THE CELL AND ITS FUNCTION

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A typical cell has two major parts: the **nucleus** and the **cytoplasm**. The nucleus is separated from the cytoplasm by a **nuclear membrane/nuclear envelop**, 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**. Protoplasm is composed mainly of five basic substances: **(A) Water:** present in most cells, except for fat cells, in a concentration of 70 to 85 %. **(B) Electrolytes**: most important ions in the cell are *potassium, magnesium, phosphate, sulfate, bicarbonate*, and smaller quantities of *sodium, chloride, and calcium*. **(C) Proteins**: after water, the most abundant substances in most cells are proteins, which normally constitute 10 to 20 % of the cell mass. These can be divided into two types; **structural proteins** and **functional proteins** (*mainly the enzymes of the cell and, in contrast to the structural proteins, are often mobile in the cell fluid*). **(D) Lipids**: important lipids are *phospholipids* and *cholesterol*, which together constitute only about 2 per cent of the total cell mass. In addition, some cells contain large quantities of *triglycerides*, also called *neutral fat*. **(E) 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. *Constitutes about 1 per cent of total cell mass but increases to as much as 3 % in muscle cells and 6 % in liver cells*. 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.

STRUCTURES OF THE CELL

The cell contains highly organized physical structures called **intracellular organelles**. They include the *membranous structures, filament and tubular structures, cytoplasm and its organelles, nucleus, nucleoli and ribosomes*.

(1) Membranous structures

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.

(A) Cell membrane: Also called the plasma membrane and envelops the cell. It is composed almost entirely of proteins, lipids bi layer and carbohydrates. The cell membrane has two types of protein (glycoprotein): **integral proteins** that protrude all the way through the membrane, and **peripheral proteins** that are attached only to one surface of the membrane. The integral proteins *provide structural channels (or pores) through which water molecules and water-soluble substances, especially ions, can diffuse* between the extracellular and intracellular fluids. Integral proteins *also act as enzymes* and can *also serve as carrier proteins* for transporting substances that otherwise could not penetrate the lipid bilayer. Integral membrane proteins *can also serve as*

receptors for water-soluble chemicals, such as peptide hormones that do not easily penetrate the cell membrane. On the other hand, *peripheral protein molecules are often attached to the integral proteins*. These peripheral proteins *function almost entirely as enzymes* or as controllers of transport of substances through the cell membrane pores. The cell membrane also contains carbohydrates (**glycocalyx**) which *occurs almost invariably in combination with proteins (glycoproteins) or lipids (glycolipids)*. Other cell membrane carbohydrate compounds called **proteoglycans**, which are mainly *carbohydrate substances bound to small protein cores*, are loosely attached to the outer surface of the cell as well. The cell membrane carbohydrate moieties have several important functions: many of them have a negative electrical charge, which gives most cells an overall negative surface charge that repels other negative objects; the glycocalyx of some cells attaches to the glycocalyx of other cells, thus attaching cells to one another; many of the carbohydrates act as receptor substances for binding hormones, such as insulin; when bound, this combination activates attached internal proteins that, in turn, activate a cascade of intracellular enzymes; some carbohydrate moieties enter into immune reactions.

(2) Cytoplasm and its 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.

(A) Endoplasmic reticulum: *The space inside the tubules and vesicles is filled with* **endoplasmic matrix**, a watery medium that is different from the fluid in the cytosol outside the 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. 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 intrareticular enzymes.

(B) Golgi apparatus: The Golgi apparatus *functions in association with the endoplasmic reticulum*. 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 organelles which break off from the golgi apparatus known as lysosomes, secretory vesicles, and other cytoplasmic components*.

(C) Lysosomes: they 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 damaged cellular structures and food particles that have been ingested by the cell and unwanted matter such as bacteria. Their activity is aided by hydrolase enzyme.

(D) Peroxisomes: First, 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. Second, *they contain oxidases* rather than hydrolases.
(E) 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.
(F) Mitochondria: they are *called the "powerhouses" of the cell*. It is involved in the synthesis of a "high-energy" substance called **adenosine triphosphate** (**ATP**). ATP is then transported out of the mitochondrion, and it diffuses throughout the cell to release its own energy wherever it is needed for performing cellular functions. 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.

(3) Filament and tubular structures of the cell
Large numbers of actin filaments frequently occur in the outer zone of the cytoplasm, called the **ectoplasm**, to form an elastic support for the cell membrane. A special type of stiff filament composed of polymerized tubulin molecules is used in all cells to construct very strong tubular structures, the microtubules. *Thus, a primary function of microtubules is to act as a cytoskeleton, providing rigid physical structures for certain parts of cells.*

(4) Nucleus: The nucleus is *the control center of the cell*. Briefly, *the nucleus contains large quantities of DNA, which are the gene*s. 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.

(5) 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.

(6) Nucleoli and formation of ribosomes: the nuclei of most cells contain one or more highly staining structures called nucleoli. The nucleolus does not have a limiting membrane. Instead, it is *simply an accumulation of large amounts of RNA and proteins* of the types found in ribosomes.

FUNCTIONAL SYSTEMS OF THE CELL (FUNCTIONS)

(1) Ingestion by cell (Endocytosis)
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 molecules* 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: 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.

Phagocytosis: Only certain cells have the capability of phagocytosis, most notably the tissue macrophages and some of the white blood cells. 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 vesicle separates from the cell membrane, leaving the vesicle in the cell interior in the same way that pinocytotic vesicles are formed.

