VOLUME ONE

MEDICAL PHYSIOLOGY

FOURTEENTH EDITION

Edited by

VERNON B. MOUNTCASTLE, M.D.

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Preface

TO FOURTEENTH EDITION

The general principles by which this textbook is organized remain those described in the preface to its twelfth edition, namely, to present mammalian physiology as an independent biologic discipline as well as a basic medical science. Two new sections appear in this edition, the first on the principles of system theory as applied to physiology and the second on the physiology of development and aging. Sixty-five chapters of the present edition either are wholly new (ten) or have been extensively revised (fifty-five); twelve chapters remain essentially as they appeared in the thirteenth edition.

This edition has been written by forty-five authors, of whom twelve have joined this effort for the first time. Forty-one of these writers are continually engaged in research and teaching in physiology. Each has taken time from that dedicated life to summarize here the present state of knowledge in a particular field of interest. Whatever value this book possesses is wholly due to the contributors' depth of understanding, skill of exposition, and devotion to the task. For this I am indebted to each.

For them and for myself I wish to thank those authors and publishers who have allowed us to reproduce illustrations previously published elsewhere.

Vernon B. Mountcastle

Preface

TO TWELFTH EDITION

The twelfth edition of *Medical Physiology* presents a cross section of knowledge of the physiologic sciences, as viewed by a group of thirty-one individuals, twenty-three of whom are actively engaged in physiologic research and teaching. Each section of the book provides statements of the central core of information in a particular field of physiology, reflecting, by virtue of the daily occupations of its authors, the questioning and explorative attitude of the investigator and indeed some of the excitement of the search. These statements vary along a continuum from those with a high probability for continuing certainty to those that are speculative but, it is hoped, of heuristic value. An attempt has been made to maintain a balanced point of view. I hope this book will convey to the student who reads it the fact that physiology is a living and changing science, continuously perfecting its basic propositions and laws in the light of new discoveries that permit new conceptual advances. The student should retain for himself a questioning attitude toward all, for commonly the most important advances are made when young investigators doubt those statements others have come to regard as absolutely true. This is not a book that sets forth in stately order a series of facts which, if learned, will be considered adequate for success in a course in physiology. Many such "facts" are likely to be obsolete before the student of physiology reaches the research laboratory, or the student of medicine the bedside. Nor is it a book that provides ready-made correlations and integrations of the various fields of physiology necessary for a comprehensive understanding of bodily function. Those integrations are an essential part of scholarly endeavor not readily gained from books alone. It is my hope, however, that study of this book, combined with laboratory experience and scholarly reflection, will provide the student with a method and an attitude that will serve him long after the concepts presented here are replaced by new and more cogent ones.

The title *Medical Physiology* has been retained, for one of the purposes of this edition, in common with earlier ones, is "to present that part of physiology which is of special concern to the medical student, the practitioner of medicine, and the medical scientist in terms of the experimental inquiries that have led to our present state of knowledge." The scope of the book was and is still broader, however, and attempts to present mammalian physiology as an independent biologic discipline as well as a basic medical science. Mammalian physiology has its base in cellular physiology and biophysics, and it is from this point of view that many of the subjects treated here are approached. Above all, mammalian physiology must deal with problems of the interactions between large populations of cells, organs, and organ systems and, finally, the integrated function of an entire animal. Physiology thus must bridge the distance from cellular biology on the one hand to systems analysis and control theory on the other: each is important and any one is incomplete without the others. This approach to the problems of internal homeostasis, of reaction to the environment, and of action upon the environment is evidenced in several sections of this book.

Of the eighty chapters composing this book, twenty-nine are wholly new in this edition; forty-five from the last edition have been extensively revised either by their original authors or by new ones. Six have been allowed to stand substantially as previously written, for these seemed to comprise as balanced and modern a survey as any presently possible. The names and affiliations of my colleagues in this effort have been

listed. They have taken time from busy lives to survey their fields of interest; for this I am greatly indebted to each. If this book possesses any worth it is in large part due to their continuing devotion to the task of its preparation.

For them and for myself I wish to thank those authors and publishers who have allowed us to reproduce illustrations previously published elsewhere.

