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UNIT I

Introduction to Physiology: The Cell and General Physiology

CHAPTER 1

Functional Organization of the Human Body and Control of the "Internal Environment"

Physiology is a branch of biology that seeks to explain the *function* of living organisms and their parts, including the physical and chemical mechanisms that are responsible for the origin, development, and progression of life. Each type of life, from the simplest virus to the largest tree or the complicated human being, has its own functional characteristics. Therefore, the vast field of physiology can be divided into viral physiology, bacterial physiology, cellular physiology, plant physiology, invertebrate physiology, vertebrate physiology, mammalian physiology, human physiology, and many more subdivisions.

Human Physiology. The science of human physiology attempts to explain the specific characteristics and mechanisms of the human body that make it a living being. The fact that we remain alive is the result of complex control systems. Hunger makes us seek food, and fear makes us seek refuge. Sensations of cold make us look for warmth. Other forces cause us to seek fellowship and to reproduce. The fact that we are sensing, feeling, and knowledgeable beings is part of this automatic sequence of life; these special attributes allow us to exist under widely varying conditions that otherwise would make life impossible.

Human physiology links the basic life sciences with medicine and integrates multiple functions of the cells, tissues, and organs into the functions of the living human being. This integration requires communication and coordination by a vast array of control systems that operate at every level—from the genes that program synthesis of molecules to the complex nervous and hormonal systems that coordinate functions of cells, tissues, and organs throughout the body. Thus, the coordinated functions of the human body are much more than the sum of its parts, and life relies on this total function. Although the main focus of this book is on normal human physiology, we also discuss, to some extent, *pathophysiology*, which is the study of disordered body function and the basis for clinical medicine.

CELLS ARE THE LIVING UNITS OF THE BODY

Each tissue or organ is an aggregate of many different cells held together by intercellular supporting structures.

Each type of cell is specially adapted to perform one or a few particular functions. For example, the red blood cells, numbering about 25 trillion in each person, transport oxygen from the lungs to the tissues. Although the red blood cells are the most abundant cell type in the body, there are also trillions of additional cells of other types that perform functions different from those of the red blood cell. The entire human body contains about 35 to 40 trillion cells.

The many cells of the body often differ markedly from one another but all have certain basic characteristics that are alike. For example, oxygen reacts with carbohydrate, fat, and protein to release the energy required for all cells to function. Furthermore, the general chemical mechanisms for changing nutrients into energy are basically the same in all cells, and all cells deliver products of their chemical reactions into the surrounding fluids.

Almost all cells also have the ability to reproduce additional cells of their own type. Fortunately, when cells of a particular type are destroyed, the remaining cells of this type usually generate new cells until the supply is replenished.

Communities of Microorganisms Living in the Body Outnumber Human Cells. In addition to human cells, trillions of microbes inhabit the body, living on the skin and in the mouth, gut, and nose. The gastrointestinal tract, for example, normally contains a complex, dynamic population of 400 to 1000 species of microorganisms that outnumber our human cells. Communities of microorganisms that inhabit the body, often called *microbiota*, can cause diseases, but most of the time they live in harmony with their human hosts and provide vital functions that are essential for survival of their hosts. Although the importance of gut microbiota for digestion of foodstuffs is widely recognized, additional roles for the body's microbes in nutrition, immunity, and other functions are just beginning to be appreciated and represent an intensive area of biomedical research.

EXTRACELLULAR FLUID—THE "INTERNAL ENVIRONMENT"

About 50% to 70% of the adult human body is fluid, mainly a water solution of ions and other substances. Although most of this fluid is inside the cells (*intracellular fluid*), about one-third is in the spaces outside the cells (*extracellular fluid*). The extracellular fluid is in constant motion throughout the body. It is transported rapidly in the circulating blood and then mixed between the blood and tissue fluids by diffusion through the capillary walls.

In the extracellular fluid are the ions and nutrients needed by the cells to maintain life. Thus, all cells live in essentially the same environment—the extracellular fluid. For this reason, the extracellular fluid is also called the *internal environment* of the body, or the *milieu intérieur*, a term introduced by the great 19th-century French physiologist Claude Bernard (1813–1878).

Maintenance of the proper concentrations of oxygen, glucose, different ions, amino acids, fatty substances, and other constituents in this internal environment is required for the cells to perform their special functions.

Differences in Extracellular and Intracellular Fluids. The extracellular fluid contains large amounts of sodium, chloride, and bicarbonate ions plus nutrients for the cells, such as oxygen, glucose, fatty acids, and amino acids. It also contains carbon dioxide that is transported from the cells to the lungs to be excreted, plus other cellular waste products that are transported to the kidneys for excretion.

