General Physiology

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Functional Organization of the Human Body

This introductory material on the human body is similar to lifting the first of many layers of wrapping of a package. You do not see the end immediately but becomes more curious what is in the package. These many layers will include initially examining the human body from the outside to cellular reproduction and development in the end.

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 system 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. ***Physiology*** *is concerned with the way these systems function and the way each contributes to the functions of the body as a whole. So physiology will deal with following three concepts:*

1. *Structure and shapes of the body parts and their functions*
2. *The hierarchy of structural organization*
3. *Homeostasis (maintenance of functional constancy)*

Human 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 simple virus to the largest tree or the complicated human being, has its own functional characteristics. Therefore, the vast field of physiology can be divided into viral physiology, bacterial physiology, cellular physiology, plant physiology, human physiology, and many more subdivisions.

In human physiology, we attempt to explain the specific characteristics and mechanisms of the human body that make it a living being. The very fact that we remain alive is almost beyond our control, for hunger makes us seek food and fear makes us seek refuge. Sensations of cold make us look for warmth. 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 exist under widely varying conditions.

Cells as the living units of the body.

The basic living unit of the body is the cell. Each organ is an aggregate of many different cells held together by intercellular supporting structures. Each type of cell is specially adapted to perform one or a few particular functions. For instance, the red blood cells, numbering 25 trillion in each human being, transport oxygen from the lungs to the tissues. Although the red cells are the most abundant of any single type of cell in the body, there are about 75 trillion additional cells of other types that perform functions different from those of the red cell. The entire body, then, contains about 100 trillion cells.

Although the many cells of the body often differ markedly from one another, all of them have certain basic characteristics that are alike. For instance, in all cells, oxygen reacts with carbohydrate, fat, and protein to release the energy required for cell function. Further, the general chemical mechanisms for changing nutrients into energy are basically the same in all cells, and all cells deliver end products of their chemical reactions into the surrounding fluids. Almost all cells also have the ability to reproduce additional cells of their own kind. Fortunately, when cells of a particular type are destroyed from one cause or another, the remaining cells of this type usually generate new cells until the supply is replenished.

Aging.

Aging is a general physiologic process that is as yet poorly understood. In the United States, life expectancy has increased from 47 years in 1900 to about 75 years today. However, this increase is due for the most part to improved treatment and prevention of infections and other causes of early death, so that more people survive into their 70s. In the meantime, the maximum human life span of 100–110 years has increased little if at all. 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.

In aging humans, declines occur in the circulating levels of some sex hormones, the adrenal androgen and growth hormone. Replacement therapy with estrogens and progesterone in women decreases the incidence of osteoporosis. Replacement therapy with testosterone 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.

Homeostasis.

The term homeostasis is used by physiologists to mean maintenance of nearly constant conditions in the internal environment. Essentially all organs and tissues of the body perform functions that help maintain these constant conditions. Many of these regulatory mechanisms operate on the principle of negative .The actual environment of the cells of the body is the interstitial component of the ECF. Since normal cell function depends on the constancy of this fluid, it is not surprising that in multicellular animals, an immense number of regulatory mechanisms have evolved to maintain it. To describe "the various physiologic arrangements which serve to restore the normal state, once it has been disturbed," W.B. Cannon coined the term ***homeostasis.*** *The buffering properties of the body fluids and the renal and respiratory adjustments to the presence of excess acid or alkali are examples of homeostatic mechanisms. There are countless other examples, and a large part of physiology feedback; deviations from a given normal set point are detected by a sensor, and signals from the sensor trigger compensatory changes that continue until the set point is again reached.*

Extracellular fluid “Internal Environment”

About 60 per cent of the adult human body is fluid, mainly a water solution of ions and other substances. Although most of this fluid is inside the cells and is called intracellular fluid, about one third is in the spaces outside the cells and is called extracellular fluid. This extracellular fluid is in constant motion throughout the body. It is transported rapidly in the circulating blood and then mixed between the blood and the tissue fluids by diffusion through the capillary walls. In the extracellular fluid are the ions and nutrients needed by the cells to maintain cell life. Thus, all cells live in essentially the same environment—the extracellular fluid. For this reason, the extracellular fluid is also called the internal environment of the body, Cells are capable of living, growing, and performing their special functions as long as the proper concentrations of oxygen, glucose, different ions, amino acids, fatty substances, and other constituents are available in this internal environment.

Differences between extracellular and intracellular fluids.

The extracellular fluid contains large amounts of sodium, chloride, and bicarbonate ions plus nutrients for the cells, such as oxygen, glucose, fatty acids, and amino acids. It also contains carbon dioxide that is being transported from the cells to the lungs to be excreted, plus other cellular waste products that are being transported to the kidneys for excretion. The intracellular fluid differs significantly from the extracellular fluid; specifically, it contains large amounts of potassium, magnesium, and phosphate ions instead of the sodium and chloride ions found in the extracellular fluid. Special mechanisms for transporting ions through the cell membranes maintain the ion concentration differences between the extracellular and intracellular fluids.

TABLE 4–1 *Composition of Extracellular and Intracellular Fluids*

	EXTRACELLULAR CONCENTRATION, mM	INTRACELLULAR CONCENTRATION,* mM
Na^+	150	15
K^+	5	150
Ca^{2+}	1	0.0001
Mg^{2+}	1.5	12
Cl^-	110	7
HCO_3^-	24	10
P_i	2	40
Amino acids	2	8
Glucose	5.6	1
ATP	0	4
Protein	0.2	4

*The intracellular concentrations differ slightly from one tissue to another, but the concentrations shown above are typical of most cells. For Ca^{2+}, values represent free concentrations. Total calcium levels, including the portion sequestered by proteins or in organelles, approach 2.5 mM (extracellular) and 1.5 mM (intracellular).

The transport and mixing system (the blood circulatory system).

Extracellular fluid is 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 intercellular spaces between the tissue cells.

Figure below shows the overall circulation of blood. 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.

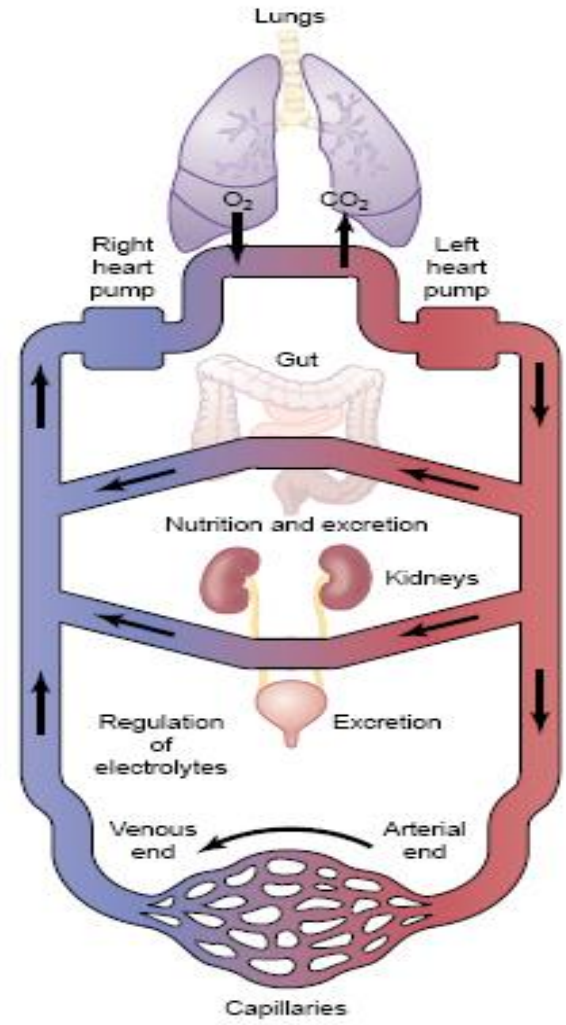
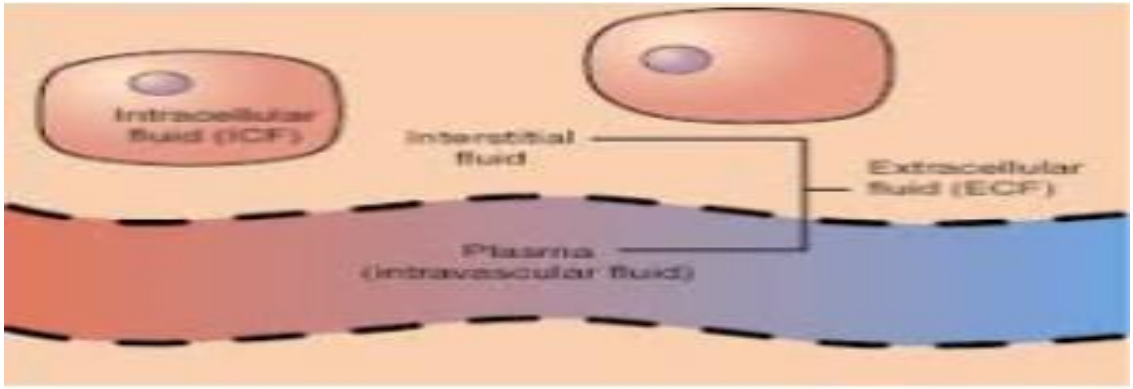
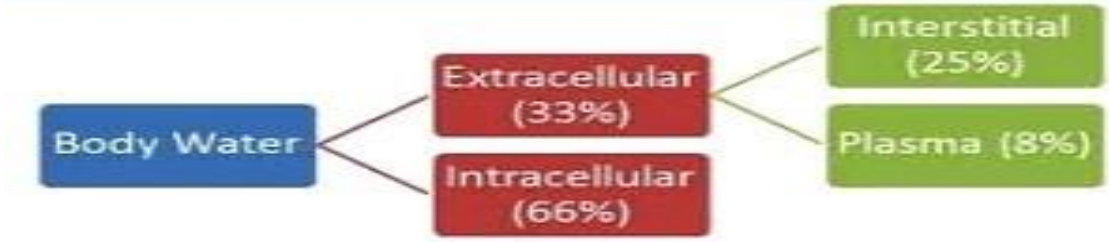


Figure 1–1

General organization of the circulatory system.





Origin of nutrients in the extracellular fluid.

1. Respiratory system.

The blood passes through the body, it also flows through the lungs. The blood picks up oxygen in the alveoli, thus acquiring the oxygen needed by the cells. The membrane between the alveoli and the lumen of the pulmonary capillaries, the alveolar membrane, is only 0.4 to 2.0 micrometers thick, and oxygen diffuses by molecular motion through the pores of this membrane into the blood in the same manner that water and ions diffuse through walls of the tissue capillaries.

2. Gastrointestinal tract.

A large portion of the blood pumped by the heart also passes through the walls of the 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.

3. Liver and other organs that perform primarily metabolic functions.

Not all substances absorbed from the gastrointestinal tract can be used in their absorbed form by the cells. 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.

4. Musculoskeletal system.

Sometimes the question is asked, how does the musculoskeletal system fit into the homeostatic functions of the body? The answer is obvious and simple: Were it not for the muscles, the body could not move to the appropriate place at the appropriate time to obtain the foods required for nutrition. The musculoskeletal system also provides motility for protection against adverse surroundings, without which the entire body, along with its homeostatic mechanisms, could be destroyed instantaneously.

Removal of metabolic end products.

1. Removal of carbon dioxide by the lungs.

At the same time that blood picks up oxygen in the lungs, carbon dioxideis released from the blood into the lung alveoli; the respiratory movement of air into and out of the lungs carries the carbon dioxide to the atmosphere. Carbon dioxide is the most abundant of all the end products of metabolism.

2. Kidneys.

Passage of the blood through the kidneys removes from the plasma most of the other substances besides carbon dioxide that are not needed by the cells. These substances 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 extracellular fluid. The kidneys perform their function by first filtering large quantities of plasma through the glomeruli into the tubules and then reabsorbing into the blood those substances needed by the body, such as glucose, amino acids, appropriate amounts of water, and many of the ions. Most of the other substances that are not needed by the body, especially the metabolic end products such as urea, are reabsorbed poorly and pass through the renal tubules into the urine.

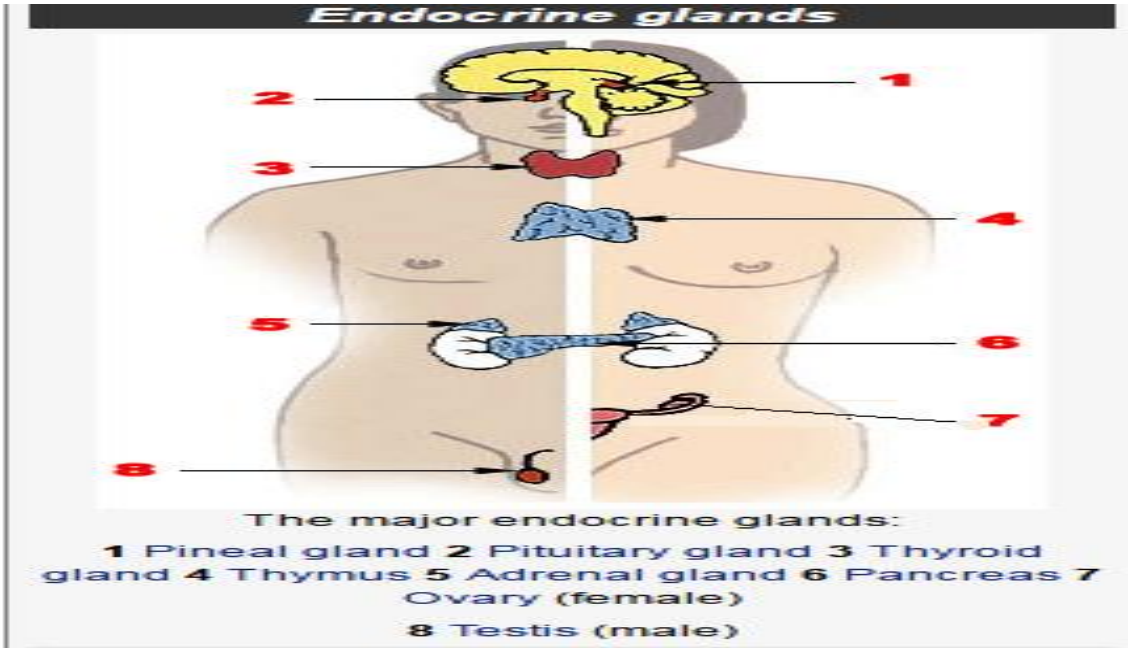
Regulation of body functions.

1. Nervous system.

The nervous system is composed of three major parts: the sensory input portion, the central nervous system (or integrative portion), and the motor output portion. Sensory receptors detect the state of the body or the state of the surroundings. For instance, receptors in the skin apprise one whenever an object touches the skin at any point. The eyes are sensory organs that give one a visual image of the surrounding area. The ears also are sensory organs. The central nervous system is composed of the brain and spinal cord. The brain can store information, generate thoughts, create ambition, and determine reactions that the body performs in response to the sensations. Appropriate signals are then transmitted through the motor output portion of the nervous system to carry out one's desires. 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 the level of pumping activity by the heart, movements of the gastrointestinal tract, and secretion by many of the body's glands.

2. 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 regulate cellular function. For instance, thyroid hormone increases the rates of most chemical reactions in all cells, thus helping to set the tempo of bodily activity. Insulin controls glucose metabolism; adrenocortical hormones control sodium ion, potassium ion, and protein metabolism; and parathyroid hormone controls bone calcium and phosphate. Thus, the hormones are a system of regulation that complements the nervous system. The nervous system regulates mainly muscular and secretory activities of the body, whereas the hormonal system regulates many metabolic functions.



Reproduction

Sometimes reproduction is not considered a homeostatic function. It does, however, help maintain homeostasis by generating new beings to take the place of those that are dying. This may sound like a permissive usage of the term homeostasis, but it illustrates that, in the final analysis, essentially all body structures are organized such that they help maintain the automaticity and continuity of life.

Control systems of the body.

The human body has thousands of control systems in it. The most intricate of these are the genetic control systems that operate in all cells to help control intracellular function as well as extracellular function. Many other control systems operate within the organs to control functions of the individual parts of the organs; others operate throughout the entire body to control the interrelations between the organs. For instance, the respiratory system, operating in association with the nervous system, regulates the concentration of carbon dioxide in the extracellular fluid. The liver and pancreas regulate the concentration of glucose in the extracellular fluid, and the kidneys regulate concentrations of hydrogen, sodium, potassium, phosphate, and other ions in the extracellular fluid.

Examples of control mechanisms.

1. Regulation of O_2 and CO_2concentrations in the extracellular fluid.

Because oxygen is one of the major substances required for chemical reactions in the cells, it is fortunate that the body has a special control mechanism to maintain an almost exact and constant oxygen concentration in the extracellular fluid. This mechanism depends principally on the chemical

characteristics of hemoglobin, which is present in all red blood cells. Hemoglobin combines with oxygen as the blood passes through the lungs. Then, as the blood passes through the tissue capillaries, hemoglobin, because of its own strong chemical affinity for oxygen, does not release oxygen into the tissue fluid if too much oxygen is already there. But if the oxygen concentration in the tissue fluid is too low, sufficient oxygen is released to re-establish an adequate concentration. Thus, regulation of oxygen concentration in the tissues is vested principally in the chemical characteristics of hemoglobin itself. This regulation is called the oxygen-buffering function of hemoglobin. Carbon dioxide concentration in the extracellular fluid is regulated in a much different way. Carbon dioxide is a major end product of the oxidative reactions in cells. If all the carbon dioxide formed in the cells continued to accumulate in the tissue fluids, the mass action of the carbon dioxide itself would soon halt all energy-giving reactions of the cells. Fortunately, a higher than normal carbon dioxide concentration in the blood excites the respiratory center, causing a person to breathe rapidly and deeply. This increases expiration of carbon dioxide and, therefore, removes excess carbon dioxide from the blood and tissue fluids. This process continues until the concentration returns to normal.

2. Regulation of arterial blood pressure.

Several systems contribute to the regulation of arterial blood pressure. One of these, the baroreceptor system, is a simple and excellent example of a rapidly acting control mechanism. In the walls of the bifurcation region of the carotid arteries in the neck, and also in the arch of the aorta in the thorax, are many nerve receptors called baroreceptors, which are stimulated by stretch of the arterial wall. When the arterial pressure rises too high, the baroreceptors send barrages of nerve impulses to the medulla of the brain. Here these impulses inhibit the vasomotor center, which in turn decreases the number of impulses transmitted from the vasomotor center through the sympathetic nervous system to the heart and blood vessels. Lack of these impulses causes diminished pumping activity by the heart and also dilation of the peripheral blood vessels, allowing increased blood flow through the vessels. Both of these effects decrease the arterial pressure back toward normal.

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.

Negative feedback nature of most control systems.

Most control systems of the body act by negative feedback, which can best be explained by reviewing some of the homeostatic control systems. In the regulation of carbon dioxide concentration, a high concentration of carbon dioxide in the extracellular fluid increases pulmonary ventilation. This, in turn, decreases the extracellular fluid carbon dioxide concentration because the lungs expire greater amounts of carbon dioxide from the body. In other words, the high concentration of carbon dioxide initiates events that decrease the concentration toward normal, which is negative to the initiating stimulus. Conversely, if the carbon dioxide concentration falls too low, this causes feedback to increase the concentration. This response also is negative to the initiating stimulus. In the arterial pressure–regulating mechanisms, a high pressure causes a series of reactions that promote a lowered pressure, or a low pressure causes a series of reactions that promote an elevated pressure. In both instances, these effects are negative with respect to the initiating stimulus. Therefore, in general, if some factor becomes excessive or deficient, a control system initiates negative feedback, which consists of a series of changes that return the factor toward a certain mean value, thus maintaining homeostasis.

Positive feedback can sometimes cause vicious cycles and death.

One might ask the question, why do essentially all control systems of the body operate by negative feedback rather than positive feedback? If one considers the nature of positive feedback, one immediately sees that positive feedback does not lead to stability but to instability and often death.

Figure below shows an example in which death can ensue from positive feedback. This figure depicts the pumping effectiveness of the heart, showing that the heart of a healthy human being pumps about 5 liters of

blood per minute. If the person is suddenly bled 2 liters, the amount of blood in the body is decreased to such a low level that not enough blood is available for the heart to pump effectively. As a result, the arterial pressure falls, and the flow of blood to the heart muscle through the coronary vessels diminishes. This results in weakening of the heart, further diminished pumping, a further decrease in coronary blood flow, and still more weakness of the heart; the cycle repeats itself again and again until death occurs. Note that each cycle in the feedback results in further weakening of the heart. In other words, the initiating stimulus causes more of the same, which is positive feedback.

Positive feedback is better known as a "vicious cycle," but a mild degree of positive feedback can be overcome by the negative feedback control mechanisms of the body, and the vicious cycle fails to develop. For instance, if the person in the aforementioned example were bled only 1 liter instead of 2 liters, the normal negative feedback mechanisms for controlling cardiac output and arterial pressure would

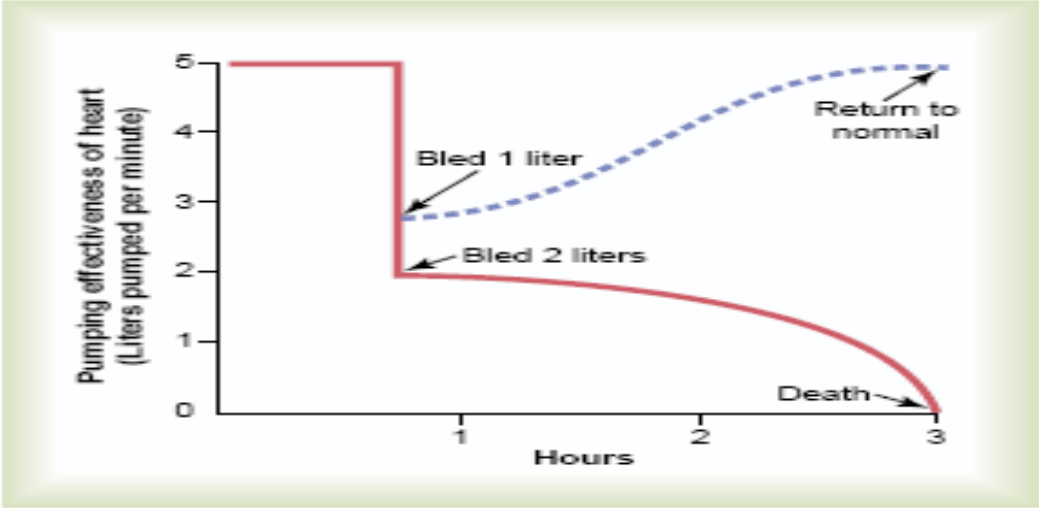


Figure 1–3

Recovery of heart pumping caused by *negative feedback* after 1 liter of blood is removed from the circulation. Death is caused by *positive feedback* when 2 liters of blood are removed.

overbalance the positive feedback and the person would recover.

Positive feedback can sometimes be useful.

In some instances, the body uses positive feedback to its advantage. Blood clotting is an example of a valuable use of positive feedback. When a blood vessel is ruptured and a clot begins to form, multiple enzymes called clotting factors are activated within the clot itself. Some of these enzymes act on other unactivated enzymes of the immediately adjacent blood, thus causing more blood clotting. This process continues until the hole in the vessel is plugged and bleeding no longer occurs. On occasion, this mechanism can get out of hand and cause the formation of unwanted clots. In fact, this is what initiates most acute heart attacks, which are caused by a clot beginning on the inside surface of an atherosclerotic plaque in a coronary artery and then growing until the artery is blocked.

Childbirth is another instance in which positive feedback plays a valuable role. When uterine contractions become strong enough for the baby's head to begin pushing through the cervix, stretch of the cervix sends signals through the uterine muscle back to the body of the uterus, causing even more powerful contractions. Thus, the uterine contractions stretch the cervix, and the cervical stretch causes stronger contractions. When this process becomes powerful enough, the baby is born. If it is not powerful enough, the contractions usually die out, and a few days pass before they begin again.

Automaticity of the body.

The purpose of this lecture has been to point out, first, the overall organization of the body and, second, the means by which the different parts of the body operate in harmony. To summarize, the 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 contributes its share to the maintenance of homeostatic conditions in the extracellular fluid, which is called the internal environment .As long as normal conditions are maintained in this internal environment, the cells of the body continue to live and function properly. Each cell benefits from homeostasis, and in turn, each cell contributes its share toward the maintenance of homeostasis. This 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; moderate dysfunction leads to sickness.

General Physiology

Dr. Ahmed talib ***Lect. 2***

The Body Fluids

The maintainenance of a relatively constant volume and a stable composition of the body fluids is essential for hoemeostasis. We enter the world in a rather soggy condition, having swallowed, excreted, and floated in amniotic fluid for months. At birth, a baby is as much as 75% water of weight, infants normally lose a little weight in the first day or two as they excrete the excess fluid. Young adult men average 55% to 60% water, women average slightly less because they have more fat, and adipose tissue is nearly free of water. Obese and elderly are as little as 45% water by weight. In average adult males, the body is composed of about 18% protein, 15% fat, 7% minerals and 60% water, known as ***total body water*** *(T.B.W.).*

About ***28 of the 42*** *liters of fluid in the body are inside the 100 trillion cells and are called* ***intracellular fluid*** *thus; the intracellular fluid constitutes about 40% of T.B.W. While* ***extracellular fluid*** *is the fluid outside the cells. Together these fluids account for about 20% of the body weight or about 14 liters in a normal 70 Kg adult. The average blood volume is about 7% of body weight or about 5 liters. About 60% plasma and 40% R.B.C. from blood (blood contain both extracellular fluid (fluid in plasma) and intracellular fluid (fluid in R.B.C.)*

Daily intake of water.

Water is added to the body by two major sources:

(1) It is ingested in the form of liquids or water in the food, which together normally add about 2100 ml/day to the body fluids.

(2) It is synthesized in the body as a result of oxidation of carbohydrates, adding about; 200 ml/day.

This provides a total water intake of about ***2300 ml/day*** *(Table below). Intake of water, however, is highly variable among different people and even within the same person on different days, depending on climate, habits, and level of physical activity.*

Daily Intake and Output of Water (ml/day)

	Normal	Prolonged, Heavy Exercise
Intake		
Fluids ingested	2100	?
From metabolism	200	200
Total intake	2300	?
Output		
Insensible—skin	350	350
Insensible—lungs	350	650
Sweat	100	5000
Feces	100	100
Urine	1400	500
Total output	2300	6600

Relative water content of various tissues.

Tissue	*Water content*	*Percentage body*
Skin	*72.0*	*18.0*
Muscle	*75.6*	*41.7*
Skeleton	*22.0*	*15.9*
Brain	*74.8*	*2.0*
Liver	*68.3*	*2.3*
Heart	*79.2*	*0.5*
Lungs	*79.0*	*0.7*
Kidney	*82.7*	*0.4*
Spleen	*75.8*	*0.2*
Blood	*83.0*	*8.0*
Intestine	*74.5*	*1.8*
Adipose	*10.0*	*10.0*

Daily loss of body water.

