Human Physiology

SIXTEENTH EDITION

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Mc Graw Hill

HUMAN PHYSIOLOGY, SIXTEENTH EDITION

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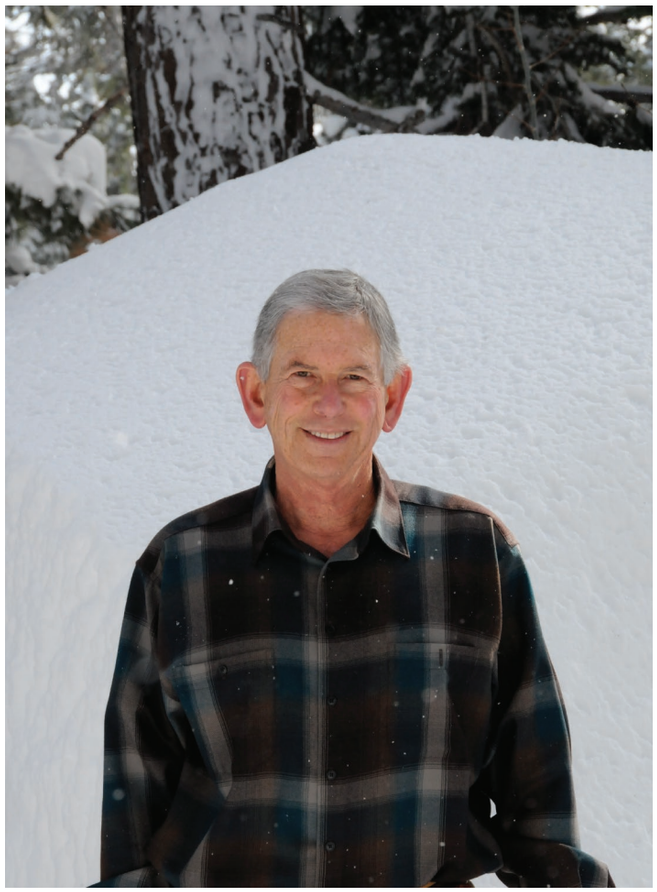
Brief Contents

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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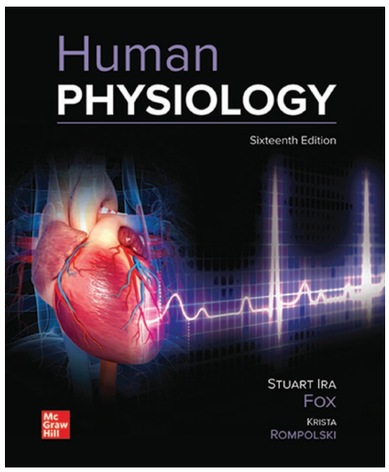
Preface

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.

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.

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.

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.

- 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.

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.

Acknowledgments

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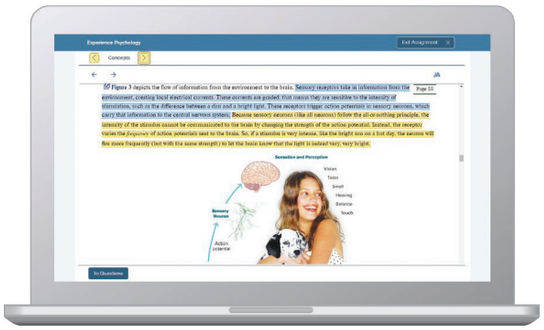

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Anatomy & Physiology Revealed® (APR) 4.0 is an interactive cadaver dissection tool to enhance lecture and lab that students can use anytime, anywhere. The result? Students are prepared for lab, engaged in the material, and utilize critical thinking.

Contents

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.

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