The intracellular fluid contains large amounts of potassium, magnesium, and phosphate ions instead of the sodium and chloride ions found in the extracellular fluid. Special mechanisms for transporting ions through the cell membranes maintain the ion concentration differences between the extracellular and intracellular fluids. These transport processes are discussed in Chapter 4.

HOMEOSTASIS—MAINTENANCE OF A STABLE INTERNAL ENVIRONMENT

In 1929, the American physiologist Walter Cannon (1871–1945) coined the term *homeostasis* to describe the *maintenance of stable conditions in the internal environment*. Homeostasis is a dynamic, rather than static, process that is continually adjusting the body's functions to maintain internal stability despite the challenges of daily life in health, as well as in disease.

Homeostasis occurs at all levels of organization in the body—from the molecular and genetic levels to the cells, tissues, organs, and the whole body. For example, the process of deoxyribonucleic acid (DNA) replication, which is necessary for production of new cells, requires assembly of around 3 to 6 billion nucleotides in correct order to form 20,000 to 25,000 genes that control formation of approximately 100,000 proteins. Each type of cell has different mechanisms that control its gene expression and protein formation. The human body has around 25 to 30 trillion cells, not including another 25 to 30 trillion microorganisms living in the body, usually in symbiosis with the body's cells. Each cell of the body, in turn, has many separate control mechanisms that regulate its function. The cells that make up a tissue communicate with each other via chemical signals and in some cases form organs that have their own internal controls. The organs communicate with each other via the *nervous system* and by releasing different substances, including *hormones* and *extracellular vesicles*; these vesicles are bound by lipids, secreted by cells into the extracellular space, and contain cargo that can alter the function of other cells and organs. How is all of this beautiful complexity that sustains life coordinated? This overall coordination is called homeostasis.

A fundamental principle of homeostasis is that *the function of the whole body is much more than the sum of its parts*. All of the organs and tissues of the body perform their functions, which together help maintain the stable conditions necessary for life. For example, the lungs provide oxygen to the extracellular fluid to replenish the oxygen used by the cells, the kidneys maintain stable ion concentrations, and the gastrointestinal system provides nutrients while eliminating waste from the body.

Body Fluid Constituents Are Normally Regulated Within a Tolerable Range of Values. The various ions, nutrients, waste products, and other constituents of the body are normally regulated within a tolerable range of values, rather than at fixed values. For some of the body's constituents, this range is extremely small. Variations in the blood hydrogen ion concentration, for example, are normally less than 5 *nanomoles/L* (0.000000005 moles/L). The blood sodium concentration is also tightly regulated, normally varying only a few *millimoles* per liter, even with large changes in sodium intake, but these variations of sodium concentration are at least 1 million times greater than for hydrogen ions.

Powerful control systems exist for maintaining concentrations of sodium and hydrogen ions, as well as for most of the other ions, nutrients, and substances in the body at levels that permit the cells, tissues, and organs to perform their normal functions, despite wide environmental variations and challenges from injury and diseases.

Much of this text is concerned with how each organ or tissue contributes to homeostasis. Normal body functions require integrated actions of cells, tissues, organs, and multiple nervous, hormonal, and local control systems that together contribute to homeostasis and good health.

Homeostatic Compensations in Diseases. *Disease* is often considered to be a state of disrupted homeostasis. However, even with diseases, homeostatic mechanisms continue to operate and maintain vital functions through multiple compensations. In some cases, these compensations may lead to major deviations of the body's functions from the normal range, making it difficult to distinguish the primary cause of the disease from the compensatory responses. For example, diseases that impair the kidneys' ability to excrete salt and water may lead to high blood pressure, which initially helps return excretion to normal so that a balance between intake and renal excretion can be maintained. This balance is needed to maintain life, but, over long periods of time, the high blood pressure can damage various organs, including the kidneys, causing even greater increases in blood pressure and more renal damage. Thus, homeostatic compensations that ensue after injury, disease, or major environmental challenges to the body may represent trade-offs that are necessary to maintain life but that, in the long term, contribute to additional abnormalities of body function. The discipline of *pathophysiology* seeks to explain how the various physiological processes are altered in diseases or injury.

This chapter outlines the different functional systems of the body and their contributions to homeostasis. We then briefly discuss the basic theory of the body's control systems that allow the functional systems to operate in support of one another.

CIRCULATION OF THE BLOOD PROVIDES MIXING AND TRANSPORT OF EXTRACELLULAR FLUID

Extracellular fluid is transported through the body in two stages. The first stage is movement of blood through the body in the blood vessels. The second is movement of fluid between the blood capillaries and the *intercellular spaces* between the tissue cells.