1. Insensible water loss.

Some of the water losses cannot be precisely regulated. For example, there is a continuous loss of water by evaporation from the respiratory tract and diffusion through the skin, which together account for about 700 ml/day of water loss under normal conditions. This is termed ***insensible water loss*** *because we are not consciously aware of it, even though it occurs continually in all living humans.*

The insensible water loss through the skin occurs independently of sweating and is present even in people who are born without sweat glands; the average water loss by diffusion through the skin is about 300 to 400 ml/day. Insensible water loss through the respiratory tract averages about 300 to 400 ml/day. As air enters the respiratory tract, it becomes saturated with moisture, to a vapor pressure of about 47 mm Hg, before it is expelled. Because the vapor pressure of the inspired air is usually less than 47 mm Hg, water is continuously lost through the lungs with respiration. In cold weather, the atmospheric vapor pressure decreases to nearly 0, causing an even greater loss of water from the lungs as the temperature decreases. This explains the dry feeling in the respiratory passages in cold weather.

2. Fluid loss in sweat.

The amount of water lost by sweating is highly variable, depending on physical activity and environmental temperature. The volume of sweat normally is about 100 ml/day, but in very hot weather or during heavy exercise, water loss in sweat occasionally increases to 1 to 2 L/hour. This would rapidly deplete the body fluids if intake were not also increased by activating the thirst mechanism.

3. Water loss in feces.

Only a small amount of water (100 ml/day) normally is lost in the feces. This can increase to several liters a day in people with severe diarrhea. For this reason, severe diarrhea can be life threatening if not corrected within a few days.

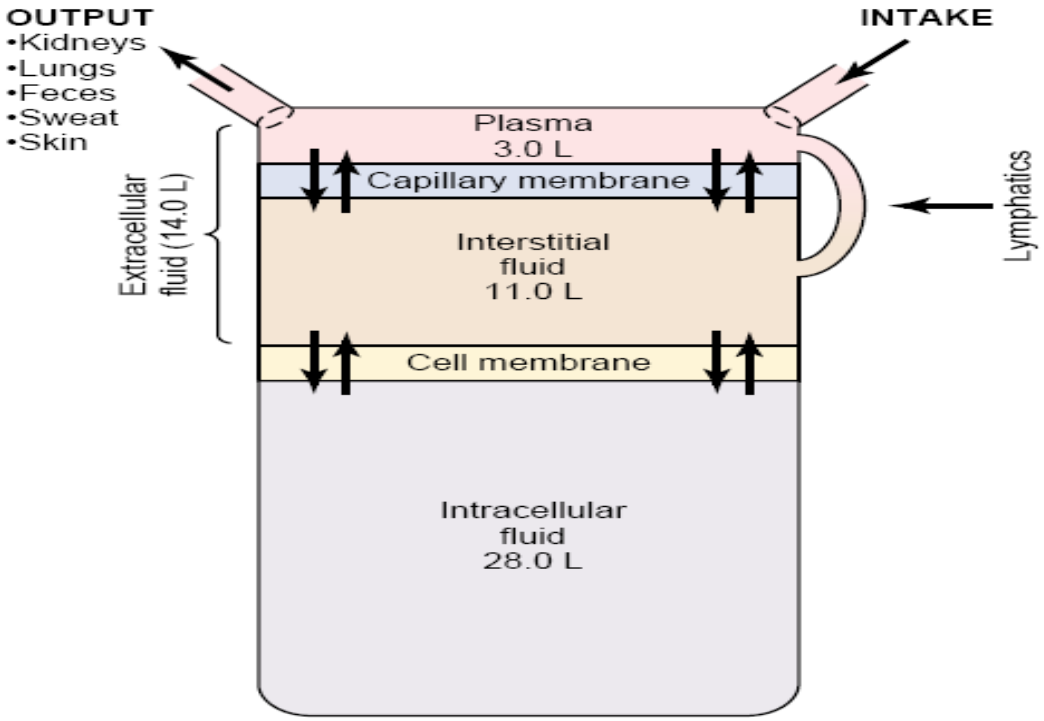
4. Water loss by the kidneys.

The remaining water loss from the body occurs in the urine excreted by the kidneys. There are multiple mechanisms that control the rate of urine excretion. In fact, the most important means by which the body maintains a balance between water intake and output, as well as a balance between intake and output of most electrolytes in the body, is by controlling the rates at which the kidneys excrete these substances. For example, urine volume can be as low as 0.5 L/day in a dehydrated person or as high as 20 L/day in a person who has been drinking tremendous amounts of water. This variability of intake is also true for most of the electrolytes of the body, such as sodium, chloride, and potassium. In some people, sodium intake may be as low as 20 mEq/day, whereas in others, sodium intake may be as high as 300 to 500 mEq/day. The kidneys are faced with the task of adjusting the excretion rate of water and electrolytes to match precisely the intake of these substances, as well as compensating for excessive losses of fluids and electrolytes that occur in certain disease states.

Body fluid compartments.

The total body fluid is distributed mainly between two compartments: the extracellular fluid and the intracellular fluid (figure below). The extracellular fluid is divided into the ***interstitial fluid*** *and the* ***blood plasma.*** *There is another small compartment of fluid that is referred to as* ***transcellular fluid****. This compartment includes fluid in the synovial, peritoneal, pericardial, and intraocular spaces, as well as the cerebrospinal 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 the plasma or interstitial fluid. All the transcellular fluids together constitute about 1 to 2 liters.*

In the average 70-kilogram adult human, the total body water is about 60 per cent of the body weight, or about 42 liters. This percentage can change, depending on age, gender, 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 associated with an increased percentage of the body weight being fat, which 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.

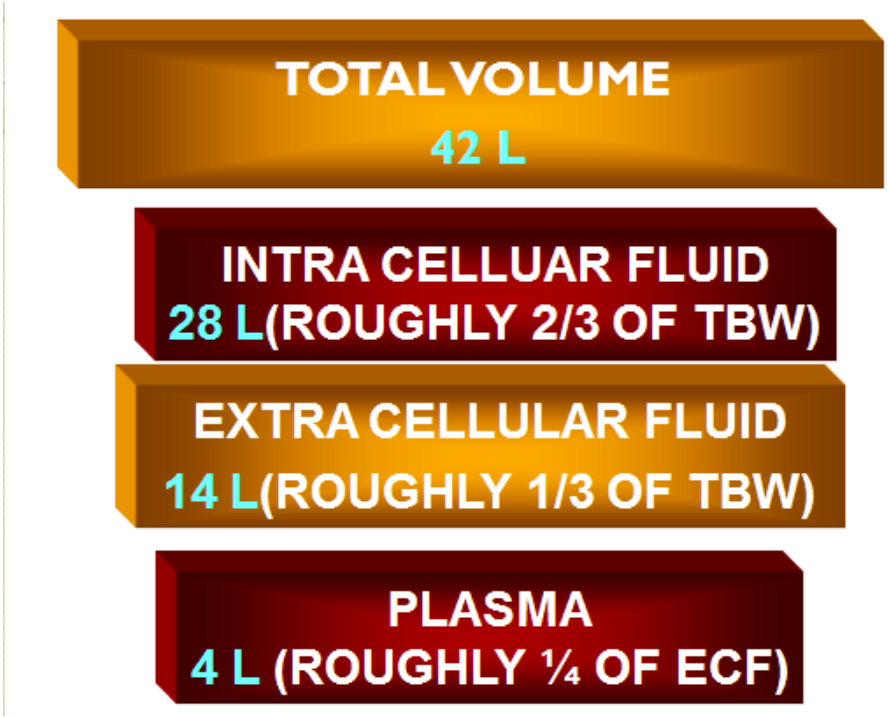


- *Intracellular fluid compartment.*

*About **28** of the 42 liters of fluid in the body are inside the 100 trillion cells and are collectively called the intracellular fluid. Thus, the intracellular fluid constitutes about **40 per cent of the total body weight** in an "average" person. The fluid of each cell contains its individual mixture of different constituents, but the concentrations of these substances are similar from one cell to another. In fact, the composition of cell fluids is remarkably similar even in different animals, ranging from the most primitive microorganisms to humans. For this reason, the intracellular fluid of all the different cells together is considered to be one large fluid compartment.*

- *Extracellular fluid compartment.*

*All the fluids outside the cells are collectively called the extracellular fluid. Together these fluids account for about **20 per cent of the body weight**, or about **14 liters** in a normal 70-kilogram adult. The two largest compartments of the extracellular fluid are the interstitial fluid, which makes up more than three fourths of the extracellular fluid, and the plasma, which makes up almost one fourth of the extracellular fluid, or about 3 liters. The plasma is the non-cellular part of the blood; it exchanges substances continuously with the interstitial fluid through the pores of the capillary membranes. These pores are highly permeable to almost all solutes in the extracellular fluid except the proteins. Therefore, the extracellular fluids are constantly mixing, so that the plasma and interstitial fluids have about the same composition except for proteins, which have a higher concentration in the plasma.*



Important constituents of the intracellular fluid.

The intracellular fluid is separated from the extracellular fluid by a cell membrane that is highly permeable to water but not to most of the electrolytes in the body. In contrast to the extracellular fluid, the intracellular fluid contains only small quantities of sodium and chloride ions and almost no calcium ions. Instead, it contains large amounts of potassium and phosphate ions plus moderate quantities of magnesium and sulfate ions, all of which have low concentrations in the extracellular fluid. Also, cells contain large amounts of protein, almost four times as much as in the plasma.

Functions of body fluid.

1. *It acts as medium for various physical processes, for example: diffusion, osmosis and filteration.*
2. *It's an essential constituent of all living cells.*
3. *By its solvent action. It provides a medium for all chemical and enzymatic reactions.*
4. *It's a good ionizing medium, so it plays an important role in regulation the PH and osmotic pressure of various body fluids.*
5. *It's essential for gases exchange of oxygen and carbon dioxides in the tissue and lungs.*
6. *It regulates the body temperature through its properties of heat absorption and distribution.*
7. *It exerts a lubricant action in potential spaces. For example; joints, pleura and pericardium.*
8. *In the eye, it acts as a refractive medium for light rays.*
9. *It acts as a vehicle for various physiological processes, for example; absorption of different foods tufts form GIT and reabsorption of various substances from renal tubule.*
10. *In cerebrospinal fluid, it acts as mechanical buffer which prevents injury of the brain.*

Hyponatremia.

Decreased plasma sodium concentration can result from ***loss of NaCl from extracellular*** *fluid or* ***excess of water to extracellular fluid.*** *A primary loss of sodium chloride result from hypo-osmotic dehydration and is associated with extracellular fluid, conditions that can cause hyponatremia owing to loss NaCl including diarrhea and vomiting ,overuse of diuretics that inhibit the ability of kidneys to conserve sodium and certain types sodium-wasting. Kidney diseases can also cause hyponatremia. Finally, Addison's disease, which results from decreased secretion of the hormone aldosterone, impairs the ability of kidneys to reabsorb sodium in extracellular fluid, a condition that referred to as hypo-osmotic over hydration.*

Hypernatremia.

Increased plasma sodium concentration can result from ***loss of water from extracellular fluid*** *or* ***excess of sodium in extracellular fluid****, this results hyper osmotic dehydration. This condition can occur from an inability to secrete antidiuretic hormone, which needed to kidneys to conserve water and result the kidneys excess excrete large amounts of the dilute urine (a disorder refered to as diabetes insipidus), causing dehydration and increased concentration of NaCl in extracellular fluid. In certain types of renal diseases, the kidneys cannot respond to antidiuretic hormone.*

Hypernatremia can also occur as a result of excessive NaCl add to the extracellular fluid. This often results in hyperosmotic over hydration, because of excess E.C. NaCl is usually associated with at least some degree of water retention by the kidney as well. Thus in analyzing abnormalities of plasma Na concentration and deciding on proper therapy, one should first determine whether the abnormality is caused by primary loss or gain of Na or primary loss or gain water.

Edema:

Edema refers to the presence of excess fluid in the body tissue. In most instances, edema occurs mainly in the extracellular fluid compartments, but it can involve intracellular fluid as well.

Intracellular edema.

Three conditions are especially prone to cause intracellular swelling:

(1) Hyponatremia.

(2) Depression of the metabolic systems of the tissues.

(3) Lack of adequate nutrition to the cells.

For example, when blood flow to a tissue is decreased, the delivery of oxygen and nutrients is reduced. If the blood flow becomes too low to maintain normal tissue metabolism, the cell membrane ionic pumps become depressed. When this occurs, sodium ions that normally leak into the interior of the cell can no longer be pumped out of the cells and the excess intracellular sodium ions cause osmosis of water into the cells. Intracellular edema can also occur in inflamed tissues. Inflammation usually increases cell membrane permeability, allowing sodium and other ions to diffuse into the interior of the cell, with subsequent osmosis of water into the cells.

Extracellular edema.

Extracellular fluid edema occurs when there is excess fluid accumulation in the extracellular spaces. There are two general causes of extracellular edema:

(1) Abnormal leakage of fluid from the plasma to the interstitial spaces across the capillaries.

(2) Failure of the lymphatics to return fluid from the interstitium back into the blood, often called ***lymphedema.*** *The most common clinical cause of interstitial fluid accumulation is excessive capillary fluid filtration.*

When lymphatic blockage occurs, edema can become especially sever because plasma proteins that leak into the interstitium have no other way to be removed. The rise in protein concentration raises the colloid osmotic pressure of interstitial fluid, which draws even more fluid out of the capillaries.

Summary of causes of extracellular edema.

A large number of conditions can cause fluid accumulation in the interstitial spaces by the abnormal leaking of fluid from the capillaries or by preventing the lymphatics from returning fluid from the interstitium back to the circulation. The following is a partial list of conditions that can cause extracellular edema by these two types of abnormalities:

I. Increased capillary pressure.

A. Excessive kidney retention of salt and water.

1. Acute or chronic kidney failure.

2. Mineralocorticoid excess.

B. High venous pressure and venous constriction.

1. Heart failure.
2. Venous obstruction.
3. Failure of venous pumps.
(a) Paralysis of muscles.
(b) Immobilization of parts of the body.
(c) Failure of venous valves.
C. Decreased arteriolar resistance.
1. Excessive body heat.
2. Insufficiency of sympathetic nervous system.
3. Vasodilator drugs.

II. Decreased plasma proteins.

A. Loss of proteins in urine (nephritic syndrome).
B. Loss of protein from denuded skin areas.
1. Burns.
2. Wounds.
C. Failure to produce proteins.
1. Liver disease (e.g., cirrhosis)
2. Serious protein or caloric malnutrition.

III. Increased capillary permeability.

A. Immune reactions that cause release of histamine and other immune products.
B. Toxins.
C. Bacterial infections.
D. Vitamin deficiency, especially vitamin C.
E. Prolonged ischemia.
F. Burns.

IV. Blockage of lymph return.

A. Cancer.
B. Infections (e.g., filaria nematodes).
C. Surgery.
D. Congenital absence or abnormality of lymphatic vessels.

Edema caused by heart failure.

In heart failure, the heart fails to pump blood normally from the veins into the arteries, this raises venous pressure and capillary pressure, causing increased capillary filtration. In addition, the arterial tends to fall, causing decreased excretion of salt and water by kidneys, which increase blood volume and further raise capillary hydrostatic pressure to cause still more edema. Also, diminished blood flow to the kidneys, stimulates secretion of rennin, causing increased formation angiotensin II and increased secretion of aldosteron, both of which cause additional ***salt and water retention*** *by the kidneys. Thus, in untreated heart failure, all these factors acting together to cause serious generalized extracellular edema.*

Safety factors that normally prevent edema

Even though many disturbances can cause edema, usually the abnormality must be severe before serious edema develops. The reason for this is that three major safety factors prevent excessive fluid accumulation in the interstitial spaces:
(1) Low compliance of the interstitium when interstitial fluid pressure is in the negative pressure range.
(2) The ability of lymph flow to increase 10- to 50-fold.

(3) Wash-down of interstitial fluid protein concentration, which reduces interstitial fluid colloid osmotic pressure as capillary filtration increases.

Edema fluid in the potential spaces is called "Effusion".

Some examples of "potential spaces" are pleural cavity, pericardial cavity, peritoneal cavity, and synovial cavities, including both the joint cavities and the bursae. Virtually all these potential spaces have surfaces that almost touch each other, with only a thin layer of fluid in between, and the surfaces slide over each other. To facilitate the sliding, a viscous proteinaceous fluid lubricates the surfaces. When edema occurs in the subcutaneous tissue adjacent to the potential spaces, edema fluid usually collects in the potential space as well, and this fluid is called effusion fluid. The abdominal cavity is especially prone to collect effusion fluid, and in this instance, the effusion is called ascites. In serious cases, 20 liters or more of ascitic fluid can accumulate. The other potential spaces, such as the pleural cavity, pericardial cavity, and joint spaces, can become seriously swollen when there is generalized edema.

Isotonic, hypotonic and hypertonic fluids.

Isotonic:

The cell will not shrink or swell because the extracellular fluid and intracellular fluid is equal and solutes cannot enter or leave the cell.

Hypotonic:

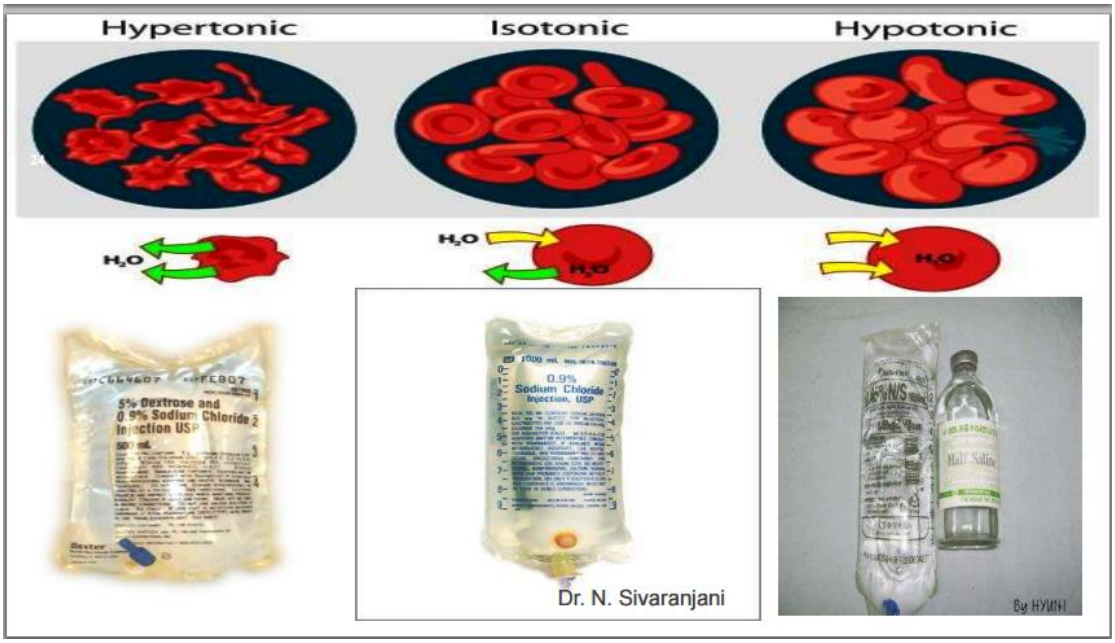
If the cell has a lower concentration of imperment solutes, water will diffuse into the cell, diluting the intracellular fluid while also concerting the extracellular fluid until both solutions have about the same osmolarity.

Hypertonic:

The cell having a higher concentration of imperment solutes, water will flow out of the cell into the extracellular fluid concentrating the intracellular fluid and diluting the extracellular fluid. In this case the cell will shrink until the two concentrations become equal.

The terms isotonic, hypotonic, and hypertonic refer to whether solutions will cause a change in cell volume. The tonicity of solutions depends on the concentration of impermeant solutes. Some solutes, however, can permeate the cell membrane. Solutions with an osmolarity the same as the cell are called ***isosmotic****, regardless of whether the solute can penetrate the cell membrane.*

The terms ***hyperosmotic*** *and* ***hypo-osmotic*** *refer to solutions that have a higher or lower osmolarity, respectively, compared with the normal extracellular fluid, without regard for whether the solute permeates the cell membrane. Highly permeating substances, such as urea, can cause transient shifts in fluid volume between the intracellular and extracellular fluids, but given enough time, the concentrations of these substances eventually become equal in the two compartments and have little effect on intracellular volume under steady-state conditions.*



Water gain and loss.

A person is in a state of fluid when daily gains and losses are equal about 2300 ml on average.

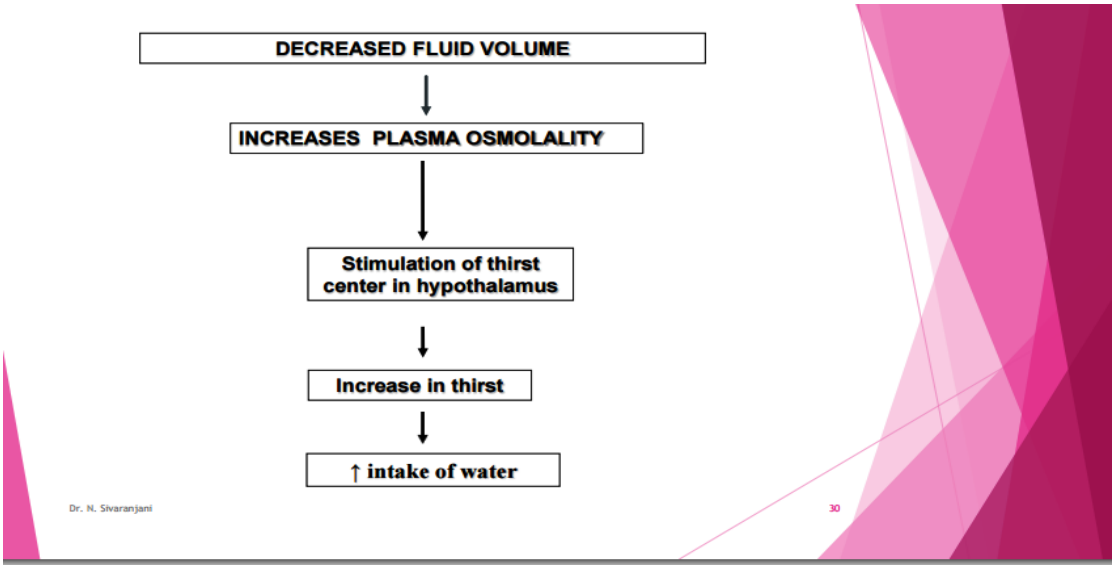
Regulation of intake.

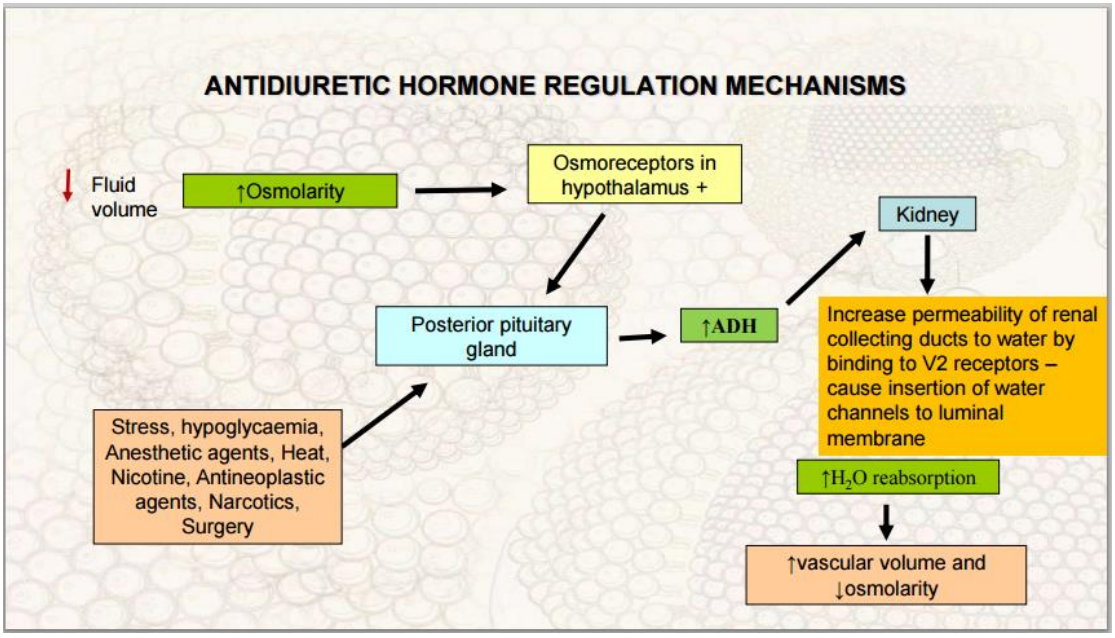
*Fluid intake is governed mainly by **thirst**, dehydration reduces the blood volume and pressure and raises osmolarity. For several reasons, this results in a smaller volume and greater viscosity of saliva. One of the reasons is that most of saliva is produced by capillary filtration, which is opposed by the lower hydrostatic pressure and higher osmolarity of the blood. Another reason is that salivation is inhibited by sympathetic output from the thirst center of the hypothalamus. The thirst center responds to stimuli of several kinds; angiotonsin II, which is produced in response to falling blood pressure, antidiuretic hormone, which is released when blood osmolarity rises, and signals from the hypothalamic osmoreceptors, neurons that continually monitor the osmolarity of the E.C.F. Reduced salivation gives us a dry, sticky-feeling mouth, but it's by no means certain that this is our primary motivation to drink.*

Regulation of output.

The only way to control water output is through variations in urine volume, it must be realized, however the kidney cannot completely prevent loss, nor can they replace lost water or electrolytes. Therefore, they never restore fluid volume or osmolarity, but in dehydration they can support existing fluid levels and slow down the rate of loss until water and electrolytes are ingested. To understand the effect of kidney on water and electrolytes balance, it's also important to bear in mind that if a substance is reabsorbed by the kidney, it's kept in the body and returned to the E.C.F. When it will be reflected in fluid volume and composition. If a substance is filtered by the glomerulus or secreted by the renal tubules and not reabsorbed, then it's excreted in the urine and lost from the body fluids. Antidiuretic hormone (ADH), however, provides a means of controlling water output independently of sodium.

In dehydration, blood volume declines and Na concentration rises. The increased osmolarity of the blood stimulates the hypothalamic osmoreceptors, which stimulates the posterior pituitary to release ADH. In response to ADH cells of collecting duct reabsorb more water and produce less urine. Na continues to be excreted, so the ratio of Na to water in the urine increases (the urine become more concentrated) by helping the kidneys retain water; ADH slow down the decline in blood volume and the rise in its osmolarity. Thus the ADH mechanism forms a negative feedback loop.





Disorders of water balance:

The body is in a state of fluid imbalance. If there is an abnormality of total body volume, fluid concentration or fluid distribution among the compartments.

Dehydration;

This condition develops when the water loss exceeds water intake due to sever sweating, prolonged vomiting and diarrhea or failure of fluid reabsorption from the GIT.

