

The Core Principles of Physiology 1.1

Learning Objectives

- Define the discipline of physiology
- Describe in general terms how each organ system contributes to homeostasis
- Define reductionism and compare it to holism
- Describe what is meant by emergent properties
- Define homeostasis
- List the four Aristotelian causes and define teleology
- Define mechanism
- Describe how evolution is a cause of human form and function
- Write equations for the conservation of mass and energy for the body
- Give an example of signaling at the organ or cellular level of organization
- List the core principles of physiology
- Contrast feed-forward or anticipatory control to negative feedback control

HUMAN PHYSIOLOGY IS THE INTEGRATED STUDY OF THE NORMAL FUNCTION OF THE HUMAN BODY

ORGAN SYSTEMS WORK TOGETHER TO PRODUCE OVERALL BODY BEHAVIOR

Almost any explanation of something begins with a description of that something's parts. The human body consists of many parts. We consider an assortment of parts that usually relate to each other in defined ways to be a **system**. In physiology, a system is usually considered to be a group of organs that serve some well-defined function of the body. The parts of these systems can be described separately, but they *work together* to produce the overall system behavior. That is, the individual behavior of the parts is *integrated* to produce overall behavior. The various organ systems and their functions in the body are summarized in [Table 1.1.1](#). These systems are further integrated to produce overall bodily function. Physiology is the study of the integrated normal function of the human body.

Each of these organ systems is essential to the survival of the organism, the living human being. It is possible

in an artificial environment to survive with a single compromised system—such as persons with failed kidneys or failed immunological systems—but these persons could not survive in natural ecosystems.

REDUCTIONISM EXPLAINS SOMETHING ON THE BASIS OF ITS PARTS

The process of explaining something on the basis of its parts is called **reductionism**. Thus the behavior of the body can be explained by the coordinated behavior of its component organ systems. In turn, each organ system can be explained in terms of the behavior of the component organs. In this reduction recursion, the behavior of the component organs can be explained by their components, the individual cells that make up the organ. These cells, in turn, can be explained by the behavior of their component subcellular organelles; the subcellular organelles can be explained by the macrochemicals and biochemicals that make up these organelles; the biochemicals can be explained by their component atoms; the atoms can be explained by their component subatomic particles; the subatomic particles can be explained by fundamental particles. According to this reductionist recursion, we might anticipate that the final explanation of our own bodies lies in the physics of the fundamental particles. Beyond being impractical, there is a growing realization that it is theoretically impossible to describe complex and complicated living beings solely on this basis of fundamental physics, because at each step in the process some information is lost.

This situation should not trouble us too much. In physics, we speak of the force of friction even though friction is not a fundamental force. It results from tremendous numbers of electromagnetic interactions between particles on two surfaces so that friction really is just a trace of all of those microscopic electromagnetic interactions onto the macroscopic bodies. The details of the surfaces produce those forces and we can experimentally reduce the force simply by polishing the surfaces that interact, making the tiny bumps and valleys on the surfaces smaller. We don't know the details of the surface and so we ignore the reality and lump all of those interactions together and call it the "force" of friction. We have lost some information and abandon the idea of recursing reductionism down to the level of fundamental physics.

TABLE 1.1.1 Organ Systems of the Body

Organ System	Function
Nervous system/endocrine system	Sensory input and integration; command and control
Musculoskeletal system	Support and movement
Cardiovascular system	Transportation between tissues and environmental interfaces
Gastrointestinal system	Digestion of food and absorption of nutrients
Respiratory system	Regulation of blood gases and exchange of gas with the air
Renal system	Regulation of volume and composition of body fluids
Integumentary system (skin)	Protection from microbial invasion, water vapor barrier, and temperature control
Reproductive system	Pass life on to the next generation
Immune system	Removal of microbes and other foreign materials

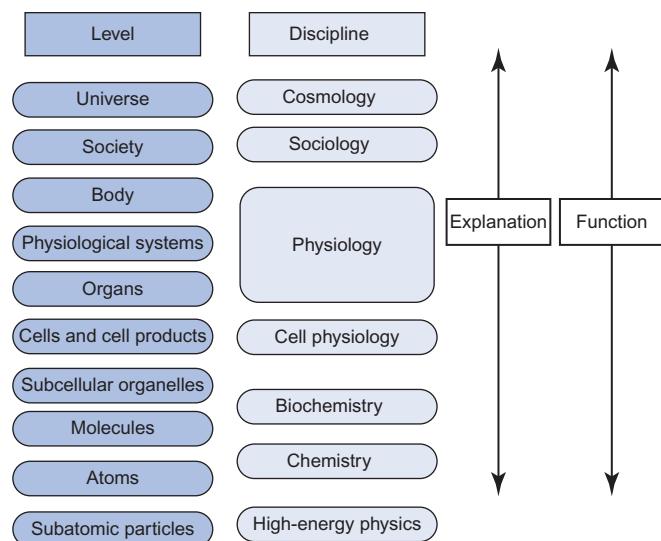


FIGURE 1.1.1 Hierarchical description of physical reality as applied to physiological systems. We attempt to “explain” something in terms of its component parts and describe a function for a part in terms of its role in the “higher” organizational entity.

PHYSIOLOGICAL SYSTEMS ARE PART OF A HIERARCHY OF LEVELS OF ORGANIZATION

The recursion of explanation described above for reductionism involves various levels of complexity in a hierarchical description of living beings, as shown in Figure 1.1.1. Understanding any particular level entails relating that level to the one immediately above it and the one immediately below it. For example, scientists studying a particular subcellular organelle can be said to have mastered it when they can explain how the function of the organelle derives from the activities of its

parts, the molecules that make it up, and how the organelle’s function is regulated by and contributes to the function of the cell.

REDUCTIONISM IS AN EXPERIMENTAL PROCEDURE; RECONSTITUTION IS A THEORETICAL PROCEDURE

The processes used in going “down” or “up” in this hierarchy are not the same. We use reductionism to explain the function of the whole in terms of its parts, by going “down” in the levels of organization. We describe the function of the parts at one level by showing how they contribute to the behavior of the larger level of organization, going “up” in Figure 1.1.1. These processes are fundamentally different. Reductionism involves actually breaking the system into its parts and studying the parts’ behavior in isolation under controlled conditions. For example, we can take a sample of tissue and disrupt its cells so that the cell membranes are ruptured. We can then isolate various subcellular organelles and study their behavior. This procedure characterizes the behavior of the subcellular organelle. Knowing the behavior of the individual parts and paying close attention to how these parts are connected, it is possible to predict system behavior from the parts’ behavior using simulation or other techniques. Because it is impossible, except in rare and limited cases, to reassemble broken systems (we cannot unscramble the egg!), we must test our ideas of subcellular function theoretically.

