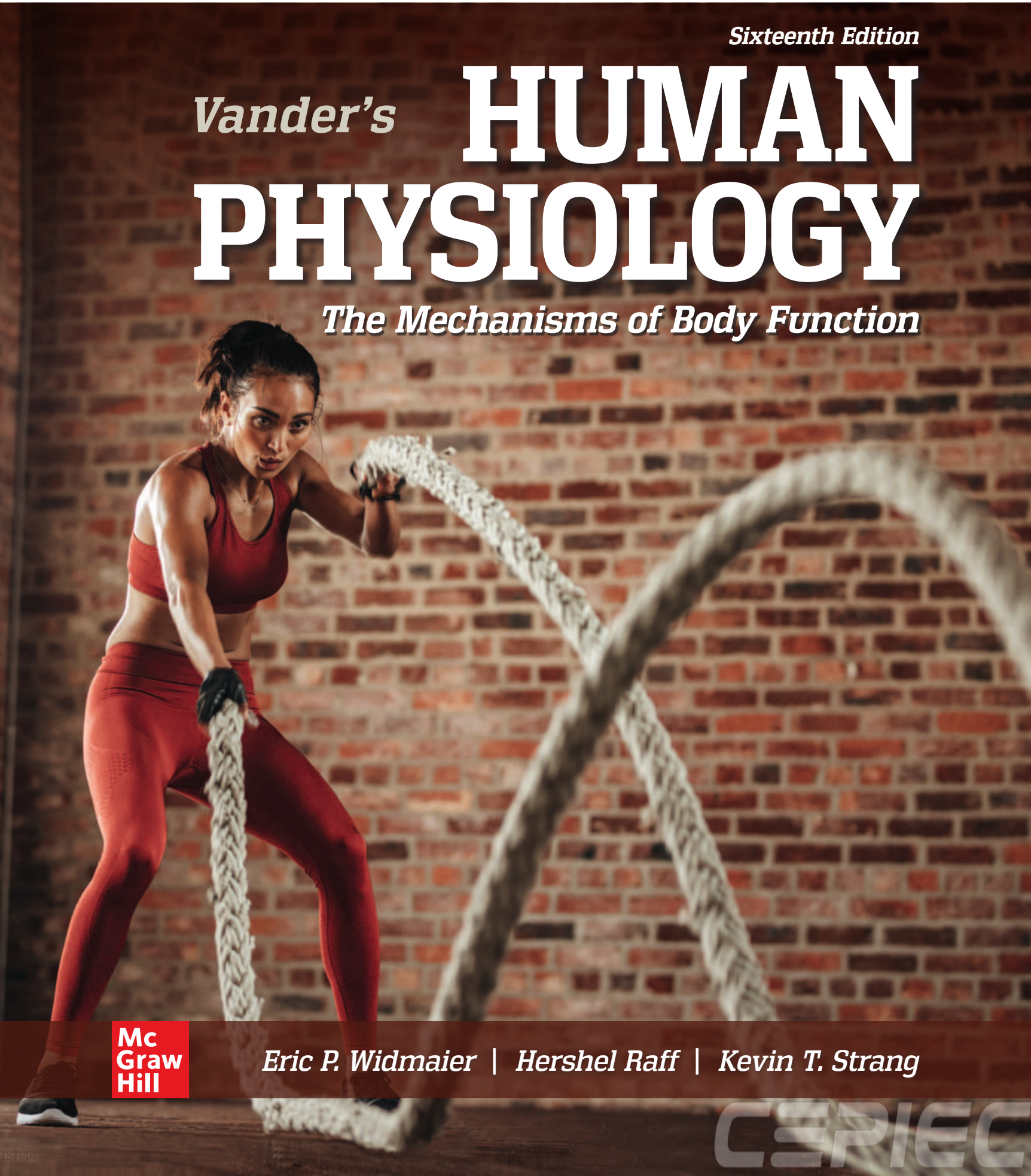
Sixteenth Edition
Vander's
HUMAN
PHYSIOLOGY
The Mechanisms of Body Function
Mc
Graw
Hill
Eric P. Widmaier | Hershel Raff | Kevin T. Strang

SIXTEENTH EDITION

VANDER'S Human Physiology

The Mechanisms of Body Function

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BOSTON UNIVERSITY

HERSHEL RAFF
MEDICAL COLLEGE OF WISCONSIN
AURORA ST. LUKE'S MEDICAL CENTER/
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UNIVERSITY OF WISCONSIN–MADISON

VANDER'S HUMAN PHYSIOLOGY

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BRIEF CONTENTS

MEET THE AUTHORS

Photo courtesy of: Maria Widmaier

ERIC P. WIDMAIER received his Ph.D. in 1984 in Endocrinology from the *University of California at San Francisco.* His postdoctoral training was in molecular endocrinology, neuroscience, and physiology at the *Worcester Foundation for Experimental Biology* in Shrewsbury, Massachusetts, and *The Salk Institute* in La Jolla, California. His research was focused on the control of body mass and metabolism in mammals, the mechanisms of hormone action, and molecular mechanisms of intestinal and hypothalamic adaptation to high-fat diets. He is currently Emeritus Professor of Biology at *Boston University,* where he has taught Human Physiology for many years, and he has been recognized with the Gitner Award for Distinguished Teaching by the College of Arts and Sciences as well as the Metcalf Prize for Excellence in Teaching by Boston University. He is the author of many scientific and lay publications, including books about physiology for the general reader. He has two grown children, Rick and Carrie; he and his wife Maria divide their time between New Hampshire and Florida.

Photo courtesy of: Tonya Limberg

HERSHEL RAFF received his Ph.D. in Environmental Physiology from the *Johns Hopkins University* in 1981 and did postdoctoral training in Endocrinology at the *University of California at San Francisco.* He is now a Professor of Medicine (Endocrinology and Molecular Medicine), Surgery, and Physiology in the School of Medicine at the *Medical College of Wisconsin*. He is Director of the Endocrine Research Laboratory at *Aurora St. Luke's Medical Center/Advocate Aurora Research Institute*. He teaches physiology and pathophysiology to medical, pharmacy, and graduate students as well as clinical fellows. At the Medical College of Wisconsin, he is the Endocrinology/Reproduction Course Director for second-year medical students. He was an inaugural inductee into the Society of Teaching Scholars, elected as a faculty member to Alpha Omega Alpha (AOA Honor Medical Society), received the Beckman Basic Science Teaching Award from the senior MD class five times, and has been one of the MCW's Outstanding Medical Student Teachers in multiple years. He is also an Adjunct Professor of Biomedical Sciences at *Marquette University.* Dr. Raff's basic research focuses on the adaptation to stress. His clinical interest focuses on pituitary and adrenal diseases, with a special focus on laboratory tests for the diagnosis of Cushing's syndrome. He resides outside Milwaukee with his wife Judy and son Jonathan.

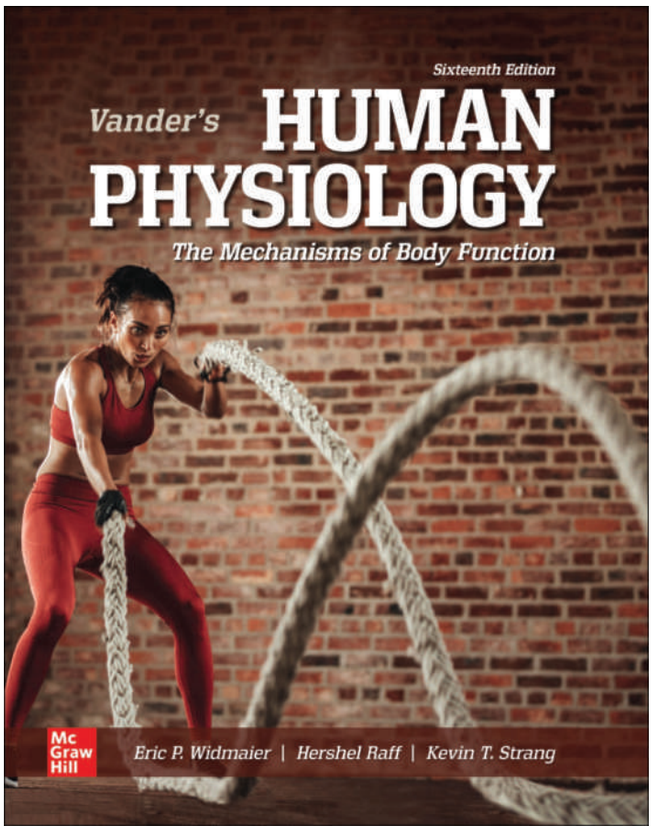
Photo courtesy of: Kevin Strang

KEVIN T. STRANG received both his Master's Degree in Zoology (1988) and his Ph.D. in Physiology (1994) from the *University of Wisconsin–Madison,* where he is now an emeritus Distinguished Faculty Associate in the Departments of Neuroscience and Kinesiology. His thesis research focused on cellular mechanisms of contractility modulation in cardiac muscle. For over 30 years he taught a large undergraduate systems physiology course as well as the first-year medical physiology course in the *UW–Madison School of Medicine and Public Health.* He was elected to UW–Madison's Teaching Academy and as a Fellow of the Wisconsin Initiative for Science Literacy. He has been a frequent guest speaker at colleges and high schools on the physiology of alcohol consumption. Twice awarded the UW Medical Alumni Association's Distinguished Teaching Award for Basic Sciences, he also received the University of Wisconsin System's Underkofler/ Alliant Energy Excellence in Teaching Award. In 2012 he was featured in *The Princeton Review* publication *The Best 300 Professors.* Interested in teaching technology, Dr. Strang has produced numerous physiology animations, some of which were adopted for use with *Vander's Human Physiology.* He has two adult children, Jake and Amy, and lives in Madison with his wife Sheryl.

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

FROM THE AUTHORS

Lifeline to success in physiology



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We are pleased to offer an integrated package of textual and digital material to deliver basic and clinical content, real-life applications, and educational technologies to students of physiology. With the sixteenth edition of *Vander's Human Physiology*, all these pieces come together to facilitate learning and enthusiasm for understanding the mechanisms of body function.

The cover of this edition reflects several areas of focus of the book, including homeostasis, exercise, and human health. These and other areas of interest are elaborated upon, beginning with Chapter 1, where the key "General Principles of Physiology," an underlying theme in the book, is first introduced. Unifying themes, such as homeostasis, are explored throughout the book at all levels of system, organ, tissue, and cellular function. As in previous editions, these themes are always related to pathophysiology through the use of compelling clinical case studies in all chapters, and a final chapter with several cases that integrate material across the entire book.

We are certain that you will find the sixteenth edition of this textbook to be the most up-to-date and comprehensive book available for students of physiology. Thank you and happy reading!

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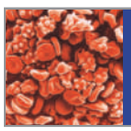

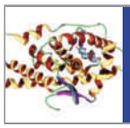

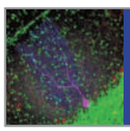

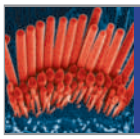

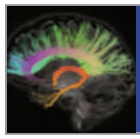

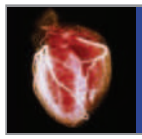

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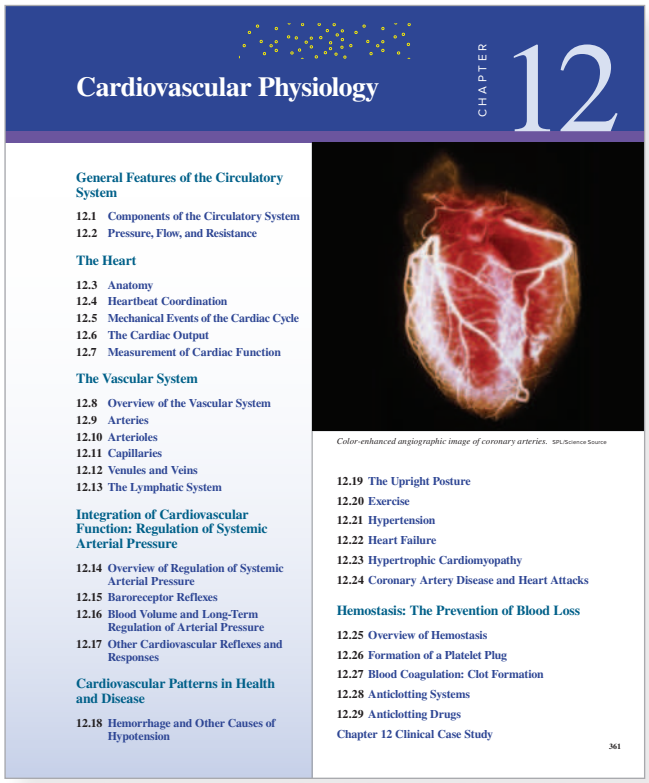
GUIDED TOUR THROUGH A CHAPTER



CHAPTER 12

Cardiovascular Physiology

General Features of the Circulatory System

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12.2 Pressure, Flow, and Resistance

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Color-enhanced angiographic image of coronary arteries. SPL/Science Source

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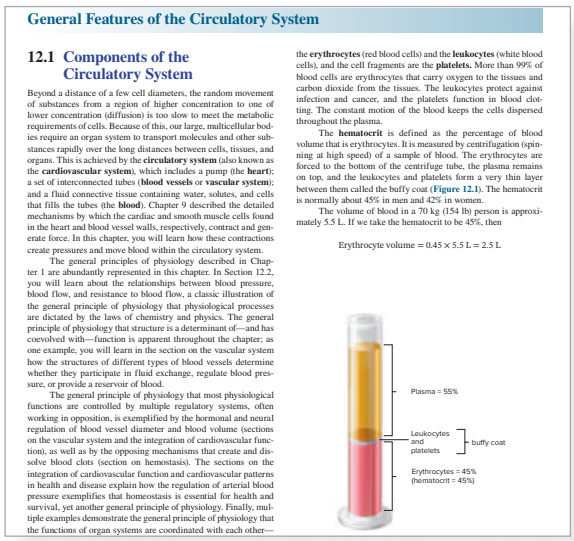
Chapter Outline

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 sixteenth 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

First introduced in the thirteenth edition to wide acclaim, 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 Dig Deeper inquiries associated with certain figures.



General Features of the Circulatory System

12.1 Components of the Circulatory System

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 12.2, 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 in the section on the vascular system 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.

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 on the vascular system and the integration of cardiovascular function), as well as by the opposing mechanisms that create and dissolve blood clots (section on hemostasis). The sections on the integration of cardiovascular function and cardiovascular patterns in health and disease explain how the 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—the **erythrocytes** (red blood cells) and the **leukocytes** (white blood cells), and the cell fragments are the **platelets.** More than 99% of blood cells are erythrocytes that carry oxygen to the tissues and carbon dioxide from the tissues. The leukocytes protect against infection and cancer, and the platelets function in blood clotting. The constant motion of the blood keeps the cells dispersed throughout the plasma.

The **hematocrit** is defined as the percentage of blood volume that is erythrocytes. It is measured by centrifugation (spinning at high speed) of a sample of blood. The erythrocytes are forced to the bottom of the centrifuge tube, the plasma remains on top, and the leukocytes and platelets form a very thin layer between them called the buffy coat (**Figure 12.1**). The hematocrit is normally about 45% in men and 42% in women.

