JOHN R. BROBECK

Physiological Basis of Medical Practice

NINTH EDITION

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PREFACE

TO FIRST EDITION

Physiology is a science in its own right and the laboratory worker who pursues his researches quite detached from medical problems need offer no apology for his academic outlook. Indeed some of the most valuable contributions to medical science have been the outcome of laboratory studies whose applications could not have been foreseen. Nevertheless, we feel that the teacher of physiology in a medical school owes it to his students, whose ultimate interest it must be conceded is in the diagnosis and treatment of disease, to emphasize those aspects of the subject which will throw light upon disorders of function. The physiologist can in this way play a part in giving the student and practitioner a vantage point from which he may gain a rational view of pathological processes.

We have endeavored to write a book which will serve to link the laboratory and the clinic, and which will therefore promote continuity of physiological teaching throughout the pre-clinical and clinical years of the under-graduate course. It is hoped that when the principles underlying diseased states are pointed out to the medical student, and he is shown how a knowledge of such principles aids in the interpretation of symptoms or in directing treatment, he will take a keener interest in physiological studies. When such studies are restricted to the classical aspects of the subject, apparently remote from clinical application, the student is likely to regard them only as a task which his teachers in their inscrutable wisdom have condemned him to perform. Too often he gains the idea, from such a course, that physiology is of very limited utility and comes to believe that, having once passed into the clinical years, most of what he has "crammed" for examination purposes may be forgotten without detriment to his more purely medical studies. Unfortunately, he does not always realize at this stage in his education how great has been the part which physiological discoveries have played in the progress of medicine, and that the practice of today has evolved from the "theories" of yesterday.

Many physiological problems can be approached only through animal experimentation. Advances in many fields, most notably in those of carbohydrate metabolism, nutrition, and endocrinology, bear witness to the fertility of this method of research. On the other hand, many problems can be elucidated only by observations upon man, and physiology has gained much from clinical research. The normal human subject as an experimental animal possesses unique advantages for many types of investigation; and in disease, nature produces abnormalities of structure and function which the physiological laboratory can imitate only in the crudest way. Within recent years the clinical physiologist, fully realizing these advantages and the opportunities afforded by the hospital wards, has contributed very largely to physiological knowledge. In many instances, clinical research has not only revealed the true nature of the underlying process in disease, but has cast a light into some dark corner of physiology as well; several examples of clinical investigation which have pointed the way

to the physiologist could be cited. In the last century, knowledge of the processes of disease was sought mainly in studies of morbid *anatomy*; biochemistry was in its infancy and many of the procedures now commonly employed for the investigation of the human subject had not been devised. Today, the student of scientific medicine is directing his attention more and more to the study of morbid *physiology* in his efforts to solve clinical problems. This newer outlook has borne fruit in many fields. It has had the beneficent result of drawing the clinic and the physiological and biochemical laboratories onto common ground from which it has often been possible to launch a joint attack upon disease. We feel that this modern trend in the field of research should be reflected in the teaching of medical students, and have therefore given greater prominence to clinical aspects of the subject than is usual in physiological texts.

In order to understand the function of an organ it is usually essential to have a knowledge of its structure. For this reason we have followed the plan of preceding the account of the physiology of a part by a short description of its morphology and, in many instances, of its nerve and blood supply. The architecture and functions of the central nervous system are so intimately related that some space has been devoted to a description of the more important fiber tracts and grey masses of the cerebrum, cerebellum and spinal cord.

We wish to thank our colleagues in physiology, biochemistry and anatomy whom we have drawn upon on so many occasions for information and advice; without their generous help the undertaking would have been an almost impossible one. We are also deeply grateful for the unstinted assistance which we have received from our friends on the clinical staff, several of whom have read parts of the text in manuscript or in proof. . . .

October 15, 1936

C.H.B.
N.B.T.

TO NINTH EDITION

We agree. In preparing this Ninth Edition we have tried to preserve all of the virtues of earlier editions, and to follow the principles set down by the original authors. We have attempted particularly to meet the needs of students in physiology courses in professional schools—medicine, dentistry and veterinary medicine—by offering a volume that is comprehensive but not encyclopedic, and that surveys physiological mechanisms related to problems encountered in clinical practice.

Nevertheless, the book has an appearance somewhat different from before. The figures are all new and, we trust, more informative. Furthermore, the nine sections have been manufactured independently so that they can be revised more easily, and so that they can be published separately as reprints from the complete volume. The edge markers serve as guides to section location, and take the place of a continuous pagination.