Symptoms of dehydration;

1. *Rapid loss of body water due to water loss and increased metabolism.*
2. *Hypotension and circulatory failure and the blood become concentrated.*
3. *The skin becomes cold, pale and the temperature is increased due to sluggish blood flow in the skin.*
4. *Nervous disturbance and sever muscle weakness.*
5. *Excessive thirst.*
6. *In infants the fontanelle of the skull become depressed.*
7. *Oliguria, which results in retention of acid metabolite and nitrogenous waste products leading to acidemia and uraemia.*

Cellular dehydration also occurs in condition of salt retention in the body due to hyperfunction of the suprarenal cortex (as result of over secretion of aldosterone hormone). In these conditions, the osmolarity of E.C.F. is increased leading to shed of the I.C.F. outwards (resulting in cellular dehydration). The

defense mechanism of the body by release of ADH which leads to water retention and stimulation of the hypothalamic thirst center which leads to increased water intake. ***Treatment;*** *Adequate amounts of isotonic saline should be I.V. infused.*

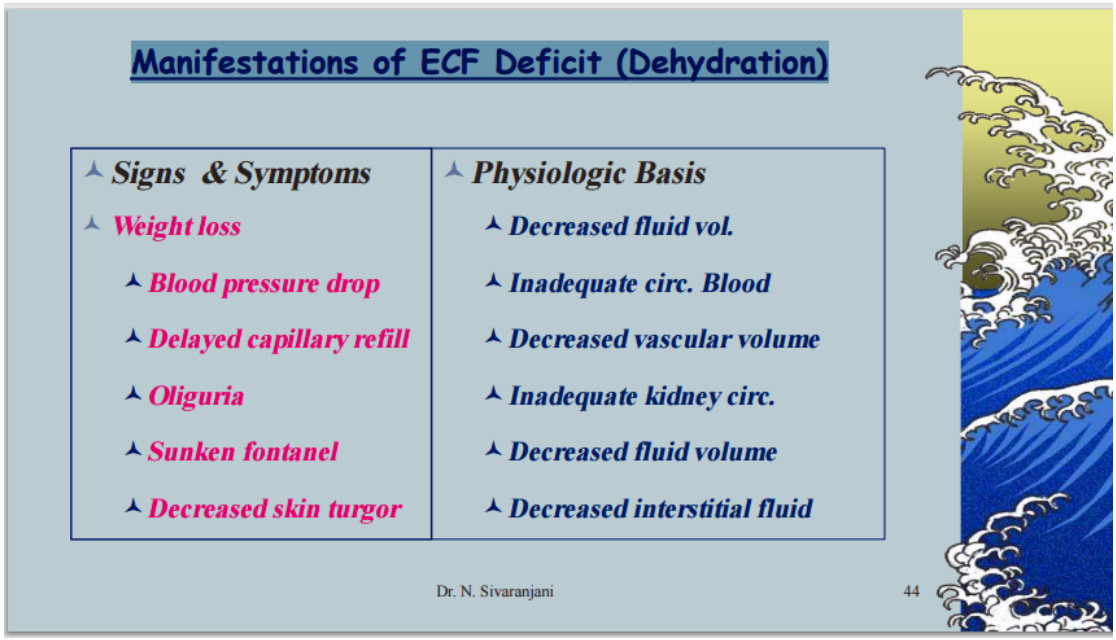
Overhydration;

This condition develops when the water intake exceeds the water loss. (e.g. when dehydrated subject is allowed to drink excess water without salt).

Symptoms of overhydration;

Overhydration leads to reduction of the osmolarity of the E.C.F. so water diffuses into the cells leading to water intoxication. The symptoms of this condition are mainly due to swelling of the brain cells and they include:

1. *Headache, restlessness, excessive salivation and vomiting.*
2. *Neurological symptoms, like asthenia, tremors and ataxia followed by convulsions, drowsiness, coma and finally death.*



Correction of overhydration;

1. *Inhibition of ADH release, which allow more water loss in the urine.*
2. *Inhibition of the thirst centre, which reduces the amount of water intake.*

Chemical composition of E.C.F.& I.C.F.:

1. Chemical composition of E.C.F.:

The main cation is sodium ion (about 142 mEq/L) and other cations include small amount of potassium, calcium and magnesium ions. The main anion is chloride ion (about 113 mEq/L) and other anions include HCO_3^-*,protein and small amount of* HPO_4^- *and* SO_4^{-2}*. Non-electrolytes include glucose, lactic acid, cholesterol. Phospholipids, urea, uric acid, creatinine and bile pigments. The PH is about 7.4 while the osmolarity is approximately 300 mosmol/L. The plasma and interstitial fluid are almost identical in composition except that the plasma contains a much higher protein 7% because the plasma protein, particularly globulins and fibrinogen cannot easily cross the capillary walls to the interstitial fluid, due to their large molecular weight.*

2. Chemical composition of I.C.F.:

The main cation is potassium ion (about 157 mEq/L). other cations include magnesium ions, small amount of sodium ions, and very little or no Ca ions. The main anion include protein (about 74 mEq/L) and HPO_4^- *with small amount of* Cl^-*,* HCO_3^-*, and* SO_4^{-2} *, the PH is about 7.2, while the osmolarity is also about 300 mosmol/L.*

Exchange between E.C.F. and I.C.F.:

Normally, cell membranes are permeable to water and their continuous exchange of fluid E.C.F. and I.C.F. But there is a difference in the constituents of the two fluids. The reasons for differences in concentrations between E.C.F. and I.C.F are:

1. Some substances that enter the cell are utilized so rapidly by the cells metabolic system such as oxygen and glucose, so that their concentration inside the cell is lower than outside the cell. These metabolic reactions create new substances inside the cell such as carbon dioxide, urea, creatinine .....etc., so their concentration is higher than E.C.F.

2. The selective transport and active transport of substances across the cell membrane is another reason for the difference in the distribution of substances in both sides of cell membrane.

Distribution of fluid volume between plasma and the interstitial fluid.

The pressure in the capillary tends to force the fluid and its dissolved substances through the capillary pores into the interstitial spaces. In contrast, the osmotic pressure caused by the plasma proteins tends to cause fluid movement by osmosis from the interstitial spaces into the blood. It's this osmotic pressure that prevents significant loss of fluid volume from the blood into interstitial spaces. The lymphatic system returns back to circulatory, the small amount of protein and fluid that leaked into the interstitial spaces.

The potential spaces fluid :(intrapleural & pericardial).

The ratio of E.C.F. / I.C.F. is higher in infants and children than in adults and this is why dehydration develops more rapidly in children. The E.C. compartment is characterized by ***homogeneity*** *of the fluid because it's always circulating even in interstitial fluid it moves from one part to another.*

The I.C. compartment is characterized by ***heterogenisity*** *of the fluid because each group of cells which represent an organ has different functions from the other groups and the composition of body fluid depends on the function of the grouping cells. The trans-cellular compartment is also heterogenisity and its composition depends on the function of grouping cell.*

Dr.Ahmed talib ***lac.1***

Physiology of the cell

Each of the 100 trillion cells in a human being is a living structure that can survive for months or many years, provided its surrounding fluids contain appropriate nutrients. To understand the function of organs and other structures of the body, it is essential that we first understand the basic organization of the cell and the functions of its component parts.

Organization of the Cell

A typical cell, as seen by the light microscope, is shown in figure below. Its two major parts are the nucleus and the cytoplasm. The nucleus is separated from the cytoplasm by a nuclear membrane, and the cytoplasm is separated from the surrounding fluids by a cell membrane, also called the plasma membrane. The different substances that make up the cell are collectively called protoplasm.

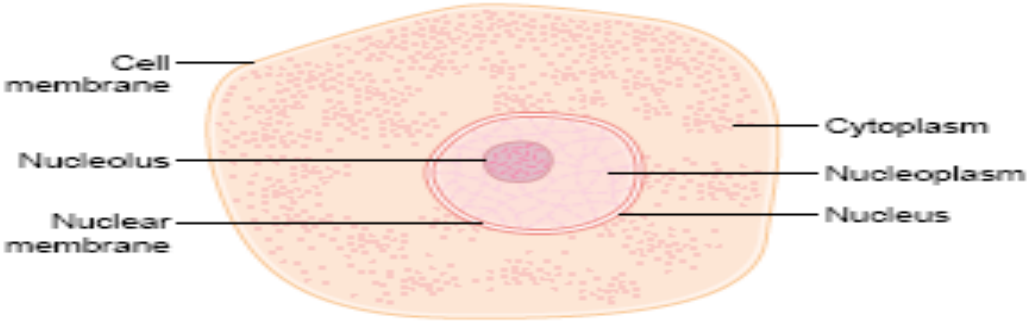


Figure 2–1

Structure of the cell as seen with the light microscope.

Protoplasm is composed mainly of five basic substances: water, electrolytes, proteins, lipids, and carbohydrates.

- ***Water.***

The principal fluid medium of the cell is water, which is present in most cells, except for fat cells, in a concentration of 70 to 85 percent. Many cellular chemicals are dissolved in the 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.

- ***Ions.***

The most important ions in the cell are potassium, magnesium, phosphate, sulfate, bicarbonate, and smaller quantities of sodium, chloride, and calcium. The ions provide inorganic chemicals for cellular reactions. Also, they are necessary for operation of some of the cellular control mechanisms. For instance, ions acting at the cell membrane are required for transmission of electrochemical impulses in nerve and muscle fibers.

- ***Proteins.***

After water, the most abundant substances in most cells are proteins, which normally constitute 10 to 20 per cent of the cell mass. These can be divided into two types:

1. Structural proteins

2. Functional proteins.

***Structural proteins** are present in the cell mainly in the form of long filaments that themselves are polymers of many individual protein molecules. A prominent use of such intracellular filaments is to form microtubules that provide the "cytoskeletons" of such cellular organelles as cilia, nerve axons, the mitotic spindles of mitosing cells, and a tangled mass of thin filamentous tubules that hold the parts of the cytoplasm and nucleoplasm together in their respective compartments. Extracellularly, fibrillar proteins are found especially in the collagen and elastin fibers of connective tissue and in blood vessel walls, tendons, ligaments, and so forth.*

***The functional proteins** are an entirely different type of protein, usually composed of combinations of a few molecules in tubular-globular form. These proteins are mainly the enzymes of the cell and, in contrast to the fibrillar proteins, are often mobile in the cell fluid. Also, many of them are adherent to membranous structures inside the cell. The enzymes come into direct contact with other substances in the cell fluid and thereby catalyze specific intracellular chemical reactions. For instance, the chemical reactions that split glucose into its component parts and then combine these with oxygen to form carbon dioxide and water while simultaneously providing energy for cellular function are all catalyzed by a series of protein enzymes.*

- ***Lipids.***

*Lipids are several types of substances that are grouped together because of their common property of being soluble in fat solvents. Especially important lipids are **phospholipids** and **cholesterol**, which together constitute only about 2 percent of the total cell mass. The significance of phospholipids and cholesterol is that they are mainly insoluble in water and, therefore, are used to form the cell membrane and intracellular*

membrane barriers that separate the different cell compartments. In addition to phospholipids and cholesterol, some cells contain large quantities of ***triglycerides****, also called neutral fat. In the fat cells, triglycerides often account for as much as 95 percent of the cell mass. The fat stored in these cells represents the body's main storehouse of energy-giving nutrients that can later be dissoluted and used to provide energy wherever in the body it is needed.*

- ### Carbohydrates.

Carbohydrates have little structural function in the cell except as parts of glycoprotein molecules, but they play a major role in nutrition of the cell. Most human cells do not maintain large stores of carbohydrates; the amount usually averages about 1 per cent of their total mass but increases to as much as 3 per cent in muscle cells and, occasionally, 6 percent in liver cells. However, carbohydrate in the form of dissolved glucose is always present in the surrounding extracellular fluid so that it is readily available to the cell. Also, a small amount of carbohydrate is virtually always stored in the cells in the form of glycogen, which is an insoluble polymer of glucose that can be depolymerized and used rapidly to supply the cells' energy needs.

Physical Structure of the Cell

The cell is not merely a bag of fluid, enzymes, and chemicals; it also contains highly organized physical structures, called intracellular organelles. The physical nature of each organelle is as important as the cell's chemical constituents for cell function. For instance, without one of the organelles, the mitochondria, more than 95 per cent of the cell's energy release from nutrients would cease immediately. The most important organelles and other structures of the cell are shown in figure below.

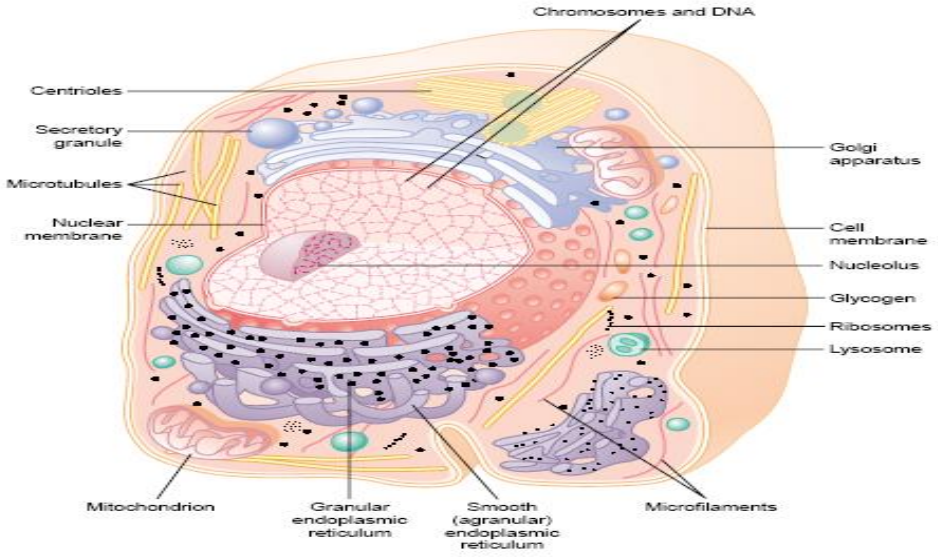


Figure 2–2

Reconstruction of a typical cell, showing the internal organelles in the cytoplasm and in the nucleus.

Membranous structures of the cell.

Most organelles of the cell are covered by membranes composed primarily of lipids and proteins. These membranes include the cell membrane, nuclear membrane, membrane of the endoplasmic reticulum, and membranes of the mitochondria, lysosomes, and Golgi apparatus. The lipids of the membranes provide a barrier that impedes the movement of water and water-soluble substances from one cell compartment to another because water is not soluble in lipids. However, protein molecules in the membrane often do penetrate all the way through the membrane, thus providing specialized pathways, often organized into actual pores, for passage of specific substances through the membrane. Also, many other membrane proteins are enzymes that catalyze a multitude of different chemical reactions.

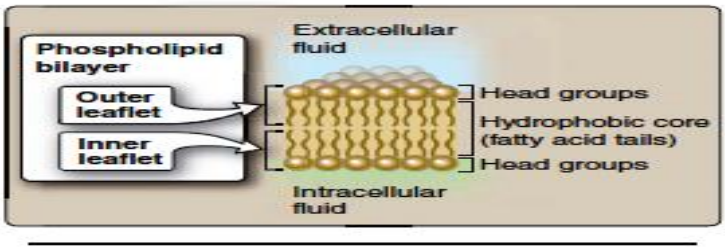
Cell membrane.

The cell membrane (also called the plasma membrane), which envelops the cell, is a thin, pliable, elastic structure only 7.5 to 10 nanometers thick. It is composed almost entirely of proteins and lipids. The

approximate composition is proteins, 55 percent; phospholipids, 25 percent; cholesterol, 13 percent; other lipids, 4 percent; and carbohydrates, 3 percent.

Lipid Barrier of the Cell Membrane :-

Membranes contain three predominant types of lipid: ***phospholipids, cholesterol, and glycolipids. All are amphipathic in nature, meaning*** *that they have a polar (hydrophilic) region and a nonpolar (hydrophobic) region. The polar region is referred to as the* ***head group*** *(hydrophilic)* ***. The****(hydrophobic)or non polar region is usually composed of fatty acid* ***"tails" of variable*** *length. When the membrane is assembled, the lipids naturally gather into a continuous bilayer as in the Figure. The polar head groups gather at the internal and external surfaces where the two layers interface with ICF and ECF, respectively. The hydrophobic tail groups dangle down from the head groups to form the fatty membrane core. Although the two halves of the bilayer are closely apposed, there is no significant lipid exchange between the two membrane leaflets.*



Plasma Membrane

Integral and Peripheral Cell Membrane Proteins:-

There are two types of cell membrane proteins: ***integral proteins*** that protrude all the way through the membrane and ***peripheral proteins*** that are attached only to one surface of the membrane and do not penetrate all the way through.

Integral proteins

1- Many of the integral proteins provide structural channels (or pores) through which water molecules and watersoluble substances, especially ions, can diffuse between the extracellular and intracellular fluids**.**

2- proteins act as carrier proteins for transporting substances that otherwise could not penetrate the lipid bilayer**.**

3- proteins can also serve as receptors for water-soluble chemicals, such as peptide hormones, that do not easily penetrate the cell membrane.

4- enzymes (catalyze chemical reactions).

Peripheral proteins

1- Enzymes**.**

2- controllers of transport of substances through the cell membrane "pores".

The Membrane Carbohydrates—The Cell "Glycocalyx." :-

Membrane carbohydrates occur in combination with proteins or lipids in the form of glycoproteins or glycolipids. It has several important functions:

(1) Have a negative electrical charge,

(2) The glycocalyx of some cells attaches to the glycocalyx of other cells.

(3) Act as receptor substances for binding hormones.

(4) Some carbohydrate types enter into immune reactions.

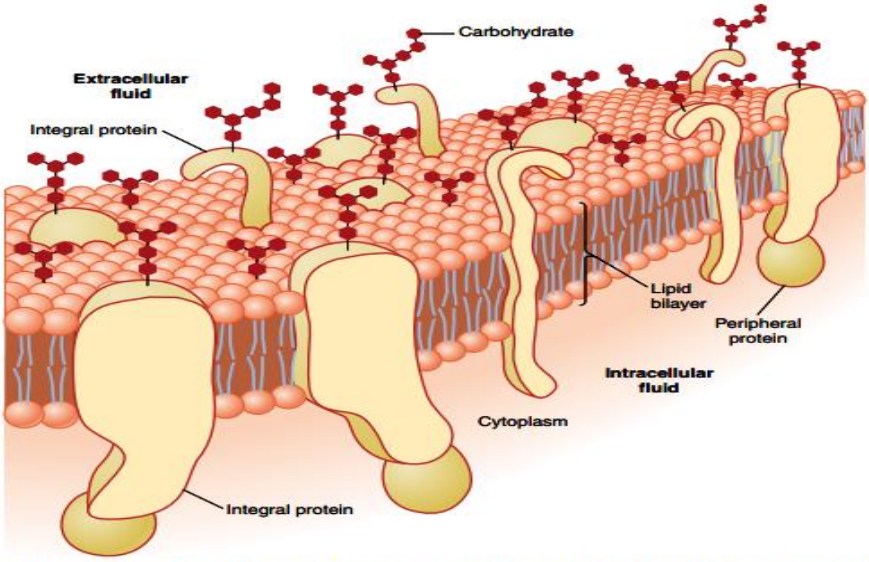


Figure 2-3 Structure of the cell membrane, showing that it is composed mainly of a lipid bilayer of phospholipid molecules, but with large numbers of protein molecules protruding through the layer. Also, carbohydrate moieties are attached to the protein molecules on the outside of the membrane and to additional protein molecules on the inside. (Redrawn from Lodish HF, Rothman JE: The assembly of cell membranes. Sci Am 240:48, 1979. Copyright George V. Kevin.)

Cytoplasm and Its organelles.

The cytoplasm is filled with both minute and large dispersed particles and organelles. The clear fluid portion of the cytoplasm in which the particles are dispersed is called ***cytosol****; this contains mainly dissolved proteins, electrolytes, and glucose. Dispersed in the cytoplasm are neutral fat globules, glycogen granules, ribosomes, secretory vesicles, and five especially important organelles: the endoplasmic reticulum, the Golgi apparatus, mitochondria, lysosomes, and peroxisomes.*

- Endoplasmic reticulum.

Network of tubular and flat vesicular structures in the cytoplasm; this is the endoplasmic reticulum. The tubules and vesicles interconnect with one another. Also, their walls are constructed of lipid bilayer membranes that contain 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 the cell membrane area.

- Ribosomes and the granular endoplasmic reticulum.

Attached to the outer surfaces of many parts of the endoplasmic reticulum are large numbers of minute granular particles called ribosomes. Where these are present, the reticulum is called the granular endoplasmic reticulum. The ribosomes are composed of a mixture of RNA and proteins, and they function to synthesize new protein molecules in the cell.

- Agranular endoplasmic reticulum.

Part of the endoplasmic reticulum has no attached ribosomes. This part is called the agranular, or smooth, endoplasmic reticulum. The agranular reticulum functions for the synthesis of lipid substances and for other processes of the cells promoted by intra reticular enzymes.

- Golgi apparatus.

The Golgi apparatus, shown in Figure below, is closely related to the endoplasmic reticulum. It has membranes similar to those of the agranular endoplasmic reticulum. It usually is composed of four or more stacked layers of thin, flat, enclosed vesicles lying near one side of the nucleus. This apparatus is prominent in secretory cells, where it is located on the side of the cell from which the secretory substances are extruded.

The Golgi apparatus functions in association with the endoplasmic reticulum. As shown below, small "transport vesicles" (also called endoplasmic reticulum vesicles, or ER vesicles) continually pinch off from the endoplasmic reticulum and shortly thereafter fuse with the Golgi apparatus. In this way, substances entrapped in the ER vesicles are transported from the endoplasmic reticulum to the Golgi apparatus. The

transported substances are then processed in the Golgi apparatus to form lysosomes, secretory vesicles, and other cytoplasmic components.

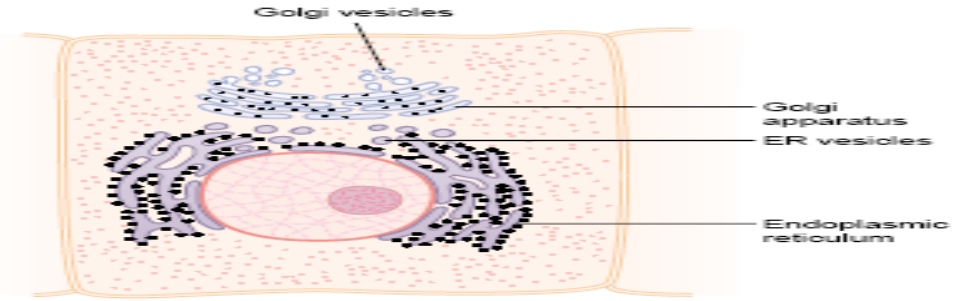


Figure 2–5

A typical Golgi apparatus and its relationship to the endoplasmic reticulum (ER) and the nucleus.

Lysosomes

Lysosomes, shown in the figure above, are vesicular organelles that form by breaking off from the Golgi apparatus and then dispersing throughout the cytoplasm. The lysosomes provide `an intracellular digestive system that allows the cell to digest:

(1) Damaged cellular structures.

(2) Food particles that have been ingested by the cell.

(3) Unwanted matter such as bacteria.

The lysosome is quite different in different types of cells, but it is usually 250 to 750 nanometers in diameter. It is surrounded by a typical lipid bilayer membrane and is filled with large numbers of small granules which are protein aggregates of as many as 40 different hydrolase (digestive) enzymes. A hydrolytic enzyme is capable of splitting an organic compound into two or more parts by combining hydrogen from a water molecule with one part of the compound and combining the hydroxyl portion of the water molecule with the other part of the compound. For instance, protein is hydrolyzed to form amino acids, glycogen is hydrolyzed to form glucose, and lipids are hydrolyzed to form fatty acids and glycerol. 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. However, some conditions of the cell break the membranes of some of the lysosomes, allowing release of the digestive enzymes. These enzymes then split the organic substances with which they come in contact into small, highly diffusible substances such as amino acids and glucose.

- Peroxisomes

Peroxisomes are similar physically to lysosomes, but they are different in two important ways.

1. *they are believed to be formed by self-replication (or perhaps by budding off from the smooth endoplasmic reticulum) rather than from the Golgi apparatus.*
2. *they contain oxidases rather than hydrolases.*

Several of the oxidases are capable of combining oxygen with hydrogen ions derived from different intracellular chemicals to form hydrogen peroxide (H_2O_2). Hydrogen peroxide is a highly oxidizing substance and 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 alcohola person drinks is detoxified by the peroxisomes of the liver cells in this manner.

- Secretory Vesicles

One of the important functions of many cells is secretion of special chemical 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****. Figure below shows typical secretory vesicles inside pancreatic acinar cells; these vesicles store protein proenzymes (enzymes that are not yet activated). The proenzymes are secreted later 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.*

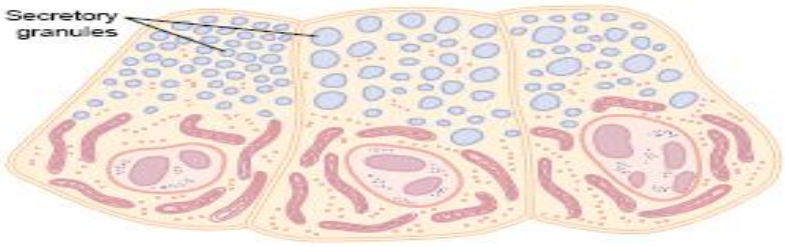


Figure 2–6

Secretory granules (secretory vesicles) in acinar cells of the pancreas.

Mitochondria

The mitochondria, shown in figures below are called the "powerhouses" of the cell. Without them, cells would be unable to extract enough energy from the nutrients, and essentially all cellular functions would cease. Mitochondria are present in all areas of each cell's cytoplasm, but the total number per cell varies from less than a hundred up to several thousand, depending on the amount of energy required by the cell. Further, the mitochondria are concentrated in those portions of the cell that are responsible for the major share of its energy metabolism. They are also variable in size and shape. Some are only a few hundred nanometers in diameter and globular in shape, whereas others are elongated as large as 1 micrometer in diameter and 7 micrometers long; still others are branching and filamentous. Mitochondria are self-replicative, which means that one mitochondrion can form a second one, a third one, and so on, whenever there is a need in the cell for increased amounts of ATP.

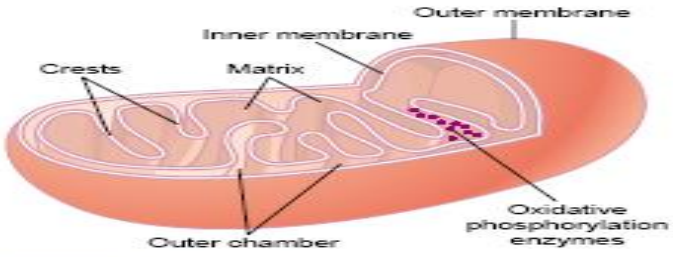


Figure 2–7

Structure of a mitochondrion. (Modified from DeRobertis EDP, Saez FA, DeRobertis EMF: Cell Biology, 6th ed. Philadelphia: WB Saunders, 1975.)