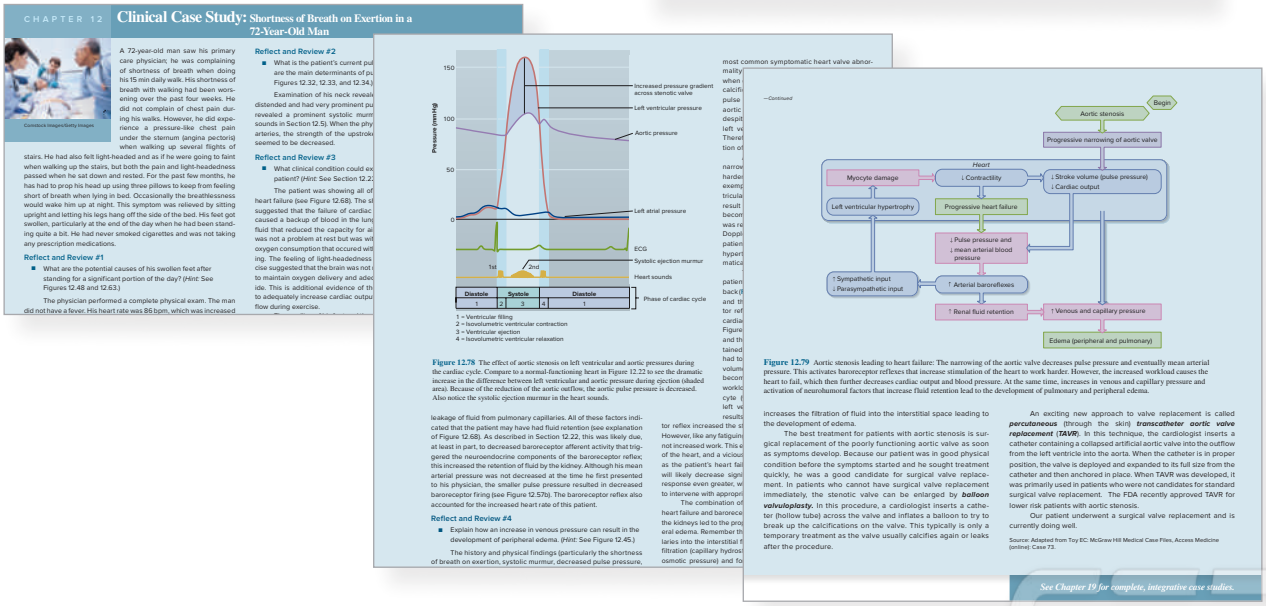
The volume of blood in a 70 kg (154 lb) person is approximately 5.5 L. If we take the hematocrit to be 45%, then

$$\text{Erythrocyte volume} = 0.45 \times 5.5\ \text{L} = 2.5\ \text{L}$$

Plasma = 55%
Leukocytes and platelets — buffy coat
Erythrocytes = 45% (hematocrit = 45%)

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" questions and at least one figure or table in every case study.



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

A 72-year-old man saw his primary care physician; he was complaining of shortness of breath when doing his 15 min daily walk. His shortness of breath with walking had been worsening over the past four weeks. He did not complain of chest pain during his walks. However, he did experience a pressure-like chest pain under the sternum (angina pectoris) when walking up several flights of stairs. He had also felt light-headed and as if he were going to faint when walking up the stairs, but both the pain and light-headedness passed when he sat down and rested. For the past few months, he has had to prop his head up using three pillows to keep from feeling short of breath when lying in bed. Occasionally the breathlessness would wake him up at night. This symptom was relieved by sitting upright and letting his legs hang off the side of the bed. His feet got swollen, particularly at the end of the day when he had been standing quite a bit. He had never smoked cigarettes and was not taking any prescription medications.

Reflect and Review #1

- What are the potential causes of his swollen feet after standing for a significant portion of the day? (*Hint:* See Figures 12.48 and 12.63.)

The physician performed a complete physical exam. The man did not have a fever. His heart rate was 86 bpm, which was increased

Reflect and Review #2

- What is the patient's current pul… are the main determinants of pu… Figures 12.32, 12.33, and 12.34.)

Examination of his neck reveal… distended and had very prominent pu… revealed a prominent systolic murm… sounds in Section 12.5). When the phy… arteries, the strength of the upstrok… seemed to be decreased.

Reflect and Review #3

- What clinical condition could ex… patient? (*Hint:* See Section 12.2…

The patient was showing all of… heart failure (see Figure 12.68). The s… suggested that the failure of cardiac… caused a backup of blood in the lun… fluid that reduced the capacity for ai… was not a problem at rest but was wi… oxygen consumption that occured wh… ing. The feeling of light-headedness… cise suggested that the brain was not … to maintain oxygen delivery and adeq… ide. This is additional evidence of th… to adequately increase cardiac output… flow during exercise.

Increased pressure gradient across stenotic valve
Left ventricular pressure
Aortic pressure
Left atrial pressure
ECG
Systolic ejection murmur
Heart sounds
Phase of cardiac cycle
Diastole | Systole | Diastole
1 = Ventricular filling
2 = Isovolumetric ventricular contraction
3 = Ventricular ejection
4 = Isovolumetric ventricular relaxation

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.

leakage of fluid from pulmonary capillaries. All of these factors indicated that the patient may have had fluid retention (see explanation of Figure 12.68). As described in Section 12.22, this was likely due, at least in part, to decreased baroreceptor afferent activity that triggered the neuroendocrine components of the baroreceptor reflex; this increased the retention of fluid by the kidney. Although his mean arterial pressure was not decreased at the time he first presented to his physician, the smaller pulse pressure resulted in decreased baroreceptor firing (see Figure 12.57b). The baroreceptor reflex also accounted for the increased heart rate of this patient.

Reflect and Review #4

- Explain how an increase in venous pressure can result in the development of peripheral edema. (*Hint:* See Figure 12.45.)

The history and physical findings (particularly the shortness of breath on exertion, systolic murmur, decreased pulse pressure,

—Continued
Begin
Aortic stenosis
Progressive narrowing of aortic valve
Heart
Myocyte damage
↓ Contractility
↓ Stroke volume (pulse pressure)
↓ Cardiac output
Left ventricular hypertrophy
Progressive heart failure
↓ Pulse pressure and ↓ mean arterial blood pressure
↑ Sympathetic input
↓ Parasympathetic input
↑ Arterial baroreflexes
↑ Renal fluid retention
↑ Venous and capillary pressure
Edema (peripheral and pulmonary)

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 neurohumoral factors that increase fluid retention lead to the development of pulmonary and peripheral edema.

increases the filtration of fluid into the interstitial space leading to the development of edema.

The best treatment for patients with aortic stenosis is surgical replacement of the poorly functioning aortic valve as soon as symptoms develop. Because our patient was in good physical condition before the symptoms started and he sought treatment quickly, he was a good candidate for surgical valve replacement. In patients who cannot have surgical valve replacement immediately, the stenotic valve can be enlarged by ***balloon valvuloplasty.*** In this procedure, a cardiologist inserts a catheter (hollow tube) across the valve and inflates a balloon to try to break up the calcifications on the valve. This typically is only a temporary treatment as the valve usually calcifies again or leaks after the procedure.

An exciting new approach to valve replacement is called ***percutaneous*** (through the skin) ***transcatheter aortic valve replacement*** (***TAVR***). In this technique, the cardiologist inserts a catheter containing a collapsed artificial aortic valve into the outflow from the left ventricle into the aorta. When the catheter is in proper position, the valve is deployed and expanded to its full size from the catheter and then anchored in place. When TAVR was developed, it was primarily used in patients who were not candidates for standard surgical valve replacement. The FDA recently approved TAVR for lower risk patients with aortic stenosis.

Our patient underwent a surgical valve replacement and is currently doing well.

Source: Adapted from Toy EC, McGraw Hill Medical Case Files, Access Medicine (online) Case 73.

See Chapter 19 for complete, integrative case studies.

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.

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	Capacitance vessels that are sites of migration of leukocytes from the blood into tissues during inflammation and infection.
Veins	Low-resistance, high-capacitance vessels carrying blood 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.

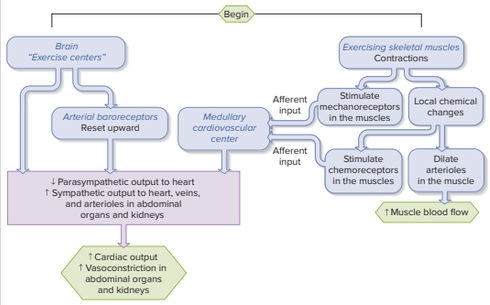


Figure 12.66 Control of the cardiovascular system during exercise. The primary outflow to the sympathetic and parasympathetic neurons is via pathways from "exercise centers" in the brain. Afferent input from mechanoreceptors and chemoreceptors in the exercising muscles and from reset arterial baroreceptors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

DIG DEEPER: General Principle of Physiology

- 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 found in Appendix A.

Dig Deeper Inquiries

The authors have continued to refine and expand the number of higher Bloom's-level critical thinking questions linked with many figures from all chapters. These concept checks were introduced in a different form 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 Dig Deeper inquiries make great exam questions. Numerous Dig Deeper inquiries are linked with General Principles of Physiology, 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.

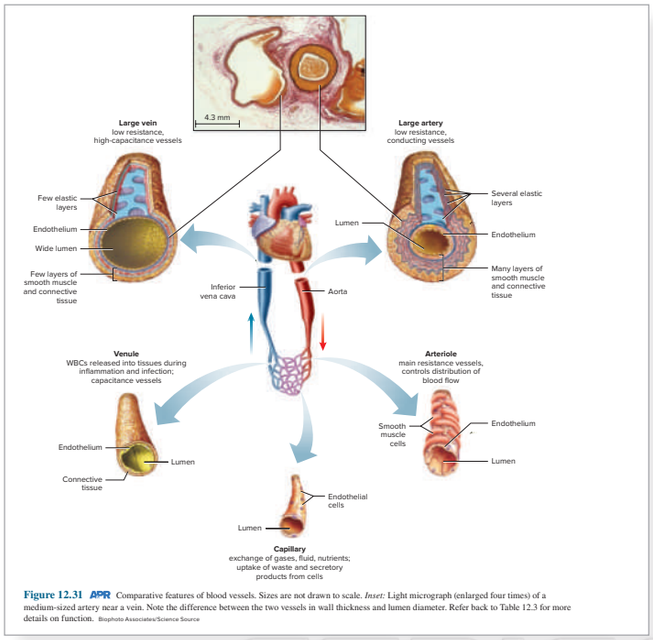


Figure 12.31 APR Comparative features of blood vessels. Sizes are not drawn to scale. *Inset:* Light micrograph (enlarged four times) of a medium-sized artery near a vein. Note the difference between the two vessels in wall thickness and lumen diameter. Refer back to Table 12.3 for more details on function. Biophoto Associates/Science Source

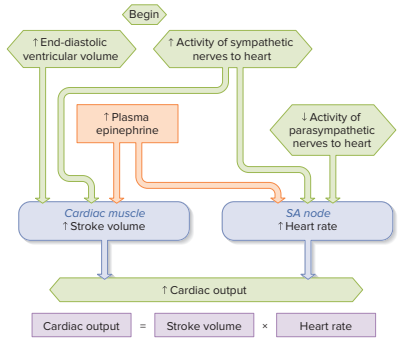


Figure 12.30 Major factors involved in increasing cardiac output. Reversal of all arrows in the boxes would illustrate how cardiac output can be decreased.

DIG DEEPER

- 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 found in Appendix A.

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.

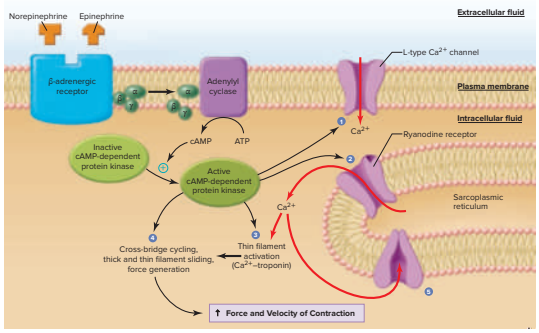


Figure 12.29 APR Mechanisms of sympathetic effects on cardiac muscle cell contractility. In some of the pathways, the kinase phosphorylates accessory proteins that are not shown.

Adrenergic receptors activate a G-protein-coupled cascade that includes the production of cAMP and activation of a protein kinase. A number of proteins involved in excitation–contraction coupling are phosphorylated by the kinase, which enhances contractility. These proteins include the following (numbers keyed in figure):

1. L-type Ca^{2+} channels in the plasma membrane
2. the ryanodine receptor and associated proteins in the sarcoplasmic reticulum membrane
3. thin filament proteins—in particular, troponin
4. thick filament proteins associated with the cross-bridges
5. proteins involved in pumping Ca^{2+} back into the sarcoplasmic reticulum

Due to these alterations, cytosolic Ca^{2+} concentration increases more quickly and reaches a greater value during excitation, Ca^{2+} returns to its pre-excitation value more quickly following excitation, and the rates of cross-bridge activation and cycling are accelerated. The net result is the stronger, faster contraction observed during sympathetic activation of the heart.

There is little parasympathetic innervation of the ventricles, so the parasympathetic system normally has a negligible direct effect on ventricular contractility.

Uniform Color-Coded Illustrations Keyed to the Text

Color-coding is effectively used to promote learning. For example, there are specific colors for extracellular fluid, intracellular fluid, muscle filaments, and transporter molecules. In addition, in figures with complex processes the color-coded numerals associated with each step are keyed using the same coding in the main text.

Multilevel Perspective

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

End of Section Study and Review

At the end of numbered sections throughout the book, you will find a feature that is new to the sixteenth edition called **Study and Review.** These are bulleted lists of the major points covered in a section, followed by an assessment. Many of the latter are multipart, critical thinking questions, asking students first to recall information and then to apply it.

Study and Review 12.2

- **Blood flow between two points:** analogous to electrical current in **Ohm's law** describing electrical circuits
  - directly proportional to pressure difference
  - inversely proportional to resistance
- **Resistance**
  - directly proportional to the **viscosity** of the blood and length of the blood vessel
  - inversely proportional to the fourth power of the vessel radius (most important determinant of resistance and blood flow to each organ)

Review Question: *What are the three determinants of resistance to flow, and which is varied physiologically to alter blood flow?* ***(Answer found in Appendix A.)***

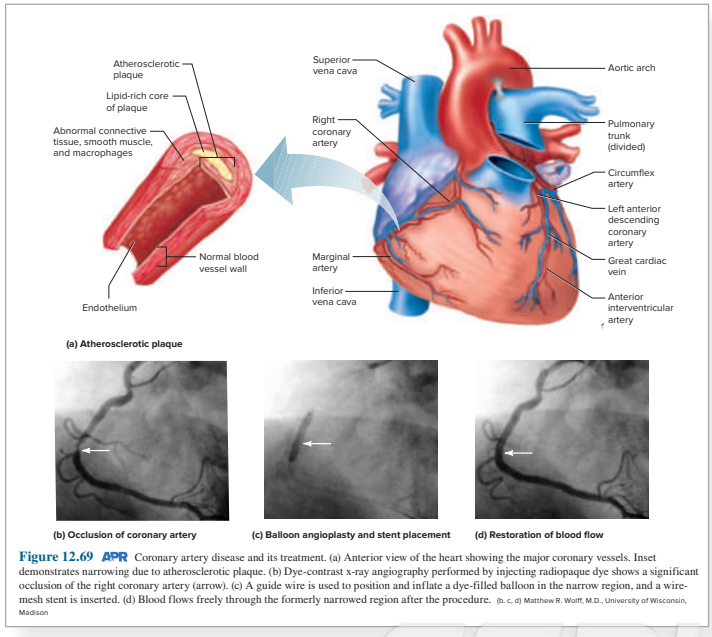
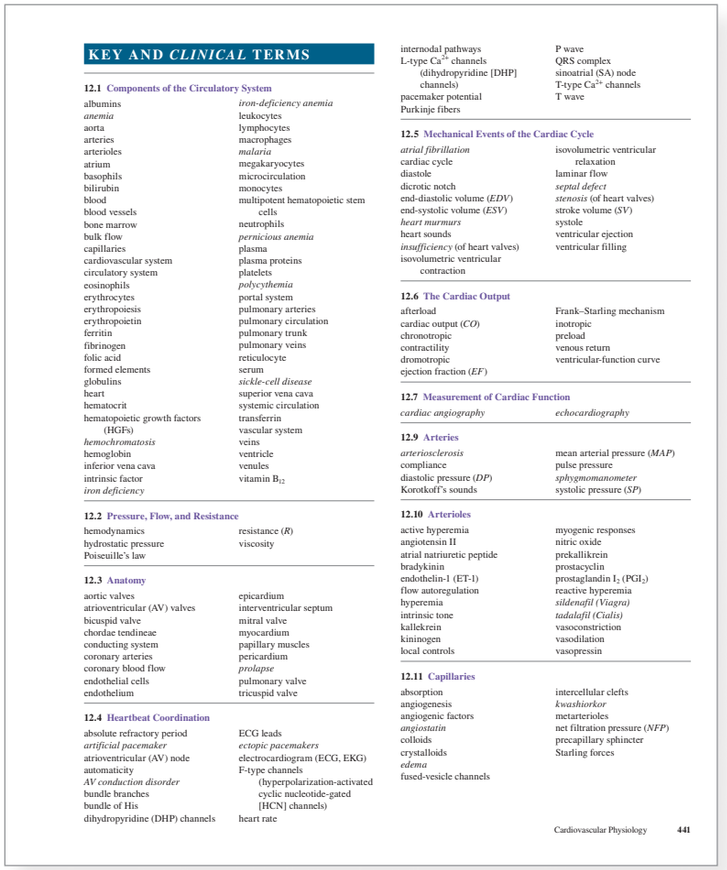


Figure 12.69 APR Coronary artery disease and its treatment. (a) Anterior view of the heart showing the major coronary vessels. Inset demonstrates narrowing due to atherosclerotic plaque. (b) Dye-contrast x-ray angiography performed by injecting radiopaque dye shows a significant occlusion of the right 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. (b, c, d) Matthew R. Wolff, M.D., University of Wisconsin, Madison

End of Chapter

At the end of the chapters, you will find

- An alphabetized list of all key terms and clinical terms in the chapter, organized by numbered section.
- 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 Assessments that test a 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 term or semester.



