms.

(Ref. Ganong 21th Edition; page-84)

Motor Unit

All the muscle fibres innervated by a single motor nerve fibre are called a motor unit.

Autonomic Nervous System

Division and root value :

Autonomic nervous system divides into-

1. Sympathetic nervous system.
2. Parasympathetic nervous system.
    1. *Sympathetic nervous system :* Originates in the spinal cord between the segments of T_1 and L_2 or thoraco-lumbar out flow.
    2. *Parasympathetic nervous system :* Originates as cranio-sacral out flow. The cranial nerves are III, VII, IX and X. The spinal verves are S_2 to S_4.

Synthesis of acetylcholine

Acetylcholine is synthesized in the body by the interaction of acetylCoA and Choline in the presence of enzyme choline acetyl transferase. The aeetyl CoA comes from acetic acid and CoASH in presence of ATP and enzyme acetyl thiokinase.

Acetic acid + CoA SH $\xrightarrow{\text{Acetyl thiokinase}}$ Acetyl CoA

AcetylCoA+Choline $\xrightarrow{\text{Choline acetyltransferase}}$ Acetyl choline.

(Ref.Guyton 11th Edition; Page-751)

Synthesis of norepinephrine and epinephrine :

The basic steps of norepinephrine and epinephrine synthesis are-

1. At first amino acid tyrosin is actively transported from the circulation into the axoplasm of terminal ending of sympathetic nerve fibres.
2. Tyrosin $\xrightarrow{\text{Hydroxylation (Hydroxylase)}}$ DOPA
3. DOPA $\xrightarrow{\text{Decarboxylation (Decarboxylase)}}$ Dopamine
4. Transport of dopamine inside the chromaffin vesicles.
5. Dopamine $\xrightarrow{\text{Hydroxylation (Hydroxylase)}}$ Nor-epinephrine

In the adrenal medulla, this reaction goes still one step further to transform about 80 percent of the norepinephrine into epinephrine, as follows :

6. Nor-epinephrine $\xrightarrow{\text{Methylation (N-Methyltransferase)}}$ Epinephrine.

(Ref. Guyton 11th Edition; Page 751)

Cholenergic receptors

A. *Necotinic receptors* :: Located in the synapse between the pre and post ganglionic neurones of both sympathetic and parasympathetic system. It is so called because its function is that of nicotine.

B. *Muscarinic receptors :* Found in all the effector cells stimulated by the post ganglionic neurones of the parasympathetic nervous system. It is so called because it collect from muscarine, a poisonous substance of fungus.

(Ref. Guyton 11th Edition; Page 752)

Adrenergic receptors

A. Alpha receptors which again divides into α_1 and α_2

B. Beta receptors which also divides into β_1 and β_2.

(Ref. Guyton 11th Edition; Page 752)

Functions of beta receptors :

1. Vasodilatation (β_2)
2. Cardioacceleration (β_1)
3. Increased myocardial strength (β_1)
4. Intestinal relaxation (β_2)

5. Uterus relaxation (β_2)
6. Bronchodilatation (β_2)
7. Calorigenesis (β_2)
8. Glycogenolysis (β_2)
9. Lipolysis (β_1)
10. Bladder wall relaxation (β_2).

(Ref. Guyton 11th Edition; Page-753)

Functions of alpha receptors :

1. Vasoconstriction
2. Iris dilatation
3. Intestinal relaxation
4. Intestinal sphincter contraction
5. Pilomotor contraction
6. Bladder spincter contraction.

(Ref. Guyton 10th Edition; Page-753)

Cyclic AMP

i. *Definition* : cAMP is cyclic adenosine 3',5' monophosphate.

ii. *Formation* : It is formed from ATP by the action of the enzyme *adenylyl cyclase*

iii. *Fate* : It is converted to physiologically inactive 5'-AMP by the action of the enzyme *phosphodiesterase*.

iv. *Mechenism of action* : Cyclic AMP activates one of the cyclic nucleotide dependent protein kinases (*protein kinase A*) that, like protein kinase C, catalyzes the phosphorylation of proteins, changing their conformation and altering their activity.

Example : A typical example is the activation of phosphorylase kinase in the liver by epinephrine via cAMP and protein kinase A.

In addition, the active catalytic subunit of PKA moves to the nucleus and phosphorylates the cAMP-responsive element-binding protein (CREB). This transcription factor then binds to DNA and alters transcription of a number of genes.

v. *Metabolism* : Cyclic AMP is metabolised by a phosphodiesterase. This phosphodiesterase is inhibited by methylxanthines such as caffeine and theophyline; consequently, these compounds augment hormonal and transmitter effects mediated via cAMP.

(Ref. Ganong 22th edition, Page 42)

Q. 00. **Write short notes on- chromosome.**

i. *Definition* : Chromosomes are deeply stained thread like structures within the nucleus of each animal cell.

ii. *Chromosomes number* : 46 or 23 pairs
   a. Autosomes : 22 pairs
   b. Sexchromosomes : 1 pair (XX or XY).

iii. *Structure of chromosome* : Each choromosome is composed of a double helix of DNA along with histone and non-histone proteins. The DNA-protein complex exists as a highly coiled or folded structure.
   a. The *non-histone* proteins are DNA and RNA polymerases, gene regulatory proteins and HMG (high mobility group) proteins.
   b. The *histones* are the most abundant group of basic proteins which help packaging of chromosomal DNA. There are five histone proteins according to the concentration of arginine and lysine residues : H1,H2A, H2B, H3, and H4.

iv. *Function* : Chromosomes act as carries of units of inheritance in the form of genes of nuclear DNA. Genes are borne by the chromosomes in linear series as parts of specific DNA molecules.

DNA

It is a complex protein of high molecular weight consisting of deoxyribose, phosphoric acid, and four bases (2 purines and 2 pyrimidines). DNA is found mainly in the chromosomes of the cell nucleus.

