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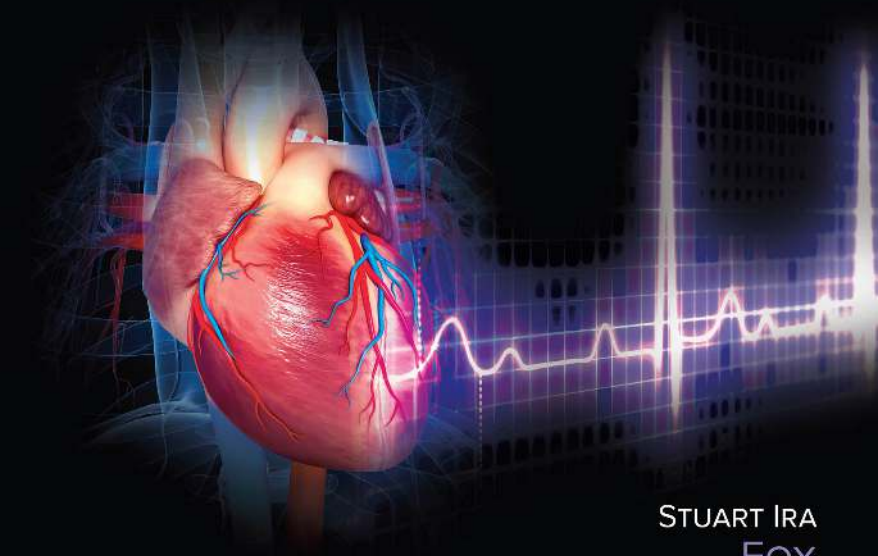
Human PHYSIOLOGY

Sixteenth Edition



STUART IRA FOX

KRISTA ROMPOLSKI

Mc Graw Hill

Human Physiology

SIXTEENTH EDITION

STUART IRA FOX
Pierce College

Krista Rompolski
Moravian College

Mc Graw Hill

ISTUDY

HUMAN PHYSIOLOGY

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Brief Contents

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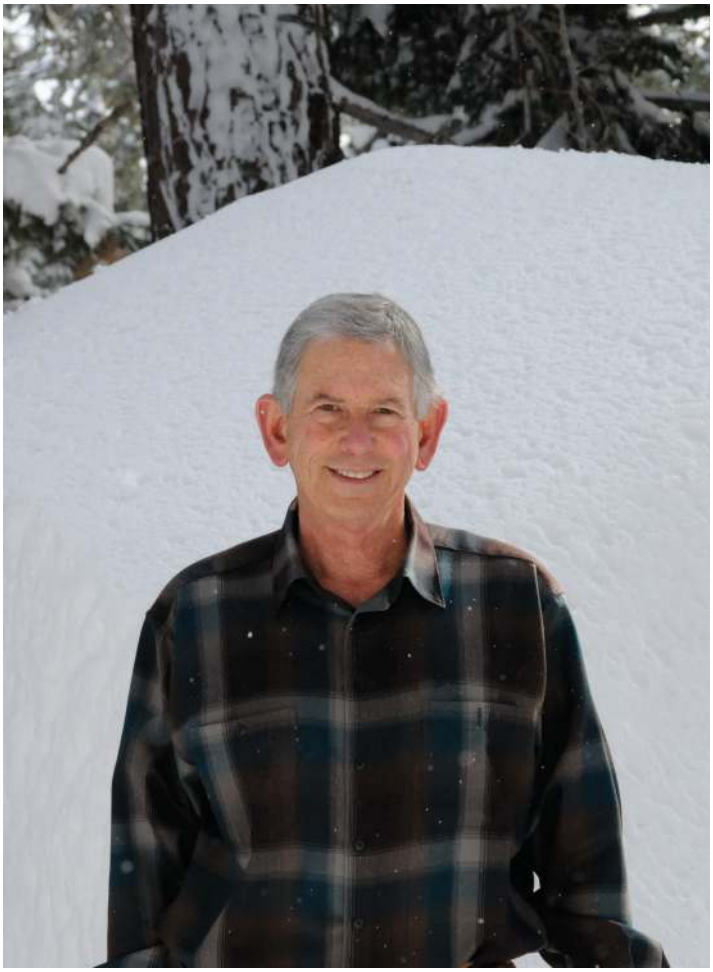
About the Authors

Stuart Ira Fox earned a Ph.D. in human physiology from the Department of Physiology, School of Medicine, at the University of Southern California, after earning degrees at the University of California at Los Angeles (UCLA); California State University, Los Angeles; and UC Santa Barbara. He has spent most of his professional life teaching at Los Angeles City College; California State University, Northridge; and Pierce College, where he has won numerous teaching awards, including several Golden Apples. Stuart has authored forty-two editions of seven textbooks, which are used worldwide and have been translated into several languages, and two novels. When not engaged in professional activities, he likes to hike, fly fish, and cross-country ski in the Eastern Sierra Nevada Mountains.

To my wife, Ellen; and to Laura, Jacob, and Kayleigh. For all the important reasons.



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Krista Lee Rompolski earned her Ph.D. in exercise physiology from the University of Pittsburgh, Department of Health and Physical Activity, after earning her bachelor's and master's degrees from Bloomsburg University, near her birthplace of Mount Carmel, PA. Krista is currently an associate professor of Physical Therapy at Moravian College in Bethlehem, PA, where she teaches Gross Anatomy and Pathophysiology to the Physical Therapy students, as well as Anatomy and Physiology to undergraduate Health Sciences students. Prior to joining Moravian College, Krista taught Anatomy, Physiology, Pathophysiology, and clinical research courses at Drexel University for seven years.

To the bravest person I know, my husband, Dan, for always reminding me of what matters most.

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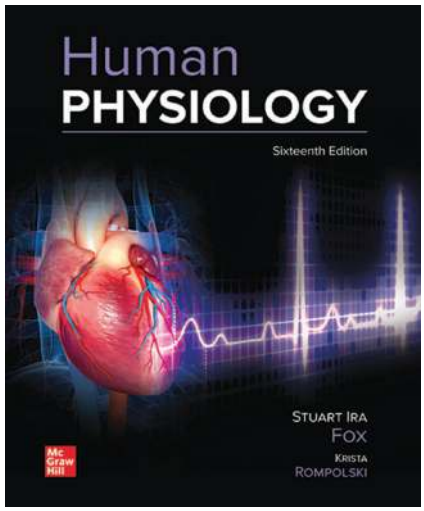
Preface

The Story of the Sixteenth Edition



Stuart Fox, Ph.D., wrote the first edition (published 1983) to help students understand the concepts of human physiology, and this objective has remained the guiding principle through all of the subsequent editions. All editions have been lauded for their readability, the currency of the information, and the clarity of the presentation. The sixteenth edition continues this tradition by presenting human physiology in the most current, readable, and student-oriented way possible.

This sixteenth edition marks a major addition to *Human Physiology*: Krista Rompolski, Ph.D. (Moravian College) has contributed significantly to the revision of chapters 8 and 18. As a very active physiology educator, Krista brings a new perspective and her own expertise to make this edition an even more exciting revision. This was achieved while maintaining the book's tradition of remaining readable, accessible, and useful to students.

To create this landmark sixteenth edition, Stuart had the support of Krista Rompolski as coauthor and a superb team at McGraw-Hill. This team includes Matthew Garcia, Melisa Seegmiller, Sherry Kane, Brent Dela Cruz, Joan Weber, Angela FitzPatrick, Valerie Kramer, Jim Connely, Kristine Rellihan, Beth Blech, and Lori Hancock. We are all incredibly grateful to the many reviewers who provided their time and expertise to critically examine individual chapters and be Board of Adviser partners. These reviewers and advisers are listed on the pages that follow.

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Guided Tour

WHAT MAKES THIS TEXT A MARKET LEADER?

Clinical Applications—No Other Human Physiology Text Has More!

The framework of this textbook is based on integrating clinically germane information with knowledge of the body's physiological processes. Examples of this abound throughout the book.

CLINICAL INVESTIGATION

Sheryl, an active 78-year-old, suddenly became greatly fatigued and disoriented while skiing. When she was brought to the hospital, blood tests revealed elevated levels of LDH, AST, ALT, and the MB isoform of CK.

