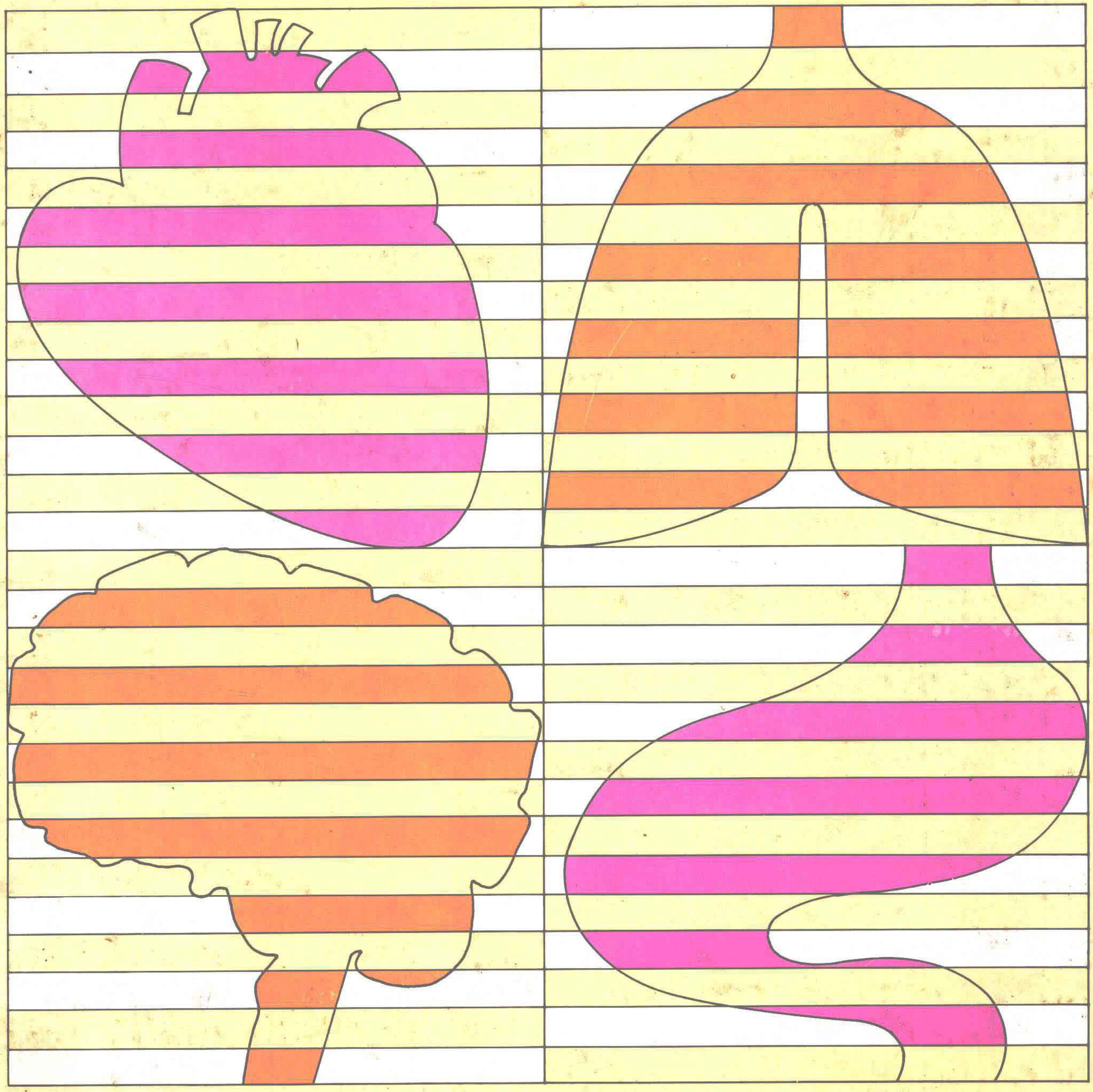
Basic Physiology for the Health Sciences

Second Edition

Edited by
Ewald E. Selkurt, Ph.D.



Basic Physiology for the Health Sciences

SECOND EDITION

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Preface

The Second Edition of *Basic Physiology for the Health Sciences* has adhered to the policy adopted for the first edition: to treat the various topics at a level consonant with the interests of advanced undergraduate students in the allied health, nursing, and other paramedical professions. Undergraduate biologic science students as well will find the text useful. Students of medicine and dentistry will find it valuable collateral reading.