***Cell Cytoskeleton—Filament and Tubular Structures*:-**

The fibrillar proteins of the cell are usually organized into filaments or tubules. These originate as precursor protein molecules synthesized by ribosomes in the cytoplasm. The precursor molecules then polymerize to form filaments

General Cell Structure & Function:-

Component	Structure	Function
Plasma (cell) membrane	Membrane composed of double layer of phospholipids in which proteins are embedded	Surrounds, holds cell together & gives its form; controls passage of materials into & out of cell
Cytoplasm	Fluid, jellylike substance b/w cell membrane & nucleus in which organelles are suspended	Serves as matrix substance in which chemical reactions occur.
Endoplasmic reticulum	System of interconnected membrane-forming canals &	**Agranular** (smooth) ER metabolizes nonpolar compounds & stores Ca^{2+} in

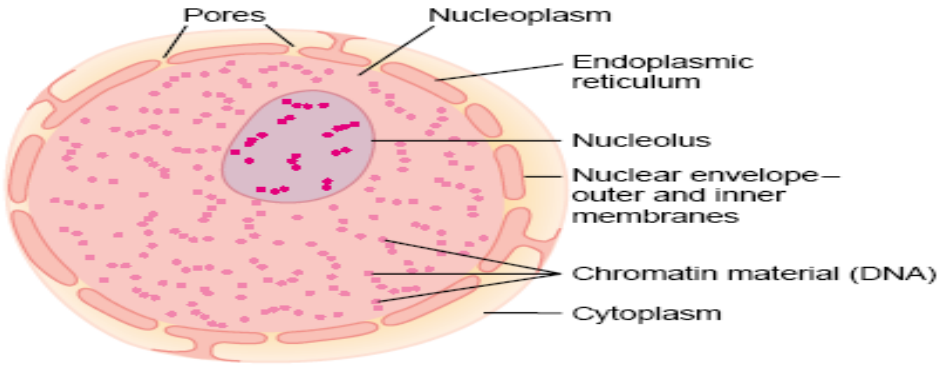
	tubules	striated muscle cells; **granular** (rough) ER assists in protein sysnthesis
Ribosomes	Granular particles composed of protein & RNA	Synthesize proteins
Golgi complex	Cluster of flattened membranous sacs	Synthesizes carbohydrates & packages molecules for secretion. Secretes lipids & glycoproteins
Lysosomes	Membranous sacs	Digest foreign molecules & damaged organelles
Peroxisomes	Spherical membranous vesicles	Contain enzymes that detoxify harmful molecules & break down hydrogen peroxide
Mitochondria	Membranous sacs with folded inner partitions	Release energy from food molecules & transform energy into usable ATP

Dr.Ahmed talib ***lac.2***

Physiology of the cell

Nucleus

The nucleus is the control center of the cell. Briefly, the nucleus contains large quantities of DNA, which are the genes. The genes determine the characteristics of the cell's proteins, including the structural proteins, as well as the intracellular enzymes that control cytoplasmic and nuclear activities. The genes also control and promote reproduction of the cell itself. The genes first reproduce to give two identical sets of genes; then the cell splits by a special process called mitosis to form two daughter cells, each of which receives one of the two sets of DNA genes.



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Nuclear Membrane

The nuclear membrane, also called the nuclear envelope, is actually two separate bilayer membranes, one inside the other. The outer membrane is continuous with the endoplasmic reticulum of the cell cytoplasm, and the space between the two nuclear membranes is also continuous with the space inside the endoplasmic reticulum, as shown in Figure above. The nuclear membrane is penetrated by several thousand nuclear pores.

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 involves simple movement through the membrane caused by the random motion of the molecules of the substance; substances move either through cell membrane pores or, in the case of lipid soluble substances, through the lipid matrix of the membrane. Active transport involves the actual carrying of a substance through the membrane by a physical protein structure that penetrates all the way through the membrane. These active transport mechanisms are so important to cell function.

Very large particles enter the cell by a specialized function of the cell membrane called endocytosis. The principal forms of endocytosis are pinocytosis and phagocytosis. Pinocytosis means ingestion of minute particles that form vesicles of extracellular fluid and particulate constituents inside the cell cytoplasm. Phagocytosis means ingestion of large particles, such as bacteria, whole cells, or portions of degenerating tissue.

- Pinocytosis.

Pinocytosis occurs continually in the cell membranes of most cells, but it is especially rapid in some cells. For instance, it occurs so rapidly in macrophages that about 3 percent of the total macrophage membrane is engulfed in the form of vesicles each minute. Even so, the pinocytotic vesicles are so small usually only 100 to 200 nanometers in diameter that most of them can be seen only with the electron microscope. Pinocytosis is the only means by which most large macromolecules, such as most protein molecules, can enter cells. In fact, the rate at which pinocytotic vesicles form is usually enhanced when such macromolecules attach to the cell membrane.

Figure 2-11 demonstrates the successive steps of pinocytosis, showing three molecules of protein attaching to the membrane. 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. The receptors generally are concentrated in small pits on the outer surface of the cell membrane, called ***coated pits***. On the inside of the cell membrane beneath these pits is a latticework of fibrillar protein called ***clathrin,*** as well as other proteins, perhaps including contractile filaments of *actin* and *myosin*. Once the protein molecules have bound with the receptors, the surface properties of the local membrane change in such a way that the entire pit invaginates inward and the fibrillar proteins surrounding the invaginating pit cause its borders to close over the attached proteins, as well as over a small amount of extracellular fluid. Immediately thereafter, the invaginated portion of the membrane breaks away from the surface of the cell, forming a ***pinocytotic vesicle*** inside the cytoplasm of the cell.

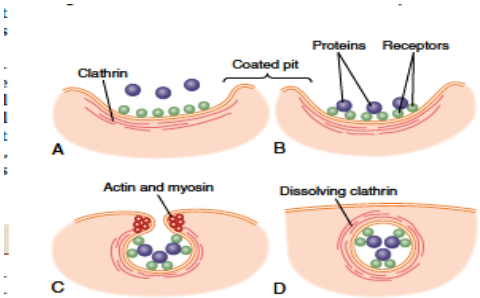


Figure 2-11 Mechanism of pinocytosis.

- Phagocytosis.

Phagocytosis occurs in much the same way as pinocytosis, except that it involves large particles rather than molecules. Only certain cells have the capability of phagocytosis, most notably the tissue macrophages and some of the white blood cells. Phagocytosis is initiated when a particle such as a bacterium, a dead cell, or tissue debris binds with receptors on the surface of the phagocyte. In the case of bacteria, each bacterium 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. This intermediation of antibodies is called opsonization.

Phagocytosis occurs in the following steps:

1. The cell membrane receptors attach to the surface ligands of the particle.

2. The edges of the membrane around 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 occurs suddenly in a zipper-like manner to form a closed phagocytic vesicle.

3. Actin and other contractile fibrils in the cytoplasm surround the phagocytic vesicle and contract around its outer edge, pushing the vesicle to the interior.

4. The contractile proteins then pinch the stem of the vesicle so completely that the vesicleseparates from the cell membrane, leaving the vesicle in the cell interior in the same way that pinocytotic vesicles are formed.

Transport of substances through the cell membrane

Figure below gives the approximate concentrations of important electrolytes and other substances in the extracellular fluid and intracellular fluid. Note that the extracellular fluid contains a large amount of sodium but only a small amount of potassium. Exactly the opposite is true of the intracellular fluid. Also, the extracellular fluid contains a large amount of chloride ions, whereas the intracellular fluid contains very little. But the concentrations of phosphates and proteins in the intracellular fluid are considerably greater than those in the extracellular fluid. These differences are extremely important to the life of the cell.

The lipid barrier of the cell membrane, and cell membrane transport proteins.

The structure of the membrane covering the outside of every cell of the body is discussed previously, This membrane consists almost entirely of a lipid bilayer, but it also contains large numbers of protein molecules in the lipid, many of which penetrate all the way through the membrane, as shown in figure below. The lipid bilayer is not miscible with either the extracellular fluid or the intracellular fluid. Therefore, it constitutes a barrier against movement of water molecules and water-soluble substances between the extracellular and intracellular fluid compartments. However, as demonstrated below by the leftmost arrow, a few substances can penetrate this lipid bilayer, diffusing directly through the lipid substance itself; this is true mainly of lipid-soluble substances. The protein molecules in the membrane have entirely different properties for transporting substances. Their molecular structures interrupt the continuity of the lipid bilayer, constituting an alternative pathway through the cell membrane. Most of these penetrating proteins, therefore, can function as transport proteins. Different proteins function differently. Some have watery spaces all the way through the molecule and allow free movement of water as well as selected ions or molecules; these are called ***channel proteins****. Others, called* ***carrier proteins****, bind with molecules or ions that are to be transported; conformational changes in the protein molecules then move the substances through the interstices of the protein to the other side of the membrane. Both the channel proteins and the carrier proteins are usually highly selective in the types of molecules or ions that are allowed to cross the membrane.*

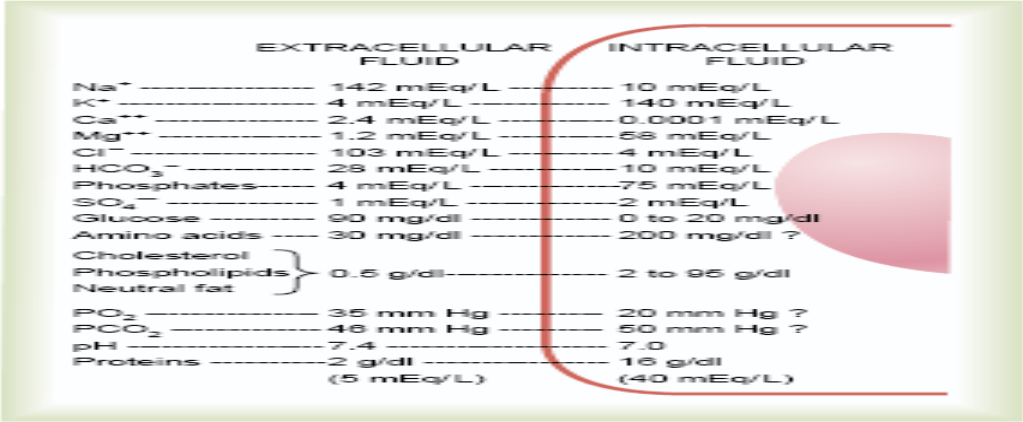


Figure 4–1

Chemical compositions of extracellular and intracellular fluids.

Diffusion versus active transport.

Transport through the cell membrane, either directly through the lipid bilayer or through the proteins, occurs by one of two basic processes: ***diffusion*** *or* ***active transport****. Although there are many variations of these*

basic mechanisms, diffusion means random molecular movement of substances molecule by molecule, either through intermolecular spaces in the membrane or in combination with a carrier protein. The energy that causes diffusion is the energy of the normal kinetic motion of matter. By contrast, active transport means movement of ions or other substances across the membrane in combination with a carrier protein in such a way that the carrier protein causes the substance to move against an energy gradient, such as from a low-concentration state to a high-concentration state. This movement requires an additional source of energy besides kinetic energy.

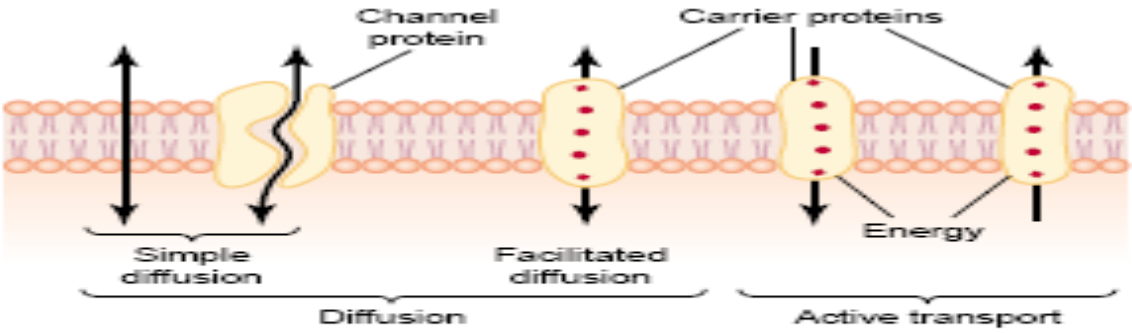


Figure 4–2

Transport pathways through the cell membrane, and the basic mechanisms of transport.

Diffusion.

All molecules and ions in the body fluids, including water molecules and dissolved substances, are in constant motion, each particle moving its own separate way. Motion of these particles is what physicists call "heat" the greater the motion, the higher the temperature and the motion never ceases under any condition except at ***absolute zero temperature****. When a moving molecule, A, approaches a stationary molecule, B, the electrostatic and other nuclear forces of molecule A repel molecule B, transferring some of the energy of motion of molecule A to molecule B. Consequently, molecule B gains kinetic energy of motion, while molecule A slows down, losing some of its kinetic energy. Thus, a single molecule in a solution bounces among the other molecules first in one direction, then another, then another, and so forth, randomly bouncing thousands of times each second.* ***This continual movement of molecules among one another in liquids or in gases is called diffusion****. Ions diffuse in the same manner as whole molecules, and even suspended colloid particles diffuse in a similar manner, except that the colloids diffuse far less rapidly than molecular substances because of their large size.*

Diffusion through the cell membrane.

Diffusion through the cell membrane is divided into two subtypes called ***simple diffusion*** *and* ***facilitated diffusion. Simple diffusion*** *means that kinetic movement of molecules or ions occurs through a membrane opening or through intermolecular spaces without any interaction with carrier proteins in the membrane. The rate of diffusion is determined by the amount of substance available, the velocity of kinetic motion, and the number and sizes of openings in the membrane through which the molecules or ions can move.* ***Facilitated diffusion*** *requires interaction of a carrier protein. The carrier protein aids passage of the molecules or ions through the membrane by binding chemically with them and shuttling them through the membrane in this form. Simple diffusion can occur through the cell membrane by two pathways:*

(1) Through the interstices of the lipid bilayer if the diffusing substance is lipid soluble.

(2) Through watery channels that penetrate all the way through some of the large transport proteins, as shown to the left in the same figure above.

Diffusion of lipid-soluble substances through the lipid bilayer.

One of the most important factors that determines how rapidly a substance diffuses through the lipid bilayer is the lipid solubility of the substance. For instance, the lipid solubilities of oxygen, nitrogen, carbon dioxide, and alcohols are high, so that all these can dissolve directly in the lipid bilayer and diffuse through the cell

membrane in the same manner that diffusion of water solutes occurs in a watery solution. For obvious reasons, the rate of diffusion of each of these substances through the membrane is directly proportional to its lipid solubility. Especially large amounts of oxygen can be transported in this way; therefore, oxygen can be delivered to the interior of the cell almost as though the cell membrane did not exist.

Diffusion of water and other lipid-insoluble molecules through protein channels.

Even though water is highly insoluble in the membrane lipids, it readily passes through channels in protein molecules that penetrate all the way through the membrane. The rapidity with which water molecules can move through most cell membranes is astounding. As an example, the total amount of water that diffuses in each direction through the red cell membrane during each second is about 100 times as great as the volume of the red cell itself. Other lipid-insoluble molecules can pass through the protein pore channels in the same way as water molecules if they are water soluble and small enough. However, as they become larger, their penetration falls off rapidly. For instance, the diameter of the urea molecule is only 20 per cent greater than that of water, yet its penetration through the cell membrane pores is about 1000 times less than that of water. Even so, given the astonishing rate of water penetration, this amount of urea penetration still allows rapid transport of urea through the membrane within minutes.

Diffusion through protein channels, and gating of these channels.

Computerized three-dimensional reconstructions of protein channels have demonstrated tubular pathways all the way from the extracellular to the intracellular fluid. Therefore, substances can move by simple diffusion directly along these channels from one side of the membrane to the other. The protein channels are distinguished by two important characteristics:

(1) They are often selectively permeable to certain substances

(2) Many of the channels can be opened or closed by gates.

- Selective permeability of protein channels.

Many of the protein channels are highly selective for transport of one or more specific ions or molecules. This results from the characteristics of the channel itself, such as its diameter, its shape, and the nature of the electrical charges and chemical bonds along its inside surfaces. To give an example, one of the most important of the protein channels, the so called sodium channel, is only 0.3 by 0.5 nanometer in diameter, but more important, the inner surfaces of this channel are strongly negatively charged, as shown by the negative signs inside the channel proteins in the top panel of Figure below. These strong negative charges can pull small dehydrated sodium ions into these channels, actually pulling the sodium ions away from their hydrating water molecules. Once in the channel, the sodium ions diffuse in either direction according to the usual laws of diffusion. Thus, the sodium channel is specifically selective for passage of sodium ions. Conversely, another set of protein channels is selective for potassium transport, shown in the lower panel of figure below. These channels are slightly smaller than the sodium channels, only 0.3 by 0.3 nanometer, but they are not negatively charged, and their chemical bonds are different. Therefore, no strong attractive force is pulling ions into the channels, and the potassium ions are not pulled away from the water molecules that hydrate them. The hydrated form of the potassium ion is considerably smaller than the hydrated form of sodium because the sodium ion attracts far more water molecules than does potassium. Therefore, the smaller hydrated potassium ions can pass easily through this small channel, whereas the larger hydrated sodium ions are rejected, thus providing selective permeability for a specific ion.

- Gating of protein channels.

Gating of protein channels provides a means of controlling ion permeability of the channels. This is shown in both panels of figure below for selective gating of sodium and potassium ions. It is believed that some of the gates are actual gate like extensions of the transport protein molecule, which can close the opening of the channel or can be lifted away from the opening by a conformational change in the shape of the protein molecule itself. The opening and closing of gates are controlled in two principal ways:

1. Voltage gating.

In this instance, the molecular conformation of the gate or of its chemical bonds responds to the electrical potential across the cell membrane. For instance, in the top panel of figure below, when there is a strong negative charge on the inside of the cell membrane, this presumably could cause the outside sodium gates to remain tightly closed; conversely, when the inside of the membrane loses its negative charge, these gates would open suddenly and allow tremendous quantities of sodium to pass inward through the sodium pores. This is the basic mechanism for eliciting action potentials in nerves that are responsible for nerve signals. In the bottom panel of figure, the potassium gates are on the intracellular ends of the potassium channels, and they open when the inside of the cell membrane becomes positively charged. The opening of these gates is partly responsible for terminating the action potential.

2. Chemical (ligand) gating.

Some protein channel gates are opened by the binding of a chemical substance (a ligand) with the protein; this causes a conformational or chemical bonding change in the protein molecule that opens or closes the gate. This is called chemical gating or ligand gating. One of the most important instances of chemical gating is the effect of ***acetylcholine*** *on the so-called acetylcholine channel. Acetylcholine opens the gate of this channel, providing a negatively charged pore about 0.65 nanometer in diameter that allows uncharged molecules or positive ions smaller than this diameter to pass through. This gate is exceedingly important for the transmission of nerve signals from one nerve cell to another and from nerve cells to muscle cells to cause muscle contraction.*

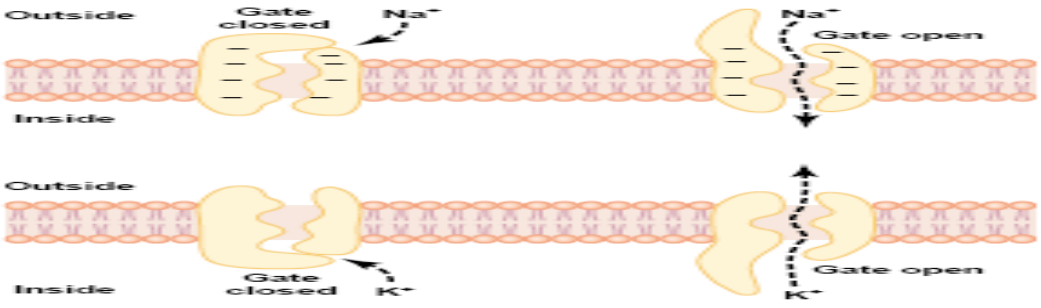


Figure 4–4

Transport of sodium and potassium ions through protein channels. Also shown are conformational changes in the protein molecules to open or close "gates" guarding the channels.

Facilitated diffusion.

Facilitated diffusion is also called ***carrier-mediated diffusion*** *because a substance transported in this manner diffuses through the membrane using a specific carrier protein to help. That is, the carrier facilitates diffusion of the substance to the other side. Facilitated diffusion differs from simple diffusion in the following important way: Although the rate of simple diffusion through an open channel increases proportionately with the concentration of the diffusing substance, in facilitated diffusion the rate of diffusion approaches a maximum, called V_{max}, as the concentration of the diffusing substance increases. This difference between simple diffusion and facilitated diffusion is demonstrated as the concentration of the diffusing substance increases, the rate of simple diffusion continues to increase proportionately, but in the case of facilitated diffusion, the rate of diffusion cannot rise greater than the V_{max}level.*

Factors that affect net rate of diffusion.

By now it is evident that many substances can diffuse through the cell membrane. What is usually important is the net rate of diffusion of a substance in the desired direction. This net rate is determined by several factors.

1. Effect of concentration difference on net diffusion through a membrane.

If a cell membrane with a substance in high concentration on the outside and low concentration on the inside., The rate at which the substance diffuses inward is proportional to the concentration of molecules on the outside, because this concentration determines how many molecules strike the outside of the membrane each second. Conversely, the rate at which molecules diffuse outward is proportional to their concentration

inside the membrane. Therefore, the rate of net diffusion into the cell is proportional to the concentration on the outside minus the concentration on the inside.

2. Effect of a pressure difference across the membrane.

At times, considerable pressure difference develops between the two sides of a diffusible membrane. This occurs, for instance, at the blood capillary membrane in all tissues of the body. The pressure is about 20 mm Hg greater inside the capillary than outside. Pressure actually means the sum of all the forces of the different molecules striking a unit surface area at a given instant. Therefore, when the pressure is higher on one side of a membrane than on the other, this means that the sum of all the forces of the molecules striking the channels on that side of the membrane is greater than on the other side. In most instances, this is caused by greater numbers of molecules striking the membrane per second on one side than on the other side. The result is that increased amounts of energy are available to cause net movement of molecules from the high-pressure side toward the low-pressure side.

3- Effect of Membrane Electrical Potential on Diffusion of Ions—The "Nernst Potential."

If an electrical potential is applied across the membrane, the electrical charges of the ions cause them to move through the membrane even though no concentration difference exists to cause movement. At normal body temperature (37°C), the electrical difference that will balance a given concentration difference of univalent ions such as sodium (Na^+) ions—can be determined from the following formula, called the Nernst equation:

$$\text{EMF (in millivolts)} = \pm 61 \log \frac{C_1}{C_2}$$

Osmosis across selectively permeable membranes—"Net Diffusion" of Water

By far the most abundant substance that diffuses through the cell membrane is water. Enough water ordinarily diffuses in each direction through the red cell membrane per second to equal about 100 times the volume of the cell itself. Yet, normally, the amount that diffuses in the two directions is balanced so precisely that zero net movement of water occurs. Therefore, the volume of the cell remains constant. However, under certain conditions, a concentration difference for water can develop across a membrane, just as concentration differences for other substances can occur. When this happens, net movement of water does occur across the cell membrane, causing the cell either to swell or to shrink, depending on the direction of the water movement. ***This process of net movement of water caused by a concentration difference of water is called osmosis.*** *To give an example of osmosis, let us assume the conditions shown in figure below, with pure water on one side of the cell membrane and a solution of sodium chloride on the other side. Water molecules pass through the cell membrane with ease, whereas sodium and chloride ions pass through only with difficulty. Therefore, sodium chloride solution is actually a mixture of permeant water molecules and nonpermeant sodium and chloride ions, and the membrane is said to be selectively permeable to water but much less so to sodium and chloride ions. Yet the presence of the sodium and chloride has displaced some of the water molecules on the side of the membrane where these ions are present and, therefore, has reduced the concentration of water molecules to less than that of pure water. As a result, in the example of figure below, more water molecules strike the channels on the left side, where there is pure water, than on the right side, where the water concentration has been reduced. Thus, net movement of water occurs from left to right—that is, osmosis occurs from the pure water into the sodium chloride solution.*

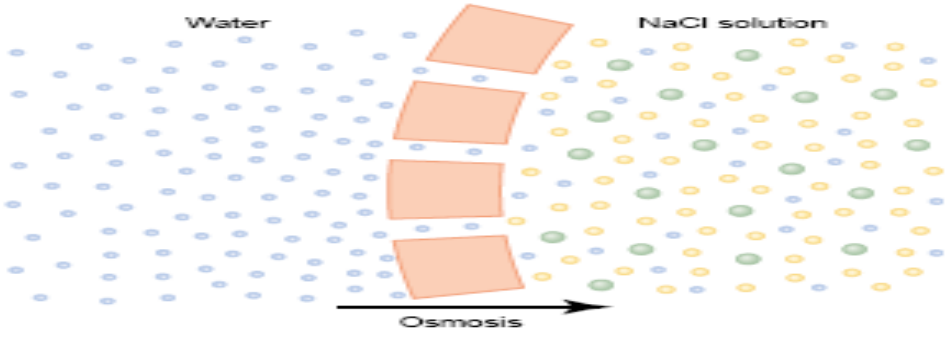
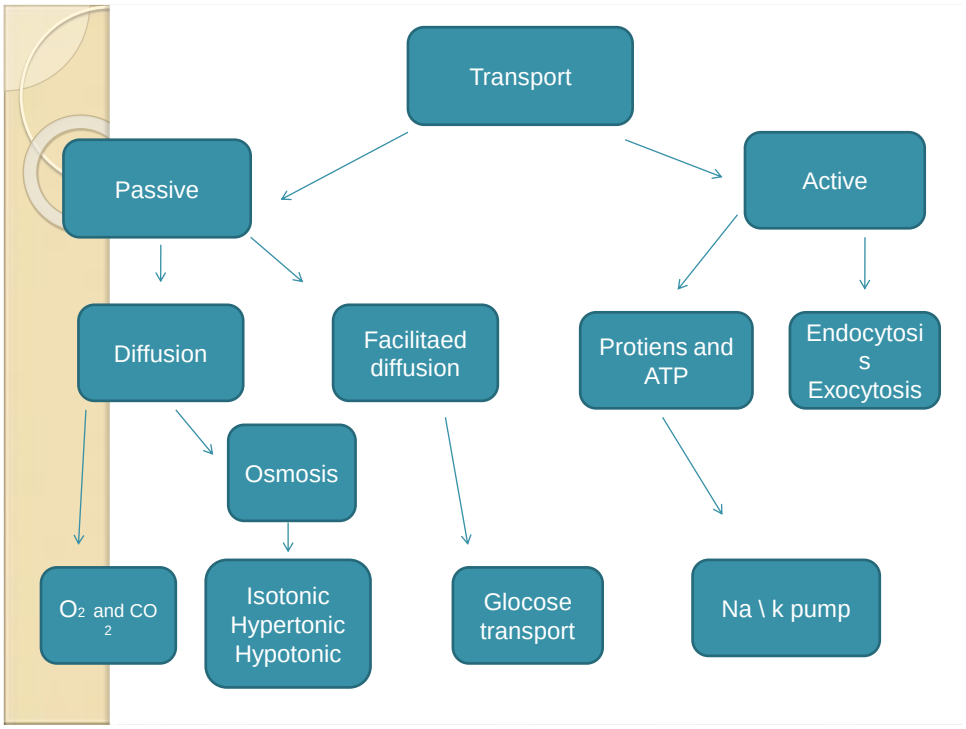


Figure 4–9

Osmosis at a cell membrane when a sodium chloride solution is placed on one side of the membrane and water is placed on the other side.



Physiology of the cell

Dr. Ahmed Talib Lec.3

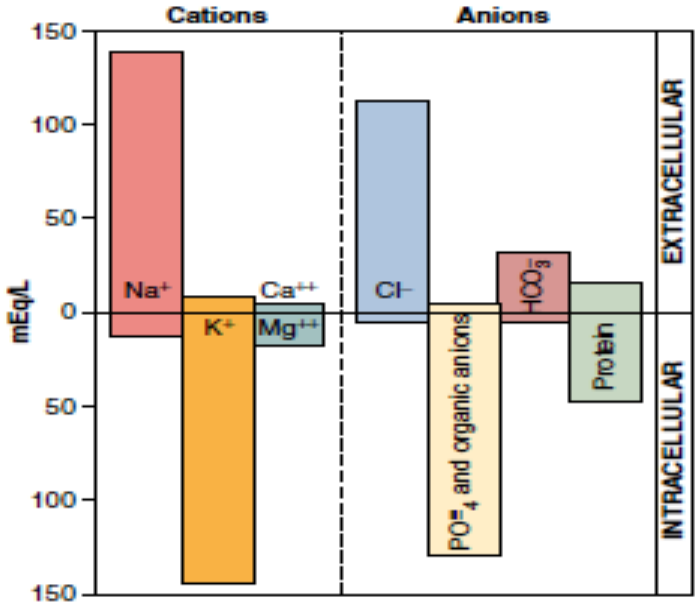
Important constituents Of Extracellular fluid:-

The extracellular fluid, including the plasma and the interstitial fluid, contains large amounts of sodium and chloride ions, reasonably large amounts of bicarbonate ions, but only small quantities of potassium, calcium, magnesium, phosphate, and organic acid ions. This allows the cells to remain continually bathed in a fluid that contains the proper concentration of electrolytes and nutrients for optimal cell function.

