CHAPTER 1

Homeostasis:

A Framework for Human Physiology

Coping with changes in external temperature and oxygen levels even in extreme conditions are examples of homeostasis.

The purpose of this chapter is to provide an orientation to the subject of human physiology and the central role of homeostasis in the study of this science. The mountain climbers shown here and on the cover of the textbook are experiencing numerous challenges that must be met by their hearts, lungs, and other organs. An understanding of the functions of these and other organs of the body also requires knowledge of the structures and relationships of the body parts. For this reason, this chapter also introduces the way the body is organized into cells, tissues, organs, organ systems, and fluid compartments. Lastly, several "General Principles of Physiology" are introduced. These serve as unifying themes throughout the textbook, and the reader is encouraged to return to them often to see how they apply to the material covered in subsequent chapters. ■

1.1 The Scope of Human Physiology

Physiology is the study of how living organisms function. At one end of the spectrum, it includes the study of individual molecules—for example, how a particular protein's shape and electrical 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. . . ."

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

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

1.2 How Is the Body Organized?

The simplest structural units into which a complex multicellular organism can be divided and still retain the functions characteristic of life are called **cells** (**Figure 1.1**). Each human being begins as a single cell, a fertilized egg, which divides to create two cells, each of which divides in turn to result in four cells, and so on. If cell multiplication were the only event occurring, the end result would be a spherical mass of identical cells. During development, however, each cell becomes specialized for the performance of a particular function, such as producing force and movement or generating electrical signals. The process of transforming an unspecialized cell into a specialized cell is known as **cell differentiation,** the study of which is one of the most exciting areas in biology today. About 200 distinct kinds of cells can be identified in the body in terms of differences in structure and function. When cells are classified according to the broad types of function they perform, however,

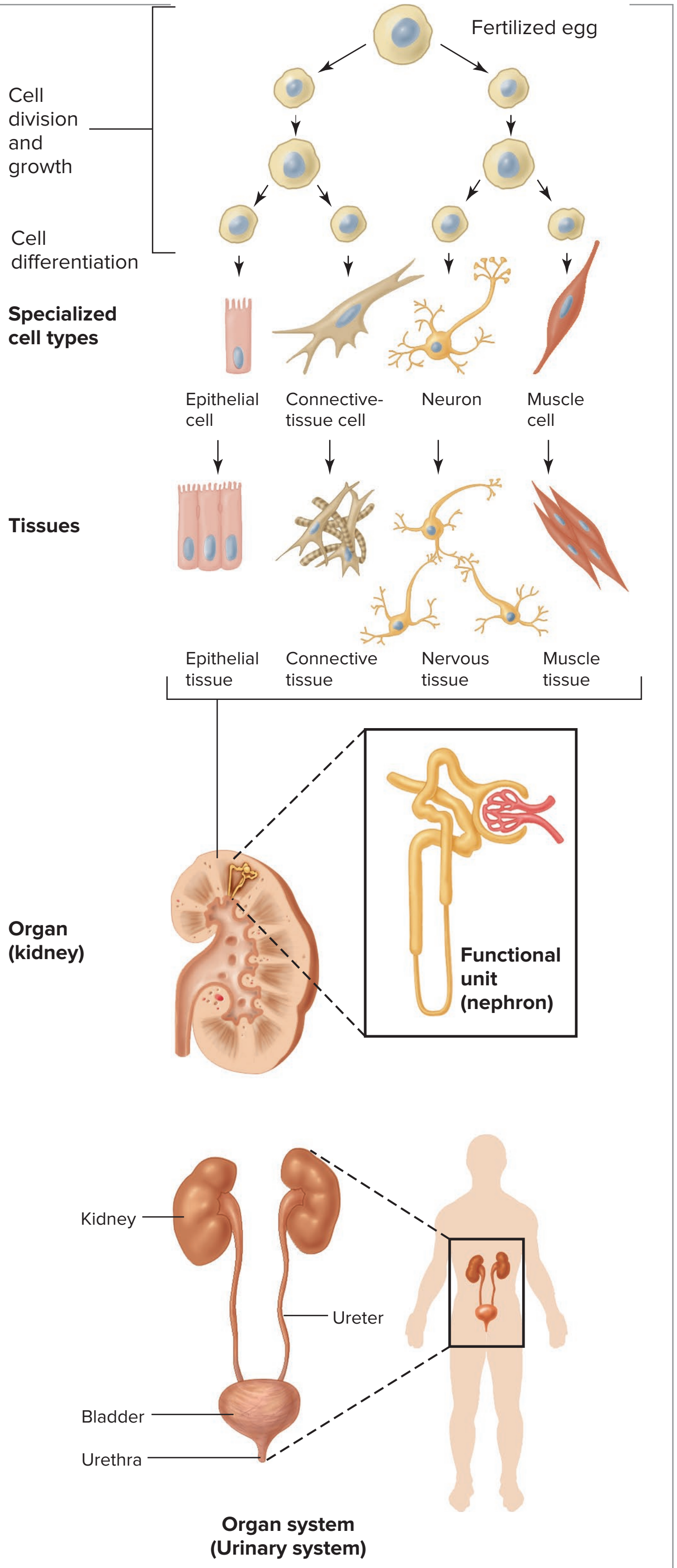


Figure 1.1 Levels of cellular organization. The nephron is not drawn to scale.

four major categories emerge: (1) muscle cells, (2) neurons, (3) epithelial cells, and (4) connective-tissue cells. In each of these functional categories, several cell types perform variations of the specialized function. For example, there are three types of muscle cells—skeletal, cardiac, and smooth. These cells differ from each other in shape, in the mechanisms controlling their contractile activity, and in their location in the various organs of the body, but each of them is a muscle cell.