Vernon B. Mountcastle

Contents

I

CELLULAR PHYSIOLOGY

ROBERT D. DeVOE and PETER C. MALONEY

1 Principles of cell homeostasis

Cells are semiautonomous units of tissue; isolated cells can survive for long periods of time in tissue culture media that mimic their normal environments. The intracellular environments are very different from the fluids around cells, however, and there are constant exchanges of metabolites, waste products, and other substances between a cell and its environment. For this molecular traffic to be possible, the cell cannot wall itself off altogether. On the other hand, it must have some barrier between its different internal and external environments simply in order to survive. The problem all cells face, therefore, is how to surround themselves with barriers (cell membranes) that allow desired substances to pass in and out while maintaining their own internal constancies. The maintenance of this constancy is what is meant by cell homeostasis.

Cells of epithelial tissues face additional problems. Parts of their surfaces border the body's relatively constant internal environment and parts the body's much more variable external environment. Across epithelial cells pass food, water, and oxygen for the body as well as wastes from the body. In the face of this molecular traffic, these cells must maintain their internal homeostasis, too. They do this by the same means as do nonepithelial cells. Indeed, the transepithelial traffic results from specializations of mechanisms used by all cells for homeostasis. Therefore cell homeostasis will be discussed primarily for the general case, with some of the epithelial specializations presented at the end of this chapter.

The beginning point here is this boundary between a cell and its environment. A "typical" cell (in fact, an epithelial cell) is depicted in Fig. 1-1, *A*, but for initial purposes it may be simplified to the hollow shell depicted in Fig. 1-1, *B*. This shell consists of a uniform cell membrane that surrounds a fluid of one composition and is itself surrounded by a fluid of a different composition. By way of illustration, the ionic compositions of intra- and extracellular fluids are given for a number of cells in Table 1-1 (with some other quantities that will be explained later). Proceeding from values given in this table and by reference to Fig. 1-1, *B*, the basic principles of cell homeostasis that will be developed in this chapter are sixfold.

First, water is in general in osmotic equilibrium across cell membranes and easily passes back and forth across them. Second, large internal organic molecules, both charged and uncharged, are retained within the cell. At nearly neutral intracellular pH values, their net charges are negative. They are designated collectively in Fig. 1-1, *B*, as P^-. Third, the presence of osmotically active organic molecules held within the cell by the membrane must be balanced by the external presence of some substance(s) impeded by the membrane from entering the cell. If this were not the case, the cell could not be in osmotic equilibrium. By and large, this external substance is sodium, shown in Fig. 1-1, *B*, in large concentration outside and in low concentration inside. Fourth, since the net charge on the internal organic ions is negative, some cation must be present to give electroneutrality within the cell. For most cells, the predominant intracellular cation tends to be potassium. This is shown in Fig. 1-1, *B*, as a large internal potassium concentration and a low external concentration. Fifth, there is a negative potential difference between the inside and the outside of the cell. This membrane potential, as it is called, is primarily due to the tendency of potassium ion to equalize its internal and external concentrations by diffusing out of the cell, thus upsetting electroneutrality across the membrane. The effect of the inside negative membrane potential, combined with internal indiffusible anions, is the greater or lesser exclusion of mobile negative ions, particularly chloride, from the cell interior. Conversely, further outward movements of potassium ion are