Important Constituents of the Intracellular Fluid :-

The intracellular fluid is separated from the extracellular fluid by a cell membrane that is highly permeable to water but not to most of the electrolytes in the body. In contrast to the extracellular fluid, the intracellular fluid contains ions ***large amounts of potassium and phosphate ions plus moderate quantities of magnesium and sulfate ions. Also, cells contain large amounts of***

protein, almost four times as much as in the plasma. only ***small quantities of sodium and chloride ions and*** almost **no calcium.**



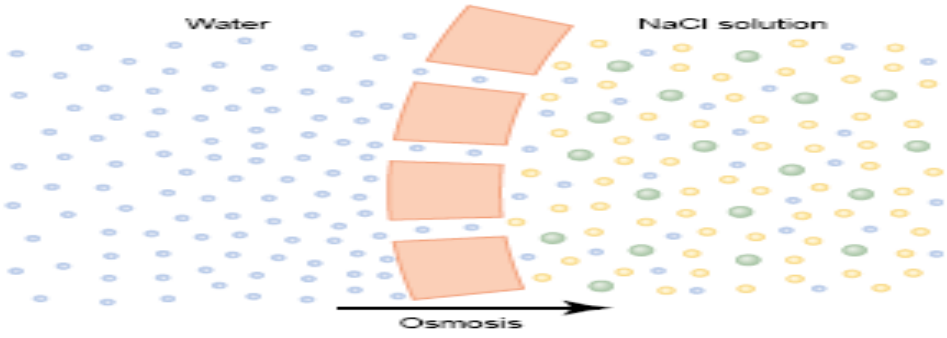


Figure 4–9

Osmosis at a cell membrane when a sodium chloride solution is placed on one side of the membrane and water is placed on the other side.

Osmotic pressure.

If in figure above pressure were applied to the sodium chloride solution, osmosis of water into this solution would be slowed, stopped, or even reversed. The exact amount of pressure required to stop osmosis is called the osmotic pressure of the sodium chloride solution The principle of a pressure difference opposing osmosis is demonstrated in figure below, which shows a selectively permeable membrane separating two columns of fluid, one containing pure water and the other containing a solution of water and any solute that will not penetrate the membrane. Osmosis of water from chamber B into chamber A causes the levels of the fluid columns to become farther and farther apart, until eventually a pressure difference develops between the two sides of the membrane great enough to oppose the osmotic effect. The pressure difference across the membrane at this point is equal to the osmotic pressure of the solution that contains the non diffusible solute.

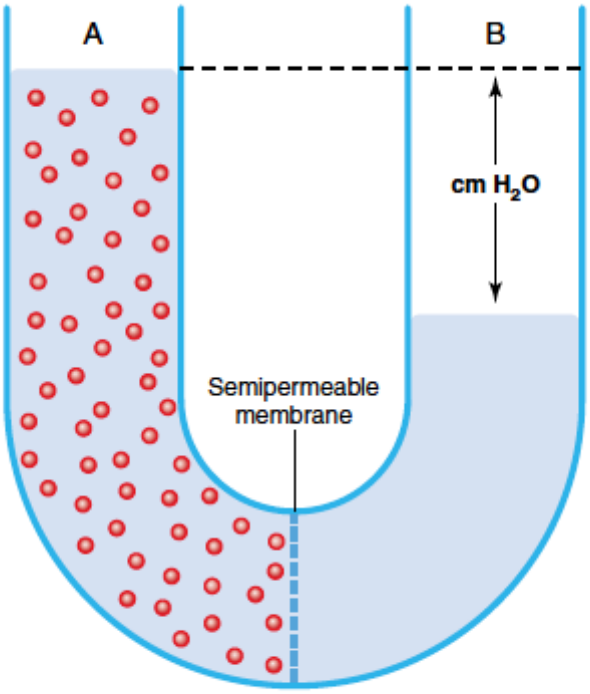


Figure 4-11 Demonstration of osmotic pressure caused by osmosis at a semipermeable membrane.

Basic Principles of Osmosis and Osmotic Pressure :-

Osmosis is the net diffusion of water across a selectively permeable membrane from a region of high water concentration to one that has a lower water concentration. When a solute is added to pure water, this reduces the concentration of water in the mixture. Thus, the higher the solute concentration in a solution, the lower the water concentration. Further, water diffuses from a region of low solute concentration (high water concentration) to one with a high solute concentration (low water concentration). Thus, if a solute such as sodium chloride is added to the extracellular fluid, water rapidly diffuses from the cells through the cell membranes into the extracellular fluid until the water concentration on both sides of the membrane becomes equal. Conversely, if a solute such as sodium chloride is removed from the extracellular fluid, water diffuses from the extracellular fluid through the cell membranes and into the cells. The rate of diffusion of water is called the rate of osmosis.

Importance of Number of Osmotic Particles (Molar Concentration) in Determining Osmotic Pressure:-

The osmotic pressure exerted by particles in a solution, whether they are molecules or ions, is determined by the number of particles per unit volume of fluid, not by the mass of the particles. The reason for this is that each particle in a solution, regardless of its mass, exerts, on average, the same amount of pressure against the membrane. That is, large particles, which have greater mass (m) than small particles, move at slower velocities (v). The small particles move at higher velocities in such a way that their average kinetic energies

$$k=\frac{mv^2}{2}$$

(k), determined by the equation n
are the same for each small particle as for each large particle. Consequently, the factor that determines the osmotic pressure of a solution is the concentration of the solution in terms of number of particles (which is the same as its molar concentration if it is a nondissociated molecule), not in terms of mass of the solute.

"Osmolality"—the osmole:-

To express the concentration of a solution in terms of numbers of particles, the unit called the ***osmole*** *is used in place of grams. One osmole is 1 gram molecular weight of osmotically active solute. Thus, 180 grams of glucose, which is 1 gram molecular weight of glucose, is equal to 1osmole of glucose because glucose does not dissociate into ions. Conversely, if a solute dissociates into two ions, 1 gram molecular weight of the*

solute will become 2 osmoles because the number of osmotically active particles is now twice as great as is the case for the non-dissociated solute. Therefore, when fully dissociated,1 gram molecular weight of sodium chloride,58.5 grams, is equal to 2 osmoles. Thus, a solution that has 1 osmole of solute dissolved in each kilogram of water is said to have an osmolality of 1 osmole per kilogram, and a solution that has1/1000 osmole dissolved per kilogram has an osmolality of 1 milliosmole per kilogram. The normal osmolality of the extracellular and intracellular fluids is about 300 milliosmoles per kilogram of water.

Relation of osmolality to osmotic pressure.

At normal body temperature, 37°C, a concentration of 1 osmole perliter will cause 19,300 mm Hg osmotic pressure in the solution. Likewise, 1 milliosmole per liter concentrationis equivalent to 19.3 mm Hg osmotic pressure. Multiplying this value by the 300 milliosmolar concentration of the body fluids gives a total calculated osmotic pressure of the body fluids of 5790 mm Hg.

The measured value for this, however, averages only about 5500 mm Hg. The reason for this difference is that many of the ions in the body fluids, such as sodium and chloride ions, are highly attracted to one another; consequently, they cannot move entirely unrestrained in the fluids and create their full osmotic pressure potential. Therefore, on average, the actual osmotic pressure of the body fluids is about 0.93 times the calculated value.

Relation Between Moles and Osmoles :-

the water concentration of a solution depends on the number of solute particles in the solution. The total number of particles in a solution is measured in ***osmoles.*** *One osmole (osm) is equal to 1 mole (mol)* (6.02×10^{23}) *of solute particles. a solution containing 1 mole of glucose in each liter has a concentration of 1 osm/L. Thus, the term osmole refers to the number of osmotically active particles in a solution rather than to the molar concentration. The term* ***milliosmole (mOsm), which equals 1/1000 osmole,*** *is commonly used.*

Osmolality and Osmolarity :-

The osmolal concentration of a solution is called ***osmolality when the concentration is expressed as osmoles per kilogram of water;*** *it is called* ***osmolarity when it is expressed as osmoles per liter of solution.***

The term Osmolarity.

Because of the difficulty of measuring kilograms of water in a solution, which is required to determine osmolality, osmolarity, which is the osmolar concentration expressed as osmoles per liter of solution rather than osmoles per kilogram of water, is used instead. Although, strictly speaking, it is osmoles per kilogram of water (osmolality) that determines osmotic pressure, for dilute solutions such as those in the body, the quantitative differences between osmolarity and osmolality are less than 1 per cent. Because it is far more practical to measure osmolarity than osmolality, this is the usual practice in almost all physiologic studies.

Active transport of Substances through membranes.

At times, a large concentration of a substance is required in the intracellular fluid even though the extracellular fluid contains only a small concentration. This is true, for instance, for potassium ions. Conversely, it is important to keep the concentrations of other ions very low inside the cell even though their concentrations in the extracellular fluid are great. This is especially true for sodium ions. Neither of these two effects could occur by simple diffusion, because simple diffusion eventually equilibrates concentrations on the two sides of the membrane. Instead, some energy source must cause excess movement of potassium ions to the inside of cells and excess movement of sodium ions to the outside of cells. When a cell membrane moves molecules or ions "uphill" against a concentration gradient (or "uphill" against an electrical or pressure gradient), the process is called ***active transport****. Different substances that are actively transported through at least some cell membranes include sodium ions, potassium ions, calcium ions, iron ions, hydrogen ions, chloride ions, iodide ions, urate ions, several different sugars, and most of the amino acids.*

Primary active transport and secondary active transport.

*Active transport is divided into two types according to the source of the energy used to cause the transport: primary active transport and secondary active transport. In **primary active transport**, the energy is derived directly from breakdown of adenosine triphosphate (ATP) or of some other high-energy phosphate compound. In **secondary active transport**, the energy is derived secondarily from energy that has been stored in the form of ionic concentration differences of secondary molecular or ionic substances between the two sides of a cell membrane, created originally by primary active transport. In both instances, transport depends on carrier proteins that penetrate through the cell membrane, as is true for facilitated diffusion. However, in active transport, the carrier protein functions differently from the carrier in facilitated diffusion because it is capable of imparting energy to the transported substance to move it against the electrochemical gradient. Following are some examples of primary active transport and secondary active transport, with more detailed explanations of their principles of function.*

Primary active transport.

Sodium-potassium pump.

*Among the substances that are transported by primary active transport are sodium, potassium, calcium, hydrogen, chloride, and a few other ions. The active transport mechanism that has been studied in greatest detail is the sodium-potassium (Na^+-K^+) pump, a transport process that pumps sodium ions outward through the cell membrane of all cells and at the same time pumps potassium ions from the outside to the inside. This pump is responsible for maintaining the sodium and potassium concentration differences across the cell membrane, as well as for establishing a negative electrical voltage inside the cells. Figure below shows the basic physical components of the Na^+-K^+ pump. The carrier protein is a complex of two separate globular proteins: a larger one called the **α** subunit, with a molecular weight of about 100,000, and a smaller one called the **ß** subunit, with a molecular weight of about 55,000. Although the function of the smaller protein is not known (except that it might anchor the protein complex in the lipid membrane), the larger protein has three specific features that are important for the functioning of the pump:*

1. It has three receptor sites for binding sodium ions on the portion of the protein that protrudes to the inside of the cell.

2. It has two receptor sites for potassium ions on the outside.

3. The inside portion of this protein near the sodium binding sites has ATPase activity.

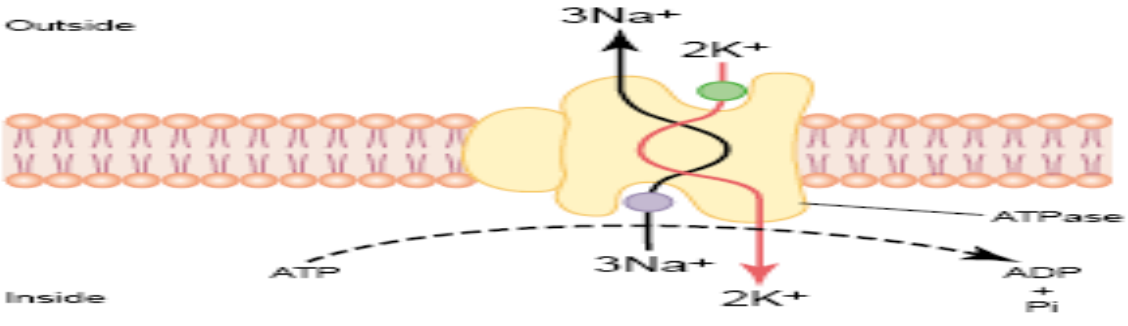


Figure 4–11

Postulated mechanism of the sodium-potassium pump. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Pi, phosphate ion.

Importance of the Na^+-K^+pump for controlling cell volume.

One of the most important functions of the Na^+-K^+ pump is to control the volume of each cell. Without function of this pump, most cells of the body would swell until they burst. The mechanism for controlling the volume is as follows: Inside the cell are large numbers of proteins and other organic molecules that cannot escape from the cell. Most of these are negatively charged and therefore attract large numbers of potassium, sodium, and other positive ions as well. All these molecules and ions then 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. Note again that this device 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 net loss of ions out of the cell, which initiates osmosis of water out of the cell as well. 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.

Primary active transport of calcium ions

Another important primary active transport mechanism is the calcium pump. Calcium ions are normally maintained at extremely low concentration in the intracellular cytosol of virtually all cells in the body, at a 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 intracellular vesicular organelles of the cell, such as the sarcoplasmic reticulum of muscle cells and the mitochondria in all cells. In each of these instances, the carrier protein penetrates the membrane and functions as an enzyme ATPase, having the same capability to cleave ATP as the ATPase of the sodium carrier protein. The difference is that this protein has a highly specific binding site for calcium instead of for sodium.

Primary Active Transport of Hydrogen Ions:-

At two places in the body, primary active transport of hydrogen ions is important: (1) in the gastric glands of the stomach and (2) 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 ends of the gastric gland parietal cells, the hydrogen ion concentration is increased as much as a millionfold and then released into the stomach along with chloride ions to form hydrochloric acid. In the renal tubules 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 from the blood into the urine for the purpose of eliminating excess hydrogen ions from the body fluids. The hydrogen ions can be secreted into the urine against a concentration gradient of about 900-fold.

Secondary active transport— Co-Transport and Counter-Transport

When sodium ions are transported out of cells by primary active transport, a large concentration gradient of sodium ions across the cell membrane usually develops—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 appropriate conditions, this diffusion energy of sodium can 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, 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.*

***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 to the exterior surface of the membrane, while the substance to be counter-transported binds to the interior projection of the carrier protein. Once both have bound, a conformational change occurs, and energy released by the sodium ion moving to the interior causes the other substance to move to the exterior.*

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 co-transport, as shown in Figure below Note that 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 high on the outside and low inside, which provides energy for the transport. A special property of the transport protein is that a conformational change to allow sodium movement to the interior will not occur until a glucose molecule also attaches. When they both become attached, the conformational change takes place automatically, and the sodium and glucose are transported to the inside of the cell at the same time. Hence, this is a sodium-glucose co-transport mechanism. Sodium-glucose co-transporters are especially important mechanisms in transporting glucose across renal and intestinal epithelial cells . 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 through the epithelial cells of the intestinal tract and the renal tubules of the kidneys to promote absorption of these substances into the blood .Other important co-transport mechanisms in at least some cells include co-transport of chloride ions, iodine ions, iron ions, and urate ions.

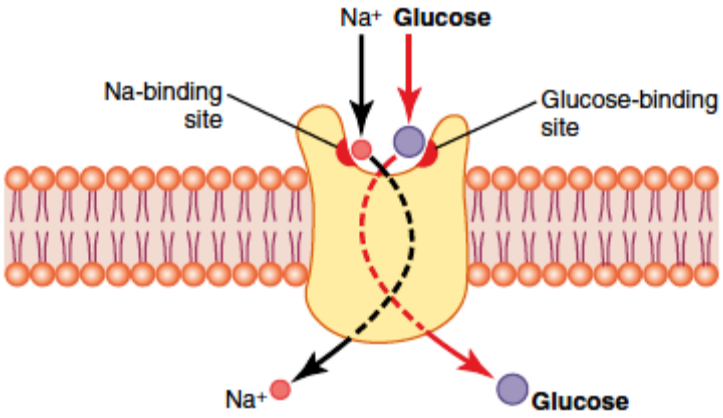


Figure 4-13 Postulated mechanism for sodium co-transport of glucose.

Sodium Counter-Transport of Calcium and Hydrogen Ions:-

Two especially important counter-transport mechanisms (transport in a direction opposite to the primary ion) are sodium-calcium counter-transport and sodium-hydrogen counter-transport Figure belew. Sodium-calcium counter-transport occurs through all or almost all cell membranes, with sodium ions moving to 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. 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 cell, while hydrogen ions are counter-transported into the tubule lumen. As a mechanism for concentrating hydrogen ions, counter-transport is not nearly as powerful as the primary active transport of hydrogen ions that occurs in the more distal renal tubules, but it can transport extremely large numbers of hydrogen ions, thus making it a key to hydrogen ion control in the body fluids.

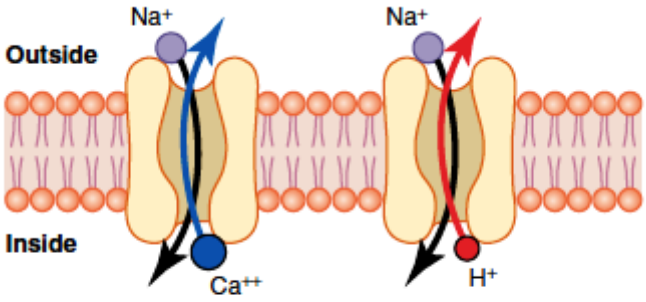
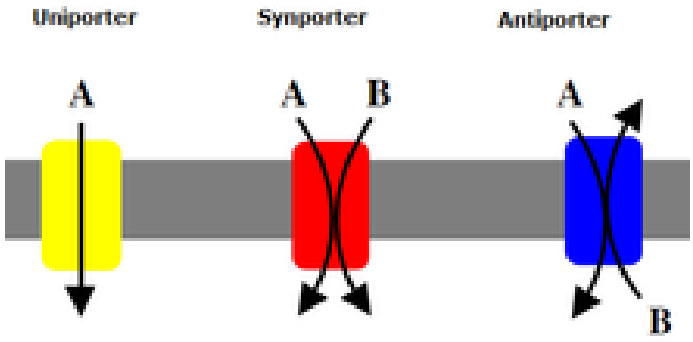


Figure 4-14 Sodium counter-transport of calcium and hydrogen ions.



Active transport through cellular sheets.

At many places in the body, substances must be transported all the way through a cellular sheet instead of simply through the cell membrane. Transport of this type occurs through the

(1) Intestinal epithelium.

(2)Epithelium of the renal tubules.

(3) Epithelium of all exocrine glands.

(4) Epithelium of the gallbladder.

(5) Membrane of the choroid plexus of the brain and other membranes.

The basic mechanism for transport of a substance through a cellular sheet is:

(1) Active transport through the cell membrane on one side of the transporting cells in the sheet.

(2) Either simple diffusion or facilitated diffusion through the membrane on the opposite side of the cell.

The brush border on the luminal surfaces of the cells is permeable to both sodium ions and water. Therefore, sodium and water diffuse readily from the lumen into the interior of the cell. Then, at the basal and lateral membranes of the cells, sodium ions are actively transported into the extracellular fluid of the surrounding connective tissue and blood vessels. This creates a high sodium ion concentration gradient across these membranes, which in turn causes osmosis of water as well. Thus, active transport of sodium ions at the basolateral sides of the epithelial cells results in transport not only of sodium ions but also of water. These are the mechanisms by which almost all the nutrients, ions, and other substances are absorbed into the blood from the intestine; they are also the way the same substances are reabsorbed from the glomerular filtrate by the renal tubules.

Active transport through cellular sheets

Mechanism:

1) Active transport occurs on one side of transporting cells in the sheet & then

2) Either simple diffusion or facilitated diffusion through the membrane on opposite side of cell.

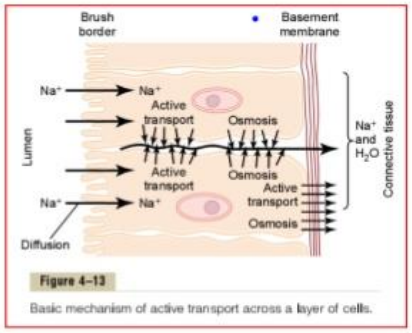


Figure 4–13
Basic mechanism of active transport across a layer of cells.

Cell Function and Cell Reproduction

Virtually everyone knows that the genes, located in the nuclei of all cells of the body, control heredity from parents to children, but most people do not realize that these same genes also control day-today function of all the body's cells. The genes control cell function by determining which substances are synthesized within the cell—which structures ,which enzymes, which chemicals. Figure below shows the general schema of genetic control. Each gene, which is a nucleic acid called deoxyribonucleic acid (DNA), automatically controls the formation of another nucleic acid, ribonucleic acid (RNA); this RNA then spreads throughout the cell to control the formation of a specific protein. Because there are more than 30,000 different genes in each cell, it is theoretically possible to form a very large number of different cellular proteins.

Some of the cellular proteins are structural proteins, which, in association with various lipids and carbohydrates, form the structures of the various intracellular organelles. However, by far the majority of the proteins are enzymes that catalyze the different chemical reactions in the cells. For instance, enzymes promote all the oxidative reactions that supply energy to the cell, and they promote synthesis of all the cell chemicals, such as lipids, glycogen ,and adenosine triphosphate (ATP).

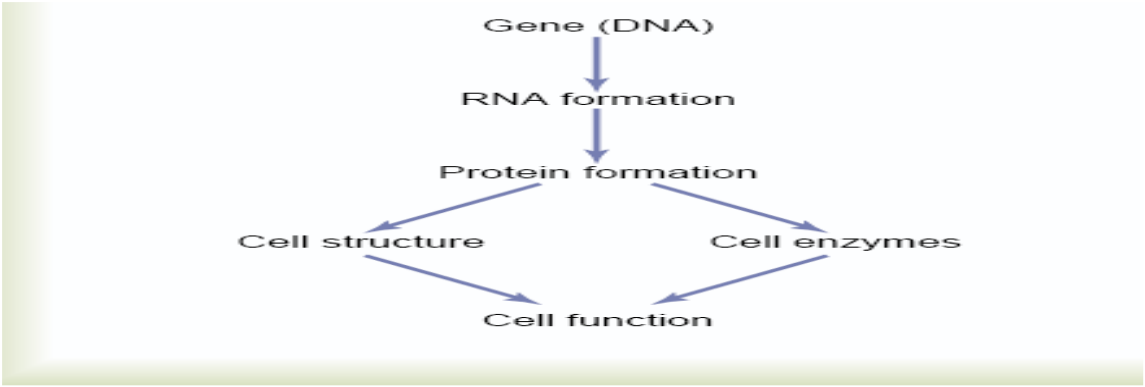


Figure 3–1

General schema by which the genes control cell function.

Genes in the cell nucleus.

In the cell nucleus, large numbers of genes are attached end on end in extremely long double-stranded helical molecules of DNA having molecular weights measured in the billions. A very short segment of a molecule is composed of several simple chemical compounds bound together in a regular pattern.

- Basic building blocks of DNA.

The basic chemical compounds involved in the formation of DNA include:

(1) Phosphoric acid.

(2) A sugar called deoxyribose.

*(3) Four nitrogenous bases (two purines, **adenine** and **guanine**, and two pyrimidines, **thymine** and **cytosine**).*

The phosphoric acid and deoxyribose form the two helical strands that are the backbone of the DNA molecule, and the nitrogenous bases lie between the two strands and connect them, as illustrated in figure below.

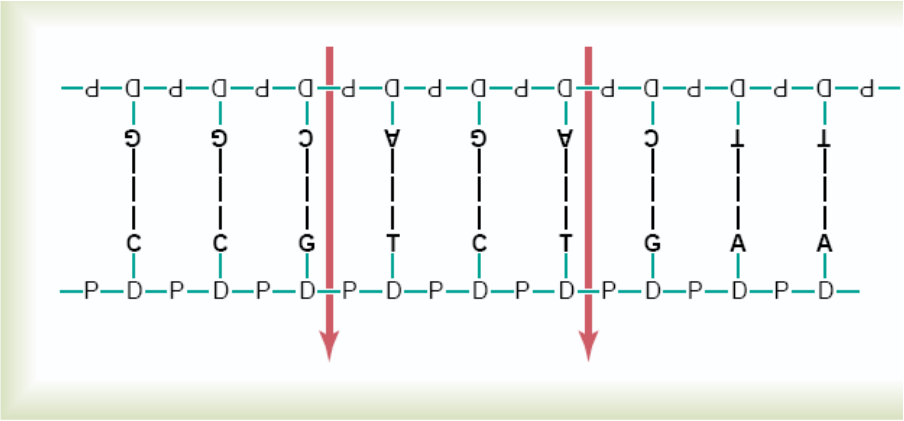


Figure 3–6

Arrangement of deoxyribose nucleotides in a double strand of DNA.

Nucleotides.

*The first stage in the formation of DNA is to combine one molecule of phosphoric acid, one molecule of deoxyribose, and one of the four bases to form an **acidic nucleotide**. Four separate nucleotides are thus formed, one for each of the four bases: deoxyadenylic, deoxythymidylic, deoxyguanylic, and deoxycytidylic acids.*

Organization of the nucleotides to form two strands of DNA.

*Figure above shows the manner in which multiple numbers of nucleotides are bound together to form two strands of DNA. The two strands are, in turn, loosely bonded with each other by weak cross-linkages, illustrated in that figure above by the central dashed lines. Note that the backbone of each DNA strand is comprised of alternating phosphoric acid and deoxyribose molecules. In turn, purine and pyrimidine bases are attached to the sides of the deoxyribose molecules. Then, by means of loose **hydrogen bonds** (dashed lines) between the purine and pyrimidine bases, the two respective DNA strands are held together. But note the following:*

*1. Each purine base **adenine** of one strand bonds with a pyrimidine base **thymine** of the other strand.*

*2. Each purine base **guanine** always bonds with a pyrimidine base **cytosine**.*

Thus, in figure above the sequence of complementary pairs of bases is CG,CG,GC,TA,CG,TA,GC,AT,andAT. Because of the looseness of the hydrogen bonds ,the two strands can pull apart with ease, and they do so many times during the course of their function in the cell.

To put the DNA of figure above into its proper physical perspective, one could merely pick up the two ends and twist them into a helix. Ten pairs of nucleotides are present in each full turn of the helix in the DNA molecule.

Genetic code.