A minimum of anatomic details has been included, on the assumption that the student will have had a separate course in anatomy or appropriate grounding in the structure of the body in other biology courses. Biochemical and biophysical concepts have been included when necessary, but mathematical treatment has been minimized. A particular effort has been made to clarify all discussions of chemistry, physics, and mathematics. Although basic concepts as they relate to normal human physiology have been emphasized, frequent opportunities have been taken to extrapolate from this foundation to the concepts of pathophysiology and clinical physiology. The style is didactic; discussion of controversial issues has been minimized.

Changes have been made in the format to facilitate the teaching and learning processes. The text is organized into 14 chapters. Each chapter is preceded by an outline of the main topics discussed, to assist the reader to review the key concepts. Each chapter concludes with review questions and an annotated list of suggested reading. The comprehensive glossary is a new feature, introduced as an aid to readers' understanding of key terms.

We are greatly indebted to our secretaries, Nancy Wagner and Ann Hollingsworth, for their valuable assistance. Appreciation is due as well to Phil Wilson and Maureen Hardebeck for their many fine illustrations. Assisting also were Jayn Montgomery and Brent Bauer of the Indiana University School of Medicine Illustrations Department.

E. E. S.

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Basic Physiology for the Health Sciences

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1

Cellular Function and Fundamentals of Physiology

ALAN R. FREEMAN

The simplest organisms of the animal kingdom are the protozoa, exemplified by the ameba and paramecium, each composed of one cell. As organisms progressed phylogenetically from these unicellular forms to multicellular animals such as sponges and hydra, the complexity of their function also increased.

In a similar sense, the human body, though an enormously complex system in its total function, can be seen to be made up of more elementary subsystems. If the simplest element of these systems is considered to be the cell, then one can regard this unit as organized into tissues and organs, which are in turn organized into systems of interacting tissues and organs ultimately assembled in the body system as a whole. The term *system* is used here to mean an arrangement of biologic components organized so as to function as a self-regulating unit.

Since systematic operation is so inherent to biologic function, it would be useful to point out some important features of the preceding definition by using a familiar analogy, a home heating system (Fig. 1-1). To begin with, this system has been constructed to maintain a desired room temperature. For this purpose, fuel, such as oil, gas, or coal, is presented as the *input* to the furnace. In burning the fuel the furnace converts the chemical energy of the fuel to heat, which is the *output* of the furnace. The furnace is termed an *effector*, as it effects environmental changes. The process of converting one form of energy to another is generally called *transduction* and does not apply only to this system. Other forms of transduction will be mentioned later in the text. The heat in turn raises the room temperature. If there were no other elements in the system except the furnace, the temperature would continue to rise until discomfort necessitated manual shutdown of the furnace.

It would appear to be desirable to provide a way for the system to be self-regulating. This brings in the concept of *feedback,* that is, information as to whether the room temperature has reached a desirable level must somehow be fed back to the furnace so that it can remain on or go off as the

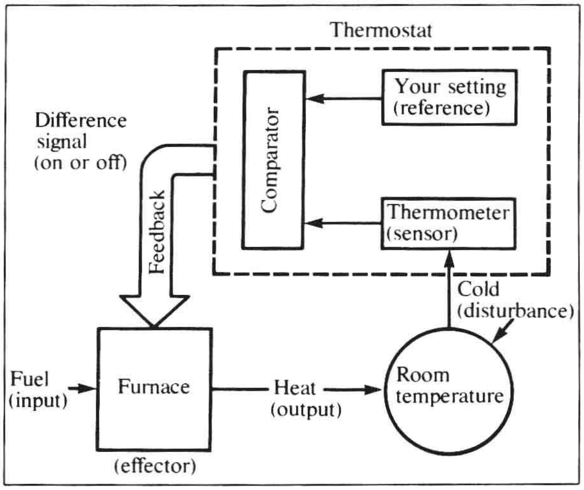

Fig. 1-1. Home heating system model for system function. Heat produced by the furnace elevates the room temperature. Disturbances such as cold tend to lower temperature. The thermostat detects differences between actual room temperature and the desired level. If room temperature is lower than the reference setting, an "on" signal is fed back to the furnace. The system is thereby self-regulating.