Fig. 1.1 shows the overall circulation of blood. All the blood in the circulation traverses the entire circuit an average of once each minute when the body is at rest and as many as six times each minute when a person is extremely active.

As blood passes through blood capillaries, continual exchange of extracellular fluid occurs between the plasma portion of the blood and the interstitial fluid that fills the intercellular spaces. This process is shown in **Fig. 1.2**. The capillary walls are permeable to most molecules in the blood plasma, with the exception of plasma proteins, which are too large to pass through capillaries readily. Therefore, large amounts of fluid and its dissolved constituents *diffuse* back and forth between the blood and the tissue spaces, as shown by the arrows in **Fig. 1.2**.

This process of diffusion is caused by kinetic motion of the molecules in the plasma and the interstitial fluid. That is, the fluid and dissolved molecules are continually moving and bouncing in all directions in the plasma and fluid in the intercellular spaces, as well as through capillary pores. Few cells are located more than 50 micrometers from a capillary, which ensures diffusion of almost any substance from the capillary to the cell within a few seconds. Thus, the extracellular fluid everywhere in the body—including plasma and interstitial fluid—is continually being mixed, thereby maintaining homogeneity of extracellular fluid throughout the body.

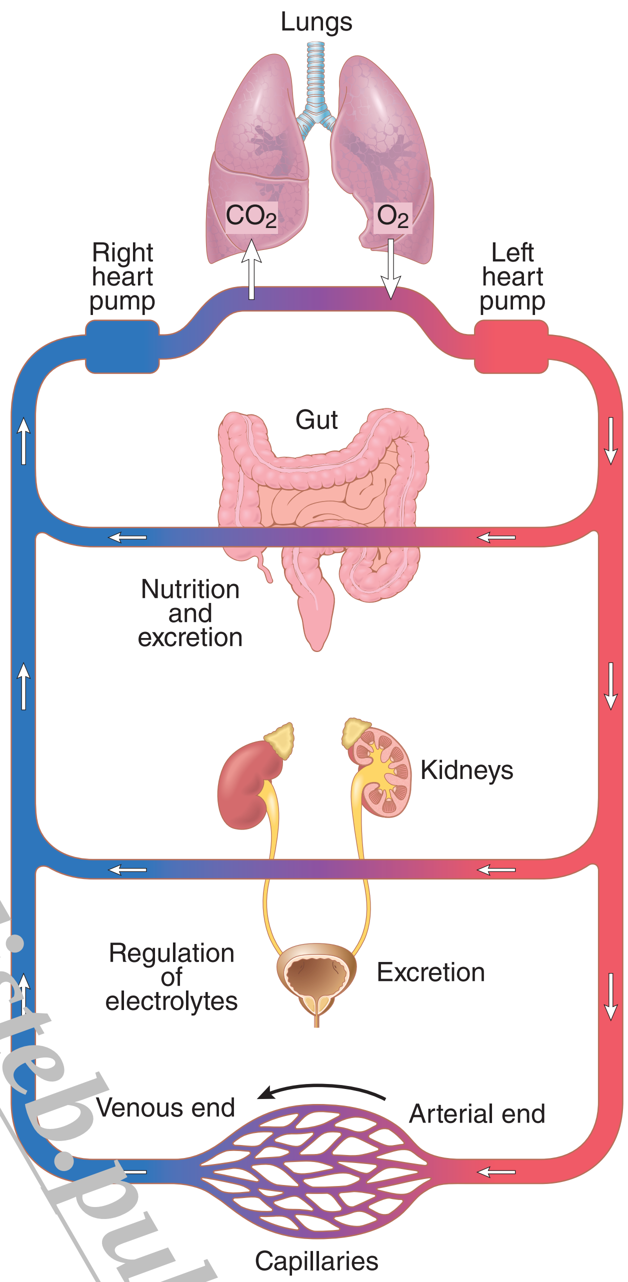

Figure 1.1 General organization of the circulatory system.

ORIGIN OF NUTRIENTS IN THE EXTRACELLULAR FLUID

Respiratory System. **Fig. 1.1** shows that each time blood passes through the body, it also flows through the lungs, picking up *oxygen* in alveoli and acquiring oxygen needed by cells. The membrane between the alveoli and the lumen of the pulmonary capillaries, the *alveolar membrane*, is only 0.4 to 2.0 micrometers thick, and oxygen rapidly diffuses by molecular motion through this membrane into the blood.

