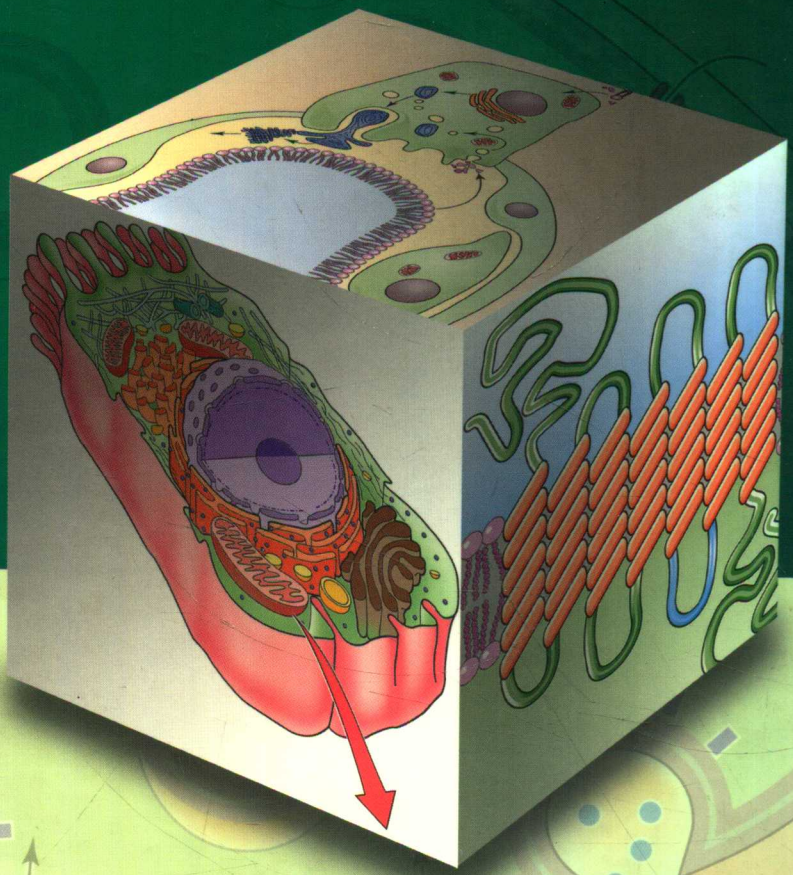
Walter F. Boron
Emile L. Boulpaep

MEDICAL PHYSIOLOGY

second edition



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Medical Physiology

A Cellular and Molecular Approach

SECOND EDITION

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PREFACE TO THE SECOND EDITION

We are very grateful for the enthusiastic reception with which the academic community received the first edition of our book. In producing this second edition, three guiding principles have remained the same as before. First, create a modern textbook of physiology that provides the expertise of several authors but the consistency of a single pen. Second, weave an integrative story that extends from the level of DNA and proteins to the level of cells, tissues, and organs, and finally to the interaction among organ systems. Third, illustrate important physiological principles with examples from pathophysiology, thereby putting physiology in a clinical context. In addition, we have strived to improve the book along the lines suggested by our readers. Moreover, we have updated the material—reflecting new molecular insights—as well as the presentation of this material. The result is two new chapters, new authors for seven chapters, the reordering or reorganization of several chapters, and—throughout the book—countless improvements to the text. In addition, the second edition includes 65 new or redrawn figures as well as enhancements to 488 others.

In Section II (The Physiology of Cells and Molecules), fresh insights into genetics led to substantial revisions in Chapter 4 (Regulation of Gene Expression). Moreover, advances in genomics and the understanding of genetic diseases led to the creation of new tables to organize families of transporter proteins in Chapters 5 (Transport of Solutes and Water) and ion channels in Chapter 6 (Electrophysiology of the Cell Membrane).

