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GUYTON AND HALL TEXTBOOK OF MEDICAL PHYSIOLOGY

THIRTEENTH EDITION

JOHN E. HALL

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13TH EDITION

Guyton and Hall Textbook of Medical Physiology

John E. Hall, PhD
Arthur C. Guyton Professor and Chair
Department of Physiology and Biophysics
Director, Mississippi Center for Obesity Research
University of Mississippi Medical Center
Jackson, Mississippi

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1600 John F. Kennedy Blvd.
Ste 1800
Philadelphia, PA 19103-2899

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To

My Family

For their abundant support, for their patience and understanding, and for their love

To

Arthur C. Guyton

For his imaginative and innovative research
For his dedication to education
For showing us the excitement and joy of physiology
And for serving as an inspirational role model

Preface

The first edition of the *Textbook of Medical Physiology* was written by Arthur C. Guyton almost 60 years ago. Unlike most major medical textbooks, which often have 20 or more authors, the first eight editions of the *Textbook of Medical Physiology* were written entirely by Dr. Guyton, with each new edition arriving on schedule for nearly 40 years. Dr. Guyton had a gift for communicating complex ideas in a clear and interesting manner that made studying physiology fun. He wrote the book to help students learn physiology, not to impress his professional colleagues.

I worked closely with Dr. Guyton for almost 30 years and had the privilege of writing parts of the ninth and tenth editions. After Dr. Guyton's tragic death in an automobile accident in 2003, I assumed responsibility for completing the subsequent editions.

For the thirteenth edition of the *Textbook of Medical Physiology*, I have the same goal as for previous editions—to explain, in language easily understood by students, how the different cells, tissues, and organs of the human body work together to maintain life.

This task has been challenging and fun because our rapidly increasing knowledge of physiology continues to unravel new mysteries of body functions. Advances in molecular and cellular physiology have made it possible to explain many physiology principles in the terminology of molecular and physical sciences rather than in merely a series of separate and unexplained biological phenomena.

The *Textbook of Medical Physiology*, however, is not a reference book that attempts to provide a compendium of the most recent advances in physiology. This is a book that continues the tradition of being written for students. It focuses on the basic principles of physiology needed to begin a career in the health care professions, such as medicine, dentistry, and nursing, as well as graduate studies in the biological and health sciences. It should also be useful to physicians and health care professionals who wish to review the basic principles needed for understanding the pathophysiology of human disease.

I have attempted to maintain the same unified organization of the text that has been useful to students in the past and to ensure that the book is comprehensive enough that students will continue to use it during their professional careers.

My hope is that this textbook conveys the majesty of the human body and its many functions and that it stimulates students to study physiology throughout their careers. Physiology is the link between the basic sciences and medicine. The great beauty of physiology is that it integrates the individual functions of all the body's different cells, tissues, and organs into a functional whole, the human body. Indeed, the human body is much more than the sum of its parts, and life relies upon this total function, not just on the function of individual body parts in isolation from the others.

This brings us to an important question: How are the separate organs and systems coordinated to maintain proper function of the entire body? Fortunately, our bodies are endowed with a vast network of feedback controls that achieve the necessary balances without which we would be unable to live. Physiologists call this high level of internal bodily control *homeostasis*. In disease states, functional balances are often seriously disturbed and homeostasis is impaired. When even a single disturbance reaches a limit, the whole body can no longer live. One of the goals of this text, therefore, is to emphasize the effectiveness and beauty of the body's homeostasis mechanisms as well as to present their abnormal functions in disease.

Another objective is to be as accurate as possible. Suggestions and critiques from many students, physiologists, and clinicians throughout the world have checked factual accuracy as well as balance in the text. Even so, because of the likelihood of error in sorting through many thousands of bits of information, I wish to issue a further request to all readers to send along notations of error or inaccuracy. Physiologists understand the importance of feedback for proper function of the human body; so, too, is feedback important for progressive improvement of a textbook of physiology. To the many persons who have already helped, I express sincere thanks. Your feedback has helped to improve the text.