Components of DNA :

i. Sugar : 2-deoxy-D-ribose
ii. Acid moiety : Phosphoric acid
iii. Bases :
   a. Purines : Adenine & Guanine
   b. Pyrimidines : Cytosine & Thymine

Function of DNA :

The genetic information store in the nucleotide sequence of DNA serves two purposes-

i. It is the source of information for the synthesis of all protein molecules of the cell & organism.
ii. It provides the information inherited by daughter cells or offspring.

(Ref. Guyton 11th Edition)

RNA

RNA (Ribonucleic acid) is a polymer of purine & pyrimidine ribonucleotides linked together by 3, 5, - phosphodiaster bridge. RNA is found mainly in the cytoplasm & nucleolus.

Components of RNA :

i. Sugar : D-ribose
ii. Acid moiety : Phosphoric acid
iii. Bases :
   a. Purines : Adenine & Guanine
   b. Pyrimidines : Cytosine & uracil.

Types of RNA :

1. *Messenger RNA (m RNA) :* Which carries the genetic code to the cytoplasm for controlling the formation of the proteins.
2. *Transfer RNA (t RNA) :* Which transports activated amino

Trait	DNA	RNA
1. Bases	1. Adenine, guanine, cytosine and thymine.	1. Adenine, guanine, cytosine and uracil.
2. Sugar moiety	2. Deoxyribose.	2. D-ribose
3. Structure	3. Have 2 strands of antiparallel double helical molecule.	3. Single-stranded molecules.
4. Situation	4. Solely intranuclear and mitrochondrial.	4. Both extra & intranuclear (cytoplasm & nucleolus).
5. Functions	5. i. Carry genetic information from one generation of cells to the next & undergo mutation. ii. Concerned with source of information protein synthesis.	5. i. Carry no genetic information & undergo no mutation. ii. Concerned with protein synthesis.

acids to the ribosomes to be used in assembling the protein molecules.

3. *Ribosomal RNA (r RNA) :* Which along with about 75 different proteins, forms the ribosomes, the physical and chemical structure on which protein molecules are actually assembled.

Functions of RNA : It is involved in protein synthesis.

(Ref. Guyton 11th Edition; Page 31)

Transcription

Assembly of the RNA molecule from activated nucleotides using the DNA strand as a template- the process is called transcription.

(Ref. Guyton & Hall-11th edition; Page-33)

Assembly of the RNA molecule is accomplished by DNA under the influence of the enzyme RNA polymerase.

Translation

The process of formation of proteins on the ribosomes is called translation.

(Ref. Guyton& Hall-1th Edition; page-33)

Aging

i. Introduction : Aging is a general physiologic process that is as yet poorly understood. Life expectancy has increased is due for the most part to improved treatment and prevention of infections and other causes of early death.

ii. *Effects and theories of aging* : Aging affects cells and the systems made up of them, as well as tissue components such as collagen, and numerous theories have been advanced to explain the phenomenon.

a. *One theory of aging* holds that tissues age as a result of random mutations in the DNA of somatic cells, with consequent introduction of cumulative abnormalities.

b. *Others* hold that cumulative abnormalities are produced by increased cross-linkage of collagen and other proteins, possibly as the end result of the nonenzymatic combination of glucose with amino groups on these molecules.

c. *A third theory* envisions aging as the cumulative result of damage to tissues by free radicals formed in them. It is interesting in this regard that species with longer life spans produce more *superoxide dismutase*, an enzyme that inactivates oxygen-free radicals.

iii. *Prolongation of aging* : It is now established that in experimental animals, a chronically decreased caloric intake prolongs life, and this could be true in humans as well. One possible explanation for this effect of *caloric restriction* is decreased metabolism, with decreased formation of protein cross-links and decreased production of free radicals. It may be relevant in this regard that in yeasts, worms, and flies, mutations in the homologs of one of the mammalian insulin pathways causes a dramatic prolongation of their life span. However, the exact cause of the lengthened life span produced by caloric restriction remains to be determined.

iv. *Hormonal effects in aging* : In aging humans, there are declines in the circulating levels of some sex hormones, the adrenal androgen dehydroepiandrosterone and its sulfate, and growth hormone. Replacement therapy with estrogens and progesterone in women decreases the incidence of osteoporosis and heart disease. Replacement therapy with testosterone, dehydroepiandrosterone, and growth hormone each has some salutary effects, but each also has undesirable side effects, and there is little if any evidence that they prolong life.

(Ref. Ganong 22th edition, Page-48, 49)

Directions : *Write T for true & F for false against* each of the following statement.

Introduction

Q. 01. **Objectives of learning of physiology are**
- T a. to acquire knowledge about the formation of human body.
- T b. to understand the functions of different organs.
- T c. to know the mechanisms of functions.
- T d. to understand the purpose of the function.
- T e. to understand the co-ordination of different organs.

Q. 02. **Human cell**
- T a. provides structural and functional unit
- T b. is bounded by cell membrane
- F c. is composed of bio-molecules only
- F d. forms internal environment
- F e. is a prokaryotic cell.

Q. 03. **Cells are held together by**
- T a. intercellualar supporting structure.
- F b. fusion.
- F c. positive pressure in the interstitium.
- F d. electrostatic force.
- F e. chemical bond.

Q. 04. **Common characteristics of all cells include**
- T a. multiplication.
- T b. energy production.
- T c. energy consumption.
- T d. waste product removal.
- F e. detoxification of toxic substances.

Q. 05. **Structural protein includes**
- T a. contractile protein.
- T b. microtubules.
- T c. collagen fibres.
- F d. transport proteins.
- F e. immunoglobulin.

Q. 06. **Carbohydrate in cell plays important role in**
- T a. nutrition.
- T b. energy storage.
- F c. cellular structure.
- F d. cellular synthetic process.
- F e. enzymatic activity.

Q. 07. ***The normal basal acid output is***
- T b. 5-10 mmol/hr
- F a. 1-2 mmol/hr
- F c. 10-15 mmol/hr
- F d. 20-25 mnol/hr
- F e. 2-5 mnol/hr.