situation demands. Since information about temperature is desired, a thermometer is needed as a *sensor* of the information. The thermometer is another kind of transducer, as it changes heat to mechanical energy. The desired comfort setting is made by manually adjusting the *reference* of the system, the thermostat. A device called a *comparator* reads the signals of both the reference point and the thermometer. If there is a difference between these two, e.g., if the thermometer reading is below the reference setting, this indicates that the room temperature is below the desired level, and the "difference signal" tells the furnace to remain on. The furnace continues to generate heat until the comparator detects no difference in signal between the thermometer and the reference setting. Since no difference signal is then sent to the furnace, the unit is turned off. There is no need for further operation of the system unless disturbances in the room, such as an open window, alter the temperature or the reference setting is changed.

The body possesses many physiologic systems that are the same in principle as the one just described. The body's own temperature regulating system is a good example. These systems will be investigated in later chapters.

The self-regulating aspect of body systems is a manifestation of the tendency of biologic systems to maintain a particular environment (*homeostasis*), seen at all levels of system function from the single cell to the whole animal. The homeostatic nature of body systems will be revealed continually throughout the study of physiology.

Though it is difficult to define specifically the nature of physiologic function, two characteristic properties, transduction and translocation, are usually present in physiologic systems. As mentioned earlier, transduction involves the transformation of energy from one form to another. *Translocation* involves movement either of material or of information from one location in space to another. In this chapter, specific examples of these two properties will be presented.

Disease may alter the normal performance of physiologic systems at any level of body organization. It is the concern of those involved in the health field to aid in the restoration of normal function. In this and future chapters the principles of physiology, the disturbances in physiologic systems in major disease states, and the means indicated for restoration of normal function will be correlated.

The Cell

The cell is considered the simplest element of a physiologic system. Both the properties of cells themselves and the manner in which they are organized into higher systems determine overall function; in this respect the terms *functional organization* and *structure-function relationship* are useful. To illustrate this point, let us consider the muscle cell as the basic unit of muscular systems. Though the work of a single muscle cell is simply to contract, variations in the organization of muscle cells result in different functions. Thus a skeletal muscle system moves the legs, for example, while the heart muscle system pumps the blood. In contrast, the cells of the nervous system do not con-

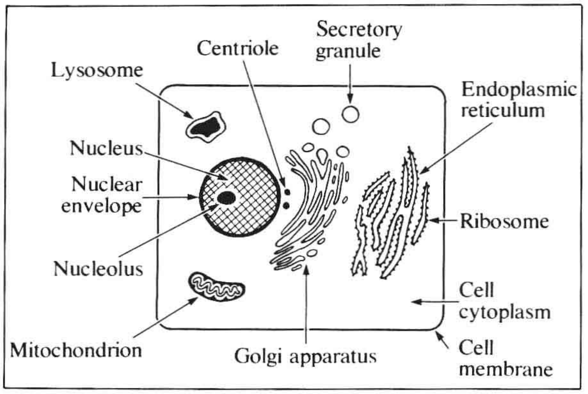

Fig. 1-2. Schematic display of a cell. The structures designated are typical inclusions found within the cell body (soma) of many cell types but do not accurately represent the details of any particular cell. Some cells are modified for special function and show marked differences in structure. These include nerve and muscle cells and will be discussed elsewhere in the text.

tract but rather have properties specialized for electrical function. The functional organization of these cells makes the enormously complicated operation of the nervous system possible.

STRUCTURE-FUNCTION RELATIONSHIP

Figure 1-2 is a diagram of a typical cell body. A brief review of the significant aspects of the cell structure-function relationship follows.

NUCLEUS. The nucleus of a cell is the particle, or organelle, present in all cells that undergo mitosis, or division into two identical parts. Within the nucleus are the chromosomes, containing deoxyribonucleic acid (DNA). Genetic information is transferred to ribonucleic acid (RNA), often contained within the nucleolus (see Fig. 1-2). The RNA-bearing information concerning protein synthesis leaves the nucleus through the porous nuclear envelope and enters the cell cytoplasm. Recall that the centrioles (two in number), which in most cells lie outside of but near the nucleus, are involved in cell division. At the start of mitosis the pair of centrioles undergoes division. The two pairs of elements then separate to become the poles of the mitotic spindle.