Gastrointestinal Tract. A large portion of the blood pumped by the heart also passes through the walls of the gastrointestinal tract. Here different dissolved nutrients,

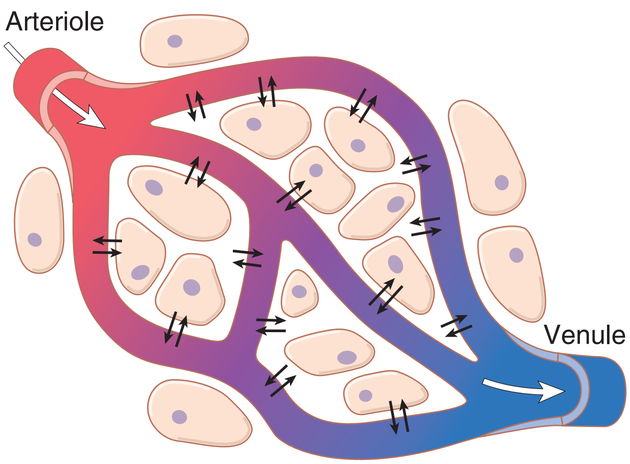

Figure 1.2 Diffusion of fluid and dissolved constituents through the capillary walls and interstitial spaces.

including *carbohydrates, fatty acids*, and *amino acids*, are absorbed from ingested food into the extracellular fluid of the blood.

Liver and Other Organs That Perform Primarily Metabolic Functions. Not all substances absorbed from the gastrointestinal tract can be used in their absorbed form by the cells. The liver changes the chemical compositions of many of these substances to more usable forms, and other tissues of the body—fat cells, gastrointestinal mucosa, kidneys, and endocrine glands—help modify the absorbed substances or store them until they are needed. The liver also eliminates certain waste products produced in the body and toxic substances that are ingested.

Musculoskeletal System. How does the musculoskeletal system contribute to homeostasis? Were it not for the muscles, the body could not move to obtain the foods required for nutrition. The musculoskeletal system also provides motility that, along with its other homeostatic mechanisms, protects the entire body against adverse surroundings.

REMOVAL OF METABOLIC END PRODUCTS

The Lungs Remove Carbon Dioxide. At the same time that blood picks up oxygen in the lungs, *carbon dioxide* is released from the blood into lung alveoli; the respiratory movement of air into and out of the lungs carries carbon dioxide to the atmosphere. Carbon dioxide is the most abundant of all the metabolism products.

Kidneys. Passage of blood through the kidneys removes most of the other substances from the plasma besides carbon dioxide that are not needed by cells. These substances include different end products of cellular metabolism, such as urea and uric acid, as well as excesses of ions and water from the food that accumulate in the extracellular fluid.

The kidneys perform these functions first by filtering large quantities of plasma through the glomerular capillaries into the tubules and then reabsorbing into the blood substances needed by the body, such as glucose, amino acids, appropriate amounts of water, and many of the ions. Most of the other substances that are not needed by the body, especially metabolic waste products such as urea and creatinine, are reabsorbed poorly and pass through the renal tubules into the urine.

Gastrointestinal Tract. Undigested material that enters the gastrointestinal tract and some waste products of metabolism are eliminated in the feces.

Liver. Among the many functions of the liver is detoxification or removal of ingested drugs and chemicals. The liver secretes many of these wastes into the bile to be eventually eliminated in the feces.

REGULATION OF BODY FUNCTIONS

Nervous System. The nervous system is composed of three major parts—the *sensory input portion*, the *central nervous system* (or *integrative portion*), and the *motor output portion*. Sensory receptors detect the state of the body and its surroundings. For example, receptors in the skin alert us whenever an object touches the skin. The eyes are sensory organs that give us a visual image of the surrounding area. The ears permit us to detect sounds. The central nervous system is composed of the brain and spinal cord. The brain stores information, generates thoughts, creates ambition, and determines reactions that the body performs in response to the sensations. Appropriate signals are then transmitted through the motor output portion of the nervous system to carry out one's desires.

An important segment of the nervous system is called the *autonomic system*. It operates at a subconscious level and controls many functions of internal organs, including the level of pumping activity by the heart, movements of the gastrointestinal tract, and secretion by many of the body's glands.

Hormone Systems. Located in the body are *endocrine glands*, organs and tissues that secrete chemical substances called *hormones*. Hormones are transported in the extracellular fluid to other parts of the body to help regulate cellular function. For example, *thyroid hormone* increases the rates of most chemical reactions in all cells, thus helping set the tempo of bodily activity. *Insulin* controls glucose metabolism, *adrenocortical hormones* control sodium and potassium ions and protein metabolism, and *parathyroid hormone* controls bone calcium and phosphate. Thus, the hormones provide a regulatory system that complements the nervous system. The nervous system controls many muscular and secretory activities of the body, whereas the hormonal system regulates many metabolic functions. The nervous and hormonal systems normally work together in a coordinated manner to control essentially all the organ systems of the body.