(2) Digestion of pinocytotic and phagocytic foreign substances inside the cell

Almost immediately after a pinocytotic or phagocytic vesicle appears inside a cell, one or more lysosomes become attached to the vesicle and empty their acid hydrolases to the inside of the vesicle. Thus, a digestive vesicle is formed inside the cell cytoplasm in which the vesicular hydrolases begin hydrolyzing the proteins, carbohydrates, lipids, and other substances in the vesicle. What is left of the digestive vesicle, called the residual body, represents indigestible substances. In most instances, this is finally excreted through the cell membrane by a process called **exocytosis**, which is essentially the opposite of endocytosis. Thus, the pinocytotic and phagocytic vesicles containing lysosomes can be called the digestive organs of the cells.

Functions of the lysosomes: tissues of the body often regress to a smaller size. For instance, this occurs in the uterus after pregnancy, in muscles during long periods of inactivity, and in mammary glands at the end of lactation. Lysosomes are responsible for much of this regression. Another special role of the lysosomes is removal of damaged cells or damaged portions of cells from tissues. Damage to the cell (caused by heat, cold, trauma, chemicals, or any other factor) induces lysosomes to rupture. The released hydrolases immediately begin to digest the surrounding organic

substances. If the damage is slight, only a portion of the cell is removed, followed by repair of the cell. If the damage is severe, the entire cell is digested, a process called autolysis. In this way, the cell is completely removed, and a new cell of the same type ordinarily is formed by mitotic reproduction of an adjacent cell to take the place of the old one. The lysosomes also contain bactericidal agents that can kill phagocytized bacteria before they can cause cellular damage. These agents include (1) **lysozyme**, which dissolves the bacterial cell membrane; (2) **lysoferrin**, which binds iron and other substances before they can promote bacterial growth; and (3) acid at a pH of about 5.0, which activates the hydrolases and inactivates bacterial metabolic systems.

(3) Synthesis and formation of cellular structure (by endoplasmic reticulum and Golgi apparatus)

Most synthesis begins in the endoplasmic reticulum. The products formed there are then passed on to the Golgi apparatus, where they are further processed before being released into the cytoplasm.

Specific functions of the endoplasmic reticulum (ER)

(a) Granular endoplasmic reticulum is responsible for protein synthesis (b) Smooth endoplasmic reticulum is responsible for lipid synthesis (c) ER provides the enzymes that control glycogen breakdown when glycogen is to be used for energy (d) ER provides a vast number of enzymes that are capable of detoxifying substances, such as drugs, that might damage the cell.

Specific functions of the Golgi apparatus (GA)

(a) It has the capability of synthesizing certain carbohydrates (hyaluronic acid and chondroitin sulfate) that cannot be formed in the endoplasmic reticulum. A few of the many functions of hyaluronic acid and chondroitin sulfate in the body are as follows: (i) they are the major components of proteoglycans secreted in mucus and other glandular secretions; (ii) they are the major components of the ground substance outside the cells in the interstitial spaces, acting as filler between collagen fibers and cells; and (iii) they are principal components of the organic matrix in both cartilage and bone (b) Golgi apparatus helps also in the processing of secretions of the endoplasmic reticulum (C) also, GA helps in the formation of vesicles such as secretory vesicles and lysosomes (d) also, GA aids in the use of intracellular vesicles to replenish cellular membranes. For instance, the cell membrane loses much of its substance every time it forms a phagocytic or pinocytotic vesicle, and the vesicular membranes of the Golgi apparatus continually replenish the cell membrane.

(4) Extraction of energy from nutrients (function of the mitochondria)

Almost all these oxidative reactions occur inside the mitochondria, and the energy that is released is used to form the high-energy compound called adenosine triphosphate (ATP). Then, ATP, not the original foodstuffs, is used throughout the cell to energize almost all the subsequent intracellular metabolic reactions. It is important to note that ATP is a nucleotide composed of (i) the nitrogenous base adenine (ii) the pentose sugar ribose, and (iii) three phosphate radicals

LOCOMOTION OF CELLS

By far the most important type of movement that occurs in the body is that of the muscle cells in skeletal, cardiac, and smooth muscle, which constitute almost 50 % of the entire body mass. Two other types of movement are ameboid locomotion and ciliary movement which occur in other cells.

Ameboid movement

Ameboid movement *is movement of an entire cell in relation to its surroundings*, especially in response to stimuli such as movement of white blood cells through tissues. Two effects are essential for forward movement of the cell. The *first effect is attachment of the pseudopodium to surrounding tissues* so that it becomes fixed in its leading position, while the remainder of the cell body is pulled forward toward the point of attachment. The *second essential effect for locomotion is to provide the energy required to pull the cell body in the direction of the pseudopodium.* The whole process is energized by the high-energy compound ATP. The *most important initiator of ameboid locomotion is the process called chemotaxis. Any chemical substance that causes chemotaxis to occur is called a chemotactic substance.* Most cells that exhibit ameboid locomotion move toward the source of a chemotactic substance (that is, from an area of lower concentration toward an area of higher concentration) which is called *positive chemotaxis*. Some cells move away from the source, which is called *negative chemotaxis*. The most common cells to exhibit ameboid locomotion in the human body are the *white blood cells* when they move out of the blood into the tissues in the form of tissue macrophages. Also, fibroblasts move into a damaged area to help repair the damage. Finally, cell locomotion is especially important in development of the embryo and fetus after fertilization of an ovum. For instance, embryonic cells often must migrate long distances from their sites of origin to new areas during development of special structures.