HOLISM PROPOSES THAT THE BEHAVIOR OF THE PARTS IS ALTERED BY THEIR CONTEXT IN THE WHOLE

Holism conveys the idea that the parts of an organism are interconnected and that each part affects others. The parts cannot be studied in isolation because important aspects of their behavior depend solely on their interaction with other parts. Reductionism seems to imply that the whole is the sum of the parts, whereas holism suggests that the whole is greater than the sum of the parts. The system takes on new properties, **emergent properties**, that arise from complex interactions among the parts. Examples of emergent properties include **self-replication**. The ability of cells to form daughter cells is a system property that does not belong to any one part but belongs to the entire system. Consciousness is also an emergent property that arises from neuronal function but at a much higher level of organization.

PHYSIOLOGICAL SYSTEMS OPERATE AT MULTIPLE LEVELS OF ORGANIZATION SIMULTANEOUSLY

It should be clear from Figure 1.1.1 that all the levels of organization simultaneously operate in the living human being. Processes occur at the molecular, subcellular, cellular, organ, and system levels simultaneously and dynamically.

THE BODY CONSISTS OF CAUSAL MECHANISMS THAT OBEY THE LAWS OF PHYSICS AND CHEMISTRY

When we say that we explain something, usually we mean that we can trace the output of the system—its behavior—to some cause. That is, we can seamlessly trace cause and effect from some starting point to some ending point. Aristotle (384–322 BC) posited four different kinds of causality:

1. Material Cause

A house is a house **because** of the boards, nails, shingles, and so on that make it up. We are what we are **because** of the cells and the cell products that make us up.

2. Efficient Cause

A house is a house **because** of the laborers who assembled the materials to make the house. We are what we are because of the developmental processes that produced us and **because** of all of the experiences we have had that alter us.

3. Formal Cause

A house is a house **because** of the blueprint that directed the laborers to assemble the materials in a particular way. We are what we are **because** of the DNA that directs our cells to make some proteins and not others, and because of epigenetic effects—those effects resulting from the environment interacting with the genome.

4. Final Cause

A house is a house **because** someone needed shelter. We are what we are **because**...

The final cause for humans has a variety of possible answers. This is the only cause that addresses the idea of a purpose. We make a house for a purpose: to provide someone with shelter. What is the purpose of human beings? This cause asks the question of why rather than how.

TELEOLOGY IS AN EXPLANATION IN REFERENCE TO A FINAL CAUSE

A description or explanation of a system based on the reference to the final cause is called a teleological explanation. Teleology has long been ridiculed by scientists because it appears to reverse the scientific notion of cause and effect. In normal usage, cause-and-effect linkages describe only the efficient cause. When a force acts on something, that something reacts in a predictable way. Its predictability is encoded in physical law. Teleology describes the behavior in terms of its final purpose, and not its driving force, which reverses the cause-and-effect link.

HOW? QUESTIONS ADDRESS CAUSAL LINKAGES. WHY? QUESTIONS ADDRESS FUNCTION

To clarify this process, let us ask some questions about blood pressure. How does your body regulate the average arterial blood pressure? This answer takes some time to develop fully (see Unit 5) but we can simplify the

answer by saying: by increasing or decreasing the caliber of the arteries, by increasing or decreasing the output of the heart, and by increasing or decreasing the volume of fluid in the arteries. All of these actions—and more—interact to determine the arterial blood pressure. All of these parts to the answer involve actions, and actions are efficient causes. For example, increasing or decreasing the caliber of the arteries depends on a complicated network of signaling pathways and biochemical reactions, but each starts with a cause and ends with an effect. Now we ask: why does your body regulate average arterial pressure at the level it does? The answer is again not so simple but we can simplify it as: to assure perfusion of the tissues. This addresses a purpose. In this sense, it is teleological, but it also makes sense to us. It is not that the cardiovascular system *knows* what it is doing, but its operation has been selected to produce the desired output. Within the framework of the body, organs do serve a purpose and that purpose is their function. All of the functions listed in Table 1.1.1 are final causes for the organ systems.

HUMAN BEINGS ARE NOT MACHINES BUT STILL OBEY PHYSICAL LAW

Aristotle had a different idea about the mind. He posited that the mind was not a material entity, much like an idea is not a material thing. He posited that the mind was what perceived, imagined, thought, emoted, desired, felt pain, reasoned, remembered, and controlled the body. This philosophy in which the mind controls behavior is called **mentalism**. These ideas went largely unchallenged until the Renaissance. René Descartes (1596–1650) wrote a book, *Treatise on Man*, in which he tried to explain how the nonmaterial mind might interact with the material body. In this process, he constructed mechanical analogues to explain sensation and command of movement. He thought that the operation of all things, however complex, could be explained by some **mechanism**. Each mechanism consists of a sequence of events that link an initial causal input to an effect that becomes the cause of the next step in the mechanism. In this view, human beings are very complex machines that obey natural law. In the late 1800s, W.O. Atwater (1844–1907) built a calorimeter to study heat production, gas exchange, and fuel consumption in humans. He found that the energy output of humans matched the chemical energy of the food consumed, within narrow experimental error. This result confirmed that the law of conservation of energy held for the transformation of energy by the human body as well as for inanimate transformations.

IS THERE A GHOST IN THE MACHINE?