PROTECTIVE SYSTEMS OF THE BODY

Immune System. The immune system includes white blood cells, tissue cells derived from white blood cells, the thymus, lymph nodes, and lymph vessels that protect the body from pathogens such as bacteria, viruses, parasites, and fungi. The immune system provides a mechanism for the body to carry out the following: (1) distinguish its own cells from harmful foreign cells and substances; and (2) destroy the invader by *phagocytosis* or by producing *sensitized lymphocytes* or specialized proteins (e.g., *antibodies*) that destroy or neutralize the invader.

Integumentary System. The skin and its various appendages (including the hair, nails, glands, and other structures) cover, cushion, and protect the deeper tissues and organs of the body and generally provide a boundary between the body’s internal environment and the outside world. The integumentary system is also important for temperature regulation and excretion of wastes, and it provides a sensory interface between the body and the external environment. The skin generally comprises about 12% to 15% of body weight.

REPRODUCTION

Although reproduction may not seem to be a homeostatic function, it helps maintain homeostasis by generating new beings to take the place of those that are dying. This may sound like a permissive usage of the term *homeostasis*, but it illustrates that in the final analysis, essentially all body structures are organized to help maintain the automaticity and continuity of life.

CONTROL SYSTEMS OF THE BODY

The human body has thousands of control systems. Some of the most intricate of these systems are genetic control systems that operate in all cells to help regulate intracellular and extracellular functions. This subject is discussed in Chapter 3.

Many other control systems operate *within the organs* to regulate functions of the individual parts of the organs; others operate throughout the entire body *to control the communication and interrelationships among the organs*. For example, the respiratory system, operating in association with the nervous system, regulates carbon dioxide concentration in the extracellular fluid. The liver and pancreas control glucose concentration in the extracellular fluid, and the kidneys regulate concentrations of hydrogen, sodium, potassium, phosphate, and other ions in the extracellular fluid.

EXAMPLES OF CONTROL MECHANISMS

Regulation of Oxygen and Carbon Dioxide Concentrations in the Extracellular Fluid. Because oxygen is required for chemical reactions in cells, the body has a special control mechanism to maintain an almost exact and constant oxygen concentration in the extracellular fluid. This mechanism depends principally on the chemical characteristics of *hemoglobin*, which is present in red blood cells. Hemoglobin combines with oxygen as blood passes through the lungs. Then, as blood passes through the tissue capillaries, hemoglobin, because of its own strong chemical affinity for oxygen, does not release oxygen into the tissue fluid if too much oxygen is already there. However, if oxygen concentration in the tissue fluid is too low, sufficient oxygen is released to reestablish an adequate concentration. Thus, regulation of oxygen concentration in the tissues relies to a great extent on the chemical characteristics of hemoglobin. This regulation is called the *oxygen-buffering function of hemoglobin*.

Carbon dioxide concentration in the extracellular fluid is regulated in a much different way. Carbon dioxide is a major end product of oxidative reactions in cells. If all the carbon dioxide formed in the cells continued to accumulate in the tissue fluids, all energy-giving reactions of the cells would cease. Fortunately, a higher than normal carbon dioxide concentration in the blood *excites the respiratory center*, causing a person to breathe rapidly and deeply. This deep rapid breathing increases expiration of carbon dioxide and removes excess carbon dioxide from the blood and tissue fluids. This process continues until the concentration returns to normal.

Regulation of Arterial Blood Pressure. Several systems contribute to arterial blood pressure regulation. One of these, the *baroreceptor system*, is an excellent example of a rapidly acting control mechanism (Fig. 1.3). In the walls of the bifurcation region of the carotid arteries in the neck and in the arch of the aorta in the thorax, are many nerve receptors called *baroreceptors* that are stimulated

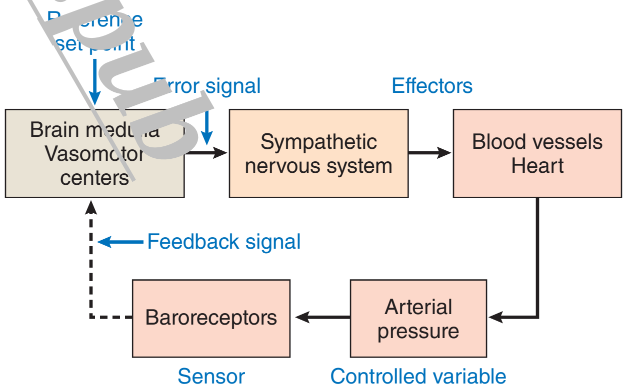

Figure 1.3 Negative feedback control of arterial pressure by the arterial baroreceptors. Signals from the sensor (baroreceptors) are sent to the medulla of the brain, where they are compared with a reference set point. When arterial pressure increases above normal, this abnormal pressure increases nerve impulses from the baroreceptors to the medulla of the brain, where the input signals are compared with the set point, generating an error signal that leads to decreased sympathetic nervous system activity. Decreased sympathetic activity causes dilation of blood vessels and reduced pumping activity of the heart, which return arterial pressure toward normal.