Some of the new terms and concepts you will encounter include:

- Enzymes, isoenzymes, coenzymes, and cofactors
- LDH, AST, ALT, and CK

Clinical Application Boxes are in-depth boxed essays that explore relevant topics of clinical interest and are placed at key points in the chapter to support the surrounding material. Subjects covered include pathologies, current research, pharmacology, and a variety of clinical diseases.

LIFESTYLE APPLICATION

Metabolic syndrome is a combination of abnormal measurements—including central obesity (excess abdominal fat), hypertension (high blood pressure), insulin resistance (prediabetes), type 2 diabetes mellitus, high plasma triglycerides, and high LDL cholesterol—that greatly increase the risk of coronary heart disease, stroke, diabetes mellitus, and other conditions. The incidence of metabolic syndrome has increased alarmingly in recent years because of the increase in obesity. Eating excessive calories, particularly in the form of sugars (including high fructose corn syrup), stimulates insulin secretion. Insulin then promotes the uptake of blood glucose into adipose cells, where (through lipogenesis) it is converted into stored triglycerides (see figs. 5.12 and 5.13). Conversely, the lowering of insulin secretion, by diets that prevent the plasma glucose from rising sharply, promotes lipolysis (the breakdown of fat) and weight loss.

Learning Outcomes are numbered for easy referencing in digital material!

LEARNING OUTCOMES

After studying this section, you should be able to:

2. Describe the aerobic cell respiration of glucose through the citric acid cycle.

3. Describe the electron transport system and oxidative phosphorylation, explaining the role of oxygen in this process.

CLINICAL INVESTIGATIONS IN ALL CHAPTERS!

Chapter-Opening Clinical Investigations, Clues, and Summaries are diagnostic case studies found in each chapter. Clues are given throughout and the case is finally resolved at the end of the chapter.

CLINICAL APPLICATION

When diseases damage tissues, some cells die and release their enzymes into the blood. The activity of these enzymes, reflecting their concentrations in the blood plasma, can be measured in a test tube by adding their specific substrates. Because an increase in certain enzymes in the blood can indicate damage to specific organs, such tests may aid the diagnosis of diseases. For example, an increase in a man's blood levels of acid phosphatase may result from disease of the prostate (table 4.1).

Lifestyle Application Boxes are readings that explore physiological principles as applied to well-being, sports medicine, exercise physiology, and aging. They are also placed at relevant points in the text to highlight concepts just covered in the chapter.

Systems Interactions pages at the end of chapters have been a tradition of this textbook since the earliest editions. Now, with this sixteenth edition, a new Systems Interactions icon has been added for the first time to relevant major sections of the in-chapter text. These alert readers to those sections that specifically discuss how the chapter's body system interacts with other systems in the service of total body function. The new Systems Interactions icon also signals essay questions in the end-chapter Review Activities that ask students about specific interactions of the discussed body systems.

Learning Outcome numbers are tied directly to **Checkpoint numbers!**

CHECKPOINTS

2a. Compare the fate of pyruvate in aerobic and anaerobic cell respiration.

2b. Draw a simplified citric acid cycle and indicate the high-energy products.

3a. Explain how NADH and $FADH_2$ contribute to oxidative phosphorylation.

3b. Explain how ATP is produced in oxidative phosphorylation.

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New to This Edition

CHAPTER CHANGES IN THE SIXTEENTH EDITION OF HUMAN PHYSIOLOGY

The following list includes relatively major changes in each chapter and does not include changes involving a sentence or two, word or phrase changes, or label changes in figures.

All Chapters

- Boxes on Exercise Applications changed to Lifestyle Applications throughout.
- Chapters 8 and 18 modified extensively by Krista Rompolski, Ph.D.
- Section subheadings that specifically deal with interactions between different body systems are called out and identified with a distinctive Systems Interactions icon.
- Review Activities questions that relate to the Systems Interactions are identified with the Systems Interactions icons.

Chapter 1

- Modifications in section on Scientific Method.
- New citation in Table 1.1 for the 2019 Nobel Prize in Physiology or Medicine.
- Modifications in section on The Primary Tissues.
- Modifications in the section on the skin.

Chapter 2

- Additional information added to the section on buffers.

Chapter 3

- New description of glycocalyx added.
- Explanation of lysosomes and autophagy rewritten and updated.
- Information on mitochondria updated and expanded.
- Expanded and updated information in the section describing the genome, genes, and genetic expression.
- Description of CRISPR-Cas9 updated.
- Section on epigenetic inheritance expanded and updated.

Chapter 4

- Updated and expanded information on gene therapy and genome editing.
- New information added to on specific autosomal recessive diseases added to the Clinical Applications box on phenylketonuria.
- Chemical structure of NADH in figure 4.17 modified.

Chapter 5

- Information about the uses of the lactic acid pathway expanded and updated.
- Information about the respiratory complexes expanded.
- Respiratory complexes identified in figure 5.9.
- Added information on essential amino acids.

Chapter 6

- Expanded explanation of carrier proteins and channel proteins, with different listing order.
- Addition of a description of the importance of Na+ in body fluid osmolality.
- Legend for figure 6.16 rewritten.
- New discussion of sodium-coupled glucose transporters (SGLT 1 and 2).
- Added description of autocrine signaling.

Chapter 7

- Updated and expanded description of microglia.
- Updated discussion of oligodendrocytes.
- Updated discussion of central nervous system (CNS) axon regeneration.
- Expanded and updated discussion of astrocytes.
- Expanded and updated discussion of CNS capillaries with addition of pericytes.
- Updated and expanded discussion of the endogenous opioids.

Chapter 8

- Clinical Investigation updated throughout the chapter.
- Description of cerebrospinal fluid formation updated.
- Figure 8.5 updated for most up-to-date terminology.
- Updated description of autism spectrum disorder.
- New research on the clinical applications of PET scans and fMRI.
- Addition of glymphatic system and its association with sleep and neurodegenerative disease.
- Updated Clinical Application box on Huntington's disease and Parkinson's disease.
- Added information on the subthalamic nucleus.
- Updated and expanded description on Wernicke's aphasia and conduction aphasia.
- Arcuate fasciculus added as a label on figure 8.14.
- New discussion on the amygdaloid body and the famous patient "S.M."
- New evidence on metabolic activity of neurons as well as activity in the hippocampus during memory consolidation.
- Updated and additional research on the genetics, pathogenesis, and prevention of Alzheimer's disease.
- Expanded discussion on the role of limbic system structures in learning and memory formation.
- Addition of the 2017 Nobel Prize in Physiology or Medicine, which led to the discovery of circadian clock genes in humans.
- Updated discussion in a Lifestyle Application box on benzodiazepine prescription, use, and abuse.
- Table 8.6 updated for accuracy on cranial nerve composition and function.

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New to This Edition

- New figure of the cranial nerves added to Section 8.6.
- Additional information provided on the structure and function of the anterior corticospinal tracts.

Chapter 9

- Figure 9.11 updated and modified for increased accuracy.
- Legend for figure 9.11 updated and expanded.

Chapter 10

- Updated and expanded description of neural pathways for somesthetic sensation.
- New Clinical Application box on the gate control theory of pain.
- Descriptions of the "labeled line" concept of taste transmission updated and expanded.
- Updated and expanded discussion of the physiology of sour taste.
- Descriptions of the structure and functions of the cupula in the semicircular canals updated and expanded.
- Addition of motion sickness explanation.
- Description of sensorineural deafness updated and expanded.
- Figure 10.37 modified to show the direction of light.
- Description of intrinsically photosensitive retinal ganglion cells added.

Chapter 11

- Updated discussion of the role of heat shock proteins in steroid hormone action.
- Updated discussion in a Clinical Applications box of the Her2 receptor and the action of Herceptin in the treatment of breast cancer.
- Figure 11.11 labels modified, and legend expanded and updated.
- Description of the osmoreceptor neurons and control of ADH secretion updated and expanded.
- Heading Hypothalamic Control of the Anterior Pituitary given a Systems Interactions icon.
- Heading Functions of the Adrenal Cortex given a Systems Interactions icon.
- Stages of the General Adaptation Syndrome description expanded and updated.
- Heading Pancreatic Islets given a Systems Interactions icon.
- Three new questions regarding Systems Interactions added to the Test Your Understanding section of the Review Activities.