Q. 08. **Which amino acid can proteinate and deproteinate at neutral pH is**
- T a. Histidine
- F b. Serine
- F c. Proline
- F d. Glycine
- F d. Alanine.

Q. 09. **Autoregulation is seen in**
- T a. Muscles
- T b. Kidneys
- T c. Brain
- F d. Liver
- F e. All of the above.

Q. 10. **Cell shape & motility are provided by**
- T a. Microtubules
- F b. Microfilaments
- F c. Golgi apparatus
- F d. Nucleus
- F e. ER.

ECF & ICF

Q. 11. **Total body water (in a subject having 70 kg body wt) is**
- T a. 42 L
- F b. 4200 ml
- F c. 30 L
- F d. 15 L
- F e. 28 L.

Q. 12. **Oedema may be due to**
- T a. increased hydrostatic pressure in the capillary.
- T b. decreased colloidal osmotic pressure.
- F c. decreased hydrostatic pressure in the capillary.
- F d. increased colloidal osmotic pressure.
- F e. decreased lymphatic obstruction.

Q. 13. **ECF contain large amount of**
- T a. Na^+
- T b. Cl^-
- T c. HCO_3^-
- F d. Mg^{++}
- F e. K^+

Q. 14. **Concentration of Na^+ ion outside the cell is**
- T a. 142 mEq/L.
- F b. 145 mEq/L.
- F c. 140 mEq/L
- F d. 100 mEq/L
- F e. 120 mEq/L

Q. 15. **Concentration of K^+ inside the cell is**
- T a. 140 mEq/L
- F b. 15 mEq/L
- F c. 45 mEq/L
- F d. 155 mEq/L
- F e. 150 mEq/L

Q. 16. **Concentration of Cl^- outside the cell is**
- T a. 103 mEq/L
- F b. 15 mEq/L
- F c. 45 mEq/L
- F d. 113 mEq/L
- F e. 123 mEq/L

Q. 17. ***ECF forms what percentage of body weight***
- T a. 25%
- F b. 10%
- F c. 33%
- F d. 60%
- F e. 30%.

Q. 18. **Most diffusible ion in excitable tissue is**
- T a. Cl^-
- F b. Na^+
- F c. K^+
- F d. PO_4^-
- F b. Ca^{++}.

Q. 19. **The majority of body sodium is present in**
- T a. Extracellular fluid
- F a. Bone.
- F c. Intracellular fluid
- F d. Plasma
- F d. Blood.

Q. 20. **Content of Na^+ in ringer lactate is - - meq/L**
- T a. 130
- F b. 154
- F c. 121
- F d. 144
- F c. 115

Q. 21. **Total body sodium in meq/Kg is**
- T a. 58
- F b. 41
- F c. 70.7
- F d. 91.0
- F b. 52

Q. 22. **Plasma sodium concentration is**
- T a. 140 meq/L
- F b. 120 meq/L
- F c. 3.5 meq/L
- F d. 110 meq/L
- F c. 130 meq/L

Q. 23. **Sodium channels are specifically blocked by**
- T a. Tekadotoxin
- F b. Nifedipirie
- F c. Tetra Ethyl Lead
- F d. Choline
- F b. All of the above.

Q. 24. **Potassium is maximum in**
- T a. Plasma
- F b. Cell
- F c. Interstitium
- F d. Bone
- F e. Skin.

Q. 25. **Plasma K constitute what percentage of total body potassium:**
- T a. 0.4%
- F b. 7.6%
- F c. 10.4
- F d. 89.6%
- F e. 1.6%

Q. 26. **If potassium levels are 39 mg% calculate the same in meq/L**
- T a. 10
- F b. 1
- F c. 3.9
- F d. 100
- F e. 13

Q. 27. **Potassium content in colonic secretion is**

T a. 30 meq/L
F b. 10 meq/L
F c. 15 meq/L
F d. 50 meq/L
F e. 45 meq/L.

Q. 28. **Which secretion contributes to the maximum amount of potassium**
T a. Salivary
F b. Gastric
F c. Pancreatic
F d. Biliary
F e. Lacrimal.

Q. 29. **Highest concentration of potassium is seen in**
T a. Saliva
F b. Gastric juice
F d. Bile
F d. Pancreatic secretion
F e. Lacrimal.

Q. 30. **What is the useful function of nitrogen in the body?**
T a. Prevents atelectasis
T b. Decreases rate of combustion
T c. Delays alveolar collapse
T d. All of the above
F e. None of the above

Q. 31. **N_2 has a role in body as it**
T a. Prevents atelectesis
F b. Decreases rate of combustion
F c. Delays alveolar collapse
F d. All of the above
F e. None of the above.

Q. 32. **Fluoride ions act by inhibiting**
T a. Enolase
F b. Cytochrome oxidase
F c. Carbonic anhydrase
F d. Hexokinase
F e. None of the above.

Q. 33. **Deficiency of which vitamin is not known in newborns**
T a. E
F b. C
F c. D
F d. K
F e. A

Q. 34. **Highest concentration of vitamin C in the body is found in the**
T a. Adrenal cortex
F b. Liver
F c. Kidney
F d. Spleen.
F d. Gall bladder.

Homeostasis

Q. 35. **Homeostasis means**
T a. keeping relative constancy of internal environment.
F b. stasis of fluid flow.
F c. rapid change of internal environment.
F d. slow change of internal environment.
F e. away from optimal environment.

Q. 36. **The control system in our body includes**
T a. buffer system.
T b. nervous system.
T c. genetic control system.
F d. urogenital system.
F e. integumentary system.

Q. 37. **Principles of control systems are**
T a. negative feed back.
T b. positive feed back.
T c. feed forward feedback.
T d. adaptive feed back.
F e. reflex action.

Q. 38. **Basic regulatory mechanism for intracellular biochemical activities are**
T a. enzyme regulation.
T b. genetic regulation.
F c. nervous regulation.
F d. hormone regulation.
F e. metabolic regulation.