KEY AND *CLINICAL* TERMS

12.1 Components of the Circulatory System

albumins
anemia
aorta
arteries
arterioles
atrium
basophils
bilirubin
blood
blood vessels
bone marrow
bulk flow
capillaries
cardiovascular system
circulatory system
eosinophils
erythrocytes
erythropoiesis
erythropoietin
ferritin
fibrinogen
folic acid
formed elements
globulins
heart
hematocrit
hematopoietic growth factors (HGFs)
hemochromatosis
hemoglobin
inferior vena cava
intrinsic factor
iron deficiency
iron-deficiency anemia
leukocytes
lymphocytes
macrophages
malaria
megakaryocytes
microcirculation
monocytes
multipotent hematopoietic stem cells
neutrophils
pernicious anemia
plasma
plasma proteins
platelets
polycythemia
portal system
pulmonary arteries
pulmonary circulation
pulmonary trunk
pulmonary veins
reticulocyte
serum
sickle-cell disease
superior vena cava
systemic circulation
transferrin
vascular system
veins
ventricle
venules
vitamin B_{12}

12.2 Pressure, Flow, and Resistance

hemodynamics
hydrostatic pressure
Poiseuille's law
resistance (*R*)
viscosity

12.3 Anatomy

aortic valves
atrioventricular (AV) valves
bicuspid valve
chordae tendineae
conducting system
coronary arteries
coronary blood flow
endothelial cells
endothelium
epicardium
interventricular septum
mitral valve
myocardium
papillary muscles
pericardium
prolapse
pulmonary valve
tricuspid valve

12.4 Heartbeat Coordination

absolute refractory period
artificial pacemaker
atrioventricular (AV) node
automaticity
AV conduction disorder
bundle branches
bundle of His
dihydropyridine (DHP) channels
ECG leads
ectopic pacemakers
electrocardiogram (ECG, EKG)
F-type channels (hyperpolarization-activated cyclic nucleotide-gated [HCN] channels)
heart rate
internodal pathways
L-type Ca^{2+} channels (dihydropyridine [DHP] channels)
pacemaker potential
Purkinje fibers
P wave
QRS complex
sinoatrial (SA) node
T-type Ca^{2+} channels
T wave

12.5 Mechanical Events of the Cardiac Cycle

atrial fibrillation
cardiac cycle
diastole
dicrotic notch
end-diastolic volume (*EDV*)
end-systolic volume (*ESV*)
heart murmurs
heart sounds
insufficiency (of heart valves)
isovolumetric ventricular contraction
isovolumetric ventricular relaxation
laminar flow
septal defect
stenosis (of heart valves)
stroke volume (*SV*)
systole
ventricular ejection
ventricular filling

12.6 The Cardiac Output

afterload
cardiac output (*CO*)
chronotropic
contractility
dromotropic
ejection fraction (*EF*)
Frank–Starling mechanism
inotropic
preload
venous return
ventricular-function curve

12.7 Measurement of Cardiac Function

cardiac angiography
echocardiography

12.9 Arteries

arteriosclerosis
compliance
diastolic pressure (*DP*)
Korotkoff's sounds
mean arterial pressure (*MAP*)
pulse pressure
sphygmomanometer
systolic pressure (*SP*)

12.10 Arterioles

active hyperemia
angiotensin II
atrial natriuretic peptide
bradykinin
endothelin-1 (ET-1)
flow autoregulation
hyperemia
intrinsic tone
kallekrein
kininogen
local controls
myogenic responses
nitric oxide
prekallikrein
prostacyclin
prostaglandin I_2 (PGI_2)
reactive hyperemia
sildenafil (Viagra)
tadalafil (Cialis)
vasoconstriction
vasodilation
vasopressin

12.11 Capillaries

absorption
angiogenesis
angiogenic factors
angiostatin
colloids
crystalloids
edema
fused-vesicle channels
intercellular clefts
kwashiorkor
metarterioles
net filtration pressure (*NFP*)
precapillary sphincter
Starling forces

Cardiovascular Physiology 441

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.

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.
3. If all plasma membrane Ca^{2+} channels in contractile cardiac muscle cells were blocked with a drug, what would happen to the muscle's action potentials and contraction? *Hint:* See Figure 12.15.
4. A person with a heart rate of 40 has no P waves but normal QRS complexes on the ECG. What is the explanation? *Hint:* See Figures 12.19 and 12.22 and remember the source of the P wave.
5. A person has a left ventricular systolic pressure of 180 mmHg and an aortic systolic pressure of 110 mmHg. What is the explanation? *Hint:* See Figure 12.22.
6. A person has a left atrial pressure of 20 mmHg and a left ventricular pressure of 5 mmHg during ventricular filling. What is the explanation? *Hint:* See Figures 12.21 and 12.22.
7. A patient is taking a drug that blocks beta-adrenergic receptors. What changes in cardiac function will the drug cause? *Hint:* See Figure 12.29 and Table 12.5 and think about the effect of these receptors on heart rate and contractility.
8. What is the mean arterial pressure in a person with a systolic pressure of 160 mmHg and a diastolic pressure of 100 mmHg? *Hint:* See Figure 12.34a.

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*?

UPDATES AND ADDITIONS

NEW TO THIS EDITION

The sixteenth edition of *Vander's Human Physiology* has been thoroughly revised with an eye toward updating information and presenting that information in a format that is most readily assimilated and retained by the reader. To that end, several new design elements that improve the effectiveness of the text as a *learning tool* have been developed. These elements include:

- offset, bulleted lists of such items as anatomical features, to provide an immediate visual reference and study guide
- offset, numbered lists of processes that are best understood in stepwise fashion
- reduction of long segments of text into smaller, more manageable chunks
- artwork that is keyed by color-coded symbols to the text
- standardization of artwork across chapters (for example, the inclusion and style of captions in multipart figures)
- the inclusion of over 200 brief, bulleted lists of major concepts at the end of each numbered section. These lists are called **Study and Review,** which reflects their purpose. An assessment at the end of each of these handy study guides is usually a mix of recall and application and is designed to encourage readers to stop and think about that section's material before proceeding to the next section.

Selected Chapter-by-Chapter Changes in This Edition

In general, every chapter has been carefully and thoroughly updated and edited for new content, improved illustrations, accuracy, and readability. A few examples of some specific changes are given below as representative of the overall approach to the sixteenth edition.

Chapter 1 The description of reflexes has been expanded.

Chapter 3 The formation of lactate and its role in metabolism has been further elucidated.

Chapter 4 The process of primary active transport is now illustrated in a color-coded figure that is keyed to the text. An expanded description of osmosis, its similarities and differences from simple diffusion, and its relation to entropy has now been included.

Chapter 6 Figures illustrating the processes involved in the establishment of a resting membrane potential, action potentials, EPSPs, and IPSPs have been redrawn for greater quantitative accuracy, with color-coded numbers keyed to the text.

Chapter 7 The response of single opponent color ganglion cells to different wavelengths of light has been redrawn for clarity.

Chapter 8 The classes and names of anti-anxiety and antidepressant drugs have been updated to reflect current trends in medicine.

Chapter 9 Figures illustrating the cross-bridge cycle in skeletal muscle cells, the mechanism of action of Ca^{2+} in the cross-bridge cycle, and contraction of smooth muscle cells have been color-coded and keyed to the text.

Chapter 10 The description of Parkinson's disease and treatments has been updated.

Chapter 11 The use of anti-inflammatory glucocorticoids in the treatment of COVID-19 is now included.

Chapter 12 New discussion and figure on lymphedema has been included.

Chapter 13 The use of anti-inflammatory glucocorticoids in the treatment of lung inflammation in COVID-19 is discussed.

Chapter 14 Sections on incontinence and on kidney transplantation have been updated.

Chapter 17 New and updated information has been added to sections on opiate suppression of the hypothalamic-pituitary-gonadal axis; nausea and vomiting of pregnancy and hyperemesis gravidum; contraception; minipuberty, including effects of estrogen in the female infant; and factors involved in development of a dominant follicle. A new figure and updated text have been added to the section on spermatogenesis.

Chapter 18 A new illustration of SARS-CoV-2 is included. New information regarding pathological effects of SARS-CoV-2, and the role of interferons in combatting the virus, are also included. New subsections for myeloid cells and lymphoid cells have been added. The description of regulatory T-cells has been expanded.

Chapter 19 Updated information has been added on glioblastoma multiforme.

ACKNOWLEDGMENTS

In this sixteenth 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 sixteenth edition. Any errors that may remain are solely the responsibility of the authors.

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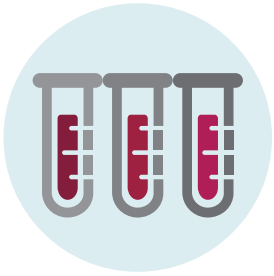

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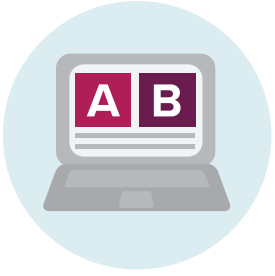

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Homeostasis:

A Framework for Human Physiology

CHAPTER 1

Coping with changes in external temperature and oxygen levels even in extreme conditions are examples of homeostasis. Andre Schoenherr/Stone/Getty Images

The purpose of this chapter is to provide an orientation to the subject of human physiology and the central role of homeostasis—the maintenance of a stable internal environment—in the study of this science. The mountain climbers shown here are experiencing numerous challenges that must be met by their hearts, lungs, and other organs. For example, their hearts need to work harder to pump more blood each minute to their muscles, their lungs must maximize the amount of oxygen brought into the blood, and they must maintain their body temperature in the cold environment. An understanding of these processes 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 charge, if any, 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 function 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."

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 pathophysiology 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.

A related field of science is anatomy, which is the study of the structures of body parts. Throughout this text, we will typically provide an overview of the anatomy of body parts, such as the lungs, kidneys, brain, and others. Without a basic understanding of structures, it would be difficult to understand physiology because, as we will see, the structures of objects determine their functions. For this reason, 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.

Study and Review 1.1

- **Physiology:** study of the functions of the body parts
- **Pathophysiology:** study of disease states (physiological dysfunction)

Review Question: *Distinguish between anatomy, physiology, and pathophysiology. How are they related?* ***(Answer found in Appendix A.)***

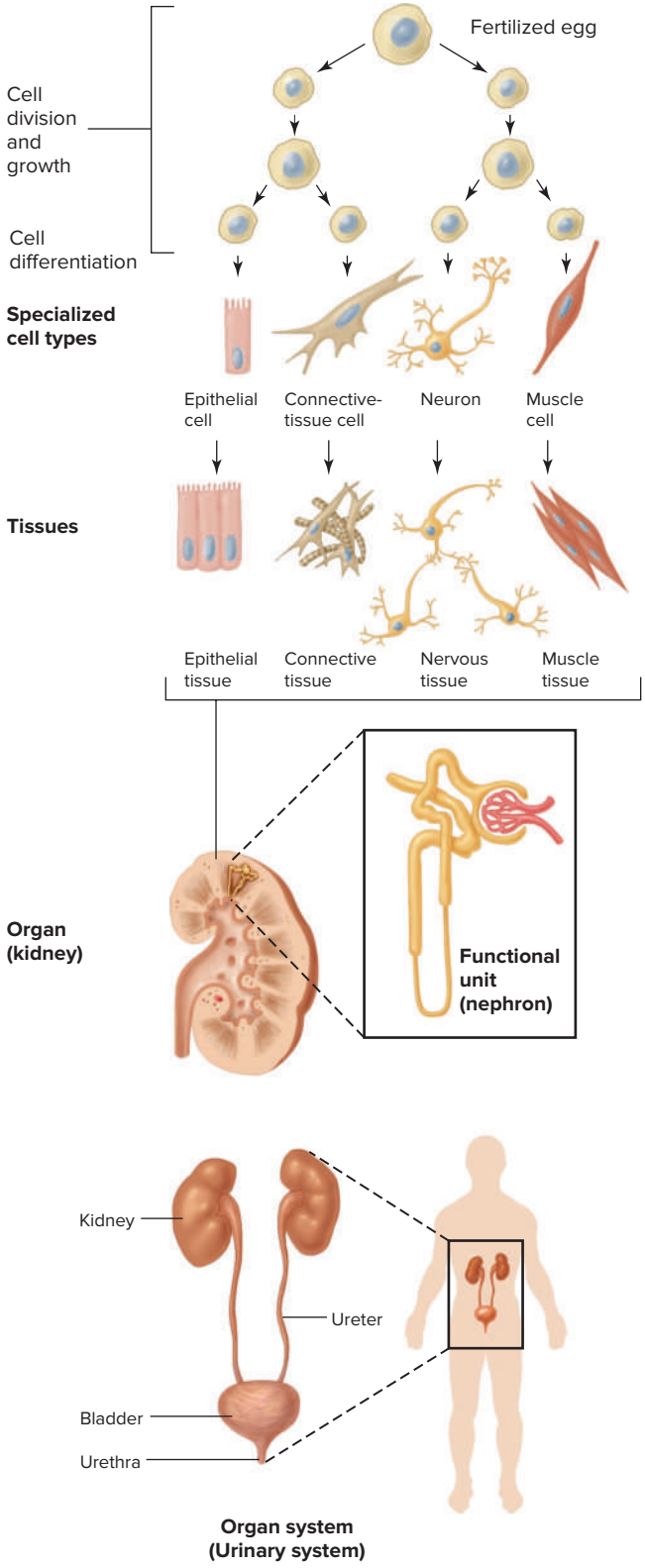


Figure 1.1 Levels of cellular organization. The nephron is not drawn to scale.

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,** one of the most exciting areas of study 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:

- **muscle cells**
- **neurons**
- **epithelial cells**
- **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 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:

- **muscle tissue**
- **nervous tissue**
- **epithelial tissue**
- **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.

As you will see shortly, 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, 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 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 make up part of the walls of 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 Chapters 9 and 12.

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 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

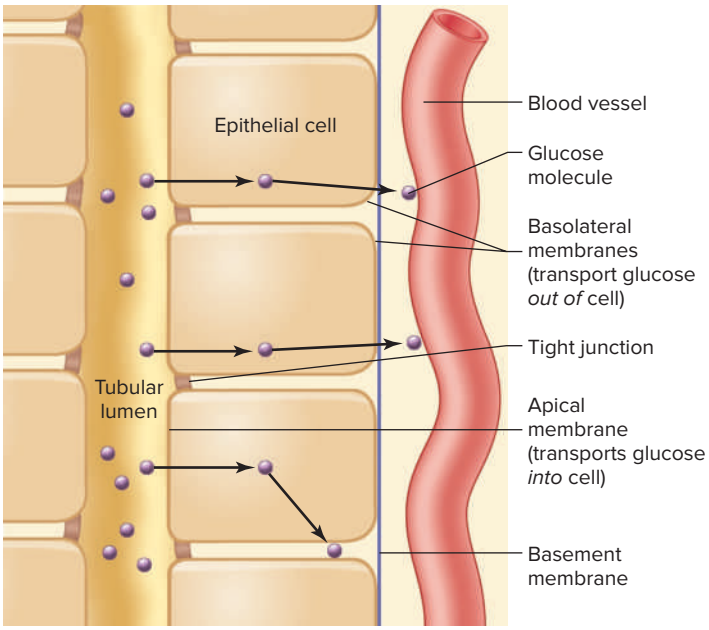


Figure 1.2 Epithelial tissue lining the inside of a structure such as a kidney tubule. The basolateral side of the cell is attached to a basement membrane. Each side of the cell can perform different functions, as in this example in which glucose is transported across the epithelium, first directed into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

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 a kidney tubule, 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:

- provides a scaffold for cellular attachments
- 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,** insoluble proteins including ropelike **collagen fibers** and rubberband-like **elastin fibers.** Others are 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:

- a series of small tubes, each composed of a simple epithelium
- blood vessels, whose walls contain varying quantities of smooth muscle and connective tissue
- extensions from neurons that end near the muscle and epithelial cells
- 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 comprised of 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 critical 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.