In Section III (The Nervous System), new molecular developments led to major changes in Chapter 15 (Sensory Transduction). In Section IV (The Cardiovascular System), we have added new Chapter 18 on Blood. In Section V (The Respiratory System), we have shifted some pulmonary function tests into Chapter 26 (Organization of the Respiratory System). In Section VI (The Urinary System), genomic progress led to a new table on amino-acid transporters. In Section VII (The Gastrointestinal System), Chapter 45 (Nutrient Digestion and Absorption) now contains a section on nutritional requirements. In Section VIII (The Endocrine System), we have renamed Chapter 48 to Endocrine Regulation of Growth and Body Mass to reflect updated coverage of the regulation of appetite. In Section IX (The Reproductive System), we have modified figures to clarify mitosis versus meiosis in males versus meiosis in females, as well as to clarify the development of the follicle. Finally, in Section X (The Physiology of Cells and Molecules), we have largely rewritten Chapter 58 (Metabolism), with special emphasis on energy interconversion (e.g., gluconeogenesis); energy capture after ingestion of carbohydrate, protein, or fats; and the integrative response to fasting. Moreover, we have added new Chapter 62 (The Physiology of Aging).

To create the second edition, we recruited as new authors several outstanding scientist-educators: Lloyd Cantley (Chapter 3), Gerald Shulman and Kitt Petersen (Chapter 58), John Stitt (Chapter 59), Arthur DuBois (Chapter 61), and Edward Masoro (Chapter 62). In addition, two previous authors picked up additional chapters: Edward Moczydlowski (Chapter 9) and Steven Segal (Chapter 60).

Online Access. The Web site **www.StudentConsult.com** offers the reader access to the online edition of the textbook, with the ability to search, bookmark, post notes, download highlighted text to a handheld device, access all of the images in the book, and more. The hundreds of "mouse" icons  in the text direct the reader to "webnotes" that likewise are available on the **Student Consult** website. These webnotes provide derivations of mathematical equations, amplification of concepts, supplementary details, additional clinical illustrations, and links that may be of interest (e.g., biographies of famous physiologists).

Acknowledgments. A textbook is the culmination of successful collaborations among many individuals. First, we thank our authors. Second, we thank Philine Wangemann, who made invaluable suggestions for the Vestibular and Auditory Transduction subchapter in Chapter 15. Third, we thank our colleagues who provided advice on parts of the book: Samuel Cukierman, Sarah Garber, and Mark Shapiro (Chapters 6-8); R. John Solaro and John Walsh (Chapter 9); T. Richard Nichols (Chapter 16); Don McCrimmon and Frank Powell (Chapter 32); Franz Beck, Gerhard Burkhardt, Bruce Koeppen, Patricia Preisig, Luis Reuss, James Schafer, Jurgen Schnermann, James Wade, and Carsten Wagner (Chapters 33-40); Mark Donowitz (Chapter 44); Charles Mansbach (Chapter 45); as well as Harold Behrman and Richard Ehrenkranz (Chapters 53-57).

We thank all of our readers who sent us their suggestions.

At the art studio Dartmouth Publishing Inc, we thank Stephanie Davidson for developing new figures and updating others, while maintaining the textbook's aesthetic appeal originally established by JB Woolsey and Associates.

At Elsevier, we are very grateful to William R. Schmitt, Acquisitions Editor, for his trust and endurance. Andrew Hall, Developmental Editor, was the project's communica-

tions hub, responsible for coordinating all parties working on the textbook, and for assembling the many elements that comprised the final product. His meticulous care was indispensable. We thank Sharon Lee, Project Manager, for overseeing production of the textbook.

Finally, at Yale University and Case Western Reserve University we thank Charleen Bertolini, who used every ounce of her friendly, good-humored, and tenacious personality to keep our authors—and us—on track.

As we did in the First Edition, we again invite the reader to enjoy learning physiology. If you are pleased with our effort, tell others. If not, tell us.

PREFACE TO THE FIRST EDITION

We were intrigued by an idea suggested to us by W.B. Saunders: write a modern textbook of physiology that combines the expertise of a multi-author book with the consistency of a single pen. Our approach has been, first, to recruit as writers mainly professors who teach medical physiology at the Yale University School of Medicine, and then to recast the professors' manuscripts in a uniform style. After much effort, we now present our book, which we hope will bring physiology to life and at the same time be a reliable resource for students.

Target Audience. We wrote *Medical Physiology* primarily as an introductory text for medical students, although it should also be valuable for students in the allied health professions and for graduate students in the physiological sciences. The book should continue to be useful for the advanced medical student who is learning pathophysiology and clinical medicine. Finally, we hope that physicians in training, clinical fellows, and clinical faculty will find the book worthwhile for reviewing principles and becoming updated on new information pertinent for understanding the physiological basis of human disease.

