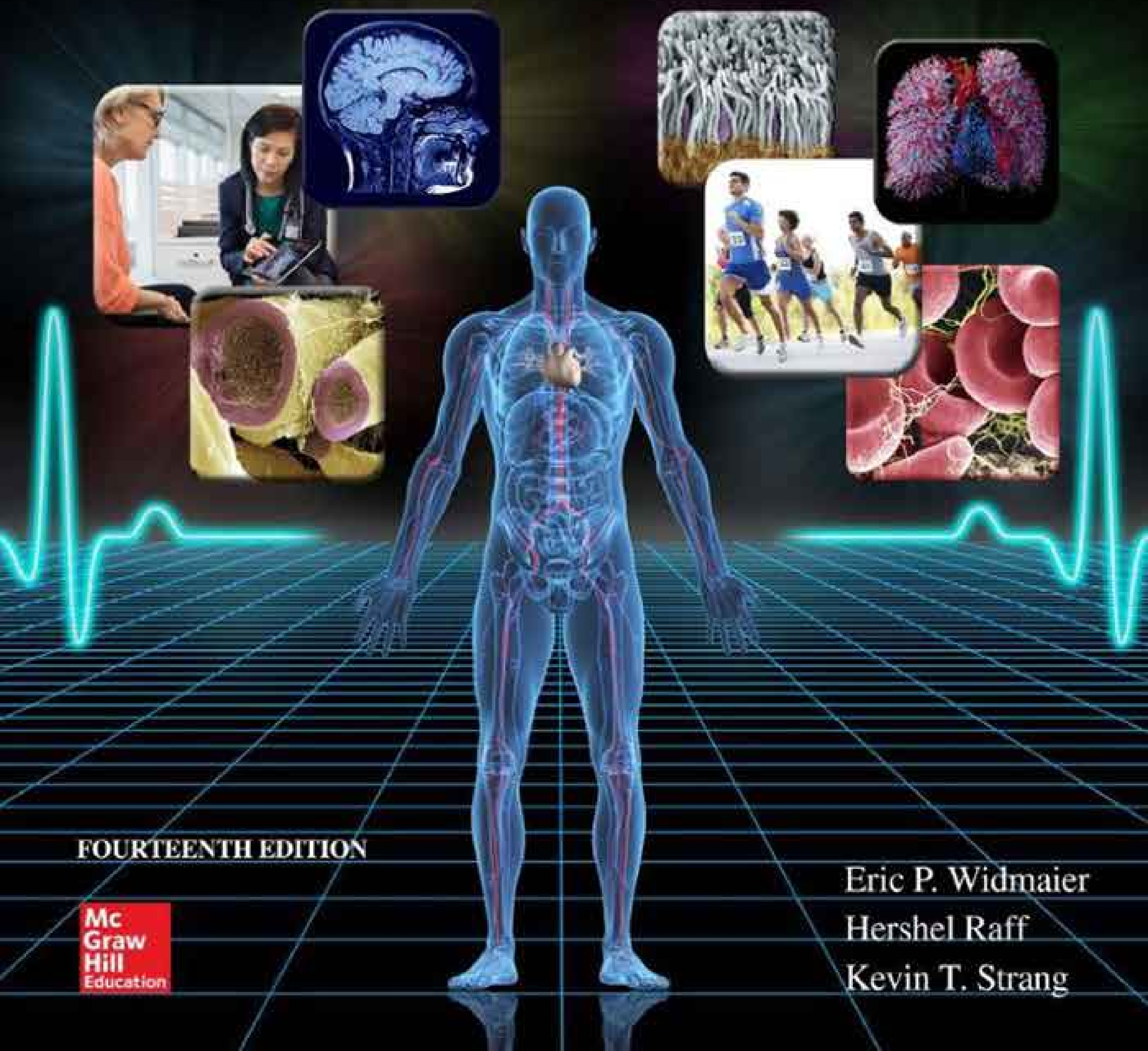
Vander's HUMAN PHYSIOLOGY

THE MECHANISMS OF BODY FUNCTION



FOURTEENTH EDITION

Eric P. Widmaier
Hershel Raff
Kevin T. Strang

Mc Graw Hill Education

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VANDER'S Human Physiology

The Mechanisms of Body Function

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TO OUR FAMILIES: MARIA, CAROLINE, AND RICHARD; JUDY AND JONATHAN; SHERYL, JAKE, AND AMY

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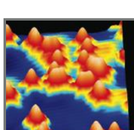

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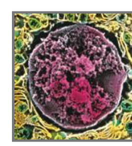

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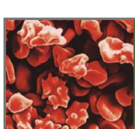

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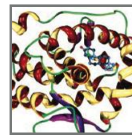

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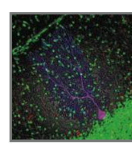

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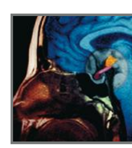

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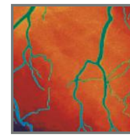

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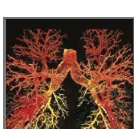

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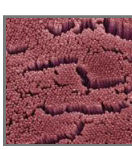

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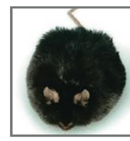

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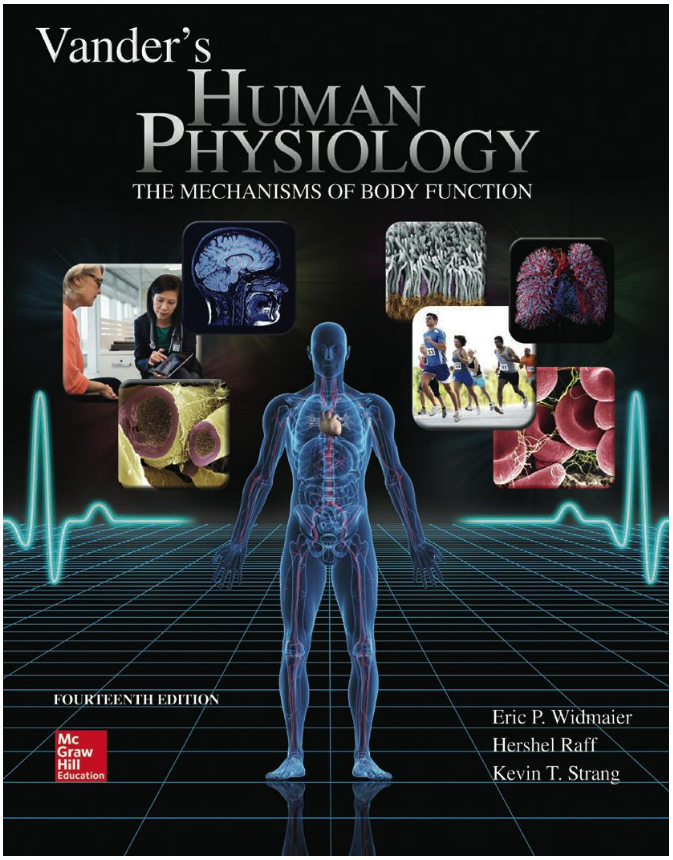
From the Authors

Lifeline to success in physiology



We are delighted to present a series of pedagogical features to help deliver clinical application, current cases, and educational technologies. With *Vander's Human Physiology,* all the pieces flow together creating your *lifeline to success in physiology.*

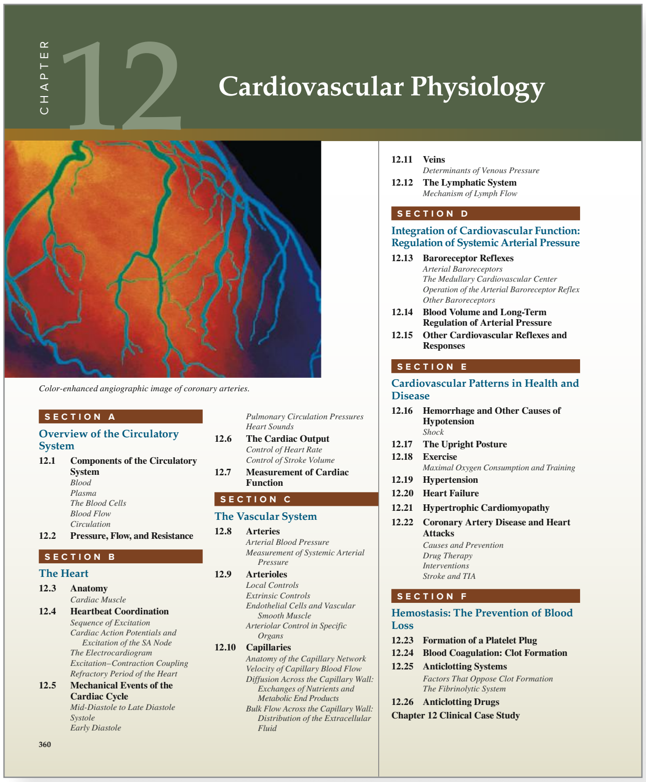
The cover of this edition reflects that lifeline—the ECG. It also represents major themes of the textbook: homeostasis, integration of cellular and molecular function with organ systems, pathophysiology, and exercise.

These themes and others are introduced in Chapter 1 as "General Principles of Physiology." These principles have been integrated throughout the remaining chapters in order to continually reinforce their importance. Each chapter opens with a preview of those principles that are particularly relevant for the material covered in that chapter. The principles are then reinforced when specific examples arise within a chapter.

Finally, assessments are provided at the end of each chapter to provide immediate feedback for students to gauge their understanding of the chapter material and its relationship to physiological principles. These assessments tend to require analytical and critical thinking; answers are provided in an appendix.

As textbooks become more integrated with digital content, McGraw-Hill Education has provided *Vander's Human Physiology* with cutting-edge digital content that continues to expand and develop. We are pleased to announce that Kevin Strang, one of the textbook authors, has taken on the role of Digital Author. Understanding the importance of content, we felt it critical that someone totally vested in the text also be vested in the digital components. We know you will see a vast improvement in the fourteenth edition's digital offerings.

Guided Tour Through a Chapter


CHAPTER 12

Cardiovascular Physiology

Color-enhanced angiographic image of coronary arteries.

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Chapter Outline

Every chapter starts with an introduction giving the reader a brief overview of what is to be covered in that chapter. Included in the introduction for the fourteenth edition is a feature that provides students with a preview of those General Principles of Physiology (introduced in Chapter 1) that will be covered in the chapter.

General Principles of Physiology

General Principles of Physiology have been integrated throughout each chapter in order to continually reinforce their importance. Each chapter opens with a preview of those principles that are particularly relevant for the material covered in that chapter. The principles are then reinforced when specific examples arise within a chapter, including Physiological Inquiries associated with certain figures.