We wish to thank the editors and the staff of The Williams and Wilkins Company for their counsel and cooperation in this effort to present a textbook that is both attractive and easy for readers to use.

August 1, 1972

For the Editors
J.R.B.

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CONTENTS

Section 1
GENERAL PHYSIOLOGICAL PROCESSES
Edited by Irving L. Schwartz

Section 2
DIGESTION
Edited by N. C. Hightower, Jr., and Henry D. Janowitz

Section 3
CIRCULATION
Edited by David K. Detweiler

Section 4
BLOOD AND LYMPH
Edited by Eugene P. Cronkite

Section 5
THE EXCRETION OF URINE
Edited by Robert W. Berliner

Section 6
RESPIRATION
Edited by William B. Youmans and Arthur A. Siebens

Section 7
ENDOCRINE CONTROL SYSTEMS
Edited by Howard E. Morgan

Section 8
SENSATION
Edited by John Lott Brown

Section 9
NEURAL CONTROL SYSTEMS
Edited by John R. Brobeck

1

General Physiological Processes

1 / BY WAY OF INTRODUCTION—THE CELL

A multicellular organism is a society of cells which, like the units of any society, manifest division of labor, specialization, and mutual interaction according to a set of rules and centralized controls. Consider the levels of organization of the human organism. *Atoms* are combined in different ways to yield *monomers* (amino acids, nucleotides, sugars) which are the building blocks of biological *polymers* (proteins, nucleic acids, polysaccharides). These macromolecules are combined with smaller molecules to form *organelles* (subcellular units with distinctive function and morphology), which in turn are combined to form cells. The study of mammalian physiology involves the dynamic interrelationships among cells, tissues, and organs and reaches ultimately to the level of the organism as a whole. In this chapter we will consider the structure and function of the organelles which comprise the cell. One group of organelles is bounded by a limiting membrane; a second group is not so delimited. The former group encompasses the nucleus, endoplasmic reticulum, Golgi apparatus, lysosome, peroxisome, and mitochondrion—and in this category we also include the plasma (outer) membrane of the cell as a whole. The group of organelles that are not bounded by a membrane includes the chromosomes, nucleoli, microtubules, microfilaments, and centrioles.

Although there was some knowledge of the cell boundary and subcellular organelles prior to the advent of the electron microscope, the complicated ultrastructure of intracellular membrane systems was unforeseen (Fig. 1.1).

The following two membrane properties are particularly significant in accounting for differences of function among the various membrane-delimited subcellular organelles: *1*) the property of selective permeability which establishes and maintains compartments of specific character within the cell; and 2) the ability to provide a matrix which lends its surface as well as its interior for the arrangement of an ordered sequence of molecules (enzymes, cofactors, carriers) in a functionally meaningful pattern.

Cell Membrane

The cell membrane is a permeability barrier. If a cell is placed in hypotonic solution and if it contains molecules which cannot penetrate its outer membrane, it will swell; conversely it will shrink if placed in a hypertonic medium. In both instances water moves down its concentration gradient (chap 2). Thus, the cell behaves as an osmometer. Nonpolar molecules (gases, lipids) move freely across the membrane; polar molecules penetrate the membrane much less readily and indeed it is the selective permeability of the plasma membrane to certain ions which determine the excitability characteristics of nerve and muscle cells.

COMPOSITION OF THE CELL MEMBRANE

Although the general chemical nature of the membrane found at the cell boundary was predicted on the basis of physiological data, the detailed molecular structure of the membrane is not yet known. Models of cell membranes prepared by combining their lipid and protein constituents (partly known from chemical analysis of purified cell membrane preparations) exhibit some physiological characteristics similar to those of natural membranes. The role of lipid-lipid interactions in membrane structure has been at the center of attention because such interactions can explain much of the presently known phenomena of membrane transport. Quantitative studies of isolated cell membranes revealed that enough lipid is present to be arranged as a bilayer coating the cell. Artificial mixtures of extracted cellular polar lipids (lecithin, phospholipid, and steroids) under appropriate conditions will form a biomolecular layer