Q. 39. **Negative feed back means**
T a. center sending negative signal to appropriate organ.
T b. a reversible phenomenon.
T c. opposite of initiating signal.
F d. center receiving negative information from periphey.
F e. acceleration of initiating factor.

Q. 40. **Sickness of a cell results from**
T b. moderate dysfuncition.
T e. cellular injury.
F a. mild dysfunction.
F c. extreme dysfunction.
F d. loss of all fucntion.

Q. 41. **Increased blood osmolality**
T a. can occur as a result of dehydration.
T d. may cause cellular dehydration.
F b. causes decreased blood osmotic pressure.

F c. is accompanied by a lower ADH level.
F e. can produce oedema.

Cell membrane

Q. 42. **Cell membrane**
T a. maintains the intracellular environment
T b. contains receptor protein and ion channel.
F c. separates blood from extracellular fluid.
F d. is composed of organic and inorganic substances.
F e. serves as a defensive layer against invasion of foreign particle.

Q. 43. **Lipid barriers of cell membrane**
T a. prevent passage of water soluble substances
T b. are fluid in nature
T c. are consist of hydrophilic and hydrophobic region
F d. do not allow passage of N_2, O_2, CO_2
F e. are composed of phospholipid only

Q. 44. **Membrane protein acts as**
T a. structural element
T b. transporter of molecules
T c. an enzyme
F d. normal metabolic fuel
F e. cellular defense system

Q. 45. **Integral proteins acts as**
T a. transporters of ions.
T b. enzymes.
F c. transporters of water.
F d. transporters of lipids.
F e. receptors for antigen.

Q. 46. **Cells are bordered at their surface by**
T a. plasma membrane.
F b. a layer of protein.
F c. layer of carbohydrate.
F d. layer of lipid.
F e. cell wall.

Q. 47. **Receptors proteins are found in**
T a. the cell membrane.
T b. cytosol.
F c. nucleus.
F d. endoplasmic reticulum.
F e. golgi apparatus.

Q. 48. **On weight basis, the membrane contains protein and lipid in the ratio of**
T a. 2:1
F b. 1:2
F c. 1:1
F d. 4:1
F e. 2:3

Cell organalles

Q. 49. **The discrete functional parts of a cell are called**
T a. organelles.
F b. molecule.
F c. ions.
F d. organs.
F e. membrane.

Q. 50. **The organelle that contains digestive enzyme are**
T a. lysosomes.
F b. mitochondria.
F c. peroxisomes.
F d. endoplasmic reticulum.
F e. golgi apparatus.

Q. 51. **Cellular digestive function is served by**
T a. lysosome
F b. mitochondria
F c. golgi apparatus
F d. nucleus
F e. ribosome

Q. 52. **Protein packaging and vesicle forming organelles are :**
T a. golgi apparatus.
F b. rough endoplasmic reticulum.
F c. smooth endoplasmic reticulum.
F d. ribosome.
F e. lysosome.

Q. 53. **Organelle containing hydrolytic enzymes is :**
T a. lysosome.
F b. mitochondrion.
F c. endoplasmic reticulum.
F d. golgi apparatus.
F e. peroxisome.

Q. 54. **The organelles that store intracellular Ca^{++} are :**
T a. endoplasmic reticulum.
T b. mitochondria.
F c. ribosome.
F d. golgi apparatus.
F e. lysosome.

Q. 55. **The network of dividing and uniting channels distributed in cytoplasm is known as**
T a. endoplasmic reticulum.
F b. cytoskeleton.
F c. microtrabecular lattice.

F d. intracellular network.
F e. fibrin network.

Q. 56. **Ribosome synthesizes**
T a. proteins.
F b. nucleic acid.
F c. aminoacids.
F d. sugars.
F e. ATP.

Q. 57. **Ribosomes are**
T a. composed of proteins and RNA.
T b. the site of protein synthesis.
T c. granular particles.
F d. membranous organelles.
F e. associated with smooth endoplasmic reticulum.

Q. 58. **Ribosome is made up of**
T a. protein.
T b. RNA.
F c. phospholipid.
F d. steroid hormones.
F e. cholesterol.

Q. 59. **Lysosome has enzymes namely**
T a. ribonuclease.
T b. cathepsins.
T c. deoxyribonuclease.
F b. glycosides.
F e. phosphate esters.

Q. 60. **Lysosomal enzymes are**
T a. ribonuclease.
T b. cathepsins.
T c. deoxyribonuclease.
F d. phosphate esters.
F e. glycosides.

Q. 61. **Lysosomes**
T a. are membrane bound structure.
T b. can cause inflammation.
T c. are formed by Golgi apparatus.
T d. may form phagosome.
F e. originates from nucleosome.

Q. 62. **Peroxisomes originates from**
T a. smooth endoplasmic reticulum.
F b. golgi apparatus.
F c. rough endoplasmic reticulum.
F d. mitochondrial membrane.
F e. cell membrane.

Q. 63. **Mitochondrion**
T a. stores Ca^{++} ion.
T b. has its own DNA.
T c. is a chemical power plant.
F d. is round shaped organelle.
F e. contains proteolytic enzyme.

Q. 64. **Regarding endoplasmic reticulum**
T a. in muscle they are termed as sarcoplasmic reticulum.
T b. it is a cytoplasmic membranous organelle.
F c. the smooth endoplasmic reticulum is concerned with protein synthesis.
F d. the rough endoplasmic reticulum is concerned with lipid synthesis.
F e. the ribosomes are attached with smooth endoplas mic reticulum.

Q. 65. **The human cell nucleus**
T a. has a skeleton of five filaments.
T b. is necessary for cell division.
T c. has a membrane which is permeable to nucleic acid.
F d. in somatic cell contains 44 chromosomes.
F e. stores genetic materials in the nucleolus.

Q. 66. **Secretory vesicles are important store for**
T a. protein hormones.
T b. extracellular enzyme.
F c. intracellular enzyme.
F d. steroid hormone.
F e. ATP.

Q. 67. **Vesicle**
T a. is a membrane bound sac.
T b. transports large molecules.
F c. transports ions.
F d. transports substances following concentration gradient.
F e. can traverse the cell membrane.