Chapter 12

- Clinical Application box on muscular dystrophy updated.
- Updated and expanded discussion of titin in muscle contraction.
- Updated and expanded discussion of muscle fatigue.
- New discussion of the myokine irisin added.
- New Lifestyle Application box added regarding the healthful consequences of a change from a sedentary to a more active lifestyle.
- Updated discussion of muscle satellite cells.
- Updated information on muscle spindle.
- Heading Skeletal Muscle Reflexes given a Systems Interactions icon.
- Single-Unit and Multi-Unit Smooth Muscle heading given a Systems Interactions icon.
- Autonomic Innervation of Smooth Muscles heading given a Systems Interactions icon.
- New Systems Interactions question added to the Review Activities.

Chapter 13

- Updated information on aplastic anemia in the Clinical Applications box on anemias.
- Updated information on the origin of platelets.
- Updated information on thrombopoietin.
- Updated information on hemophilia A and B.
- Figure 13.23 labels and legend modified to emphasize mechanical correlates of electrical activity.
- Cardioprotective effects of exercise added to a Lifestyle Application box.
- Updated information on potential repairs of myocardial infarction.
- Updated information on ECG changes in myocardial infarction.
- New information added on paroxysmal supraventricular tachycardia.
- New information on pericytes added.

Chapter 14

- Expanded and updated discussion of the control of cardiac rate.
- Heading Regulation of Blood Volume by the Kidneys given a Systems Interactions icon.
- Heading Extrinsic Regulation of Blood Flow given a Systems Interactions icon.
- Updated discussion of changes in coronary blood flow with exercise.
- Updated and expanded explanation of how aerobic exercise improves cardiovascular health.
- Heading Baroreceptor Reflex given a Systems Interactions icon.
- Updated discussion of hypertension.
- Table 14.8 updated to display latest classification system for hypertension.
- Updated discussion of septic shock.
- Three new Systems Interactions questions added to the Review Activities.

Chapter 15

- Updated information on danger-associated molecular patterns (DAMPs).
- Updated information on macrophages.
- Expanded and updated explanation of the causes and functions of a fever.
- Expanded and updated description of the sources and functions of gamma interferon.
- Updated and expanded description of neutrophil actions in an infection.
- Expanded and updated information on regulatory T lymphocytes.
- Updated information on sepsis in a Clinical Applications box.

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- Updated and expanded explanation of the nature of B cell clones in the development of secondary immune responses.
- Updated information on immunological competence and immunological tolerance.
- Updated and expanded information on chimeric antigen receptors and immune checkpoint blockade in the treatment of cancer.
- Updated information on the viral causes of cancer.
- New information on anaphylaxis.

Chapter 16

- Updated and expanded description of control of the vocal cords.
- New information about lower respiratory tract infections added.
- Updated and expanded information about how allergens stimulate asthma.
- Description of the role of the pons in the control of breathing updated.
- Updated description of the role of the central chemoreceptors in the control of breathing.
- New description of the hypoxic ventilatory response.
- Updated and expanded description of obstructive sleep apnea.
- New discussion of cardiovascular changes during breath-holding and hyperventilation.
- New information added about treatments for sickle cell anemia and thalassemia.
- Heading Principles of Acid–Base Balance gets Systems Interactions icon.
- Expanded and updated description of the role of the kidneys in assisting the lungs in the control of acid–base balance.
- Updated and expanded discussion of the mechanisms of acclimatization to high altitude.
- New Systems Interactions question added to the Review Activities.

Chapter 17

- Updated and expanded explanation of autoregulation of renal blood flow and tubuloglomerular feedback.
- Expanded and updated description of the secretion of ADH.
- Figure 17.21 modified to show reabsorption from and secretion into blood vessels.
- Heading Role of Aldosterone in Na^+/K^+ Balance given a Systems Interactions icon.
- Figure 17.25 modified to show reabsorption from and secretion into blood vessels.
- Heading Renal Acid–Base Regulation given a Systems Interaction icon.
- Figure 17.29 modified to show Na^+ being cotransported with bicarbonate out of the proximal tubule.
- Added explanation of sodium-bicarbonate cotransport from proximal tubule.
- Updated and expanded explanation of the renal generation of bicarbonate and ammonia.
- Updated description of acute mountain sickness.
- Two new Systems Interactions questions added to the Review Activities.

Chapter 18

- Clinical Investigation updated throughout the chapter.
- Updated descriptions of the mucosal and serosal layers of the alimentary tract.
- New detail included on the nerve composition of the vagus nerve.
- Clinical Application box on Barrett's esophagus updated to include the role of esophageal stem cells in the development of esophageal cancer.
- Clinical Application box on gastroesophageal reflux disease (GERD) updated to include additional risk factors.
- Discussion on celiac disease added to the updated Clinical Application box on lactose intolerance.
- New and expanded description of the function of the interconnected cells of Cajal in the stomach and intestines.
- Additional information on the structure of the large intestine.
- Label for taenia coli added to figure 18.16.
- Section on Intestinal Microbiota revitalized with new headings and up-to-date research on its development, role in immune function, metabolism and disease development.
- Clinical Application box on inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) updated to include distinguishing features of ulcerative colitis and Chron's disease.
- Updated description of salt and water transport in the large intestine.
- Description on the steps of defecation reflex updated.
- Clinical Application box on cirrhosis, nonalcoholic fatty liver disease, and liver diseases caused by chronic alcohol use updated.
- Table 18.3 updated to include storage functions of the liver.
- Legend for figure 18.22 on metabolism of heme and bilirubin updated for more detail and accuracy.
- Urobilinogen changed to sterocobilin in text and figure 18.23 for accuracy in terminology.
- Updated and expanded description of the metabolism and circulation of bile acids and the role of bile acids in the secretion of hormones by the small intestine.
- Lifestyle Application on exercise and the timing of meals updated to include the autonomic nervous system's influence on digestion during exercise.
- New information added to the structure and function of the enteric nervous system.
- New information on the role of secretin in metabolism of brown adipose tissue.
- Updated explanation of the transport of chylomicrons by the lacteals of the intestinal villi.

Chapter 19

- Updated and expanded discussion of the development of adipose tissue.
- New discussion of subcutaneous adipose tissue, visceral fat, and ectopic fat.
- New heading, Hormonal Signals from the GI Tract.

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New to This Edition

- Updated and expanded discussion of enteroendocrine regulation of hunger.
- Information on leptin and obesity updated.
- New information on meal-induced thermogenesis added.
- Description of thermoregulation updated and expanded.
- Updated and expanded description regarding insulin and glucagon during the postabsorptive state.
- Updated and expanded section on the role of autonomic nerves in pancreatic islet regulation.
- Updated and expanded description of insulin action during the absorptive state.
- Updated explanation of increased metabolism stimulated by thyroxine.
- New information added regarding psychosocial effects on children's levels of growth hormone and IGF-1.
- New and expanded description of the regulation of osteoclast development.
- Updated description of the effects of sex steroids on osteoblasts and osteoclasts.
- New and updated information added regarding the effects of osteocalcin.

Chapter 20

- Updated information on anti-Müllerian hormone.
- Updated information added on the mechanisms of the pubertal growth spurt.
- Updated information added regarding the 5 α-reduced androgens.
- New and updated information regarding the role of estradiol in male physiology.
- New and expanded description of primary follicles and anti-Müllerian hormone in adult women.
- New and updated information regarding polycystic ovarian syndrome.
- Updated information added regarding the sperm's contribution to the mitochondria of the zygote.
- New paragraph added distinguishing the embryonic and fetal stages of development.
- Current information added regarding the use of iPS cells in regenerative medicine.

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Acknowledgments

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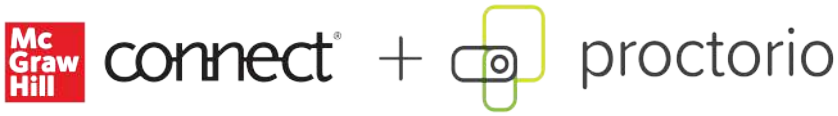

New remote proctoring and browser-locking capabilities, hosted by Proctorio within Connect, provide control of the assessment environment by enabling security options and verifying the identity of the student.