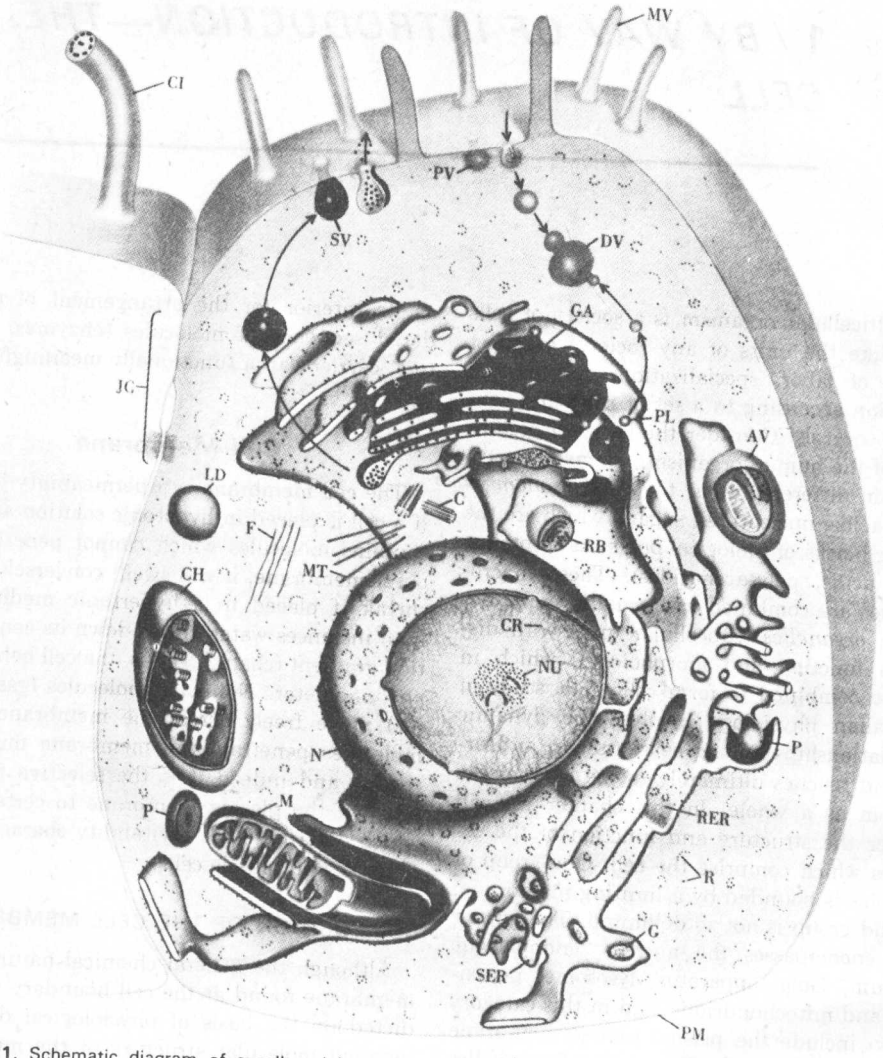

Fig. 1.1. Schematic diagram of a cell and its organelles drawn to reveal their three-dimensional structure. *AV*, autophagic vacuole; *C*, centriole; *CH*, chloroplast; *CI*, cilium; *CR*, chromatin; *DV*, digestion vacuole; *F*, microfilaments; *G*, glycogen; *GA*, Golgi apparatus; *JC*, junctional complex; *LD*, lipid droplet; *M*, mitochondrion; *MT*, microtubules; *MV*, microvillus; *N*, nucleus; *NU*, nucleolus; *P*, peroxisome; *PL*, primary lysosome; *PM*, plasma membrane; *PV*, pinocytosis vesicle; *R*, ribosomes and polysomes; *RB*, residual body; *RER*, rough endoplasmic reticulum; *SER*, smooth endoplasmic reticulum; *SV*, secretion vacuole. The organelles have been drawn only roughly to scale. Also, the sizes and relative amounts of different organelles can vary considerably from one cell type to another. For example, only plant cells show chloroplasts, and among animal cells only a few types show peroxisomes. (× 58,000.) (From Novikoff and Holtzman, 1970.)

spontaneously. Presumably the polar (hydrophilic) ends of the lipids form the two outer borders making them available for interaction with other polar molecules such as proteins (Fig. 1.2). On a weight basis membranes contain a significantly larger amount of protein than lipid (ratio up to 4:1); however, due to the high molecular weight of proteins, this relationship is reversed on a molar basis (protein: lipid ranging from 1 to 10:100). At least some of the protein must be present in a globular rather than extended form; unfolding of enzymic protein results in loss of activity. In fact, some of the proteins are probably not restricted to the surfaces of the plasma membranes but rather extend into the bimolecular lipid layer.