Q. 68. **Receptors proteins are found in**
T a. cytosol.
T b. the cell membrane.
F c. nucleus.
F d. endoplasmic reticulum.
F e. golgi apparatus.

Q. 69. **Nissl's substance is composed of**
T a. Rough endoplasmic reticulum
F b. Nerve cell vesicles
F c. Aggregated mitochondria
F d. Deposits of pigmented granules
F c. Mitochondria.

Q. 70. **Marker of Golgi apparatus**
T a. Galactosyl transferase
F b. Acetyl CoA synthase

F c. Pyruvate kinase
F d. Malonyl Co A
F d. Lactate dehydrogenase.

Membrane trnasport

Q. 71. **Transport mechanisms for large particle through the cell membrane are**
T a. exocytosis.
T b. pinocytosis.
F c. osmosis.
F d. primary active transport.
F e. facilitated diffusion.

Q. 72. **Ionized calcium is**
T a. required for coagulation of blood.
T b. needed for contraction of muscle.
T c. required for neuromuscular transmission.
T d. present in sarcoplasmic reticulum.
F e. required for relaxation of muscle.

Q. 73. **The cell obtains nutrients and other substances from the surrounding fluid by means of**
T a. pump.
T b. ingestion of small vesicle that contain ECF.
T c. ingestion of large particles.
F d. limited molecular movement.
F e. a process called exocytosis.

Q. 74. **Processes for difusion of vesicle with cell membrane are :**
T a. Exocytosis.
F b. Pinocytosis.
F c. Endocytosis.
F d. Phagocytosis.
F e. Internalization.

Q. 75. **Processes stopped due to lack of ATP formation are**
T a. overlapping of actin and myosin.
T b. movement of Na^+ out of the cells.
F c. osmosis.
F d. movement of K^+ out of a cell.
F e. exocytosis.

Q. 76. **Substances that can diffuse easily through cell membrane are**
T a. steroid
F b. Na^+
F c. glucose
F d. protein
F e. insulin.

Q. 77. **The rate of diffusion of a particle across a membrane will increase if**
T a. the concentration gradient of the particles increase.
T b. the lipid solubility of the particle increases.
F c. the area of the membrane decreases.
F d. the thickness of the membrane increases.
F e. the size of the particle increases.

Q. 78. **With regard to osmosis across the cell membrane**
T a. increased intracellular hydrostatic pressure would help to oppose osmotic swelling.
T b. water moves along its own concentration gradient.
T c. cells will swell in hypotonic solution.
F d. increased extra cellular hydorstratic pressure would help to oppose osmotic swelling.
F e. water moves up against its concentration gradient

Q. 79. **Facilitated diffusion**
T a. is crrier mediated transport.
T b. is always down hill movements.
F c. is always uphill movement.
F d. does not require energy.
F e. requires energy from ATP.

Q. 80. **Facilitated diffusion**
T a. transports from higher to lower concentration.
T b. is a passive process.
F c. transport lipid soluble substances.
F d. is associated with ATP splitting by ATPase system.
F e. is a form of counter transport.

Q. 81. **Carrier mediated facilitated diffusion**
T a. is used for cellular uptake of blood glucose
T b. transports substances by changing molecular conformation of carrier protein
F c. is a form of active transport
F d. uses cellular ATP.
F e. transports molecules against their concentration gradient

Q. 82. **Concerning the Sodium-Pump**
T a. high energy phosphate bonds can support the operation of the Na^+ pump.
F b. the rate of Na^+ pumping is independent of the internal. Na^+ pump.
F c. the operation of the Na^+ pump is independent of K^+ influx.
F d. the sodium pump is not affected by change in temperature.
F e. the process can be explained in terms of facilitated diffusion.

Q. 83. **By Na^+-K^+ pump**
T a. constant pumping activity is carried out in all cells
T b. cell volume is maintained

F c. Na^+ is actively transported into the cell
F d. K^+ is actively transported out of the cell
F e. equal number of Na^+-K^+ are transported

Q. 84. **Inactivation of the Na^+-K^+ pump will cause**
T a. an increase in the intracellular volume.
F b. an increase in the intracellular potassium concentration.
F c. hyperpolarization of the membrane potential.
F d. an increase in the excitability of nerve cells.
F e. an increase in the flow of sodium out of the cell.

Q. 85. **Transport of Na^+ across the cell membrane occurs by**
T a. diffusion.
T b. primary active transport.
T c. secondary active transport.
F d. osmosis.
F e. filtration.

Q. 86. **Characteristic of voltage gated Na^+ channel include**
T a. both gates remain open for a short period.
T b. it opens with inactivation gate in open state.
T c. it closes with activation gate remaining open.
F d. it opens with inactivation gate with closed state.
F e. it closes with closure of activation gate.

Q. 87. **Voltage gated K^+ channel**
T a. remains closed at resting membrane potential.
T b. has activation gate only.
T c. opens with depolarization.
F d. opens with hyperpolarization.
F e. has activation and inactivation gates.

Q. 88. **Voltage gate Ca^{++} channel**
T a. takes part in action potential.
T b. is permeable to Na^+
F c. is permeable to K^+
F d. is synonamous with Ca^+ pump.
F e. is a fast channel.

Q. 89. **The emetocytosis or reverse pinocytosis requires which ion**
T a. Mg
F b. Na
F c. K
F d. Ca
F e. Cl.

Q. 90. **When solvent is moving in one direction, the solvent tends to drag along some molecules of solute. This is called**
T a. Solvent drug
F b. Filtration
F c. Osmosis
F d. Donnan effect
F e. All of the above.

Q. 91. **All are true about Sodium-Potassium pump**
T a. Needs ATP
T b. Is inactive at 40° C
T c. Is electrogenic
T d. Requires enzymes
F e. Needed for generation of action potential

Q. 92. **Not true regarding Na-K pump is**
F a. Pumps Na against a gradient intracellular
T b. 3 Na exchanged for 2 K
F c. Increases in intracellular Na.
F d. Hypocalcemia inhibits the pump
F e. Non of the above.