by stretch of the arterial wall. When arterial pressure rises too high, the baroreceptors send increased nerve impulses to the medulla of the brain. Here, these impulses inhibit the *vasomotor center*, which in turn decreases the number of impulses transmitted from the vasomotor center through the sympathetic nervous system to the heart and blood vessels. Reduced sympathetic nervous activity diminishes pumping activity of the heart and dilates peripheral blood vessels. Both these effects decrease the arterial pressure, moving it back toward normal.

Conversely, a decrease in arterial pressure below normal relaxes the stretch receptors, allowing the vasomotor center to become more active than usual, thereby causing vasoconstriction and increased heart pumping. The initial decrease in arterial pressure thus initiates negative feedback mechanisms that raise arterial pressure back toward normal.

Normal Ranges and Physical Characteristics of Important Extracellular Fluid Constituents

Table 1.1 lists some important constituents of extracellular fluid, along with their normal values, normal ranges, and maximum limits without causing death. Note the narrowness of the normal range for most of these constituents. Values outside these ranges are often caused by illness, injury, or major environmental challenges.

Most important are the limits beyond which abnormalities can cause death. For example, an increase in the body temperature of only 11°F (7°C) above normal can lead to a vicious cycle of increasing cellular metabolism that destroys the cells. Note also the narrow range for acid–base balance in the body, with a normal pH value of 7.4 yet lethal values only about 0.5 higher or lower than the normal value. Whenever the potassium ion concentration decreases to less than one-third normal, paralysis may result from the inability of the nerves to carry signals. Alternatively, if potassium ion concentration increases to two or more times normal, the heart muscle is likely to be severely depressed. Also, when the calcium ion concentration falls below about one-half normal, a person is likely to experience tetanic contraction of muscles throughout the body because of the spontaneous generation of excess nerve impulses in peripheral nerves. When the glucose concentration falls below one-half normal, a person frequently exhibits extreme mental irritability and sometimes even has convulsions.

These examples give one an appreciation for the necessity of the vast numbers of control systems that keep the body operating in health. In the absence of any one of these controls, serious body malfunction or death can result.

CHARACTERISTICS OF CONTROL SYSTEMS

The aforementioned examples of homeostatic control mechanisms are only a few of the many thousands in the body, all of which have some common characteristics, as explained in this section.

Many Control Systems Operate By Negative Feedback

Most control systems of the body act by *negative feedback*, which can be explained by reviewing some of the homeostatic control systems mentioned previously. In the regulation of carbon dioxide concentration, a high concentration of carbon dioxide in the extracellular fluid increases pulmonary ventilation. This, in turn, decreases extracellular fluid carbon dioxide concentration because the lungs expire greater amounts of carbon dioxide from the body. Thus, the high concentration of carbon dioxide initiates events that decrease the concentration toward normal, which is *negative* to the initiating stimulus. Conversely, a carbon dioxide concentration that falls too low results in feedback to increase the concentration. This response is also negative to the initiating stimulus.

In the arterial pressure–regulating mechanisms, a high pressure causes a series of reactions that promote compensatory reductions in pressure, whereas a low pressure causes a series of reactions that promote increased pressure. In both cases, these effects are negative with respect to the initiating stimulus.

Table 1.1 Important Constituents and Physical Characteristics of Extracellular Fluid

Constituent	Normal Value	Normal Range	Approximate Short-Term Nonlethal Limit	Unit
Oxygen (venous)	40	25–40	10–1000	mm Hg
Carbon dioxide (venous)	45	41–51	5–80	mm Hg
Sodium ion	142	135–145	115–175	mmol/L
Potassium ion	4.2	3.5–5.3	1.5–9.0	mmol/L
Calcium ion	1.2	1.0–1.4	0.5–2.0	mmol/L
Chloride ion	106	98–108	70–130	mmol/L
Bicarbonate ion	24	22–29	8–45	mmol/L
Glucose	90	70–115	20–1500	mg/dL
Body temperature	98.4 (37.0)	98–98.8 (37.0)	65–110 (18.3–43.3)	°F (°C)
Acid–base (venous)	7.4	7.3–7.5	6.9–8.0	pH

Therefore, in general, if some factor becomes excessive or deficient, a control system initiates *negative feedback*, which consists of a series of changes that return the factor toward a certain mean value, thus maintaining homeostasis.