The importance of DNA lies in its ability to control the formation of proteins in the cell. It does this by means of the so-called ***genetic code****. That is, when the two strands of a DNA molecule are split apart, this exposes the purine and pyrimidine bases projecting to the side of each DNA strand, and these projecting bases form the genetic code.*

The genetic code consists of successive ***"triplets"*** *of bases—that is, each three successive bases is a* ***code word****. The successive triplets eventually control the sequence of amino acids in a protein molecule that is to be synthesized in the cell. Note in figure above that the top strand of DNA, reading from left to right, has the genetic code GGC, AGA, CTT, the triplets being separated from one another by the arrows. As we follow this genetic code through figures below we see that these three respective triplets are responsible for successive placement of the three amino acids, proline, serine, and glutamic acid, in a newly formed molecule of protein.*

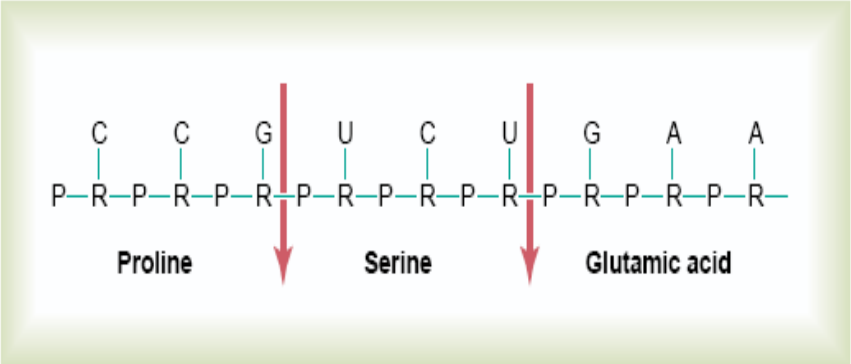


Figure 3–8

Portion of an RNA molecule, showing three RNA "codons"—CCG, UCU, and GAA—which control attachment of the three amino acids *proline*, *serine*, and *glutamic acid*, respectively, to the growing RNA chain.

Physiology of the cell

Dr. Ahmed talib Lec.4

The process of transcription.

Because the DNA is located in the nucleus of the cell, yet most of the functions of the cell are carried out in the cytoplasm, there must be some means for the DNA genes of the nucleus to control the chemical reactions of the cytoplasm. This is achieved through the intermediary of another type of nucleic acid, RNA, the formation of which is controlled by the DNA of the nucleus. The code is transferred to the RNA; this process is ***called transcription****. The RNA, in turn, diffuses from the nucleus through nuclear pores into the cytoplasmic compartment, where it controls protein synthesis.*

Synthesis of RNA

During synthesis of RNA, the two strands of the DNA molecule separate temporarily; one of these strands is used as a template for synthesis of an RNA molecule.The code triplets in the DNA cause formation of complementary code triplets ***(called codons)*** *in the RNA; these codons, in turn, will control the sequence of amino acids in a protein to be synthesized in the cell cytoplasm.*

- ### Basic building blocks of RNA.

The basic building blocks of RNA are almost the same as those of DNA, except for two differences.

1. The sugar deoxyribose is not used in the formation of RNA. In its place is another sugar of slightly different composition, ***ribose****, containing an extra hydroxyl ion appended to the ribose ring structure.*

2.Thymine is replaced by another pyrimidine, ***uracil****.*

- ### Formation of RNA nucleotides.

The basic building blocks of RNA form RNA nucleotides, exactly as previously described for DNA synthesis. Here again, four separate nucleotides are used in the formation of RNA. These nucleotides contain the bases

adenine, guanine, cytosine, and uracil. Note that these are the same bases as in DNA, except that uracil in RNA replaces thymine in DNA.

- Activation of the RNA nucleotides.

The next step in the synthesis of RNA is "activation" of the RNA nucleotides by an enzyme, ***RNA polymerase****. This occurs by adding to each nucleotide two extra phosphate radicals to form triphosphates. These last two phosphates are combined with the nucleotide by high-energy phosphate bonds derived from ATP in the cell. The result of this activation process is that large quantities of ATP energy are made available to each of the nucleotides, and this energy is used to promote the chemical reactions that add each new RNA nucleotide at the end of the developing RNA chain.*

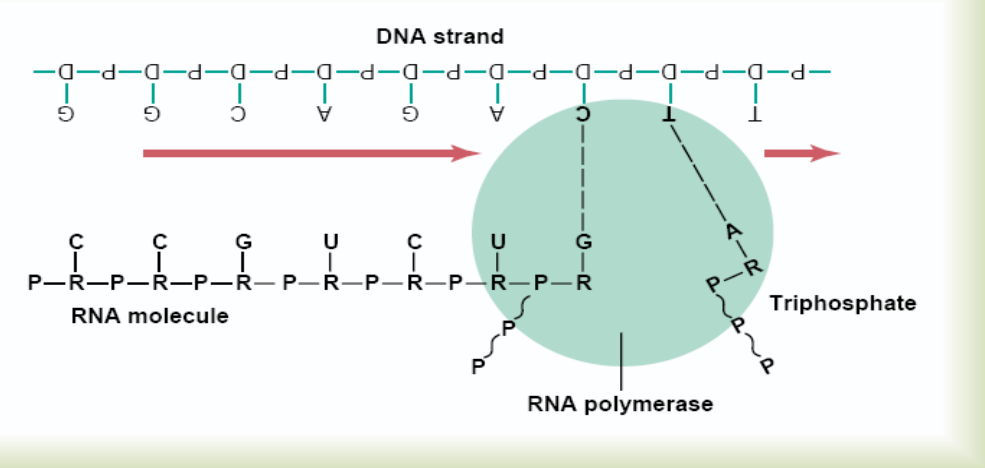


Figure 3–7

Combination of ribose nucleotides with a strand of DNA to form a molecule of RNA that carries the genetic code from the gene to the cytoplasm. The *RNA polymerase* enzyme moves along the DNA strand and builds the RNA molecule.

Assembly of the RNA chain from activated nucleotides.

RNA chain is assembled from activated nucleotides by using the DNA strand as a template—the process of Transcription. Assembly of the RNA molecule is accomplished in the manner shown in figure above under the influence of an enzyme, RNA polymerase. This is a large protein enzyme that has many functional properties necessary for formation of the RNA molecule. They are as follows:

1. *In the DNA strand immediately ahead of the initial gene is a sequence of nucleotides called the promoter. The RNA polymerase has an appropriate complementary structure that recognizes this promoter and becomes attached to it. This is the essential step for initiating formation of the RNA molecule.*

2. *After the RNA polymerase attaches to the promoter, the polymerase causes unwinding ofabout two turns of the DNA helix and separation of the unwound portions of the two strands.*

3. *Then the polymerase moves along the DNA strand, temporarily unwinding and separating the two DNA strands at each stage of its movement.*

As it moves along, it adds at each stage a new activated RNA nucleotide to the end of the newly forming RNA chain by the following steps:

A. *First, it causes a hydrogen bond to form between the end base of the DNA strand and the base of an RNA nucleotide in the nucleoplasm.*

B. *Then, one at a time, the RNA polymerase breaks two of the three phosphate radicals away from each of these RNA nucleotides ,liberating large amounts of energy from the broken high-energy phosphate bonds; this energy is used to cause covalent linkage of the remaining phosphate on the nucleotide with the ribose on the end of the growing RNA chain.*

C. *When the RNA polymerase reaches the end of the DNA gene, it encounters a new sequence of DNA nucleotides called the chain-terminating sequence; this causes the polymerase and the newly formed RNA chainto break away from the DNA strand. Then the polymerase can be used again and again toform still more new RNA chains.*

D. *As the new RNA strand is formed, its weak hydrogen bonds with the DNA template breakaway, because the DNA has a high affinity for rebonding with its own complementary DNA strand. Thus, the RNA chain is forced away from the DNA and is released into the nucleoplasm.*

Thus, the code that is present in the DNA strand is eventually transmitted in complementary form to the RNA chain. The ribose nucleotide bases always combine with the deoxyribose bases in the following combinations:

DNA Base	RNA Base
guanine	***cytosine***
cytosine	***guanine***
adenine	***uracil***
thymine	***adenine***

Types of RNA.

There are four different types of RNA, each of which plays an independent andentirely different role in protein formation:

***1. Messenger RNA**, which carries the genetic code tothe cytoplasm for controlling the type of protein formed.*

***2. Transfer RNA,** which transports activated amino acids to the ribosomes to be used in assembling the protein molecule.*

***3. Ribosomal RNA**, which, along with about 75different proteins, forms ribosomes, the physicaland chemical structures on which protein molecules are actually assembled.*

***4. MicroRNA (miRNA)**, which are single-stranded RNA molecules of 21 to 23 nucleotides that can regulate gene transcription and translation.*

1. Messenger RNA—The Codons

Messenger RNA molecules are long, single RNA strands that are suspended in the cytoplasm. These molecules are composed of several hundred to several thousand RNA nucleotides in unpaired strands, and they contain codons that are exactly complementary to the code triplets of the DNA genes. Figures above shows a small segment of a molecule of messengerRNA. Its codons are CCG,UCU, and GAA. These arethe codons for the amino acids proline, serine, and glutamicacid.

*There are several RNA codons for the 20 common amino acidsfound in protein molecules, most of theamino acids are represented by more than one codon; also, one codon represents the signal "start manufacturingthe protein molecule," and three codons represent "stop manufacturing the protein molecule." these two types of codons are designated CI for **"chain-initiating"** and CT for **"chain-terminating."***

2. Transfer RNA—The Anticodons

Another type of RNA that plays an essential role in protein synthesis is called transfer RNA, because it transfers amino acid molecules to protein molecules as the protein is being synthesized. Each type of transfer RNA combines specifically with 1 of the 20 amino acids that are to be incorporated into proteins. The transfer RNA then acts as a carrier to transport its specific type of amino acid to the ribosomes, where protein molecules are forming. In the ribosomes, each specific type of transfer RNA recognizes a particular codon on the messenger RNA and thereby delivers the appropriate amino acid to the appropriate place in the chain of the newly forming protein molecule .Transfer RNA, which contains only about 80 nucleotides, is a relatively small molecule in comparison with messenger RNA. It is a folded chain of nucleotides with a cloverleaf appearance .At one end of the molecule is always an adenylic acid; it is to this that the transported amino acid attaches at a hydroxyl group of the ribose in the adenylic acid.

*Because the function of transfer RNA is to cause attachment of a specific amino acid to a forming protein chain, it is essential that each type of transfer RNA also have specificity for a particular codon in the messenger RNA. The specific code in the transfer RNA that allows it to recognize a specific codon is again a triplet of nucleotide bases and is called an **anticodon**.* This is located approximately in the middle of the tRNA molecule (at the bottom of the cloverleaf configuration shown in Figure 3-9). During formation of the protein molecule, the anticodon bases combine loosely by hydrogen bonding with the codon bases of the mRNA. In this way, the respective amino acids are lined up one after another along the mRNA chain, thus establishing the appropriate sequence of amino acids in the newly forming protein molecule.

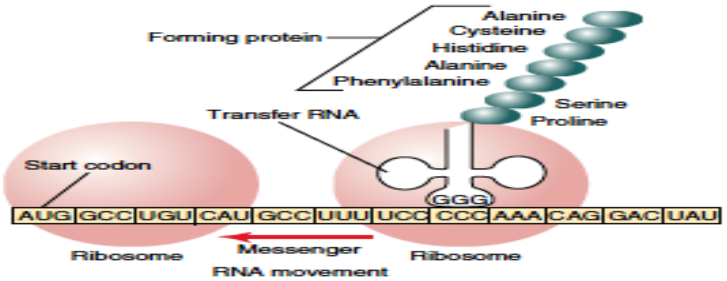


Figure 3-9. A messenger RNA strand is moving through two ribosomes. As each "codon" passes through, an amino acid is added to the growing protein chain, which is shown in the right-hand ribosome. The transfer RNA molecule transports each specific amino acid to the newly forming protein.

3. Ribosomal RNA

The third type of RNA in the cell is ribosomal RNA; it constitutes about 60 per cent of the ribosome. The remainder of the ribosome is protein, containing about 75 types of proteins that are both structural proteins and enzymes needed in the manufacture of protein molecules. The ribosome is the physical structure in the cytoplasm on which protein molecules are actually synthesized. However, it always functions in association with the other two types of RNA as well: transfer RNA transports amino acids to the ribosome for incorporation into the developing protein molecule, whereas messenger RNA provides the information necessary for sequencing the amino acids in proper order for each specific type of protein to be manufactured. Thus, the ribosome acts as a manufacturing plant in which the protein molecules are formed.

4. Micro RNA

A fourth type of RNA in the cell is miRNA. These are short (21 to 23 nucleotides) single-stranded RNA fragments that regulate gene expression. The miRNAs are encoded from the transcribed DNA of genes, but they are not translated into proteins and are therefore often called noncoding RNA. The miRNAs are processed by the cell into molecules that are complementary to mRNA and act to decrease gene expression. Generation of miRNA sinvolves special processing of longer primary precursor RNAs called pri-miRNAs, which are the primary transcripts of the gene. The pri-miRNAs are then processed in the cell nucleus by the microprocessor complex to premiRNAs, which are 70 nucleotide stem-loop structures. These pre-miRNAs are then further processed in the cytoplasm by a specific dicer enzyme that helps assemble an RNA-induced silencing complex (RISC) and generates miRNAs.

The miRNAs regulate gene expression by binding to the complementary region of the RNA and promoting repression of translation or degradation of the mRNA before it can be translated by the ribosome. miRNAs are believed to play an important role in the normal regulation of cell function, and alterations in miRNA function have been associated with diseases such as cancer and heart disease.

Another type of microRNA is small interfering RNA(siRNA), also called silencing RNA or short interfering RNA. The siRNAs are short, double-stranded RNA molecules,20 to 25 nucleotides in length, that interfere with the expression of specific genes. siRNAs generally refer to synthetic miRNAs and can be administered to silence expression of specific genes. They are designed to avoid the nuclear processing by the microprocessor complex, and after the siRNA enters the cytoplasm it activates the RISC silencing complex, blocking the translation of mRNA. Because siRNAs can be tailored for any specific sequence in the gene, they can be used to block translation of any mRNA and therefore expression by any gene for which the nucleotide sequence is known. Some researchers have proposed that siRNAs may become useful therapeutic tools to silence genes that contribute to the pathophysiology of diseases.

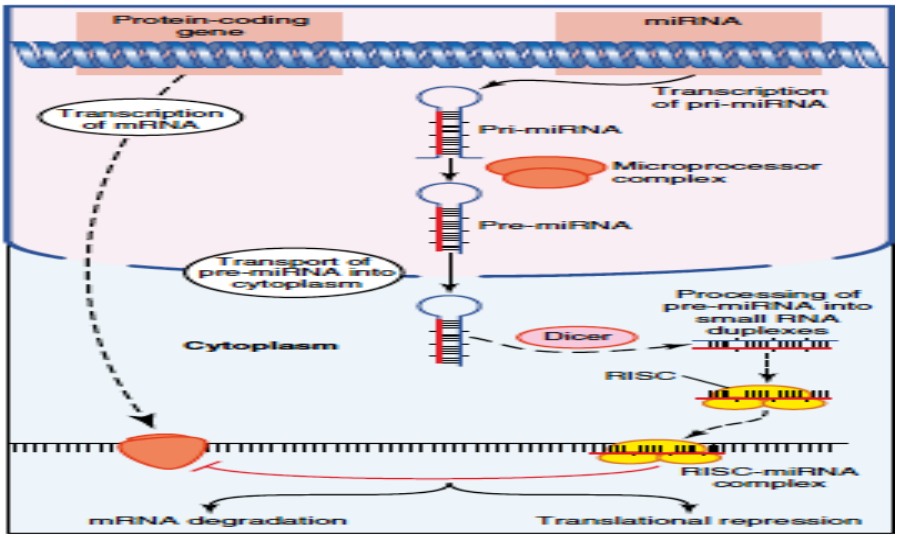


Figure 3–10. Regulation of gene expression by microRNA (miRNA). Primary miRNA (pri-miRNA), the primary transcripts of a gene processed in the cell nucleus by the microprocessor complex to pre-miRNAs. These pre-miRNAs are then further processed in the cytoplasm by *dicer*, an enzyme that helps assemble an RNA-induced silencing complex (RISC) and generates miRNAs. The miRNAs regulate gene expression by binding to the complementary region of the RNA and repressing translation or promoting degradation of the mRNA before it can be translated by the ribosome.

Formation of ribosomes in the nucleolus.

The DNA genes for formation of ribosomal RNA are located in five pairs of chromosomes in the nucleus, and each of these chromosomes contains many duplicates of these particular genes because of the large amounts of ribosomal RNA required for cellular function.

As the ribosomal RNA forms, it collects in the nucleolus, a specialized structure lying adjacent to the chromosomes. When large amounts of ribosomal RNA are being synthesized, as occurs in cells that manufacture large amounts of protein, the nucleolus is a large structure, whereas in cells that synthesize little protein, the nucleolus may not even be seen. Ribosomal RNA is specially processed in the nucleolus, where it binds with "ribosomal proteins" to form granular condensation products that are primordial subunits of ribosomes. These subunits are then released from the nucleolus and transported through the large pores of the nuclear envelope to almost all parts of the cytoplasm. After the subunits enter the cytoplasm, they are assembled to form mature, functional ribosomes. Therefore, proteins are formed in the cytoplasm of the cell, but not in the cell nucleus, because the nucleus does not contain mature ribosomes.

Formation of proteins on the ribosomes—The process of "Translation"

When a molecule of messenger RNA comes in contact with a ribosome, it travels through the ribosome, beginning at a predetermined end of the RNA molecule specified by an appropriate sequence of RNA bases called the ***"chain-initiating" codon.*** *Then, while the messenger RNA travels through the ribosome, a protein molecule is formed— a process called* ***translation.*** *Thus, the ribosome reads the codons of the messenger RNA in much the same way that a tape is "read" as it passes through the playback head of a tape recorder. Then, when a "stop" (or* ***"chain-terminating") codon*** *slips past the ribosome, the end of a protein molecule is signaled and the protein molecule is freed into the cytoplasm.*

Polyribosomes.

A single messenger RNA molecule can form protein molecules in several ribosomes at the same time because the initial end of the RNA strand can pass to a successive ribosome as it leaves the first. The protein molecules are in different stages of development in each ribosome. As a result, clusters of ribosomes frequently occur, 3 to 10 ribosomes being attached to a single messenger RNA at the same time. These clusters are called ***polyribosomes*** *.It is especially important to note that a messenger RNA can cause the formation of a protein molecule in any ribosome; that is, there is no specificity of ribosomes for given types of protein. The ribosome is simply the physical manufacturing plant in which the chemical reactions take place.*

Many ribosomes attach to the endoplasmic reticulum.

In previous study it was noted that many ribosomes become attached to the endoplasmic reticulum. This occurs because the initial ends of many forming protein molecules have amino acid sequences that immediately attach to specific receptor sites on the endoplasmic reticulum; this causes these molecules to

penetrate the reticulum wall and enter the endoplasmic reticulum matrix. This gives a granular appearance to those portions of the reticulum where proteins are being formed and entering the matrix of the reticulum.
Figure 3-11 shows the functional relation of messenger RNA to the ribosomes and the manner in which the ribosomes attach to the membrane of the endoplasmic reticulum. Note the process of translation occurring in several ribosomes at the same time in response to the same strand of messenger RNA. Note also the newly forming polypeptide (protein) chains passing through the endoplasmic reticulum membrane into the endoplasmic matrix.
Yet it should be noted that except in glandular cells in which large amounts of protein-containing secretory vesicles are formed, most proteins synthesized by the ribosomes are released directly into the cytosol instead of into the endoplasmic reticulum. These proteins are enzymes and internal structural proteins of the cell.

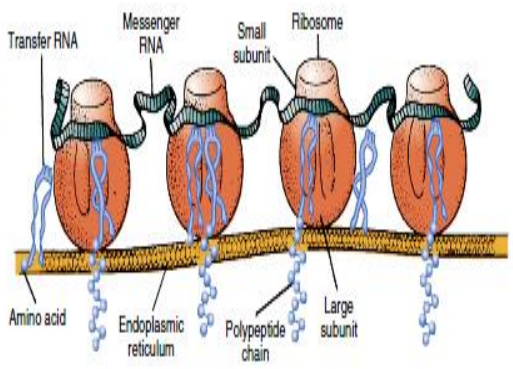


Figure 3-11. Physical structure of the ribosomes, as well as their functional relation to messenger RNA, transfer RNA, and the endoplasmic reticulum during the formation of protein molecules. (Courtesy Dr. Don W. Fawcett, Montana.)

Chemical steps in protein synthesis.

Some of the chemical events that occur in synthesis of a protein molecule are shown in figure below.This figure shows representative reactions for three separate amino acids, AA1, AA2, and AA20. The stages of the reactions are the following:
(1) *Each amino acid is activated by a chemical process in which ATP combines with the amino acid to form an adenosine monophosphate complex with the amino acid, giving up two high-energy phosphate bonds in the process.*
(2) *The activated amino acid, having an excess of energy, then combines with its specific transfer RNA to form an amino acid–tRNA complex and, at the same time, releases the adenosine monophosphate.*
(3) *The transfer RNA carrying the amino acid complex then comes in contact with the messenger RNA molecule in the ribosome, where the anticodon of the transfer RNA attaches temporarily to its specific codon of the messenger RNA, thus lining up the amino acid in appropriate sequence to form a protein molecule. Then, under the influence of the enzyme peptidyl transferase (one of the proteins in the ribosome), peptide bonds are formed between the successive amino acids, thus adding progressively to the protein chain. These chemical events require energy from two additional high-energy phosphate bonds, making a total of four high-energy bonds used for each amino acid added to the protein chain. Thus, the synthesis of proteins is one of the most energy-consuming processes of the cell.*

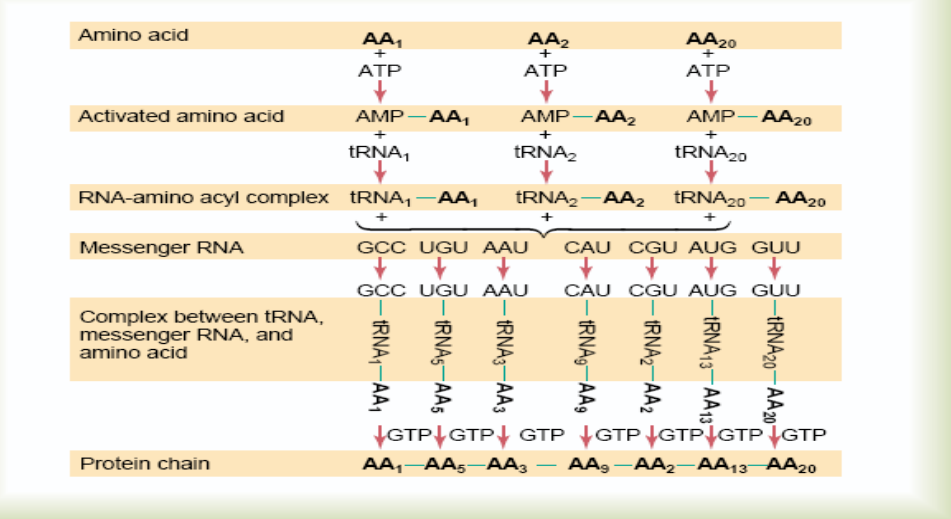
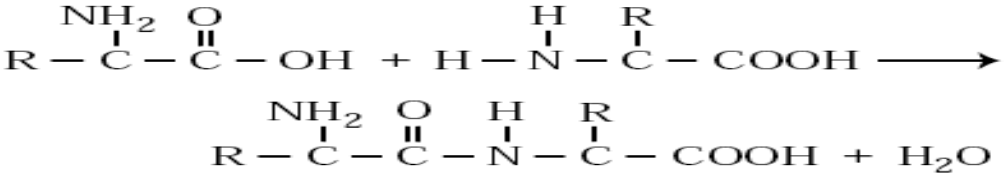


Figure 3–11

Chemical events in the formation of a protein molecule.

Peptide Linkage.

The successive amino acids in the protein chain combine with one another according to the typical reaction:



In this chemical reaction, a hydroxyl radical (OH^-) is removed from the COOH portion of the first amino acid, and a hydrogen (H^+) of the NH2 portion of the other amino acid is removed. These combine to form water, and the two reactive sites left on the two successive amino acids bond with each other, resulting in a single molecule. This process is called ***peptide linkage****. As each additional amino acid is added, an additional peptide linkage is formed.*

Dr. Ahmed Talib Lec.5

Cell Function and Reproduction

Control of intracellular function by enzyme regulation.

In addition to control of cell function by genetic regulation, some cell activities are controlled by intra cellular inhibitors or activators that act directly on specific intracellular enzymes. Thus, enzyme regulation represents a second category of mechanisms by which cellular biochemical functions can be controlled.

- *Enzyme inhibition.*

Some chemical substances formed in the cell have direct feedback effects in inhibiting the specific enzyme systems that synthesize them. Almost always the synthesized product acts on the first enzyme in a sequence, rather than on the subsequent enzymes, usually binding directly with the enzyme and causing an allosteric conformational change that inactivates it. One can readily recognize the importance of inactivating the first enzyme: this prevents buildup of intermediary products that are not used. Enzyme inhibition is another example of negative feedback control; it is responsible for controlling intracellular concentrations of multiple amino acids ,purines, pyrimidines, vitamins, and other substances.

- ## Enzyme activation.

Enzymes that are normally inactive often can be activated when needed. An example of this occurs when most of the ATP has been depleted in a cell. In this case, a considerable amount of cyclicadenosine monophosphate (cAMP) begins to be formed as a breakdown product of the ATP; the presence of this cAMP, in turn, immediately activates the glycogen-splitting enzyme phosphorylase, liberating glucose molecules that are rapidly metabolized and their energy used for replenishment of the ATP stores. Thus, cAMP acts as an enzyme activator for the enzyme phosphorylase and thereby helps control intracellular ATP concentration.

Another interesting instance of both enzyme inhibition and enzyme activation occurs in the formation of the purines and pyrimidines. These substances are needed by the cell in approximately equal quantities for formation of DNA and RNA. When purines are formed, they inhibit the enzymes that are required for formation of additional purines. However, they activate the enzymes for formation of pyrimidines. Conversely ,the pyrimidines inhibit their own enzymes but activate the purine enzymes. In this way, there is continual cross-feed between the synthesizing systems for these two substances, resulting in almost exactly equal amounts of the two substances in the cells at all times.

Summary.

In summary, there are two principal methods by which cells control proper proportions and proper quantities of different cellular constituents:

(1) The mechanism of genetic regulation.

(2) The mechanism of enzyme regulation.

The genes can be either activated or inhibited, and likewise, the enzyme systems can be either activated or inhibited .These regulatory mechanisms most often function as feedback control systems that continually monitor the cell's biochemical composition and make corrections as needed. But on occasion, substances from without the cell also control the intracellular biochemical reactions by activating or inhibiting one or more of the intracellular control systems.

The DNA-genetic system also controls cell reproduction.

Cell reproduction is another example of the ubiquitous role that the DNA-genetic system plays in all life processes .The genes and their regulatory mechanisms determine the growth characteristics of the cells and also when or whether these cells will divide to form new cells. In this way, the all-important genetic system controls each stage in the development of the human being, from the single-cell fertilized ovum to the whole functioning body. Thus, if there is any central theme to life, it is the DNA-genetic system.

Life cycle of the cell.