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, including most of those regulated by the endocrine system; 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

Study and Review 1.2

- **Cells:** simplest structural units into which a complex multicellular organism can be divided and still retain the functions characteristic of life
- **Cell differentiation:** formation of four general types of specialized cells
  - **Muscle cells:** generate the mechanical activities that produce force and movement; 3 types include **skeletal, cardiac,** and **smooth muscle** cells
  - **Neurons:** initiate and conduct electrical signals
  - **Epithelial cells:** form barriers and selectively secrete and absorb ions and organic molecules; basolateral surface rests on a basement membrane
  - **Connective-tissue cells:** connect, anchor, and support the structures of the body; form the **extracellular matrix,** which consists of fibers such as collagen and elastin

Study and Review 1.2—*continued*

- **Tissues:** aggregates of differentiated cells with similar properties; correspond to the four general types of specialized cells
- **Organs:** composed of two or more of the four kinds of tissues
  - Many organs contain multiple, small, similar **functional units.**
- **Organ system:** group of organs that perform an overall function

Review Question: *It is a simplification to refer to organ systems as if they function independently from each other. Why? Refer to Table 1.1 and give two or three examples of how the functions of different organ systems overlap.* ***(Answer found in Appendix A.)***

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 three compartments:

- **Intracellular fluid** is the fluid contained within all the cells of the body and accounts for about 67% of all the water in the body.
- **Plasma** is the fluid portion of blood in which blood cells are suspended, and accounts for about 7% of total-body water.
- **Interstitial fluid** is the fluid that lies around and between cells (in the space known as the **interstitium**) and makes up about 26% of total-body water.

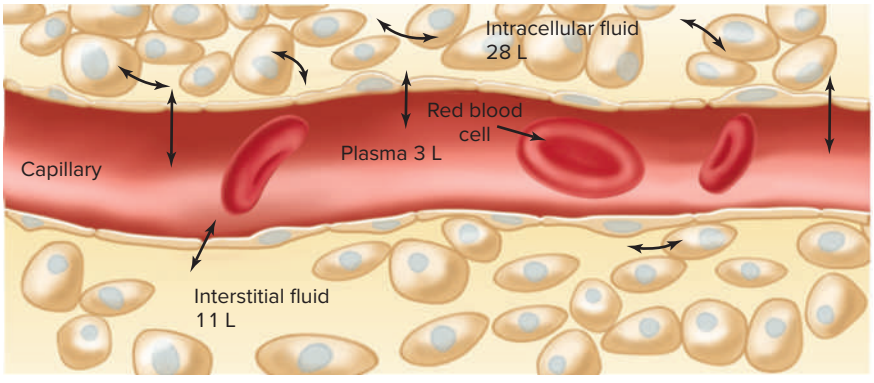
Together, the plasma and interstitial fluid comprise the **extracellular fluid** of the body. Therefore, the total volume of extracellular fluid is the sum of the plasma and interstitial fluid volumes. **Figure 1.3** summarizes the relative volumes of water in the different fluid compartments of the 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 an essentially homogeneous solute composition. In contrast, the composition of the extracellular fluid is very different from that of the intracellular fluid.

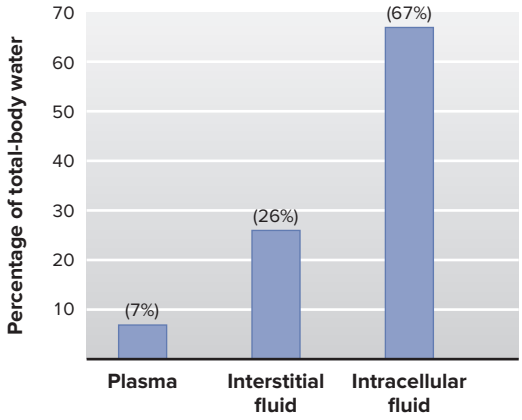
Maintaining differences in fluid composition between intracellular and extracellular fluid compartments is an important way in which cells regulate their own activity. For example, intracellular fluid contains many different proteins that are important in regulating cellular events such as growth and metabolism. These proteins must be 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.



(a) Movements of water between body fluid compartments



(b) Relative amounts of water in body fluid compartments

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.

DIG DEEPER

- 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 found in Appendix A.

Study and Review 1.3

- **Extracellular fluid:** composed of the interstitial fluid (the fluid between cells [within the space called the **interstitium**]) and the plasma (noncellular portion of blood)
  - **Interstititial fluid:** ~75%–80% of the extracellular fluid
  - **Plasma:** ~20%–25% of the extracellular fluid
- Interstitial fluid and plasma have similar composition except plasma contains a much greater concentration of protein.
- **Intracellular fluid:** the fluid inside cells
- **Internal environment:** total-body fluid, made up of 2/3 intracellular fluid and 1/3 extracellular fluid
- Different compositions of the compartments reflect the activities of the barriers separating them.

Review Question: *If a person were to receive a wound that resulted in significant loss of blood, which body fluid compartment would be immediately affected? How might a health care professional restore fluid to that compartment?* ***(Answer found in Appendix A.)***

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 plasma 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).

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 does not provide a full 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, by regulating the uptake of glucose from the blood into organs such as muscles. However, 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 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.

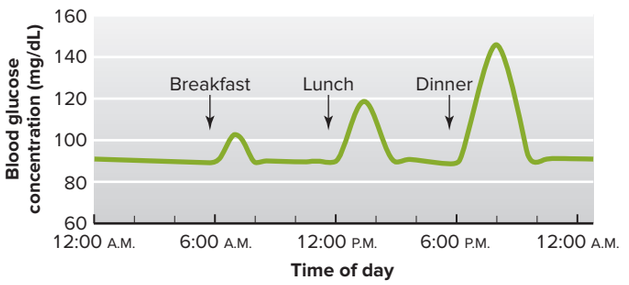


Figure 1.4 Changes in blood glucose concentration during a typical 24 h period. Note that glucose concentration increases after each meal, more so after larger meals, and then returns to the premeal concentration in a short while. The profile shown here is that of a person who is homeostatic for blood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

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 (Na^+) in the blood remains within 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").

Study and Review 1.4

- **Internal environment:** the extracellular fluid
- **Homeostasis:** the process of maintaining a stable internal environment
  - When homeostasis is disturbed for one variable, other variables will compensate.
- **Dynamic constancy:** a given variable may fluctuate in the body in the short term, but is stable and predictable in the long term

Review Question: *What is meant by "dynamic constancy"? How does it relate to homeostasis, and what is one physiological variable described in this section that illustrates this concept?* ***(Answer found in Appendix A.)***

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 internal environment 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 at 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 the room 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 more or less 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 stable, homeostatic 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.

All homeostatic control systems operate around a set point. There are set points for blood pressure, plasma ion concentrations, total-body water, and so on. 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.*

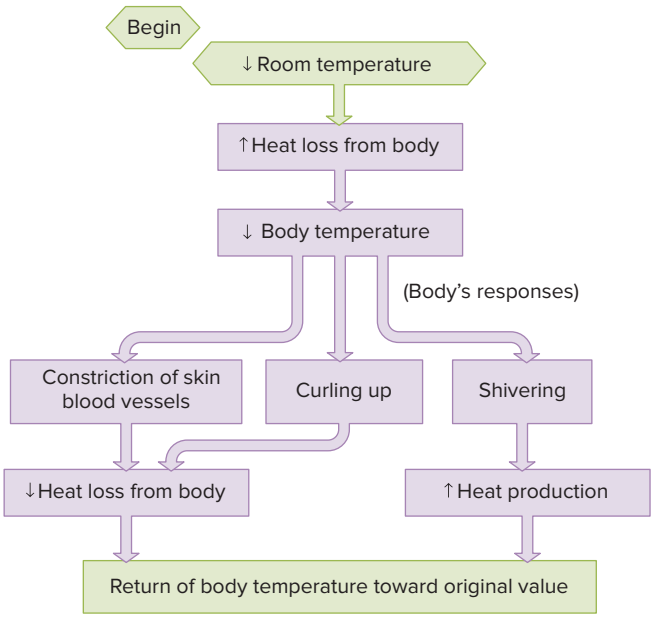


Figure 1.5 A homeostatic control system maintains body temperature when room temperature decreases. This flow diagram is typical of those used throughout this book to illustrate homeostatic systems, and several conventions should be noted. The "Begin" sign indicates where to start. The arrows next to 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.

The first homeostatic response is that blood vessels to the skin become constricted (narrowed), reducing the amount of blood flowing through the skin. This decreases heat loss from the warm blood across the skin and out to the environment and helps slow the loss of heat from the body. At a room temperature of 5°C, however, blood vessel constriction cannot by itself eliminate the extra heat loss from the body. 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, thereby restoring body temperature homeostasis.

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**. (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. In other words, an initial change in a particular variable subsequently leads to an even greater change in that variable.

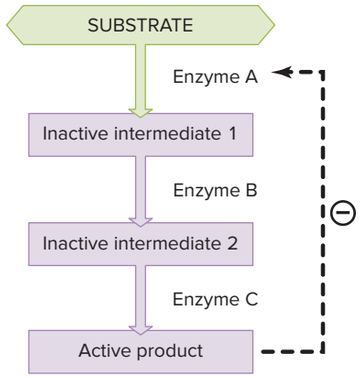


Figure 1.6 Hypothetical example of negative feedback (as denoted by the circled minus sign and dashed feedback line) occurring within a set of sequential chemical reactions. By inhibiting the activity of the first enzyme involved in the formation of a product, the product can regulate the rate of its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

DIG DEEPER

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

Answer found in Appendix A.

This is counter to 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 detail in Chapter 12, is the process of blood clotting (**Figure 1.7**). When a blood vessel is ruptured, damaged cells in the vessel wall release chemicals into the blood that attract platelets to the injury site and activate them. Platelets are fragments of cells that stick together and form clots that seal a wound. Once activated, platelets themselves then release additional activating chemicals, which activate more platelets, and so on. The cycle finally stops once the wound is fully sealed with a clot.

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 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.

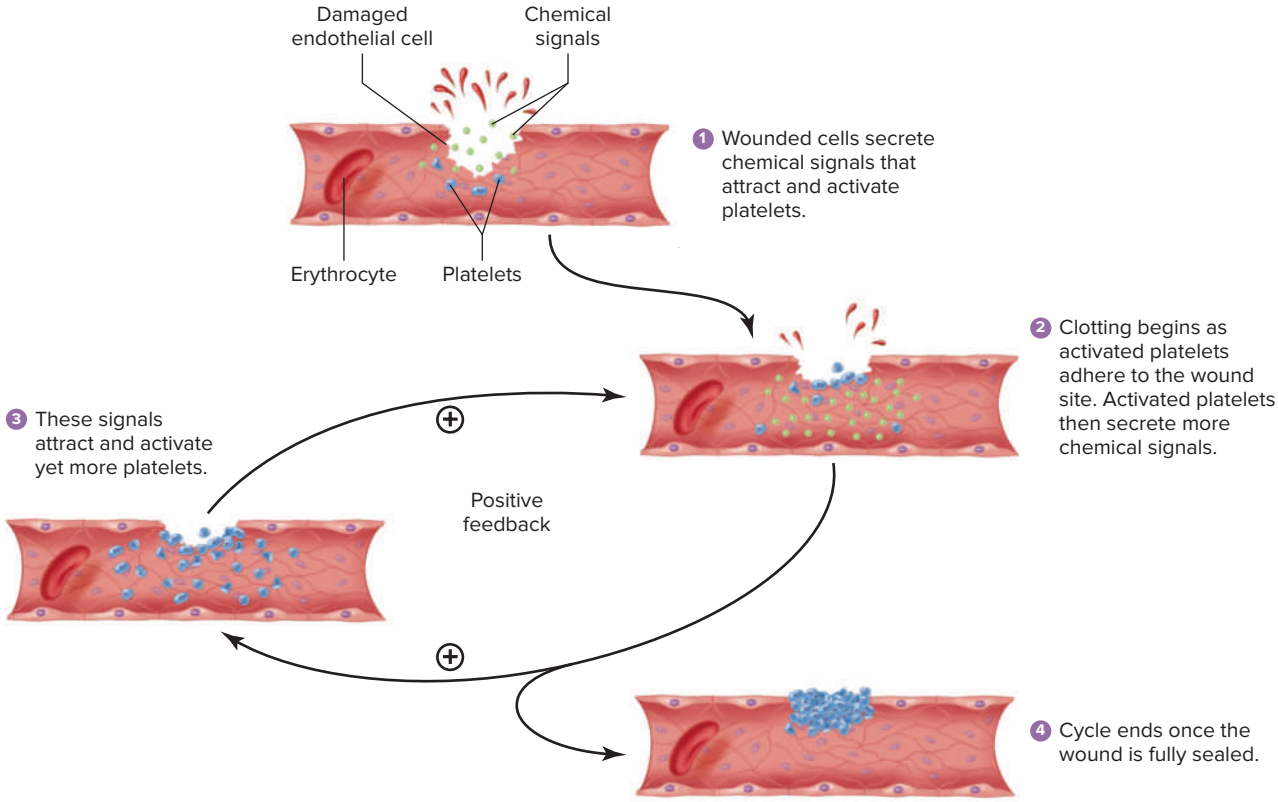


Figure 1.7 Positive feedback as illustrated by the clotting process in blood. Damaged endothelial cells (a type of epithelial cells) in the lining of a blood vessel secrete chemical signals that attract and activate platelets, tiny cell fragments that form clots. As clotting begins, the activated platelets produce chemical signals of their own, attracting and activating more platelets to the wound site, which then produce yet more chemical signals, and so on. The cycle ends when the wound is fully sealed. (Most details of the clotting process are omitted for clarity; you can look ahead to Figure 12.71 for details.)

For example, the set point for body temperature is higher during the day, when we are active, 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 is **feedforward regulation,** in which changes in regulated variables are anticipated and prepared for before they actually occur. Control of body temperature is a

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.

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 regulation 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.

Study and Review 1.5

- **Homeostasis** results from the operation of compensatory control systems.
  - Homeostasis is a **steady state** in which a variable is unchanging but only as long as energy is provided (**equilibrium** does not require input of energy).
- **Negative feedback control system:** minimizes changes from the **set point** of a system, leading to stability
  - A change in a regulated variable brings about responses that move the variable in the direction opposite to the original change.
- **Positive feedback:** accelerates a process by moving a variable further from a set point
- **Homeostatic control systems** minimize changes but cannot maintain complete constancy of a regulated variable.
- **Feedforward regulation:**
  - anticipates changes in a regulated variable
  - fine-tunes homeostatic responses
  - minimizes fluctuations in the regulated variable

Review Question: *Distinguish between negative feedback, positive feedback, and feedforward regulation. Which of the three is least likely to contribute to homeostasis, and why?* ***(Answer found in Appendix A.)***

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*. In the narrowest sense of the word, a **reflex** is a specific, involuntary, "built-in" response to a particular stimulus. Some reflexes involve muscular activity, such as the familiar knee-jerk reflex, or the startle reflex that follows when we are surprised by a loud noise. Other reflexes occur without our conscious awareness and involve internal homeostatic responses such as those described in this chapter. For example, you are generally not aware of reflexive changes in blood pressure.

Many responses 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.

The pathway mediating a reflex is known as the **reflex arc,** and its components are shown in **Figure 1.8**. A **stimulus** is defined as a detectable change in the internal or external environment, such as a change in temperature, plasma potassium concentration, or blood pressure. A **receptor** detects the environmental change. A stimulus acts upon a receptor to produce a signal that is relayed to an **integrating center.** The signal travels between the receptor and the integrating center along the **afferent pathway** (the general term *afferent* means "to carry to," in this case, to the integrating center).

An integrating center often receives signals from many receptors, some of which may respond to quite different types of stimuli. Thus, the output of an integrating center reflects the net effect of the total afferent input—that is, it represents an integration of numerous bits of information.