Content of the Textbook. Aside from Part I, which is a brief introduction to the discipline of physiology, the book consists of nine major Parts. Part II (Physiology of Cells and Molecules) reflects that, increasingly, the underpinnings of modern physiology have become cellular and molecular. Chapters 2, 4, and 5 would not be present in a traditional physiology text. Chapter 2 (Functional Organization of the Cell), Chapter 4 (Signal Transduction), and Chapter 5 (Regulation of Gene Expression) provide the essentials of cell biology and molecular biology necessary for understanding cell and organ function. The other chapters in Part II cover the *cellular* physiology of transport, excitability, and muscle—all of which are classic topics for traditional physiology texts. In this book we have extended each of these subjects to the *molecular* level. The remainder of the book will frequently send the reader back to the principles introduced in Part II.

Parts III to IX address individual organ systems. In each case, the first chapter provides a general introduction to the system. Part III (Cellular Physiology of the Nervous System) is untraditional in that it deliberately omits those aspects of the physiology of the central nervous system that neuroscience courses generally treat and that require extensive knowledge of neuroanatomical pathways. Rather, Part III focuses on cellular neurophysiology, including synaptic transmission in the nervous system, sensory transduction, and neural circuits. In addition, Part III also treats two subjects—the autonomic nervous system and the neuronal microenvironment—that are important for understanding other physiological systems. Finally, Part X (The Physiology of Everyday Life) is an integrated, multisystem approach to metabolism, temperature regulation, exercise, and adaptations to special environments.

Emphasis of the Textbook. Some important aspects of physiology remain as fundamentally important today as when the pioneers of physiology discovered them a century or more ago. These early observations were generally phenomenological descriptions that physiologists have since been trying to understand at a mechanistic level. Where possible, a goal of this textbook is to extend this understanding all the way to the cell and molecule. Moreover, although some areas are evolving rapidly, we have tried to be as up to date as practical. To make room for the cellular and molecular bricks, we have omitted some classic experimental observations, especially when they were of a "black-box" nature.

Just as each major Part of the textbook begins with an introductory chapter, each chapter generally first describes—at the level of the whole body or organ system (e.g., the kidney)—how the body performs a certain task and/or controls a certain parameter (e.g., plasma K^+ concentration). As appropriate, our discussion then progresses in a reductionistic fashion from organ to tissue to cell and organelles, and ultimately to the molecules that underlie the physiology. Finally, most chapters include a discussion of how the body regulates the parameter of interest at all levels of integration, from molecules to the whole body.

Creating the Textbook. The first draft of each chapter was written by authors with extensive research and/or teaching experience in that field. The editors, sitting shoulder to shoulder at a computer, then largely rewrote all chapters line by line. The goal of this exercise was for the reader to recognize, throughout the entire book, a single voice—a unity provided by consistency in style, in organization, in the sequence for presenting concepts, and in terminology and notation, as well as in consistency in the expression of standard values (e.g., a cardiac output of 5 liters/min). The editors also attempted to minimize overlap among chapters by making extensive use of cross references (by page, figure, or table number) to principles introduced elsewhere in the book.

After the first round of editing, Dr. Malcolm Thaler—a practicing physician and accomplished author in his own right—improved the readability of the text and sometimes

added clinical examples. Afterwards, the editors again went through the entire text line by line to decide on the material to be included in specific illustrations, and to match the main text of the book with the content of each figure. The editors then traveled to Philadelphia to visit the art studio of JB Woolsey and Associates. Over many visits, John Woolsey and the editors together developed the content and format for each of the approximately 760 full-color illustrations used in the textbook. These meetings were unique intellectual and pedagogical dialogues concerning the design of the figures. To a large extent, the figures owe their pedagogical style to the creativity of John Woolsey.

The illustrations evolved through several iterations of figure editing, based on suggestions from both the editors and authors. This evolution, as well as text changes requested by authors, led to yet a third round of editing of the entire book, often line by line. Throughout this seemingly endless process, our goal has been to achieve the proper balance among reader friendliness, depth, and accuracy.