The core principle of physiology that states the human body is a mechanism strikes at the heart of the concept of **vitalism**. Vitalism states that living things cannot be described in mechanistic terms alone, and that some organizing force or vital principle forever distinguishes living things from nonliving things. For human beings, we could call this the soul and be in reasonable agreement with the vitalists. So far, science has found

no reliable, scientific verification that the human body violates any physical law. The existence of emergent properties gives credence to the idea of vitalism. Emergent properties are new properties that arise from complex systems because of their complexity and topology—the way that subsystems are connected. These emergent properties do not appear to be predictable. That is, we cannot see how we would predict their emergence given the fundamental laws of physics. Examples of these emergent properties are life itself and consciousness. These properties appear to arise from interactions of parts that appear to obey physical law alone, but how these properties arise remains mysterious. These emergent properties are system properties, not mechanism properties. Because of overwhelming evidence that specific deficits in brain function produce specific deficits in mental function, we have come to believe that the brain somehow produces the mystical thing that is conscious and self-aware. This thing is not material in the ordinary sense of the word, just like an idea is not a material thing. The new mind–body problem is the inverse of Descartes's mind–body problem: how can a material thing (the brain) produce the nonmaterial thing that we identify as *self*. Is this relationship a one-way street, or does the mind have a reciprocal effect on the brain? Although these are extremely important questions, most physiologists take a narrower aim of explaining only those phenomena for which we have satisfactory mechanistic models and attempt to extend the range to include all physiologic phenomena, including consciousness.

UNDERSTANDING A SYSTEM IS EQUIVALENT TO MAKING A MODEL OF IT

What we have been discussing so far is what it means to say that we understand something. The something we are trying to understand we will label "the real system." To understand this system, we make a model of it in a process that we will call **encoding** (B in Figure 1.1.2). The model does not have to remain solely in our minds. It could be written down as a set of equations or as a computer algorithm, for example. In the real system, perturbations cause changes in the real system. This **causal link** (A in Figure 1.1.2) between perturbation and effect is what we desire to predict or explain using

FIGURE 1.1.2 The modeling relation. The real system is characterized by causal links, A, that correspond to the behavior of the real system to external or internal perturbation. The real system is converted by an encoding step to a model (B). In the model, the response of the model to a perturbation is determined as an inference (C). The behavior of the model is then decoded (D) in the last step in testing the validity of the model. When $B + C + D = A$, the model has successfully predicted the behavior of the real system and we say that it is a valid model. Adapted from R. Rosen, *Theoretical Biology and Complexity*, 1985, Academic Press, NY.

the model. In the model, the cause is also encoded, and its predicted effect we will call an **inference** (C in Figure 1.1.2). That is, some perturbation of the model is predicted to cause some effect in the model. When we **decode** this effect (D in Figure 1.1.2), the inference of the model is translated as our prediction of the behavior of the real system. A correct model is one that correctly predicts the behavior of the real system. That is

$$[1.1.1] \quad A = B + C + D$$

THE CORE PRINCIPLES OF PHYSIOLOGY

The rest of this chapter will discuss several Core Principles of Physiology. These are:

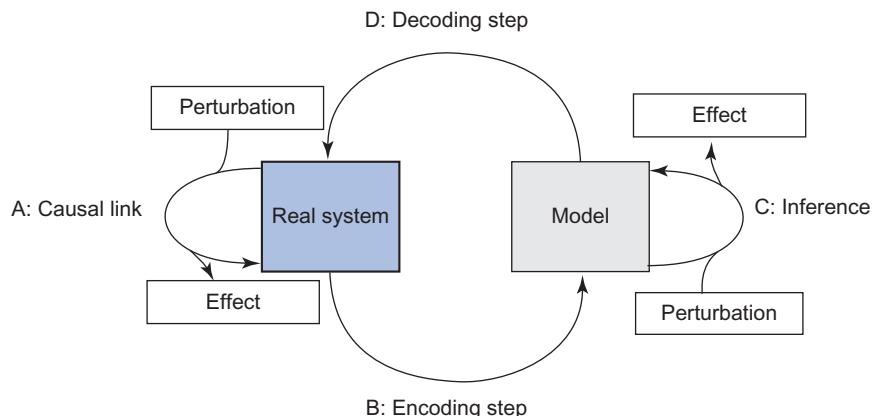
- Cells are the organizational unit of Life.
- Homeostasis is a central theme of physiology.
- We have evolved from prior life forms and our pedigree is revealed in our genome.
- Physiological systems transform matter and energy while obeying the conservation laws.
- Coordinated command and control requires signaling at all levels of organization.
- Control systems using negative feedback, positive feedback, anticipatory and threshold mechanisms.

CELLS ARE THE ORGANIZATIONAL UNIT OF LIFE

THE CELL THEORY IS A UNIFYING PRINCIPLE OF BIOLOGY

The cell theory states that all biological organisms are composed of cells; cells are the unit of life and all life come from preexisting life. The cell theory is so established today that it forms one of the unifying principles of biology.

The word *cell* was first used by Robert Hooke (1635–1703) when he looked at cork with a simple microscope and found what appeared to be blocks of material making up the cork. The term today describes a microscopic unit of life that separates itself from its surroundings by a thin partition, the cell membrane.



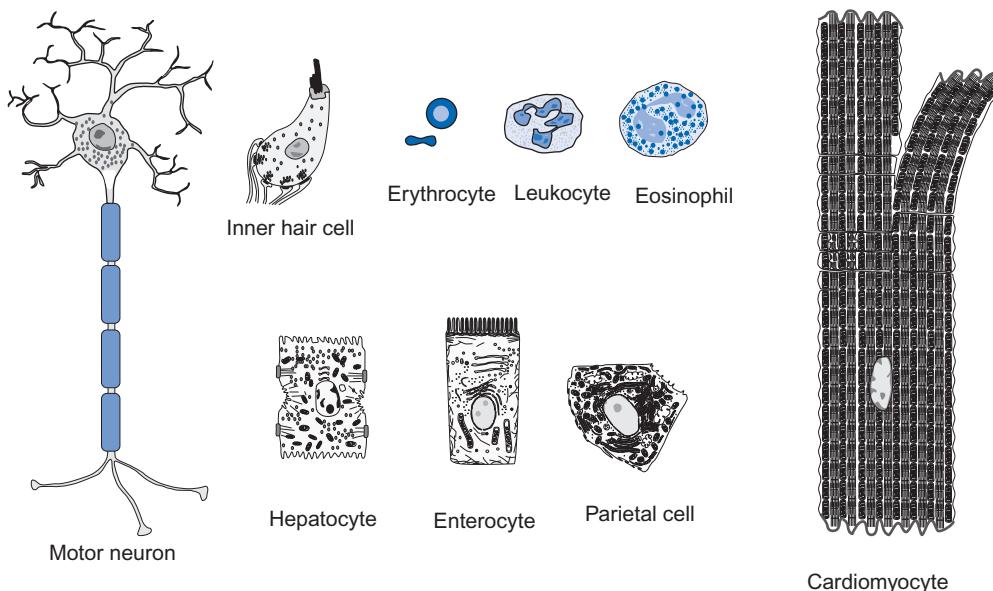


FIGURE 1.1.3 Examples of the different cells that populate the human body. Motor neurons such as the one illustrated are found in the ventral horn of the spinal cord. The inner hair cells are found in the cochlea and form part of our response to sound. Erythrocytes, leukocytes, and eosinophils are all found in the blood. Cells typically are not colored but may be seen in color by their adsorption of histological stains. Hepatocytes in the liver help package nutrients, form bile, and detoxify foreign chemicals. The enterocytes line the small intestine and absorb nutrients from the food into the blood. The parietal cells secrete HCl in the stomach. The cardiomyocyte shown is a ventricular cell whose contraction contributes to the pumping action of the heart. This is a small sampling of the diversity of cell forms in the human body.