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

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

Muscle Cells and Tissue

As noted earlier, there are three types of muscle cells. These cells form skeletal, cardiac, or smooth muscle tissue. All **muscle cells** are specialized to generate mechanical force. Skeletal muscle cells are attached through other structures to bones and produce movements of the limbs or trunk. They are also attached to skin, such as the muscles producing facial expressions. Contraction of skeletal muscle is under voluntary control, which simply means that you can choose to contract a skeletal muscle whenever you wish. Cardiac muscle cells are found only in the heart. When cardiac muscle cells generate force, the heart contracts and consequently pumps blood into the circulation. Smooth muscle cells 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 Chapter 9.

Neurons and Nervous Tissue

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

Epithelial Cells and Epithelial Tissue

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

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

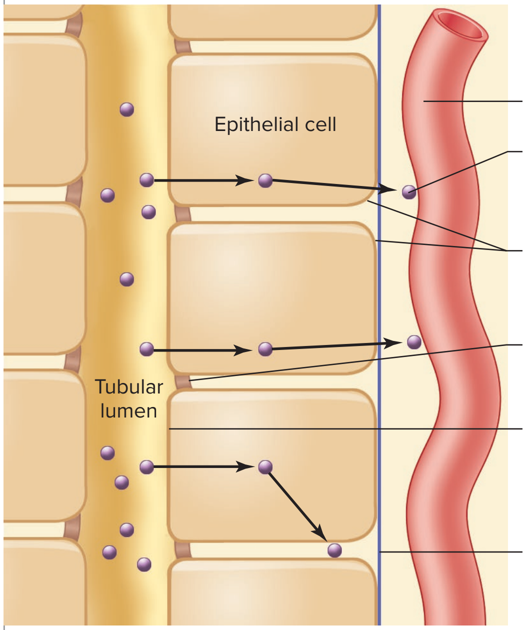


Figure 1.2 Epithelial tissue lining the inside of a structure such as a kidney tubule. The basolateral side of the cell is attached to a basement membrane. Each side of the cell can perform different functions, as in this example in which glucose is transported across the epithelium, first directed into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

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

Connective-Tissue Cells and Connective Tissue

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

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

Some of the proteins of the ECM are known as **fibers,** 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 (1) a series of small tubes, each composed of a simple epithelium; (2) blood vessels, whose walls contain varying quantities of smooth muscle and connective tissue; (3) extensions from neurons that end near the muscle and epithelial cells; and (4) a loose network of connective-tissue elements that are interspersed throughout the kidneys and include the protective capsule that surrounds the organ.

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

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

1.3 Body Fluid Compartments

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

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

TABLE 1.1	Organ Systems of the Body	
System	**Major Organs or Tissues**	**Primary Functions**
Circulatory	Heart, blood vessels, blood	Transport of blood throughout the body
Digestive	Mouth, salivary glands, pharynx, esophagus, stomach, small and large intestines, anus, pancreas, liver, gallbladder	Digestion and absorption of nutrients and water; elimination of wastes
Endocrine	All glands or organs secreting hormones: pancreas, testes, ovaries, hypothalamus, kidneys, pituitary, thyroid, parathyroids, adrenals, stomach, small intestine, liver, adipose tissue, heart, and pineal gland; and endocrine cells in other organs	Regulation and coordination of many activities in the body, including growth, metabolism, reproduction, blood pressure, water and electrolyte balance, and others
Immune	White blood cells and their organs of production	Defense against pathogens
Integumentary	Skin	Protection against injury and dehydration; defense against pathogens; regulation of body temperature
Lymphatic	Lymph vessels, lymph nodes	Collection of extracellular fluid for return to blood; participation in immune defenses; absorption of fats from digestive system
Musculoskeletal	Cartilage, bone, ligaments, tendons, joints, skeletal muscle	Support, protection, and movement of the body; production of blood cells
Nervous	Brain, spinal cord, peripheral nerves and ganglia, sense organs	Regulation and coordination of many activities in the body; detection of and response to changes in the internal and external environments; states of consciousness; learning; memory; emotion; others
Reproductive	Male: testes, penis, and associated ducts and glands Female: ovaries, fallopian tubes, uterus, vagina, mammary glands	Male: production of sperm; transfer of sperm to female Female: production of eggs; provision of a nutritive environment for the developing embryo and fetus; nutrition of the infant
Respiratory	Nose, pharynx, larynx, trachea, bronchi, lungs	Exchange of carbon dioxide and oxygen; regulation of hydrogen ion concentration in the body fluids
Urinary	Kidneys, ureters, bladder, urethra	Regulation of plasma composition through controlled excretion of ions, water, and organic wastes