A brief explanation is needed about several features of the thirteenth edition. Although many of the chapters have been revised to include new principles of physiology and new figures to illustrate these principles, the text length has been closely monitored to limit the book size so that it can be used effectively in physiology courses for medical students and health care professionals. Many of the figures have also been redrawn and are in full color. New references have been chosen primarily for their presentation of physiological principles, for the quality of their own references, and for their easy accessibility. The selected bibliography at the end of the chapters lists papers mainly from recently published scientific journals that can be freely accessed from the PubMed site at http://www.ncbi.nlm.nih.gov/pubmed/. Use of these references, as well as cross-references from them, can give the student almost complete coverage of the entire field of physiology.

The effort to be as concise as possible has, unfortunately, necessitated a more simplified and dogmatic presentation of many physiological principles than I normally would have desired. However, the bibliography can be used to learn more about the controversies and unanswered questions that remain in understanding the complex functions of the human body in health and disease.

Another feature is that the print is set in two sizes. The material in large print constitutes the fundamental physiological information that students will require in virtually all of their medical activities and studies. The material in small print and highlighted with a pale blue background is of several different kinds: (1) anatomic, chemical, and other information that is needed for immediate discussion but that most students will learn in more detail in other courses; (2) physiological information of special importance to certain fields of clinical medicine; and (3) information that will be of value to those students who may wish to study particular physiological mechanisms more deeply.

I wish to express sincere thanks to many persons who have helped to prepare this book, including my colleagues in the Department of Physiology and Biophysics at the University of Mississippi Medical Center who provided valuable suggestions. The members of our faculty and a brief description of the research and educational activities of the department can be found at http://physiology.umc.edu/. I am also grateful to Stephanie Lucas for excellent secretarial services and to James Perkins for excellent illustrations. Michael Schenk and Walter (Kyle) Cunningham also contributed to many of the illustrations. I also thank Elyse O'Grady, Rebecca Gruliow, Carrie Stetz, and the entire Elsevier team for continued editorial and production excellence.

Finally, I owe an enormous debt to Arthur Guyton for the great privilege of contributing to the *Textbook of Medical Physiology* for the past 25 years, for an exciting career in physiology, for his friendship, and for the inspiration that he provided to all who knew him.

John E. Hall

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By John E. Hall, PhD, Arthur C. Guyton Professor and Chair, Department of Physiology and Biophysics, Director, Mississippi Center for Obesity Research, University of Mississippi Medical Center, Jackson, Mississippi

UNIT I - Introduction to Physiology: The Cell and General Physiology

UNIT II - Membrane Physiology, Nerve, and Muscle

UNIT III - The Heart

UNIT IV - The Circulation

UNIT V - The Body Fluids and Kidneys

UNIT XIII - Metabolism and Temperature Regulation

68. Metabolism of Carbohydrates and Formation of Adenosine Triphosphate
69. Lipid Metabolism
70. Protein Metabolism
71. The Liver as an Organ
72. Dietary Balances; Regulation of Feeding; Obesity and Starvation; Vitamins and Minerals
73. Energetics and Metabolic Rate
74. Body Temperature Regulation and Fever

UNIT XIV - Endocrinology and Reproduction

75. Introduction to Endocrinology
76. Pituitary Hormones and Their Control by the Hypopthalamus
77. Thyroid Metabolic Hormones
78. Adenocortical Hormones
79. Insulin, Glucagon, and Diabetes Mellitus
80. Parathyroid Hormone, Calcitonin, Calcium and Phosphate Metabolism, Vitamin D, Bone, and Teeth
81. Reproductive and Hormonal Functions of the Male (and Function of the Pineal Gland)
82. Female Physiology Before Pregnancy and Female Hormones
83. Pregnancy and Lactation
84. Fetal and Neonatal Physiology

UNIT XV - Sports Physiology

85. Sports Physiology

CHAPTER 1

Functional Organization of the Human Body and Control of the "Internal Environment"

Physiology is the science that seeks to explain the physical and chemical mechanisms that are responsible for the origin, development, and progression of life. Each type of life, from the simplest virus to the largest tree or the complicated human being, has its own functional characteristics. Therefore, the vast field of physiology can be divided into viral physiology, bacterial physiology, cellular physiology, plant physiology, invertebrate physiology, vertebrate physiology, mammalian physiology, human physiology, and many more subdivisions.

Human Physiology. The science of *human physiology* attempts to explain the specific characteristics and mechanisms of the human body that make it a living being. The fact that we remain alive is the result of complex control systems. Hunger makes us seek food, and fear makes us seek refuge. Sensations of cold make us look for warmth. Other forces cause us to seek fellowship and to reproduce. The fact that we are sensing, feeling, and knowledgeable beings is part of this automatic sequence of life; these special attributes allow us to exist under widely varying conditions, which otherwise would make life impossible.