Most biologists believe that life arose spontaneously from inanimate matter, but the details of how this could have happened remain unknown, and the time scale was long. Rudolf Virchow, a German pathologist (1821–1902), famously wrote “omnis cellula e cellula”—all cells come from other cells—meaning that spontaneous generation of living things from inanimate matter does not occur over periods as short as our lifetimes.

CELLS WITHIN THE BODY SHOW A MULTITUDE OF FORMS

Large multicellular organisms such as ourselves consist of a vast number of different cells that share some features but vary in size, structure, biochemical makeup, and functions. A sampling of the spectrum of cells that make up the body is illustrated in Figure 1.1.3. Almost all cells in the body have a **cell membrane**, also called the **plasma membrane**, and most contain a nucleus. The simplest cell in the human is probably the **erythrocyte**, which is the only cell in the body that lacks a nucleus.

THE DIVERSITY OF CELLS IN THE BODY DERIVES FROM DIFFERENTIAL EXPRESSION OF THE GENOME

The outward appearance and behavior of an organism define its **phenotype**, which is related to but not identical to the organism's genetic material, its **genotype**. The genotype consists of the set of alternate forms of genes, called **alleles**, that the organism has, and these alternate forms of genes are further defined by the sequence of nucleotides in their DNA. DNA is the genetic material

that is passed on through the generations. It determines the kind of proteins that cells can produce, and these materials make up the phenotype. The **genome** is the entirety of the hereditary information, including all of the genes and regions of the DNA that are not involved in producing proteins. Nearly all cells in the body contain the entire genome. The exceptions include the erythrocytes and the reproductive cells. Those cells that are not reproductive cells are called **somatic** cells (from the Greek *soma*, meaning *body*). Thus the great majority of body cells are somatic cells, and they all contain the same amount and kind of DNA. The astounding diversity of the types of human cells derives from their expression of different parts of the genome. Here expression means using DNA to produce proteins.

THE CONCEPT OF HOMEOSTASIS IS A CENTRAL THEME OF PHYSIOLOGY

EXTRACELLULAR FLUID SURROUNDS ALL SOMATIC CELLS

As described above, each cell in the body is surrounded by a cell membrane that defines the limits of the cell and separates the interior of the cell from its exterior. The interior consists of a number of subcellular organelles suspended in a fluid, the **intracellular fluid**. The exterior consists of an extracellular matrix that holds things in place and an **extracellular fluid**. The extracellular fluid has two components: the plasma and the interstitial fluid. The plasma is that part of the extracellular fluid that is contained in the blood vessels. The interstitial fluid is that part of the extracellular fluid between the cells and the walls of the vasculature. Nearly all cells of the body come in intimate contact

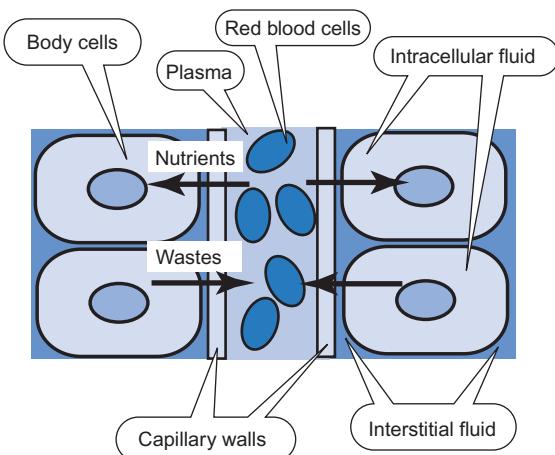


FIGURE 1.1.4 Relationship between cells and the extracellular fluid. All cells of the body are surrounded by a thin layer of extracellular fluid from which they immediately derive nutrients such as amino acids, sugars, and oxygen, and to which they discharge wastes such as carbon dioxide and other end products of metabolism. Nutrients are delivered to the cells and waste products are removed through the circulation, which does not make direct contact with the interstitial fluid, but is separated from it by the walls of the vascular system.

with the extracellular fluid. The last step in the delivery of nutrients and the first step in removal of wastes is achieved through the extracellular fluid (see Figure 1.1.4). The extracellular fluid was called the *milieu interieur*, or the internal environment, by the great French physiologist, Claude Bernard (1813–1878). Survival of the cells depends on the maintenance of a constant internal environment. The maintenance of a constant internal environment is called homeostasis, which is literally translated as *same standing*. Contributing to the maintenance of a constant internal environment appears to be the “goal” (or final cause or purpose) of many physiological systems, and this homeostasis is the central theme of physiology.

EVOLUTION IS AN EFFICIENT CAUSE OF THE HUMAN BODY WORKING OVER LONGTIME SCALES

EVOLUTION WAS POSTULATED TO EXPLAIN THE DIVERSITY OF LIFE FORMS

Charles Darwin (1809–1892) wrote *On The Origin of Species* in 1858 as his attempt to explain the origin of the tremendous variety of animals and plants in today’s ecosystems. He noted that any one species consists of a population of individuals that are capable of breeding among themselves but not with members of other species. The similarity among members of a species defines the species; the differences between them define the individual. These outward appearances constitute the phenotype, as described earlier, which arises from the response of the genotype to the environment. Some of the individual members of a species are better suited to their environment than others and produce more offspring as a consequence. With sufficient time, the frequency of genotypes represented in the population

would shift to those better suited to the environment. New variations in the genotype arise by mutation. Over geological time, such natural selection gradually changes the population. Darwin believed that such slow changes in the genetic makeup of populations could eventually produce new species, and he termed this slow formation of new species evolution.