Cilia and ciliary movement

A second type of cellular motion, ciliary movement, is a *whiplike movement of cilia on the surfaces of cell*s. This occurs in only two places in the human body: on the surfaces of the *respiratory airways* and on the inside surfaces of the *uterine tubes (fallopian tubes)* of the reproductive tract. In the nasal cavity and lower respiratory airways, the whiplike motion of cilia causes a layer of mucus to move at a rate of about 1 cm/min toward the pharynx, in this way continually clearing these passageways of mucus and particles that have become trapped in the mucus. In the uterine tubes, the cilia cause slow movement of fluid from the ostium of the uterine tube toward the uterus cavity; this movement of fluid transports the ovum from the ovary to the uterus. Each cilium is an outgrowth of a structure that lies immediately beneath the cell membrane, called the basal body of the cilium.

TRANSPORT OF SUBSTANCES THROUGH THE CELL MEMBRANE

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*. 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. *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, activ*e 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.

1) 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.

A) Simple diffusion: can occur through the cell membrane by two pathways: (i) through the interstices of the lipid bilayer if the diffusing substance is lipid soluble, and (ii) through watery channels that penetrate all the way through some of the large transport proteins. 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.

Gating of Protein Channels

Gating of protein channels provides a means of controlling ion permeability of the channels. The mechanisms include (i) **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*. (ii) **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.

B) 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 Vmax, as the concentration of the diffusing substance increases*. *Among the most important substances that cross cell membranes by facilitated diffusion are glucose and most of the amino acids.*

Factors affecting 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.

a) Concentration difference: the rate of net diffusion into the cell is proportional to the concentration on the outside minus the concentration on the inside, or: Net diffusion μ (Co - Ci) in which Co is concentration outside and Ci is concentration inside.

b) Electrical potential (Nernst potential): At normal body temperature (37°C), the electrical difference that will balance a given concentration difference of univalent ions (Na+) can be determined from the following formula, called the Nernst equation: EMF = $\pm$ 61 log c1/c2 in which EMF is the electromotive force (voltage) between side 1 and side 2 of the membrane, C1 is the concentration on side 1, and C2 is the concentration on side 2. This equation is extremely important in understanding the transmission of nerve impulses.

c) Pressure difference: 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. 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.

C) Osmosis across selectively permeable membranes (Net Diffusion of Water): 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 with pure water on one side of the cell membrane and a solution of sodium chloride on the other side. Thus, net movement of water occurs from left to right, that is, osmosis occurs from the pure water into the sodium chloride solution.

2) 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. Active transport is divided into two types according to the source of the energy used to cause the transport:

(a) Primary 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. (b) **Secondary active transport**; here, *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. 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. 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.

In both instances (primary and secondary active transport), 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.

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. 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.

Calcium Pump: 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.

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. Note that the transport carrier protein has two binding sites on its exterior side, one for sodium and one for glucose. 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 co-transport of the amino acids occurs in the same manner as for glucose, except that it uses a different set of transport proteins. 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.

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. 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.

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, and (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, and then (2) either simple diffusion or facilitated diffusion through the membrane on the opposite side of the cell.

MEMBRANE POTENTIALS

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
discussion is concerned with membrane potentials generated both at rest and during action by nerve and muscle cells.

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. The important factors in the establishment of the normal resting membrane potential of –90 millivolts are as follows; potassium diffusion potential, sodium diffusion through the nerve membrane and Na^{+}-K^{+} pump. In 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.

Nerve action potentials

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 action potential is comprised of various stages which include;

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.

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 are immediately neutralized by the inflowing positively charged sodium ions, with the potential rising rapidly in the positive direction. This is called depolarization. Simply put, depolarization is due to sodium ion conductance which takes sodium ion (positive ion) into the cell.

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. Simply put, repolarization is due to potassium ion conductance which takes potassium ion (positive ion) out of the cell. This is usually facilitated by the **voltage-gated sodium and potassium channels**. In the **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. In the **inactivation of sodium channel**, the same increase in voltage that opens the activation gate also closes the inactivation gate. Therefore, after the sodium channel has remained open for a few seconds, 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

fiber's first repolarizing. In the **potassium channel**, 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 seconds.

Initiation, threshold and propagation of action potential

The initiation of action potential is brought about (initiated) by a positive-feedback vicious cycle which opens the sodium channels. When the number of Na+ ions entering the fiber becomes greater than the number of K+ ions leaving the fiber, sudden rise in membrane potential of 15 to 30 millivolts (from -90 millivolts to about -65 millivolts) usually occur leading to the explosive development of an action potential. This level of –65 millivolts is said to be the **threshold for stimulation**. A very weak stimulus at point A causes the membrane potential to change from –90 to –85 millivolts, but this is not a sufficient change for the automatic regenerative processes of the action potential to develop. At point B, the stimulus is greater, but again, the intensity is still not enough. The stimulus does, however, disturb the membrane potential locally for as long as 1

millisecond or more after both of these weak stimuli. These local potential changes are called acute local potentials, and when they fail to elicit an action potential, they are called **acute subthreshold potentials.** An excitable membrane has no single direction of propagation, but the action potential travels in all directions away from the stimulus until the entire membrane has become depolarized. Once an action potential has been elicited at any point on the membrane of a normal fiber, the depolarization process travels over the entire membrane if conditions are right, or it does not travel at all if conditions are not right. This is called the **all-or-nothing principle**. Therefore, for continued propagation of an impulse to occur, the ratio of action potential to threshold for excitation must at all times be greater than 1. This "greater than 1" requirement is called the **safety factor for propagation**.

Rhythmicity of some excitable tissues (repetitive discharge)

Repetitive self-induced discharges occur normally in the heart, in smooth muscle, and in many of the neurons of the central nervous system. These rhythmical discharges cause (1) the rhythmical beat of the heart, (2) rhythmical peristalsis of the intestines, and (3) such neuronal events as the rhythmical control of breathing. The excessive outflow of potassium ions carries tremendous numbers of positive charges to the outside of the membrane, leaving inside the fiber considerably more negativity than would otherwise occur. This continues for nearly a second after the preceding action potential is over, thus drawing the membrane potential nearer to the potassium Nernst potential. This is a state called **hyperpolarization**. As long as this state exists, self–re-excitation will not occur. But the excess potassium conductance (and the state of hyperpolarization) gradually disappears, thereby allowing the membrane potential again to increase up to the threshold for excitation. Then, suddenly, a new action potential results, and the process occurs again and again.