Special Features. Compared with other major textbooks of physiology, a much larger fraction of the space in this book is devoted to illustrations. Thus, although our textbook may appear thick, it actually has fewer text words than most other leading medical physiology books. Virtually all illustrations in our book are in full color, conceived de novo, with consistent style and pedagogy. Many of the figures feature "dialogue balloons" that tell a story. The illustrations are also available in digital format on the Evolve Web site (http://evolve.elsevier.com/productPages/s_417.html) for use in the classroom.

The textbook makes considerable use of clinical boxes—highlighted on a color background—that present examples of diseases illustrating important physiological principles. The text includes over 2000 cross references that send the reader from the current page to specific pages, figures, or tables elsewhere in the book for relevant concepts or data. The text also includes hundreds of web icons, which direct the reader to our website at **http://www.wbsaunders.com/MERLIN/BandB/**. These web links provide derivations of mathematical equations, amplification of concepts, material that was deleted for the sake of brevity from earlier drafts of the textbook, and clinical illustrations not included in the clinical boxes.

The website will also contain several other features, including summaries for each subchapter, an expanded list of references (sometimes with direct links to the primary literature), other links that may be of interest to the physiology student (e.g., biographies of famous physiologists), late-breaking scientific developments that occur after publication of the book, and—alas—the correction of errors. Finally, we invite the reader to visit our website to comment on our book, to point out errors, and to make other helpful suggestions.

Acknowledgments. A textbook is the culmination of successful collaborations among many individuals. First, we would like to thank our authors. Second, we acknowledge the expert input of Dr. Malcolm Thaler, both in terms of style and clinical insight. We also thank Dr. Thaler for emphasizing the importance of telling a "good story." The textbook's aesthetic appeal is largely attributable to JB Woolsey and Associates, particularly John Woolsey and Joel Dubin.

At W.B. Saunders, we are especially thankful to William R. Schmitt—Acquisitions Editor—for his trust and patience over the years that this book has been in gestation. At the times when the seas were rough, he steered a safe course. Melissa Dudlick—Developmental Editor at W.B. Saunders—was the project's nerve center, responsible for day-to-day communication among all parties working on the textbook, and for assembling all of the many components that went into making the final product. Her good humor and careful attention to detail greatly facilitated the creation of the textbook. We thank Frank Polizzano—Publishing Services Manager at W.B. Saunders—for overseeing production of the textbook.

Before this textbook was completed, the author of Part X (The Physiology of Everyday Life), Ethan Nadel, passed away. We are indebted to those who generously stepped up to carefully check the nearly finished manuscripts for the final four chapters: Dr. Gerald Shulman for Chapter 57, Dr. John Stitt for Chapter 58, the late Dr. Carl Gisolfi for Chapter 59, and Dr. Arthur DuBois for Chapter 60. In addition, Dr. George Lister provided expert advice for Chapter 56. We are also grateful to Dr. Bruce Davis for researching the sequences of the polypeptide hormones, to Mr. Duncan Wong for expert information-technology services, and to Mrs. Leisa Strohmaier for administrative assistance.

We now invite the reader to enjoy the experience of learning physiology. If you are pleased with our effort, tell others. If not, tell us.

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SECTION

INTRODUCTION

CHAPTER 1

FOUNDATIONS OF PHYSIOLOGY

Emile L. Boulpaep and Walter F. Boron

WHAT IS PHYSIOLOGY?

Physiology is the dynamic study of life. Physiology describes the "vital" functions of living organisms and their organs, cells, and molecules. For centuries, the discipline of physiology has been closely intertwined with medicine. Although physiology is not primarily concerned with structure—as is the case of anatomy, histology, and structural biology—structure and function are inextricably linked because the living structures perform the functions.

For some, physiology is the function of the whole person (e.g., exercise physiology). For many practicing clinicians, physiology may be the function of an individual organ system, such as the cardiovascular, respiratory, or gastrointestinal system. For still others, physiology may focus on the cellular principles that are common to the function of all organs and tissues. This last field has traditionally been called general physiology, a term that is now supplanted by "cellular and molecular physiology." Although one can divide physiology according to varying degrees of reductionism, it is also possible to define a branch of physiology—for example, comparative physiology—that focuses on differences and similarities among different species. Indeed, comparative physiology may deal with all degrees of reductionism, from molecule to whole organism. In a similar way, medical physiology deals with how the human body functions, which depends on how the individual organ systems function, which depends on how the component cells function, which in turn depends on the interactions among subcellular organelles and countless molecules. Thus, medical physiology takes a global view of the human body; but in doing so, it requires an integrated understanding of events at the level of molecules, cells, and organs.