EVOLUTION RESULTS FROM CAUSE AND EFFECT SUMMED OVER LONGTIME PERIODS

Evolution is like a higher level on the hierarchy of cause-and-effect relationships. As an example, consider a mutation that alters the structure of a critical protein located in a selected group of cells in the body that enhances the function of these cells. The mutation causes an altered protein, which in turn causes enhanced behavior of the organism. This altered behavior of the organism causes greater success in reproduction. Over time, greater success in reproduction replaces the less-fit genotype with the mutated, superior genotype. Thus evolution results from thousands of independent cause-and-effect linkages played out over a population of individuals, over longtime periods.

EVOLUTION WORKS ON PREEEXISTING FORMS: COMPARATIVE GENOMICS REVEALS PEDIGREE

At some time in the distant past, there was no life on earth. The origin of life is unknown and, in some sense, how it arose is not a scientific question because we cannot test any hypothesis of events in the past. We can, however, search for the trace of past events in the world today, much like a detective searches for clues to determine what happened earlier. This search has some of the character of an experiment. In this way, the fossil record illuminates the march of evolution to the present day. Similarly, we carry traces of our evolution in our own genome in the form of “fossil genes.” Because evolution works on preexisting forms, and because the multicellular organism plan entails the same challenges to homeostasis, and the same problems of cell maintenance, the genomes for many diverse animals and plants share profound similarities. For this reason, similarities in the genome can be used to trace the evolution of the proteins and shed light on the pedigree of species.

EVOLUTION TAILORS THE PHENOTYPE TO THE ECOSYSTEM

Humans live and reproduce within the context of an ecosystem. Our evolution has occurred because of our fit, or lack of it, with a specific environment. This explains some of the diversity of human forms within our species. Skin color and overall body shape, for example, are adaptations that arose to better fit the different levels of sunlight and air temperatures at different latitudes. Evolution has prepared us to meet the challenges of our environment but has not prepared us for unusual challenges. For example, we are adapted to survive short periods without water or longer periods without food, but we cannot do without air even for short periods.

ROBUSTNESS MEASURES THE ABILITY OF THE BODY TO RESPOND TO ENVIRONMENTAL CHALLENGES

A robust system is one that continues to function even when faced with difficult challenges. A fragile system fails easily. Engineered systems aim for a degree of robustness and usually achieve that end by adding redundant or back-up control systems and by building in safety factors. These systems are robust for some kinds of failure while remaining vulnerable to others. For example, autopilot systems in aircraft use multiple computers with different programs so that failure of one does not cause failure of the entire system. But these systems remain vulnerable to general power failure. We also have redundant or reserve function for several physiological systems. We have two kidneys, yet generally we can survive with only one. Liver, intestine, brain, and heart have more functional capacity than generally used so that we can survive if part of these organs fails. Strokes and heart attacks damage parts of the brain or the heart, respectively. Persons who suffer these cardiovascular accidents often recover much of their function, depending on the degree of damage and its location. If the damage is severe or involves a critical area, the victim may be permanently impaired or they may die. History is replete with astonishing stories of the tenacity of humans for life under amazingly harsh conditions. On the other hand, history also tells of the crumbling of civilizations when exposed to unfamiliar pathogens. Thus the human body may surprise us either because of its robustness or its fragility.

REGULATION OF THE GENOME MAY EXPLAIN THE FAST PACE OF EVOLUTION

There is a growing realization among evolutionary biologists that mutations in the genes that encode for somatic proteins—the ones that make us up—are only a small part of the story and cannot account for the rapid pace of evolution. Instead, much of evolution is accounted for in the genes that regulate the expression of other genes. Many modern birds, for example, do not have teeth. Yet it is possible experimentally to induce birds to make teeth, because they retain the genes for making teeth but also have genes that suppress the expression of the genes for teeth. Many diverse groups of animals share most of the genes involved in body building but differ in how and when these genes are used. The result is the differing body forms that are found in the animal kingdom.

EVOLUTION HELPS LITTLE IN EXPLAINING THE NORMAL FUNCTION OF THE BODY

Although evolution is one of the few unifying principles of biology and is one cause of the structure and function of the human body, it answers the question of the efficient cause of the body on a different time scale than the normal operating time scale of the body. Evolution

does not aid us very much when trying to explain how our bodies work on a minute-to-minute basis. Instead, we look to control theory to explain the normal functioning of the human body.

LIVING BEINGS TRANSFORM ENERGY AND MATTER

Repair, maintenance, growth, activity, and reproduction all require input of energy and matter in the form of food. The gastrointestinal system breaks down the food, which is absorbed into the blood and distributed among the tissues according to need. The available building blocks must be transformed into cellular or extracellular components, and all of this metabolism requires energy. The energy comes from the oxidation of food and subsequent production of wastes. In addition to this conversion of chemical energy of one compound to another, we also transform chemical energy into other forms of energy, including electrical and mechanical energy. These processes obey physical and chemical laws that govern the transformation of energy and matter. In particular, we can write two equations that describe overall mass and energy balance in the body:

$$\begin{aligned} M_{\text{in}} &= M_{\text{out}} + \Delta M_{\text{body}} \\ M_{\text{food}} + M_{\text{drink}} + M_{\text{inspiredair}} &= M_{\text{feces}} + M_{\text{urine}} + M_{\text{expiredair}} \\ &\quad + M_{\text{exfoliation}} + \Delta M_{\text{body}} \end{aligned} \quad [1.1.2]$$

where M indicates mass and the subscripts indicate the origin of the mass (in = input; out = output; most of these are self-explanatory) and ΔM_{body} indicates change in body mass. These equations describe mass balance and simply indicate that all of the mass that enters the body must either stay there (ΔM_{body}) or exit the body through one of several routes. A similar equation can be written for energy balance:

$$\begin{aligned} E_{\text{in}} &= E_{\text{out}} + \Delta E_{\text{body}} \\ E_{\text{food}} + E_{\text{drink}} + E_{\text{inspiredair}} &= E_{\text{feces}} + E_{\text{urine}} + E_{\text{expiredair}} \\ &\quad + E_{\text{exfoliation}} + \Delta E_{\text{body}} + E_{\text{heat}} \\ &\quad + E_{\text{work}} \end{aligned} \quad [1.1.3]$$

The overall mass and energy balance is shown schematically in [Figure 1.1.5](#).

