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The Foundation

For students receiving their initial exposure to the life sciences, physiology is the study of how living things work. It is the bedrock of the biomedical sciences. As the American Physiological Society expresses it, physiology is the science of life. Physiology is an analytical, experimental, investigative, and quantitative science. For the medical student completing an MD degree, or any student in the life sciences preparing to see patients, physiology is the basis of human medicine, historically and in the present. Each year a Nobel Prize is awarded in physiology or medicine. No other life science, past or present, has such a distinction.

The physiological approach to problem solving is the mechanistic approach. Physiologists use the words *mechanism* and *mechanistic* when they discuss the functions of living things. Mechanisms of function are studied by physiologists at the molecular, cellular, organ system, and whole animal levels. In the twenty-first century, the challenge for the physiologist is to study life integratively, for example, from the molecular to the organ systems levels. The modern physiologist is also encouraged to work translationally. In other words, if their research has relevance to modern human medicine, what happens in the laboratory must be quickly transferable to the clinic. Although the idea of translational physiology is relatively recent, one of the best examples occurred in the first two decades of the twentieth century when insulin was discovered. In only a matter of weeks between its isolation and purification, insulin was used in a diabetic human subject. From that first trial in a young man in Toronto, use of insulin had an immediate and global impact on human suffering from diabetes.

Structure and Function

Once the student understands what physiology is, it becomes easier, in many cases, to grasp the mechanistic approach by studying the relation of function to structure. Examples abound of how structure and function are interrelated in the human body (see table 1.1).

Understanding the functions of the body is enhanced by first understanding corresponding structures. In addition, learning medically relevant scientific prefixes, suffixes, and some simple definitions will help both the student and the clinician with physiology. Anatomy, simply stated, is the structure or morphology of a tissue, organ, organ system, or whole animal. The morphology of a living thing can and does change with time and other conditions. Consider, for example, the morphology of a tadpole and contrast it with that of the mature frog. Alternatively, the primitive spermatogonium looks nothing like the mature spermatozoan, that is, the reproductively capable sperm cell. The spermatogonium lacks a tail and well-defined head with acrosome. Metamorphosis, such as that experienced by the tadpole or spermatogonium, happens because of development, differentiation, growth, and proliferation of cells, tissues, organs, and organ systems. Stated simply, anatomy is what we have and physiology is how we use it. Or, anatomy is the cut and chiseled appearance of the conditioned athlete's back and shoulders, biceps, and abdomen. Physiology is the mechanisms by which those same muscles develop force, shorten, and lift a load.

An ideal example of the relationship between structure and function is found in striated muscle. Muscle in human bodies can be subdivided into two broad categories, striated and nonstriated. Striated muscle is so named because when viewed under powerful transmission and scanning electron microscopes,

TABLE 1.1

Examples in human physiology where structure (anatomy, morphology) is related to function

Structure	*Function*
Striated muscle (skeletal, cardiac)	shortening and contraction, development of force, movement of a load
Nephron (kidney)	filters plasma, reabsorbs ultrafiltrate, secretes molecules, excretes urine
Alveolar airway	exchanges the respiratory gases oxygen and carbon dioxide with blood
Circulatory systems	manage/distribute flow (arteries, arterioles), exchange (capillaries), collect (veins)
Epiglottis	controlled by the swallowing reflex, minimizes/prevents choking

these cells have alternating light and dark bands called striations. Examples of striated muscles, among many others, include the biceps and the “six pack” muscles of the abdomen, as well as the ventricles and atria of the heart. Striated muscle is further divided into cardiac and noncardiac or skeletal. All other muscle types are considered nonstriated because they lack the pattern of alternating light and dark bands. One example of a nonstriated muscle would be the vascular smooth muscle that is found in the walls of most blood vessels. Figure 1.1 is an example of striated muscle as seen through an electron microscope at a magnification of 10,000 times.

Striated muscle, whether skeletal or cardiac, is characterized by the well-defined striations shown in figure 1.1. Many such striations occur inside a single muscle cell, also called a myocyte or muscle fiber. The myocyte’s cell membrane is called the sarcolemma. The sarcolemma separates the interior contents of the cell from the extracellular fluids. Each muscle cell also has a dense concentration of mitochondria, the metabolic motors of the cell. The light and dark bands are composed of smaller units called thick and thin filaments. Thick filaments (dark bands) are polymers of the protein myosin and thin filaments (light bands) are made from actin chains. There are many other functional proteins associated with thick and thin filaments, but their description is beyond the purposes of this book.