> Beyond a distance of a few cell diameters, the random movement of substances from a region of higher concentration to one of lower concentration (diffusion) is too slow to meet the metabolic requirements of cells. Because of this, our large, multicellular bodies require an organ system to transport molecules and other substances rapidly over the long distances between cells, tissues, and organs. This is achieved by the **circulatory system** (also known as the **cardiovascular system**), which includes a pump (the **heart**); a set of interconnected tubes (**blood vessels** or **vascular system**); and a fluid connective tissue containing water, solutes, and cells that fills the tubes (the **blood**). Chapter 9 described the detailed mechanisms by which the cardiac and smooth muscle cells found in the heart and blood vessel walls, respectively, contract and generate force. In this chapter, you will learn how these contractions create pressures and move blood within the circulatory system.
>
> The general principles of physiology described in Chapter 1 are abundantly represented in this chapter. In Section A, you will learn about the relationships between blood pressure, blood flow, and resistance to blood flow, a classic illustration of the general principle of physiology that physiological processes are dictated by the laws of chemistry and physics. The general principle of physiology that structure is a determinant of—and has coevolved with—function is apparent throughout the chapter; as one example, you will learn how the structures of different types of blood vessels determine whether they participate in fluid exchange, regulate blood pressure, or provide a reservoir of blood (Section C). The general principle of physiology that most physiological functions are controlled by multiple regulatory systems, often working in opposition, is exemplified by the hormonal and neural regulation of blood vessel diameter and blood volume (Sections C and D), as well as by the opposing mechanisms that create and dissolve blood clots (Section F). Sections D and E explain how regulation of arterial blood pressure exemplifies that homeostasis is essential for health and survival, yet another general principle of physiology. Finally, multiple examples demonstrate the general principle of physiology that the functions of organ systems are coordinated with each other; for example, the circulatory and urinary systems work together to control blood pressure, blood volume, and sodium balance. ■

Clinical Case Studies

The authors have drawn from their teaching and research experiences and the clinical experiences of colleagues to provide students with real-life applications through clinical case studies in each chapter. They have been redesigned to incorporate the format of Chapter 19. You will now find "Reflect and Review" in every case study.

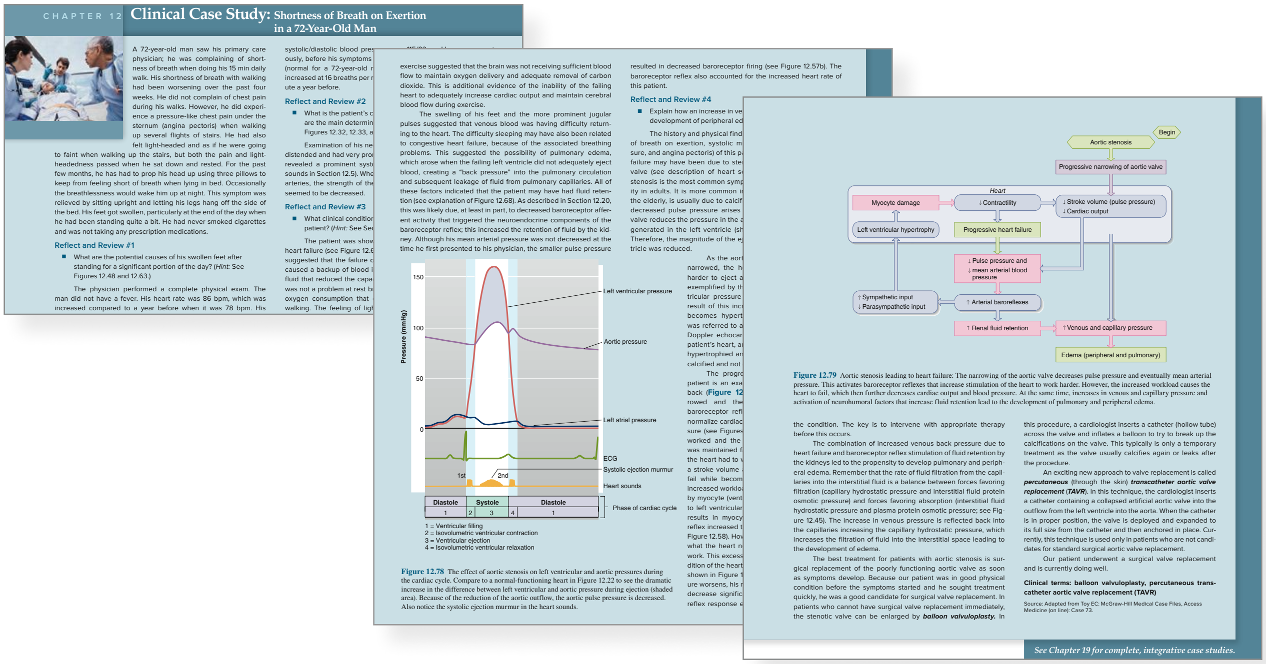

CHAPTER 12 Clinical Case Study: Shortness of Breath on Exertion in a 72-Year-Old Man

Figure 12.78 The effect of aortic stenosis on left ventricular and aortic pressures during the cardiac cycle. Compare to a normal-functioning heart in Figure 12.22 to see the dramatic increase in the difference between left ventricular and aortic pressure during ejection (shaded area). Because of the reduction of the aortic outflow, the aortic pulse pressure is decreased. Also notice the systolic ejection murmur in the heart sounds.

Figure 12.79 Aortic stenosis leading to heart failure: The narrowing of the aortic valve decreases pulse pressure and eventually mean arterial pressure. This activates baroreceptor reflexes that increase stimulation of the heart to work harder. However, the increased workload causes the heart to fail, which then further decreases cardiac output and blood pressure. At the same time, increases in venous and capillary pressure and activation of neurohormonal factors that increase fluid retention lead to the development of pulmonary and peripheral edema.

See Chapter 19 for complete, integrative case studies.

TABLE 12.3	The Circulatory System
Component	**Function**
Heart	
Atria	Chambers through which blood flows from veins to ventricles. Atrial contraction adds to ventricular filling but is not essential for it.
Ventricles	Chambers whose contractions produce the pressures that drive blood through the pulmonary and systemic vascular systems and back to the heart.
Vascular system	
Arteries	Low-resistance tubes conducting blood to the various organs with little loss in pressure. They also act as pressure reservoirs for maintaining blood flow during ventricular relaxation.
Arterioles	Major sites of resistance to flow; responsible for regulating the pattern of blood-flow distribution to the various organs; participate in the regulation of arterial blood pressure.
Capillaries	Major sites of nutrient, gas, metabolic end product, and fluid exchange between blood and tissues.
Venules	Sites of nutrient, metabolic end product, and fluid exchange between blood and tissues.
Veins	Low-resistance conduits for blood flow back to the heart. Their capacity for blood is adjusted to facilitate this flow.
Blood	
Plasma	Liquid portion of blood that contains dissolved nutrients, ions, wastes, gases, and other substances. Its composition equilibrates with that of the interstitial fluid at the capillaries.
Cells	Includes erythrocytes that function mainly in gas transport, leukocytes that function in immune defenses, and platelets (cell fragments) for blood clotting.

Summary Tables

Summary tables are used to bring together large amounts of information that may be scattered throughout the book or to summarize small or moderate amounts of information. The tables complement the accompanying figures to provide a rapid means of reviewing the most important material in the chapter.

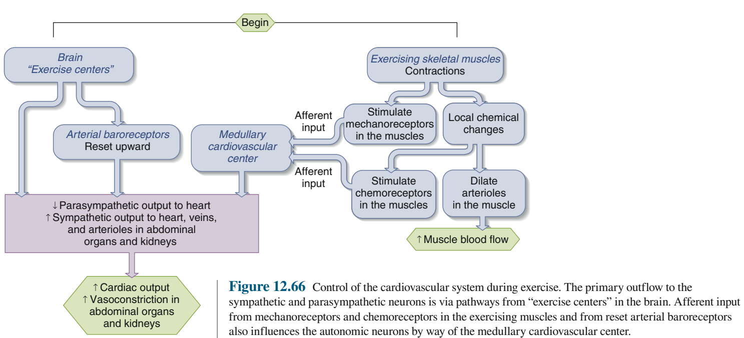


Figure 12.66 Control of the cardiovascular system during exercise. The primary outflow to the sympathetic and parasympathetic neurons is via pathways from "exercise centers" in the brain. Afferent input from mechanoreceptors and chemoreceptors in the exercising muscles and from reset arterial baroreceptors also influences the autonomic neurons by way of the medullary cardiovascular center.

PHYSIOLOGICAL INQUIRY

- How do the homeostatic responses during exercise highlight the general principle of physiology described in Chapter 1 that the functions of organ systems are coordinated with each other?

Answer can be found at end of chapter.

Physiological Inquiries

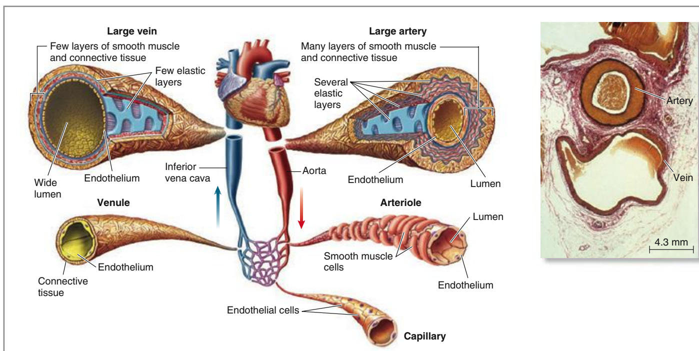
The authors have continued to refine and expand the number of critical-thinking questions based on many figures from all chapters. These concept checks were introduced in the eleventh edition and continue to prove extremely popular with users of the textbook. They are designed to help students become more engaged in learning a concept or process depicted in the art. These questions challenge a student to analyze the content of the figure and, occasionally, to recall information from previous chapters. Many of the questions also require quantitative skills. Many instructors find that these Physiological Inquiries make great exam questions. New to the fourteenth edition, numerous Physiological Inquiries are now linked with General Principles of Physiology (introduced in the thirteenth edition), providing students with two great learning tools in one!

Anatomy and Physiology REVEALED® (APR) Icon

APR icons are found in figure legends. These icons indicate that APR related content is available to reinforce and enhance learning of the material.

Descriptive Art Style

A realistic three-dimensional perspective is included in many of the figures for greater clarity and understanding of concepts presented.



APR **Figure 12.31** Comparative features of blood vessels. Sizes are not drawn to scale. *Inset:* Light micrograph (enlarged four times) of a medium-sized artery near a vein. Note the difference between the two vessels in wall thickness and lumen diameter.

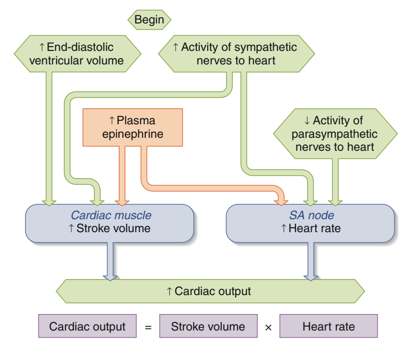


Figure 12.30 Major factors involved in increasing cardiac output. Reversal of all arrows in the boxes would illustrate how cardiac output can be decreased.

PHYSIOLOGICAL INQUIRY

- Recall from Figure 12.12 that parasympathetic nerves do not innervate the ventricles. Does this make it impossible for parasympathetic activity to influence stroke volume?

Answer can be found at end of chapter.

Flow Diagrams

Long a hallmark of this book, extensive use of flow diagrams is continued in this edition. They have been updated to assist in learning.

Key to Flow Diagrams

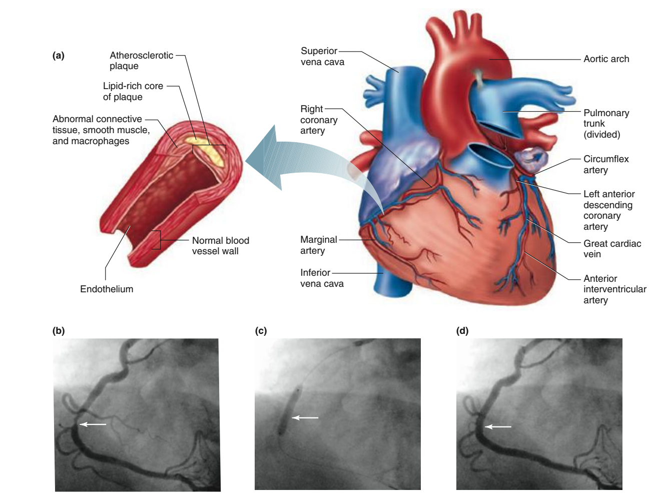
- The beginning boxes of the diagrams are color-coded green.
- Other boxes are consistently color-coded throughout the book.
- Structures are always shown in three-dimensional form.