FUNCTION FOLLOWS FORM

Almost all processes carried out by the body, at all levels of organization, depend on the three-dimensional structure of some component. The structure both

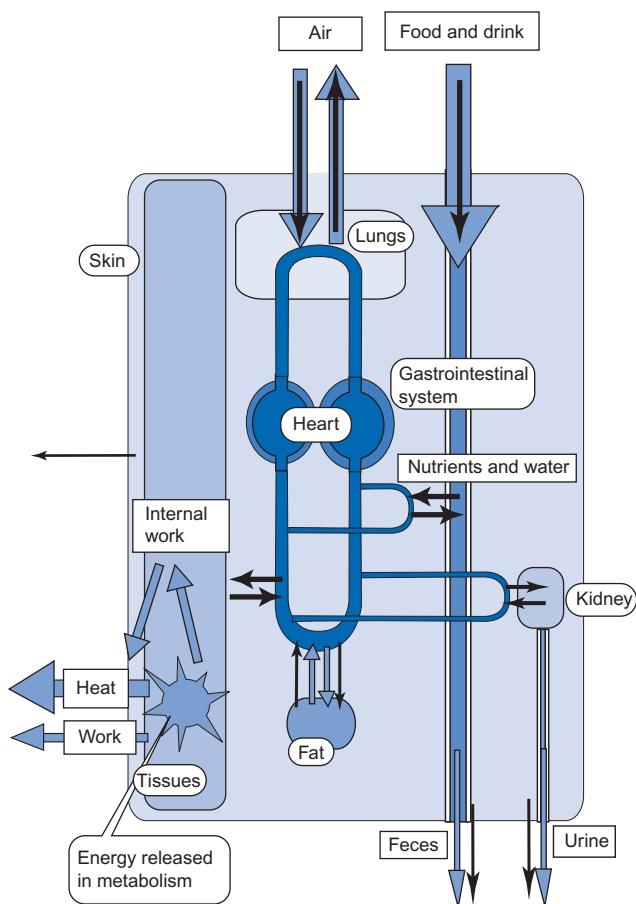


FIGURE 1.1.5 Overall mass and energy balance in the body. The lighter arrows indicate energy transfer. The black arrows denote transfer of mass. The chemical energy of the ingested food is released by oxidation in metabolism, as indicated by the starburst in the tissues. This released chemical energy is used for internal work, which usually eventually degrades to heat, for external work and for storage in the chemical energy of body components such as glycogen and fat. Growth also entails a form of storage of ingested mass and chemical energy. The laws of conservation of mass and energy (in ordinary chemical reactions) require that the matter and energy that enter the body must be equal to the matter and energy that leave the body plus any change in the matter and energy content of the body.

enables function and constrains it, by determining what can be done and how fast it can be accomplished. These structural considerations apply at the molecular level, at which the three-dimensional shape of protein surfaces determines what binds to the protein, how it is chemically altered, and how it interacts with other surfaces. These structural considerations apply at the subcellular level, at which the organelles themselves can compartmentalize chemicals and so determine or limit rates of reactions by regulating transfer between the compartments. Structural considerations are also important at the tissue level, at which the topology or spatial distribution of cellular processes allows countercurrent flows, for example, that are crucial in clearing metabolites from the blood or concentrating the urine. Structural considerations are important at the organ

system level at which the structure and arrangement of nerves and tissues is vital for the proper coordination of activity such as the heart beat or gastrointestinal motility. As another example, both the lungs and the gastrointestinal tract involve transfer of gas or nutrients from the environment to the blood. Both lungs and intestine have enormous surface areas and thin barriers—consequences of their structure—to maximize the rate of transport.

COORDINATED COMMAND AND CONTROL REQUIRES SIGNALING AT ALL LEVELS OF ORGANIZATION

Success of an organism requires adaptive responses to change in the environment. This, in turn, requires sensory apparatus that senses both the external environment (exteroceptors) and the interior environment (interoreceptors). These originate signals that pass either to nearby cells or to the central nervous system either for specific, reflex responses or for global responses. These signals are important at all levels of organization. At the subcellular level, these signals regulate the activities of subcellular components such as the expression of specific genes or the regulation of the rates of energy transformation. At the tissue level, local signals can regulate smooth muscle contraction to regulate blood flow within the organ or secretion into ducts; at the organ system level, signals traveling through the blood (hormones) or over nerves can coordinate activity of the system. At the whole organism level, signals at all levels must be used to adapt to whole-body responses such as running to avoid predators. Coordinating command and control for muscle contraction using sensory information from the environment (exteroceptors) and from the muscle (interoreceptors) is illustrated in [Figure 1.1.6](#). Signaling at the cellular level is illustrated schematically in [Figure 1.1.7](#).

MANY CONTROL SYSTEMS OF THE BODY USE NEGATIVE FEEDBACK LOOPS

One of the main themes of physiological control systems comprises a negative feedback loop. This consists of controlled parameters such as plasma calcium concentration, body temperature, plasma glucose concentration, and plasma pH, a sensor for that parameter, a comparator, and an effector. For many physiologically controlled parameters, there is a set point or reference (see [Figure 1.1.8](#)). This is the desired value for the controlled parameter. Its value can change under some circumstances. When the controlled parameter varies from its set point, the variation is detected by the sensor and comparator. The comparator then engages some effector or actuator mechanism to correct the departure of the parameter from its normal, set-point value. An example of this is core body temperature, whose normal set-point value is about 37°C . Whenever heat loss exceeds heat production, body temperature falls below the set point and the person shivers. In this case, the sensor