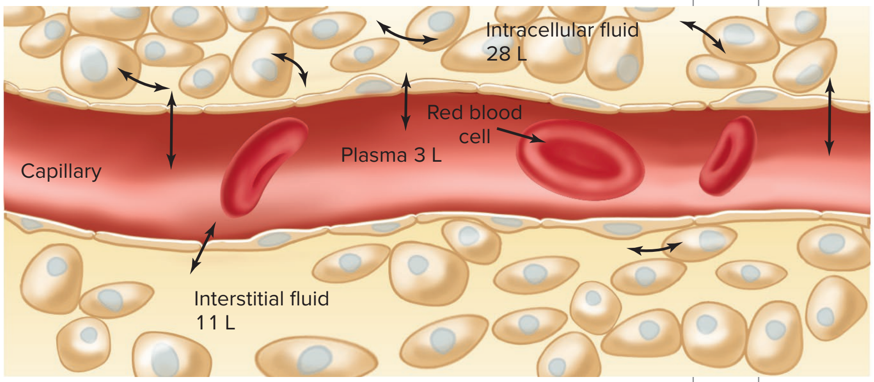
retained within the intracellular fluid and are not required in the extracellular fluid.

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

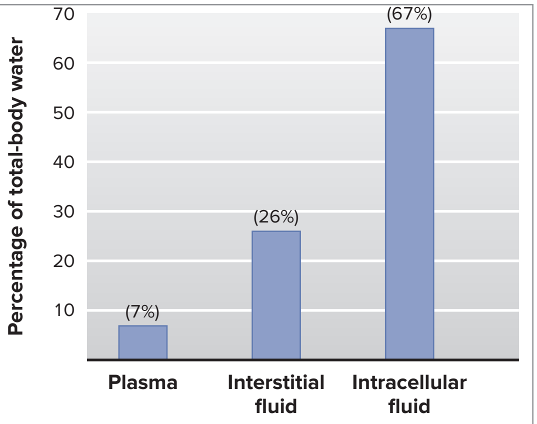
With this understanding of the structural organization of the body, we turn to a description of how balance is maintained in the internal environment of the body.

1.4 Homeostasis: A Defining Feature of Physiology

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



(a)



(b)

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

PHYSIOLOGICAL INQUIRY

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

Answer can be found at end of chapter.

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

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

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

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

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

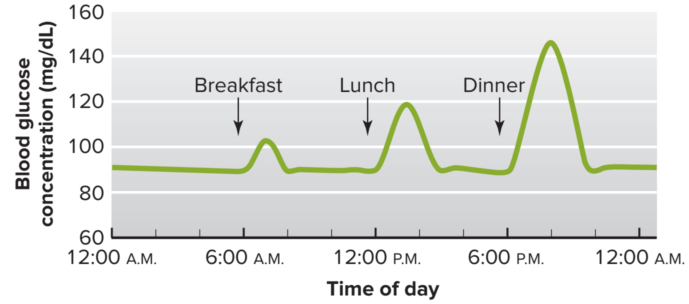


Figure 1.4 Changes in blood glucose concentration during a typical 24 h period. Note that glucose concentration increases after each meal, more so after larger meals, and then returns to the premeal concentration in a short while. The profile shown here is that of a person who is homeostatic for blood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

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

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

1.5 General Characteristics of Homeostatic Control Systems

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

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

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

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

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

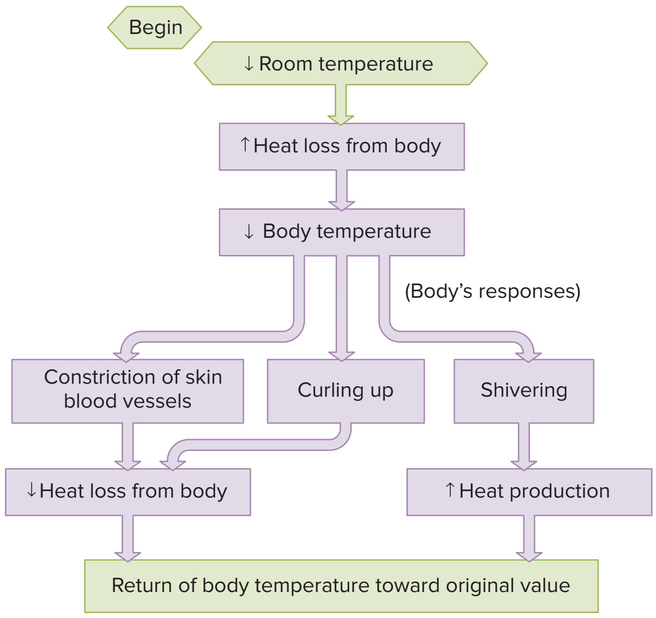


Figure 1.5 A homeostatic control system maintains body temperature when room temperature decreases. This flow diagram is typical of those used throughout this book to illustrate homeostatic systems, and several conventions should be noted. The "Begin" sign indicates where to start. The arrows next to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

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

Feedback Systems

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

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

Negative feedback may occur at the organ, cellular, or molecular level. For instance, negative feedback regulates many enzymatic processes, as shown in schematic form in **Figure 1.6**. (An enzyme is a protein that catalyzes chemical reactions.)