The structural and functional unit of the striated muscle is the sarcomere, which is composed of any two adjacent dark lines running through corresponding light bands. Greater detail of the striations can be studied by further magnifying

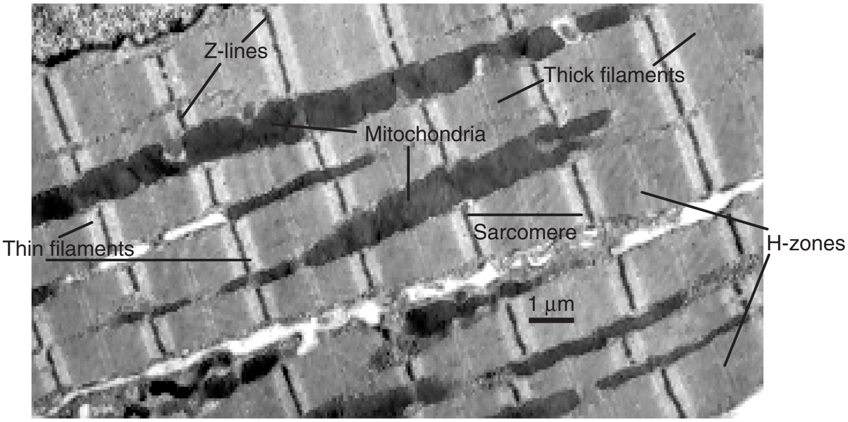

FIGURE 1.1 Electron micrograph (magnified about 10,000 times) showing cardiac striated muscle in the left ventricle of the guinea pig heart. Note the pattern of alternating light (with dark Z-lines running through the center) and dark bands (gray areas labeled thick filaments). Similar patterns are found in the hearts of all mammals, including humans. Note the sarcomeres.

(Merrill, unpublished data)

the structures shown in figure 1.1. We hypothesize that striated muscles contract and create force when the filaments slide over each other (we have not seen it occur, even though we can see the fibers in a microscope). Thin filaments, attached at adjacent Z-lines, slide towards each other and over interposed thick filaments. Thick and thin filaments do not change length, but the sarcomere shortens. Because of the structure and proximity of apposing thick and thin filaments, coupled with the physiology and biochemistry of the sarcomere, as filaments pass each other, energy is released, muscles shorten, force is generated, and a load is lifted (see figure 1.2).

A simple analogy of the sliding filament theory is interlacing the fingers of both hands. With fingers extended and the tips of index fingers touching each other, spread the fingers and then slide the apposing sets of fingers past one another about an inch, keeping the two index fingers fixed. With fingers in this position, note (1) the distance between the two palms, (2) the extent of overlap of the fingers, and (3) the thickness of the region of overlap versus the areas of the fingers that are not overlapped. The thick region corresponds to the area of a sarcomere where the thick and thin filaments overlap. The region of the fingers that do not overlap represent the non-overlapping thin filaments of the sarcomere, and where they are connected to the palms represents their points of attachment at the Z-lines. Now if you slide the fingers closer together, you can visualize how the sliding filament hypothesis of muscle contraction works.

Skeletal muscles are activated to contract by motor nerves that innervate them. A muscle fiber and its associated motor nerve is called a motor unit. The greater the number of motor units firing, the more force a muscle can generate. For example, a person lifting weights with 20-pound dumbbells in each hand will activate fewer motor units than they will using 40-pound dumbbells. The

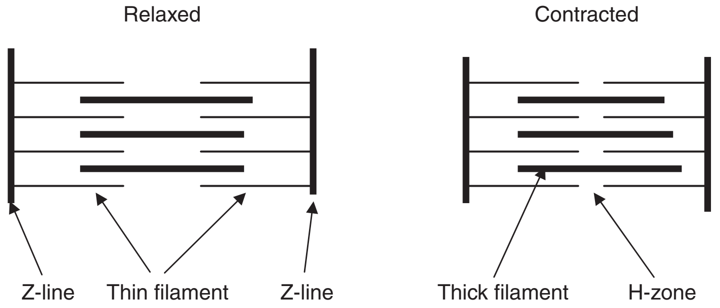

FIGURE 1.2 Relaxed (left) and contracted (right) sarcomeres. These illustrate the sliding-filament theory for muscle contraction (both cardiac and skeletal). Note the extent of overlap of thick and thin filaments under the two conditions. Note also that the lengths of the thick and thin filaments do not change during contraction (only sarcomere length changes).

heavier the weight, the greater the number of motor units recruited. Repeating such motion with progressively increasing weights during an eight- to twelve-week period will cause an increased size of each muscle cell in the affected region (*hypertrophy*). Some weight training (stretching) activities can also increase the number of cells (*hyperplasia*).

A second example of how understanding structure can enhance the understanding of function is the kidney. While the kidneys perform several important physiological functions, one of their main purposes is to filter the blood. In filtering the blood, potentially toxic waste products of metabolism are eliminated—for example, urea—and the balance of body water and electrolytes is maintained. The structural and functional unit of the mammalian kidney is the *nephron*. This word gives rise to the name of a clinician who studies kidney disease, a nephrologist. Nephrology is the study of renal disease. Figure 1.3 illustrates the mammalian nephron. Each of the two kidneys in the human body is constructed of a million plus nephrons. Each nephron is composed of vascular and tubular structures that are important to kidney function.