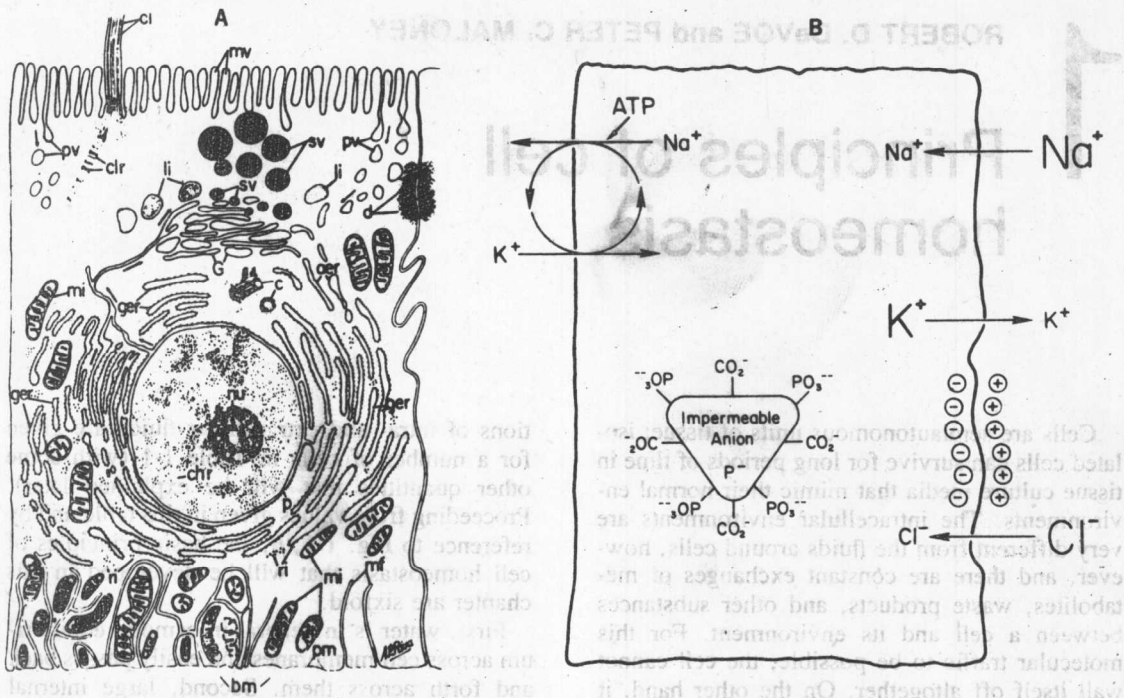

Fig. 1-1. **A,** Diagram of ultrastructure of ideal animal cell. (See De Robertis et al.[4] for key to details.) **B,** "Hollow-shell" depiction of plasma membrane around cell, ionic movements and electrical potential across membrane, and relative concentrations of substances on either side (shown by relative sizes of lettering). (A From De Robertis et al.[4])

Table 1-1. Some representative values for intracellular and extracellular ionic concentrations (in millimoles per liter cell water or extracellular volume) and equilibrium and resting potentials (in millivolts)

	Squid giant axon	Frog sartorius muscle	Human red blood cell
Intracellular concentrations (mM/L)			
$[Na^+]_i$	78.0	13.0	19.0
$[K^+]_i$	396.0	138.0	136.0
$[Mg^{++}]_i$	11.0	16.0	6.0
$[Ca^{++}]_i$	0.4	3.0	0.0
$[Cl^-]_i$	104.0	2.0	78.0
Extracellular concentrations (mM/L)			
$[Na^+]_o$	462.0	108.0	155.0
$[K^+]_o$	22.0	2.5	5.0
$[Mg^{++}]_o$	56.0	1.0	1.0
$[Ca^{++}]_o$	11.0	2.0	2.5
$[Cl^-]_o$	586.0	76.0	112.0
Equilibrium potentials (mV)			
E_{Na}	+45	+53	+55
E_K	−73	−101	−86
E_{Cl}	−44	−92	−9
Resting potentials—V_m (mV)	−73	−92	−6 to −10

retarded, whereas the slow tendency of sodium ions to enter the cell down its concentration gradient is accelerated. Sixth, and finally, in order to prevent even a slow net inward movement of sodium, which would upset the osmotic equilibrium, cells utilize metabolic energy to transport, or pump, the excess sodium out of the cell. In most instances, there is a linked inward movement of potassium ions to maintain the internal potassium concentration.