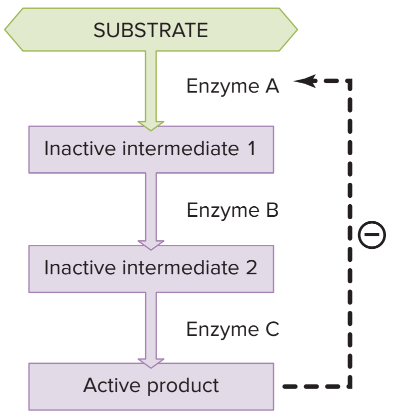


Figure 1.6 Hypothetical example of negative feedback (as denoted by the circled minus sign and dashed feedback line) occurring within a set of sequential chemical reactions. By inhibiting the activity of the first enzyme involved in the formation of a product, the product can regulate the rate of its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

PHYSIOLOGICAL INQUIRY

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

Answer can be found at end of chapter.

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

Not all forms of feedback are negative. In some cases, **positive feedback** accelerates a process, leading to an "explosive" system. This is counter to the general physiological principle of homeostasis, because positive feedback has no obvious means of stopping. Not surprisingly, therefore, positive feedback is much less common in nature than negative feedback. Nonetheless, there are examples in physiology in which positive feedback is very important. One well-described example, which you will learn about in 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, moreover, 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 physiologically reset to a new value. A common example is fever, the increase in body temperature that occurs in response to infection and that is somewhat analogous to raising the setting of a thermostat in a room. The homeostatic control systems regulating body temperature are still functioning during a fever, but they maintain the temperature at an increased value. This regulated increase in body temperature is adaptive for fighting the infection, because elevated temperature inhibits proliferation of some pathogens. In fact, this is why a fever is often preceded by chills and shivering. The set point for body temperature has been reset to a higher value, and the body responds by shivering to generate heat.

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

Although the resetting of a set point is adaptive in some cases, in others it simply reflects the clashing demands of different regulatory systems. This brings us to one more generalization. It is not possible for everything to be held constant by homeostatic

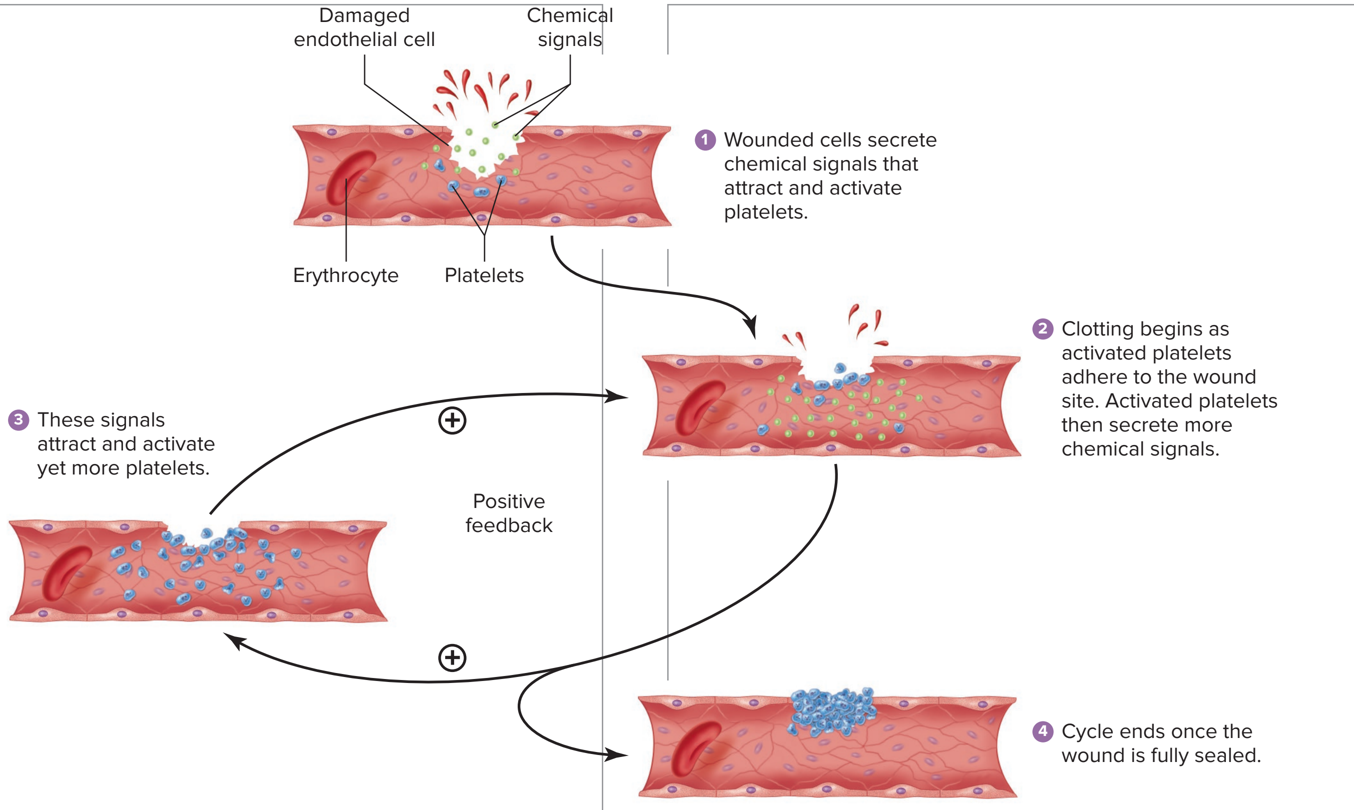


Figure 1.7 Positive feedback as illustrated by the clotting process in blood. Damaged endothelial cells (a type of epithelial cells) in the lining of a blood vessel secrete chemical signals that attract and activate platelets, tiny cell fragments that form clots. As clotting begins, the activated platelets 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.).