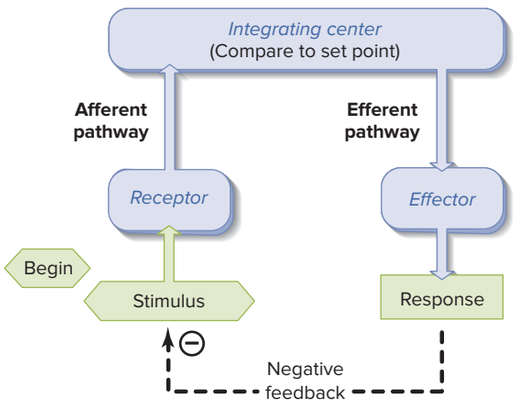


Figure 1.8 General components of a reflex arc that functions as a negative feedback control system. The response of the system has the effect of counteracting or eliminating the stimulus.

The output of an integrating center is sent to the last component of the system, known as an **effector.** The actions of the effector constitute the overall response of the system. The information going from an integrating center to an effector is like a command directing the effector to alter its activity. This information travels along the **efferent pathway** (the general term *efferent* means "to carry away from," in this case, away from the integrating center).

Thus far, we have described the reflex arc as the sequence of events linking a stimulus to a response. If the response produced by the effector causes a decrease in the magnitude of the stimulus that triggered the sequence of events, then the reflex leads to negative feedback and we have a typical homeostatic control system. Not all reflexes are associated with such feedback. For example, the smell of food stimulates the stomach to secrete molecules that are important for digestion, but these molecules do not eliminate our perception of the smell of food (the stimulus).

Figure 1.9 demonstrates the components of a negative feedback homeostatic reflex arc in the process of thermoregulation. The temperature receptors are the endings of certain neurons in various parts of the body. These receptors generate electrical signals in the neurons at a rate determined by the temperature. These electrical signals are conducted by nerves containing processes from the neurons—the afferent pathway—to the brain, where the integrating center for temperature regulation is located. The integrating center, in turn, sends signals out along neurons in other nerves that cause skeletal muscles and the muscles in skin blood vessels to contract. The nerves to the muscles are the efferent pathway, and the muscles are the effectors. The dashed arrow and the negative sign indicate the negative feedback nature of the reflex.

Almost all body cells can act as effectors in homeostatic reflexes. Muscles and glands, however, are the major effectors of biological control systems. In the case of glands, for example, the effector may be a hormone secreted into the blood. As will be described in detail in Chapter 11, a **hormone** is a type of chemical messenger secreted into the blood by cells of the endocrine system (see Table 1.1). Hormones may act on many different cells simultaneously because they circulate throughout the body.

Traditionally, the term *reflex* was restricted to situations in which the receptors, afferent pathway, integrating center, and efferent pathway were all parts of the nervous system, as in the thermoregulatory reflex. However, the principles are essentially the same when a blood-borne chemical messenger, rather than a nerve, serves as the efferent pathway, or when a hormone-secreting gland serves as the integrating center.

In our use of the term *reflex,* therefore, we include hormones as reflex components. Moreover, depending on the specific nature of the reflex, the integrating center may reside either in the nervous system or in a gland. In addition, a gland may act in more than one way in a reflex. For example, when the glucose concentration in the blood is increased, this is detected by gland cells

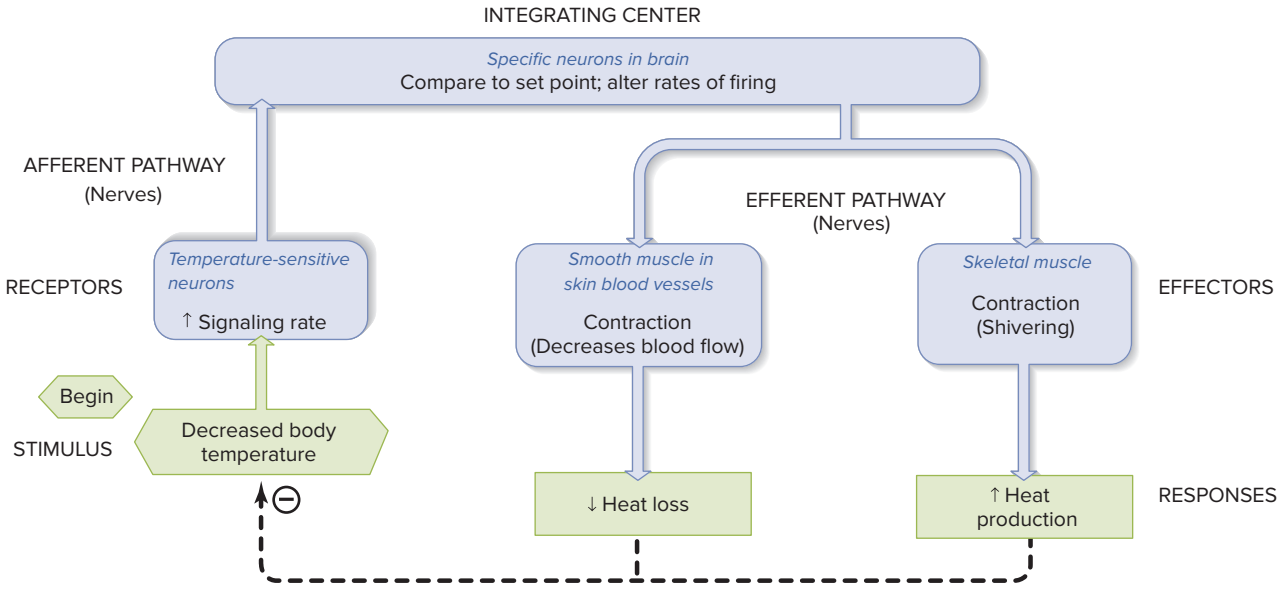


Figure 1.9 Reflex for minimizing the decrease in body temperature that occurs on exposure to a reduced external environmental temperature. This figure provides the internal components for the reflex shown in Figure 1.5. The dashed arrow and the ⊖ indicate the negative feedback nature of the reflex, denoting that the reflex responses cause the decreased body temperature to return toward normal. An additional flow-diagram convention is shown in this figure: Blue boxes always denote events that are occurring in anatomical structures (labeled in blue italic type in the upper portion of the boxes).

DIG DEEPER

- What might happen to the efferent pathway in this control system if body temperature *increased* above normal?

Answer found in Appendix A.

in the pancreas (receptor). These same cells then release the hormone insulin (effector) into the blood, which decreases the blood glucose concentration.

Local Homeostatic Responses

In addition to reflexes, another group of biological responses, called **local homeostatic responses,** is of great importance for homeostasis. These responses are initiated by a change in the external or internal environment (that is, a stimulus), and they induce an alteration of cell activity with the net effect of counteracting the stimulus. Like a reflex, therefore, a local response is the result of a sequence of events proceeding from a stimulus. Unlike a reflex, however, the entire sequence occurs only in the area of the stimulus. For example, when cells of a tissue become very metabolically active, they secrete substances into the interstitial fluid that dilate (widen) local blood vessels. The resulting increased blood flow increases the rate at which nutrients and oxygen are delivered to that area, and the rate at which wastes are removed. The significance of local responses is that they provide individual areas of the body with mechanisms for local self-regulation.

Study and Review 1.6

- **Reflex:** specific, involuntary, unpremeditated response to a stimulus
  - typically innate but some can be **learned** or **acquired**
- **Reflex arc:** stimulus → receptor → afferent pathway → integrating center → efferent pathway → effector → response
- **Local homeostatic responses:**
  - involve stimulus–response sequences
  - occur only in the area of the stimulus (no nerves or hormones directly involved)

Review Question: *What might happen to a reflex arc in an individual in whom the effectors for that reflex were not functional?* ***(Answer found in Appendix A.)***

1.7 The Role of Intercellular Chemical Messengers in Homeostasis

Essential to reflexes and local homeostatic responses—and therefore to homeostasis—is the ability of cells to communicate with one another. In this way, cells in the brain, for example, can be made aware of the status of activities of structures outside the brain, such as the heart, and help regulate those activities to meet new homeostatic challenges. In the majority of cases, intercellular communication is performed by chemical messengers. There are four categories of such messengers: hormones, neurotransmitters, paracrine substances, and autocrine substances (**Figure 1.10**).

As noted earlier, a hormone is a chemical messenger that enables the hormone-secreting cell to communicate with other cells,

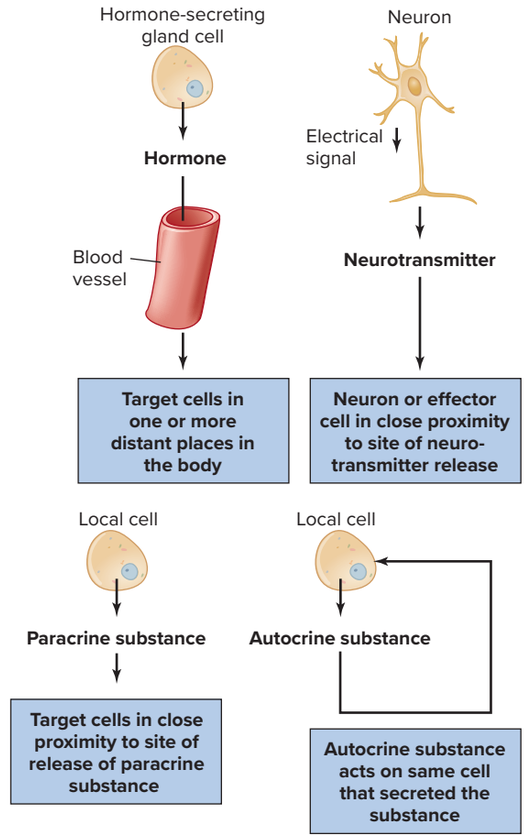


Figure 1.10 Categories of chemical messengers. With the exception of autocrine messengers, all messengers act between cells—that is, *inter*cellularly.

with the blood acting as the delivery system. The cells on which hormones act are called the hormone's target cells. Hormones are produced in and secreted from **endocrine glands**—such as the gonads, pancreas, and thyroid gland—or in scattered cells that are distributed throughout an organ. They have important functions in essentially all physiological processes, including growth, reproduction, metabolism, mineral balance, and blood pressure, and several of them are produced whenever homeostasis is threatened.

In contrast to hormones, **neurotransmitters** are chemical messengers that are released from the endings of neurons onto other neurons, muscle cells, or gland cells. A neurotransmitter diffuses through the extracellular fluid separating the neuron and its target cell; it is not released into the blood like a hormone. Neurotransmitters and their functions in neuronal signaling and brain function will be covered in Chapter 6. In the context of homeostasis, they form the signaling basis of many reflexes, as well as having a vital role in the compensatory responses to a wide variety of challenges, such as the requirement for increased heart and lung function during exercise.

Chemical messengers participate not only in reflexes but also in local responses. Chemical messengers involved in local communication between cells are known as **paracrine substances** (or agents). Paracrine substances are synthesized by cells and released, once given the appropriate stimulus, into the extracellular fluid. They then diffuse to neighboring cells, some of which are their target cells. Given this broad definition, neurotransmitters

could be classified as a subgroup of paracrine substances, but by convention they are not. Once they have performed their functions, paracrine substances are generally inactivated by locally existing enzymes and therefore they do not enter the bloodstream in large quantities. Paracrine substances are produced throughout the body; an example of their key role in homeostasis that you will learn about in Chapter 15 is their ability to fine-tune the amount of acid produced by cells of the stomach in response to eating food.

There is one category of local chemical messengers that are not *inter*cellular messengers—that is, they do not communicate *between* cells. Rather, the chemical is secreted by a cell into the extracellular fluid and then acts upon the very cell that secreted it. Such messengers are called **autocrine substances** (or agents) (see Figure 1.10). Frequently, a messenger may serve both paracrine and autocrine functions simultaneously—that is, molecules of the messenger released by a cell may act locally on adjacent cells as well as on the same cell that released the messenger. This type of signaling is commonly found in cells of the immune system (Chapter 18).

A point of great importance must be emphasized here to avoid later confusion. A neuron, endocrine gland cell, and other cell types may all secrete the same chemical messenger. In some cases, a particular messenger may sometimes function as a neurotransmitter, a hormone, or a paracrine or autocrine substance. Norepinephrine, for example, is not only a neurotransmitter in the brain; it is also produced as a hormone by cells of the adrenal glands.

All types of intercellular communication described thus far in this section involve secretion of a chemical messenger into the extracellular fluid. However, there are two important types of chemical communication between cells that do not require such secretion. The first type occurs via gap junctions, which are physical linkages connecting the cytosol between two cells (see Chapter 3). Molecules can move directly from one cell to an adjacent cell through gap junctions without entering the extracellular fluid. In the second type, the chemical messenger is not actually released from the cell producing it but rather is located in the plasma membrane of that cell. For example, the messenger may be a plasma membrane protein with part of its structure extending into the extracellular space. When the cell encounters another cell type capable of responding to the message, the two cells link up via the membrane-bound protein. This type of signaling, sometimes termed *juxtacrine,* is of particular importance in the growth and differentiation of tissues as well as in the functioning of cells that protect the body against pathogens (Chapter 18). It is one way in which similar types of cells "recognize" each other and form tissues.

Study and Review 1.7

- **Intercellular communication:** cell-to-cell communication facilitates homeostasis
  - essential to reflexes and local responses
  - achieved by **neurotransmitters, hormones** (many of which are secreted from **endocrine glands**), **paracrine substances,** or **autocrine substances**
  - also occurs to a lesser extent through gap junctions or cell-bound messengers

Review Question: *Explain how intercellular communication facilitates the maintenance of homeostasis.* ***(Answer found in Appendix A.)***

1.8 Processes Related to Homeostasis

Adaptation and Acclimatization

The term **adaptation** denotes a characteristic that favors survival in specific environments. Common examples in humans include the ability of certain individuals to digest lactose in milk, and the protection against the dangerous effects of ultraviolet light conferred by dark skin. Homeostatic control systems are also inherited biological adaptations and allow an individual to adapt to encountered environmental changes. In addition, in some cases the effectiveness of such systems can be enhanced by prolonged exposure to an environmental change. This type of adaptation—the improved functioning of an already existing homeostatic system—is known as **acclimatization.**

Let us take sweating in response to heat exposure as an example of an adaptation and perform a simple experiment. On day 1, we expose a person for 30 minutes (min) to an elevated temperature and ask her to do a standardized exercise test. Body temperature increases, and sweating begins after a certain period of time. The sweating provides a mechanism for increasing heat loss from the body and therefore tends to minimize the increase in body temperature in a hot environment. The volume of sweat produced under these conditions is measured. Then, for a week, our subject enters the heat chamber for 1 or 2 hours (h) per day and exercises. On day 8, her body temperature and sweating rate are again measured during the same exercise test performed on day 1. The striking finding is that the subject begins to sweat sooner and much more profusely than she did on day 1. As a consequence, her body temperature does not increase to nearly the same degree. The subject has become acclimatized to the heat. She has undergone a beneficial change induced by repeated exposure to the heat and is now better able to respond to heat exposure.

Acclimatizations are usually reversible. If, in the example just described, the daily exposures to heat are discontinued, our subject's sweating rate will revert to the preacclimatized value within a relatively short time.

The precise anatomical and physiological changes that bring about increased capacity to withstand change during acclimatization are highly varied. Typically, they involve an increase in the number, size, or sensitivity of one or more of the cell types in the homeostatic control system that mediates the basic response.

Biological Rhythms

As noted, a striking characteristic of many body functions is the rhythmic changes they manifest. The most common type is the **circadian rhythm,** which cycles approximately once every 24 h. Waking and sleeping, body temperature, hormone concentrations in the blood, the excretion of ions into the urine, and many other functions undergo circadian variation; an example of one type of rhythm is shown in **Figure 1.11**.