The general filtering function of the nephron is crudely analogous to the kitchen sink and its plumbing and purposes. The main function of a kitchen sink filled with hot water and detergent is to eliminate waste from glassware, utensils, and pots and pans. The dirty dishwater and its contents eventually get flushed into the kitchen plumbing. However, before they enter the plumbing,

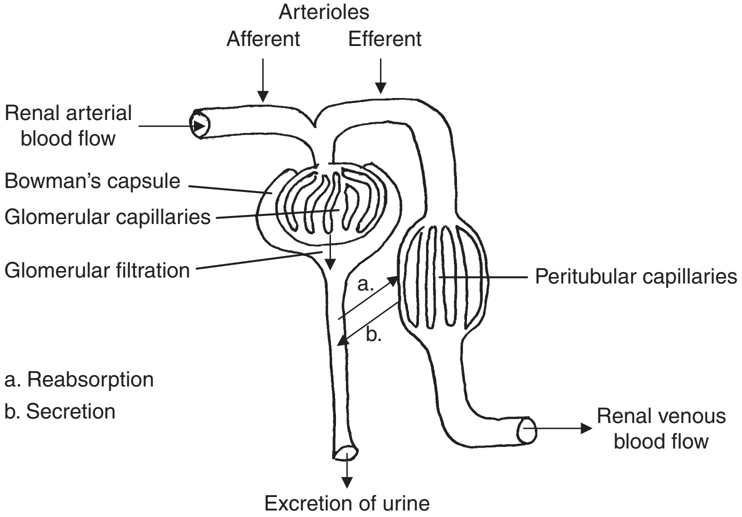

FIGURE 1.3 The mammalian nephron, the basic functional unit of the kidney. Note the basic renal functions of glomerular filtration, reabsorption, secretion, and excretion. Note also the proximities of afferent and efferent arterioles and glomerular and peritubular capillaries.

the waste products and dirty water must pass through a removable sink drain or filter. This drain is designed to allow water to flow across freely but to trap larger waste particles, which can be disposed of in the garbage.

Nephron function is similar. Each nephron has an arterial blood supply that is analogous to the faucet that supplies water to the sink. The nephron has a drain or filter called the glomerular filtration apparatus. It allows water and other small molecules to pass freely into the Bowman's capsule and the tubular nephron (sink gooseneck and house plumbing). The filtration barrier is composed of the wall of small blood vessels called glomerular capillaries. The capillaries have pores in their walls and the walls are overlaid by cells called podocytes. Together, the porous glomerular capillaries and overlaying podocytes form the glomerular filtration barrier. This barrier prevents large molecules from getting out of the renal blood and into the nephron tubules.

As renal arterial blood flows into the glomerular capillaries, water and its smallest solutes are forced from the blood vessels into the tubules of the nephron. Blood pressure and other factors such as the molecular radius of a particular solute and electrical charges on solutes and the filtration barrier determine which solutes get filtered and which ones remain inside the blood vessels. The total process is called glomerular filtration, and its rate can be determined experimentally and clinically. The glomerular filtration rate, abbreviated GFR, is one of the most important indicators of kidney function.

The filtered fluid and its nonaqueous component are referred to as ultrafiltrate, and once it is inside the renal tubules it will either be excreted as urine (renal excretion), or it will be reabsorbed into the capillaries surrounding the nephrons, a process called tubular reabsorption. On occasion, solutes get secreted out of the peritubular capillaries and into the renal tubules. For any given solute in the renal arterial blood, the net effects of filtration, reabsorption, and secretion ultimately determine the composition and volume of urine. As a rule, if a solute gets filtered and is not reabsorbed, it will be excreted as urine. Also, if a solute gets filtered but is completely reabsorbed, it will not appear in the urine. Finally, a solute can appear in the urine without having been filtered at the glomerular capillaries. In this case, that solute had to be secreted by the peritubular capillaries in order to appear in the urine.

One can check the physiological efficiency of these several processes by rapidly consuming a large quantity of water, say a pint or two in ten to fifteen minutes. If you are observant, you will note two things. First, the yellow hue of the urine before consuming the water was darker than it will be two or three hours after drinking. Secondly, the need to urinate after consuming the water will most likely be greater than before. This results as the kidneys reabsorb less water and try to restore body water volume and osmolarity to their physiological states. I will have much more to say about this in chapter 6 on renal function.

Homeostasis, Equilibrium, and the Steady State

In addition to understanding the differences between structure and function and how they interrelate, there are other fundamental physiological concepts that are key to body function. Among the most important of these are the concepts of homeostasis, equilibrium, and the physiological steady state. The term *homeostasis* was coined by the American physiologist Walter B. Cannon (1871–1945). In one of his books, *The Wisdom of the Body,* Cannon described the body's ability to maintain the status quo, and he applied that ability to all known functions of the tissues and organ systems. For contemporary physiologists, homeostasis is the maintenance of static or constant conditions in the internal environment.