control systems. In our earlier example, body temperature was maintained despite large swings in ambient temperature, but only because the homeostatic control system brought about large changes in skin blood flow and skeletal muscle contraction. Moreover, because so many properties of the internal environment are closely interrelated, it is often possible to keep one property relatively stable only by moving others away from their usual set point. This is what we mean by "clashing demands," which explains the phenomenon mentioned earlier about the interplay between body temperature and water balance during exercise.

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

Feedforward Regulation

Another type of regulatory process often used in conjunction with feedback systems is **feedforward,** in which changes in regulated variables are anticipated and prepared for before they actually occur. Control of body temperature is a good example of a feedforward process. The temperature-sensitive neurons that trigger

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.

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.

1.6 Components of Homeostatic Control Systems

Reflexes

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

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

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

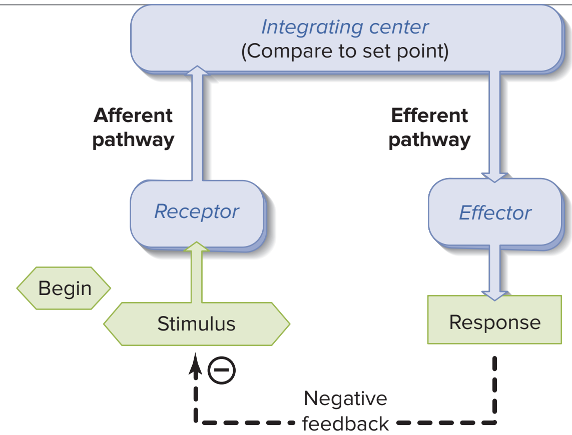


Figure 1.8 General components of a reflex arc that functions as a negative feedback control system. The response of the system has the effect of counteracting or eliminating the stimulus.

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.

The output of an integrating center is sent to the last component of the system, whose change in activity constitutes the overall response of the system. This component is known as an **effector.** 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. They 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

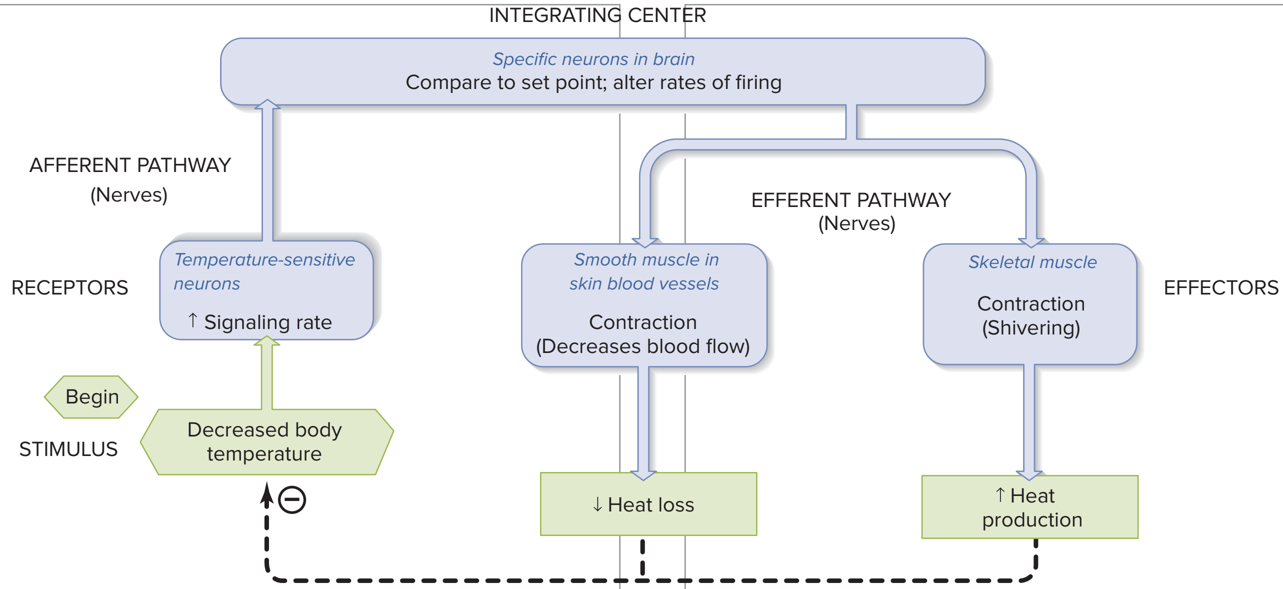


Figure 1.9 Reflex for minimizing the decrease in body temperature that occurs on exposure to a reduced external environmental temperature. This figure provides the internal components for the reflex shown in Figure 1.5. The dashed arrow and the ⊖ indicate the negative feedback nature of the reflex, denoting 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 box).