ENDOPLASMIC RETICULUM. The endoplasmic reticulum, made up of tiny membrane-bounded tubules, contains a granular portion that consists of RNA incorporated into ribosomes. Ribosomes, also made up of subunits, are the site of protein synthesis. The nongranular or smooth portion of the endoplasmic reticulum is involved in hormone synthesis in some cells and in others plays an important role in removal or uptake of material from the cytoplasm.

GOLGI APPARATUS. The Golgi apparatus, which is a mixture of tubules and vesicles, is involved in preparing the protein secretions of certain cells, and, accordingly, is believed to be the site of origin of secretory granules that act as storage sites for such protein materials. The Golgi system may also be important in delivering certain protein elements to the cell membrane, thereby helping to maintain its structure and function.

LYSOSOMES. Lysosomes contain certain "digestive" enzymes, the acid hydrolases, which break down material that may be present in excessive amounts in the cytoplasm. They may act both on protein material such as collagen and on carbohydrates such as glycogen. In addition to their role in maintaining the normal cell environment, lysosomes are involved in removing the remnants of dead cells (autolysis).

MITOCHONDRIA. Mitochondria are the site of energy production and contain enzymes of the citric acid cycle. Recall that, through the process of oxidative phosphorylation, the high-energy phosphate compound adenosine triphosphate (ATP) is formed. A certain amount of lipid and protein synthesis also occurs within the mitochondria.

It should be noted here that each of these subcellular components, i.e., the nucleus, endoplasmic reticulum, Golgi apparatus, lysosomes, and mitochondria, is a physiologic system, since translocation of information (genetic code) or material (biochemical substances) is associated with function. Indeed, the total unitary cell system is the integrated performance of all these functional elements, and, accordingly, this area of function is termed *cell physiology*.

Aspects of Cell Physiology

As does any machine designed to carry out function, the human body uses energy in this process. Thus, basic to function is the ability of cells to produce, store, and utilize energy. Since our bodies are essentially chemical machines, the system must carry out this task utilizing biochemical processes. In this regard, energy is stored in the manufacture of compounds that require a large amount of energy input for their synthesis. Conversely, when these substances are broken down, they are capable of releasing this "stored" energy to be available for function.

Adenosine triphosphate (ATP), a chemical compound of major importance, is present in every cell. It is necessary for all biologic functions, ranging from the carrying out of thought processes by the nervous system to the contraction of the muscles in everyday situations.

It follows from this that a portion of the food we eat is utilized by the body in the formation of this energy-rich compound. As shown in Fig. 1-3, the final step in the synthesis of the high-energy phosphate substance ATP is the addition of a phosphate group to adenosine diphosphate (ADP).

Adenosine triphosphate is manufactured from ADP within the mitochondria by a process called *oxidative phosphorylation*. This process allows storage of chemical energy in the ATP molecule for later use by functional elements of the cell. Conversely, when ATP is split, or "hydrolyzed," energy stored within the molecule is released to the particular system requiring that energy to function.

Mentioned earlier was the idea that some fraction of our food intake is destined to become ATP. We will treat in more detail a single example of this process.

An important substance in our daily nourishment is the sugar contained in many foods. As a consequence of digestion and absorption, glucose appears in the bloodstream. This substance may then be carried via the blood to individual cells of the body. Many cells contain within their plasma

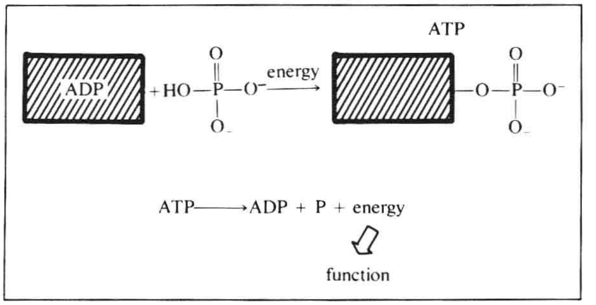

Fig. 1-3. Formation and utilization of ATP. ATP is formed from ADP and inorganic phosphate in the presence of energy. The high-energy phosphate of ATP may then be hydrolyzed to yield energy for function. ADP and inorganic phosphate are produced in the process.

membrane a transport system designed to transfer sugars such as glucose from the blood to the intracellular cytoplasm. This transport system is discussed later in this chapter and is outlined in Fig. 1-9. Once it appears in the cytoplasm, glucose undergoes cellular metabolism, as diagramed in Fig. 1-4. While in the cytoplasm, glucose undergoes *anaerobic metabolism*, or *glycolysis*. The term *anaerobic metabolism* implies that glucose is transformed to other substances by mechanisms not directly involving oxygen. Not shown in Fig. 1-4 is the fact that a series of biochemical reactions is involved in the breakdown of glucose to the three-carbon compound pyruvic acid. Significant in the process is that two molecules of ATP are generated. Thus, glycolysis provides the cell with a moderate amount of high-energy phosphates.