Uniform Color-Coded Illustrations

Color-coding is effectively used to promote learning. For example, there are specific colors for extracellular fluid, the intracellular fluid, muscle filaments, and transporter molecules.

Multilevel Perspective

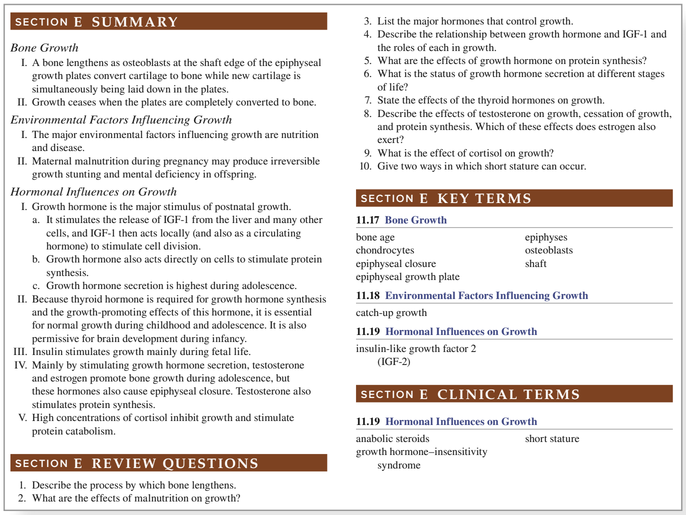
Illustrations depicting complex structures or processes combine macroscopic and microscopic views to help students see the relationships between increasingly detailed drawings.



AP|R **Figure 12.69** Coronary artery disease and its treatment. (a) Anterior view of the heart showing the major coronary vessels. Inset demonstrates narrowing due to atherosclerotic plaque. (b) Dye-contrast x-ray angiography performed by injecting radiopaque dye shows a significant occlusion of the right coronary artery (arrow). (c) A guide wire is used to position and inflate a dye-filled balloon in the narrow region, and a wire-mesh stent is inserted. (d) Blood flows freely through the formerly narrowed region after the procedure. Photos (b), (c), and (d) courtesy of Matthew R. Wolff, M.D.

End of Section

At the end of sections throughout the book, you will find a summary, review questions, key terms, and clinical terms.



SECTION E SUMMARY

Bone Growth

I. A bone lengthens as osteoblasts at the shaft edge of the epiphyseal growth plates convert cartilage to bone while new cartilage is simultaneously being laid down in the plates.
II. Growth ceases when the plates are completely converted to bone.

Environmental Factors Influencing Growth

I. The major environmental factors influencing growth are nutrition and disease.
II. Maternal malnutrition during pregnancy may produce irreversible growth stunting and mental deficiency in offspring.

Hormonal Influences on Growth

I. Growth hormone is the major stimulus of postnatal growth.
   a. It stimulates the release of IGF-1 from the liver and many other cells, and IGF-1 then acts locally (and also as a circulating hormone) to stimulate cell division.
   b. Growth hormone also acts directly on cells to stimulate protein synthesis.
   c. Growth hormone secretion is highest during adolescence.
II. Because thyroid hormone is required for growth hormone synthesis and the growth-promoting effects of this hormone, it is essential for normal growth during childhood and adolescence. It is also permissive for brain development during infancy.
III. Insulin stimulates growth mainly during fetal life.
IV. Mainly by stimulating growth hormone secretion, testosterone and estrogen promote bone growth during adolescence, but these hormones also cause epiphyseal closure. Testosterone also stimulates protein synthesis.
V. High concentrations of cortisol inhibit growth and stimulate protein catabolism.

SECTION E REVIEW QUESTIONS

1. Describe the process by which bone lengthens.
2. What are the effects of malnutrition on growth?
3. List the major hormones that control growth.
4. Describe the relationship between growth hormone and IGF-1 and the roles of each in growth.
5. What are the effects of growth hormone on protein synthesis?
6. What is the status of growth hormone secretion at different stages of life?
7. State the effects of the thyroid hormones on growth.
8. Describe the effects of testosterone on growth, cessation of growth, and protein synthesis. Which of these effects does estrogen also exert?
9. What is the effect of cortisol on growth?
10. Give two ways in which short stature can occur.

SECTION E KEY TERMS

11.17 Bone Growth

bone age
chondrocytes
epiphyseal closure
epiphyseal growth plate
epiphyses
osteoblasts
shaft

11.18 Environmental Factors Influencing Growth

catch-up growth

11.19 Hormonal Influences on Growth

insulin-like growth factor 2 (IGF-2)

SECTION E CLINICAL TERMS

11.19 Hormonal Influences on Growth

anabolic steroids
growth hormone–insensitivity syndrome
short stature

End of Chapter

At the end of the chapters, you will find

- Recall and Comprehend Questions that are designed to test student comprehension of key concepts.
- Apply, Analyze, and Evaluate Questions that challenge the student to go beyond the memorization of facts to solve problems and to encourage thinking about the meaning or broader significance of what has just been read.
- General Principles Assessment questions that test the student's ability to relate the material covered in a given chapter to one or more of the General Principles of Physiology described in Chapter 1. This provides a powerful unifying theme to understanding all of physiology and is also an excellent gauge of a student's progress from the beginning to the end of a semester.
- Answers to the Physiological Inquiries in that chapter.

CHAPTER 12 TEST QUESTIONS *Recall and Comprehend* — *Answers appear in Appendix A.*

These questions test your recall of important details covered in this chapter. They also help prepare you for the type of questions encountered in standardized exams. Many additional questions of this type are available on Connect and LearnSmart.

1. Hematocrit is increased
   a. when a person has a vitamin B_{12} deficiency.
   b. by an increase in secretion of erythropoietin.
   c. when the number of white blood cells is increased.
   d. by a hemorrhage.
   e. in response to excess oxygen delivery to the kidneys.
2. The principal site of erythrocyte production is
   a. the liver.
   b. the kidneys.
   c. the bone marrow.
   d. the spleen.
   e. the lymph nodes.
3. Which of the following contains blood with the lowest oxygen content?
   a. aorta
   b. left atrium
   c. right ventricle
   d. pulmonary veins
   e. systemic arterioles
4. If other factors are equal, which of the following vessels would have the lowest resistance?
   a. length = 1 cm, radius = 1 cm
   b. length = 4 cm, radius = 1 cm
   c. length = 8 cm, radius = 1 cm
   d. length = 1 cm, radius = 2 cm
   e. length = 0.5 cm, radius = 2 cm
5. Which of the following correctly ranks pressures during isovolumetric contraction of a normal cardiac cycle?
   a. left ventricular > aortic > left atrial
   b. aortic > left atrial > left ventricular
   c. left atrial > aortic > left ventricular
   d. aortic > left ventricular > left atrial
   e. left ventricular > left atrial > aortic
6. Considered as a whole, the body's capillaries have
   a. smaller cross-sectional area than the arteries.
   b. less total blood flow than in the veins.
   c. greater total resistance than the arterioles.
   d. slower blood velocity than in the arteries.
   e. greater total blood flow than in the arteries.

9. What is mainly responsible for the delay between the atrial and ventricular contractions?
   a. the shallow slope of AV node pacemaker potentials
   b. slow action potential conduction velocity of AV node cells
   c. slow action potential conduction velocity along atrial muscle cell membranes
   d. slow action potential conduction in the Purkinje network of the ventricles
   e. greater parasympathetic nerve firing to the ventricles than to the atria
10. Which of the following pressures is closest to the mean arterial blood pressure in a person whose systolic blood pressure is 135 mmHg and pulse pressure is 50 mmHg?
   a. 110 mmHg
   b. 78 mmHg
   c. 102 mmHg
   d. 152 mmHg
   e. 85 mmHg
11. Which of the following would help restore homeostasis in the first few moments after a person's mean arterial pressure became elevated?
   a. a decrease in baroreceptor action potential frequency
   b. a decrease in action potential frequency along parasympathetic neurons to the heart
   c. an increase in action potential frequency along sympathetic neurons to the heart
   d. a decrease in action potential frequency along sympathetic neurons to arterioles
   e. an increase in total peripheral resistance
12. Which is *false* about L-type Ca^{2+} channels in cardiac ventricular muscle cells?
   a. They are open during the plateau of the action potential.
   b. They allow Ca^{2+} entry that triggers sarcoplasmic reticulum Ca^{2+} release.
   c. They are found in the T-tubule membrane.
   d. They open in response to depolarization of the membrane.
   e. They contribute to the pacemaker potential.
13. Which correctly pairs an ECG phase with the cardiac event responsible?
   a. P wave: depolarization of the ventricles
   b. P wave: depolarization of the AV node
   c. QRS wave: depolarization of the ventricles
   d. QRS wave: repolarization of the ventricles
   e. T wave: repolarization of the atria

CHAPTER 12 TEST QUESTIONS *Apply, Analyze, and Evaluate* — *Answers appear in Appendix A.*

These questions, which are designed to be challenging, require you to integrate concepts covered in the chapter to draw your own conclusions. See if you can first answer the questions without using the hints that are provided; then, if you are having difficulty, refer back to the figures or sections indicated in the hints.

1. A person is found to have a hematocrit of 35%. Can you conclude that there is a decreased volume of erythrocytes in the blood? Explain. *Hint:* See Figure 12.1 and remember the formula for hematocrit.
2. Which would cause a greater increase in resistance to flow, a doubling of blood viscosity or a halving of tube radius? *Hint:* See equation 12-2 in Section 12.2.

CHAPTER 12 TEST QUESTIONS *General Principles Assessment* — *Answers appear in Appendix A.*

These questions reinforce the key theme first introduced in Chapter 1, that general principles of physiology can be applied across all levels of organization and across all organ systems.

1. A general principle of physiology states that *information flow between cells, tissues, and organs is an essential feature of homeostasis and allows for integration of physiological processes.* How is this principle demonstrated by the relationship between the circulatory and endocrine systems?
2. The left AV valve has only two large leaflets, while the right AV valve has three smaller leaflets. It is a general principle of physiology that *structure is a determinant of—and has coevolved with—function.* Although it is unknown why the two valves differ in structure in this way, what difference in the functional demands of the left side of the heart might explain why there is one less valve leaflet than on the right side?
3. Two of the body's important fluid compartments are those of the interstitial fluid and plasma. How does the liver's production of plasma proteins interact with those compartments to illustrate the general principle of physiology, *Controlled exchange of materials occurs between compartments and across cellular membranes?*

CHAPTER 12 ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS

Figure 12.1 The hematocrit would be 33% because the red blood cell volume is the difference between total blood volume and plasma volume (4.5 − 3.0 = 1.5 L), and hematocrit is determined by the fraction of whole blood that is red blood cells (1.5 L/4.5 L = 0.33, or 33%).

Figure 12.6 The major change in blood flow would be an increase to certain abdominal organs, notably the stomach and small intestines. This change would provide the additional oxygen and nutrients required to meet the increased metabolic demands of digestion and absorption of the breakdown products of food. Blood flow to the brain and other organs would not be expected to change significantly, but there might be a small increase in blood flow to the skeletal muscles associated with chewing and swallowing. Consequently, the total blood flow in a resting person during and following a meal would be expected to increase.