PHYSIOLOGICAL INQUIRY

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

Answer can be found at end of chapter.

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

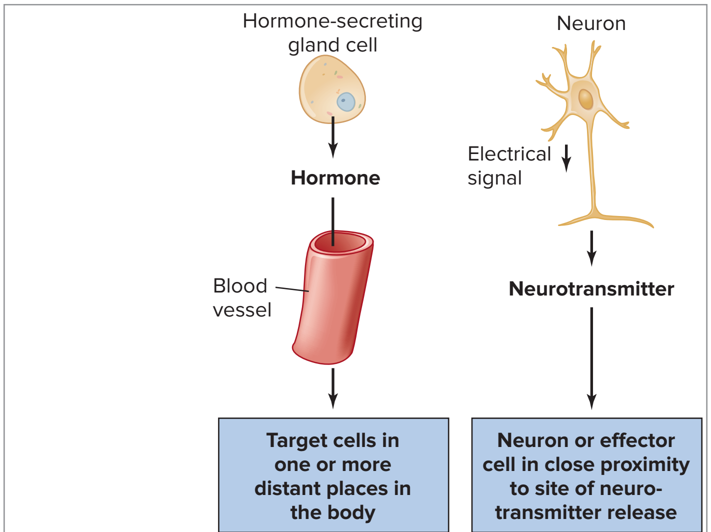
Local Homeostatic Responses

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.

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, 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 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** or in scattered cells



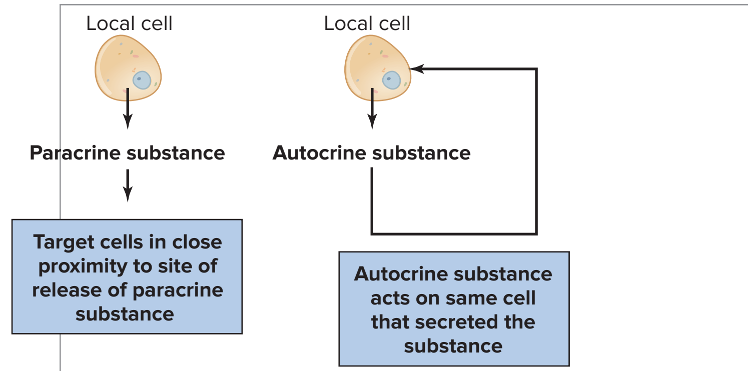


Figure 1.10 Categories of chemical messengers. With the exception of autocrine messengers, all messengers act between cells—that is, *inter*cellularly.

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 type 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.

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 earlier, 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* 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

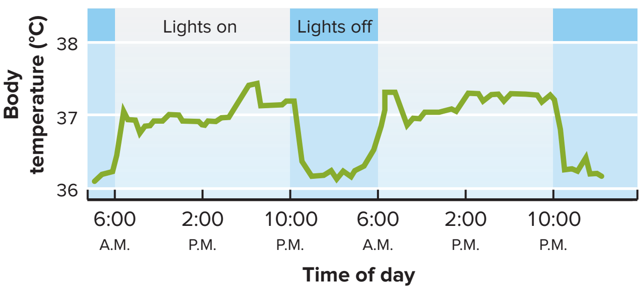


Figure 1.11 Circadian rhythm of body temperature in a human subject with room lights on (open bars at top) for 16 h, and off (blue bars at top) for 8 h. Note the increase in body temperature that occurs just prior to lights on, in anticipation of the increased activity and metabolism that occur during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

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.

The light–dark cycle is the most important environmental time cue in our lives—but not the only one. Others include external environmental temperature, meal timing, and many social cues. Thus, if several people were undergoing the experiment just described in isolation from each other, their free-running rhythms would be somewhat different, but if they were all in the same room, social cues would entrain all of them to the same rhythm.

Environmental time cues also function to **phase-shift** rhythms—in other words, to reset the internal clock. Thus, if you fly west or east to a different time zone, your sleep–wake cycle and other circadian rhythms slowly shift to the new light–dark cycle. These shifts take time, however, and the disparity between external time and internal time is one of the causes of the symptoms of jet lag—a disruption of homeostasis that leads to gastrointestinal disturbances, decreased vigilance and attention span, sleep problems, and a general feeling of malaise.

Similar symptoms occur in workers on permanent or rotating night shifts. These people generally do not adapt to their schedules even after several years because they are exposed to the usual outdoor light–dark cycle (normal indoor lighting is too dim to function as a good entrainer). In recent experiments, night-shift workers were exposed to extremely bright indoor lighting while they worked and they were exposed to 8 h of total darkness during the day when they slept. This schedule produced total adaptation to night-shift work within 5 days.

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 that 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 the figure 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.

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: (1) Loss exceeds gain, so that the total amount of the substance in the body is decreasing, and the person is in **negative balance;** (2) gain exceeds loss, so that the total amount of the substance in the body is increasing, and the person is in **positive balance;** and (3) 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, and 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.