Special characteristics of signal transmission in nerve trunks

The large fibers are **myelinated**, and the small ones are **unmyelinated**. The average nerve trunk contains about twice as many unmyelinated fibers as myelinated fibers. The central core of the fiber is the **axon**, and the membrane of the axon is the membrane that actually conducts the action potential. The axon is filled in its center with **axoplasm**, which is a viscid intracellular fluid. Surrounding the axon is a **myelin sheath** that is often much thicker than the axon itself. The myelin sheath is deposited around the axon by **Schwann cells** (function of the Schwann cell is to insulate nerve fibers). At the juncture between each two successive Schwann cells along the axon, a small uninsulated area only 2 to 3 micrometers in length remains where ions still can flow with ease through the axon membrane between the extracellular fluid and the intracellular fluid inside the axon. This area is called the **node of Ranvier**. About once every 1 to 3 millimeters along the length of the myelin sheath is a node of Ranvier. Even though almost no ions can flow through the thick

myelin sheaths of myelinated nerves, they can flow with ease through the nodes of Ranvier. Therefore, action potentials occur only at the nodes. Yet the action potentials are conducted from node to node, this is called **saltatory conduction**. That is, electrical current flows through the surrounding extracellular fluid outside the myelin sheath as well as through the axoplasm inside the axon from node to node, exciting successive nodes one after another. Saltatory conduction is of value for two reasons. First, by causing the depolarization process to jump long intervals along the axis of the nerve fiber, this mechanism increases the velocity of nerve transmission in myelinated fibers as much as 5- to 50-fold. Second, saltatory conduction conserves energy for

the axon because only the nodes depolarize, allowing perhaps 100 times less loss of ions than would otherwise be necessary, and therefore requiring little metabolism for reestablishing the sodium and potassium concentration differences across the membrane after a series of nerve impulses. Still another feature of saltatory conduction in large myelinated fibers is the following: The excellent insulation afforded by the myelin membrane and the 50- fold decrease in membrane capacitance allow repolarization to occur with very little transfer of ions.

Refractory period after an action potential, during which a new stimulus cannot be elicited
A new action potential cannot occur in an excitable fiber as long as the membrane is still depolarized from the preceding action potential. The reason for this is that shortly after the action potential is initiated, the sodium channels (or calcium channels, or both) become inactivated, and no amount of excitatory signal applied to these channels at this point will open the inactivation gates. The only condition that will allow them to reopen is for the membrane potential to return to or near the original resting membrane potential level. Then, within another small fraction of a second, the inactivation gates of the channels open, and a new action potential can be initiated. *The period during which a second action potential cannot be elicited, even with a strong stimulus, is called the* **absolute refractory period.**

Inhibition of excitability (stabilizers and local anesthetics)
Membrane-stabilizing factors, can decrease excitability. For instance, a high extracellular fluid calcium ion concentration decreases membrane permeability to sodium ions and simultaneously reduces excitability. Therefore, calcium ions are said to be a **stabilizer**. Among the most important stabilizers are the many substances used clinically as **local anesthetics**, including procaine and tetracaine. *Most of these act directly on the activation gates of the sodium channels, making it much more difficult for these gates to open, thereby reducing membrane excitability (simply put, they block/inhibit the opening of sodium ion channel)*. When excitability has been reduced so low that the ratio of action potential strength to excitability threshold (called the safety factor) is reduced below 1.0, nerve impulses fail to pass along the anesthetized nerves.

Recording membrane potentials and action potentials
For practical purposes, the only common type of meter that is capable of responding accurately to the rapid membrane potential changes is the *cathode ray oscilloscope*. The cathode ray tube itself is composed basically of an electron gun and a fluorescent screen against which electrons are fired. In addition to the electron gun and fluorescent surface, the cathode ray tube is provided with two sets of electrically charged plates; one set positioned on the two sides of the electron beam, and the other set positioned above and below.

PHYSIOLOGIC ANATOMY OF THE SKELETAL MUSCLE

Skeletal muscles are specialized contractile tissues which function to move an organism’s body. In most skeletal muscles, each fiber extends the entire length of the muscle. Except for about 2 per cent of the fibers, each fiber is usually innervated by only one nerve ending, located near the middle of the fiber. The **sarcolemma** is the cell membrane of the muscle fiber. The sarcolemma consists of a true cell membrane, called the plasma membrane, and an outer coat made up of a thin layer of polysaccharide material that contains numerous thin collagen fibrils. Each muscle

fiber contains several hundred to several thousand myofibrils made up of **myosin** (thick) and **actin** (thin) filaments (The actin filament also contains another protein, tropomyosin.). The ends of the actin filaments are attached to a Z-disc. The portion of the myofibril (or of the whole muscle fiber) that lies between two successive Z-discs is called a **sarcomere**. The side-by-side relationship between the myosin and actin filaments is difficult to maintain. This is achieved by a large number of filamentous molecules of a protein called **titin filaments**. The spaces between the myofibrils are filled with intracellular fluid called **sarcoplasm**, containing large quantities of potassium, magnesium, and phosphate, plus multiple protein enzymes. Also present are tremendous numbers of **mitochondria** (which supplies energy in form of ATP to the contacting myofibrils) that lie parallel to the myofibrils. Also in the sarcoplasm surrounding the myofibrils of each muscle fiber is an extensive reticulum called the sarcoplasmic reticulum. Skeletal muscles in the body can be found in the arm, head, hand, chest, larynx, leg, thigh, neck, scalp, eye, vertebral column, abdomen, nose, mouth, tongue, pharynx and back.