Figure 12.8 No. The flow on side *B* would be doubled, but still less than that on side *A*. The summed wall area would be the same in both sides. The formula for circumference of a circle is $2\pi r$; so the wall circumference in side *A* would be $2 \times 3.14 \times 2 = 12.56$; for the two tubes on side *B*, it would be $(2 \times 3.14 \times 1) + (2 \times 3.14 \times 1) = 12.56$. However, the total cross section through which flow occurs would be larger in side *A* than in side *B*. The formula for cross-sectional area of a circle is πr^2, so the area of side *A* would be $3.14 \times 2^2 = 12.56$, whereas the summed area of the tubes in side *B* would be $(3.14 \times 1^2) + (3.14 \times 1^2) = 6.28$. Thus, even with two outflow tubes on side *B*, there would be more flow through side *A*

Figure 12.11 A: If this diagram included a systemic portal vessel, the order of structures in the lower box would be: aorta → arteries → arterioles →

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Anatomy & Physiology REVEALED (aprevealed.com): A fascinating view inside real human bodies that also incorporates animations to help you understand cardiovascular physiology.

Updates and Additions

In addition to updating material throughout the text to reflect cutting-edge changes in physiology and medicine, the authors have introduced the following:

- **The test questions at the end of each chapter include dozens of new, revised, or updated questions. In addition, they are now organized according to Bloom's taxonomy and reflect a range of cognitive skills from recall to synthesis. Those questions at the highest Bloom level have hints provided to guide the student back to a relevant figure, table, or section in the text or to prompt their thinking along specific lines.**
- **The chapters have been carefully examined for opportunities to break up challenging text into smaller, more manageable portions. To that end, the authors have introduced nearly 100 new subheadings throughout the chapters where they can best help students instantly recognize the key topics covered in a given section of text.**
- **The Clinical Case Studies at the end of each chapter have been expanded to follow the format of Chapter 19. Each Clinical Case Study now has several "Reflect and Review" questions interspersed within the case. These are opportunities for students to connect aspects of the physiology in each case with material they learned earlier in that chapter or even in earlier chapters. It is a great way to make connections and to learn to appreciate the integrative nature of physiology. These additions will help reinforce the importance of knowledge of physiological principles to pathophysiology.**
- **All of the Clinical Case Studies now include flow charts, clinical photos, or other artwork to help the students navigate through these sophisticated, real-life medical cases.**
- **As part of our ongoing effort to present physiology to beginning students in as clear and complete a manner possible, we have added dozens of new or revised pieces of art to the text to maximize the instructional value of the illustrations and to provide updated information that reflects the exciting discoveries in physiology that continually demonstrate the dynamic nature of this field of science.**
- **Finally, the popularity of a new feature introduced in the thirteenth edition called "General Principles of Physiology" prompted us to reference these principles more frequently where relevant in each chapter. These principles have also been incorporated into 32 new Physiological Inquiries associated with figures throughout the text. This combines two valuable instructional features of the text that foster an integrated approach to learning physiology. We are gratified to hear from instructors and users of the book that this conceptual approach to mastering physiology has proven to be of such benefit.**
- **We are very pleased to have been able to incorporate real student data points and input, derived from thousands of our LearnSmart users, to help guide our revision. LearnSmart Heat Maps provided a quick visual snapshot of usage of portions of the text and the relative difficulty students experienced in mastering the content. With these data, we were able to hone not only our text content but also the LearnSmart probes.**

Chapter 1 A new flow chart that describes the sequence of events occurring in the chapter-ending case study has been added. Two additional figures have been revised and updated, and five new test questions have been added to the end of the chapter.

Chapter 2 A new image of a blood smear that includes sickled erythrocytes has been added. Three additional figures and tables have been updated and revised. Four new test questions have been added.

Chapter 3 New material on motile and nonmotile cilia and ciliopathies has been added. A new figure on ATP synthesis has been added. A new flow chart illustrating the effect of furanocuramin ingestion on the intestinal absorption of medicines has been added to the case study at the end of the chapter. Five additional figures have been updated or modified for improved visual clarity.

Chapter 4 A new figure depicting the difference between transcellular and paracellular water and solute movement has been added, and a new micrograph comparing normal and swollen erythrocytes has been added to the case study at the end of the chapter. Three additional figures have been updated or revised.

Chapter 5 A new figure depicting the general domain structure of intracellular receptors has been added. A new table has been added to the case study to illustrate the mechanisms of target cell insensitivity to ligands. Two additional figures have been updated or revised. The text has been reorganized in places for improved clarity.

Chapter 6 New figures of an image of a brain from a patient with multiple sclerosis, an illustration of an electrical synapse, and a micrograph of a cross section of a nerve have been added. Sixteen additional figures have been revised or updated. Numerous subheadings have been added to the text to break complex topics into more manageable segments. The description of brain anatomy has been reorganized to match adult structures with structures during development. The description of resting membrane potential has been revised for clarity.

Chapter 7 Numerous subheadings have been added to the text to break up complex topics into more manageable segments. The major pathologies of the eye are now discussed together in a new subsection. A new figure showing the Epley maneuver has been added to the case study, and eight additional figures have been updated or revised.

Chapter 8 Two figures have been updated or revised, and the text has been carefully edited for updated information.

Chapter 9 In addition to five revised figures, a new flow chart figure has been added to the case study at the end of the chapter to illustrate the events of malignant hyperthermia. Numerous subheadings have been added to the text to break complex topics into more manageable segments. The description of smooth muscle anatomy has been revised for better understanding.

Chapter 10 In addition to revised figures, a new image of *C. tetani* has been added to the case study at the end of the chapter.

Chapter 11 In addition to four updated or revised figures, a new figure illustrating the pathophysiology of acromegaly has been added to the case study at the end of the chapter.

Chapter 12 The chapter has been reorganized to introduce basic information on blood earlier in the chapter. The discussion of the Purkinje fibers and their function in cardiac electrophysiology has been updated. Seven figures and two tables have been updated or revised. A completely new case study with two new figures has been added to the end of the chapter. Numerous subheadings have been added to the text to break up complex topics into more manageable segments.

Chapter 13 A new figure providing details about the muscles of respiration during inspiration and expiration has been added, and three other figures or tables have been updated or revised.

Chapter 14 In addition to six revised or updated figures, a new figure illustrated the anatomy of the human kidney has been added. New text describing the effects of vasopressin on the osmolarity of the renal medulla has been added.

Chapter 15 A new figure showing intestinal microvilli has been added, and twelve figures have been revised and improved. Numerous subheadings have been introduced to help streamline complex material.

Chapter 16 Four figures have been modified and new subheadings have been introduced.

Chapter 17 New and revised text has been added to the sections on contraception, menopause, and relaxin. A new figure illustrating the pathophysiology of prolactinoma has been added, and nine figures and tables have been modified or updated to reflect new information or to improve presentation.

Chapter 18 One new figure (micrograph of the ebola virus) has been added, and four figures have been updated or revised. Five new Physiological Inquiries have been added to select figures.

Chapter 19 The text has been carefully edited to reflect current trends in the diagnosis and treatment of the pathologies presented in each case study.

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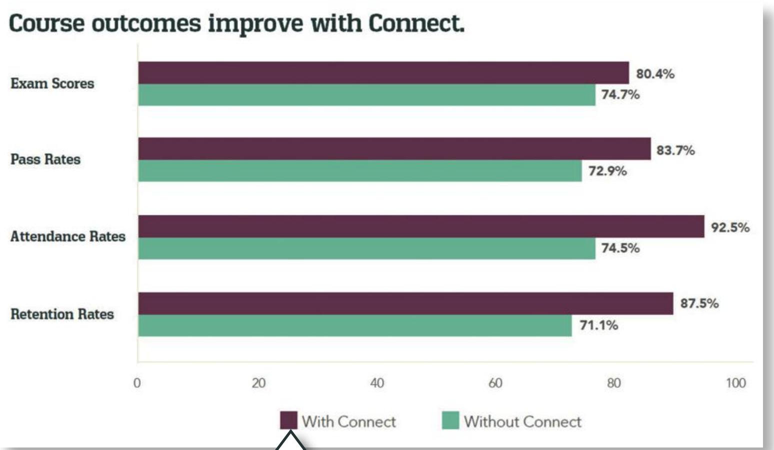

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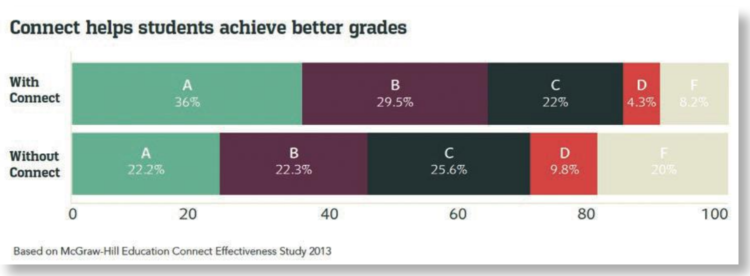

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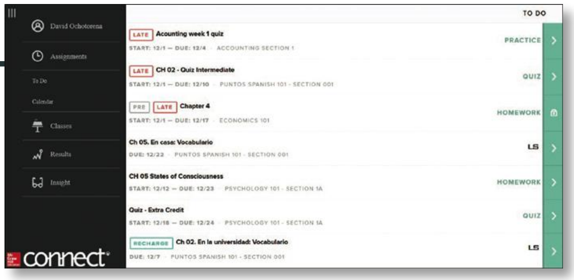

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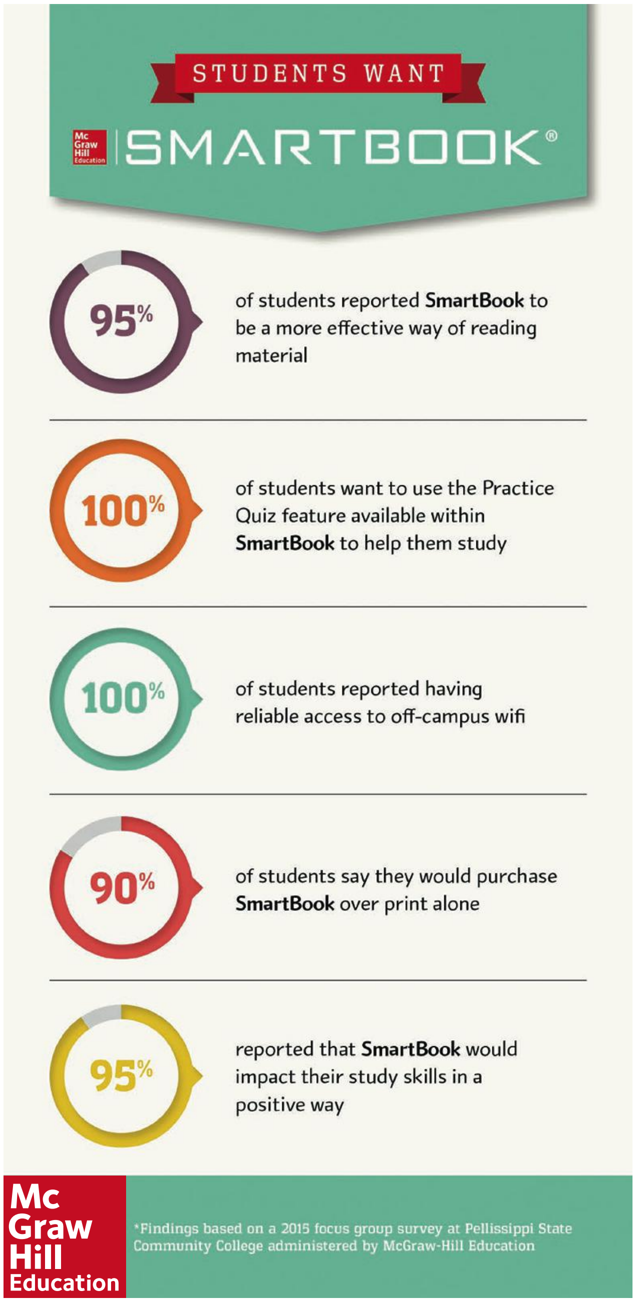