1.9 General Principles of Physiology

When you undertake a detailed study of the functions of the human body, several fundamental, general principles of physiology are repeatedly observed. 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

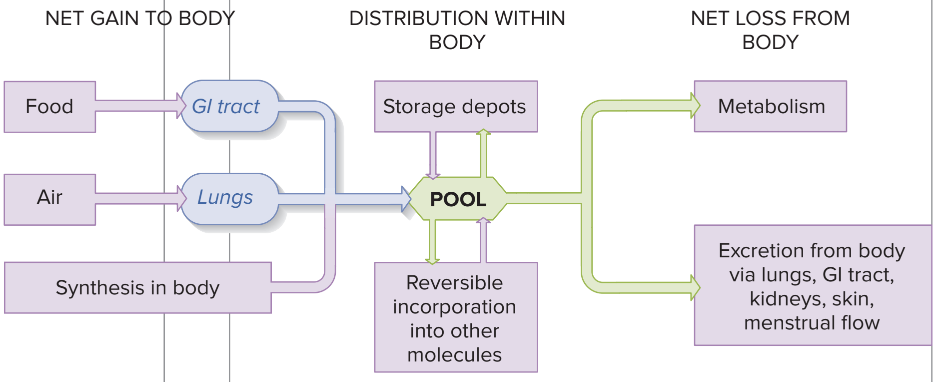


Figure 1.12 Balance diagram for a chemical substance.

then be tested with assessments at the end of the chapter and in Physiological Inquiry 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. ■

SUMMARY

The Scope of Human Physiology

I. Physiology is the study of how living organisms work. Physiologists are interested in the regulation of body function.
II. The study of disease states is pathophysiology.

How Is the Body Organized?

I. Cells are the simplest structural units into which a complex multicellular organism can be divided and still retain the functions characteristic of life.
II. Cell differentiation results in the formation of four general categories of specialized cells:
   a. Muscle cells generate the mechanical activities that produce force and movement.
   b. Neurons initiate and conduct electrical signals.
   c. Epithelial cells form barriers and selectively secrete and absorb ions and organic molecules.
   d. Connective-tissue cells connect, anchor, and support the structures of the body.

III. Specialized cells associate with similar cells to form tissues: muscle tissue, nervous tissue, epithelial tissue, and connective tissue.
IV. Organs are composed of two or more of the four kinds of tissues arranged in various proportions and patterns. Many organs contain multiple, small, similar functional units.
V. An organ system is a collection of organs that together perform an overall function.

Body Fluid Compartments

I. The body fluids are enclosed in compartments.
   a. The extracellular fluid is composed of the interstitial fluid (the fluid between cells) and the blood plasma. Of the extracellular fluid, 75%–80% is interstitial fluid, and 20%–25% is plasma.
   b. Interstitial fluid and plasma have essentially the same composition except that plasma contains a much greater concentration of protein.
   c. Extracellular fluid differs markedly in composition from the fluid inside cells—the intracellular fluid.
   d. Approximately one-third of body water is in the extracellular compartment, and two-thirds is intracellular.
II. The differing compositions of the compartments reflect the activities of the barriers separating them.

Homeostasis: A Defining Feature of Physiology

I. The body's internal environment is the extracellular fluid.
II. The function of organ systems is to maintain a stable internal environment—this is called homeostasis.
III. Numerous variables within the body must be maintained homeostatically. When homeostasis is lost for one variable, it may trigger a series of changes in other variables.

General Characteristics of Homeostatic Control Systems

I. Homeostasis denotes the stable condition of the internal environment that results from the operation of compensatory homeostatic control systems.
   a. In a negative feedback control system, a change in the variable being regulated brings about responses that tend to push the variable in the direction opposite to the original change. Negative feedback minimizes changes from the set point of the system, leading to stability.
   b. Homeostatic control systems minimize changes in the internal environment but cannot maintain complete constancy.
   c. Feedforward regulation anticipates changes in a regulated variable, improves the speed of the body's homeostatic responses, and minimizes fluctuations in the level of the variable being regulated.

Components of Homeostatic Control Systems

I. The components of a reflex arc are the receptor, afferent pathway, integrating center, efferent pathway, and effector. The pathways may be neural or hormonal.
II. Local homeostatic responses are also stimulus–response sequences, but they occur only in the area of the stimulus, with neither nerves nor hormones involved.

The Role of Intercellular Chemical Messengers in Homeostasis

I. Intercellular communication is essential to reflexes and local responses and is achieved by neurotransmitters, hormones, and paracrine or autocrine substances. Less common is intercellular communication through either gap junctions or cell-bound messengers.

Processes Related to Homeostasis

I. Acclimatization is an improved ability to respond to an environmental stress. The improvement is induced by prolonged exposure to the stress with no change in genetic endowment.
II. Biological rhythms provide a feedforward component to homeostatic control systems.
   a. The rhythms are internally driven by brain pacemakers but are entrained by environmental cues, such as light, which also serve to phase-shift (reset) the rhythms when necessary.
   b. In the absence of cues, rhythms free-run.
III. The balance of substances in the body is achieved by matching inputs and outputs. Total-body balance of a substance may be negative, positive, or stable.

General Principles of Physiology

I. Several fundamental, general principles of physiology are important in understanding how the human body functions at all levels of structure, from cells to organ systems. These include, among others, such things as homeostasis, information flow, coordination between the function of different organ systems, and the balance of matter and energy.