Gain of a Control System. The degree of effectiveness with which a control system maintains constant conditions is determined by the *gain* of negative feedback. For example, let us assume that a large volume of blood is transfused into a person whose baroreceptor pressure control system is not functioning, and the arterial pressure rises from the normal level of 100 mm Hg up to 175 mm Hg. Then, let us assume that the same volume of blood is injected into the same person when the baroreceptor system is functioning, and this time the pressure increases by only 25 mm Hg. Thus, the feedback control system has caused a "correction" of −50 mm Hg, from 175 mm Hg to 125 mm Hg. There remains an increase in pressure of +25 mm Hg, called the "error," which means that the control system is not 100% effective in preventing change. The gain of the system is then calculated by using the following formula:

$$\text{Gain} = \frac{\text{Correction}}{\text{Error}}$$

Thus, in the baroreceptor system example, the correction is −50 mm Hg, and the error persisting is +25 mm Hg. Therefore, the gain of the person's baroreceptor system for control of arterial pressure is −50 divided by +25, or −2. Thus, the baroreceptor system corrects about two-thirds of the initial disturbance and increases or decreases in arterial pressure are only one-third as much as would occur if this control system were not present.

The gains of some other physiological control systems are much greater than that of the baroreceptor system. For example, the gain of the system controlling internal body temperature when a person is exposed to moderately cold weather is about −33. Therefore, one can see that the temperature control system is much more effective than the baroreceptor pressure control system.

Feed-Forward and Adaptive Control Systems Anticipate Changes

Later in this text, when we study the nervous system, we shall see that this system contains great numbers of interconnected control mechanisms. Some are simple feedback systems similar to those already discussed. Many are not. For example, some movements of the body occur so rapidly that there is not enough time for nerve signals to travel from the peripheral parts of the body all the way to the brain and then back to the periphery again to control the movement. Therefore, the brain uses a mechanism called *feed-forward control* to cause required muscle contractions. Sensory nerve signals from the moving parts apprise the brain about whether the movement is performed correctly. If not, the brain corrects the feed-forward signals that it sends to the muscles the *next* time the movement is required. Then, if still further correction is necessary, this process will be performed again for subsequent movements. This process is called *adaptive control*. Adaptive control, in a sense, is delayed negative feedback.

Positive Feedback May Cause Vicious Cycles and Death

Why do most control systems of the body operate by negative feedback or feed-forward rather than by positive feedback? If one considers the nature of positive feedback, it is obvious that positive feedback leads to instability rather than stability and, in some cases, can cause death.

Fig. 1.4 shows an example in which death can ensue from positive feedback. This figure depicts the pumping effectiveness of the heart, showing the heart of a healthy human pumping about 5 liters of blood per minute. If the person suddenly bleeds a total of 2 liters, the amount of blood in the body is decreased to such a low level that not enough blood is available for the heart to pump effectively. As a result, the arterial pressure falls, and the flow of blood to the heart muscle through the coronary vessels diminishes. This scenario results in weakening of the heart, further diminished pumping, further decrease in coronary blood flow, and still more weakness of the heart; the cycle repeats itself again and again until death occurs. Note that each cycle in the feedback results in further weakening of the heart. In other words, the initiating stimulus causes more of the same, which is *positive feedback*.

Positive feedback is sometimes known as a "vicious cycle," but a mild degree of positive feedback can be overcome by the negative feedback control mechanisms of the body, and the vicious cycle then fails to develop. For example, if the person in the aforementioned example bleeds only 1 liter instead of 2 liters, the normal negative feedback mechanisms for controlling cardiac output and arterial pressure can counterbalance the positive feedback, and the person can recover, as shown by the dashed curve of **Fig. 1.4**.

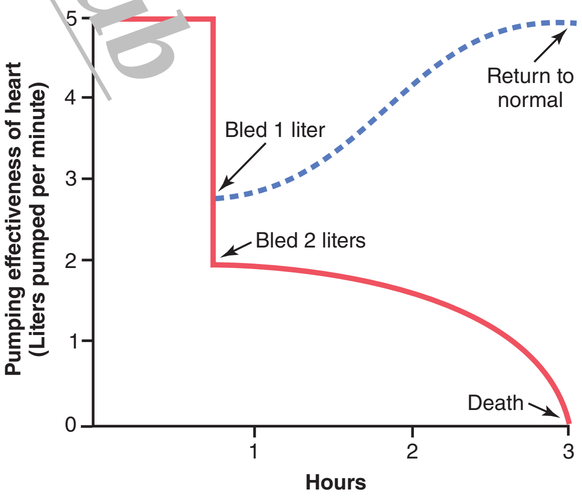

Figure 1.4 Recovery of heart pumping caused by negative feedback after 1 liter of blood is removed from the circulation. Death is caused by positive feedback when 2 or more liters of blood are removed.