Pyruvic acid is subsequently acted on within the mitochondria by the process known as *aerobic metabolism*. This is accomplished by a series of chemical reactions called the *tricarboxylic acid (TCA) cycle*. Here, three-carbon acids are oxidized ultimately to carbon dioxide and water. Oxygen is utilized directly during this procedure. The TCA cycle is biochemically coupled to another process (*oxidative phosphorylation*), which results in the production of 36 molecules of ATP. Thus we see that aerobic metabolism is much more efficient in terms of high-energy phosphate compound pro-

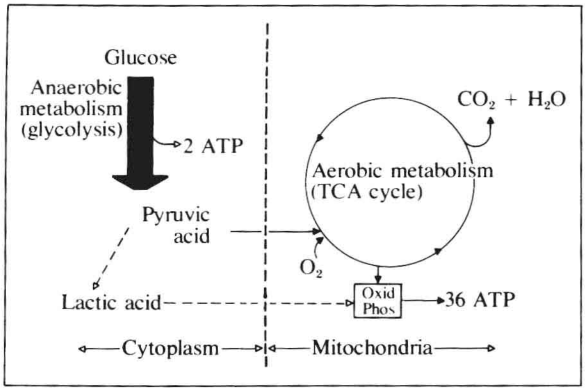

Fig. 1-4. Cellular energy metabolism. In the cell cytoplasm, glucose undergoes anaerobic metabolism (glycolysis) to become pyruvic acid. Within the mitochondria, pyruvic acid is aerobically metabolized via the TCA cycle to CO_2 and water. ATP is formed during both glycolysis and aerobic oxidation, with the latter being much more productive. Under conditions of low oxygen levels, pyruvic acid may be transformed to lactic acid, which in turn may result in ATP formation.

duction than is anaerobic metabolism. It would be reasonable to suppose, then, that under normal circumstances the cell would utilize both glycolysis and the TCA cycle to generate energy for function. Though this is true, the body may be placed in certain situations in which the oxygen supply is limited.

Vigorous exercise is an example of a situation in which an oxygen deficit may occur. If oxygen is being consumed for function at a rate faster than the cardiopulmonary system can supply it, one would expect the TCA cycle to operate at a proportionally lower rate. When this occurs, the usual pathway for pyruvate metabolism is altered and pyruvate is not taken up as rapidly as usual by the oxidative processes within the mitochondria. Thus there tends to be a relative accumulation of pyruvic acid in the cytoplasm. Under these conditions, appropriate enzymes may convert excess pyruvate to lactic acid. Lactic acid may in turn enter the oxidative phosphorylation process to produce ATP. However, the latter process is not nearly so efficient as the usual metabolic pathway and results in a significant accumulation of lactic acid within the cell. This accumulation can be so great as to result in leakage of this compound out of the cell and into the blood, a condition termed *lactic acidemia*.

Thus conditions resulting in insufficient oxygen within the body would in turn result in either the localized or systemic appearance of lactic acid. Such a condition, if severe enough, may cause a disruption of normal function. Lactic acid, for example, may be implicated in cramping of exercising muscles and is involved in the pain experienced by heart attack victims when an area of the heart is deprived of its normal oxygen supply.

Thus the cells of our body contain mechanisms for the production of energy over a wide range of both normal and abnormal states.

Summary

1. Energy for physiologic function is derived from the high-energy phosphate compound ATP.
2. In releasing its stored energy, ATP is broken down to ADP.
3. Cellular energy metabolism involves an anaerobic phase (glycolysis) and an aerobic component (TCA cycle).
4. During glycolysis, glucose is converted to pyruvic acid without direct use of oxygen.
5. Pyruvic acid is broken down within the mitochondria in the TCA cycle to CO_2 and H_2O utilizing direct oxidation.
6. The TCA cycle is much more efficient than glycolysis, producing 18 times more ATP via the process of oxidative phosphorylation.
7. Under conditions of oxygen deprivation, pyruvic acid is transformed into lactic acid, which in turn may be involved in ATP production via oxidative phosphorylation.
8. The lactic acid system is less efficient in energy production than pyruvic acid system and may result in causing muscle cramps and pain under certain conditions.