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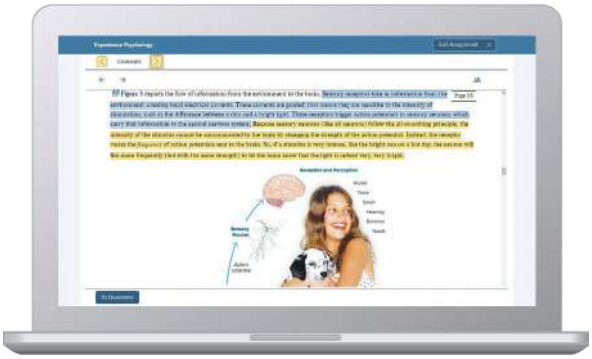

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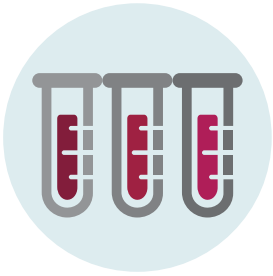

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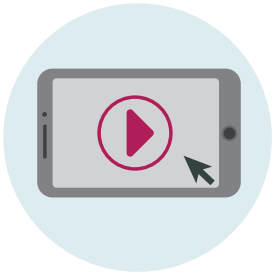
Ph.I.L.S. 4.0 (Physiology Interactive Lab Simulations) software is the perfect way to reinforce key physiology concepts with powerful lab experiments. **The result? Students gain critical thinking skills and are better prepared for lab.**



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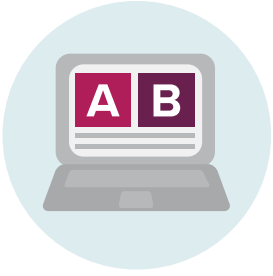

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*Statistic courtesy of The New England Journal of Higher Education

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Anatomy & Physiology Revealed® (APR) 4.0 is an interactive cadaver dissection tool to enhance lecture and lab that students can use anytime, anywhere. **The result? Students are prepared for lab, engaged in the material, and utilize critical thinking.**

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1 The Study of Body Function

CLINICAL INVESTIGATION

As you study the sections of this chapter, you can see how your new knowledge can be applied to interesting health issues that may be important to know in your future career as a health professional. This can add zest to your studies and increase your motivation to truly understand physiological concepts, rather than to simply memorize facts for examinations. Each chapter begins with a medical mystery for you to solve, using information in the text of that chapter and "Clinical Investigation Clues" within the chapter.

For example, suppose Linda goes for a medical examination where her body temperature is measured, and she gives a fasting blood sample to test for glucose. Your first Clinical Investigation challenge is to determine the medical significance of these physiological tests.

CHAPTER OUTLINE

1.1 INTRODUCTION TO PHYSIOLOGY

Human physiology is the study of how the human body functions, with emphasis on specific cause-and-effect mechanisms. Knowledge of these mechanisms has been obtained experimentally through applications of the scientific method.

LEARNING OUTCOMES

After studying this section, you should be able to:

1. Describe the scientific study of human physiology.
2. Describe the characteristics of the scientific method.

Physiology (from the Greek *physis* = nature; *logos* = study) is the study of biological function—of how the body works, from molecular mechanisms within cells to the actions of tissues, organs, and systems, and how the organism as a whole accomplishes particular tasks essential for life. In the study of physiology, the emphasis is on mechanisms—with questions that begin with the word *how* and answers that involve cause-and-effect sequences. These sequences can be woven into larger and larger stories that include descriptions of the structures involved (anatomy) and that overlap with the sciences of chemistry and physics.

The separate facts and relationships of these cause-and-effect sequences are derived empirically from experimental evidence. Explanations that seem logical are not necessarily true; they are only as valid as the data on which they are based, and they can change as new techniques are developed and further experiments are performed. The ultimate objective of physiological research is to understand the normal functioning of cells, organs, and systems. A related science—*pathophysiology*—is concerned with how physiological processes are altered in disease or injury.

Pathophysiology and the study of normal physiology complement one another. For example, a standard technique for investigating the functioning of an organ is to observe what happens when the organ is surgically removed from an experimental animal or when its function is altered in a specific way. This study is often aided by "experiments of nature"—diseases—that involve specific damage to the functioning of an organ. The study of disease processes has thus aided our understanding of normal functioning, and the study of normal physiology has provided much of the scientific basis of modern medicine. This relationship is recognized by the Nobel Prize committee, whose members award prizes in the category "Physiology or Medicine."

The physiology of invertebrates and of different vertebrate groups is studied in the science of *comparative physiology.* Much of the knowledge gained from comparative physiology has benefited the study of human physiology. This is because animals, including humans, are more alike than they are different. This is especially true when comparing humans with other mammals. The small differences in physiology between humans and other mammals can be of crucial importance in the development of pharmaceutical drugs (discussed later in this section), but these differences are relatively slight in the overall study of physiology.

Scientific Method

All of the information in this text has been gained by people applying the **scientific method.** Although many different techniques are involved when people apply the scientific method, all share three attributes: (1) confidence that the natural world, including ourselves, is ultimately explainable in terms we can understand; (2) descriptions and explanations of the natural world that are honestly based on observations and that could be modified or refuted by other observations; and (3) humility, or the willingness to accept the fact that we could be wrong. If further study should yield conclusions that refuted all or part of an idea, the idea would have to be modified accordingly. In order for the scientific enterprise to function, its practitioners must honestly report their data and observations and be willing to modify their ideas, sometimes long-held and cherished, in response to new scientific information. Practicing scientists may not always display these attributes, but the validity of the large body of scientific knowledge that has been accumulated—as shown by the technological applications and the predictive value of scientific hypotheses—is ample testimony to the fact that the scientific method works.

The scientific method involves specific steps. After certain observations regarding the natural world are made, a **hypothesis** is formulated. In order for this hypothesis to be scientific, it must be capable of being refuted by experiments or other observations of the natural world. For example, one might hypothesize that people who exercise regularly have a lower resting pulse rate than other people. Experiments are conducted, or other observations are made, and the results are analyzed. Conclusions are then drawn as to whether the new data either refute or support the hypothesis. If the hypothesis survives such testing, it might be incorporated into a more general **theory.** Scientific theories are thus not simply conjectures; they are statements about the natural world that incorporate a number of hypotheses that have been supported by scientific evidence. They serve as a logical framework by which these hypotheses can be interrelated and provide the basis for predictions that may as yet be untested.

The hypothesis in the preceding example is scientific because it is *testable;* the pulse rates of 100 athletes and 100 sedentary people could be measured, for example, to see if there were statistically significant differences. If there were, the statement that athletes, on the average, have lower resting pulse rates than other people would be justified *based on these data.* One must still be open to the fact that this conclusion could be wrong. Before the discovery could become generally accepted as fact, other scientists would have to consistently replicate the results. Scientific theories are based on *reproducible* data.

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It is quite possible that when others attempt to replicate the experiment, their results will be slightly different. They may then construct scientific hypotheses that the differences in resting pulse rate also depend on other factors, such as the nature of the exercise performed. When scientists attempt to test these hypotheses, they will likely encounter new problems requiring new explanatory hypotheses, which then must be tested by additional experiments.

In this way, a large body of highly specialized information is gradually accumulated, and a more generalized explanation (a scientific theory) can be formulated. This explanation will almost always be different from preconceived notions. People who follow the scientific method will then appropriately modify their concepts, realizing that their new ideas will probably have to be changed again in the future as additional experiments are performed.

Use of Measurements, Controls, and Statistics

Suppose you wanted to test the hypothesis that a regular exercise program causes people to have a lower resting heart rate. First, you would have to decide on the nature of the exercise program. Then, you would have to decide how the heart rate (or pulse rate) would be measured. This is a typical problem in physiology research because the testing of most physiological hypotheses requires quantitative **measurements.**

The group that is subject to the testing condition—in this case, exercise—is called the **experimental group.** A measurement of the heart rate for this group would be meaningful only if it is compared to that of another group, known as the **control group.** How shall this control group be chosen? Perhaps the subjects could serve as their own controls—that is, a person's resting heart rate could be measured before and after the exercise regimen. If this isn't possible, a control group could be other people who do not follow the exercise program. The choice of control groups is often a controversial aspect of physiology studies. In this example, did the people in the control group really refrain from *any* exercise? Were they comparable to the people in the experimental group with regard to age, sex, ethnicity, body weight, health status, and so on? You can see how difficult it could be in practice to get a control group that could satisfy any potential criticism.