In addition to lipid and protein, carbohydrate appears to be associated with the cell membrane as lipopolysaccharide and as protein-polysaccharide. The carbohydrate moieties of the membrane serve to modify the electrical charge at its surface and provide specific surface-binding sites. Cytochemically demonstrable polysaccharide and protein is associated with many cell surfaces as an extracellular layer. In some places, particularly at luminal surfaces, this layer forms a fuzzy coat—often referred to as a glycocalyx (Fig. 1.3)—which may act as a crude filter and/or facilitate the attachment of molecules for endocytic (see below) transport across the cell membrane.

STRUCTURE OF UNIT MEMBRANE

A pattern generally found in almost all cellular membranes prepared for microscopy by conventional techniques consists of three layers, two electron-dense layers on either side of a single electron-lucent layer (Fig. 1.3 and 1.4). This is termed a *unit membrane*. Electron microscopic examination of osmium tetroxide-fixed, sectioned tissue shows the cell membrane to be 70 to 100 Å wide. The electron-lucent line in the unit membrane is thought to represent the lipid layer. Hydrophobic bonding in the lipid bilayer region may make it inaccessible to osmium deposition. Thus, the two electron-dense lines would result from deposition of osmium at the surfaces of this bilayer. There is much physiological evidence to suggest that the lipid bilayer is interrupted by hydrophilic molecules (Fig. 1.2*A*) which connect the two outer surfaces of the membrane and provide transmembrane channels (a few Å in width) for transfers of water molecules and ions (chap. 2).

Evidence for the unit membrane structure has been provided by x-ray diffraction patterns

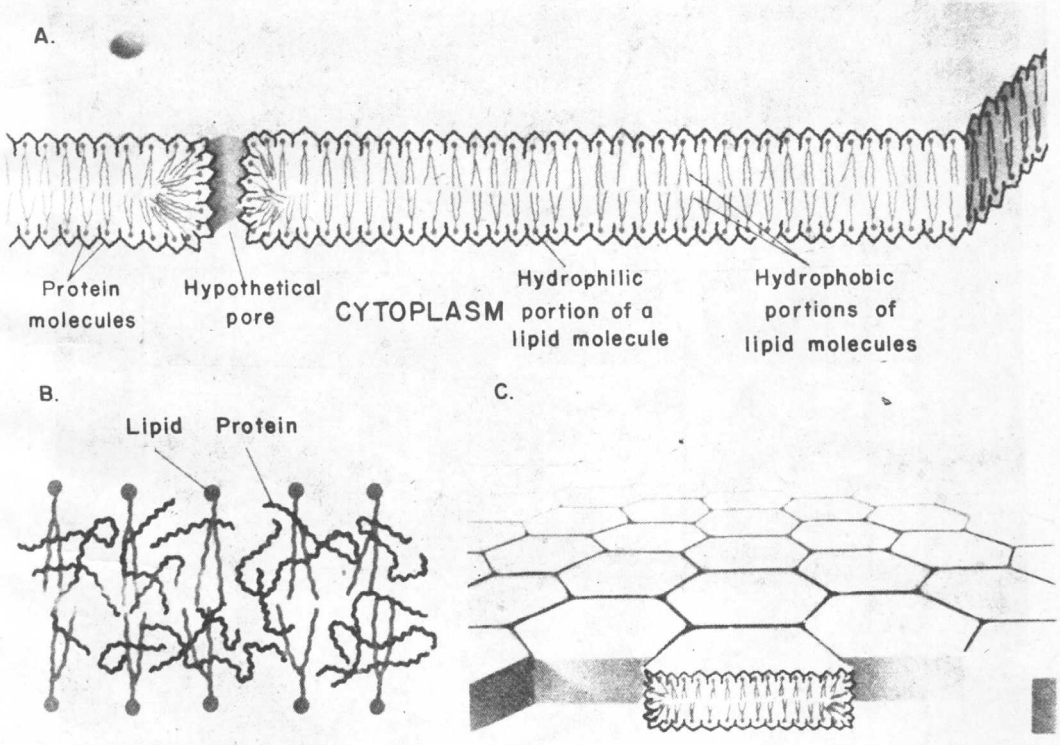

Fig. 1.2. Diagram of various models of the cell membrane. *A* represents the classic biomolecular lipid leaflet coated by protein; note inclusion of a hypothetical hydrophilic pore. *B* represents a less ordered protein component found within the lipid bilayer. *C* represents a mosaic of subunits each made up of lipid bilayers with protein or other hydrophilic molecules forming the borders. All of these forms of the membrane (and others) could be present simultaneously and in different proportions under different conditions. (From Novikoff and Holtzman, 1970.)