Physiology is the mother of several biological sciences, having given birth to the disciplines of biochemistry, biophysics, and neuroscience as well as their corresponding scientific societies and journals. Thus, it should come as no surprise that the boundaries of physiology are not sharply delineated. Conversely, physiology has its unique attributes. For example, physiology has evolved over the centuries from a more qualitative to a more quantitative science. Indeed, many of the leading physiologists were—and still are—trained as chemists, physicists, mathematicians, or engineers.

Physiological Genomics Is the Link Between the Organ and the Gene

The life of the human body requires not only that individual organ systems do their jobs but also that these organ systems work "hand in hand" with each other. They must share information. Their actions must be interdependent. The cells within an organ or a tissue often share information, and certainly the individual cells must act in concert to perform the proper function of the organ or tissue. In fact, cells in one organ must often share information with cells in another organ and make decisions that are appropriate for the health of the individual cell as well as for the health of the whole person.

In most cases, the sharing of information between organs and between cells takes place at the level of atoms or molecules. Cell-to-cell messengers or intracellular messengers may be atoms such as H^+ or K^+ or Ca^{2+}. The messengers may also be more complex chemicals. A cell may release a molecule that acts on a neighboring cell or that enters the bloodstream and acts on other cells a great distance away. In other cases, a neuron may send an axon a centimeter or even a meter away and rapidly modulate, through a neurotransmitter molecule, the activity of another cell or another organ. Cells and organs must interact with one another, and the method of communication is almost always molecular.

The grand organizer—the master that controls the molecules, the cells, and the organs and the way they interact—is the genome. Traditionally, the discipline of physiology has, in its reductionistic journey, always stopped at about the level of cells and certain subcellular organelles as well as their component and controlling molecules. The discipline of physiology left to molecular biology and molecular genetics the business of how the cell controls itself through its DNA. The modern discipline of physiology has become closely intertwined with molecular biology, however, because DNA encodes the proteins in which physiologists are most interested. Very often, physiologists painstakingly develop elegant

strategies for cloning of the genes relevant to physiology. Sometimes, brute force approaches, such as the Human Genome Project in the United States, hand the physiologist a candidate gene, homologous to one of known function, on a silver platter. In still other cases, molecular biologists may clone a gene with no known function. In this case, it may be up to the physiologist to determine the *function* of the gene product, that is, to determine its *physiology*.

Physiological genomics (or functional genomics) is a new branch of physiology devoted to understanding of the roles that genes play in physiology. Traditionally, physiologists have moved in a reductionistic direction from organ to cell to molecule to gene. One of the most fascinating aspects of physiological genomics is that it has closed the circle and linked organ physiology directly with molecular biology. Perhaps one of the most striking examples is the knockout mouse. Knocking out the gene encoding a protein that, according to conventional wisdom, is very important will sometimes have no obvious effect or sometimes unexpected effects. It is up to the physiologist, at least in part, to figure out why. It is perhaps rather sobering to consider that to truly understand the impact of a transgene or a knockout on the physiology of a mouse, one would have to carefully re-evaluate the totality of mouse physiology. To grasp the function of a gene product, the physiologist must retrace the steps up the reductionistic road and achieve an integrated understanding of that gene's function at the level of the cells, organs, and whole body. Physiology is unique among the basic medical sciences in that it is both broad in its scope (i.e., it deals with multiple systems) and integrative in its outlook.

In some cases, important physiological parameters, such as blood pressure, may be under the control of many genes. Certain polymorphisms in several of these many genes could have a cumulative effect that produces high blood pressure. How would one identify which polymorphisms of which genes may underlie high blood pressure? This sort of complex problem does not easily lend itself to a physiologist's controlled studies. One approach would be to study a population of people, or strains of experimental animals, and use statistical tools to determine which polymorphisms correlate with high blood pressure in a population. Indeed, epidemiologists use statistical tools to study group effects in populations. However, even after the identification of variants in various genes, each of which may make a small contribution to high blood pressure, the physiologist has an important role. First, the physiologist, performing controlled experiments, must determine whether a particular genetic variant does indeed have at least the potential to modulate blood pressure. Second, the physiologist must determine the mechanism of the effect.