General mechanism of muscle contraction

The initiation and execution of muscle contraction occur in the following sequential steps: (1) An action potential travels along a motor nerve to its endings on muscle fibers. (2) At each ending, the nerve secretes a small amount of the neurotransmitter substance acetylcholine. (3) The acetylcholine acts on a local area of the muscle fiber membrane to open multiple "acetylcholinegated" channels through protein molecules floating in the membrane. (4) Opening of the acetylcholine-gated channels allows large quantities of sodium ions to diffuse to the interior of the muscle fiber membrane. This initiates an action potential at the membrane. (5) The action potential travels along the muscle fiber membrane in the same way that action potentials travel along nerve fiber membranes. (6) The action potential depolarizes the muscle membrane, and much of the action potential electricity flows through the center of the muscle fiber. Here it causes the sarcoplasmic reticulum to release large quantities of calcium ions that have been stored within this reticulum. (7) The calcium ions initiate attractive forces between the actin and myosin filaments, causing them to slide alongside each other, which is the contractile process. (8) After a fraction of a second, the calcium ions are pumped back into the sarcoplasmic reticulum by a Ca++ membrane pump, and they remain stored in the reticulum until a new muscle action potential comes along; this removal of calcium ions from the myofibrils causes the muscle contraction to cease.

Molecular mechanism of muscle contraction

a) Troponin and Its Role in Muscle Contraction: Attached intermittently along the sides of the tropomyosin molecules are still other protein molecules called troponin. These are actually complexes of three loosely bound protein subunits, each of which plays a specific role in controlling muscle contraction. One of the subunits (troponin I) has a strong affinity for actin, another (troponin T) for tropomyosin, and a third (troponin C) for calcium ions. This complex is believed to attach the tropomyosin to the actin. The strong affinity of the troponin for calcium ions is believed to initiate the contraction process.

b) Interaction between the "activated" actin filament and the myosin cross-bridges/the "walk-along" theory of contraction: It is postulated that when a head (of a crossbridge) attaches to an active site, this attachment simultaneously causes profound changes in the intramolecular forces between the head and arm of its cross-bridge. The new alignment of forces causes the head to tilt toward the arm and to drag the actin filament along with it. This tilt of the

head is called the **power stroke.** Then, immediately after tilting, the head automatically breaks away from the active site. Next, the head returns to its extended direction. In this position, it combines with a new active site farther down along the actin filament; then the head tilts again to cause a new power stroke, and the actin filament moves another step. Thus, the heads of the crossbridges bend back and forth and step by step walk along the actin filament, pulling the ends of two successive actin filaments toward the center of the myosin filament.

Characteristics of whole muscle contraction

Many features of muscle contraction can be demonstrated by eliciting single **muscle twitches**. This can be accomplished by instantaneous electrical excitation of the nerve to a muscle or by passing a short electrical stimulus through the muscle itself, giving rise to a single, sudden contraction lasting for a fraction of a second. Muscle contraction is said to be **isometric** when the muscle does not shorten during contraction and **isotonic** when it does shorten but the tension on the muscle remains constant throughout the contraction. The muscles that react rapidly are composed mainly of **fast fibers** with only small numbers of the slow variety. Conversely, the muscles that respond slowly but with prolonged contraction are composed mainly of **slow fibers**. The differences between these two types of fibers are as follows; **Fast Fibers.** (1) Large fibers for great strength of contraction. (2) Extensive sarcoplasmic reticulum for rapid release of calcium ions to initiate contraction. (3) Large amounts of glycolytic enzymes for rapid release of energy by the glycolytic process. (4) Less extensive blood supply because oxidative metabolism is of secondary importance. (5) Fewer mitochondria, also because oxidative metabolism is secondary. **Slow Fibers.** (1) Smaller fibers. (2) Also innervated by smaller nerve fibers. (3) More extensive blood vessel system and capillaries to supply extra amounts of oxygen. (4) Greatly increased numbers of mitochondria, also to support high levels of oxidative metabolism. (5) Fibers contain large amounts of myoglobin, an iron containing protein similar to hemoglobin in red blood cells. Myoglobin combines with oxygen and stores it until needed; this also greatly speeds oxygen transport to the mitochondria. The myoglobin gives the slow muscle a reddish appearance and the name **red muscle,** whereas a deficit of red myoglobin in fast muscle gives it the name **white muscle.**

Muscle hypertrophy and atrophy

When the total mass of a muscle increases, this is called **muscle hypertrophy.** When it decreases, the process is called **muscle atrophy.** Virtually all muscle hypertrophy results from an increase in the number of actin and myosin filaments in each muscle fiber, causing enlargement of the individual muscle fibers; this is called simply **fiber hypertrophy.** Hypertrophy occurs to a much greater extent when the muscle is loaded during the contractile process. Only a few strong contractions each day are required to cause significant hypertrophy within 6 to 10 weeks. When a muscle remains unused for many weeks, the rate of decay of the contractile proteins is more rapid
than the rate of replacement. Therefore, muscle atrophy occurs.