Another possible criticism could be bias in the way that the scientists perform the measurements. This bias could be completely unintentional; scientists are human, after all, and they may have invested months or years in this project. To prevent such bias, the person doing the measurements often does not know if a subject is part of the experimental or the control group. This is known as a *blind measurement.*

Now suppose the data are in and it looks like the experimental group indeed has a lower average resting heart rate than the control group. But there is overlap—some people in the control group have measurements that are lower than some people in the experimental group. Is the difference in the average measurements of the groups due to a real physiological difference, or is it due to chance variations in the measurements? Scientists attempt to test the *null hypothesis* (the hypothesis that the difference is due to chance) by employing the mathematical tools of **statistics.** If the statistical results so warrant, the null hypothesis can be rejected and the experimental hypothesis can be deemed to be supported by this study.

The statistical test chosen will depend on the design of the experiment, and it can also be a source of contention among scientists in evaluating the validity of the results. Because of the nature of the scientific method, "proof" in science is always provisional. Some other researchers, employing the scientific method in a different way (with different measuring techniques, experimental procedures, choice of control groups, statistical tests, and so on), may later obtain different results. The scientific method is thus an ongoing enterprise.

The results of the scientific enterprise are written up as research articles, and these must be reviewed by other scientists who work in the same field before they can be published in **peer-reviewed journals.** More often than not, the reviewers will suggest that certain changes be made in the articles before they can be accepted for publication.

Examples of such peer-reviewed journals that publish articles in many scientific fields include *Science* (www.sciencemag.org/), *Nature* (www.nature.com/nature/), and *Proceedings of the National Academy of Sciences* (www.pnas.org/). Review articles on physiology can be found in *Annual Review of Physiology* (physiol.annualreviews.org/), *Physiological Reviews* (journals.physiology.org), and *Physiology* (physiologyonline.physiology.org). Medical research journals, such as the *New England Journal of Medicine* (content.nejm.org/) and *Nature Medicine* (www.nature.com/nm/), also publish articles of physiological interest. There are also many specialty journals in areas of physiology such as neurophysiology, endocrinology, and cardiovascular physiology.

Students who wish to look online for scientific articles published in peer-reviewed journals that relate to a particular subject can do so at the National Library of Medicine website, *PubMed* (www.ncbi.nlm.nih.gov/entrez/query.fcgi).

Development of Pharmaceutical Drugs

The development of new pharmaceutical drugs can serve as an example of how the scientific method is used in physiology and its health applications. The process usually starts with basic physiological research, often at cellular and molecular levels. Perhaps a new family of drugs is developed using cells in tissue culture (*in vitro,* or outside the body). For example, cell physiologists studying membrane transport may discover that a particular family of compounds blocks membrane channels for calcium ions (Ca^{2+}). Because of their knowledge of physiology, other scientists may predict that a drug of this nature might be useful in the treatment of hypertension (high blood pressure). This drug may then be tried in animal experiments.

If a drug is effective at extremely low concentrations *in vitro* (in cells cultured outside of the body), there is a chance

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that it may work *in vivo* (in the body) at concentrations low enough not to be toxic (poisonous). This possibility must be thoroughly tested utilizing experimental animals, primarily rats and mice. More than 90% of drugs tested in experimental animals are too toxic for further development. Only in those rare cases when the toxicity is low enough may development progress to human/clinical trials.

Biomedical research is often aided by **animal models** of particular diseases. These are strains of laboratory rats and mice that are genetically susceptible to particular diseases that resemble human diseases. Research utilizing laboratory animals typically takes several years and always precedes human (clinical) trials of promising drugs. It should be noted that this length of time does not include all of the years of "basic" physiological research (involving laboratory animals) that provided the scientific foundation for the specific medical application.

In **phase I clinical trials,** the drug is tested on healthy human volunteers. This is done to test its toxicity in humans and to study how the drug is "handled" by the body: how it is metabolized, how rapidly it is removed from the blood by the liver and kidneys, how it can be most effectively administered, and so on. If significant toxic effects are not observed, the drug can proceed to the next stage. In **phase II clinical trials,** the drug is tested on the target human population (for example, those with hypertension). Only in those exceptional cases where the drug seems to be effective but has minimal toxicity does testing move to the next phase. **Phase III trials** occur in many research centers across the country to maximize the number of test participants. At this point, the test population must include a sufficient number of subjects of both sexes, as well as people of different ethnic groups. In addition, people are tested who have other health problems besides the one that the drug is intended to benefit. For example, those who have diabetes in addition to hypertension would be included in this phase. If the drug passes phase III trials, it goes to the Food and Drug Administration (FDA) for approval. **Phase IV trials** test other potential uses of the drug. These "post-marketing studies" often reveal problems with the drug that were not previously evident.

Less than 10% of the tested drugs make it all the way through clinical trials to eventually become approved and marketed. This low success rate does not count those that fail after approval because of unexpected toxicity, nor does it take into account the great amount of drugs that fail earlier in research before clinical trials begin. Notice the crucial role of basic research, using experimental animals, in this process. Virtually every prescription drug on the market owes its existence to such research.

CHECKPOINTS

1. How has the study of physiology aided, and been aided by, the study of diseases?

2a. Describe the steps involved in the scientific method. What would qualify a statement as unscientific?

2b. Describe the different types of trials a new drug must undergo before it is "ready for market."

1.2 HOMEOSTASIS AND FEEDBACK CONTROL

The regulatory mechanisms of the body can be understood in terms of a single shared function: that of maintaining constancy of the internal environment. A state of relative constancy of the internal environment is known as homeostasis, maintained by negative feedback loops.

LEARNING OUTCOMES

After studying this section, you should be able to:

3. Define homeostasis, and identify the components of negative feedback loops.

4. Explain the role of antagonistic effectors in maintaining homeostasis, and the nature of positive feedback loops.

5. Give examples of how negative feedback loops involving the nervous and endocrine systems help to maintain homeostasis.

History of Physiology

The Greek philosopher Aristotle (384–322 B.C.) speculated on the function of the human body, but another ancient Greek, Erasistratus (304–250 B.C.), is considered to be the first to study physiology because he attempted to apply physical laws to understand human function. Galen (A.D. 130–210) wrote widely on the subject and was considered the supreme authority until the Renaissance. Physiology became a fully experimental science with the revolutionary work of the English physician William Harvey (1578–1657), who demonstrated that the heart pumps blood through a closed system of vessels.

However, the originator of modern physiology is the French physiologist Claude Bernard (1813–1878), who observed that the *milieu intérieur* (internal environment) remains remarkably constant despite changing conditions in the external environment. In a book titled *The Wisdom of the Body,* published in 1932, the American physiologist Walter Cannon (1871–1945) coined the term **homeostasis** to describe this internal constancy. Cannon further suggested that the many mechanisms of physiological regulation have but one purpose—the maintenance of internal constancy. In the early 1950s, James Hardin extended Cannon's concept by proposing that homeostatic mechanisms maintain each physiological variable within a normal range by comparing its value to a desired, or *set point,* value (as will be described shortly).

Most of our present knowledge of human physiology has been gained in the twentieth century. However, new knowledge in the twenty-first century is being added at an ever more rapid pace, fueled in more recent decades by the revolutionary growth of molecular genetics and its associated biotechnologies, and by the availability of more powerful computers and other equipment. A very brief history of twentieth- and

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twenty-first-century physiology, limited by space to only two citations per decade, is provided in table 1.1.

Most of the citations in table 1.1 indicate the winners of Nobel Prizes. The **Nobel Prize in Physiology or Medicine** (a single prize category) was first awarded in 1901 to Emil Adolf von Behring, a pioneer in immunology who coined the term *antibody* and whose many other discoveries included the use of serum (containing antibodies) to treat diphtheria. Many scientists who might deserve a Nobel Prize never receive one, and the prizes are given for particular achievements and not others (Einstein didn't win his Nobel Prize in Physics for relativity, for example) and are often awarded many years after the discoveries were made. Nevertheless, the awarding of the Nobel Prize in Physiology or Medicine each year is a celebrated event in the biomedical community, and the awards can be a useful yardstick for tracking the course of physiological research over time.