What do biological rhythms have to do with homeostasis? They add an anticipatory component to homeostatic control systems—in effect, a feedforward system operating without detectors. The negative feedback homeostatic responses we described earlier in this chapter are *corrective* responses. They are initiated *after*

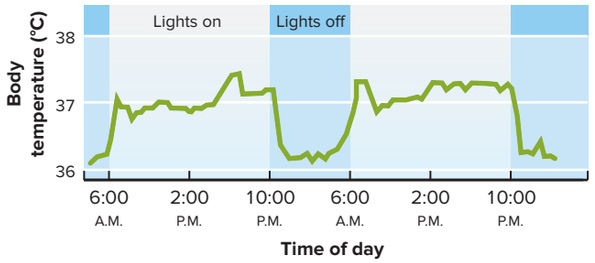


Figure 1.11 Circadian rhythm of body temperature in a human subject with room lights on (open bars at top) for 16 h, and off (blue bars at top) for 8 h. Note the increase in body temperature that occurs just prior to lights on, in anticipation of the increased activity and metabolism that occur during waking hours. Source: Moore-Ede, Martin C., Sulzman, Frank M., and Fuller, Charles A., *The Clocks that Time Us*. Harvard University Press, 1982.

the steady state of the individual has been perturbed. In contrast, biological rhythms enable homeostatic mechanisms to be utilized immediately and automatically by activating them at times when a challenge is *likely* to occur but before it actually does occur—for example, body temperature increases prior to waking in a person on a typical sleep–wake cycle. This allows the metabolic machinery of the body to operate most efficiently immediately upon waking, because metabolism (chemical reactions) is to some extent temperature dependent. During sleep, metabolism is slower than during the active hours, and therefore body temperature decreases at that time. A crucial point concerning most body rhythms is that they are internally driven. Environmental factors do not drive the rhythm but rather provide the timing cues important for **entrainment,** or setting of the actual hours of the rhythm. A classic experiment will clarify this distinction.

Subjects were put in experimental chambers that completely isolated them from their usual external environment, including knowledge of the time of day. For the first few days, they were exposed to a 24 h rest–activity cycle in which the room lights were turned on and off at the same times each day. Under these conditions, their sleep–wake cycles were 24 h long. Then, all environmental time cues were eliminated, and the subjects were allowed to control the lights themselves. Immediately, their sleep–wake patterns began to change. On average, bedtime began about 30 min later each day, and so did wake-up time. Thus, a sleep–wake cycle persisted in the complete absence of environmental cues. Such a rhythm is called a **free-running rhythm.** In this case, it was approximately 24.5 h rather than 24. This indicates that cues are required to entrain or set a circadian rhythm to 24 h.

What is the neural basis of body rhythms? In the part of the brain called the hypothalamus a specific collection of neurons (the suprachiasmatic nucleus) functions as the principal **pacemaker,** or time clock, for circadian rhythms. How it keeps time independent of any external environmental cues is not fully understood, but it appears to involve the rhythmic turning on and off of critical genes in the pacemaker cells.

The pacemaker receives input from the eyes and many other parts of the nervous system, and these inputs mediate the entrainment effects exerted by the external environment. In turn, the pacemaker sends out neural signals to other parts of the brain, which then influence the various body systems, activating some and inhibiting others. One output of the pacemaker goes to the **pineal gland,** a gland within the brain, which secretes the hormone **melatonin.** These neural signals from the pacemaker cause the pineal gland to secrete melatonin during darkness but not during daylight. It has been hypothesized, therefore, that melatonin may act as an important mediator to influence other organs either directly or by altering the activity of the parts of the brain that control these organs.

Balance of Chemical Substances in the Body

Many homeostatic systems regulate the balance between addition and removal of a chemical substance from the body. **Figure 1.12** is a generalized schema of the possible pathways involved in maintaining such balance. The **pool** occupies a position of central importance in the balance sheet. It is the body's readily available quantity of the substance and is often identical to the amount present in the extracellular fluid. The pool receives substances and redistributes them to all the pathways.

The pathways on the left of Figure 1.12 are sources of net gain to the body. A substance may enter the body through the gastrointestinal (GI) tract or the lungs. Alternatively, a substance may be synthesized within the body from other materials.

The pathways on the right of the figure are causes of net loss from the body. A substance may be lost in the urine, feces, expired air, or menstrual fluid, as well as from the surface of the body as skin, hair, nails, sweat, or tears. The substance may also be chemically altered by enzymes and thus removed by metabolism.

The central portion of Figure 1.12 illustrates the distribution of the substance within the body. The substance may be taken from the pool and accumulated in storage depots—such as the accumulation of fat in adipose tissue. Conversely, it may leave the storage depots to reenter the pool. Finally, the substance may be incorporated reversibly into some other molecular structure, such as fatty acids into plasma membranes. Incorporation is reversible because the substance is liberated again whenever the more complex structure is broken down. This pathway is distinguished from storage in that the incorporation of the substance into other molecules produces new molecules with specific functions.

Substances do not necessarily follow all pathways of this generalized schema. For example, minerals such as Na^+ cannot be synthesized, do not normally enter through the lungs, and cannot be removed by metabolism.

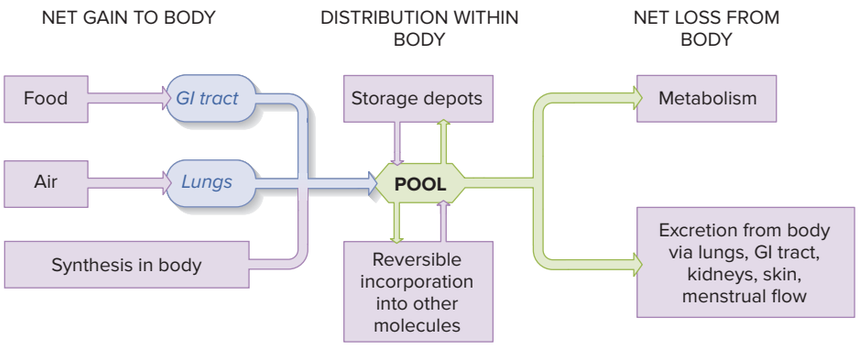


Figure 1.12 Balance diagram for a chemical substance.

The orientation of Figure 1.12 illustrates two important generalizations concerning the balance concept: (1) During any period of time, total-body balance depends upon the relative rates of net gain and net loss to the body; and (2) the pool concentration depends not only upon the total amount of the substance in the body but also upon exchanges of the substance *within* the body.

For any substance, three states of total-body balance are possible:

- Loss exceeds gain, so that the total amount of the substance in the body is decreasing, and the person is in **negative balance.**
- Gain exceeds loss, so that the total amount of the substance in the body is increasing, and the person is in **positive balance.**
- Gain equals loss, and the person is in **stable balance.**

Clearly, a stable balance can be upset by a change in the amount being gained or lost in any single pathway in the schema. For example, increased sweating can cause severe negative water balance. Conversely, stable balance can be restored by homeostatic control of water intake and output.

Let us take the balance of calcium ions (Ca^{2+}) as another example. The concentration of Ca^{2+} in the extracellular fluid is critical for normal cellular functioning, notably muscle cells and neurons, but also for the formation and maintenance of the skeleton. The vast majority of the body's Ca^{2+} is present in bone. The control systems for Ca^{2+} balance target the intestines and kidneys such that the amount of Ca^{2+} absorbed from the diet is balanced with the amount excreted in the urine. During infancy and childhood, however, the net balance of Ca^{2+} is positive, and Ca^{2+} is deposited in growing bone. In later life, especially in women after menopause (see Chapter 17), Ca^{2+} is released from bones faster than it can be deposited, and that extra Ca^{2+} is lost in the urine. Consequently, the bone pool of Ca^{2+} becomes smaller, the rate of Ca^{2+} loss from the body exceeds the rate of intake, and Ca^{2+} balance is negative.

In summary, homeostasis is a complex, dynamic process that regulates the adaptive responses of the body to changes in the external and internal environments. To work properly, homeostatic systems require a sensor to detect the environmental change as well as a means to produce a compensatory response. Because compensatory responses require muscle activity, behavioral changes, or synthesis of chemical messengers such as hormones, homeostasis is achieved by the expenditure of energy. The nutrients that provide this energy, as well as the cellular structures and chemical reactions that release the energy stored in the chemical bonds of the nutrients, are described in the following two chapters.

Study and Review 1.8

- **Adaptation:** any characteristic that favors survival in a specific environment; many are inheritable, such as homeostatic control systems
- **Acclimatization:** improved functioning of an already existing homeostatic system
  - induced by prolonged exposure to a stress with no change in genetic endowment
  - typically reversible

Study and Review 1.8 — *continued*

- **Circadian rhythms:** biological functions with a cycle of approximately 24 h
  - feedforward component to homeostatic control systems
  - internally driven by pacemakers
  - entrained by light
  - **free run** without entrainment
- **Total-body (mass) balance:** matching inputs and outputs of a substance in the body
  - can be negative (net loss), positive (net gain), or stable (loss = gain)

Review Question: *Distinguish between acclimatization and adaptation. Considering organ systems and referring back to Table 1.1 if necessary, what are one or two general adaptations that are important for our ability to survive in a terrestrial environment?* ***(Answer found in Appendix A.)***

1.9 General Principles of Physiology

This chapter has highlighted several fundamental and recurring themes or principles in physiology. Recognizing these principles and how they manifest in the different organ systems can provide a deeper understanding of the integrated function of the human body. To help you gain this insight, beginning with Chapter 2, the introduction to each chapter will highlight the general principles demonstrated in that chapter. Your understanding of how to apply the following general principles of physiology to a given chapter's content will then be assessed at the end of the chapter and in Dig Deeper questions associated with certain figures.

1. ***Homeostasis is essential for health and survival.*** The ability to maintain physiological variables such as body temperature and blood sugar concentrations within normal ranges is the underlying principle upon which all physiology is based. Keys to this principle are the processes of feedback and feedforward. Challenges to homeostasis may result from disease or from environmental factors such as famine or exposure to extremes of temperature.
2. ***The functions of organ systems are coordinated with each other.*** Physiological mechanisms operate and interact at the levels of cells, tissues, organs, and organ systems. Furthermore, the different organ systems in the human body do not function independently of each other. Each system typically interacts with one or more others to control a homeostatic variable. A good example that you will learn about in Chapters 12 and 14 is the coordinated activity of the circulatory and urinary systems in regulating blood pressure. This type of coordination is often referred to as "integration" in physiological contexts.
3. ***Most physiological functions are controlled by multiple regulatory systems, often working in opposition.*** Typically, control systems in the human body operate such that a given variable, such as heart rate, receives both stimulatory and inhibitory signals. As you will learn in detail in Chapter 6, for example, the nervous system sends both types of signals to the heart; adjusting the ratio of stimulatory to inhibitory

signals allows for fine-tuning of the heart rate under changing conditions such as rest or exercise.

4. ***Information flow between cells, tissues, and organs is an essential feature of homeostasis and allows for integration of physiological processes.*** Cells can communicate with nearby cells via locally secreted chemical signals; a good example of this is the signaling between cells of the stomach that results in acid production, a key feature of the digestion of proteins (see Chapter 15). Cells in one structure can also communicate long distances using electrical signals or chemical messengers such as hormones. Electrical and hormonal signaling will be discussed throughout the textbook and particularly in Chapters 6, 7, and 11.
5. ***Controlled exchange of materials occurs between compartments and across cellular membranes.*** The movement of water and solutes—such as ions, sugars, and other molecules—between the extracellular and intracellular fluid is critical for the survival of all cells, tissues, and organs. In this way, important biological molecules are delivered to cells and wastes are removed and eliminated from the body. In addition, regulation of ion movements creates the electrical properties that are crucial to the function of many cell types. These exchanges occur via several different mechanisms, which are introduced in Chapter 4 and are reinforced where appropriate for each organ system throughout the book.
6. ***Physiological processes are dictated by the laws of chemistry and physics.*** Throughout this textbook, you will encounter some simple chemical reactions, such as the reversible binding of oxygen to the protein hemoglobin in red blood cells (Chapter 13). The basic mechanisms that regulate such reactions are reviewed in Chapter 3. Physical laws, too, such as gravity, electromagnetism, and the relation between the diameter of a tube and the flow of liquid through the tube, help explain things like why we may feel light-headed upon standing too suddenly (Chapter 12, but also see the Clinical Case Study that follows in this chapter), how our eyes detect light (Chapter 7), and how we inflate our lungs with air (Chapter 13).
7. ***Physiological processes require the transfer and balance of matter and energy.*** Growth and the maintenance of homeostasis require regulation of the movement and transformation of energy-yielding nutrients and molecular building blocks between the body and the environment and between different regions of the body. Nutrients are ingested (Chapter 15), stored in various forms (Chapter 16), and ultimately metabolized to provide energy that can be stored in the bonds of ATP (Chapters 3 and 16). The concentrations of many inorganic molecules must also be regulated to maintain body structure and function—for example, the Ca^{2+} found in bones (Chapter 11). One of the most important functions of the body is to respond to changing demands, such as the increased requirement for nutrients and oxygen in exercising muscle. This requires a coordinated allocation of resources to regions that most require them at a particular time. The mechanisms by which the organ systems of the body recognize and respond to changing demands is a theme you will encounter repeatedly in Chapters 6 through 19.
8. ***Structure is a determinant of—and has coevolved with—function.*** The form and composition of cells, tissues, organs, and organ systems determine how they interact with each other and with the physical world. Throughout the text, you will see examples of how different body parts converge in their structure to accomplish similar functions. For example, enormous elaborations of surface areas to facilitate membrane transport and diffusion can be observed in the circulatory (Chapter 12), respiratory (Chapter 13), urinary (Chapter 14), digestive (Chapter 15), and reproductive (Chapter 17) systems.

Study and Review 1.9

- **General principles of physiology:** include homeostasis; information flow; coordination between the functions of different organ systems; transfer of matter and energy; structure determines function; physiological processes follow the laws of chemistry and physics

Review Question: *Refer back to Figure 1.9. Which general principles of physiology are depicted by the reflexes that control body temperature homeostasis?* ***(Answer found in Appendix A.)***

CHAPTER 1

Clinical Case Study: Loss of Consciousness in a 64-Year-Old Man While Gardening on a Hot Day

Comstock Images/Getty Images

Throughout this text, you will find a feature at the end of each chapter called the "Clinical Case Study." These segments reinforce what you have learned in that chapter by applying it to real-life examples of different medical conditions. The clinical case studies will increase in complexity as you progress through the text and will enable you to integrate recent material from a given chapter with information learned in previous chapters. In this first clinical case study, we examine a serious and potentially life-threatening condition that can occur in individuals in whom body temperature homeostasis is disrupted. All of the material presented in this clinical case study will be explored in depth in subsequent chapters, as you learn the mechanisms that underlie the pathologies and compensatory responses illustrated here in brief. Notice as you read that the first two general principles of physiology described earlier are particularly relevant to this case. *It is highly recommended that you return to this case study as a benchmark at the end of your semester; we are certain that you will be amazed at how your understanding of physiology has grown in that time.*

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A 64-year-old, fair-skinned man in good overall health spent a very hot, humid summer day gardening in his backyard. After several hours in the sun, he began to feel light-headed and confused as he knelt over his vegetable garden. Although earlier he had been perspiring profusely and appeared flushed, his sweating had eventually stopped. Because he also felt confused and disoriented, he could not recall for how long he had not been perspiring, or even how long it had been since he had taken a drink of water. He called to his wife, who was alarmed to see that his skin had since turned a pale-blue color. She asked her husband to come indoors, but he fainted as soon as he tried to stand. The wife called for an ambulance, and the man was taken to a hospital and diagnosed with a condition called heatstroke. What happened to this man that would explain his condition? How does it relate to homeostasis?

Reflect and Review #1

- Review the homeostatic control of body temperature in Figure 1.5. Based on that, what would you expect to occur to skin blood vessels when a person first starts feeling warm?

As you learned in this chapter, body temperature is a physiological function that is under homeostatic control. If body temperature decreases, heat production increases and heat loss decreases, as illustrated in Figures 1.5 and 1.9. Conversely, as in our example here, if body temperature increases, heat production decreases and heat loss increases. When our patient began gardening on a hot, humid day, his body temperature began to increase. At first, the blood vessels in his skin dilated, making him appear flushed and helping him dissipate heat across his skin. In addition, he perspired heavily. As you will learn in Chapter 16, perspiration is an important mechanism by which the body loses heat; it takes considerable heat to evaporate water from the surface of the skin, and the source of that heat is from the body. However, as you likely know from personal experience, evaporation of water from the body is less effective in humid environments, which makes it more dangerous to exercise when it is not only hot but also humid.