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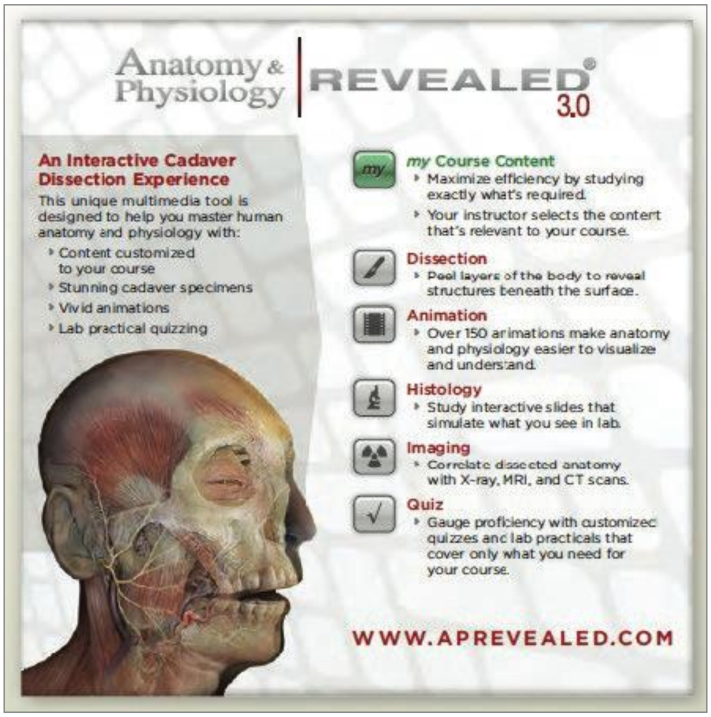

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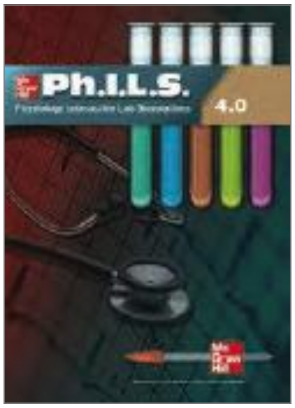

Ph.I.L.S. 4.0 has been updated! Users have requested and we are providing five new exercises (Respiratory Quotient, Weight & Contraction, Insulin and Glucose Tolerance, Blood Typing, and Anti-Diuretic Hormone). Ph.I.L.S. 4.0 is the perfect way to reinforce key physiology concepts with powerful lab experiments. Created by Dr. Phil Stephens at Villanova University, this program offers 42 laboratory simulations that may be used to supplement or substitute for wet labs. All 42 labs are self-contained experiments—no lengthy instruction manual required. Users can adjust variables, view outcomes, make predictions, draw conclusions, and print lab reports. This easy-to-use software offers the flexibility to change the parameters of the lab experiment. There is no limit!

Acknowledgments

In this fourteenth edition of *Vander's Human Physiology,* we are very excited to have been able to use real student data points derived from thousands of users to help guide our revision path. We are also deeply thankful to the following individuals for their contributions to the fourteenth edition. Any errors that may remain are solely the responsibility of the authors.

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Eric P. Widmaier
Hershel Raff
Kevin T. Strang

Homeostasis:

A Framework for Human Physiology

CHAPTER 1

1.1 The Scope of Human Physiology

1.2 How Is the Body Organized?

Muscle Cells and Tissue
Neurons and Nervous Tissue
Epithelial Cells and Epithelial Tissue
Connective-Tissue Cells and Connective Tissue
Organs and Organ Systems

1.3 Body Fluid Compartments

1.4 Homeostasis: A Defining Feature of Physiology

1.5 General Characteristics of Homeostatic Control Systems

Feedback Systems
Resetting of Set Points
Feedforward Regulation

1.6 Components of Homeostatic Control Systems

Reflexes
Local Homeostatic Responses

1.7 The Role of Intercellular Chemical Messengers in Homeostasis

1.8 Processes Related to Homeostasis

Adaptation and Acclimatization
Biological Rhythms
Balance of Chemical Substances in the Body

1.9 General Principles of Physiology

Chapter 1 Clinical Case Study

Maintenance of body temperature is an example of homeostasis.

The purpose of this chapter is to provide an orientation to the subject of human physiology and the central role of homeostasis in the study of this science. An understanding of the functions of the body also requires knowledge of the structures and relationships of the body parts. For this reason, this chapter also introduces the way the body is organized into cells, tissues, organs, organ systems, and fluid compartments. Lastly, several "General Principles of Physiology" are introduced. These serve as unifying themes throughout the textbook, and the reader is encouraged to return to them often to see how they apply to the material covered in subsequent chapters.

1.1 The Scope of Human Physiology

Physiology is the study of how living organisms function. At one end of the spectrum, it includes the study of individual molecules—for example, how a particular protein's shape and electrical properties allow it to function as a channel for ions to move into or out of a cell. At the other end, it is concerned with complex processes that depend on the integrated functions of many organs in the body—for example, how the heart, kidneys, and several glands all work together to cause the excretion of more sodium ions in the urine when a person has eaten salty food.

Physiologists are interested in function and integration—how parts of the body work together at various levels of organization and, most importantly, in the entire organism. Even when physiologists study parts of organisms, all the way down to individual molecules, the intention is ultimately to apply the information they gain to understanding the function of the whole body. As the nineteenth-century physiologist Claude Bernard put it, "After carrying out an analysis of phenomena, we must . . . always reconstruct our physiological synthesis, so as to see the *joint action* of all the parts we have isolated. . . ."

Finally, in many areas of this text, we will relate physiology to human health. Some disease states can be viewed as physiology "gone wrong," or **pathophysiology,** which makes an understanding of physiology essential for the study and practice of medicine. Indeed, many physiologists are actively engaged in research on the physiological bases of a wide range of diseases. In this text, we will give many examples of the basic physiology that underlies disease. A handy index of all the diseases and medical conditions discussed in this text, and their causes and treatments, appears in Appendix B.

We turn first to an overview of the anatomical organization of the human body, including the ways in which the cells of the body are organized into higher levels of structure. As we will see throughout the text, the structures of objects—such as the heart, lungs, or kidneys—determine in large part their functions.

1.2 How Is the Body Organized?

The simplest structural units into which a complex multicellular organism can be divided and still retain the functions characteristic of life are called **cells** (**Figure 1.1**). Each human being begins as a single cell, a fertilized egg, which divides to create two cells, each of which divides in turn to result in four cells, and so on. If cell multiplication were the only event occurring, the end result would be a spherical mass of identical cells. During development, however, each cell becomes specialized for the performance of a particular function, such as producing force and movement or generating electrical signals. The process of transforming an unspecialized cell into a specialized cell is known as **cell differentiation,** the study of which is one of the most exciting areas in biology today. About 200 distinct kinds of cells can be identified in the body in terms of differences in structure and function. When cells are classified according to the broad types of function they perform, however, four major categories emerge: (1) muscle cells, (2) neurons, (3) epithelial cells, and (4) connective-tissue cells. In each of these functional categories, several cell types perform variations of the specialized function. For example, there are three types of muscle cells—skeletal, cardiac, and smooth. These cells differ from each other in shape, in the mechanisms controlling their

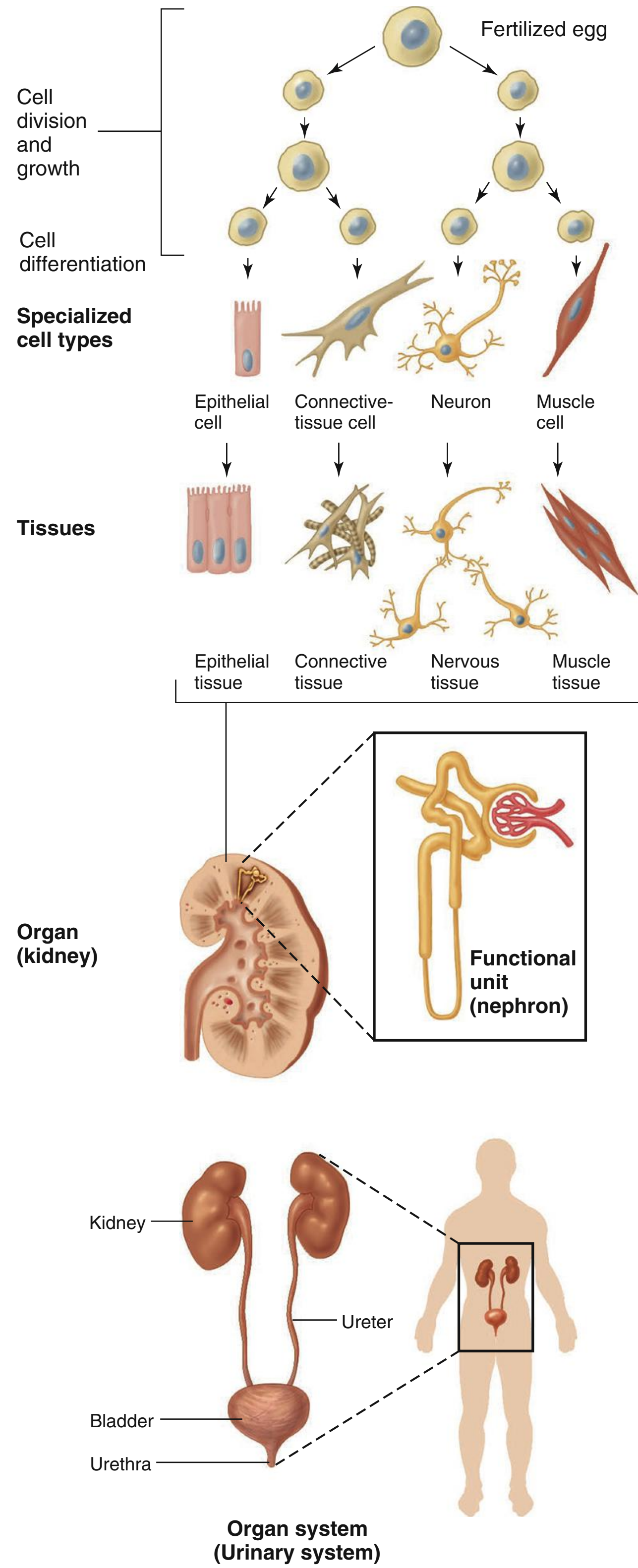

Figure 1.1 Levels of cellular organization. The nephron is not drawn to scale.

contractile activity, and in their location in the various organs of the body, but each of them is a muscle cell.

In addition to differentiating, cells migrate to new locations during development and form selective adhesions with other cells to produce multicellular structures. In this manner, the cells of the body arrange themselves in various combinations to form a hierarchy of organized structures. Differentiated cells with similar properties aggregate to form **tissues.** Corresponding to the four general categories of differentiated cells, there are four general types of tissues: (1) **muscle tissue,** (2) **nervous tissue,** (3) **epithelial tissue,** and (4) **connective tissue.** The term *tissue* is used in different ways. It is formally defined as an aggregate of a single type of specialized cell. However, it is also commonly used to denote the general cellular fabric of any organ or structure—for example, kidney tissue or lung tissue, each of which in fact usually contains all four types of tissue.

One type of tissue combines with other types of tissues to form **organs,** such as the heart, lungs, and kidneys. Organs, in turn, work together as **organ systems,** such as the urinary system (see Figure 1.1). We turn now to a brief discussion of each of the four general types of cells and tissues that make up the organs of the human body.