REVIEW QUESTIONS

1. Describe the levels of cellular organization and state the four major types of cells and tissues.
2. List the organ systems of the body and give one-sentence descriptions of their functions.
3. Name the two fluids that constitute the extracellular fluid. What are their relative proportions in the body?
4. What is one way in which the composition of intracellular and extracellular fluids differ?
5. Describe several important generalizations about homeostatic control systems, including the difference between steady state and equilibrium.
6. Contrast feedforward, positive feedback, and negative feedback.
7. List the components of a reflex arc.
8. What is the basic difference between a local homeostatic response and a reflex?
9. List the general categories of intercellular messengers and briefly describe how they differ.
10. Describe the conditions under which acclimatization occurs. Are acclimatizations passed on to a person's offspring?
11. Define *circadian rhythm*. Under what conditions do circadian rhythms become free running?
12. How do phase shifts occur?
13. What is the most important environmental cue for entrainment of circadian rhythms?
14. Draw a figure illustrating the balance concept in homeostasis.
15. Make and keep a list of the general principles of physiology. See if you can explain what is meant by each principle. To really see how well you've learned physiology at the end of your course, remember to return to the list you've made and try this exercise again at that time giving as many examples of each principle as you can.

KEY TERMS

1.1 The Scope of Human Physiology

pathophysiology	physiology

1.2 How Is the Body Organized?

basement membrane	epithelial cells
cell differentiation	epithelial tissue
cells	epithelium
collagen fibers	extracellular matrix
connective tissue	fibers
connective-tissue cells	functional units
elastin fibers	muscle cells

muscle tissue	organ systems
nerve	organs
nervous tissue	tissues
neuron	

1.3 Body Fluid Compartments

extracellular fluid	interstitium
internal environment	intracellular fluid
interstitial fluid	plasma

1.4 Homeostasis: A Defining Feature of Physiology

dynamic constancy	homeostasis

1.5 General Characteristics of Homeostatic Control Systems

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

1.6 Components of Homeostatic Control Systems

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

1.7 The Role of Intercellular Chemical Messengers in Homeostasis

autocrine substances	paracrine substances
endocrine glands	target cells
neurotransmitters	

1.8 Processes Related to Homeostasis

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

CHAPTER 1

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

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.*

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

—Continued next page

—*Continued*

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.

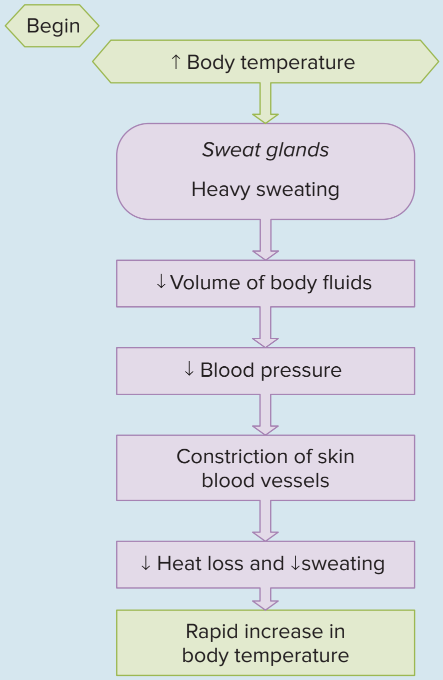


Figure 1.13 Sequence of events that occurred in the man described in this case study.

See Chapter 19 for complete, integrative case studies.

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. In the absence of any environmental cues, a circadian rhythm is said to be
   a. entrained.
   b. in phase.
   c. free running.
   d. phase-shifted.
   e. no longer present.
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 (in the Clinical Case Study in this chapter).

CHAPTER 1 ANSWERS TO PHYSIOLOGICAL INQUIRY QUESTIONS

Figure 1.3 Approximately one-third of total-body water is in the extracellular compartments. If water makes up 60% of a person's body weight, then the water in extracellular fluid makes up approximately 20% of body weight (because $0.33 \times 0.60 = 0.20$).

Figure 1.6 Removing negative feedback in this example would result in an increase in the amount of active product formed, and eventually the amount of available substrate would be greatly depleted.

Figure 1.9 If body temperature were to increase, the efferent pathway shown in this diagram would either turn off or become reversed. For example, shivering would not occur (muscles may even become more relaxed than usual), and blood vessels in the skin would not constrict. Indeed, in such a scenario, skin blood vessels would dilate to bring warm blood to the skin surface, where the heat could leave the body across the skin. Heat loss, therefore, would be increased.

ONLINE STUDY TOOLS

connect

Test your recall, comprehension, and critical thinking skills with interactive questions about homeostasis assigned by your instructor. Also access McGraw-Hill LearnSmart®/SmartBook® and Anatomy & Physiology REVEALED from your McGraw-Hill Connect® home page.

LEARNSMART

Do you have trouble accessing and retaining key concepts when reading a textbook? This personalized adaptive learning tool serves as a guide to your reading by helping you discover which aspects of homeostasis you have mastered, and which will require more attention.

Anatomy & Physiology REVEALED
aprevealed.com

A fascinating view inside real human bodies that also incorporates animations to help you understand homeostasis, the central idea of physiology.