Cells Live in a Highly Protected Milieu Intérieur

In his lectures on the phenomena of life, Claude Bernard wrote in 1878 on the conditions of the constancy of life, which he considered a property of higher forms of life. According to Bernard, animals have two environments: the milieu extérieur that physically surrounds the whole organism; and the milieu intérieur, in which the tissues and cells of the organism live. This internal environment is neither the air nor the water in which an organism lives but rather—in the case of the human body—the well-controlled liquid environment that Bernard called "the organic liquid that circulates and bathes all the anatomic elements of the tissues, the lymph or the plasma." In short, this internal environment is what we today call the extracellular fluid. He argued that physiological functions continue in a manner indifferent to the changing environment because the milieu intérieur isolates the organs and tissues of the body from the vagaries of the physical conditions of the environment. Indeed, Bernard described the milieu intérieur as if an organism had placed itself in a greenhouse.

According to Bernard's concept of milieu intérieur, some fluids contained within the body are not really inside the body at all. For example, the *contents* of the gastrointestinal tract, sweat ducts, and renal tubules are all outside the body. They are all continuous with the milieu extérieur.

Bernard compares a complex organism to an ensemble of anatomical elements that live together inside the milieu intérieur. Therefore, in Part II of this textbook, we examine the physiology of these cells and molecules. In Chapter 2 ("Functional Organization of the Cell"), we begin our journey through physiology with a discussion of the biology of the cells that are the individual elements of the body. Chapter 3 ("Signal Transduction") discusses how cells communicate directly through gap junctions or indirectly by molecules released into the extracellular fluid. These released molecules can bind to receptors on the cell membrane and initiate signal transduction cascades that can modify gene transcription (a genomic response) and a wide range of other cell functions (nongenomic responses). Alternatively, these released molecules can bind to receptors in the cytoplasm or nucleus and alter the transcription of genes. In Chapter 4 ("Regulation of Gene Expression"), we examine the response of the nucleus. Chapter 5 ("Transport of Solutes and Water") addresses how the plasma membrane separates the cell interior from Bernard's milieu intérieur and establishes the composition of the cell interior. In the process of establishing the composition of the intracellular fluid, the plasma membrane also sets up ion and voltage gradients across itself. Excitable cells—mainly nerve and muscle cells—can exploit these gradients for the long-distance "electrical" transmission of information. The property of "excitability," which requires both the perception of a change (a signal) and the reaction to it, is the topic of Chapters 6 to 9. In Part III, we examine how the nervous system exploits excitability to process information.

Another theme developed by Bernard was that the "fixité du milieu intérieur" (the constancy of the extracellular fluid) is the condition of "free, independent life." He explains that organ differentiation is the exclusive property of higher organisms and that each organ contributes to "compensate and equilibrate" against changes in the external environment. In that sense, each of the systems discussed in Parts IV to VIII permits the body to live within an adverse external environment because the cardiovascular system, the respiratory system, the urinary system, the gastrointestinal system, and the endocrine system create and maintain a constant internal environment. Individual cell types in various organ systems act in concert to support the constancy of the internal milieu, and the internal milieu in

turn provides these cells with a culture medium in which they can thrive.

The discipline of physiology also deals with those characteristics that are the property of a living organism as opposed to a nonliving organism. Four fundamental properties distinguish the living body. First, only living organisms exchange matter and energy with the environment to continue their existence. Several organ systems of the body participate in these exchanges. Second, only living organisms can receive signals from their environment and react accordingly. The principles of sensory perception, processing by the nervous system, and reaction are discussed in the chapters on excitability and the nervous system. Third, what distinguishes a living organism is the life cycle of growth and reproduction, as discussed in the chapters on reproduction (Part IX). Finally, the living organism is able to adapt to changing circumstances. This is a theme that is developed throughout this textbook but especially in the chapters on everyday life (Part X).