Positive Feedback Can Sometimes Be Useful. The body sometimes uses positive feedback to its advantage. Blood clotting is an example of a valuable use of positive feedback. When a blood vessel is ruptured, and a clot begins to form, multiple enzymes called *clotting factors* are activated within the clot. Some of these enzymes act on other inactivated enzymes of the immediately adjacent blood, thus causing more blood clotting. This process continues until the hole in the vessel is plugged and bleeding stops. On occasion, this mechanism can get out of hand and cause the formation of unwanted clots. In fact, this is what initiates most acute heart attacks, which can be caused by a clot beginning on the inside surface of an atherosclerotic plaque in a coronary artery and then growing until the artery is blocked.

Childbirth is another situation in which positive feedback is valuable. When uterine contractions become strong enough for the baby's head to begin pushing through the cervix, the stretched cervix sends signals through the uterine muscle back to the body of the uterus, causing even more powerful contractions. Thus, the uterine contractions stretch the cervix, and cervical stretch causes stronger contractions. When this process becomes powerful enough, the baby is born. If they are not powerful enough, the contractions usually die out, and a few days pass before they begin again.

Another important use of positive feedback is for the generation of nerve signals. Stimulation of the membrane of a nerve fiber causes slight leakage of sodium ions through sodium channels in the nerve membrane to the fiber's interior. The sodium ions entering the fiber then change the membrane potential, which, in turn, causes more opening of channels, more change of potential, still more opening of channels, and so forth. Thus, a slight leak becomes an explosion of sodium entering the interior of the nerve fiber, which creates the nerve action potential. This action potential, in turn, causes electrical current to flow along the outside and inside of the fiber and initiates additional action potentials. This process continues until the nerve signal goes all the way to the end of the fiber.

In each case in which positive feedback is useful, the positive feedback is part of an overall negative feedback process. For example, in the case of blood clotting, the positive feedback clotting process is a negative feedback process for the maintenance of normal blood volume. Also, the positive feedback that causes nerve signals allows the nerves to participate in thousands of negative feedback nervous control systems.

Thus, one can see how complex the feedback control systems of the body can be. A person's life depends on all of them. Therefore, much of this text is devoted to discussing these life-giving mechanisms, as well as some of the positive feedbacks that can lead to progressive diseases or even death.

PHYSIOLOGICAL VARIABILITY

Although some physiological variables, such as plasma concentrations of potassium, calcium, and hydrogen ions, are tightly regulated, others, such as body weight and adiposity, show wide variation among different individuals and even in the same individual at different stages of life. Blood pressure, cardiac pumping, metabolic rate, nervous system activity, hormones, and other physiological variables change throughout the day as we move about and engage in normal daily activities. Some variables follow a *circadian rhythm*, a regular recurring cycle of changes every 24 hours, as discussed in Chapter 59. Therefore, when we discuss "normal" values, it is with the understanding that many of the body's control systems are constantly reacting to perturbations and that variability may exist even in the same individual, depending on the time of day, and among different individuals, depending on body weight and height, diet, age, sex, environment, genetics, and other factors.

For simplicity, discussion of physiological functions often focuses on the "average" 70-kg lean young male. However, the American male no longer weighs an average of 70 kg; he now weighs over 88 kg, and the average American female weighs over 76 kg, more than the average male in the 1960s. Body weight has also increased substantially in most other industrialized countries during the past 40 to 50 years.

Age-related and ethnic or racial differences in physiology also have important influences on body composition, physiological control systems, and pathophysiology of diseases. For example, total body water is about 60% to 65% of body weight in lean young males and about 50% to 55% in lean young females, although there is considerable variation among individuals. As a person grows and ages, this percentage gradually decreases, partly because aging is usually associated with declining skeletal muscle mass and increasing fat mass. Aging may also cause a decline in the function and effectiveness of some organs and physiological control systems.

These sources of physiological variability—sex differences, aging, and ethnic differences—are complex but important considerations when discussing normal physiology and the pathophysiology of diseases.

SEX DIFFERENCES IN PHYSIOLOGY AND PATHOPHYSIOLOGY

The term *sexual dimorphism* has traditionally been used to describe two distinct and nonoverlapping traits of males and females from the same species. In humans, sexually dimorphic anatomical features include, for example, the gonads (e.g., testes and ovaries) and the internal and external genitals. However, beyond obvious differences related to reproduction and some physical traits, important sex differences exist for a broad range of physiological