It can thus be seen that there are three points at which cells can control the states they will achieve in homeostasis by means of metabolic, synthetic, or other activity. These are (1) the permeabilities of their membranes to water, ions, and nonelectrolytes; (2) the osmolarities and amounts of charge of internal organic molecules; and (3) the rate of ion transport. Even in a given cell, one or more of these may be a variable, depending on physiologic activity. Thus nerve cells, which like other cells have low membrane permeabilities to sodium, transiently increase this permeability during the generation of action potentials. Cells such as those in kidney collecting tubules have water permeabilities that are under

endocrine control. Oxygenation and deoxygenation of hemoglobin in erythrocytes, which occur as these cells transport oxygen and carbon dioxide to and from tissues, respectively, involve changes in internal anionic charge and hence in internal ionic distributions. Rates of ion transport may depend on internal ion concentrations or, in some epithelial cells, on hormones. It should thus be understood that there may be many different combinations of membrane permeabilities, internal anions, and ion transport mechanisms that cells use both to maintain themselves and to carry out their physiologic functions.

Whatever the particular combination that a given cell has evolved, it will result in homeostasis, a steady-state condition in which there are no *net* molecular movements of consequence into and out of the cell. There will be molecular traffic across the membrane, but the movement of osmotically active particles into the cell must be matched by an equal outward movement if the cell is to stay in osmotic equilibrium. In general, since cell membranes show selectivity toward each chemical species, this means that the inward movement of a given substance must be matched by an equal outward movement, unless it is consumed. Again, since the major osmotically active substances in body fluids are the three principal ions sodium, chloride, and potassium, the matched movements in question will be of these ions. Movement of any substance across a membrane per unit of time is called its *flux*, and the flux per 1 cm^2 unit area has the dimensions of moles per second per square centimeter. For a steady state, then, the outflux of each ion (and water) must be of the same size but opposite in sign (i.e., direction) to the influx; the net flux, their sum, must be zero. (This is as true for epithelial cells as for other cells, but in epithelial cells there may be a net transcellular flux. In this case, what enters at one cell border may leave at a different border.)

To complete this initial picture of cell homeostasis, recall that the *causes* of inward and outward movements of substances can be both the tendencies of these substances to distribute themselves according to concentration and electrical differences across the cell membrane and the use of metabolic energy by the cell to transport substances. The term "passive fluxes" is used to describe movements of substances due to kinetic forces, i.e., concentration gradients, electrical potential gradients (in the case of ions), and other gradients such as pressure and temperature. When influxes and outfluxes of a substance are both solely passive and equal to each other, that substance is in equilibrium across the membrane. As stated earlier, water is thought to be in equilibrium across cell membranes,[111] and in resting muscle in situ, chloride may likewise be in equilibrium.[11] However, there is, in addition, an *active transport* of ions such as sodium and potassium across cell membranes that results from the expenditure of metabolic energy by the cell. Intuitively it can be seen that if, for example, sodium ions are transported out of a cell interior, the negative organic anions are left behind. Therefore there will be movements of the other ions to reestablish electroneutrality. Thus active transport of only one ion out of a cell, with given amounts of internal indiffusible anion and with given membrane permeabilities to the various ions, can result in extensive redistributions of other ions as well. In general the process of this redistribution cannot be observed; what is usually seen is the final result. Nonetheless, cell homeostasis may be approached as the study of what active fluxes there are and hence what the requisite concentration and electrical gradients there must be in order to set up, across the membrane in question, the passive fluxes that will just balance the active fluxes. Once this is done, the distributions of ions (and water) can be determined from the necessity for electrical neutrality and for osmotic equilibrium, that is, for the distribution that will bring these other substances into equilibrium.

To proceed further, it is necessary to consider first the structure of membranes and how, to the extent known, they exert their selective effects on the movements of water, ions, and nonelectrolytes into and out of cells. Second, considerable emphasis will be given to the manner in which ions and water move under concentration and electrical gradients, which themselves are established by ion pumps. Initially, emphasis will be placed on the homeostasis of individual cells—their ionic and water distributions and how these affect membrane potentials and ionic equilibriums. Finally, the properties of the active transport mechanisms will be discussed, since these are the key to understanding the ultimate ionic and water distributions seen in cells.

COMPOSITION AND STRUCTURE OF CELL MEMBRANES

Cell membranes undeniably differ from one cell to another. A common structural basis now appears to be the fluid mosaic model,[15,115] diagrammed in Fig. 1-2. In this, about 70% of the membrane surface is a lipid bilayer[46] with integral, amphipathic proteins (having both hydro-