Excitation of neuromuscular junction

Each nerve ending makes a junction, called the **neuromuscular junction**, with the muscle fiber near its midpoint. The action potential initiated in the muscle fiber by the nerve signal travels in both directions toward the muscle fiber ends. With the exception of about 2 per cent of the muscle fibers, there is only one such junction per muscle fiber. The nerve fiber forms a complex of branching nerve terminals that invaginate into the surface of the muscle fiber but lie outside

the muscle fiber plasma membrane. The entire structure is called the **motor end plate**. The invaginated membrane is called the **synaptic gutter or synaptic trough**, and the space between the terminal and the fiber membrane is called the **synaptic space or synaptic cleft.** At the bottom of the gutter are numerous smaller folds of the muscle membrane called **subneural clefts**, which greatly increase the surface area at which the synaptic transmitter can act**.** In the axon terminal are many mitochondria that supply adenosine triphosphate (ATP), the energy source that is used for synthesis of an excitatory transmitter **acetylcholine.** In the synaptic space are large quantities of the enzyme acetylcholinesterase, which destroys acetylcholine a few milliseconds after it has been released from the synaptic vesicles. However, stimulation of the nerve fiber at rates greater than 100 times per second for several minutes often diminishes the number of acetylcholine vesicles so much that impulses fail to pass into the muscle fiber. This is called **fatigue** of the neuromuscular
junction. Drugs that enhance or **stimulate transmission at the muscle fiber** include methacholine, carbachol, and nicotine (they all have the same effect on the muscle fiber as does acetylcholine). Drugs that stimulate transmission at neuromuscular junction by **inactivating acetylcholinesterase** include neostigmine, physostigmine, and diisopropyl fluorophosphates. Drugs that **block transmission at the neuromuscular junction** includes tubocurarine. **Myasthenia gravis** is muscle paralysis because of inability of the neuromuscular junctions to transmit enough signals from the nerve fibers to the muscle fibers. Therefore, it is believed that myasthenia gravis is an autoimmune disease in which the patients have developed immunity against their own acetylcholine-activated ion channels.

PHYSIOLOGIC ANATOMY OF SMOOTH MUSCLE

Smooth muscles are composed of small muscle fibers when compared to skeletal muscles. For the sake of simplicity, smooth muscle can generally be divided into two major types; multi-unit smooth muscle and unitary (or single-unit) smooth muscle. **Multi-unit smooth muscle:** This type of smooth muscle is composed of discrete, separate smooth muscle fibers. Each fiber operates independently of the others and often is innervated by a single nerve ending, as occurs for skeletal muscle fibers. Further, the outer surfaces of these fibers, like those of skeletal muscle fibers, are covered by a thin layer of basement membrane–like substance, a mixture of fine collagen and glycoprotein that helps insulate the separate fibers from one another. The most important characteristic of multi-unit smooth muscle fibers is that each fiber can contract independently of the others, and their control is exerted mainly by nerve signals. **Unitary (or single-unit) smooth muscle:** it means a mass of hundreds to thousands of smooth muscle fibers that contract together as a single unit. The fibers usually are arranged in sheets or bundles, and their cell membranes are adherent to one another at multiple points so that force generated in one muscle fiber can be transmitted to the next. In addition, the cell membranes are joined by many **gap junctions** through which ions can flow freely from one muscle cell to the next so that action potentials or simple ion flow without action potentials can travel from one fiber to the next and cause the muscle fibers to contract together. This type of smooth muscle is also known as **syncytial smooth muscle** because of its syncytial interconnections among fibers. It is also called **visceral smooth muscle** because it is found in the walls of most viscera of the body, including the gut, bile ducts, ureters, uterus, and many blood vessels. In contrast, a major share of control of unitary smooth muscle is exerted by non-nervous stimuli.

Chemical basis for smooth muscle contraction

Smooth muscle contains both **actin** and **myosin filaments,** having chemical characteristics similar to those of the actin and myosin filaments in skeletal muscle. It does not contain the normal troponin complex that is required in the control of skeletal muscle contraction, so the mechanism for control of contraction is different. Chemical studies have shown that actin and myosin filaments derived from smooth muscle interact with each other in much the same way that they do in skeletal muscle. Further, the contractile process is activated by calcium ions, and adenosine triphosphate (ATP) is degraded to adenosine diphosphate (ADP) to provide the energy for contraction.

Physical basis for smooth muscle contraction

Large numbers of actin filaments are attached to **dense bodies** (the dense bodies of smooth muscle serve the same role as the Z discs in skeletal muscle)**.** Some of these bodies are attached to the cell membrane. Others are dispersed inside the cell. Some of the membrane dense bodies of adjacent cells are bonded together by intercellular protein bridges. It is mainly through these bonds that the force of contraction is transmitted from one cell to the next. The value of this organization is that it allows smooth muscle cells to contract as much as 80 % of their length instead of being limited to less than 30 %, as occurs in skeletal muscle.

Latch mechanism for prolonged holding of contractions of smooth muscle: Once smooth muscle has developed full contraction, the amount of continuing excitation usually can be reduced to far less than the initial level, yet the muscle maintains its full force of contraction. Further, the energy consumed to maintain contraction is often minuscule, sometimes as little as 1/300 the energy required for comparable sustained skeletal muscle contraction. This is called the **latch mechanism.** The importance of the latch mechanism is that it can maintain prolonged tonic contraction in smooth muscle for hours with little use of energy. Little continued excitatory signal is required from nerve fibers or hormonal sources.

Regulation of contraction

As is true for skeletal muscle, the initiating stimulus for smooth muscles contraction is an increase in intracellular calcium ions. Yet smooth muscle does not contain troponin, the regulatory protein that is activated by calcium ions to cause skeletal muscle contraction. In place of troponin, smooth muscle cells contain a large amount of another regulatory protein called **calmodulin.** Activation and subsequent contraction occur in the following sequence: (1) The calcium ions bind with calmodulin. (2) The calmodulin-calcium combination joins with and activates **myosin kinase,** a phosphorylating enzyme. (3) One of the light chains of each myosin head, called the **regulatory chain,** becomes phosphorylated in response to this myosin kinase. When this chain is not phosphorylated, the attachment-detachment cycling of the myosin head with the actin filament does not occur. But when the regulatory chain is phosphorylated, the head has the capability of binding repetitively with the actin filament and proceeding through the entire cycling process of intermittent “pulls,” the same as occurs for skeletal muscle, thus causing muscle contraction.