Homeostatic Mechanisms—Operating Through Sophisticated Feedback Control Mechanisms—Are Responsible for Maintaining the Constancy of the Milieu Intérieur

Homeostasis is the control of a vital parameter. The body carefully controls a seemingly endless list of vital parameters. Examples of tightly controlled parameters that affect nearly the whole body are arterial pressure and blood volume. At the level of the milieu intérieur, tightly regulated parameters include body core temperature and plasma levels of oxygen, glucose, potassium ions (K^+), calcium ions (Ca^{2+}), and hydrogen ions (H^+). Homeostasis also occurs at the level of the single cell. Thus, cells regulate many of the same parameters that the body as a whole regulates: volume, the concentrations of many small inorganic ions (e.g., Na^+, Ca^{2+}, H^+), and energy levels (e.g., ATP).

One of the most common themes in physiology is the **negative feedback mechanism** responsible for homeostasis. Negative feedback requires at least four elements. First, the system must be able to sense the vital parameter (e.g., glucose) or something related to it. Second, the system must be able to compare the input signal with some internal reference value called a set-point, thereby forming a difference signal. Third, the system must multiply the error signal by some proportionality factor (i.e., the gain) to produce some sort of output signal (e.g., release of insulin). Fourth, the output signal must be able to activate an effector mechanism (e.g., glucose uptake and metabolism) that opposes the source of the input signal and thereby brings the vital parameter closer to the set-point (e.g., decrease of blood glucose levels to normal). Sometimes the body controls a parameter, in part, by cleverly employing positive feedback loops.

A single feedback loop often does not operate in isolation but rather as part of a larger network of controls. Thus, a complex interplay may exist among feedback loops within single cells, within a tissue, within an organ or organ system, or at the level of the whole body. After studying these individual feedback loops in isolation, the physiologist may find that two feedback loops act either synergistically or antagonistically. For example, insulin lowers blood glucose levels, whereas epinephrine and cortisol have the opposite effect. Thus, the physiologist must determine the relative weights of feedback loops in **competition** with one another. Finally, the physiologist must also establish **hierarchy** among various feedback loops. For example, the hypothalamus controls the anterior pituitary, which controls the adrenal cortex, which releases cortisol, which helps control blood glucose levels.

Another theme of homeostasis is **redundancy**. The more vital a parameter is, the more systems that the body mobilizes to regulate it. If one system should fail, others are there to help maintain homeostasis. It is probably for this reason that genetic knockouts sometimes fail to have their expected deleterious effects. The result of many homeostatic systems controlling many vital parameters is a milieu intérieur with a stable composition.

Whether at the level of the milieu intérieur or the cytoplasm of a single cell, homeostasis occurs at a price: energy. When a vital parameter (e.g., the blood glucose level) is well regulated, that parameter is not in equilibrium. **Equilibrium** is a state that does not involve energy consumption. Instead, a well-regulated parameter is generally in a **steady state**. That is, its value is constant because the body or the cell carefully matches actions that lower the parameter value with other actions that raise it. The net effect is that the vital parameter is held at a constant value.

An important principle in physiology, to which we have already alluded, is that each cell plays a specialized role in the overall function of the body. In return, the body—which is the sum of all these cells—provides the milieu intérieur appropriate for the life of each cell. As part of the bargain, each cell or organ must respect the needs of the body as a whole and not run amok for its own greedy interests. For example, during exercise, the system that controls body core temperature sheds heat by elaborating sweat for evaporation. However, the production of sweat ultimately reduces blood volume. Because the body as a whole places a higher **priority** on the control of blood volume than on the control of body core temperature, at some point the system that controls blood volume will instruct the system that controls body core temperature to reduce the production of sweat. Unfortunately, this juggling of priorities works only if the individual stops exercising; if not, the result may be heat stroke.

The **adaptability** of an organism depends on its ability to alter its response. Indeed, flexible feedback loops are at the root of many forms of physiological adaptation. For instance, at sea level, experimentally lowering the level of oxygen (the sensory stimulus) in the inspired air causes an increase in breathing (the response). However, after **acclimatization** at high altitude to low oxygen levels, the same low level of oxygen (the same sensory stimulus) causes one to breathe much faster (a greater response). Thus, the response may depend on the previous history and therefore the "state" of the system. In addition to acclimatization, genetic factors can also contribute to the ability to respond to an environmental stress. For example, certain populations of humans who have lived for generations at high altitude withstand hypoxia better than lowlanders do, even after the lowlanders have fully acclimatized.