The sources of perspiration are the sweat glands, which are located beneath the skin and which secrete a salty solution through ducts to the surface of the skin. The fluid in sweat comes from the extracellular fluid compartment, which, as you have learned, consists of the plasma and interstitial fluid compartments (see Figure 1.3). Consequently, the profuse sweating that initially occurred in this man caused his extracellular fluid levels to decrease. In fact, the fluid levels decreased so severely that the amount of blood available to be pumped out of his heart with each heartbeat also decreased. The relationship between fluid volume and blood pressure is an important one that you will learn about in detail in Chapter 12. Generally speaking, if extracellular fluid levels decrease, blood pressure decreases as a consequence. This explains why our subject felt light-headed, particularly when he tried to stand up too quickly. As his blood pressure decreased, the ability of his heart to pump sufficient blood against gravity up to his brain also decreased; when brain cells are deprived of blood flow, they begin to malfunction. Suddenly standing only made matters worse. Perhaps you have occasionally experienced a little of this light-headed feeling when you have jumped out of a chair or bed and stood up too quickly. Normally, your nervous system quickly compensates for the effects of gravity on blood flowing up to the brain, as will be described in Chapters 6 and 12. In a person with decreased blood volume and pressure, however, this compensation may not happen and the person can lose consciousness. After fainting and falling, the man's head and heart were at the same horizontal level; consequently, blood could more easily reach his brain.

Another concern is that the salt (ion) concentrations in the body fluids changed. If you have ever tasted the sweat on your upper lip on a hot day, you know that it is somewhat salty. That is because sweat is derived from extracellular fluid, which as you have learned is a watery solution of ions (derived from salts, such as NaCl) and other substances. Sweat, however, is slightly more dilute than extracellular fluid because more water than ions is secreted from sweat glands. Consequently, the more heavily one perspires, the more concentrated the extracellular fluid becomes. In other words, the total amount of water and ions in the extracellular fluid decreases with perspiration, but the remaining fluid is "saltier." Heavy perspiration, therefore, not only disrupts fluid balance and blood pressure homeostasis but also has an impact on the balance of the ions in the body fluids, notably Na^+, K^+, and Cl^-. A homeostatic balance of ion concentrations in the body fluids is absolutely essential for normal heart and brain function, as you will learn in Chapters 4 and 6. As the man's ion concentrations changed, therefore, the change affected the activity of the cells of his brain.

Reflect and Review #2

- Refer to Figure 1.12. Was the man in a positive or negative balance for total-body Na^+?

Why did the man stop perspiring, and why did his skin turn pale? To understand this, we must consider that several homeostatic variables were disrupted by his activities. His body temperature increased, which initially resulted in heavy sweating. As the sweating continued, it resulted in decreased fluid levels and a negative balance of key ion concentrations in his body; this contributed to a decrease in mental function, and he became confused. As his body fluid levels continued to decrease, his blood pressure also decreased, further endangering brain function. At this point, the homeostatic control systems were essentially in competition. Though it is potentially life threatening for body temperature to *increase* too much, it is also life threatening for blood pressure to *decrease* too much. Eventually, many of the blood vessels in regions of the body that are not immediately required for survival—such as the skin—began to constrict, or close off. By doing so, the more vital organs of the body—such as the brain—could receive sufficient blood. This is why the man's skin turned a pale blue, because the amount of oxygen-rich blood flowing to the surface of his skin was decreased. Unfortunately, although this compensatory mechanism

helped protect the man's brain and other vital organs by providing the necessary blood flow to them, the reduction in blood flow to the skin made it increasingly more difficult to dissipate heat from the body to the environment. It also made it more difficult for sweat glands in the skin to obtain the fluid required to produce sweat. The man gradually decreased perspiring and eventually stopped sweating altogether. At that point, his body temperature spiraled out of control and he was hospitalized (**Figure 1.13**).

This case illustrates a critical feature of homeostasis that you will encounter throughout this textbook and that was emphasized in this chapter. Often, when one physiological variable—such as body temperature—is disrupted, the compensatory responses initiated to correct that disruption cause, in turn, imbalances in other variables. These secondary imbalances must also be compensated for, and the significance of each imbalance must be "weighed" against the others. In this example, the man was treated with intravenous fluids made up of a salt solution to restore his fluid levels and concentrations, and he was immersed in a cool bath and given cool compresses to help reduce his body temperature. Although he recovered, many people do not survive heatstroke because of its profound impact on homeostasis.

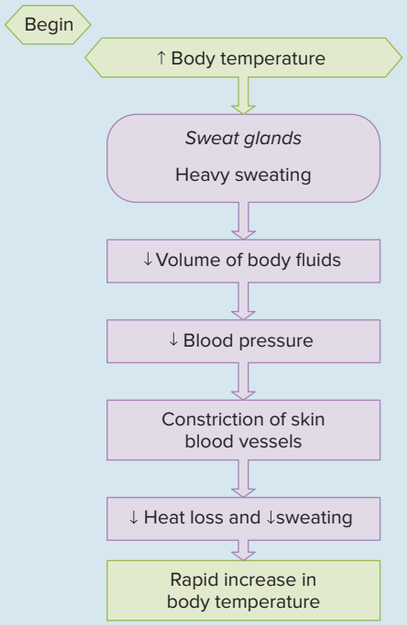


Figure 1.13 Sequence of events that occurred in the man described in this case study.

See Chapter 19 for complete, integrative case studies.

KEY AND *CLINICAL* TERMS

1.1 The Scope of Human Physiology

pathophysiology
physiology

1.2 How Is the Body Organized?

basement membrane
cell differentiation
cells
collagen fibers
connective tissue
connective-tissue cells
elastin fibers
epithelial cells
epithelial tissue
epithelium
extracellular matrix (ECM)
fibers
functional units
muscle cells
muscle tissue
nerve
nervous tissue
neuron
organs
organ system
tissues

1.3 Body Fluid Compartments

extracellular fluid
internal environment
interstitial fluid
interstitium
intracellular fluid
plasma

1.4 Homeostasis: A Defining Feature of Physiology

dynamic constancy
homeostasis

1.5 General Characteristics of Homeostatic Control Systems

equilibrium
feedforward regulation
homeostatic control systems
negative feedback
positive feedback
set point
steady state

1.6 Components of Homeostatic Control Systems

acquired reflexes
afferent pathway
effector
efferent pathway
hormone
integrating center
learned reflexes
local homeostatic responses
receptor
reflex
reflex arc
stimulus

1.7 The Role of Intercellular Chemical Messengers in Homeostasis

autocrine substances
endocrine glands
neurotransmitters
paracrine substances

1.8 Processes Related to Homeostasis

acclimatization
adaptation
circadian rhythm
entrainment
free-running rhythm
melatonin
negative balance
pacemaker
pineal gland
pool
positive balance
stable balance

CHAPTER 1 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. Which of the following is one of the four basic cell types in the body?
   a. respiratory
   b. epithelial
   c. endocrine
   d. integumentary
   e. immune
2. Which of the following is *incorrect*?
   a. Equilibrium requires a constant input of energy.
   b. Positive feedback is less common in nature than negative feedback.
   c. Homeostasis does not imply that a given variable is unchanging.
   d. Fever is an example of resetting a set point.
   e. Efferent pathways carry information away from the integrating center of a reflex arc.
3. In a reflex arc initiated by touching a hand to a hot stove, the effector belongs to which class of tissue?
   a. nervous
   b. connective
   c. muscle
   d. epithelial
4. Which is correct?
   a. Circadian rhythms can only free-run; they cannot be fixed to some environmental cue.
   b. Being able to perceive color is an example of an acclimatization.
   c. Eating a very salty meal will create a period of positive sodium balance in the blood.
   d. Drinking an excess of water will create a negative balance of water in the body.
   e. Acclimatization requires a modification of a person's genetic makeup.
5. Most of the water in the human body is found in
   a. the interstitial fluid compartment.
   b. the intracellular fluid compartment.
   c. the plasma compartment.
   d. the total extracellular fluid compartment.
6. The type of tissue involved in many types of transport processes, and which often lines the inner surfaces of tubular structures, is called _____.
7. All the fluid found outside cells is collectively called _____ fluid, and consists of _____ and _____ fluid.
8. Physiological changes that occur in anticipation of a future change to a homeostatic variable are called _____ processes.
9. A _____ is a chemical factor released by cells that acts on neighboring cells without having to first enter the blood.
10. When loss of a substance from the body exceeds its gain, a person is said to be in _____ balance for that substance.

CHAPTER 1 TEST QUESTIONS *Apply, Analyze, and Evaluate*

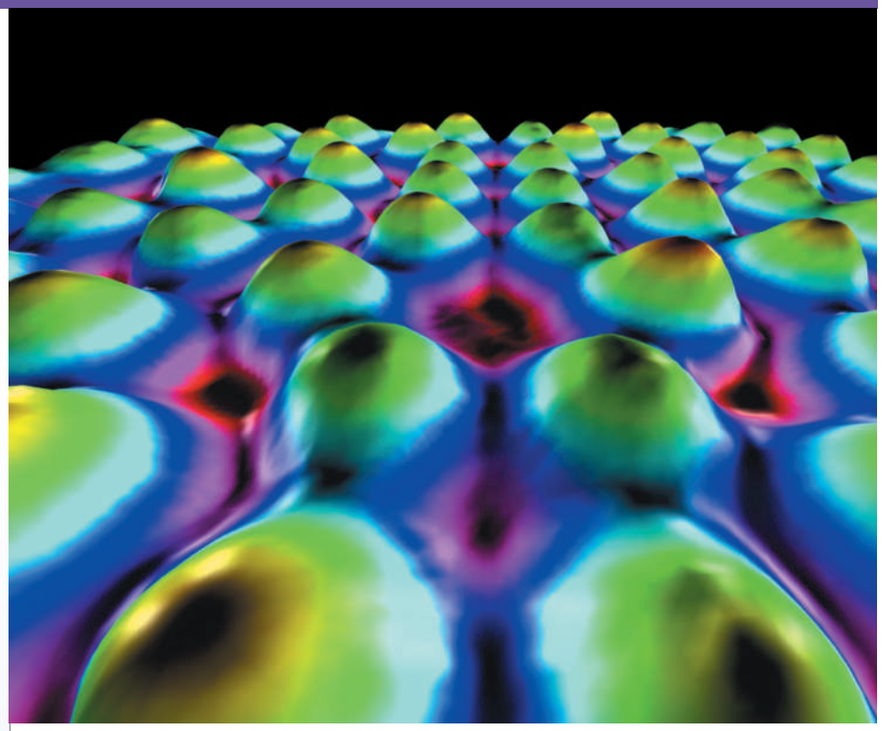
Answers appear in Appendix A.

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. The Inuit of Alaska and Canada have a remarkable ability to work in the cold without gloves and not suffer decreased skin blood flow. Does this prove that there is a genetic difference between the Inuit and other people with regard to this characteristic? *Hint:* Refer back to "Adaptation and Acclimatization" in Section 1.8.
2. Explain how an imbalance in any given physiological variable may produce a change in one or more *other* variables. *Hint:* For help, see Section 1.4 and Figure 1.13.

Chemical Composition of the Body and Its Relation to Physiology

CHAPTER 2



Scanning tunneling micrograph of individual silicon atoms on a silicon chip.
Andrew Dunn/Alamy Stock Photo

In Chapter 1, you were introduced to the concept of homeostasis, in which variables such as the concentrations of many chemicals in the blood are maintained within a normal range. To fully appreciate the mechanisms by which homeostasis is achieved, we must first understand the basic chemistry of the human body, including the key features of atoms and molecules that contribute to their ability to interact with one another. Such interactions form the basis for processes as diverse as maintaining a healthy pH of the body fluids, determining which molecules will bind to or otherwise influence the function of other molecules, forming functional proteins that mediate numerous physiological processes, and maintaining energy homeostasis.

In this chapter, we also will describe the distinguishing characteristics of some of the major organic molecules in the human body. The specific functions of these molecules in physiology will be introduced here and discussed more fully in subsequent chapters where appropriate. This chapter will provide you with the knowledge required to best appreciate the significance of one of the general principles of physiology introduced in Chapter 1, namely that physiological processes are dictated by the laws of chemistry and physics. ■

2.1 Atoms

The units of matter that form all chemical substances are called **atoms.** Each type of atom—carbon, hydrogen, oxygen, and so on—is called a **chemical element.** A one- or two-letter symbol is used as an abbreviated identification for each element. Although more than 100 elements occur naturally or have been synthesized in the laboratory, only 24 (**Table 2.1**) have been clearly identified as essential for the function of the human body and are therefore of particular interest to physiologists.

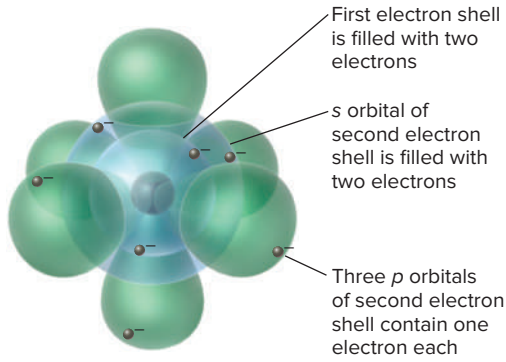
Components of Atoms

The chemical properties of atoms can be described in terms of three subatomic particles—**protons, neutrons,** and **electrons.** The protons and neutrons are confined to a very small volume at the center of an atom called the **atomic nucleus.** The electrons revolve in orbitals at various distances from the nucleus. Each orbital can hold up to two electrons and no more. The larger the atom, the more electrons it contains, and therefore the more orbitals that exist around the nucleus. Orbitals are found in regions known as electron shells; additional shells exist at greater and greater distances from the nucleus as atoms get bigger. An atom such as carbon has more shells than does hydrogen with its lone electron, but fewer than an atom such as iron, which has a greater number of electrons.

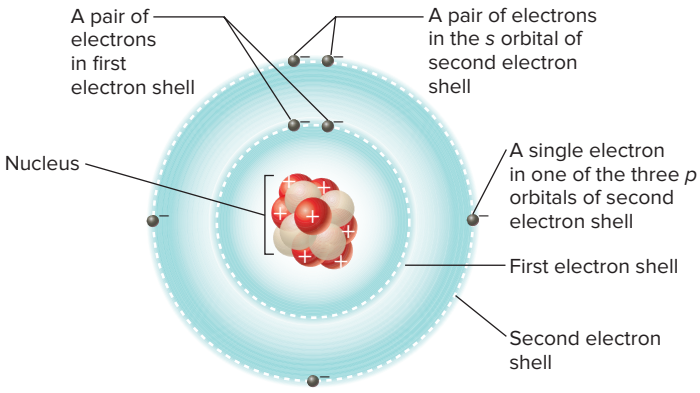
The first, innermost shell of any atom can hold up to two electrons in a single, spherical ("*s*") orbital (**Figure 2.1a**). Once the lone orbital of the innermost shell is filled, electrons begin to fill the second shell. The second shell can hold up to eight electrons; the first two electrons fill a spherical orbital, and subsequent electrons fill three additional, propeller-shaped ("*p*") orbitals. Additional shells can accommodate further orbitals; this will happen once the inner shells are filled. For simplicity, we will ignore the distinction between *s* and *p* orbitals and represent the shells of an atom in two dimensions as shown in **Figure 2.1b** for nitrogen.

TABLE 2.1 Essential Chemical Elements in the Body (Neo-Latin Terms in Italics)

Element	Symbol
Major Elements: 99.3% of Total Atoms in the Body	
Hydrogen	H (63%)
Oxygen	O (26%)
Carbon	C (9%)
Nitrogen	N (1%)
Mineral Elements: 0.7% of Total Atoms in the Body	
Calcium	Ca
Phosphorus	P
Potassium	K (*kalium*)
Sulfur	S
Sodium	Na (*natrium*)
Chlorine	Cl
Magnesium	Mg
Trace Elements: Less Than 0.01% of Total Atoms in the Body	
Iron	Fe (*ferrum*)
Iodine	I
Copper	Cu (*cuprum*)
Zinc	Zn
Manganese	Mn
Cobalt	Co
Chromium	Cr
Selenium	Se
Molybdenum	Mo
Fluorine	F
Tin	Sn (*stannum*)
Silicon	Si
Vanadium	V



(a) Nitrogen atom showing electrons in orbitals



(b) Simplified depiction of a nitrogen atom (seven electrons: two electrons in first electron shell, five in second electron shell)

Figure 2.1 APR Arrangement of subatomic particles in an atom, shown here for nitrogen. (a) Negatively charged electrons orbit around a nucleus consisting of positively charged protons and (except for hydrogen) uncharged neutrons. Up to two electrons may occupy an orbital, shown here as regions in which an electron is likely to be found. The orbitals exist within electron shells at progressively greater distances from the nucleus as atoms get bigger. The first electron shell contains only a single orbital; progressively distant shells may contain a different number of orbitals. (b) Simplified, two-dimensional depiction of a nitrogen atom, showing a full complement of two electrons in its innermost shell and five electrons in its second, outermost shell. Orbitals are not depicted using this simplified means of illustrating an atom.

