Thirteenth edition

MEDICAL PHYSIOLOGY

Edited by

VERNON B. MOUNTCASTLE

Volume one

VOLUME ONE

MEDICAL PHYSIOLOGY

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PREFACE

The general principles on which this textbook is organized are those described in the preface to its twelfth edition. An extensive revision of that book has been made for the present edition. Completely new sections appear on endocrinology, renal physiology and the regulation of the internal milieu, gastrointestinal physiology, and the autonomic nervous system. Chapters on new subjects appear in several other sections as well. This edition thus contains twenty-eight chapters that are wholly new. The elimination and combination of others has reduced to seventy-three the eighty chapters of the twelfth edition, printed in approximately the same space. Each of the remaining forty-five chapters has been substantially revised and in many cases rewritten to take into account advances in the relevant fields of physiology since 1968.

This edition has been written by thirty-eight authors, of whom seventeen have joined this endeavor for the first time. Each is busily engaged in the work of research and teaching in physiology; each has taken time from that dedicated life to summarize here the state of knowledge in his particular field of interest. Whatever value the result of our common effort may possess is wholly due to their depth of understanding and skill in exposition and their devotion to the task. For this I am greatly 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.

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I

CELLULAR PHYSIOLOGY

1

ROBERT D. DeVOE

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 internal environments of cells are very different from the fluids around them, 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.

The beginning point here is therefore this boundary between a cell and its environment. A "typical" cell is depicted in Fig. 1-1, *A*, but for our 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 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. 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, the charge on the internal organic ions is, in the aggregate, negative, and some cation must be present to give electroneutrality within the cell. As sodium is impeded by the membrane from entering but potassium is less impeded, the predominant intracellular cation tends to be potassium. This is shown in Fig. 1-1, *B*, as a large internal potassium concentration

Table 1-1. Some representative values for intracellular and extracellular ionic concentrations (in mM/L cell water or extracellular volume), equilibrium potentials, and resting potentials

	Squid giant axon	Frog sartorius muscle	Human red blood cell
Intracellular concentrations			
Na	65.0	13.0	19.0
K	344.0	138.0	136.0
Mg	10.0	14.0	5.5
Ca	3.5	5.0	0.0
Cl	80.0	3.0	78.0
Extracellular concentrations*			
Na	460.0	110.0	155.0
K	10.0	2.5	5.0
Mg	53.0	1.0	2.2
Ca	10.0	2.0	5.0
Cl	540.0	90.0	112.0
SO_4	25.0	2.0	1.0
Equilibrium potentials			
E_{Na}	+49	+ 55	+55
E_K	−89	−101	−86
E_{Cl}	−48	− 86	− 9
Resting potentials	−77	− 99	−6 to −10

*Values for squid giant axon are concentrations in seawater; values for frog sartorius muscle and human red blood cell are concentrations in plasma.

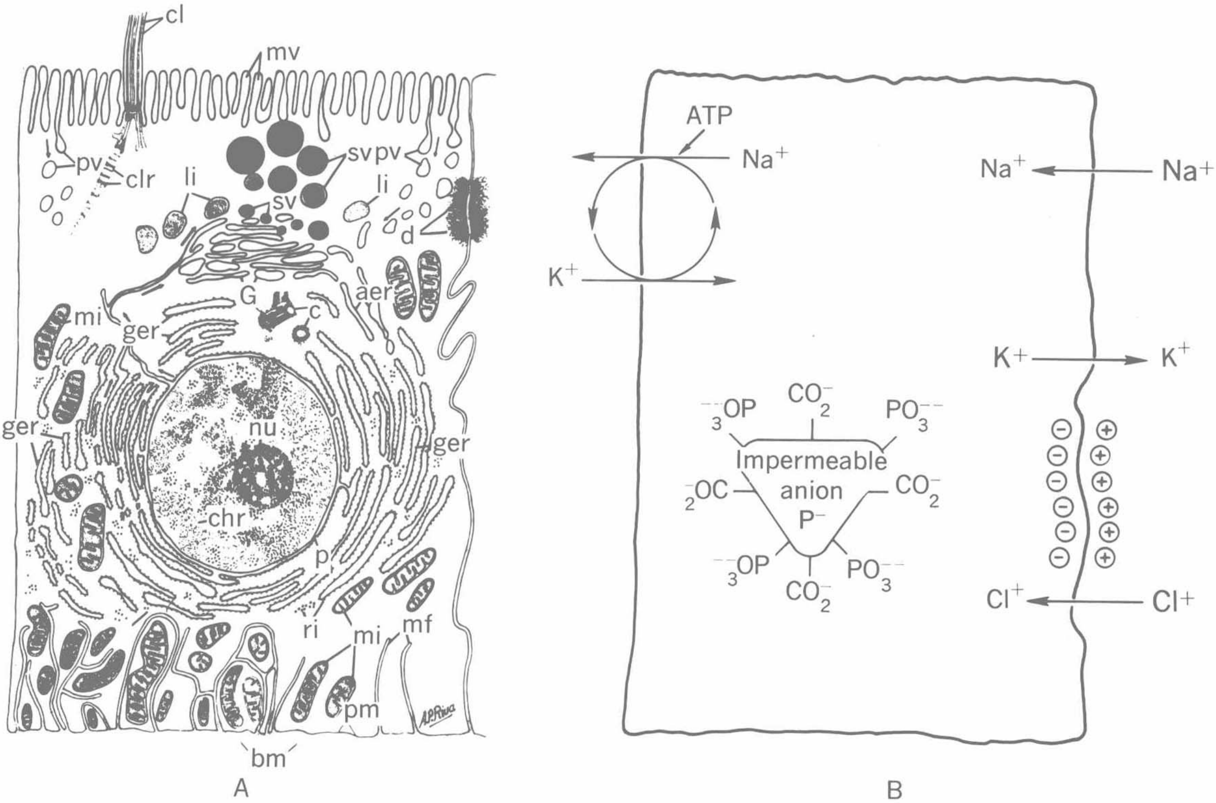

Fig. 1-1. A, Diagram of ultrastructure of ideal animal cell. (See De Robertis et al.[2a] for key to details.) **B,** "Hollow-shell" depiction of plasma membrane around cell, ionic movements and electric potential across membrane, and relative concentrations of substances on either side (shown by relative sizes of lettering.) (**A** From De Robertis et al.[2a])

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 due to the tendency of a potassium ion, especially, to equalize its internal and external concentrations by diffusing out of the cell, thus upsetting electroneutrality across the membrane. In any event, the effect of the negative membrane potential is to exclude negative ions, particularly chloride, from the cell interior, while accelerating the slow tendency of sodium to equalize *its* internal and external concentrations by diffusing into the cell. 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 many instances there is a linked inward movement of potassium ions when this is necessary 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. Oxidation and reduction 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, in-