Muscle Cells and Tissue

As noted earlier, there are three types of muscle cells. These cells form skeletal, cardiac, or smooth muscle tissue. All **muscle cells** are specialized to generate mechanical force. Skeletal muscle cells are attached through other structures to bones and produce movements of the limbs or trunk. They are also attached to skin, such as the muscles producing facial expressions. Contraction of skeletal muscle is under voluntary control, which simply means that you can choose to contract a skeletal muscle whenever you wish. Cardiac muscle cells are found only in the heart. When cardiac muscle cells generate force, the heart contracts and consequently pumps blood into the circulation. Smooth muscle cells surround many of the tubes in the body—blood vessels, for example, or the tubes of the gastrointestinal tract—and their contraction decreases the diameter or shortens the length of these tubes. For example, contraction of smooth muscle cells along the esophagus—the tube leading from the pharynx to the stomach—helps "squeeze" swallowed food down to the stomach. Cardiac and smooth muscle tissues are said to be "involuntary" muscle, because you cannot consciously alter the activity of these types of muscle. You will learn about the structure and function of each of the three types of muscle cells in Chapter 9.

Neurons and Nervous Tissue

A **neuron** is a cell of the nervous system that is specialized to initiate, integrate, and conduct electrical signals to other cells, sometimes over long distances. A signal may initiate new electrical signals in other neurons, or it may stimulate a gland cell to secrete substances or a muscle cell to contract. Thus, neurons provide a major means of controlling the activities of other cells. The incredible complexity of connections between neurons underlies such phenomena as consciousness and perception. A collection of neurons forms nervous tissue, such as that of the brain or spinal cord. In some parts of the body, cellular extensions from many neurons are packaged together along with connective tissue (described shortly); these neuron extensions form a **nerve,** which carries the signals from many neurons between the nervous system and other parts of the body. Neurons, nervous tissue, and the nervous system will be covered in Chapter 6.

Epithelial Cells and Epithelial Tissue

Epithelial cells are specialized for the selective secretion and absorption of ions and organic molecules, and for protection. These cells are characterized and named according to their unique shapes, including cuboidal (cube-shaped), columnar (elongated), squamous (flattened), and ciliated. Epithelial tissue (known as an **epithelium**) may form from any type of epithelial cell. Epithelia may be arranged in single-cell-thick tissue, called a simple epithelium, or a thicker tissue consisting of numerous layers of cells, called a stratified epithelium. The type of epithelium that forms in a given region of the body reflects the function of that particular epithelium. For example, the epithelium that lines the inner surface of the main airway, the trachea, consists of ciliated epithelial cells (see Chapter 13). The beating of these cilia helps propel mucus up the trachea and into the mouth, which aids in preventing airborne particles and pollutants from reaching the sensitive lung tissue.

Epithelia are located at the surfaces that cover the body or individual organs, and they line the inner surfaces of the tubular and hollow structures within the body, such as the trachea just mentioned. Epithelial cells rest on an extracellular protein layer called the **basement membrane,** which (among other functions) anchors the tissue (**Figure 1.2**). The side of the cell anchored to the basement membrane is called the basolateral side; the opposite side, which typically faces the interior (called the lumen) of a structure such as the trachea or the tubules of the kidneys, is called the apical

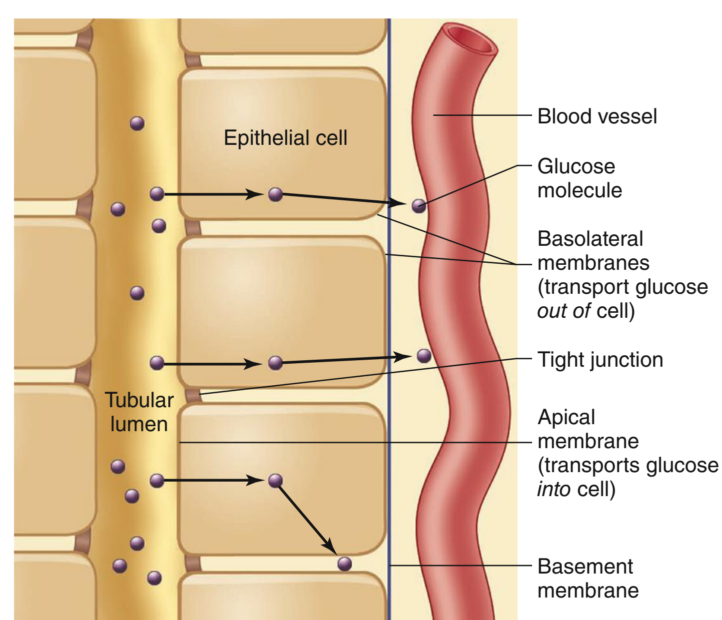

Figure 1.2 Epithelial tissue lining the inside of a structure such as a kidney tubule. The basolateral side of the cell is attached to a basement membrane. Each side of the cell can perform different functions, as in this example in which glucose is transported across the epithelium, first directed into the cell, and then directed out of the cell.

side. A defining feature of many epithelia is that the two sides of all the epithelial cells in the tissue may perform different physiological functions. In addition, the cells are held together along their lateral surfaces between the apical and basolateral membranes by extracellular barriers called tight junctions (look ahead to Figure 3.9, b and c, for a depiction of tight junctions). Tight junctions function as selective barriers regulating the exchange of molecules. For example, as shown in Figure 1.2 for the kidney tubules, the apical membranes transport useful solutes such as the sugar glucose from the tubule lumen into the epithelial cell; the basolateral sides of the cells transport glucose out of the cell and into the surrounding fluid where it can reach the bloodstream. The tight junctions prevent glucose from leaking "backward."

Connective-Tissue Cells and Connective Tissue

Connective-tissue cells, as their name implies, connect, anchor, and support the structures of the body. Some connective-tissue cells are found in the loose meshwork of cells and fibers underlying most epithelial layers; this is called loose connective tissue. Another type called dense connective tissue includes the tough, rigid tissue that makes up tendons and ligaments. Other types of connective tissue include bone, cartilage, and adipose (fat-storing) tissue. Finally, blood is a type of fluid connective tissue. This is because the cells in the blood have the same embryonic origin as other connective tissue, and because the blood connects the various organs and tissues of the body through the delivery of nutrients, removal of wastes, and transport of chemical signals from one part of the body to another.

An important function of some connective tissue is to form the **extracellular matrix** (ECM) around cells. The ECM consists of a mixture of proteins; polysaccharides (chains of sugar molecules); and, in some cases, minerals, specific for any given tissue. The ECM serves two general functions: (1) It provides a scaffold for cellular attachments; and (2) it transmits information in the form of chemical messengers to the cells to help regulate their activity, migration, growth, and differentiation.

Some of the proteins of the ECM are known as **fibers,** including ropelike **collagen fibers** and rubberband-like **elastin fibers.** Others are and a mixture of nonfibrous proteins that contain carbohydrate. In some ways, the ECM is analogous to reinforced concrete. The fibers of the matrix, particularly collagen, which constitutes as much as one-third of all bodily proteins, are like the reinforcing iron mesh or rods in the concrete. The carbohydrate-containing protein molecules are analogous to the surrounding cement. However, these latter molecules are not merely inert packing material, as in concrete, but function as adhesion or recognition molecules between cells. Thus, they are links in the communication between extracellular messenger molecules and cells.

Organs and Organ Systems

Organs are composed of two or more of the four kinds of tissues arranged in various proportions and patterns, such as sheets, tubes, layers, bundles, and strips. For example, the kidneys consist of (1) a series of small tubes, each composed of a simple epithelium; (2) blood vessels, whose walls contain varying quantities of smooth muscle and connective tissue; (3) extensions from neurons that end near the muscle and epithelial cells; and (4) a loose network of connective-tissue elements that are interspersed throughout the kidneys and include the protective capsule that surrounds the organ.

Many organs are organized into small, similar subunits often referred to as **functional units,** each performing the function of the organ. For example, the functional unit of the kidney, the nephron, contains the small tubes mentioned in the previous paragraph. The total production of urine by the kidneys is the sum of the amounts produced by the 2 million or so individual nephrons.

Finally, we have the organ system, a collection of organs that together perform an overall function (see Figure 1.1). For example, the urinary system consists of the kidneys; the urinary bladder; the ureters, the tubes leading from the kidneys to the bladder; and the urethra, the tube leading from the bladder to the exterior. **Table 1.1** lists the components and functions of the organ systems in the body. It is important to recognize, however, that organ systems do not function "in a vacuum." That is, they function together to maintain a healthy body. As just one example, blood pressure is controlled by the circulatory, urinary, nervous, and endocrine systems working together.

1.3 Body Fluid Compartments

Another useful way to think about how the body is organized is to consider body fluid compartments. When we refer to "body fluid," we are referring to a watery solution of dissolved substances such as oxygen, nutrients, and wastes. This solution is present within and around all cells of the body, and within blood vessels, and is known as the **internal environment.** Body fluids exist in two major compartments, intracellular fluid and extracellular fluid. **Intracellular fluid** is the fluid contained within all the cells of the body and accounts for about 67% of all the fluid in the body. Collectively, the fluid present in the blood and in the spaces surrounding cells is called **extracellular fluid,** that is, all the fluid that is outside of cells. Of this, only about 20%–25% is in the fluid portion of blood, which is called the **plasma,** in which the various blood cells are suspended. The remaining 75%–80% of the extracellular fluid, which lies around and between cells, is known as the **interstitial fluid.** The space containing interstitial fluid is called the **interstitium.** Therefore, the total volume of extracellular fluid is the sum of the plasma and interstitial fluid volumes. **Figure 1.3** summarizes the relative volumes of water in the different fluid compartments of the body. Water accounts for about 55%–60% of body weight in an adult.

As the blood flows through the smallest of blood vessels in all parts of the body, the plasma exchanges oxygen, nutrients, wastes, and other substances with the interstitial fluid. Because of these exchanges, concentrations of dissolved substances are virtually identical in the plasma and interstitial fluid, except for protein concentration (which, as you will learn in Chapter 12, remains higher in plasma than in interstitial fluid). With this major exception, the entire extracellular fluid may be considered to have a homogeneous solute composition. In contrast, the composition of the extracellular fluid is very different from that of the intracellular fluid. Maintaining differences in fluid composition across the cell membrane is an important way in which cells regulate their own activity. For example, intracellular fluid contains many different proteins that are important in regulating cellular events such as growth and metabolism. These proteins must be

TABLE 1.1 Organ Systems of the Body

System	Major Organs or Tissues	Primary Functions
Circulatory	Heart, blood vessels, blood	Transport of blood throughout the body
Digestive	Mouth, salivary glands, pharynx, esophagus, stomach, small and large intestines, anus, pancreas, liver, gallbladder	Digestion and absorption of nutrients and water; elimination of wastes
Endocrine	All glands or organs secreting hormones: pancreas, testes, ovaries, hypothalamus, kidneys, pituitary, thyroid, parathyroids, adrenals, stomach, small intestine, liver, adipose tissue, heart, and pineal gland; and endocrine cells in other organs	Regulation and coordination of many activities in the body, including growth, metabolism, reproduction, blood pressure, water and electrolyte balance, and others
Immune	White blood cells and their organs of production	Defense against pathogens
Integumentary	Skin	Protection against injury and dehydration; defense against pathogens; regulation of body temperature
Lymphatic	Lymph vessels, lymph nodes	Collection of extracellular fluid for return to blood; participation in immune defenses; absorption of fats from digestive system
Musculoskeletal	Cartilage, bone, ligaments, tendons, joints, skeletal muscle	Support, protection, and movement of the body; production of blood cells
Nervous	Brain, spinal cord, peripheral nerves and ganglia, sense organs	Regulation and coordination of many activities in the body; detection of and response to changes in the internal and external environments; states of consciousness; learning; memory; emotion; others
Reproductive	Male: testes, penis, and associated ducts and glands Female: ovaries, fallopian tubes, uterus, vagina, mammary glands	Male: production of sperm; transfer of sperm to female Female: production of eggs; provision of a nutritive environment for the developing embryo and fetus; nutrition of the infant
Respiratory	Nose, pharynx, larynx, trachea, bronchi, lungs	Exchange of carbon dioxide and oxygen; regulation of hydrogen ion concentration in the body fluids
Urinary	Kidneys, ureters, bladder, urethra	Regulation of plasma composition through controlled excretion of ions, water, and organic wastes

retained within the intracellular fluid and are not required in the extracellular fluid.