Consider body temperature and its regulation. At any point in time, body temperature is the composite of the rates of heat production and heat loss combined with heat storage. When members of polar bear clubs in the northern hemisphere don their swimsuits and plunge into frigid waters on January 1 to ring in the New Year, homeostasis of body temperature is perturbed. While in the cold water, heat loss will outpace heat production, heat storage will decline, and body temperature will fall, even if only transiently. During the next several hours as swimmers dry off, replace their clothing, and move into a warm environment, physiological mechanisms will restore the balance among heat production, heat loss, and heat storage. When body temperature returns to preplunge levels, thermoregulatory homeostasis will have been restored.

The physiological concept of homeostasis suggests a basic mechanism for maintaining the stability of the internal milieu in the face of irregular nutrient, mineral, and water fluxes, as well as physical alterations in the environment. Homeostasis is the control of a vital parameter. The body carefully controls a seemingly endless list of vital parameters. Examples of tightly controlled parameters that affect nearly the whole body are arterial blood pressure and circulating blood volume. At the level of the internal fluids, tightly regulated parameters include body core temperature and plasma levels of oxygen, glucose, potassium ions (K^+), calcium ions (Ca^{2+}), and hydrogen ions (H^+). Homeostasis also occurs at the level of the single cell. Thus, cells regulate many of the same parameters that the body as a whole regulates: volume, the concentrations of many small inorganic ions, and energy levels such as adenosine triphosphate (ATP).

Another example of the concept of homeostasis is energy balance or maintenance of body weight. Simply stated, if the student or patient consumes more calories in a day than are expended, they are going to gain weight. Alternatively, if they expend more calories in a day than they consume, they will lose weight. If they weigh 175 pounds on day one, then consume and expend 2,000 calories per day through day thirty, they will still weigh 175 pounds on day thirty. The homeostasis of energy balance is the formula, over a lifetime, for maintaining body weight at a constant level.

Integral components of the concept of homeostasis are the ideas of equilibrium and steady states. To help explain equilibrium, imagine a washing machine, a rinse basin, and the outlet from the rinse basin into the plumbing system of a house. As the washing machine goes through a rinse cycle, it releases a large volume of rinse water into the basin. The water entering the basin exits into the house's plumbing system. If the plumbing system is clogged or restricted, and depending on the volume of the basin, the rate of entry of water into the basin exceeds the rate of exit from the basin. Under those conditions, the rinse water could overflow onto the laundry room floor. Conversely, if the plumbing system is not plugged, the rates of rinse water entering and exiting the basin are near equal and the level of water in the basin is near constant. At that precise moment in time, the two rates of water flow produce a volume of rinse water in the basin that does not change. At that moment, the entire system—washing machine, entry and exit of rinse water into the basin, and volume of water in the basin—is in a state of equilibrium. Happily, under such conditions there is no threat of the basin overfilling and the water overflowing onto the laundry room floor, that is, there is no arduous task to add to one's workload for the day.

This is the case for many of the functions of the human body. Consider the heart to be the physiological equivalent of the rinse basin. Venous blood flowing into the heart from various regions of the body, such as the head, trunk, internal organs, and limbs, is the counterpart of rinse water flowing into the basin. Arterial blood flowing away from the heart, to nourish tissues and organs of the head, trunk, and limbs, is analogous to rinse water draining the basin. If the volumes of blood flowing into and out of the heart are not equal, then either the heart or the organs will be depleted of or engorged with blood. Either condition is bad, and both cause an imbalance or disequilibrium in the cardiovascular system. Unless corrected promptly, either state can be lethal.

The heart and the vasculature, or blood vessels, acting in concert with other tissues and organ systems, have mechanisms to prevent such disequilibrium from either occurring or from lasting. This, however, can fail in disease states. Consider congestive heart failure as an example. The weakened and reduced capacity of the heart to pump blood is often caused by a heart attack, or myocardial infarction. As the heart expels less blood during each contraction, the volume of blood in the heart at the end of the following relaxation phase increases, that is, the heart becomes congested with blood. As congestion progresses, the pressures inside the heart and in the veins leading to the heart also change. This, in turn, affects arterial blood pressure. Thus, a state of disequilibrium in general circulatory hemodynamics occurs. In other words, cardiac and circulatory homeostasis is lost, the person's health deteriorates, and death can be the end result.