Q. 93. **The non-ionic diffusion in body is seen in:**
T a. Both gut and kidney
F b. Gut
F c. Kidneys
F d. All of the above.
F e. None

DNA & RNA

Q. 94. **DNA molecule**
T a. is also found in mitochondria.
T b. contains adenine with its complementary base thymine.
T c. is located in the nucleus.
T d. is double stranded.
F e. has adenine bound with guanine.

Q. 95. **After DNA has replicated the duplicate strands are called**
T a. chromomere.
T b. chromatid.
F c. centromere.
F d. chromosome.
F e. spindle fibers.

Q. 96. **DNA molecules**
T a. contain deoxyribose sugar.
T b. provide genetic code.
T c. are attached with histone.
F d. are distributed in the cytoplasm.
F e. consist of RNA molecules.

Q. 97. **Basic building blocks of DNA are**
T a. purine and pyrimidine bases.
T b. pentose sugar.
T c. phosphoric acid.

F d. amino acids.
F e. proteins.

Q. 98. **Transcription process include**
T a. base pairing of DNA.
T b. breakdown of hydrogen bond.
T c. formation of extron and intron.
F d. base pairing of RNA.
F e. splitting of DNA.

Q. 99. **RNA nucleotide that forms pair with adenine in DNA is**
T a. uracil.
F b. thymine.
F c. guanine.
F d. cytosine.
F e. tyrosine.

Q. 100. **RNA molecule**
T a. is synthesized in the nucleus.
F b. is a complementary copy of the entire DNA.
F c. migrates from nucleus to cell membrane.
F d. is double stranded structure.
F e. contains sugar deoxyribose.

Q. 101. **Role of RNA in the biosynthesis of proteins is**
T a. ending of polypeptide chain.
T b. ending of peptide chain.
T c. initiation of peptide chain.
F d. replication of single stranded RNA molecule.
F e. to control amino acid sequence of many polypeptide chain.

Q. 102. **tRNA molecule**
T a. transfers amino acid to growing polypeptide chain.
T b. is formed from DNA.
F c. is formed from m RNA.
F d. is formed from RNA.
F e. transfers RNA from nucleus to cytoplasm.

Q. 103. **Messenger RNA**
T a. migrates from nucleus to cytoplasm.
F b. carries anticodon.
F c. combines with ribosomal RNA.
F d. is arranged in helical pattern.
F e. is synthesized by translation process.

Q. 104. **RNA polymerase plays role in**
T a. DNA replication.
T b. separation of DNA strand.
T c. RNA formation.
F d. DNA synthesis.
F e. base pairing.

Q. 105. **RNA is**
T a. composed of sugar ribose.
T b. a complementary copy of the entire DNA molecule.
T c. containing hydroxyl ion present in the sugar ribose.
T d. synthesized in the nucleus.
F e. double stranded.

Q. 106. **Activation of RNA nucleotides is done by**
T a. RNA polymerase.
F b. activator protein.
F c. repressor protein.
F d. phosphorylase.
F e. ATPase.

Q. 107. **Nucleotides are**
T a. NAD.
T b. $NADPH^+$
T c. ATP.
F d. RNA.
F e. DNA.

Q. 108. **Gene**
T a. contains information for regulation of cellular activity.
T b. can be lethal for organism.
T c. transfers hereditary characteristics.
T d. can be modified by environment.
T e. can be copied.

Q. 109. ***Base Stacking of DNA is by***
T a. Hyperchromicity
F b. Linear dichromicity
F c. Hypochromicity
F d. Electrophoresis
F e. All of the above.

Action potential

Q. 110. **Action potential consists of**
T a. both depolarization and repolarization.
F b. repolarization and hyperpolarization.
F c. either depolarization or repolarization.
F d. depolarization only.
F e. repolarization only.

Q. 111. **Action potentials**
T a. inhibit further stimulation during the period of depolarization and repolarization.
T b. are produced by threshold stimulus.
T c. are composed of depolarization and repolarization phases.
F d. are associated with a repolarization phase caused by out ward movement of chloride.
F e. are produced by sub-threshold stimuli.

Q. 112. **Equilibrium potential of K^+ is**
- T a. -95 mv.
- F b. -90 mv.
- F c. -80 mv.
- F d. -85 mv.
- F e. -70 mv.

Q. 113. **Equilibrium potential of Cl^- is**
- T a. -70 mv.
- F b. -110 mv.
- F c. -80 mv.
- F d. -90 mv.
- F e. -100 mv.

Q. 114. **Equilibrium potential of Na^+ is**
- T a. +60 mv.
- F b. -60 mv.
- F c. -90 mv.
- F d. -70 mv.
- F e. 0 mv.

Q. 115. **Resting membrane potential is created due to**
- T a. exit of K^+ from the cell.
- T b. Na^+-K^+ pump.
- T c. Na^+ entry into the cell.
- T d. entry of K^+ into the cell.
- T e. exit of Na^+ from the cell.

Q. 116. **The resting membrane potential depends on the concentration gradient of**
- T a. sodium.
- T b. potassium.
- F c. calcium.
- F d. chloride.
- F e. bicarbonate.

Q. 117. **Resting membrane potential of a cell**
- T a. is close to equilibrium potential of K^+
- T b. is contributed by Na^+-K^+ pump.
- F c. indicates its excitability.
- F d. is calculated by Gold man equation.
- F e. is calculated by Nernst equation.

Q. 118. **Resting membrane potential of a spinal motor-neuron is**
- T a. -70 mv.
- F b. -80 mv.
- F c. -90 mv.
- F d. +40 mv.
- F e. -100 mv.

Q. 119. **Resting membrane potential of cardiac muscle cell is**
- T a. -85 mv.
- F b. +70 mv.
- F c. -100 mv.
- F d. -70 mv.
- F e. -100 mv.