CELLS ARE THE LIVING UNITS OF THE BODY

The basic living unit of the body is the cell. Each organ is an aggregate of many different cells held together by intercellular supporting structures.

Each type of cell is specially adapted to perform one or a few particular functions. For instance, the red blood cells, numbering about 25 trillion in each human being, transport oxygen from the lungs to the tissues. Although the red blood cells are the most abundant of any single type of cell in the body, about 75 trillion additional cells of other types perform functions different from those of the red blood cell. The entire body, then, contains about 100 trillion cells.

Although the many cells of the body often differ markedly from one another, all of them have certain basic characteristics that are alike. For instance, oxygen reacts with carbohydrate, fat, and protein to release the energy required for all cells to function. Further, the general chemical mechanisms for changing nutrients into energy are basically the same in all cells, and all cells deliver products of their chemical reactions into the surrounding fluids.

Almost all cells also have the ability to reproduce additional cells of their own kind. Fortunately, when cells of a particular type are destroyed, the remaining cells of this type usually generate new cells until the supply is replenished.

EXTRACELLULAR FLUID—THE "INTERNAL ENVIRONMENT"

About 60 percent of the adult human body is fluid, mainly a water solution of ions and other substances. Although most of this fluid is inside the cells and is called *intracellular fluid,* about one third is in the spaces outside the cells and is called *extracellular fluid.* This extracellular fluid is in constant motion throughout the body. It is transported rapidly in the circulating blood and then mixed between the blood and the tissue fluids by diffusion through the capillary walls.

In the extracellular fluid are the ions and nutrients needed by the cells to maintain life. Thus, all cells live in essentially the same environment—the extracellular fluid. For this reason, the extracellular fluid is also called the *internal environment* of the body, or the *milieu intérieur,* a term introduced more than 150 years ago by the great 19th-century French physiologist Claude Bernard (1813–1878).

Cells are capable of living and performing their special functions as long as the proper concentrations of oxygen, glucose, different ions, amino acids, fatty substances, and other constituents are available in this internal environment.

Differences Between Extracellular and Intracellular Fluids. The extracellular fluid contains large amounts of *sodium, chloride,* and *bicarbonate ions* plus nutrients for the cells, such as *oxygen, glucose, fatty acids,* and *amino acids.* It also contains *carbon dioxide* that is being transported from the cells to the lungs to be excreted, plus other cellular waste products that are being transported to the kidneys for excretion.

The intracellular fluid differs significantly from the extracellular fluid; for example, it contains large amounts of *potassium, magnesium,* and *phosphate ions* instead of the sodium and chloride ions found in the extracellular fluid. Special mechanisms for transporting ions through the cell membranes maintain the ion concentration differences between the extracellular and intracellular fluids. These transport processes are discussed in Chapter 4.

HOMEOSTASIS—MAINTENANCE OF A NEARLY CONSTANT INTERNAL ENVIRONMENT

In 1929 the American physiologist Walter Cannon (1871–1945) coined the term *homeostasis* to describe the *maintenance of nearly constant conditions in the internal environment*. Essentially all organs and tissues of the body perform functions that help maintain these relatively constant conditions. For instance, the lungs provide oxygen to the extracellular fluid to replenish the oxygen used by the cells, the kidneys maintain constant ion concentrations, and the gastrointestinal system provides nutrients.

The various ions, nutrients, waste products, and other constituents of the body are normally regulated within a range of values, rather than at fixed values. For some of the body's constituents, this range is extremely small. Variations in blood hydrogen ion concentration, for example, are normally less than 5 *nanomoles* per liter (0.000000005 moles per liter). Blood sodium concentration is also tightly regulated, normally varying only a few *millimoles* per liter even with large changes in sodium intake, but these variations of sodium concentration are at least 1 million times greater than for hydrogen ions.

Powerful control systems exist for maintaining the concentrations of sodium and hydrogen ions, as well as for most of the other ions, nutrients, and substances in the body at levels that permit the cells, tissues, and organs to perform their normal functions despite wide environmental variations and challenges from injury and diseases.