Termination of contraction

When the calcium ion concentration falls below a critical level, the aforementioned processes automatically reverse, except for the phosphorylation of the myosin head. Reversal of this requires another enzyme, **myosin phosphatase,** located in the fluids of the smooth muscle cell,

which splits the phosphate from the regulatory light chain. Then the cycling stops and contraction ceases.

Neuromuscular junction of smooth muscles

The **autonomic nerve fibers** that innervate smooth muscle generally branch diffusely on top of a sheet of muscle fibers. these fibers do not make direct contact with the smooth muscle fiber cell membranes but instead form **diffuse junctions** that secrete their transmitter substance into the matrix coating of the smooth muscle often a few nanometers to a few micrometers away from the muscle cells; the transmitter substance then diffuses to the cells. Furthermore, where there are many layers of muscle cells, the nerve fibers often innervate only the outer layer, and muscle excitation travels from this outer layer to the inner layers by action potential conduction in the muscle mass or by additional diffusion of the transmitter substance. Most of the fine terminal axons have multiple **varicosities** distributed along their axes. But, in contrast to the vesicles of skeletal muscle junctions, which always contain acetylcholine, the vesicles of the autonomic nerve fiber endings contain **acetylcholine** in some fibers and **norepinephrine** in others. Particularly in the multi-unit type of smooth muscle, the varicosities are separated from the muscle cell membrane by as little as 20 to 30 nanometers. These are called **contact junctions**, and they function in much the same way as the skeletal muscle neuromuscular junction.

Membrane potentials in smooth muscles

In the normal resting state, the intracellular potential is usually about **-50 to -60 millivolts**, which is about 30 millivolts less negative than in skeletal muscle.

Action potential in unitary smooth muscles

The action potentials of visceral smooth muscle occur in one of two forms: (1) **spike potentials** (duration of this type of action potential is 10 to 50 milliseconds) or (2) **action potentials with plateaus** (the repolarization is delayed for about a second).

Slow wave potentials in unitary smooth muscle, and spontaneous generation of action potentials: Some smooth muscle is self-excitatory. That is, action potentials arise within the smooth muscle cells themselves without an extrinsic stimulus. This often is associated with a basic **slow wave rhythm** of the membrane potential. A typical example is slow wave in a visceral smooth muscle of the gut. The importance of the slow waves is that, when they are strong enough, they can initiate action potentials. The slow waves themselves cannot cause muscle contraction, but when the peak of the negative slow wave potential inside the cell membrane rises in the positive
direction from -60 to about -35 millivolts (the approximate threshold for eliciting action potentials in most visceral smooth muscle), an action potential develops and spreads over the muscle mass. Then contraction does occur. These repetitive sequences of action potentials elicit rhythmical contraction of the smooth muscle mass. Therefore, the slow waves are called **pacemaker waves.**

Depolarization of multi-unit smooth muscle without action potentials: The smooth muscle fibers of multi-unit smooth muscle normally contract mainly in response to nerve stimuli. The transmitter substances cause depolarization of the smooth muscle membrane, and this in turn elicits contraction. Action potentials usually do not develop; the reason is that the fibers are too

small to generate an action potential. (When action potentials are elicited in *vi*sceral unitary smooth muscle, 30 to 40 smooth muscle fibers must depolarize simultaneously before a self-propagating action potential ensues.) Yet, in small smooth muscle cells, even without an action potential, the local depolarization (called the junctional potential) caused by the nerve transmitter substance itself spreads "electrotonically" over the entire fiber and is all that is needed to cause muscle contraction.

PHYSIOLOGIC ANATOMY OF CARDIAC MUSCLES

The heart is composed of three major types of cardiac muscle: **atrial muscle, ventricular muscle**, and **specialized excitatory and conductive muscle fibers**. The atrial and ventricular types of muscle contract in much the same way as skeletal muscle, except that the duration of contraction is much longer. Conversely, the specialized excitatory and conductive fibers contract only feebly because they contain few contractile fibrils; instead, they exhibit either automatic rhythmical electrical discharge in the form of action potentials or conduction of the action potentials through the heart, providing an excitatory system that controls the rhythmical beating of the heart. Further, cardiac muscle has typical myofibrils that contain **actin** and **myosin filaments** almost identical to those found in skeletal muscle; these filaments lie side by side and slide along one another during contraction in the same manner as occurs in skeletal muscle. **Intercalated discs** are actually cell membranes that separate individual cardiac muscle cells from one another. At each intercalated disc the cell membranes fuse with one another in such a way that they form permeable **communicating junctions (gap junctions)** that allow almost totally free diffusion of ions. Ions move with ease in the intracellular fluid along the longitudinal axes of the cardiac muscle fibers, so that action potentials travel easily from one cardiac muscle cell to the next, past the intercalated discs. Thus, cardiac muscle is a **syncytium** of many heart muscle cells in which the cardiac cells are so interconnected that when one of these cells becomes excited, the action potential spreads to all of them, spreading from cell to cell throughout the latticework interconnections. The heart actually is composed of two syncytiums: the **atrial syncytium** that constitutes the walls of the two atria, and the **ventricular syncytium** that constitutes the walls of the two ventricles. The atria are separated from the ventricles by fibrous tissue that surrounds the **atrioventricular (A-V) valvular openings** between the atria and ventricles. they are conducted only by way of a specialized conductive system called the **A-V bundle.**