Q. 120. **Repolarization phase**
- T a. brings an end to excitation.
- F b. raises the membrane potential level.
- F c. is caused by K^+ leak channel.
- F d. precedes depolarization.
- F e. is associated with opening of sodium& calcium channel.

Q. 121. **Rhythmic discharge of action potential is observed in**
- T a. smooth muscle in the gall bladder.
- T b. cardiac muscle.
- T c. neurons in the respiratory center.
- T d. smooth muscle of GI tract.
- F e. neurons in the vasomotor center.

Q. 122. **Saltatory conduction of nerve impulse**
- T a. is a rapid process.
- T b. is present in myelinated nerve fiber.
- F c. is a slow process.
- F d. means conduction from axon to cell body.
- F e. is present in unmyelinated nerve fiber.

Q. 123. **Propagation of action potential is responsible for**
- T a. glandular secretion.
- T b. nerve impulse.
- T c. cardiac impulse.
- T d. muscle contraction.
- F e. muscle relaxation.

Q. 124. **Threshold for action potential means**
- T a. voltage at which muscle contraction begins.
- T b. minimum depolarization of membrane requiring opening of voltage gated channels.
- F c. voltage at which repolarization begins.
- F d. slow depolarization of the membrane.
- F e. voltage that closes inactivation gate.

Q. 125. **Rhythmicity**
- T a. may be induced by low threshold leve for stimulation.
- T b. requires high membrane permeability to Na^+
- T c. requires high membrane permiability to Ca^{++}
- T d. means repetitive action potential.
- T e. means regular interval between two action potentials.

Q. 126. **Plateau in action potential**

T a. is caused by activation of slow Na^+-Ca^{++} channel.
T b. means sustained depolarization.
T c. is caused by inactivation of fast Na^+ channel.
F d. is caused by inactivation of K^+ channel.
F e. means sustained repolarization.

Q. 127. **Action potentials are produced by**
T a. Na^+ influx
F b. Na^+-K^+influx
F c. K^+ influx
F d. K^+ efflux
F d. Ca^+ efflux

Q. 128. **Resting nerve membrance is more permeable to K than to Na**
T a. 50-100 times
F b. 1-5 times
F c. 20-50 times
F d. 200-500 times
F e. 170-180 times.

Q. 129. **The ionic channels in excitable membrane are lined by**
T a. Proteins
F b. Cephalins
F c. Lipids
F d. Carbohydrates
F e. Fat.

Q. 130. **What provides most of the energy that is used to maintain a normal resting membrane potential of about 70 millivolts inside the neuronal cell?**
T a. The sodium pu mp
F b. The potassium pump
F c. The chloride pump
F d. The calcium pump
F e. Diffusion of chloride ions

Q. 131. **Chemical gradient across cell membrane is maintained chiefly by**
T a. K^+
F b. Na^+
F c. Ca^{++}
F d. Cl^-
F e. Mg^{++}.

Q. 132. **Most diffusible ion in excitable tissue is**
T a. Cl^-
F b. Na^+
F c. K^+
F d. PO_4^-
F e. Mg^{++}.

Q. 133. **The physiologically important anion other than chloride is**
T a. Bicarbonate
F b. Nitrate
F c. Phosphate
F d. Sulphate
F e. Lactate.

Q. 134. **Resting membrane potential is close to the Isoelectrical potential of**
T a. CV
F b. Na^+
F c. Mg^{++}
F d. K^+
F e. Cl^-.

Q. 135. **Resting membrane potential on nerve is determined by concentration of**
T a. Potassium
F b. Calcium
F c. Chloride
F d. Magnesium
F e. Sodium.

Q. 136. **Repolarization in isolated muscle piece fibre proceeds from**
T a. Endocardium to epicardium
F b. Epicardium to endocardium
F c. Left to right
F d. Right to left
F d. Base to apex.

Q. 137. **In excitable cells, repolarization is closely associated with, one of the following events**
T a. K efflux
F b. Na efflux
F c. Na influx
F d. K influx
F e. Cl efflux

Q. 138. **End plate potential follows which law**
T a. Depolarisation
F b. All or none law
F c. Hyperpolarisation
F d. Propagation
F e. contraction.

Q. 139. **The end plate potential is characterised by**
T a. Depolarisation
F b. Propagation
F c. All or non law
F d. Hyperpolarisation
F e. contraction.

Q. 140. **Initiation of impulse starts in**
- T d. Dendritic tree
- F a. Axon
- F b. Axon hillock + initial segment
- F c. Cell body
- T d. soma.

Muscle

Q. 141. **Resting length of muscle fibre**
- T a. is 2 mecrometer.
- T b. means unstreteched length before contraction begins.
- F c. means length of sarcomere at the end of contraction
- F d. means length of stretched muscle fiber before contraction.
- F e. is 4 micrometer.

Q. 142. **During isotonic contraction of a skeletal muscle there is shortening of**
- T a. Sarcomere.
- F b. I band.
- F c. M line.
- F d. A band.
- F e. H band.

Q. 143. **Isometric contraction**
- T a. means no change in the length of muscle fiber during contraction.
- T b. is an energy consuming process.
- F c. means change in tension of muscle fiber.
- F d. means change in the lenght of muscle fiber.
- F e. is associated with work done.

Q. 144. **Maximum efficiency of muscle contraction can be achieved by**
- T a. when velocity of contraction is 30% of the maximum velocity.
- T b. moderate velocity of contraction.
- F c. rapid rate of contraction.
- F d. maximum velocity of contraction.
- F e. slow rate of muscle contraction.

Q. 145. **Cross bridges**
- T a. contain ATPase.
- T b. split ATP before their attachment with actin.
- T c. form power stroke.
- T d. are composed of myosin.
- F e. bind to AtP after their detachment from ADP.

Q. 146. **Excitation of a muscle fiber most directly causes**
- T a. release of Ca^{++} from the sarcoplasmic reticulum.
- F b. splitting of ATP.
- F c. pulling of actin.
- F d. movement of tropomyosin.
- F e. attachment of cross bridges to actin.