Negative Feedback Loops

The concept of homeostasis has been of immense value in the study of physiology because it allows diverse regulatory mechanisms to be understood in terms of their "why" as well as their "how." The concept of homeostasis also provides a major foundation for medical diagnostic procedures. When a particular measurement of the internal environment, such as a blood measurement (table 1.2), deviates significantly from the normal range of values, it can be concluded that homeostasis is not being maintained and that the person is sick. A number of such measurements, combined with clinical observations, may allow the particular defective mechanism to be identified.

In order for internal constancy to be maintained, changes in the body must stimulate *receptors,* which function as **sensors** that can send information to an **integrating center.** This allows the integrating center to detect changes from a **set point.**

TABLE 1.1 | History of Twentieth- and Twenty-First-Century Physiology (two citations per decade)

1900	Karl Landsteiner discovers the A, B, and O blood groups.
1904	Ivan Pavlov wins the Nobel Prize for his work on the physiology of digestion.
1910	Sir Henry Dale describes properties of histamine.
1918	Earnest Starling describes how the force of the heart's contraction relates to the amount of blood in it.
1921	John Langley describes the functions of the autonomic nervous system.
1923	Sir Frederick Banting, Charles Best, and John Macleod win the Nobel Prize for the discovery of insulin.
1932	Sir Charles Sherrington and Lord Edgar Adrian win the Nobel Prize for their discoveries related to the functions of neurons.
1936	Sir Henry Dale and Otto Loewi win the Nobel Prize for the discovery of acetylcholine in synaptic transmission.
1939–47	Albert von Szent-Györgyi explains the role of ATP and contributes to the understanding of actin and myosin in muscle contraction.
1949	Hans Selye discovers the common physiological responses to stress.
1953	Sir Hans Krebs wins the Nobel Prize for his discovery of the citric acid cycle.
1954	Hugh Huxley, Jean Hanson, R. Niedergerde, and Andrew Huxley propose the sliding filament theory of muscle contraction.
1962	Francis Crick, James Watson, and Maurice Wilkins win the Nobel Prize for determining the structure of DNA.
1963	Sir John Eccles, Sir Alan Hodgkin, and Sir Andrew Huxley win the Nobel Prize for their discoveries relating to the nerve impulse.
1971	Earl Sutherland wins the Nobel Prize for his discovery of the mechanism of hormone action.
1977	Roger Guillemin and Andrew Schally win the Nobel Prize for their discoveries of the brain's production of peptide hormone.
1981	Roger Sperry wins the Nobel Prize for his discoveries regarding the specializations of the right and left cerebral hemispheres.
1986	Stanley Cohen and Rita Levi-Montalcini win the Nobel Prize for their discoveries of growth factors regulating the nervous system.
1994	Alfred Gilman and Martin Rodbell win the Nobel Prize for their discovery of the functions of G-proteins in signal transduction in cells.
1998	Robert Furchgott, Louis Ignarro, and Ferid Murad win the Nobel Prize for discovering the role of nitric oxide as a signaling molecule in the cardiovascular system.
2004	Linda B. Buck and Richard Axel win the Nobel Prize for their discoveries of odorant receptors and the organization of the olfactory system.
2012	Sir John Gurdon and Shinya Yamanaka win the Nobel Prize for their discoveries that mature cells can be reprogrammed to become pluripotent (like embryonic cells).
2019	William G. Kaelin, Gregg L. Semenza, and Peter J. Ratcliffe win the Nobel Prize for their discoveries of how cells sense the oxygen levels in their environment and initiate physiological responses.

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TABLE 1.2 | Approximate Normal Ranges for Measurements of Some Fasting Blood Values

Measurement	Normal Range
Arterial pH	7.35–7.45
Bicarbonate	24–28 mEq/L
Sodium	135–145 mEq/L
Calcium	4.5–5.5 mEq/L
Oxygen content	17.2–22.0 ml/100 ml
Urea	12–35 mg/100 ml
Amino acids	3.3–5.1 mg/100 ml
Protein	6.5–8.0 g/100 ml
Total lipids	400–800 mg/100 ml
Glucose	70–99 mg/100 ml

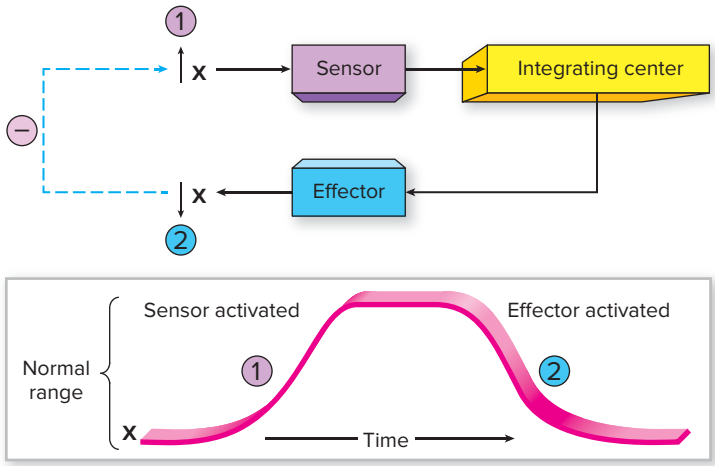

FIGURE 1.1 A rise in some factor of the internal environment (↑X) is detected by a sensor. This information is relayed to an integrating center, which causes an effector to produce a change (1) in the opposite direction (↓X). The initial deviation is thus reversed (2), completing a negative feedback loop (shown by the dashed arrow and negative sign). The numbers indicate the sequence of changes.

The set point is analogous to the temperature set on a house thermostat. In a similar manner, there is a set point for body temperature, blood glucose concentration, the tension on a tendon, and so on. The integrating center is often a particular region of the brain or spinal cord, but it can also be a group of cells in an endocrine gland. A number of different sensors may send information to a particular integrating center, which can then integrate this information and direct the responses of **effectors**—generally muscles or glands. The integrating center may cause increases or decreases in effector action to counter the deviations from the set point and defend homeostasis.

The thermostat of a house can serve as a simple example. Suppose you set the thermostat at a set point of 70° F. If the temperature in the house rises sufficiently above the set point, a sensor connected to an integrating center within the thermostat will detect that deviation and turn on the air conditioner (the effector in this example). The air conditioner will turn off when the room temperature falls and the thermostat no longer detects a deviation from the set-point temperature. However, this simple example gives a wrong impression: the effectors in the body are generally increased or decreased in activity, *not* just turned on or off. Because of this, negative feedback control in the body works far more efficiently than does a house thermostat.

If the body temperature exceeds the set point of 37° C, sensors in a part of the brain detect this deviation and, acting via an integrating center (also in the brain), stimulate activities of effectors (including sweat glands) that lower the temperature. For another example, if the blood glucose concentration falls below normal, the effectors act to increase the blood glucose. One can think of the effectors as "defending" the set points against deviations. Because the activity of the effectors is influenced by the effects they produce, and because this regulation is in a negative, or reverse, direction, this type of control system is known as a **negative feedback loop** (fig. 1.1). (Notice that in figure 1.1 and in all subsequent figures, negative feedback is indicated by a dashed line and a negative sign.)

The nature of the negative feedback loop can be understood by again referring to the analogy of the thermostat and air conditioner. After the air conditioner has been on for some time, the room temperature may fall significantly below the set point of the thermostat. When this occurs, the air conditioner will be turned off. The effector (air conditioner) is turned on by a high temperature and, when activated, produces a negative change (lowering of the temperature) that ultimately causes the effector to be turned off. In this way, constancy is maintained.

It is important to realize that these negative feedback loops are continuous, ongoing processes. Thus, a particular nerve fiber that is part of an effector mechanism may always display some activity, and a particular hormone that is part of another effector mechanism may always be present in the blood. The nerve activity and hormone concentration may decrease in response to deviations of the internal environment in one direction (fig. 1.1), or they may increase in response to deviations in the opposite direction (fig. 1.2). Changes from the normal range in either direction are thus compensated for by reverse changes in effector activity.