The life cycle of a cell is the period from cell reproduction to the next cell reproduction *.When mammalian cells are not inhibited and are reproducing as rapidly as they can, this life cycle may be as little as 10 to 30 hours. It is terminated by a series of distinct physical events called mitosis that cause division of the cell into two new daughter cells. The events of mitosis are shown in figure below. The actual stage of mitosis, however, lasts for only about 30 minutes, so that more than 95 percent of the life cycle of even rapidly reproducing cells is represented by the interval between mitosis, called* ***interphase .****Except in special conditions of rapid cellular reproduction ,inhibitory factors almost always slow or stop the uninhibited life cycle of the cell. Therefore, different cells of the body actually have life cycle periods that vary from as little as 10 hours for highly stimulated bone marrow cells to an entire lifetime of the human body for most nerve cells.*

Cell reproduction begins with replication of DNA.

As is true of almost all other important events in the cell, reproduction begins in the nucleus itself .The first step is replication (duplication) of all DNA in the chromosomes .Only after this has occurred can mitosis take place. The DNA begins to be duplicated some 5 to 10hours before mitosis, and this is completed in 4 to 8hours. The net result is two exact replicas of all DNA. These replicas become the DNA in the two new daughter cells that will be formed at mitosis. After replication of the DNA, there is another period of 1 to2

hours before mitosis begins abruptly. Even during this period, preliminary changes are beginning to take place that will lead to the mitotic process.

Chemical and physical events of DNA replication.

DNA is replicated in much the same way that RNA is transcribed in response to DNA, except for a few important differences:

1. *Both strands of the DNA in each chromosome are replicated, not simply one of them.*

2. *Both entire strands of the DNA helix are replicated from end to end, rather than small portions of them, as occurs in the transcription of RNA.*

3. *The principal enzymes for replicating DNA are a complex of multiple enzymes called* ***DNA polymerase****, which is comparable to RNA polymerase. It attaches to and moves along the DNA template strand while another enzyme ,DNA ligase, causes bonding of successive DNA nucleotides to one another, using high-energy phosphate bonds to energize these attachments.*

4. *Formation of each new DNA strand occurs simultaneously in hundreds of segments along each of the two strands of the helix until the entire strand is replicated. Then the ends of the subunits are joined together by the DNA ligase enzyme.*

5. *Each newly formed strand of DNA remains attached by loose hydrogen bonding to the original DNA strand that was used as its template .Therefore, two DNA helixes are coiled together.*

6. *Because the DNA helixes in each chromosome are approximately 6 centimeters in length and have millions of helix turns, it would be impossible for the two newly formed DNA helixes to uncoil from each other were it not for some special mechanism. This is achieved by enzymes that periodically cut each helix along its entire length, rotate each segment enough to cause separation, and then resplice the helix. Thus, the two new helixes become uncoiled.*

DNA repair, DNA proofreading, and mutation.

During the hour or so between DNA replication and the beginning of mitosis, there is a period of very activerepair and "proofreading" of the DNA strands. That is, wherever inappropriate DNA nucleotides have been matched up with the nucleotides of the original template strand, special enzymes cut out the defective areas and replace these with appropriate complementary nucleotides. This is achieved by the same DNA polymerases and DNA ligases that are used in replication .This repair process is referred to as ***DNA proofreading****.Because of repair and proofreading, the transcription process rarely makes a mistake. But when amistake is made, this is called a mutation. The mutation causes formation of some abnormal protein in the cell rather than a needed protein, often leading to abnormal cellular function and sometimes even cell death. Yet, given that there are 30,000 or more genes in the human genome and that the period from one human generation to another is about 30 years, one would expect as many as 10 or many more mutations in the passage of the genome from parent to child. As a further protection, however, each human genome is represented by two separate sets of chromosomes with almost identical genes. Therefore, one functional gene of each pair is almost always available to the child despite mutations.*

Chromosomes and their replication.

The DNA helixes of the nucleus are packaged in chromosomes. The human cell contains 46 chromosomes arranged in 23 pairs. Most of the genes in the two chromosomes of each pair are identical or almost identical to each other, so it is usually stated that the different genes also exist in pairs, although occasionally this is not the case. In addition to DNA in the chromosome, there is alarge amount of protein in the chromosome, composed mainly of many small molecules of electro positively charged ***histones****. The histones are organized into vast numbers of small, bobbin-like cores. Small segments of each DNA helix are coiled sequentially around one core after another.*

The histone cores play an important role in the regulation of DNA activity because as long as the DNA is packaged tightly, it cannot function as a template for either the formation of RNA or the replication of new

DNA. Further, some of the regulatory proteins have been shown to deco dense the histone packaging of the DNA and to allow small segments at a time to form RNA.

Several nonhistone proteins are also major components of chromosomes, functioning both as chromosomal structural proteins and, in connection with the genetic regulatory machinery, as activators, inhibitors , and enzymes. Replication of the chromosomes in their entirety occurs during the next few minutes after replication of the DNA helixes has been completed; the new DNA helixes collect new protein molecules as needed. The two newly formed chromosomes remain attached to each other (until time for mitosis) at a point called the ***centromere*** *located near their center. These duplicated but still attached chromosomes are called* ***chromatids****.*

Cell mitosis

The actual process by which the cell splits into two new cells is called mitosis. Once each chromosome has been replicated to form the two chromatids, in many cells, mitosis follows automatically within 1 or 2 hours.

- Mitotic apparatus: function of the centrioles.

One of the first events of mitosis takes place in the cytoplasm, occurring during the latter part of interphase in or around the small structures called ***centrioles****. As shown in figure below, two pairs of centrioles lie close to each other near one pole of the nucleus. (These centrioles, like the DNA and chromosomes, were also replicated during interphase, usually shortly before replication of the DNA.) Each centriole is a small cylindrical body about 0.4 micrometer long and about 0.15 micrometer in diameter, consisting mainly of nine parallel tubular structures arranged in the form of a cylinder. The two centrioles of each pair lie at right angles to each other.*

Each pair of centrioles, along with attached pericentriolar material, is called a ***centrosome****. Shortly before mitosis is to take place, the two pairs of centrioles begin to move apart from each other .This is caused by polymerization of protein micro tubules growing between the respective centriole pairs and actually pushing them apart. At the same time, other microtubules grow radially away from each of the centriole pairs, forming a spiny star, called the* ***aster****, in each end of the cell. Some of the spines of the aster penetrate the nuclear membrane and help separate the two sets of chromatids during mitosis. The complex of microtubules extending between the two new centriolepairs is called the* ***spindle****, and the entire set of microtubules plus the two pairs of centrioles is called the* ***mitotic apparatus****.*

1. Prophase.

The first stage of mitosis, called prophase, is shown in figure below (A, B, and C).While the spindle is forming, the chromosomes of the nucleus (which in interphase consist of loosely coiled strands) become condensed into well-defined chromosomes.

2. Prometaphase.

During this stage (figure below D), the growing microtubular spines of the aster fragment the nuclear envelope. At the same time, multiple microtubules from the aster attach to the chromatids at the centromeres, where the paired chromatids are still bound to each other; the tubules then pull one chromatid of each pair toward one cellular pole and its partner toward the opposite pole.

3. Metaphase.

*During metaphase (figure below E), the two asters of the mitotic apparatus are pushed farther apart. This is believed to occur because the micro tubular spines from the two asters, where they interdigitate with each other to form the mitotic spindle, actually push each other away. There is reason to believe that minute contractile protein molecules called "****motor molecules****," perhaps composed of the muscle protein actin, extend between the respective spines and, using a stepping action as in muscle, actively slide the spines in a reverse direction along each other. Simultaneously, the chromatids are pulled tightly by their attached microtubules to the very center of the cell, lining up to form the equatorial plate of the mitotic spindle.*

4. Anaphase.

During this phase (figure below F), the two chromatids of each chromosome are pulled apart at the centromere. All 46 pairs of chromatids are separated, forming two separate sets of 46 daughter chromosomes.

One of these sets is pulled toward one mitotic aster and the other toward the other aster as the two respective poles of the dividing cell are pushed still farther apart.

5. Telophase.

In telophase (figure below G and H), the two sets of daughter chromosomes are pushed completely apart. Then the mitotic apparatus dissolute , and a new nuclear membrane develops around each set of chromosomes. This membrane is formed from portions of the endoplasmic reticulum that are already present in the cytoplasm. Shortly thereafter, the cell pinches in two, midway between the two nuclei. This is caused by formation of a contractile ring of microfilaments composed of actin and probably myosin (the two contractile proteins of muscle) at the juncture of the newly developing cells that pinches them off from each other.

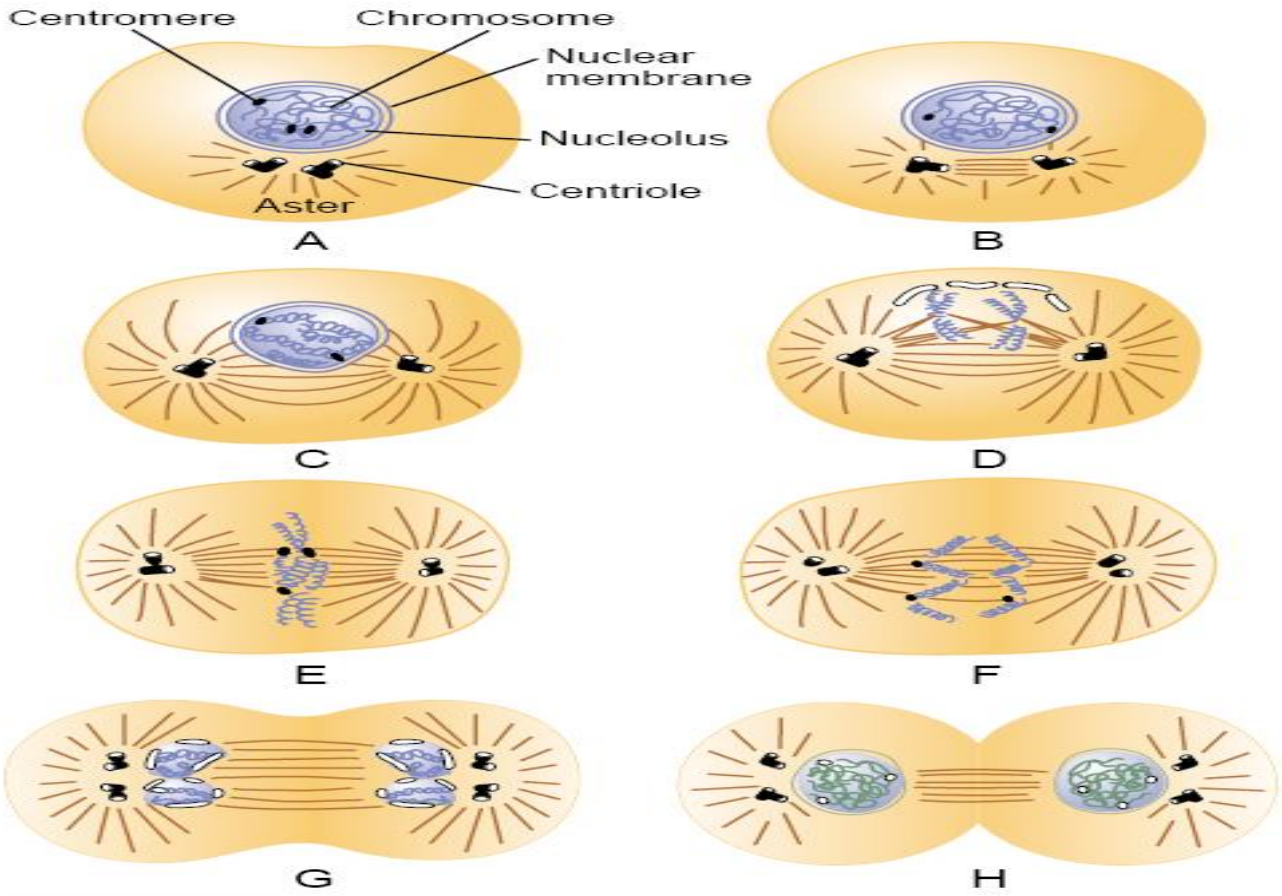


Figure 3–13

Stages of cell reproduction. *A*, *B*, and *C*, Prophase. *D*, Prometaphase. *E*, Metaphase. *F*, Anaphase. *G* and *H*, Telophase. (From Margaret C. Gladbach, Estate of Mary E. and Dan Todd, Kansas.)

Control of cell growth and cell reproduction.

We know that certain cells grow and reproduce all the time, such as the blood-forming cells of the bone marrow, the germinal layers of the skin, and the epithelium of the gut. Many other cells, however, such as smooth muscle cells, may not reproduce for many years. A few cells, such as the neurons and most striated muscle cells, do not reproduce during the entire life of a person, except during the original period of fetal life. In certain tissues, an insufficiency of some types of cells causes these to grow and reproduce rapidly until appropriate numbers of them are again available. For instance, in some young animals, seven eighths of the liver can be removed surgically, and the cells of the remaining one eighth will grow and divide until the liver mass returns almost to normal. The same occurs for many glandular cells and most cells of the bone marrow, subcutaneous tissue, intestinal epithelium, and almost any other tissue except highly differentiated cells such as nerve and muscle cells. We know little about the mechanisms that maintain proper numbers of the different types of cells in the body in spite of the theories and experiments have been explained ways in which growth can be controlled.

Regulation of cell size.

Cell size is determined almost entirely by the amount of functioning DNA in the nucleus. If replication of the DNA does not occur, the cell grows to a certain size and thereafter remains at that size. Conversely, it is possible, by use of the chemical colchicine, to prevent formation of the mitotic spindle and therefore to prevent mitosis, even though replication of the DNA continues. In this event, the nucleus contains far greater quantities of DNA than it normally does, and the cell grows proportionately larger. It is assumed that this results simply from increased production of RNA and cell proteins, which in turn cause the cell to grow larger.

Cell differentiation.

A special characteristic of cell growth and cell division is cell differentiation, which refers to changes in physical and functional properties of cells as they proliferate in the embryo to form the different bodily structures and organs. The description of an especially interesting experiment that helps explain these processes follows. When the nucleus from an intestinal mucosal cell of a frog is surgically implanted into a frog ovum from which the original ovum nucleus was removed, the result is often the formation of a normal frog. This demonstrates that even the intestinal mucosal cell, which is a well-differentiated cell, carries all the necessary genetic information for development of all structures required in the frog's body.

Therefore, it has become clear that differentiation results not from loss of genes but from selective repression of different gene promoter. In fact, electron micrographs suggest that some segments of DNA helixes wound around histone cores become so condensed that they no longer uncoil to form RNA molecules. One explanation for this is as follows: It has been supposed that the cellular genome begins at a certain stage of cell differentiation to produce a regulatory protein that forever after represses a select group of genes. Therefore, the repressed genes never function again. Regardless of the mechanism, mature human cells produce a maximum of about 8000 to 10,000 proteins rather than the potential 30,000 or more if all genes were active.

Apoptosis—programmed cell death.

The 100 trillion cells of the body are members of a highly organized community in which the total number of cells is regulated not only by controlling the rate of cell division but also by controlling the rate of cell death. When cells are no longer needed or become a threat to the organism, they undergo a suicidal programmed cell death, or ***apoptosis****. This process involves a specific proteolytic cascade that causes the cell to shrink and condense, to disassemble its cytoskeleton, and to alter its cell surface so that a neighboring phagocytic cell, such as a macrophage, can attach to the cell membrane and digest the cell. In contrast to programmed death, cells that die as a result of an acute injury usually swell and burst due to loss of cell membrane integrity, a process called cell* ***necrosis****. Necrotic cells may spill their contents, causing inflammation and injury to neighboring cells. Apoptosis, however, is an orderly cell death that results in disassembly and phagocytosis of the cell before any leakage of its contents occurs, and neighboring cells usually remain healthy.*

Apoptosis is initiated by activation of a family of proteases called caspases. These are enzymes that are synthesized and stored in the cell as inactive procaspases. The mechanisms of activation of caspases are complex, but once activated, the enzymes cleave and activate other procaspases, triggering a cascade that rapidly breaks down proteins within the cell. The cell thus dismantles itself, and its remains are rapidly digested by neighboring phagocytic cells.

A tremendous amount of apoptosis occurs in tissues that are being remodeled during development. Evenin adult humans, billions of cells die each hour in tissues such as the intestine and bone marrow and are replaced by new cells. Programmed cell death, however, is precisely balanced with the formation of new cells in healthy adults. Otherwise, the body's tissues would shrink or grow excessively. Recent studies suggest that abnormalities of apoptosis may play a key role in neurodegenerative diseases such as Alzheimer's disease, as well as in cancer and autoimmune disorders. Some drugs that have been used successfully for chemotherapy appear to induce apoptosis in cancer cells.

Cancer

Cancer is caused in all or almost all instances by mutation or by some other abnormal activation of cellular genes that control cell growth and cell mitosis. The abnormal genes are called ***oncogenes****. As many as 100 different oncogenes have been discovered .Also present in all cells are antioncogenes, which suppress the activation of specific oncogenes. Therefore, loss of or inactivation of antioncogenes can allow activation of oncogenes that lead to cancer. Only a minute fraction of the cells that mutate in the body ever lead to cancer.*

There are several reasons for this.

1. *Most mutated cells have less survival capability than normal cells and simply die.*

2.*Only a few of the mutated cells that do survive become cancerous, because even most mutated cells still have normal feedback controls that prevent excessive growth.*

3. *Those cells that are potentially cancerous are often, destroyed by the body's immune system before they grow into a cancer.*

4. *Usually several different activated oncogenes are required simultaneously to cause a cancer. For instance, one such gene might promote rapid reproduction of a cell line, but no cancer occurs because there is not a simultaneous mutant gene to form the needed blood vessels.*

Thus, chance alone is all that is required for mutations to take place, so we can suppose that a large number of cancers are merely the result of an unlucky occurrence. However, the probability of mutations can be increased many fold when a person is exposed to certain chemical, physical, or biological factors, including:

Predisposing factors.

1. *It is well known that ionizing radiation, such as x-rays, gamma rays, and particle radiation from radioactive substances, and even ultraviolet light can predispose individuals to cancer.*

2. *Chemical substances of certain types also have a high propensity for causing mutations. It was discovered long ago that various aniline dye derivatives are likely to cause cancer, so that workers in chemical plants producing such substances, if unprotected, have a special predisposition to cancer. Chemical substances that can cause mutation are called carcinogens. The carcinogens that currently cause the greatest number of deaths are those in cigarette smoke. They cause about one quarter of all cancer deaths.*

3. *Physical irritants also can lead to cancer, such as continued abrasion of the linings of the intestinal tract by some types of food. The damage to the tissues leads to rapid mitotic replacement of the cells.*

4. *In many families, there is a strong hereditary tendency to cancer. This results from the fact that most cancers require not one mutation but two or more mutations before cancer occurs. In those families that are particularly predisposed to cancer,*

5. *In laboratory animals, certain types of viruses can cause some kinds of cancer, including leukemia*

Invasive characteristic of the cancer cell.

The major differences between the cancer cell and the normal cell are the following:

(1) *The cancer cell does not respect usual cellular growth limits; the reason for this is that these cells presumably do not require all the same growth factors that are necessary to cause growth of normal cells.*

(2) *Cancer cells often are far less adhesive to one another than are normal cells. Therefore, they have a tendency to wander through the tissues, to enter the blood stream, and to be transported all through the body, where they form nidi for numerous new cancerous growths.*

(3) *Some cancers also produce angiogenic factors that cause many new blood vessels to grow into the cancer, thus supplying the nutrients required for cancer growth.*

Why do cancer cells kill?

The answer to this question usually is simple. Cancer tissue competes with normal tissues for nutrients. Because cancer cells continue to proliferate indefinitely, their number multiplying day by day, cancer cells soon demand essentially all the nutrition available to the body or to an essential part of the body. As a result, normal tissues gradually suffer nutritive death.

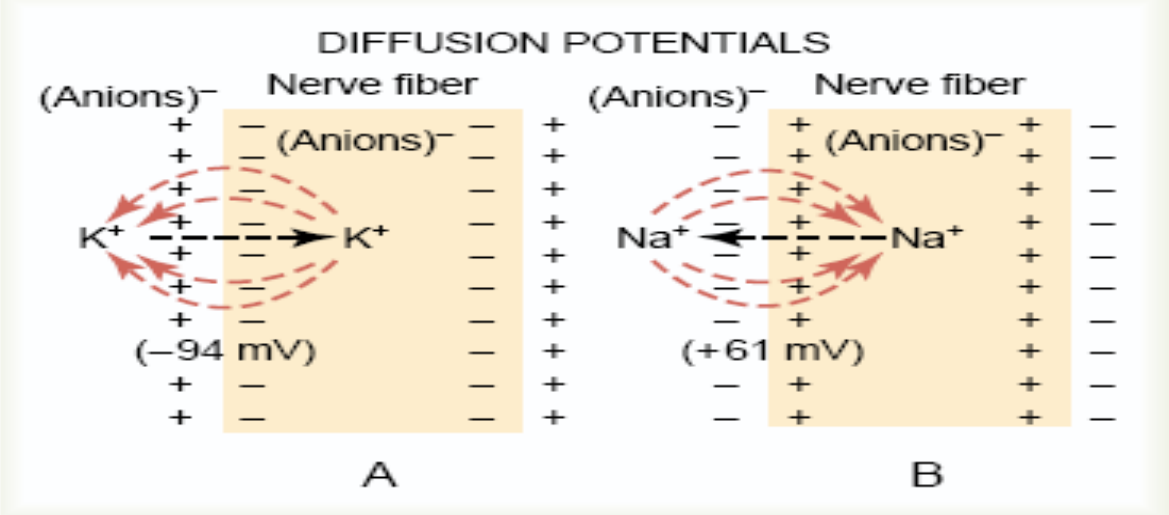
Membrane potentials and action potential

Electrical potentials exist across the membranes of virtually all cells of the body. In addition, some cells, such as nerve and muscle cells, are capable of generating rapidly changing electrochemical impulses at their membranes, and these impulses are used to transmit signals along the nerve or muscle membranes. In still other types of cells, such as glandular cells, macrophages, and ciliated cells, local changes in membrane potentials also activate many of the cells' functions. The present lecture is concerned with membrane potentials generated both at rest and during action by nerve and muscle cells.

Membrane potentials caused by diffusion.

*Diffusion potential caused by an ion concentration difference on the two sides of the membrane. In **figure below A**, the potassium concentration is great inside a nerve fiber membrane but very low outside the membrane. Let us assume that the membrane in this instance is permeable to the potassium ions but not to any other ions. Because of the large potassium concentration gradient from inside toward outside, there is a strong tendency for extra numbers of potassium ions to diffuse outward through the membrane. As they do so, they carry positive electrical charges to the outside, thus creating electropositivity outside the membrane and electronegativity inside because of negative anions that remain behind and do not diffuse outward with the potassium. Within a millisecond or so, the potential difference between the inside and outside, called the **diffusion potential**, becomes great enough to block further net potassium diffusion to the exterior, despite the high potassium ion concentration gradient. In the normal mammalian nerve fiber, the potential difference required is about 94 millivolts, with negativity inside the fiber membrane.*

***Figure below B** shows the same phenomenon as in A, but this time with high concentration of sodium ions outside the membrane and low sodium inside. These ions are also positively charged. This time, the membrane is highly permeable to the sodium ions but impermeable to all other ions. Diffusion of the positively charged sodium ions to the inside creates a membrane potential of opposite polarity to that in Figure below A, with negativity outside and positivity inside. Again, the membrane potential rises high enough within milliseconds to block further net diffusion of sodium ions to the inside; however, this time, in the mammalian nerve fiber, the potential is about 61 millivolts positive inside the fiber. Thus, in both parts of Figure below, we see that a concentration difference of ions across a selectively permeable membrane can, under appropriate conditions, create a membrane potential.*



Diffusion potential and concentration difference (Nernst potential).

*The diffusion potential level across a membrane that exactly opposes the net diffusion of a particular ion through the membrane is called the **Nernst potential** for that ion. The magnitude of this Nernst potential is determined by the ratio of the concentrations of that specific ion on the two sides of the membrane.*

The greater this ratio, the greater the tendency for the ion to diffuse in one direction, and therefore the greater the Nernst potential required to prevent additional net diffusion. The following equation, called the ***Nernst equation****, can be used to calculate the Nernst potential for any univalent ion at normal body temperature of 98.6°F (37°C):*

$$\text{EMF (millivolts)} = \pm 61 \log \frac{\text{Concentration inside}}{\text{Concentration outside}}$$

Where ***EMF*** *is* ***electromotive force****. When using this formula, it is usually assumed that the potential in the extracellular fluid outside the membrane remains at zero potential, and the Nernst potential is the potential inside the membrane. Also, the sign of the potential is positive (+) if the ion diffusing from inside to outside is a negative ion, and it is negative (–) if the ion is positive. Thus, when the concentration of positive potassium ions on the inside is 10 times that on the outside, the log of 10 is 1, so that the Nernst potential calculates to be –61 millivolts inside the membrane.*

Calculation of the diffusion potential:

Calculation of the diffusion potential when the membrane is permeable to several different ions, the diffusion potential that develops depends on three factors:

(1) The polarity of the electrical charge of each ion.

*(2) The permeability of the membrane (**P**) to each ion.*

*(3) The concentrations (**C**) of the respective ions on the inside (**i**) and outside (**o**) of the membrane.*

Thus, the following formula, called the ***Goldman equation****, or the* ***Goldman-Hodgkin-Katz equation****, gives the calculated membrane potential on the inside of the membrane when two univalent positive ions, sodium (Na^+) and potassium (K^+), and one univalent negative ion, chloride (Cl^-), are involved.*

$$\text{EMF (millivolts)} = -61 \cdot \log \frac{C_{Na^+_i} P_{Na^+} + C_{K^+_i} P_{K^+} + C_{Cl^-_o} P_{Cl^-}}{C_{Na^+_o} P_{Na^+} + C_{K^-_o} P_{K^+} + C_{Cl^-_i} P_{Cl^-}}$$

The importance and meaning of Goldman equation.

1. *Sodium, potassium, and chloride ions are the most important ions involved in the development of membrane potentials in nerve and muscle fibers, as well as in the neuronal cells in the nervous system. The concentration gradient of each of these ions across the membrane helps determine the voltage of the membrane potential.*

2. *The degree of importance of each of the ions in determining the voltage is proportional to the membrane permeability for that particular ion. That is, if the membrane has zero permeability to both potassium and chloride ions, the membrane potential becomes entirely dominated by the concentration gradient of sodium ions alone, and the resulting potential will be equal to the Nernst potential for sodium. The same holds for each of the other two ions if the membrane should become selectively permeable for either one of them alone.*

3. *A positive ion concentration gradient from inside the membrane to the outside causes electronegativity inside the membrane. The reason for this is that excess positive ions diffuse to the outside when their concentration is higher inside than outside. This carries positive charges to the outside but leaves the nondiffusible negative anions on the inside, thus creating electronegativity on the inside. The opposite effect occurs when there is a gradient for a negative ion. That is, a chloride ion gradient from the outside to the inside causes negativity inside the cell because excess negatively charged chloride ions diffuse to the inside, while leaving the nondiffusible positive ions on the outside.*

4.*The permeability of the sodium and potassium channels undergoes rapid changes during transmission of a nerve impulse, whereas the permeability of the chloride channels does not change greatly during this process. Therefore, rapid changes in sodium and potassium permeability are primarily responsible for signal transmission in nerves.*

Measuring the membrane potential.