A large segment of this text is concerned with how each organ or tissue contributes to homeostasis. Normal body functions require the integrated actions of cells, tissues, organs, and the multiple nervous, hormonal, and local control systems that together contribute to homeostasis and good health.

Disease is often considered to be a state of disrupted homeostasis. However, even in the presence of disease, homeostatic mechanisms continue to operate and maintain vital functions through multiple compensations. In some cases, these compensations may themselves lead to major deviations of the body's functions from the normal range, making it difficult to distinguish the primary cause of the disease from the compensatory responses. For example, diseases that impair the kidneys' ability to excrete salt and water may lead to high blood pressure, which initially helps return excretion to normal so that a balance between intake and renal excretion can be maintained. This balance is needed to maintain life, but over long periods of time the high blood pressure can damage various organs, including the kidneys, causing even greater increases in blood pressure and more renal damage. Thus, homeostatic compensations that ensue after injury, disease, or major environmental challenges to the body may represent a "trade-off" that is necessary to maintain vital body functions but may, in the long term, contribute to additional abnormalities of body function. The discipline of *pathophysiology* seeks to explain how the various physiological processes are altered in diseases or injury.

This chapter outlines the different functional systems of the body and their contributions to homeostasis; we then briefly discuss the basic theory of the body's control systems that allow the functional systems to operate in support of one another.

EXTRACELLULAR FLUID TRANSPORT AND MIXING SYSTEM—THE BLOOD CIRCULATORY SYSTEM

Extracellular fluid is transported through the body in two stages. The first stage is movement of blood through the body in the blood vessels, and the second is movement of fluid between the blood capillaries and the *intercellular spaces* between the tissue cells.

Figure 1-1 shows the overall circulation of blood. All the blood in the circulation traverses the entire circulatory circuit an average of once each minute when the body is at rest and as many as six times each minute when a person is extremely active.

As blood passes through the blood capillaries, continual exchange of extracellular fluid also occurs between the plasma portion of the blood and the interstitial fluid that fills the intercellular spaces. This process is shown in **Figure 1-2**. The walls of the capillaries are permeable to most molecules in the plasma of the blood, with the exception of plasma proteins, which are too large to readily pass through the capillaries. Therefore, large amounts of fluid and its dissolved constituents *diffuse* back and forth between the blood and the tissue spaces, as shown by the arrows. This process of diffusion is caused by kinetic motion of the molecules in both the plasma and the interstitial fluid. That is, the fluid and dissolved molecules are continually moving and bouncing in all directions within the plasma and the fluid in the intercellular spaces, as well as through the capillary pores. Few cells are located more than 50 micrometers from a capillary, which ensures diffusion of almost any substance from the capillary to the cell within a few seconds. Thus, the extracellular fluid everywhere in the body—both that of the