The Cell Membrane

Many membranes exist within the overall cell architecture, as exemplified by membranes of the endoplasmic reticulum and Golgi apparatus. The membrane of particular interest here, however, is that which encloses the outer boundary of the cell, separating the inside of the cell, or intracellular phase, from the outside, or extracellular phase. This is called the *plasma membrane* or, simply, *cell membrane*. The cell membrane is continuous over the entire surface of a cell and thus may cover areas that have differing functions; e.g., the nerve cell membrane encloses the cell body with its dendrites, then becomes continuous with the axon, and then bounds the terminal region of the neuron. The body (soma), axon, and terminals of nerve cells have different properties. Furthermore, these properties are intimately related to the characteristics of the cell membrane of the particular region, raising a question of whether or not the plasma membrane is chemically different in various regions.

To try to explain the diverse behavior of cell membranes, many models have been proposed. The most widely known of these is the fluid mosaic model. This plasma membrane model, which has received considerable support from physiologic and electronmicroscopic studies, is diagramed in Fig. 1-5.

The cell membrane is represented as a protein-lipid-protein matrix measuring about 75 angstrom units (Å) in thickness (Å = 1×10^{-8}, or .00000001 cm). An additional component is the globular protein within the matrix. These protein areas act like pores, which permit water to flow through them relatively easily (i.e., they are *hydrophilic* or *aqueous*) but offer resistance to the movement of ions or molecular particles larger than the water molecule. These hydrophilic pores are thought to show relative preferences for different ions. Thus, some pores allow sodium ions to move through them to the relative exclusion of other ions, while other pores permit potassium ions to flow more freely.

Cell membranes possess a great diversity of functional properties. These properties generally fall within the two major characteristics of physiologic systems, namely, translocation and transduction. This chapter will deal mainly with the property of translocation, while later ones will explore transduction more thoroughly.

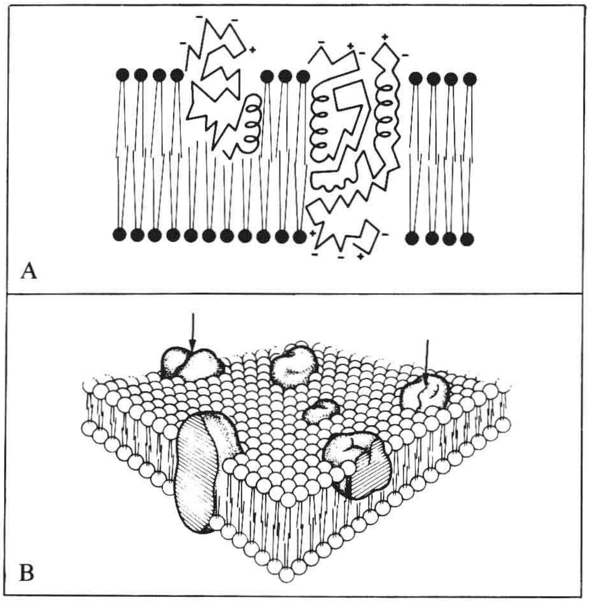

Fig. 1-5. (A) cross-sectional and (B) three-dimensional representation of the cell membrane as a fluid mosaic of lipid and globular protein. Note disposition of ionic groups in membrane proteins (A) and occurrence of oligomers (arrows in B). (Reprinted with permission from Bengt Andersson, Thirst—and brain control of water balance, Am. Sci. *59 [July 1971].)*

Cell Membrane Translocation Characteristics

As in other physiologic systems, translocation in the plasma membrane involves movement of information or material. The movement of material, that is, the manner in which organic molecules, ions, and water travel across membranes, will be considered here. There are three general kinds of movement of water, ions, and organic molecules across membranes: passive mechanisms, active transport, and engulfment.

PASSIVE MECHANISMS OF TRANSLOCATION: DIFFUSION

The process of diffusion is based entirely on the fact that molecules are always "jumping around," in a kind of movement called *random motion*. The randomly moving particle shown in Fig. 1-6A may jump in any direction with equal likelihood, or probability, as indicated by the arrows. After a