Compartmentalization is an important feature of physiology and is achieved by barriers between the compartments. The properties of the barriers determine which substances can move between compartments. These movements, in turn, account for the differences in composition of the different compartments. In the case of the body fluid compartments, plasma membranes that surround each cell separate the intracellular fluid from the extracellular fluid. Chapters 3 and 4 describe the properties of plasma membranes and how they account for the profound differences between intracellular and extracellular fluid. In contrast, the two components of extracellular fluid—the interstitial fluid and the plasma—are separated from each other by the walls of the blood vessels. Chapter 12 discusses how this barrier normally keeps most of the extracellular fluid in the interstitial compartment and restricts proteins mainly to the plasma.

With this understanding of the structural organization of the body, we turn to a description of how balance is maintained in the internal environment of the body.

1.4 Homeostasis: A Defining Feature of Physiology

From the earliest days of physiology—at least as early as the time of Aristotle—physicians recognized that good health was somehow associated with a balance among the multiple life-sustaining forces ("humours") in the body. It would take millennia, however, for scientists to determine what it was that was being balanced and how this balance was achieved. The advent of modern tools of science, including the ordinary microscope, led to the discovery that the human body is composed of trillions of cells, each of which can permit movement of certain substances—but not others—across the cell membrane. Over the course of the nineteenth and twentieth centuries, it became clear that most cells are in contact with the interstitial fluid. The interstitial fluid, in turn, was found to be in a state of flux, with water and solutes such as ions and gases moving back and forth through it between the cell interiors and the blood in nearby capillaries (see Figure 1.3a).

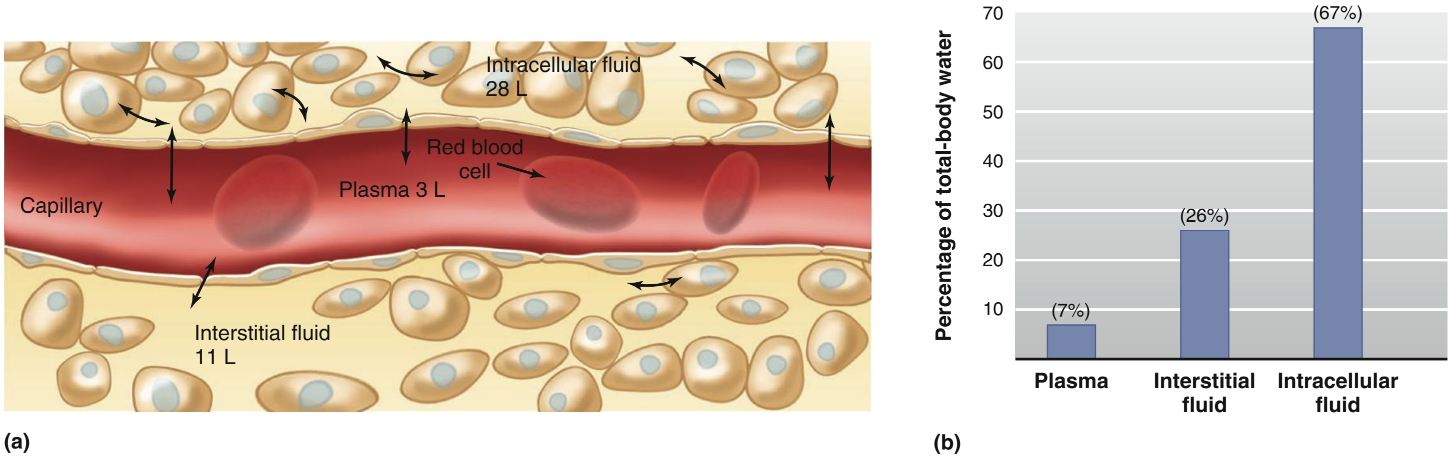

Figure 1.3 Fluid compartments of the body. Volumes are for a typical 70-kilogram (kg) (154-pound) person. (a) The bidirectional arrows indicate that fluid can move between any two adjacent compartments. Total-body water is about 42 liters (L), which makes up about 55%–60% of body weight. (b) The approximate percentage of total-body water normally found in each compartment.

PHYSIOLOGICAL INQUIRY

- What fraction of total-body water is extracellular? Assume that water constitutes 60% of a person's body weight. What fraction of a person's body weight is due to extracellular body water?

Answer can be found at end of chapter.

It was further determined by careful observation that most of the common physiological variables found in healthy organisms such as humans—blood pressure; body temperature; and blood-borne factors such as oxygen, glucose, and sodium ions, for example—are maintained within a predictable range. This is true despite external environmental conditions that may be far from constant. Thus was born the idea, first put forth by Claude Bernard, of a constant internal environment that is a prerequisite for good health, a concept later refined by the American physiologist Walter Cannon, who coined the term *homeostasis.*

Originally, **homeostasis** was defined as a state of reasonably stable balance between physiological variables such as those just described. However, this simple definition cannot give one a complete appreciation of what homeostasis entails. There probably is no such thing as a physiological variable that is constant over long periods of time. In fact, some variables undergo fairly dramatic swings around an average value during the course of a day, yet are still considered to be in balance. That is because homeostasis is a *dynamic,* not a static, process.

Consider swings in the concentration of glucose in the blood over the course of a day (**Figure 1.4**). After a typical meal, carbohydrates in food are broken down in the intestines into glucose molecules, which are then absorbed across the intestinal epithelium and released into the blood. As a consequence, the blood glucose concentration increases considerably within a short time after eating. Clearly, such a large change in the blood concentration of glucose is not consistent with the idea of a stable or static internal environment. What is important is that once the concentration of glucose in the blood increases, compensatory mechanisms restore it toward the concentration it was before the meal. These homeostatic compensatory mechanisms do not, however, overshoot to any significant degree in the opposite direction. That is, the blood glucose usually does not decrease below the premeal concentration, or does so only slightly. In the case of glucose, the endocrine system is primarily responsible for this adjustment, but a wide variety of control systems may be initiated to regulate other homeostatic processes. In later chapters, we will see how every organ of the human body contributes to homeostasis, sometimes in multiple ways, and usually in concert with each other.

Homeostasis, therefore, does not imply that a given physiological function or variable is rigidly constant with respect to time but that it fluctuates within a predictable and often narrow range. When disturbed above or below the normal range, it is restored to normal.

What do we mean when we say that something varies within a normal range? This depends on just what we are monitoring. If the oxygen and carbon dioxide levels in the arterial blood of a healthy person are measured, they barely change over the course of time, even if the person exercises. Such a system is said to be

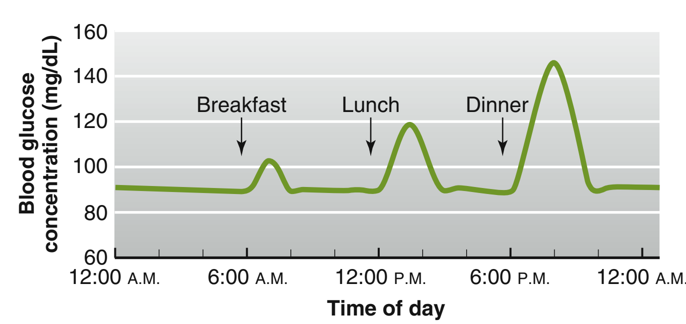

Figure 1.4 Changes in blood glucose concentration during a typical 24 h period. Note that glucose concentration increases after each meal, more so after larger meals, and then returns to the premeal concentration in a short while. The profile shown here is that of a person who is homeostatic for blood glucose, even though concentrations of this sugar vary considerably throughout the day.

tightly controlled and to demonstrate very little variability or scatter around an average value. Blood glucose concentrations, as we have seen, may vary considerably over the course of a day. Yet, if the daily average glucose concentration was determined in the same person on many consecutive days, it would be much more predictable over days or even years than random, individual measurements of glucose over the course of a single day. In other words, there may be considerable variation in glucose values over short time periods, but less when they are averaged over long periods of time. This has led to the concept that homeostasis is a state of **dynamic constancy.** In such a state, a given variable like blood glucose may vary in the short term but is stable and predictable when averaged over the long term.

It is also important to realize that a person may be homeostatic for one variable but not homeostatic for another. Homeostasis must be described differently, therefore, for each variable. For example, as long as the concentration of sodium ions in the blood remains within a few percentage points of its normal range, Na^+ homeostasis exists. However, a person whose Na^+ concentration is homeostatic may suffer from other disturbances, such as an abnormally low pH in the blood resulting from kidney disease, a condition that could be fatal. Just one nonhomeostatic variable, among the many that can be described, can have life-threatening consequences. Often, when one variable becomes significantly out of balance, other variables in the body become nonhomeostatic as a consequence. For example, when you exercise strenuously and begin to get warm, you perspire, which helps maintain body temperature homeostasis. This is important, because many cells (notably neurons) malfunction at elevated temperatures. However, the water that is lost in perspiration creates a situation in which total-body water is no longer in balance. In general, if all the major organ systems are operating in a homeostatic manner, a person is in good health. Certain kinds of disease, in fact, can be defined as the loss of homeostasis in one or more systems in the body. To elaborate on our earlier definition of *physiology,* therefore, when homeostasis is maintained, we refer to physiology; when it is not, we refer to pathophysiology (from the Greek *pathos,* meaning “suffering” or “disease”).

1.5 General Characteristics of Homeostatic Control Systems

The activities of cells, tissues, and organs must be regulated and integrated with each other so that any change in the extracellular fluid initiates a reaction to correct the change. The compensating mechanisms that mediate such responses are performed by **homeostatic control systems.**

Consider again an example of the regulation of body temperature. This time, our subject is a resting, lightly clad man in a room having a temperature of 20°C and moderate humidity. His internal body temperature is 37°C, and he is losing heat to the external environment because it is at a lower temperature. However, the chemical reactions occurring within the cells of his body are producing heat at a rate equal to the rate of heat loss. Under these conditions, the body undergoes no *net* gain or loss of heat, and the body temperature remains constant. The system is in a **steady state,** defined as a system in which a particular variable—temperature, in this case—is not changing but in which energy—in this case, heat—must be added continuously to maintain a constant condition. (Steady state differs from **equilibrium,** in which a particular variable is not changing but no input of energy is required to maintain the constancy.) The steady-state temperature in our example is known as the **set point** of the thermoregulatory system.

This example illustrates a crucial generalization about homeostasis. Stability of an internal environmental variable is achieved by the balancing of inputs and outputs. In the previous example, the variable (body temperature) remains constant because metabolic heat production (input) equals heat loss from the body (output).