The method for measuring the membrane potential is simple in theory but often difficult in practice because of the small size of most of the fibers. Figure below shows a small pipette filled with an electrolyte solution. The pipette is impaled through the cell membrane to the interior of the fiber. Then another electrode, called the ***"indifferent electrode,"*** *is placed in the extracellular fluid, and the potential difference between the inside and outside of the fiber is measured using an appropriate voltmeter. This voltmeter is a highly sophisticated electronic apparatus that is capable of measuring very small voltages despite extremely high resistance to electrical flow through the tip of the micropipette, which has a lumen diameter usually less than 1 micrometer and a resistance more than a million ohms. For recording rapid changes in the membrane potential during transmission of nerve impulses, the microelectrode is connected to an oscilloscope.*

The lower part of Figure below shows the electrical potential that is measured at each point in or near the nerve fiber membrane, beginning at the left side of the figure and passing to the right. As long as the electrode is outside the nerve membrane, the recorded potential is zero, which is the potential of the extracellular fluid. Then, as the recording electrode passes through the voltage change area at the cell membrane (called the ***electrical dipole layer****), the potential decreases abruptly to –90 millivolts. Moving across the center of the fiber, the potential remains at a steady –90-millivolt level but reverses back to zero the instant it passes through the membrane on the opposite side of the fiber. To create a negative potential inside the membrane, only enough positive ions to develop the electrical dipole layer at the membrane itself must be transported outward. All the remaining ions inside the nerve fiber can be both positive and negative, Therefore, an incredibly small number of ions needs to be transferred through the membrane to establish the normal "resting potential" of –90 millivolts inside the nerve fiber;Also, an equally small number of positive ions moving from outside to inside the fiber can reverse the potential from –90 millivolts to as much as +35 millivolts within as little as 1/10,000 of a second.*

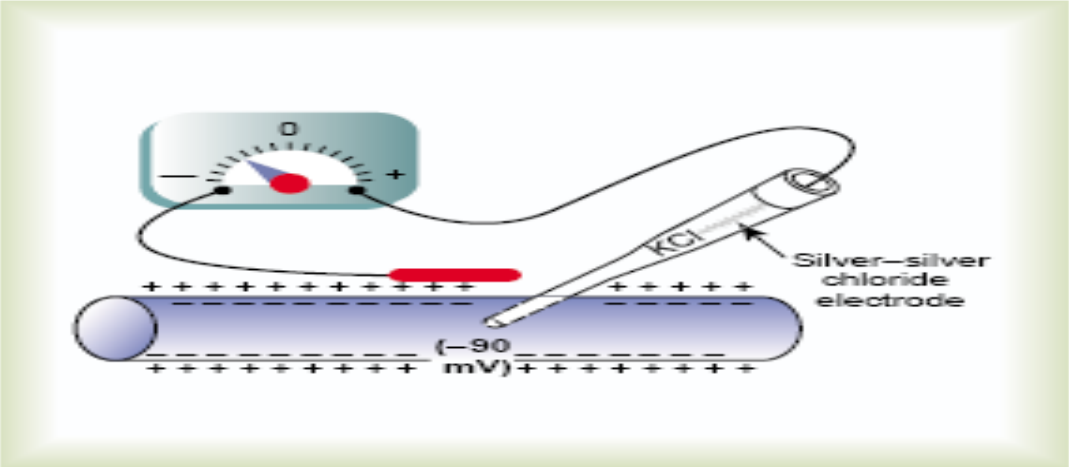


Figure 5–2

Measurement of the membrane potential of the nerve fiber using a microelectrode.

Resting Membrane Potential of Nerves

The resting membrane potential of large nerve fibers when not transmitting nerve signals is about −90 millivolts. That is, the potential *inside the fiber* is 90 millivolts more negative than the potential in the extracellular fluid on the outside of the fiber.

Active Transport of Sodium and Potassium IonsThrough the Membrane—The Sodium-Potassium (Na^+-K^+) Pump.

In previous study all cell membranes of the body have a powerful Na+-K+ pump that continually transports sodium ions to the outside of the cell and potassium ions to the inside, as illustrated on the left-hand side in Figure below Further, note that this is an *electrogenic pump* because more positive charges are pumped to the outside than to the inside (three Na+ ions to the outside for each two K+ ions to the inside), leaving a net

deficit of positive ions on the inside; this causes a negative potential inside the cell membrane. The Na+-K+ pump also causes large concentration gradients for sodium and potassium across the resting nerve membrane. These gradients are the following:

Na^+ (outside): 142 mEq/L

Na^+ (inside): 14 mEq/L

K^+ (outside): 4 mEq/L

K^+ (inside): 140 mEq/L

The ratios of these two respective ions from the inside to the outside are

$$Na^+_{inside}/Na^+_{outside} = 0.1$$

$$K^+_{inside}/K^+_{outside} = 35.0$$

Leakage of Potassium Through the Nerve Membrane.

In figure below shows a channel protein, sometimes called a *"tandem pore domain," potassium channel*, or *potassium (K+) "leak" channel,* in the nerve membrane through which potassium can leak even in a resting cell. These K+ leak channels may also leak sodium ions slightly but are far more permeable to potassium than to sodium, normally about 100 times as permeable. As discussed later, this differential in permeability is a key factor in determining the level of the normal resting membrane potential.

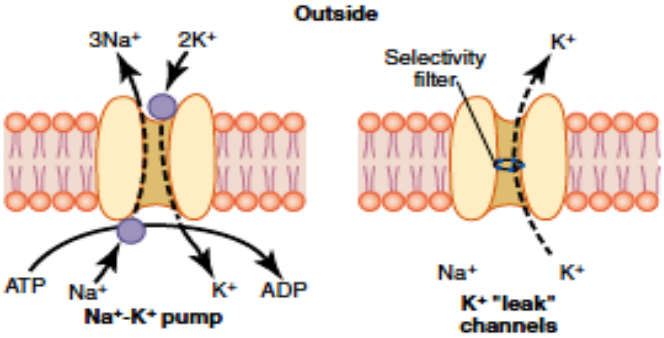


Figure 5–4 Functional characteristics of the Na^+-K^+ pump and of the K^+ "leak" channels. ADP, adenosine diphosphate; ATP, adenosine triphosphate. The K^+ "leak" channels also leak Na^+ ions into the cell slightly, but are much more permeable to K^+.

Origin of the Normal Resting Membrane Potential

In figure below shows the important factors in the establishment of the normal resting membrane potential of −90millivolts. They are as follows.

A- Contribution of the Potassium Diffusion Potential

In figure (A) we make the assumption that the only movement of ions through the membrane is diffusion of potassium ions, as demonstrated by the open channels between the potassium symbols (K+) inside and outside the membrane. Because of the high ratio of potassium ions inside to outside, 35:1, the Nernst potential corresponding to this ratio is −94 millivolts because the logarithm of 35 is 1.54, and this multiplied by −61 millivolts is −94 millivolts. Therefore, if potassium ions were the only factor causing the resting potential, the resting potential *inside the fiber* would be equal to −94 millivolts, as show in the figure .

B- Contribution of Sodium Diffusion Through the Nerve Membrane

In figure(B) shows the addition of 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. But also shown in Figure 5 is the Nernst potential for potassium diffusion of −94 millivolts. How do these interact with each other, and what will be the summated potential? This can be answered by using the Goldman equation described previously. Intuitively, one can see that if 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 its permeability to sodium. Using this value in the Goldman equation gives a potential inside the membrane of −86 millivolts, which is near the potassium potential shown in the figure.

C- Contribution of the Na^+-K^+ Pump

In Figure(C), the Na+-K+ pump is shown to provide an additional contribution to the resting potential. In this figure, there is 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 continual loss of positive charges from inside the membrane; this creates an additional degree of negativity (about −4 millivolts additional) on the inside beyond that which can be accounted for by diffusion alone. Therefore, as shown in Figure the net membrane potential with all these factors operative at the same time is about −90 millivolts.

Summary

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

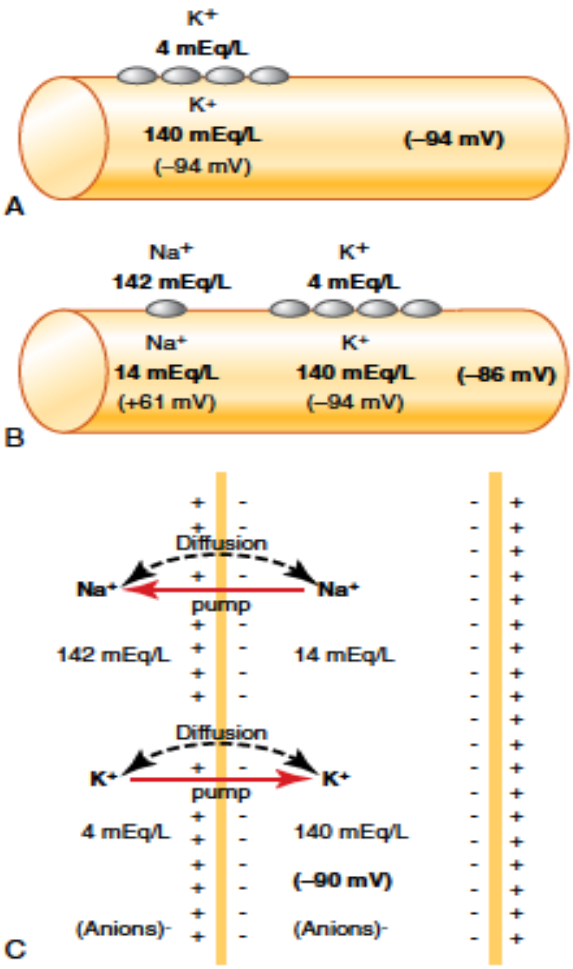
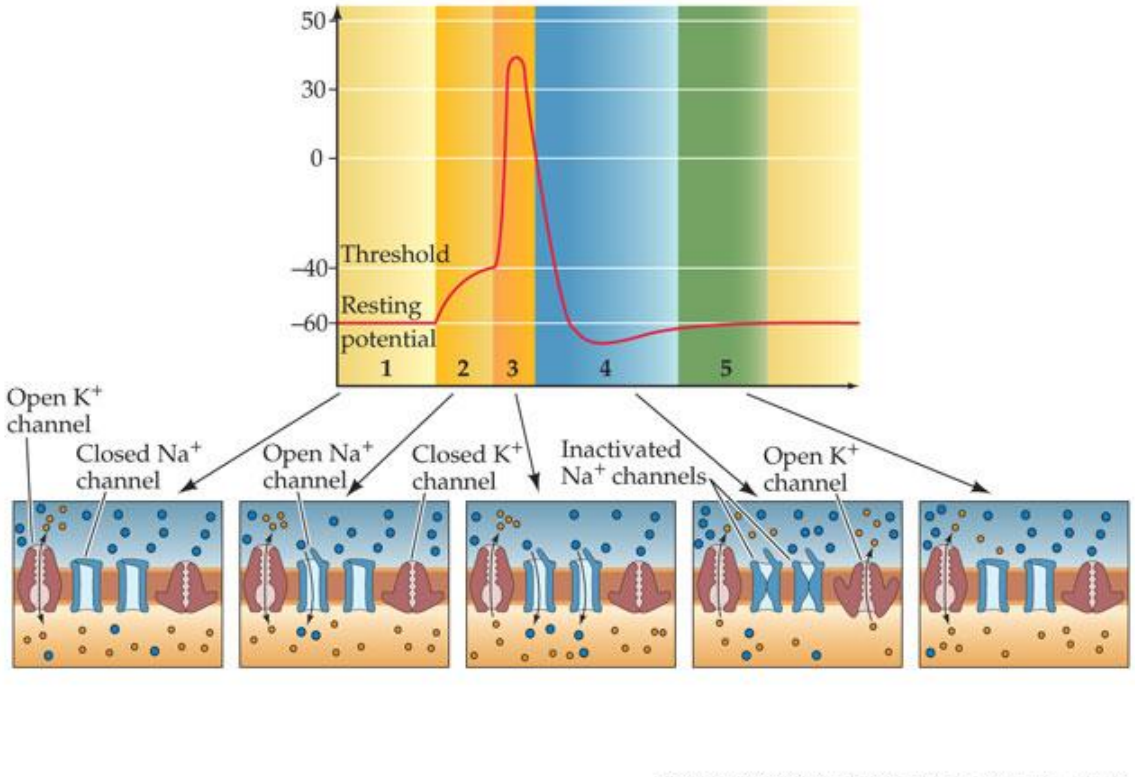


Figure 5-5 Establishment of resting membrane potentials in nerve fibers under three conditions: *A*, when the membrane potential is caused entirely by potassium diffusion alone; *B*, when the membrane potential is caused by diffusion of both sodium and potassium ions; and *C*, when the membrane potential is caused by diffusion of both sodium and potassium ions plus pumping of both these ions by the Na^+-K^+ pump.

Nerve Action Potential

Nerve signals are transmitted by action potentials, which are rapid changes in the membrane potential that spread rapidly along the nerve fiber membrane. Each action potential begins with a sudden change from the normal resting negative membrane potential to a positive potential and then ends with an almost equally rapid change back to the negative potential. To conduct a nerve signal, the action potential moves along the nerve fiber until it comes to the fiber's end. The upper panel of Figure below shows the changes that occur at the membrane during the action potential, with transfer of positive charges to the interior of the fiber at its onset and return of positive charges to the exterior at its end. The lower panel shows graphically the successive changes in membrane potential over a few 10,000ths of a second, illustrating the explosive onset of the action potential and the almost equally rapid recovery. The successive stages of the action potential are as follows.



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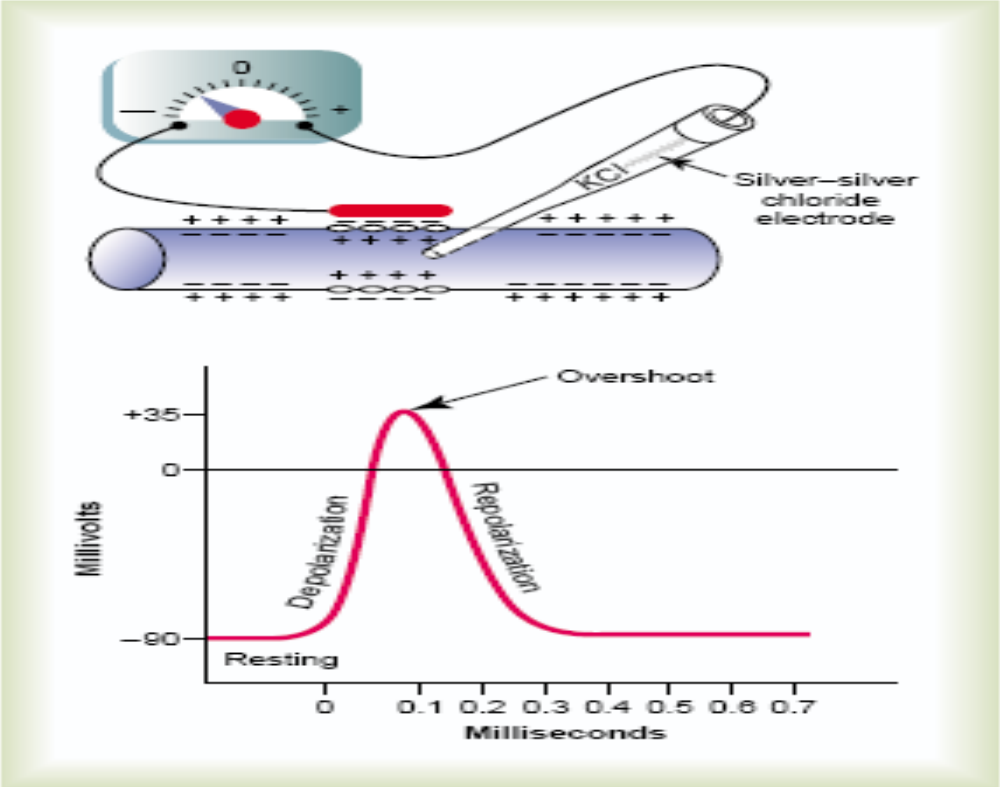


Figure 5–6

Typical action potential recorded by the method shown in the upper panel of the figure.

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 diffuse to the interior of the axon. The normal "polarized"

state of –90 millivolts is immediately neutralized by the inflowing positively charged sodium ions, with the potential rising rapidly in the positive direction. This is called ***depolarization****. In large nerve fibers, the great excess of positive sodium ions moving to the inside causes the membrane potential to actually "overshoot" beyond the zero level and to become somewhat positive. In some smaller fibers, as well as in many central nervous 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 second after the membrane becomes highly permeable to sodium ions, the sodium channels begin to close and the potassium channels open more than normal. Then, rapid diffusion of potassium ions to the exterior re-establishes the normal negative resting membrane potential. This is called ***repolarization****of the membrane.*

To explain more fully the factors that cause both depolarization and repolarization, we need to describe the special characteristics of two other types of transport channels through the nerve membrane: the voltage-gated sodium and potassium channels.

Voltage-gated sodium channel-activation and inactivation of channel

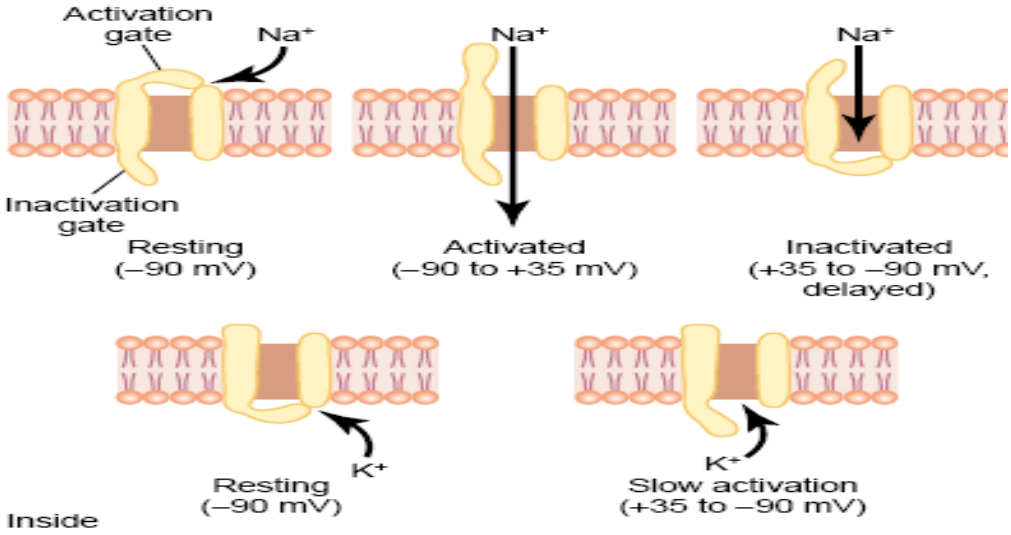
The upper panel of figure below shows the voltage-gated sodium channel in three separate states. This channel has two gates—one near the outside of the channel called the ***activation gate****, and another near the inside called the* ***inactivation gate****. The upper left of the figure depicts the state of these two gates in the normal resting membrane when the membrane potential is –90 millivolts. In this state, the activation gate is closed, which prevents any entry of sodium ions to the interior of the fiber through these sodium channels.*

- Activation of the sodium channel.

When the membrane potential becomes less negative than during the resting state, rising from –90 millivolts toward zero, it finally reaches a voltage—usually somewhere between –70 and –50 millivolts—that causes a sudden conformational change in the activation gate, flipping it all the way to the open position. This is called the ***activated state****; during this state, sodium ions can pour inward through the channel, increasing the sodium permeability of the membrane as much as 500- to 5000-fold.*

- Inactivation of the sodium channel.

The upper right panel of figure below shows a third state of the sodium channel. The same increase in voltage that opens the activation gate also closes the inactivation gate. The inactivation gate, however, closes a few 10,000ths of a second after the activation gate opens. That is, the conformational change that flips the inactivation gate to the closed state is a slower process than the conformational change that opens the activation gate. Therefore, after the sodium channel has remained open for a few 10,000ths of a second, the inactivation gate closes, and sodium ions no longer can pour to the inside of the membrane. At this point, the membrane potential begins to recover back toward the resting membrane state, which is the repolarization process. Another important characteristic of the sodium channel inactivation process is that the inactivation gate will not reopen until the membrane potential returns to or near the original resting membrane potential level. Therefore, it usually is not possible for the sodium channels to open again without the nerve fibers first repolarizing.



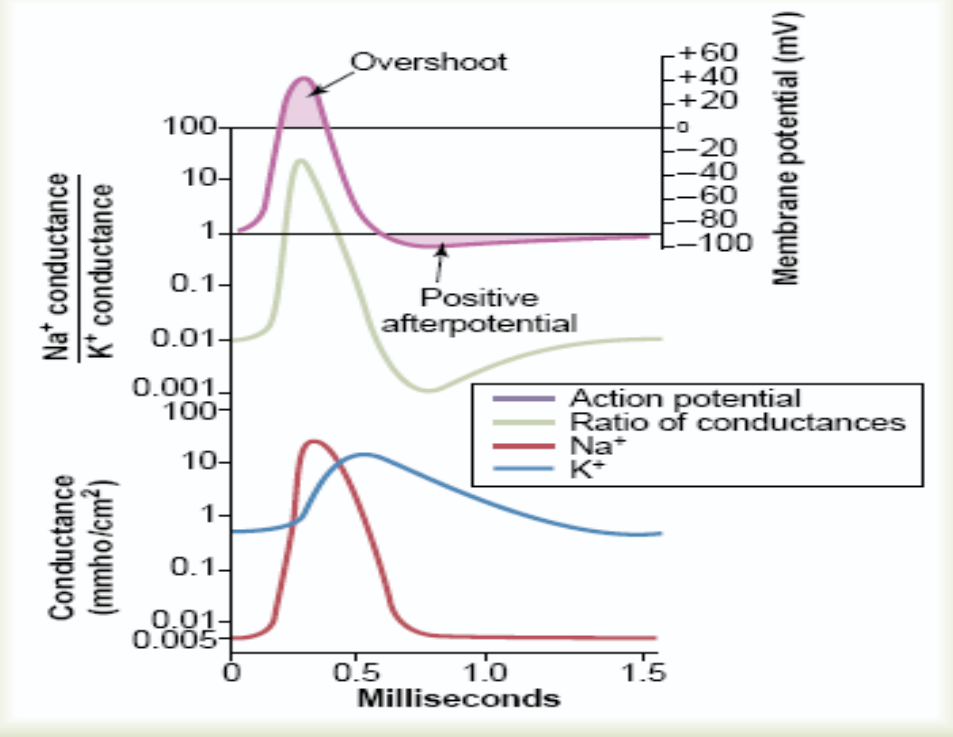
Voltage-gated potassium channel and its activation

The lower panel of Figure above shows the voltage-gated potassium channel in two states: during the resting state (left) and toward the end of the action potential (right). During the resting state, the gate of the potassium channel is closed, and potassium ions are prevented from passing through this channel to the exterior. When the membrane potential rises from –90 millivolts toward zero, this voltage change causes a conformational opening of the gate and allows increased potassium diffusion outward through the channel. However, because of the slight delay in opening of the potassium channels, for the most part, they open just at the same time that the sodium channels are beginning to close because of inactivation. Thus, the decrease in sodium entry to the cell and the simultaneous increase in potassium exit from the cell combine to speed the repolarization process, leading to full recovery of the resting membrane potential within another few 10,000ths of a second.

Summary of the events that cause the action potential.

Figure below shows in summary form the sequential events that occur during and shortly after the action potential. The bottom of the figure shows the changes in membrane conductance for sodium and potassium ions. During the resting state, before the action potential begins, the conductance for potassium ions is 50 to 100 times as great as the conductance for sodium ions. This is caused by much greater leakage of potassium ions than sodium ions through the leak channels. However, at the onset of the action potential, the sodium channels instantaneously become activated and allow up to a 5000-fold increase in sodium conductance. Then the inactivation process closes the sodium channels within another fraction of a millisecond. The onset of the action potential also causes voltage gating of the potassium channels, causing them to begin opening more slowly a fraction of a millisecond after the sodium channels open. At the end of the action potential, the return of the membrane potential to the negative state causes the potassium channels to close back to their original status, but again, only after an additional millisecond or more delay.

The middle portion of the figure below shows the ratio of sodium conductance to potassium conductance at each instant during the action potential, and above this is the action potential itself. During the early portion of the action potential, the ratio of sodium to potassium conductance increases more than 1000-fold. Therefore, far more sodium ions flow to the interior of the fiber than do potassium ions to the exterior. This is what causes the membrane potential to become positive at the action potential onset. Then the sodium channels begin to close and the potassium channels to open, so that the ratio of conductance shifts far in favor of high potassium conductance but low sodium conductance. This allows very rapid loss of potassium ions to the exterior but virtually zero flow of sodium ions to the interior. Consequently, the action potential quickly returns to its baseline level.



Roles of other ions during the action potential

Thus far, we have considered only the roles of sodium and potassium ions in the generation of the action potential. At least two other types of ions must be considered: negative anions and calcium ions.

- Impermeant negatively charged ions inside the nerve axon.

Inside the axon are many negatively charged ions (anions) that cannot go through the membrane channels. They include the anions of protein molecules and of many organic phosphate compounds, sulfate compounds, andso forth. Because these ions cannot leave the interior of the axon, any deficit of positive ions inside the membrane leaves an excess of these impermeant negative anions. Therefore, these impermeant negative ions are responsible for the negative charge inside the fiber when there is a net deficit of positively charged potassium ions and other positive ions.

- Calcium ions.

The membranes of almost all cells of the body have a calcium pump similar to the sodium pump, and calcium serves along with (or instead of) sodium in some cells to cause most of the action potential. Like the sodium pump, the calcium pump pumps calcium ions from the interior to the exterior of the cell membrane creating a calcium ion gradient of about 10,000-fold.This leaves an internal cell concentration of calcium ions of about 10–7 molar, in contrast to an external concentration of about 10–3 molar.

In addition, there are voltage-gated calcium channels.These channels are slightly permeable to sodium ions as well as to calcium ions; when they open, both calcium and sodium ions flow to the interior of the fiber. Therefore, these channels are also called ***Ca^{++}-Na^{+}channels****.The calcium channels are slow to become activated, requiring 10 to 20 times as long for activation as the sodium channels. Therefore, they are called* ***slow channels****, in contrast to the sodium channels, which are called* ***fast channels****.*

Calcium channels are numerous in both cardiac muscle and smooth muscle. In fact, in some types of smooth muscle, the fast sodium channels are hardly present, so that the action potentials are caused almost entirely by activation of slow calcium channels.

Increased Permeability of the Sodium Channels When There Is a Deficit of Calcium Ions. The concentration of calcium ions in the extracellular fluid also has a profound effect on the voltage level at which the sodium channels become activated. When there is a deficit of calcium ions, the sodium

channels become activated (opened) by a small increase of the membrane potential from its normal, very negative level. Therefore, the nerve fiber becomes highly excitable, sometimes discharging repetitively without provocation rather than remaining in the resting state. In fact, the calcium ion

concentration needs to fall only 50 percent below normal before spontaneous discharge occurs in some peripheral nerves, often causing muscle "tetany." This is sometimes lethal because of tetanic contraction of the respiratory muscles.

The probable way in which calcium ions affect the sodium channels is as follows: These ions appear to bind to the exterior surfaces of the sodium channel protein molecule. The positive charges of these calcium ions in turn alter the electrical state of the sodium channel protein itself, in this way altering the voltage level required to open the sodium gate.