Because negative feedback loops respond after deviations from the set point have stimulated sensors, the internal environment is never absolutely constant. Homeostasis is best conceived as a state of **dynamic constancy** in which conditions are stabilized above and below the set point. These conditions can be measured quantitatively, in degrees Celsius for body temperature, for example, or in milligrams per deciliter (one-tenth of a liter) for blood glucose. The set point can be taken as the average value within the normal range of measurements (fig. 1.3).

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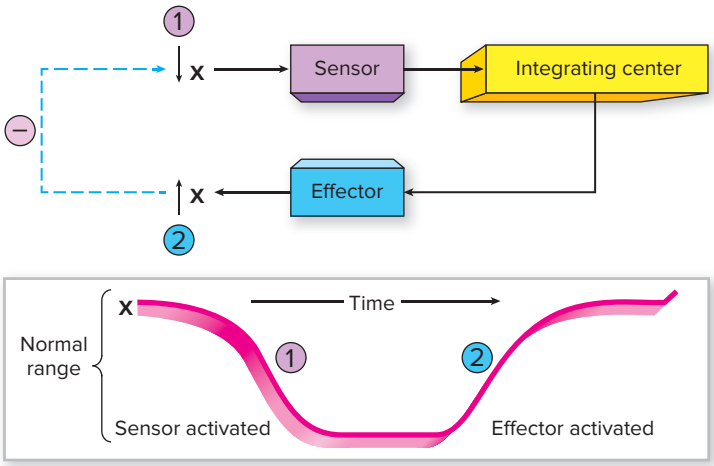

FIGURE 1.2 A fall in some factor of the internal environment (↓X) is detected by a sensor. (Compare this negative feedback loop with that shown in fig. 1.1.)

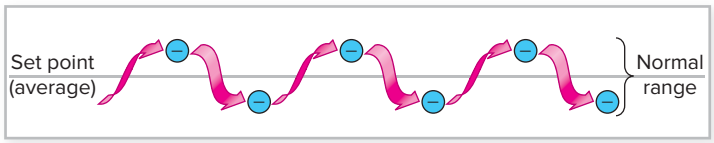

FIGURE 1.3 Negative feedback loops maintain a state of dynamic constancy within the internal environment. The completion of the negative feedback loop is indicated by negative signs.

Antagonistic Effectors

Most factors in the internal environment are controlled by several effectors, which often have antagonistic actions. Control by antagonistic effectors is sometimes described as "push-pull," where the increasing activity of one effector is accompanied by decreasing activity of an antagonistic effector. This affords a finer degree of control than could be achieved by simply switching one effector on and off.

Room temperature can be maintained, for example, by simply turning an air conditioner on and off, or by just turning a heater on and off. A much more stable temperature, however, can be achieved if the air conditioner and heater are both controlled by a thermostat. Then the heater is turned on when the air conditioner is turned off, and vice versa. Normal body temperature is maintained about a set point of 37° C by the antagonistic effects of sweating, shivering, and other mechanisms (fig. 1.4).

The blood concentrations of glucose, calcium, and other substances are regulated by negative feedback loops involving hormones that promote opposite effects. Insulin, for example, lowers blood glucose, and other hormones raise the blood glucose concentration. The heart rate, similarly, is controlled by nerve fibers that produce opposite effects: stimulation of one group of nerve fibers increases heart rate; stimulation of another group slows the heart rate.

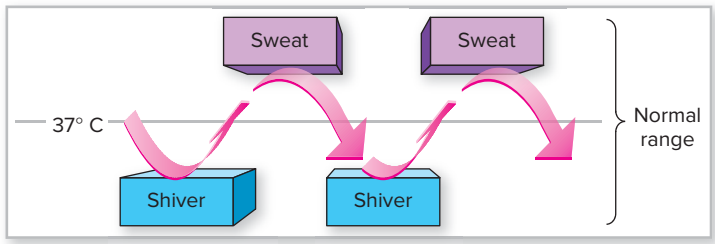

FIGURE 1.4 How body temperature is maintained within the normal range. The body temperature normally has a set point of 37° C. This is maintained, in part, by two antagonistic mechanisms—shivering and sweating. Shivering is induced when the body temperature falls too low, and it gradually subsides as the temperature rises. Sweating occurs when the body temperature is too high, and it diminishes as the body temperature falls. Most aspects of the internal environment are regulated by the antagonistic actions of different effector mechanisms.

See the *Test Your Quantitative Ability* section of the Review Activities at the end of this chapter.

Quantitative Measurements

To study physiological mechanisms, scientists must measure specific values and mathematically determine such statistics as their normal range, their averages, and their deviations from the average (which can represent the set point). For these and other reasons, quantitative measurements are basic to the science of physiology. One example of this, and of the actions of antagonistic mechanisms in maintaining homeostasis, is shown in figure 1.5. Blood glucose concentrations were measured in five healthy people before and after an injection of insulin, a hormone that acts to lower the blood glucose concentration. A graph of the data reveals that the blood glucose concentration decreased rapidly but was brought back up to normal levels within 80 minutes after the injection. This demonstrates that

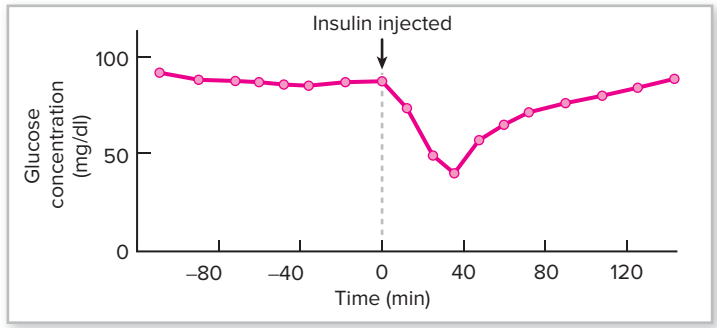

FIGURE 1.5 Homeostasis of the blood glucose concentration. Average blood glucose concentrations of five healthy individuals are graphed before and after a rapid intravenous injection of insulin. The "0" indicates the time of the injection. The blood glucose concentration is first lowered by the insulin injection, but is then raised back to the normal range (by hormones antagonistic to insulin that stimulate the liver to secrete glucose into the blood). Homeostasis of blood glucose is maintained by the antagonistic actions of insulin and several other hormones.

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negative feedback mechanisms acted to restore homeostasis in this experiment. These mechanisms involve the action of hormones whose effects are antagonistic to that of insulin—that is, they promote the secretion of glucose from the liver (see chapter 19).

Positive Feedback

Constancy of the internal environment is maintained by effectors that act to compensate for the change that served as the stimulus for their activation; in short, by negative feedback loops. A thermostat, for example, maintains a constant temperature by increasing heat production when it is cold and decreasing heat production when it is warm. The opposite occurs during **positive feedback**—in this case, the action of effectors *amplifies* those changes that stimulated the effectors. A thermostat that works by positive feedback, for example, would increase heat production in response to a rise in temperature.

It is clear that homeostasis must ultimately be maintained by negative rather than by positive feedback mechanisms. The effectiveness of some negative feedback loops, however, is increased by positive feedback mechanisms that amplify the actions of a negative feedback response. Blood clotting, for example, occurs as a result of a sequential activation of clotting factors; the activation of one clotting factor results in activation of many in a positive feedback cascade. In this way, a single change is amplified to produce a blood clot. Formation of the clot, however, can prevent further loss of blood, and thus represents the completion of a negative feedback loop that restores homeostasis.

Two other examples of positive feedback in the body are both related to the female reproductive system. One of these examples occurs when estrogen, secreted by the ovaries, stimulates the woman's pituitary gland to secrete LH (luteinizing hormone). This stimulatory, positive feedback effect creates an "LH surge" (very rapid rise in blood LH concentrations) that triggers ovulation. Interestingly, estrogen secretion after ovulation has an inhibitory, negative feedback, effect on LH secretion (this is the physiological basis for the birth control pill, discussed in chapter 20). Another example of positive feedback is contraction of the uterus during childbirth (parturition). Contraction of the uterus is stimulated by the pituitary hormone oxytocin, and the secretion of oxytocin is increased by sensory feedback from contractions of the uterus during labor. The strength of uterine contractions during labor is thus increased through positive feedback. The mechanisms involved in labor are discussed in more detail in chapter 20 (see fig. 20.50).