Now imagine that we rapidly decrease the temperature of the room, say to 5°C, and keep it there. This immediately increases the loss of heat from our subject’s warm skin, upsetting the balance between heat gain and loss. The body temperature therefore starts to decrease. Very rapidly, however, a variety of homeostatic responses occur to limit the decrease. **Figure 1.5** summarizes these responses. *The reader is urged to study Figure 1.5 and its legend carefully because the figure is typical of those used throughout the remainder of the book to illustrate homeostatic systems, and the legend emphasizes several conventions common to such figures.*

The first homeostatic response is that blood vessels to the skin become constricted (narrowed), reducing the amount of blood flowing through the skin. This reduces heat loss from the warm blood across the skin and out to the environment and helps maintain body

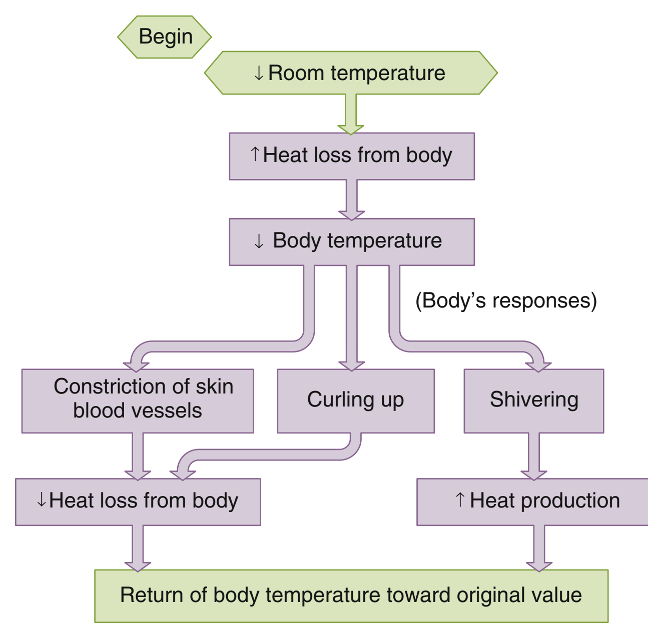

Figure 1.5 A homeostatic control system maintains body temperature when room temperature decreases. This flow diagram is typical of those used throughout this book to illustrate homeostatic systems, and several conventions should be noted. The “Begin” sign indicates where to start. The arrows next to each term within the boxes denote increases or decreases. The arrows connecting any two boxes in the figure denote cause and effect; that is, an arrow can be read as “causes” or “leads to.” (For example, decreased room temperature “leads to” increased heat loss from the body.) In general, you should add the words “tends to” in thinking about these cause-and-effect relationships. For example, decreased room temperature tends to cause an increase in heat loss from the body, and curling up tends to cause a decrease in heat loss from the body. Qualifying the relationship in this way is necessary because variables like heat production and heat loss are under the influence of many factors, some of which oppose each other.

temperature. At a room temperature of 5°C, however, blood vessel constriction cannot by itself eliminate the extra heat loss from the body. Like the person shown in the chapter-opening photo, our subject hunches his shoulders and folds his arms in order to reduce the surface area of the skin available for heat loss. This helps somewhat, but heat loss still continues, and body temperature keeps decreasing, although at a slower rate. Clearly, then, if excessive heat loss (output) cannot be prevented, the only way of restoring the balance between heat input and output is to increase input, and this is precisely what occurs. Our subject begins to shiver, and the chemical reactions responsible for the skeletal muscle contractions that constitute shivering produce large quantities of heat.

Feedback Systems

The thermoregulatory system just described is an example of a **negative feedback** system, in which an increase or decrease in the variable being regulated brings about responses that tend to move the variable in the direction opposite ("negative" to) the direction of the original change. Thus, in our example, a decrease in body temperature led to responses that tended to increase the body temperature—that is, move it toward its original value.

Without negative feedback, oscillations like some of those described in this chapter would be much greater and, therefore, the variability in a given system would increase. Negative feedback also prevents the compensatory responses to a loss of homeostasis from continuing unabated. Details of the mechanisms and characteristics of negative feedback in different systems will be addressed in later chapters. For now, it is important to recognize that negative feedback has a vital part in the checks and balances on most physiological variables.

Negative feedback may occur at the organ, cellular, or molecular level. For instance, negative feedback regulates many enzymatic processes, as shown in schematic form in **Figure 1.6**.

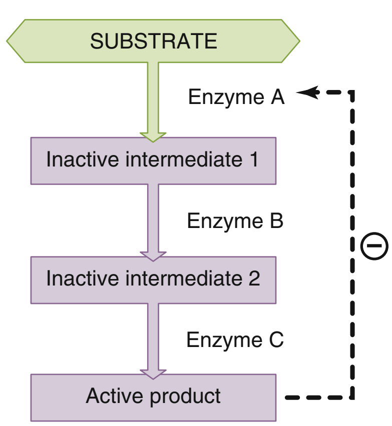

Figure 1.6 Hypothetical example of negative feedback (as denoted by the circled minus sign and dashed feedback line) occurring within a set of sequential chemical reactions. By inhibiting the activity of the first enzyme involved in the formation of a product, the product can regulate the rate of its own formation.

PHYSIOLOGICAL INQUIRY

- What would be the effect on this pathway if negative feedback was removed?

Answer can be found at end of chapter.

(An enzyme is a protein that catalyzes chemical reactions.) In this example, the product formed from a substrate by an enzyme negatively feeds back to inhibit further action of the enzyme. This may occur by several processes, such as chemical modification of the enzyme by the product of the reaction. The production of adenosine triphosphate (ATP) within cells is a good example of a chemical process regulated by feedback. Normally, glucose molecules are enzymatically broken down inside cells to release some of the chemical energy that was contained in the bonds of the molecule. This energy is then stored in the bonds of ATP. The energy from ATP can later be tapped by cells to power such functions as muscle contraction, cellular secretions, and transport of molecules across cell membranes. As ATP accumulates in the cell, however, it inhibits the activity of some of the enzymes involved in the breakdown of glucose. Therefore, as ATP concentrations increase within a cell, further production of ATP slows down due to negative feedback. Conversely, if ATP concentrations decrease within a cell, negative feedback is removed and more glucose is broken down so that more ATP can be produced.

Not all forms of feedback are negative. In some cases, **positive feedback** accelerates a process, leading to an "explosive" system. This is counter to the general physiological principle of homeostasis, because positive feedback has no obvious means of stopping. Not surprisingly, therefore, positive feedback is much less common in nature than negative feedback. Nonetheless, there are examples in physiology in which positive feedback is very important. One well-described example, which you will learn about in Chapter 17, is the process of parturition (birth). As the uterine muscles contract and a baby's head is pressed against the mother's cervix during labor, signals are relayed via nerves from the cervix to the mother's brain. The brain initiates the secretion into the blood of a molecule called oxytocin from the mother's pituitary gland. Oxytocin is a potent stimulator of further uterine contractions. As the uterus contracts even harder in response to oxytocin, the baby's head is pushed harder against the cervix, causing it to stretch more; this stimulates yet more nerve signals to the mother's brain, resulting in yet more oxytocin secretion. This self-perpetuating cycle continues until finally the baby pushes through the stretched cervix and is born.

Resetting of Set Points

As we have seen, changes in the external environment can displace a variable from its set point. In addition, the set points for many regulated variables can be physiologically reset to a new value. A common example is fever, the increase in body temperature that occurs in response to infection and that is somewhat analogous to raising the setting of a thermostat in a room. The homeostatic control systems regulating body temperature are still functioning during a fever, but they maintain the temperature at an increased value. This regulated increase in body temperature is adaptive for fighting the infection, because elevated temperature inhibits proliferation of some pathogens. In fact, this is why a fever is often preceded by chills and shivering. The set point for body temperature has been reset to a higher value, and the body responds by shivering to generate heat.

The example of fever may have left the impression that set points are reset only in response to external stimuli, such as the presence of pathogens, but this is not the case. Indeed, the set points for many regulated variables change on a rhythmic basis every day. For example, the set point for body temperature is higher during the day than at night.

Although the resetting of a set point is adaptive in some cases, in others it simply reflects the clashing demands of different regulatory systems. This brings us to one more generalization. It is not possible for everything to be held constant by homeostatic control systems. In our earlier example, body temperature was maintained despite large swings in ambient temperature, but only because the homeostatic control system brought about large changes in skin blood flow and skeletal muscle contraction. Moreover, because so many properties of the internal environment are closely interrelated, it is often possible to keep one property relatively stable only by moving others away from their usual set point. This is what we mean by "clashing demands," which explains the phenomenon mentioned earlier about the interplay between body temperature and water balance during exercise.

The generalizations we have given about homeostatic control systems are summarized in **Table 1.2**. One additional point is that, as is illustrated by the regulation of body temperature, multiple systems usually control a single parameter. The adaptive value of such redundancy is that it provides much greater fine-tuning and also permits regulation to occur even when one of the systems is not functioning properly because of disease.

Feedforward Regulation

Another type of regulatory process often used in conjunction with feedback systems is **feedforward,** in which changes in regulated variables are anticipated and prepared for before they actually occur. Control of body temperature is a good example of a feedforward process. The temperature-sensitive neurons that trigger negative feedback regulation of body temperature when it begins to decrease are located inside the body. In addition, there are temperature-sensitive neurons in the skin; these cells, in effect, monitor outside temperature. When outside temperature decreases, as in our example, these neurons immediately detect the change and relay this information to the brain. The brain then sends out signals to the blood vessels and muscles, resulting in heat conservation and increased heat production. In this manner, compensatory thermoregulatory responses are activated *before* the colder outside temperature can cause the internal body temperature to decrease. In another familiar example, the smell of food triggers nerve responses from odor receptors in the nose to the cells of the digestive system. The effect is to prepare the digestive system for the arrival of food before we even consume it, for example, by inducing saliva to be secreted in the mouth and causing the stomach to churn and produce acid. Thus, feedforward improves the speed of the body's homeostatic responses and minimizes fluctuations in the level of the variable being regulated—that is, it reduces the amount of deviation from the set point.

In our examples, feedforward regulation utilizes a set of external or internal environmental detectors. It is likely, however, that many examples of feedforward regulation are the result of a different phenomenon—learning. The first times they occur, early in life, perturbations in the external environment probably cause relatively large changes in regulated internal environmental factors, and in responding to these changes the central nervous system learns to anticipate them and resist them more effectively. A familiar form of this is the increased heart rate that occurs in an athlete just before a competition begins.

1.6 Components of Homeostatic Control Systems

Reflexes

The thermoregulatory system we used as an example in the previous section and many of the other homeostatic control systems belong to the general category of stimulus–response sequences known as *reflexes.* Although in some reflexes we are aware of the stimulus and/or the response, many reflexes regulating the internal environment occur without our conscious awareness.

In the narrowest sense of the word, a **reflex** is a specific, involuntary, unpremeditated, "built-in" response to a particular stimulus. Examples of such reflexes include pulling your hand away from a hot object or shutting your eyes as an object rapidly approaches your face. Many responses, however, appear automatic and stereotyped but are actually the result of learning and practice. For example, an experienced driver performs many complicated acts in operating a car. To the driver, these motions are, in large part, automatic, stereotyped, and unpremeditated, but they occur only because a great deal of conscious effort was spent learning them. We term such reflexes **learned** or **acquired reflexes.** In general, most reflexes, no matter how simple they may appear to be, are subject to alteration by learning.

TABLE 1.2 Some Important Generalizations About Homeostatic Control Systems
Stability of an internal environmental variable is achieved by balancing inputs and outputs. It is not the absolute magnitudes of the inputs and outputs that matter but the balance between them.
In negative feedback, a change in the variable being regulated brings about responses that tend to move the variable in the direction opposite the original change—that is, back toward the initial value (set point).
Homeostatic control systems cannot maintain complete constancy of any given feature of the internal environment. Therefore, any regulated variable will have a more or less narrow range of normal values depending on the external environmental conditions.
The set point of some variables regulated by homeostatic control systems can be reset—that is, physiologically raised or lowered.
It is not always possible for homeostatic control systems to maintain every variable within a narrow normal range in response to an environmental challenge. There is a hierarchy of importance, so that certain variables may be altered markedly to maintain others within their normal range.