Like the person who consumed and expended 2,000 calories per day for a month, and whose body weight remained constant, the person's heart that ejects all the blood it receives per cycle will produce a circulation that is also in a state of stability, the physiological steady state. Imagine yourself kicking back and reading the paper about 11 A.M. on a Sunday morning. Your homework is done, there are no midterm exams for a couple of weeks, and you are enjoying some leisure time. As you are comfortably relaxing on the couch, your respiratory rate, heart rate, body temperature, blood pressure (vital signs), and digestive functions are all in their baseline, resting conditions—their steady states. If we were to measure some of these variables, we might find your heart rate to be about seventy cycles per minute (beats per minute), your breathing rate to be about twelve cycles per minute, your body temperature to be about 38°C (98°F), and your mean arterial blood pressure to be about 100 mmHg. Now imagine an unexpected, loud knock at the front door and a frantic neighbor screaming, "My house is on fire, please help me!" The events of the next several minutes will arouse many of your physiological functions. If at the moment of greatest alarm we were to measure your vital signs, they would be elevated and perhaps even continuing to rise—they would not be in the steady state. After the fire and police departments arrive and have things under control, some time will have to pass before these physiological variables return to or near the stable conditions that prevailed before your neighbor's intrusion. During the time of alarm and increased physical activity, these physiological variables will operate under non-steady-state conditions.

Many events can disrupt the physiological steady state. These include but are not limited to periods of dynamic and static physical activity such as dancing, water skiing, and other forms of exercise; marked and/or sudden changes in environmental temperatures, such as would occur if you were marathoning in Death Valley or summiting Mount Everest; different states of consciousness such as during general anesthesia, sleep, and wakefulness; and fasting and feasting, periods of emotional distress and anger, anxiety over a misunderstood date and location of a final exam, and so forth. As students become familiar with physiology in general, they will be more cognizant of events that can influence the steady state.

Physiological Gradients

Another physiological concept of fundamental importance is that of gradients. The term is related to the words *grade* and *slope*. Any traveler driving from the east to the west coasts of the United States has crossed the Continental Divide and Rocky Mountains. Whether in Montana, Idaho, Wyoming, Utah, or Colorado, at some point the traveler will ascend and descend one or more mountain passes. Frequently the steepness of such passes is posted as a grade, for example, 6 percent or 7 percent. This means that for each 100 feet of linear distance forward, the traveler will rise or descend six or seven feet. Although plains and valley floors are already at about 5,000 feet, such as Denver, Colorado, the passes may be at elevations in excess of 10,000 or 12,000 feet, for example Eisenhower Pass. Drivers of large vehicles such as buses and semis are advised to check their brakes before descending these mountainous passes, and the novice mountain traveler might notice the runaway truck and bus ramps. A gradient is a difference. In the case of Denver and Pike's Peak the difference is about 9,000 feet.

Blood pressure is an example of a physiologically important gradient. Blood flows from regions of high pressure to regions of low pressure. That is to say, blood flow occurs, in part, as the result of pressure gradients. In our reclining newspaper reader above, the average pressure in the left ventricle at the peak of its contraction is about 100 mmHg under resting conditions. Millimeters of mercury are the units of measure used to express blood pressure. Blood pressure levels are similar in the major arteries carrying blood away from the left ventricle during systole. At the peak of excitement during the neighbor's house fire, left ventricular peak blood pressure will be elevated considerably. Blood leaving the left side of the heart eventually ends up in the right side of the heart at the right atrium. From there it goes to the right ventricle en route to the lungs. The average pressure in the right atrium of the reader at rest is less than 5 mmHg; blood flows because of an intravascular pressure gradient of $100 - 5 = 95$ mmHg. Conditions that increase this gradient (house fire) will increase blood flow, and those that decrease the gradient will decrease it.

Another physiologically important gradient is the osmotic gradient. Osmosis is the process by which charged particles such as ions influence the distribution of water between different body compartments. Ions, electrolytes, salts, and other osmotically active chemicals are those that have the ability to attract water across permeable membranes such as cell walls. Osmotically active chemicals exist in three important locations in the body: (1) inside cells, that is, the intracellular space or intracellular compartment; (2) inside blood vessels, for example, the intravascular space or intravascular compartment, an extracellular compartment; and (3) the interstitial space, also an extracellular compartment. *Interstitial* means "between the tissues" and refers to space within the body and its organ systems that is both between the cells (but outside of cells) and outside of the vascular compartment. Under homeostatic conditions, there is a balance in the amount or concentrations of osmotically active chemicals in these three spaces. Because of their abilities to attract water (osmosis), the distribution of these chemicals causes an equally important distribution of water among the three compartments. This mechanism is crucial since the balance of water and salts among the body's various compartments is critically important to the health and well-being of the individual. When either the water or osmotic gradient is upset—for example, when there is a higher concentration of osmotically active chemicals in the interstitial space than in the intracellular space—the other space is disrupted. Unless the imbalance is promptly restored by homeostatic mechanisms, net losses or gains in water and electrolytes will occur in the various compartments leading to injury and death of the tissues.

Anyone whose job requires them to stand most of the day has experienced swelling and discomfort in the feet. This is especially true in a hot environment, for example, standing on a concrete slab or asphalt during hot summer months. The swelling results from imbalances in osmolality and volume in the water compartments of the tissues of the feet. Periodically elevating the feet above the heart, even during the workday, can do wonders for the swelling and discomfort. Stress such as standing for long hours multiple days per week over years can do irreversible damage to the walls of blood vessels not only in the feet but in vessels of the lower leg as well, leading to conditions such as varicose veins and phlebitis. I will have more to say about this when I discuss kidney function later in the book (see chapter 6, “Kidneys and Renal Physiology”).