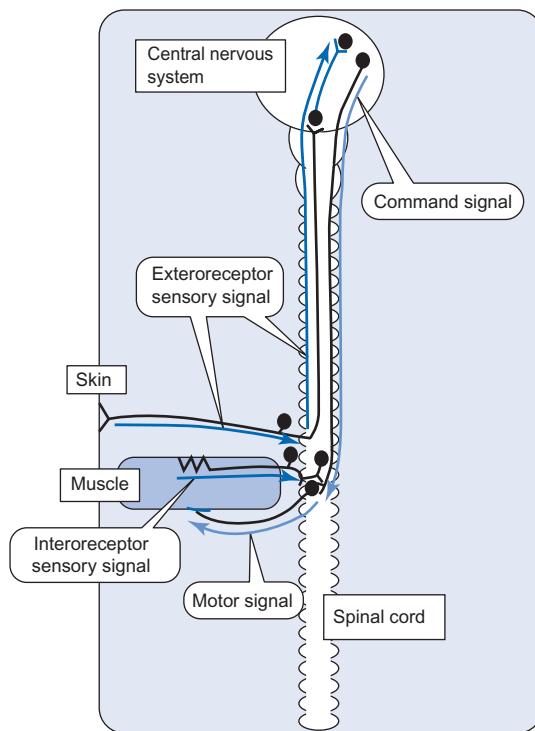


FIGURE 1.1.6 Neural signaling in the control of muscle. Neurons consist of cell bodies (dark circles) that have long processes (black lines) that bring signals into the central nervous system (dark lines with arrows) or take signals out toward the periphery (light lines with arrows). Branches at the ends of the long processes signify the junction of one neuron with another or with muscle. Neural signal transmission across these junctions is discussed in Chapter 4.2. Muscles are controlled by motor neurons whose cell bodies lie in the spinal cord. These can be activated in reflexes initiated by exteroceptors that sense perturbations on the skin and send signals to the spinal cord and eventually activate the motor neurons by a simple reflex involving just a few interneurons in the spinal cord. Muscles can also be activated by another reflex involving a stretch receptor internal to the muscle (interoreceptor). In a third pathway, motor neurons can be activated by command signals originating in the brain. Nervous control of muscle is considered in Chapters 4.4 and 4.5.

detects the temperature, the comparator determines that it has fallen below the set point, and it engages the skeletal muscles as an effector to produce heat by shivering to help raise the temperature back to the set point. In a fever, the set point is elevated and the individual feels chilled even when the temperature is elevated to, say, 40°C. When the fever “breaks,” the set point is reset back to 37°C and the person perspires because now the body temperature is elevated above the set point. When the controlled parameter varies from its set point, the variation is detected by the comparator. The comparator then engages some actuator mechanism to correct the departure of the parameter from its normal, set-point value. The controlled parameter can vary from its set point by the action of some physiological disturbance. These control systems are called negative feedback loops because the causality forms a loop ($y \Rightarrow x \Rightarrow u \Rightarrow a \Rightarrow y$) and the adjustment is typically the opposite sign, or the negative, of the disturbance. If d adds to y , the adjustment a subtracts from y ; if d subtracts from y , a adds to it. There are many systems that operate through negative feedback loops.

POSITIVE FEEDBACK CONTROL SYSTEMS HAVE DIFFERENT SIGNS FOR THE ADJUSTMENT TO PERTURBATIONS

Positive feedback systems exist for the mechanism of blood clotting, parts of the menstrual cycle, aspects of the action potential, and for parturition (child birth). In these cases, the disturbance is followed by an adjustment in the same direction of the disturbance, so that there is a rapid increase in some component. These positive feedback systems generally are self-limiting and, after the rapid increase in some component, there is a gradual return to baseline levels.

ANTICIPATORY OR FEED-FORWARD CONTROL AVOIDS WIDE SWINGS IN CONTROLLED PARAMETERS

Sometimes rapid changes in a controlled parameter can outstrip the physiological mechanisms for reacting to these changes, resulting in potentially catastrophic changes in the internal environment. To avoid this, some physiological systems anticipate changes in controlled parameters and begin to do something about it even before the parameter changes. Most wide swings in controlled parameters have to do with behavior. Eating, for example, is followed by an influx of nutrients into the blood. The nervous system prepares the gastrointestinal tract for a meal by using sensory cues—the sight, aroma, and taste of food—to induce the secretion of gastrointestinal fluids even before food is swallowed. In another example, controlled parameters including blood pH, P_{CO_2} (the partial pressure of CO₂ in the blood—a measure of CO₂ concentration) and blood P_{O_2} help regulate the depth and frequency of breathing. Negative feedback mechanisms keep these controlled parameters within narrow ranges during normal activity. During strenuous activity, there appears to be little or no error in these controlled parameters, though the depth and frequency of breathing is markedly increased. This occurs through an anticipatory response of the central nervous system in which the depth and frequency of breathing is activated simultaneously with activity.

DEVELOPMENTAL AND THRESHOLD CONTROL MECHANISMS REGULATE NONCYCLICAL AND CYCLICAL PHYSIOLOGICAL SYSTEMS

Although negative feedback control is a major theme in physiology, it does not account for a variety of important physiological events. Developmental events include the onset of puberty and menopause. Pregnancy, parturition (birth), and cyclical events such as the menstrual cycle and the sleep/wake cycle are episodic events that do not obey negative feedback mechanisms and may involve positive feedback mechanisms.

WE ARE NOT ALONE: THE MICROBIOTA

In natural ecosystems, human beings are literally covered with tiny contaminating organisms. We typically have 10 times more bacteria than body cells, but each