Q. 147. **The energy of muscle contraction is most directly obtained from**
- T a. ATP.
- F b. anaerobic respiration.
- F c. myoglobin.
- F d. creatinine phosphate.
- F e. aerobic respiration.

Q. 148. **Relationship of velocity of contraction to load applied is**
- T a. inversely proportional.
- F b. directly proportional.
- F c. negative.
- F d. neutral.
- F e. positive.

Q. 149. **The major cation directly involved in the isotonic contraction of skeletal muscle is**
- T b. Ca^{++}
- F b. Mg^{++}
- F c. H^{+}
- F d. Na^{+}
- F e. K^{+}.

Q. 150. **Ionized calcium is**
- T a. required for neuromuscular transmission.
- T b. present in sarcoplasmic reticulum.
- T c. required for coagulation of blood.
- T d. needed for contraction of muscle.
- F e. required for relaxation of muscle.

Q. 151. **Most of the ATP in red muscle is produced in**
- T a. mitochondria.
- F b. golgi apparatus.
- F c. myofilaments.
- F d. cytosol.
- F e. nucleus.

Q. 152. **The Calcium pump of striated muscle pump Ca^{++} into**
- T a. mitochondria.
- T b. sarcoplasmic reticulum.
- F c. sarcoplasm.
- F d. sarcolemma.
- F e. nucleus.

Q. 153. **A band contains**
- T a. both actin and myosin.
- F b. troponin.
- F c. z disc.
- F d. actin only.

F e. myosin only.

Q. 154. **Actin filaments**
T a. cause clot retraction.
T b. form an elastic support for cell membrane.
T c. are contactile element in platelet.
F d. are present in WBC.
F e. are present in cilia.

Q. 155. **Actin filaments are present in**
T a. in platelets.
T b. in smooth muscle cell.
F c. in fibroblast.
F d. all cell membrane.
F e. in endothelial cell.

Q. 156. **Troponin is composed of**
T a. TN-1
T b. TN-T
T c. TN-C
F d. TN-D
F e. TN-2

Q. 157. **Steps in relaxation of skeletal muscle include**
T a. cessation of interaction between actin and myosin.
T b. Ca^{++} is pumped back into sarcoplasmic reticulum.
F c. binding of acetylcholine to nicotinic receptors.
F d. discharge of motor neuron.
F e. inward spread of depolarization along T tubules.

Q. 158. **Agents causing smooth muscle contraction is**
T a. epinephrine and norepinephrine.
T b. angiotensin
F c. glycine.
F d. nitric oxide.
F e. acetylcholine.

Q. 159. **Smooth muscle possess**
T a. contractility.
T b. syncytial properties.
F c. all or none law.
F d. excitability.
F e. stair case phenomenon.

Q. 160. **Unitary smooth muscle is synonymous with**
T a. visceral smooth muscle.
T b. syncytial smooth muscle.
F c. piloerector smooth muscle.
F d. vascular smooth muscle.
F e. bronchial smooth muscle

Q. 161. **When smoth muscle is stretched within physiological limits**
T a. the membrane dopolarizes.
F b. the muscle relaxes.
F c. syncytial conduction is blocked.
F d. action potentials are not elicited.
F e. the tension that develops is due to elastic elements only.

Q. 162. **The average number of muscle fibres attached to one golgi tendon organ are**
T a. 10-15
F b. 1-3
F c. 5-10
F d. 15-75
T e. 8-10

Q. 163. **The band which disappears on muscle contraction is**
T a. H
F b. I
F c. A
F d. Z
F e. M.

Q. 164. **The band which appears on muscular contraction is**
T a. I
F b. A
F c. H
F d. M or CM
F e. A & H

Q. 165. **In severe exercise muscle spasm occurs due to**
T a. Accumulation of K^+
F b. Accumulation of acetylcholine
F c. Accumulation of ca^{++}
F d. Depletion of sodium
F e. Depletion of ATP.

Q. 166. **High twitch muscle fibres in comparison to low twitch muscle fibres are having more**
T a. Mitochondria
F b. C-AMP
F c. Cytoplasm
F d. Enzymes
F e. ER.

Q. 167. **Calmodulin activates**
T a. Muscle phosphorylase
F b. Protein kinase C
F 0. 2,3 DPG
F d. Glucokinase
F e. Depletion of ATP.

Q. 168. **Thrombosthenin is**
T a. Contractile protein
F b. Coagulation factor
F c. A thrombosis promoting protein
F d. A protein regulation platelet producting

F e. All of the above.

Q. 169. **Increased blood flow in muscle during exercise is not because of**

T a. High lactate
T b. High bicarbonate
F c. Low pH
F d. High CO_2
F e. Low PO_2

Q. 170. **A sprinter utilises in the first 3 to 4 minutes of a race**

T a. Muscle glycogen
F b. Creatinine phosphate
F c. Blood glucose
F d. None of the above
F e. All of the above

Q. 171. **In keletal muscle contraction requires**

T a. Depends on action potential
T b. Recruitment of more number of fibres produces more contraction
T c. Local tension
F d. Increase in the strength of action potential increase contraction.
F e. All of the above

Q. 172. **A unique characteristic of smooth muscle is that**

T a. It can sustain a contraction for prologed periods
F b. Calcium is not required for contraction
F c. Repetitive contractions are not possible
F d. Myosin filaments are not required
F e. ATP is required for contraction

Q. 173. **Curare in therapeutic doses**

T a. Decreases the amplitude of skeletal muscle potential
F b. Prevents propagation of action potential in skeletal muscle
F c. Enhances the action of choline esterase
F d. Enhances the action of catecholamines
F e. All of the above

Q. 174. **Muscles can withstand complete arterial occlusion for**

T a. 1 hour
F b. 1/2 hour
F c. 4-6 hours
F d. 8 hours
F e. 4 hours

Q. 175. **Smooth muscle has the following characteristic**

T a. Chronaxie is longer
F b. Threshold is higher
F c. RMP is greater
F d. Action potential is greater
F e. None of the above.