We acquire oxygen from the atmosphere and eliminate carbon dioxide into it also as a result of gradients. The amount of oxygen in any particular space can be expressed by its partial pressure (the amount of energy or force caused by oxygen molecules as they collide with one another and with the walls of containers confining them). Physiologists express the partial pressure of oxygen with the symbol PO_2. The upper-case P stands for partial pressure and O_2 is the chemist’s symbol for molecular oxygen. The greatest partial pressure of oxygen is in the atmosphere we breathe. At sea level it is about 150 mmHg. The next greatest PO_2 is in the lungs (about 105 mmHg), then in the venous blood leaving the lungs (blood that will become arterialized—the addition of oxygen to venous blood—once it reaches the left ventricle and major arteries and is pressurized to about 100 mmHg), then inside the cell (about 40 mmHg), finally in subcellular organelles (structures such as nuclei and mitochondria that are located inside cells), where the pressure is less than 40 mmHg). Thus, there is an oxygen gradient from atmosphere to subcellular organelle of more than 110 mmHg that ensures constant delivery of oxygen to where it is needed. An opposite gradient exists for carbon dioxide, a by-product of cellular metabolism that must not accumulate in the tissues. If carbon dioxide accumulates, especially in brain and other sensitive tissues, it can lead to acidosis, comatosis, and even death. Partial pressure of carbon dioxide in the cells is greater than 45 mmHg and in the lungs is less than 40 mmHg. So, for both these physiologically important, life-sustaining gases, gradients exist that ensure continuous uptake of oxygen and removal of carbon dioxide.

Physiological Reflexes

In their earliest clinical training, students become familiar with the concept of body reflexes. They are taught some very simple reflexes such as the knee-jerk reflex, but, unless enrolled in advanced physiology courses, they might not be taught the more complex reflexes such as the contralateral flexor/extensor reflexes and reflex movements of the gut wall during and after ingestion of a meal. Structurally, all reflex arcs consist of five components. They are (1) a sensory receptor, (2) a sensory or afferent nerve, (3) a central integrator, (4) a motor or efferent nerve, and (5) a motor effector or activator (see figure 1.4). Unless all five components are involved, it cannot correctly be said that a function has occurred "reflexively."

A sensory receptor is generally thought of as a cell (or group of specialized cells) that is sensitive to changes in its environment. The environmental stimuli that activate these receptors can be mechanical, electrical, thermal, or chemical, and most receptors respond to specific stimuli. For example, receptors that respond to heat and cold (thermoreceptors) do not respond to mechanical changes in their environments. Environmental stimuli refer to events outside the body, at the body surface, or inside the body. In the case of the knee-jerk reflex, the stimulus is mechanical, the deformation or changes in tissue contour caused by a hard object striking the knee. The knee-jerk mechanoreceptors are innervated (attached to sensory nerves) by neurons (nerve cells) that carry the mechanical signal, now transformed into an electrical impulse, centrally or afferently into the spinal cord. Inside the spinal cord, the signal is evaluated and integrated by interneurons (nerve cells interposed between the afferent, sensory nerves and the efferent, motor nerves, that is, the central integrator) that direct the outflow of information to the motor or efferent nerves. Finally, motor nerves carry another electrical impulse to motor effectors or activators. In the case of the knee jerk, the activators are extensor muscles that are stimulated (cause extension of the limb) and flexor muscles that are inhibited (do not oppose extension of the limb). The end result of this reflex is extension and elevation of the leg below the knee.

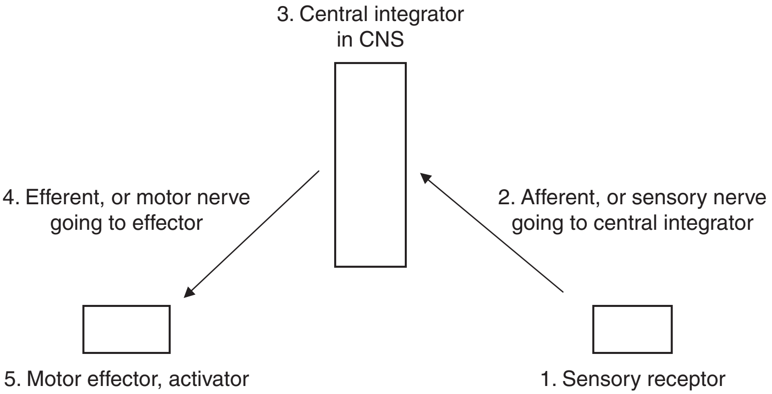

FIGURE 1.4 The five basic components of a mammalian reflex arc. Note that the physiological mechanism of the reflex begins with a sensory receptor (1) and ends with a motor effector (5).