Action potential in cardiac muscle

Intracellular potential rises from a very negative value, about -85 millivolts, between beats to a slightly positive value, about +20 millivolts, during each beat. After the initial **spike,** the membrane remains depolarized for about 0.2 second, exhibiting a **plateau** followed at the end of the plateau by abrupt repolarization. The presence of this plateau in the action potential causes ventricular contraction to last as much as 15 times as long in cardiac muscle compared to skeletal muscle. **Reasons for prolonged action potential and plateau:** In cardiac muscle, the action potential is caused by opening of two types of channels: (1) the same **fast sodium channels** as those in skeletal muscle and (2) another entirely different population of **slow calcium channels,** which are also called **calcium-sodium channels.** This second population of channels differs from the fast sodium channels in that they are slower to open and, even more important, remain open for several tenths of a second. During this time, a large quantity of both calcium and

sodium ions flows through these channels to the interior of the cardiac muscle fiber, and this maintains a prolonged period of depolarization, **causing the plateau** in the action potential. Further, the calcium ions that enter during this plateau phase activate the muscle contractile process, while the calcium ions that cause skeletal muscle contraction are derived from the intracellular sarcoplasmic reticulum. Immediately after the onset of the action potential, the permeability of the cardiac muscle membrane for potassium ions **decreases** about fivefold, an effect that does not occur in skeletal muscle. The decreased potassium permeability greatly decreases the outflux of positively charged potassium ions during the action potential plateau and thereby prevents early return of the action potential voltage to its resting level. When the slow calcium-sodium channels do close at the end of 0.2 to 0.3 second and the influx of calcium and sodium ions ceases, the membrane permeability for potassium ions also increases rapidly; this rapid loss of potassium from the fiber immediately returns the membrane potential to its resting level, thus ending the action potential. A second factor that may be partly responsible for the plateau is that the voltage-gated potassium channels are slower than usual to open, often not opening very much until the end of the plateau. This delays the return of the membrane potential toward its normal negative value of –80 to –90 millivolts.

Refractory period of cardiac muscles

The refractory period of the heart is the interval of time, during which a normal cardiac impulse cannot re-excite an already excited area of cardiac muscle. The normal refractory period of the **ventricle is 0.25 to 0.30 second**, which is about the duration of the prolonged plateau action potential. There is an additional **relative refractory period** of about 0.05 second during which the muscle is more difficult than normal to excite but nevertheless can be excited by a very strong excitatory signal. The refractory period of **atrial muscle is much shorter** than that for the ventricles (**about 0.15 second for the atria** compared with 0.25 to 0.30 second for the ventricles).

Specialized excitatory and conductive system of the heart

The specialized excitatory and conductive system of the heart that controls cardiac contractions consists of the **sinus node** (also called **sinoatrial or S-A node**), in which the normal rhythmical impulse is generated; the **internodal pathways** that conduct the impulse from the sinus node to the **atrioventricular (A-V) node**; the **A-V node**, in which the impulse from the atria is delayed before passing into the ventricles; the **A-V bundle**, which conducts the impulse from the atria into the ventricles; and the left and right bundle branches of **Purkinje fibers**, which conduct the cardiac impulse to all parts of the ventricles**.**

Automatic electrical rhythmicity of the sinus fibers: Some cardiac fibers have the capability of **self-excitation,** a process that can cause automatic rhythmical discharge and contraction. This is especially true of the fibers of the heart's specialized conducting system, including the fibers of the sinus node. For this reason, the sinus node ordinarily controls the rate of beat of the entire heart. The question we must ask is: Why does the sinus node rather than the A-V node or the Purkinje fibers control the heart's rhythmicity? The answer derives from the fact that the discharge rate of the sinus node is considerably faster than the natural self-excitatory discharge rate of either the A-V node or the Purkinje fibers. Thus, the sinus node controls the beat of the heart because its rate of rhythmical discharge is faster than that of any other part of the heart. Therefore, the sinus node is virtually always the **pacemaker** of the normal heart. A pacemaker elsewhere than the sinus node is called an **ectopic pacemaker.** An ectopic pacemaker causes an

abnormal sequence of contraction of the different parts of the heart and can cause significant debility of heart pumping.

Parasympathetic and sympathetic nerve: The heart is supplied with both sympathetic and parasympathetic nerves. The **parasympathetic nerves** (the **vagi**) are distributed mainly to the S-A and A-V nodes, to a lesser extent to the muscle of the two atria, and very little directly to the ventricular muscle. The **sympathetic nerves**, conversely, are distributed to all parts of the heart, with strong representation to the ventricular muscle as well as to all the other areas. Stimulation of the parasympathetic nerves to the heart (the vagi) causes the hormone **acetylcholine** to be released at the vagal endings. This hormone has two major effects on the heart. First, it decreases the rate of rhythm of the sinus node, and second, it decreases the excitability of the A-V junctional fibers between the atrial musculature and the A-V node, thereby slowing transmission of the cardiac impulse into the ventricles. When there is either weak or strong stimulation of the vagi, the ventricles stop beating for 5 to 20 seconds, but then some point in the Purkinje fibers, usually in the ventricular septal portion of the A-V bundle, develops a rhythm of its own and causes ventricular contraction at a rate of 15 to 40 beats per minute. This phenomenon is called **ventricular escape.**

Sympathetic stimulation causes essentially the opposite effects on the heart to those caused by vagal stimulation, as follows: First, it increases the rate of sinus nodal discharge. Second, it increases the rate of conduction as well as the level of excitability in all portions of the heart. Third, it increases greatly the force of contraction of all the cardiac musculature, both atrial and ventricular.