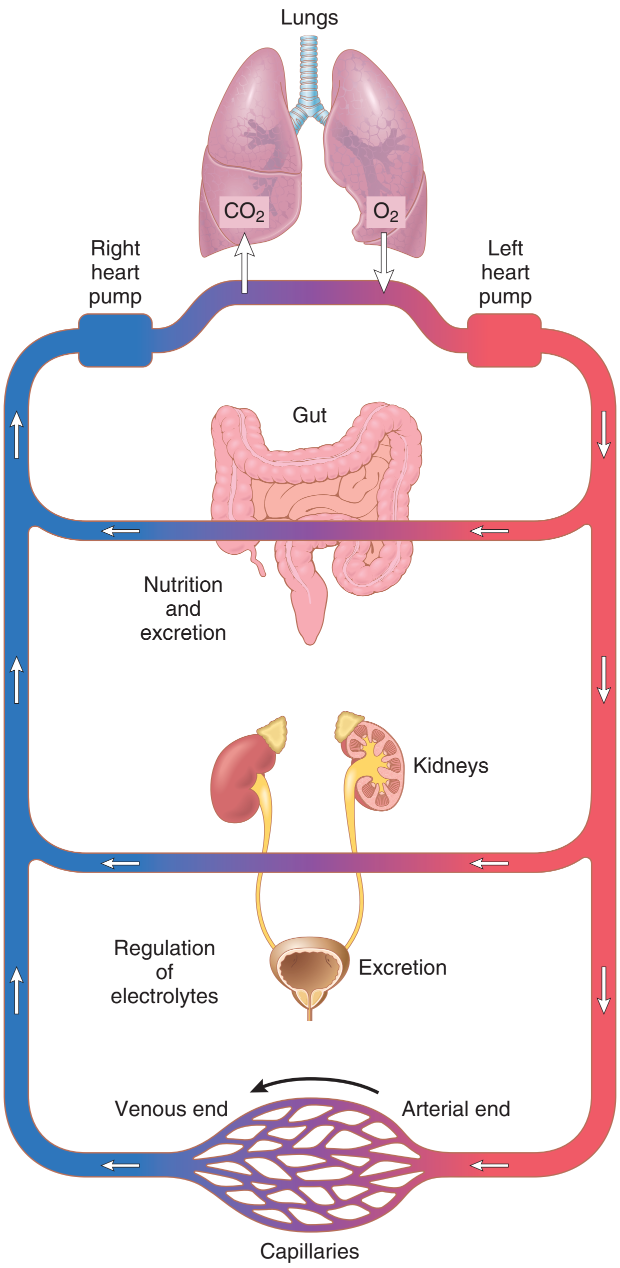

Figure 1-1. General organization of the circulatory system.

plasma and that of the interstitial fluid—is continually being mixed, thereby maintaining homogeneity of the extracellular fluid throughout the body.

ORIGIN OF NUTRIENTS IN THE EXTRACELLULAR FLUID

Respiratory System. Figure 1-1 shows that each time the blood passes through the body, it also flows through the lungs. The blood picks up *oxygen* in the alveoli, thus acquiring the oxygen needed by the cells. The membrane between the alveoli and the lumen of the pulmonary capillaries, the *alveolar membrane,* is only 0.4 to 2.0 micrometers thick, and oxygen rapidly diffuses by molecular motion through this membrane into the blood.

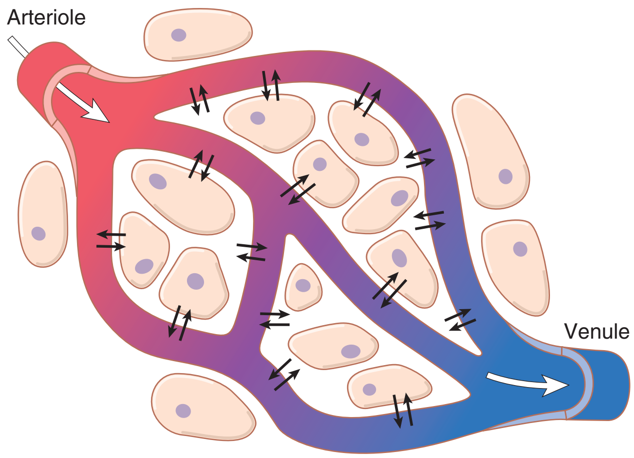

Figure 1-2. Diffusion of fluid and dissolved constituents through the capillary walls and through the interstitial spaces.

Gastrointestinal Tract. A large portion of the blood pumped by the heart also passes through the walls of the gastrointestinal tract. Here different dissolved nutrients, including *carbohydrates, fatty acids,* and *amino acids,* are absorbed from the ingested food into the extracellular fluid of the blood.

Liver and Other Organs That Perform Primarily Metabolic Functions. Not all substances absorbed from the gastrointestinal tract can be used in their absorbed form by the cells. The liver changes the chemical compositions of many of these substances to more usable forms, and other tissues of the body—fat cells, gastrointestinal mucosa, kidneys, and endocrine glands—help modify the absorbed substances or store them until they are needed. The liver also eliminates certain waste products produced in the body and toxic substances that are ingested.

Musculoskeletal System. How does the musculoskeletal system contribute to homeostasis? The answer is obvious and simple: Were it not for the muscles, the body could not move to obtain the foods required for nutrition. The musculoskeletal system also provides motility for protection against adverse surroundings, without which the entire body, along with its homeostatic mechanisms, could be destroyed.

REMOVAL OF METABOLIC END PRODUCTS

Removal of Carbon Dioxide by the Lungs. At the same time that blood picks up oxygen in the lungs, *carbon dioxide* is released from the blood into the lung alveoli; the respiratory movement of air into and out of the lungs carries the carbon dioxide to the atmosphere. Carbon dioxide is the most abundant of all the metabolism products.

Kidneys. Passage of the blood through the kidneys removes from the plasma most of the other substances