Reflex responses can aid the well-being of the organism, as demonstrated by the nociceptor reflex. Nociceptors are sensory receptors that respond to painful stimuli. Heat can be a painful stimulus. Consider small children who place their hands on hot stoves. Pain receptors in a hand are activated and initiate reflexes that both cause the withdrawal of the hand and the child's removal from the stove. Even though the contact lasted less than one second, the child still suffered a burn. Imagine the damage that would be sustained if thermoreceptors were not present and the child's hand had remained on the stove for several seconds. Examples of other reflexes, such as occur when stepping on a sharp object with a bare foot, should now be more easily understood.

Control Systems Analysis

Physiologists sometimes think and act like engineers. This is especially true when it comes to analyzing functions of the body that are regulated by "control systems." Indeed these systems are similar to and even involve components of the reflex arc. Figure 1.5 illustrates, in simplest terms, the standard physiological control system. The controller is an anatomical structure of the central nervous system, and in the case of the human cardiovascular system, the controller is located in the brain stem and is subdivided into several more discrete units. These are the vasomotor and cardiotonic centers. The vasomotor centers cause adjustments in vascular tone—the degree to which an artery, arteriole, or vein is constricted or dilated. The cardiotonic centers cause acceleration and deceleration of the heart

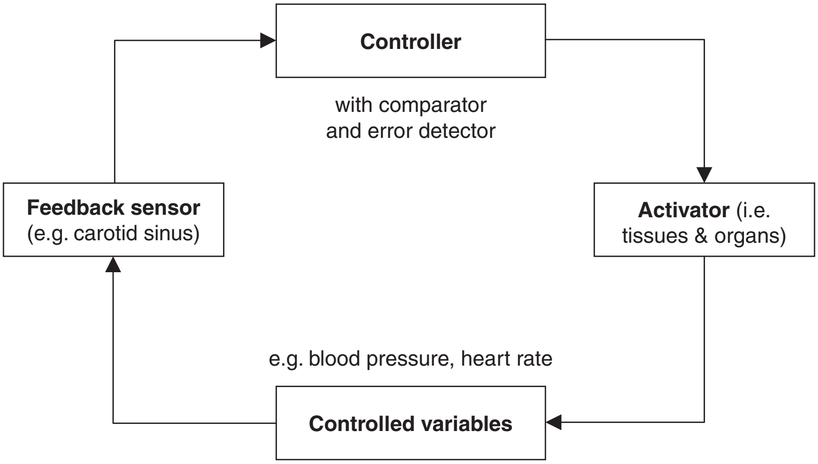

FIGURE 1.5 The physiological mechanism by which closed-loop feedback control systems work. Note that the physiological output of each component becomes the input to a subsequent component. See text for an example of how such a system behaves in controlling blood pressure.

rate, as well as increments and decrements in contractile vigor of the heart. The vasomotor center is further subdivided into vasopressor (causes elevations in blood pressure) and vasodepressor (causes decreases in blood pressure) regions.

The brain stem is a segment of the central nervous system that connects the cerebral hemispheres, spinal cord, and other components of the central nervous system (for example, the cerebellum and midbrain). The brain stem is critically important to the control and regulation of all the major organ systems of the body. Controllers within the brain stem consist of other subcomponents such as *comparators*. Comparators assess feedback signals with preexisting "set points" in the controller. Any differences between feedback signals and set points are seen as error signals and are adjusted by the entire control system. This is done to eliminate the error signal and to reestablish the set point. Output from the controller goes to "activators" (organs and tissues) and become the activator's inputs. The output of an activator is a controlled variable. Examples of controlled variables using a controller mechanism are blood pressure, heart rate, and body temperature. Controlled variables are detected by feedback sensors that send that information directly to the controller where it is compared (by the comparator) with the set point.

One example of a control system is the human cardiovascular system. Consider the short-term regulation of arterial blood pressure. Imagine that your average arterial blood pressure is 100 mmHg and that it has been at this level for several years. This means the set point in your brainstem controller is near 100 mmHg, and this value is what the comparator has been accustomed to detecting for several years. Now imagine that you are nervously seated in your dentist's chair in preparation for a root canal. Through emotionally evoked physiological mechanisms, the thought of a root canal has elevated your mean arterial blood pressure to 150 mmHg, a 50 percent increase. It has also elevated your heart rate. These changes are not good for the body, and if sustained could become pathological. For example, sustained elevated heart rates lead to excess heart work as evidenced by increased oxygen consumption. Prolonged elevation of blood pressure (hypertension) at 150 mmHg or more damages the endothelial lining of blood vessels making it easier for atherosclerosis (hardening of the arteries) to develop. That will further increase blood pressure. Moreover, the higher the blood pressure, the harder the heart has to work to circulate blood. This places undue strain on the heart and chronically predisposes to hypertrophy and failure. While transient elevations of blood pressure (dentist's chair, root canal) do little lasting damage, progressive and sustained hypertension is a leading cause of disability and death in industrialized nations. Transient changes in blood pressure and heart rate can also contribute to dangerous arrhythmias, myocardial infarction, and even sudden death.