An atom is most stable when all of the orbitals in its outermost shell are filled with two electrons each. If one or more orbitals do not have their capacity of electrons, the atom can react with other atoms and form molecules, as described later. For many of the atoms that are most important for physiology, the outer shell requires eight electrons in its orbitals in order to be filled to capacity.

Each of the subatomic particles has a different electrical charge. Protons have one unit of positive charge, electrons have one unit of negative charge, and neutrons are electrically neutral. Because the protons are located in the atomic nucleus, the nucleus has a net positive charge equal to the number of protons it contains. One of the fundamental principles of physics is that opposite electrical charges attract each other and like charges repel each other. It is the attraction between the positively charged protons and the negatively charged electrons that serves as a major force that forms an atom. The entire atom has no net electrical charge, however, because the number of negatively charged electrons orbiting the nucleus equals the number of positively charged protons in the nucleus.

Atomic Number

Each chemical element contains a unique and specific number of protons, and it is this number, known as the **atomic number,** that distinguishes one type of atom from another. For example, hydrogen, the simplest atom, has an atomic number of 1, corresponding to its single proton. As another example, calcium has an atomic number of 20, corresponding to its 20 protons. Because an atom is electrically neutral, the atomic number is also equal to the number of electrons in the atom.

Atomic Mass

Atoms have very little mass. A single hydrogen atom, for example, has a mass of only 1.67×10^{-24} g. The **atomic mass** scale indicates an atom's mass relative to the mass of other atoms. By convention, this scale is based upon assigning the carbon atom a mass of exactly 12. On this scale, a hydrogen atom has an atomic mass of approximately 1, indicating that it has one-twelfth the mass of a carbon atom. A magnesium atom, with an atomic mass of 24, has twice the mass of a carbon atom. The unit of atomic mass is known as a dalton. One dalton (d) equals one-twelfth the mass of a carbon atom.

Although the number of neutrons in the nucleus of an atom is often equal to the number of protons, many chemical elements can exist in multiple forms, called **isotopes,** which have identical numbers of protons but which differ in the number of neutrons they contain. For example, the most abundant form of the carbon atom, ^{12}C, contains six protons and six neutrons and therefore has an atomic number of 6. Protons and neutrons are approximately equal in mass, and so ^{12}C has an atomic mass of 12. The radioactive carbon isotope ^{14}C contains six protons and eight neutrons, giving it an atomic number of 6 but an atomic mass of 14. The value of atomic mass given in the standard Periodic Table of the Elements is actually an average mass that reflects the relative abundance in nature of the different isotopes of a given element.

Many isotopes are unstable; they will spontaneously emit energy or even release components of the atom itself, such as part of the nucleus. This process is known as radiation, and such isotopes are called **radioisotopes.** The special qualities of radioisotopes are of great practical benefit in the practice of medicine and the study of physiology. In one example, high-energy radiation can be focused onto cancerous areas of the body to kill cancer cells. Radioisotopes may also be useful in making diagnoses. In one common method, the sugar glucose can be chemically modified so that it contains a radioactive isotope of fluorine. When injected into the blood, the cells of all the organs of the body take up the radioactive glucose just as they would ordinary glucose. Special imaging techniques such as ***PET (positron emission tomography) scans*** can then be used to detect how much of the radioactive glucose appears in different organs (**Figure 2.2**). Because glucose is a key source of energy used by all cells, this information can be used to determine if a given organ is functioning normally or at an increased or decreased rate. For example, a PET scan that revealed decreased uptake of radioactive glucose into the heart might indicate that the blood vessels of the heart were diseased, thereby depriving the heart of nutrients. PET scans can also reveal the presence of cancer—a disease characterized by uncontrolled cell growth and increased glucose uptake.

The **gram atomic mass** of a chemical element is the amount of the element, in grams, equal to the numerical value of its atomic mass. Thus, 12 g of carbon (assuming it is all ^{12}C) is 1 gram

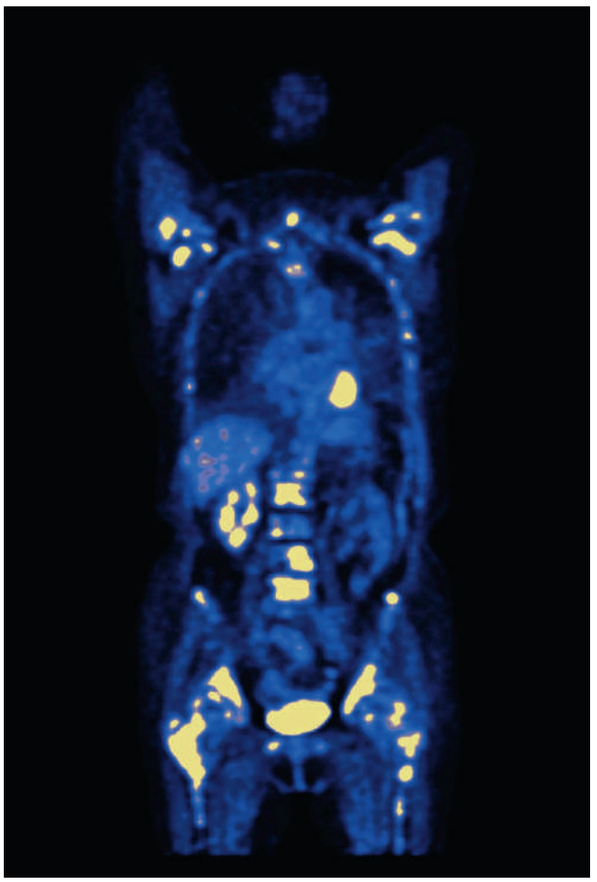


Figure 2.2 Positron emission tomography (PET) scan of a human body. In this image, radioactive glucose that has been taken up by the body's organs appears as a false color; the greater the uptake, the more intense the color. The brightest regions were found to be areas of cancer in this particular individual. Living Art Enterprises/Science Source

atomic mass of carbon, and 1 g of hydrogen is 1 gram atomic mass of hydrogen. *One gram atomic mass of any element contains the same number of atoms.* For example, 1 g of hydrogen contains 6×10^{23} atoms; likewise, 12 g of carbon, whose atoms have 12 times the mass of a hydrogen atom, also has 6×10^{23} atoms (this value is often called Avogadro's constant, or Avogadro's number, after the nineteenth-century Italian scientist Amedeo Avogadro).

Ions

As mentioned, a single atom is electrically neutral because it contains equal numbers of negative electrons and positive protons. There are instances, however, in which certain atoms may gain or lose one or more electrons; in such cases, they will then acquire a net electrical charge and become an **ion.** This may happen, for example, if an atom has an outer shell that contains only one or a few electrons; losing those electrons would mean that the next innermost shell would then become the outermost shell. This next innermost shell is complete with a full capacity of electrons and is therefore very stable (recall that each successive shell does not begin to acquire electrons until all the preceding inner shells are filled). For example, when a sodium atom (Na), which has 11 electrons, loses the lone electron in its outer shell, it becomes a sodium ion (Na^+) with a net positive charge; it still has 11 protons, but it now has only 10 electrons, 2 in its first shell and a full complement of 8 in its second, outer shell. On the other hand, a chlorine atom (Cl), which has 17 electrons, is 1 electron shy of a full outer shell. It can gain an electron and become a chloride ion (Cl^-) with a net negative charge—it now has 18 electrons but only 17 protons. Some atoms can gain or lose more than 1 electron to become ions with two or more units of net electrical charge (for example, the calcium ion Ca^{2+}).

Hydrogen and many other atoms readily form ions. Table 2.2 lists the ionic forms of some of these elements that are found in the body. Ions that have a net positive charge are called **cations,** and those that have a net negative charge are called **anions.** Because of their charge, ions are able to conduct electricity when dissolved in water; consequently, the ionic forms of mineral elements are collectively referred to as **electrolytes.** This is extremely important in physiology, because electrolytes are used to carry electrical charge across cell membranes; in this way, they serve as the source of electrical current in certain cells. You will learn in Chapters 6, 9, and 12 that such currents are critical to the ability of muscle cells and neurons to function in their characteristic ways.

Atomic Composition of the Body

Just four of the body's essential elements (see Table 2.1)—hydrogen, oxygen, carbon, and nitrogen—account for over 99% of the atoms in the body.

The seven essential **mineral elements** are the most abundant substances dissolved in the extracellular and intracellular fluids. Most of the body's calcium and phosphorus atoms, however, make up the solid matrix of bone tissue.

The 13 essential **trace elements,** so-called because they are present in extremely small quantities, are required for normal growth and function. For example, iron has a critical function in the blood's transport of oxygen, and iodine is required for the production of thyroid hormone.

Many other elements, in addition to the 24 listed in Table 2.1, may be detected in the body. These elements enter in the foods we eat and the air we breathe but are not essential for normal body function and may even interfere with normal body chemistry. For example, ingested arsenic has poisonous effects.

TABLE 2.2 Ionic Forms of Elements Most Frequently Encountered in the Body

Atom	Symbol	Ion	Chemical Symbol	Electrons Gained or Lost
Hydrogen	H	Hydrogen ion	H^+	**1 lost**
Sodium	Na	Sodium ion	Na^+	**1 lost**
Potassium	K	Potassium ion	K^+	**1 lost**
Chlorine	Cl	Chloride ion	Cl^-	**1 gained**
Magnesium	Mg	Magnesium ion	Mg^{2+}	**2 lost**
Calcium	Ca	Calcium ion	Ca^{2+}	**2 lost**

Study and Review 2.1

- **Atoms:** consist of shells of **electrons** (–) around an atomic nucleus comprised of **protons** (+) and **neutrons** (uncharged)
  - Each type of atom is a **chemical element.**
- **Atomic number:** number of protons in an atom
- **Atomic mass:** ratio of an atom's mass relative to that of a ^{12}C atom
  - **Gram atomic mass:** amount of an element, in grams, equal to numerical value of its atomic mass
- **Isotope:** a chemical element with the same number of protons but different numbers of neutrons; **radioisotopes** are unstable and emit radiation
- **Ion:** an atom that has gained (**anion**) or lost (**cation**) one or more electrons, thereby acquiring a net electrical charge
- H, O, C, and N account for over 99% of atoms in the body; remainder are **mineral elements** (e.g., Ca) and **trace elements** (e.g., Fe).

Review Question: *Iron is an important trace element for normal body function and is critical for such processes as oxygen transport in the blood. The most common form of iron has 26 protons and 30 neutrons and is not an ion. What are its atomic number and atomic mass? How many electrons does it have?* ***(Answer found in Appendix A.)***

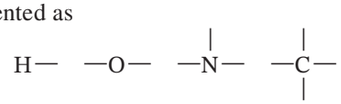
2.2 Molecules

Two or more atoms bonded together make up a **molecule.** A molecule made up of two or more different elements is called a compound, but the two terms are often used interchangeably. For example, a molecule of oxygen gas consists of two atoms of oxygen bonded together. By contrast, water is a compound that contains two hydrogen atoms and one oxygen atom. For simplicity, we will generally use the term *molecule* in this textbook. Molecules can be represented by their component atoms. In the two examples just given, a molecule of oxygen can be represented as O_2 and water as H_2O. The atomic composition of glucose, a sugar, is $C_6H_{12}O_6$, indicating that the molecule contains 6 carbon atoms, 12 hydrogen atoms, and 6 oxygen atoms. Such formulas, however, do not indicate how the atoms are linked together in the molecule. This occurs by means of chemical bonds, as described next.

Covalent Chemical Bonds

Chemical bonds between atoms in a molecule form when electrons transfer from the outer electron shell of one atom to that of another, or when two atoms with partially unfilled electron shells share electrons. The strongest chemical bond between two atoms is called a **covalent bond,** which forms when one or more electrons in the outer electron shells of each atom are shared between the two atoms (**Figure 2.3**). In the example shown in Figure 2.3, a carbon atom with two electrons in its innermost shell and four in its outer shell forms covalent bonds with four hydrogen atoms. Recall that the second shell of atoms can hold up to eight electrons. Carbon has six total electrons and only four in the second shell, because two electrons are used to fill the first shell. Therefore, it has "room" to acquire four additional electrons in its outer shell. Hydrogen has only a single electron, but like all orbitals, its single orbital can hold up to two electrons. Therefore, hydrogen also has room for an additional electron. In this example, a single carbon atom shares its four electrons with four different hydrogen atoms, which in turn share their electrons with the carbon atom. The shared electrons orbit around both atoms, bonding them together into a molecule of methane (CH_4). These covalent bonds are the strongest type of bonds in the body; once formed, they usually do not break apart unless acted upon by an energy source (heat) or an enzyme (see Chapter 3 for a description of enzymes).

As mentioned, the atoms of some elements can form more than one covalent bond and thus become linked simultaneously to two or more other atoms. Each type of atom forms a characteristic number of covalent bonds, which depends on the number of electrons in its outermost orbit. The number of chemical bonds formed by the four most abundant atoms in the body are hydrogen, one; oxygen, two; nitrogen, three; and carbon, four. When the structure of a molecule is diagrammed, each covalent bond is represented by a line indicating a pair of shared electrons. The covalent bonds of the four elements just mentioned can be represented as



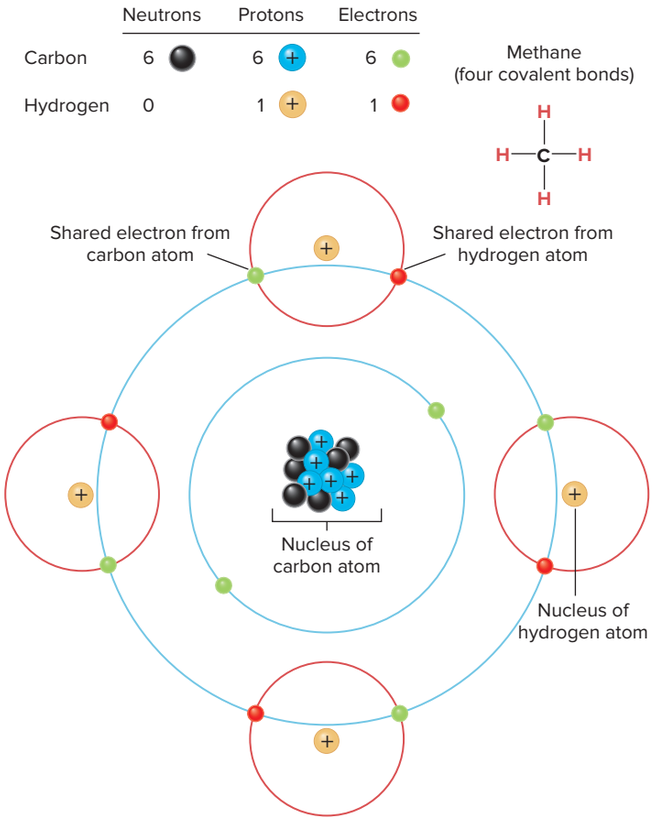


Figure 2.3 APR A covalent bond formed by sharing electrons. Hydrogen atoms have room for one additional electron in their sole orbital; carbon atoms have four electrons in their second shell, which can accommodate up to eight electrons. Each of the four hydrogen atoms in a molecule of methane (CH_4) forms a covalent bond with the carbon atom by sharing its one electron with one of the electrons in carbon. Each shared pair of electrons—one electron from the carbon and one from a hydrogen atom—forms a covalent bond. The sizes of protons, neutrons, and electrons are not to scale.

A molecule of water, H_2O, can be diagrammed as

H—O—H

In some cases, two covalent bonds—a double bond—form between two atoms when they share two electrons from each atom. Carbon dioxide (CO_2), a waste product of metabolism, contains two double bonds:

O═C═O

Note that in this molecule the carbon atom still forms four covalent bonds and each oxygen atom only two.

Polar Covalent Bonds

Not all atoms have the same ability to attract shared electrons. The measure of an atom's ability to attract electrons in a covalent bond is called its **electronegativity.** Electronegativity generally increases as the total positive charge of a nucleus increases but decreases as the distance between the outer electrons and the nucleus increases. When two atoms with different electronegativities combine to form a covalent bond, the shared electrons will