Neural and Endocrine Regulation

Homeostasis is maintained by two general categories of regulatory mechanisms: (1) those that are **intrinsic,** or "built into" the organs being regulated (such as molecules produced in the walls of blood vessels that cause vessel dilation or constriction); and (2) those that are **extrinsic,** as in regulation of an organ by the nervous and endocrine systems. The endocrine system functions closely with the nervous system in regulating and integrating body processes and maintaining homeostasis. The nervous system controls the secretion of many endocrine glands, and some hormones in turn affect the function of the nervous system. Together, the nervous and endocrine systems regulate the activities of most of the other systems of the body.

Regulation by the endocrine system is achieved by the secretion of chemical regulators called **hormones** into the blood, which carries the hormones to all organs in the body. Only specific organs can respond to a particular hormone, however; these are known as the **target organs** of that hormone.

Nerve fibers are said to *innervate* the organs that they regulate. When stimulated, these fibers produce electrochemical nerve impulses that are conducted from the origin of the fiber to its terminals in the target organ innervated by the fiber. These target organs can be muscles or glands that may function as effectors in the maintenance of homeostasis.

For example, we have negative feedback loops that help maintain homeostasis of arterial blood pressure, in part by adjusting the heart rate. If everything else is equal, blood pressure is lowered by a decreased heart rate and raised by an increased heart rate. This is accomplished by regulating the activity of the autonomic nervous system, as will be discussed in later chapters. Thus, a fall in blood pressure—produced daily as we go from a lying to a standing position—is compensated by a faster heart rate (fig. 1.6). As a consequence of this negative feedback loop, our heart rate varies as we go through our day, speeding up and slowing down, so that we can maintain homeostasis of blood pressure and keep it within limits.

Feedback Control of Hormone Secretion

The nature of the endocrine glands, the interaction of the nervous and endocrine systems, and the actions of hormones will be discussed in detail in later chapters. For now, it is sufficient to describe the regulation of hormone secretion very broadly, because it so superbly illustrates the principles of homeostasis and negative feedback regulation.

Hormones are secreted in response to specific chemical stimuli. A rise in the plasma glucose concentration, for example, stimulates insulin secretion from structures in the pancreas known as the *pancreatic islets.* Hormones are also secreted in response to nerve stimulation and stimulation by other hormones.

The secretion of a hormone can be inhibited by its own effects in a negative feedback manner. Insulin, as previously described, produces a lowering of blood glucose. Because a rise in blood glucose stimulates insulin secretion, a lowering of blood glucose caused by insulin's action inhibits further insulin secretion. This closed-loop control system is called **negative feedback inhibition** (fig. 1.7*a*).

Homeostasis of blood glucose is too important—the brain uses blood glucose as its primary source of energy—to entrust to the regulation of only one hormone, insulin. So, when blood

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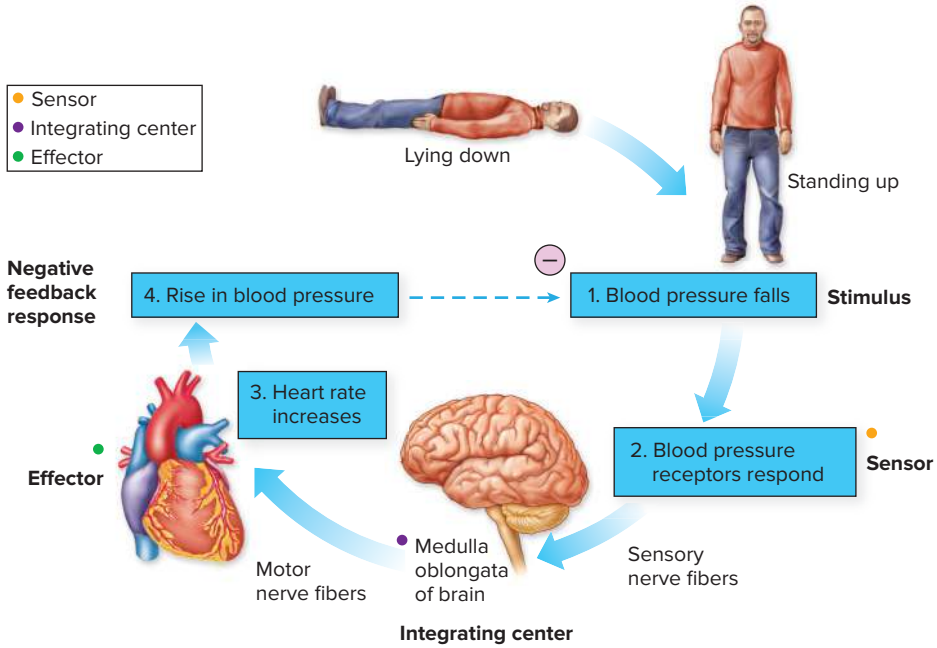

FIGURE 1.6 Negative feedback control of blood pressure. Blood pressure influences the activity of sensory neurons from the blood pressure receptors (sensors); a rise in pressure increases the firing rate, and a fall in pressure decreases the firing rate of nerve impulses. When a person stands up from a lying-down position, the blood pressure momentarily falls. The resulting decreased firing rate of nerve impulses in sensory neurons affects the medulla oblongata of the brain (the integrating center). This causes the motor nerves to the heart (effector) to increase the heart rate, helping to raise the blood pressure.

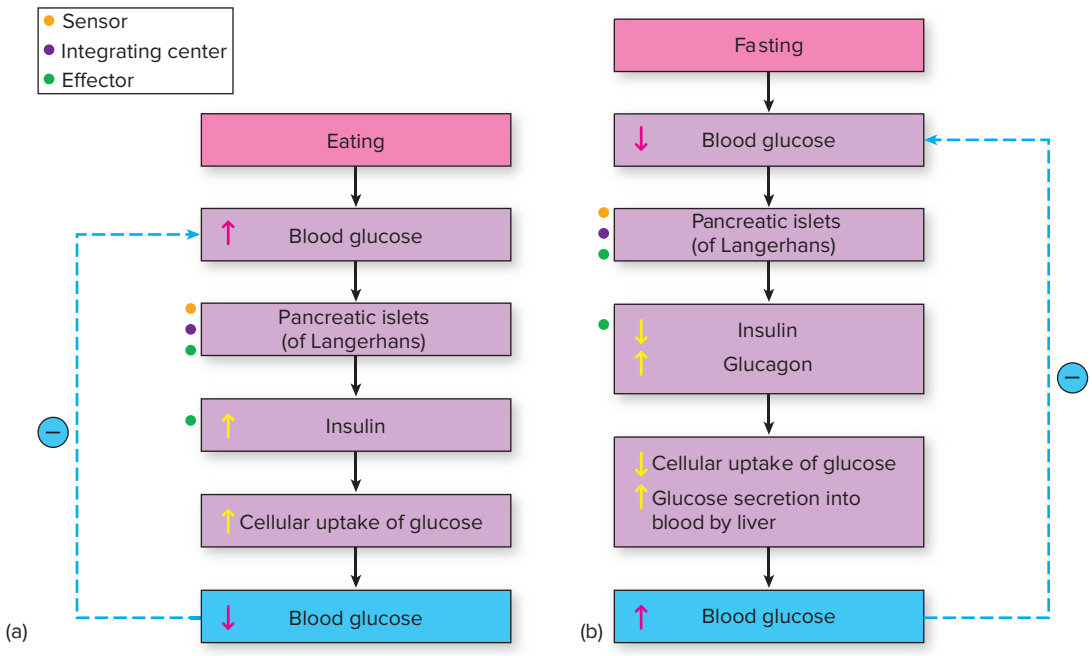

FIGURE 1.7 Negative feedback control of blood glucose. (*a*) The rise in blood glucose that occurs after eating carbohydrates is corrected by the action of insulin, which is secreted in increasing amounts at that time. (*b*) During fasting, when blood glucose falls, insulin secretion is inhibited and the secretion of an antagonistic hormone, glucagon, is increased. This stimulates the liver to secrete glucose into the blood, helping to prevent blood glucose from continuing to fall. In this way, blood glucose concentrations are maintained within a homeostatic range following eating and during fasting.

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