A feedback sensor called the *carotid baroreceptor* is located in the wall of the internal carotid artery. This is located just downstream from the point of branching of the common (main) carotid artery into the internal and external carotid arteries. This critical region of vasculature is located near the bottom of the ear and curvature of the jaw. It is just above the region of the neck where we see EMT specialists, doctors, and nurses place their fingers to detect carotid pulses in injured persons. Once the feedback information from the carotid baroreceptor arrives at the cardiovascular control center, the comparator evaluates the difference between the set point of 100 mmHg and the new feedback of 150 mmHg, and physiological adjustments are made within the activators to bring arterial pressure back to 100 mmHg. Because of physiological variability among dental patients, the above adjustments in the control system might be made while they are still in the dentist's chair. In others, the corrective actions will take several hours to complete.

Feedback and Feedforward

Control systems in humans and other mammals act primarily by negative feedback. Negative feedback is one mechanism that contributes to homeostatic maintenance of physiological variables. Consider the regulation of the concentrations of carbon dioxide in body fluids. If the concentration of carbon dioxide in the blood increases, then pulmonary ventilation will be stimulated. The increase in ventilation will cause a greater release of carbon dioxide to the atmosphere. This will reduce the concentration of carbon dioxide in the blood. In other words, an elevated concentration of carbon dioxide in the blood ultimately leads to a lower concentration of carbon dioxide, which is negative to the initiating stimulus. Conversely, if the concentration of carbon dioxide in the blood falls too low, it will impede respiration causing a feedback increase in the blood concentration of the gas. This response also is negative to the initiating event.

In the regulation of heart rate and blood pressure, elevations in either variable cause a series of events via the control systems described above that lead to reductions in heart rate and blood pressure. In both cases, the final outcome is negative to the initiating stimuli. Therefore, if some physiological variable becomes excessive or deficient, a control system initiates negative feedback, which consists of a series of changes that restores the variable to its original levels.

Positive feedback also occurs but commonly is deleterious and even lethal. Whereas negative feedback typically leads to physiological stability and maintenance of the status quo (protection of homeostasis), positive feedback leads to instability through what some call vicious cycles. Consider again the feedback regulation of arterial blood pressure. If an increase in pressure occurs, a positive feedback system would produce events that lead to a further increase in arterial pressure: an errant change in blood pressure of 100 to 150 mmHg could through positive feedback lead to an arterial blood pressure of 175 or 200 mmHg or greater. Such changes would be dangerous and, if uncorrected, fatal.

TABLE 1.2

Basic concepts of the physiology of human health

Concept	*Principle*
1. Structures and functions	Understanding structure can enhance learning functions
2. Homeostasis	Tendency to stability; the principle that systems are designed to operate at constant levels
3. Equilibrium	The principle that input and output balance one another at a level that is consistent with life and good health; maintaining the *status quo*
4. Steady state	Dynamic equilibrium; conditions when a system operates at a constant level
5. Gradients	Differences, e.g., in concentrations and pressures as a function of time and space
6. Reflexes	Interrelated functions of the five basic components of an involuntary physiological system designed to achieve specific actions
7. Feedback/feedforward	Basic principles of control systems (closed-loop) designed to maintain homeostasis of controlled variables (e.g., blood pressure, body temperature)

A third kind of control called feedforward also occurs in the human body. For example, some movements of the body occur so rapidly that there is insufficient time for peripheral (distantly located tissues relative to the central nervous system) sensory stimuli to travel all the way to the central nervous system, become integrated, and relay motor responses to the affected muscles in time to control a particular movement. In such cases, the brain uses feedforward control to cause the required muscle movements. Sensory signals from the moving parts apprise the brain in retrospect whether the appropriate movement as envisaged by the brain has been performed correctly. If not, the brain corrects the feedforward signals it sends to the muscles the next time the movement is required. If still further corrections must be made, they will be done for subsequent movements. This kind of feedforward activity by the body has also been referred to as adaptive control.

THIS CHAPTER HAS SUMMARIZED some of the fundamental principles of physiology. The first task is to understand the interrelationships between structure and function of living tissue. Then the concepts of homeostasis, equilibrium, and steady states were discussed. The importance of physiological gradients and reflexes and control systems and feedback were also discussed. While this is by no means an exhaustive list of fundamental physiological principles, it is nonetheless an important list. These principles will help the student and practitioner understand our marvelous bodies and the physiological basis of health and wholeness. For the reader who is interested in a more in-depth understanding of physiology, please see the suggested readings at the end of this and all chapters. The textbooks I have suggested are among the best and are used for teaching the physiology of medicine in medical schools in the United States and elsewhere.

Table 1.2 summarizes some of the important physiological concepts presented in this chapter.