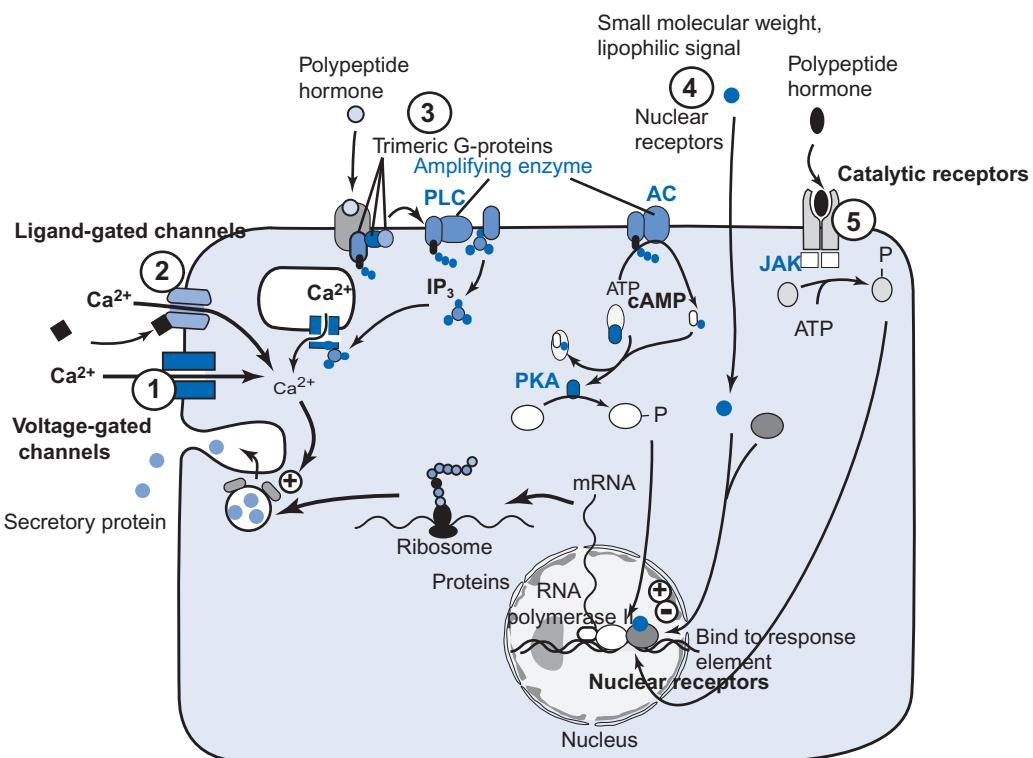


FIGURE 1.1.7 Synopsis of signaling mechanisms on the cellular level. Cells receive electrical signals that can be converted into chemical signals through voltage-gated channels (1). The voltage-gated calcium channel is shown. Chemical signals released from nearby cells can also open ion channels, producing electrical signals in the cell (2). Cells receive chemical signals in the form of polypeptide hormones that cannot penetrate the cell membrane. These can affect the cell by coupling to heterotrimeric G-proteins (3) or to catalytic receptors on the surface of the cell (5). These are coupled to amplifying enzymes or to kinases that phosphorylate intracellular proteins. Small molecular weight, permeant chemical messengers (4) can enter the cell and bind to receptors in the nucleus, which then alter the kind or amount of specific proteins made by the cell. These signaling mechanisms are discussed in detail in Chapter 2.8.

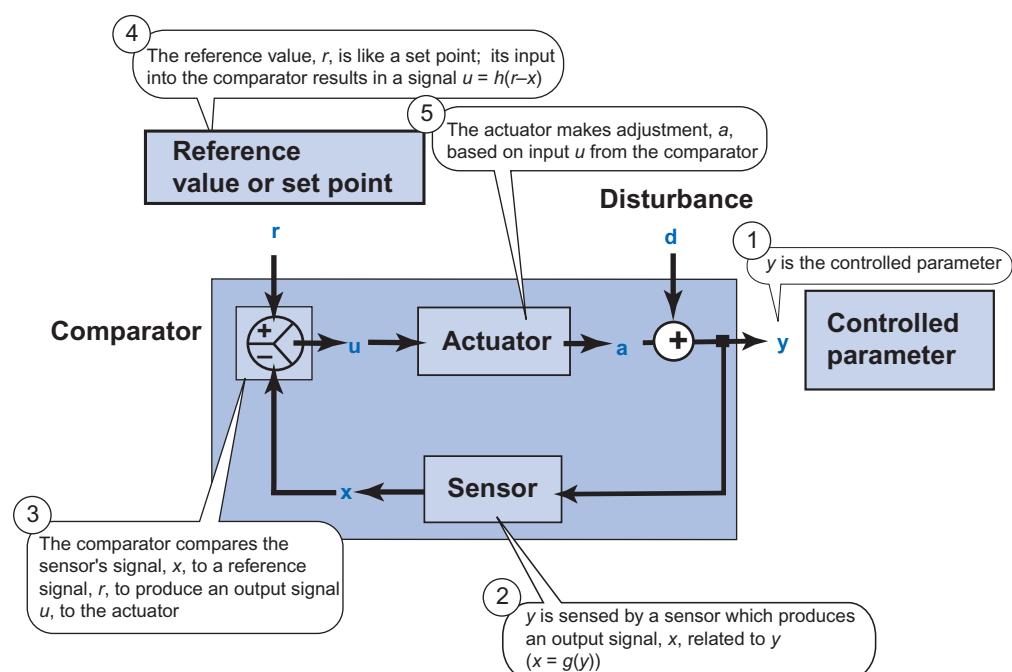


FIGURE 1.1.8 Component parts of a negative feedback loop. A controlled parameter, y , is sensed by a sensor that releases a signal that relates to the value of y ($x = g(y)$). This signal is fed into a comparator, which compares the signal x to some reference or set-point value, causing the comparator to produce a signal u that is a function of the error of x from its reference [$u = h(r - x)$], where u is the signal from the comparator, $r - x$ is the error and $h(r - x)$ gives the functional dependence of u on the error]. The signal u turns on an actuator that makes an adjustment, a , to the value of y . In negative feedback, the value of a reduces the error ($r - x$) so that the value of y returns towards its normal, set-point level. Disturbances, d , can alter the value of y and the negative feedback loop is engaged to minimize the departure of y from its set-point level.

of these is small, and so the total mass of these bacteria amounts to 0.5–1.5 kg. These organisms are present as surface contaminants, but they are the usual surface contaminants and so they can be considered to be part of us. They live on the surface of the body, and invasion within the body constitutes infection, and must be fought off by our immune systems. They live on the skin, in the oral cavity, in the airways, and in the gastrointestinal system and on the terminal parts of the reproductive system where it melds with the skin. Most of these are within the gastrointestinal system, and fully half of the feces is estimated to consist of bacteria. In addition to the bacteria, many natural ecosystems provide us with a load of other organisms: tapeworms, flukes, helminths (hookworms, pinworms, and roundworms), leeches, fleas, various fungal organisms, and a host of viruses. Although in natural ecosystems, infections with some of the multicellular parasites may be unusual, the load of bacterial contaminants is unavoidable. The aggregate of these hangers-on is called the **microbiota**. The microbiota engage signaling systems of the body and thereby alter our physiological states. This is true of the rhinoviruses that make us sneeze, thereby spreading them around to other individual hosts, and intestinal bugs that induce diarrhea, using the host signaling systems, to likewise spread them to other hosts. Evidence is accruing that even those “benevolent” strains that do not make us frankly sick still manipulate our physiology to their advantage. Thus the microbiota become part of our physiology.

PHYSIOLOGY IS A QUANTITATIVE SCIENCE

As described earlier, homeostasis refers to the maintenance of a constant internal environment, where the internal environment refers to the extracellular fluid that surrounds the cells. This internal environment is characterized by the concentration of a host of materials, and each of these concentrations has a unit and a numerical value. Many of these materials are metabolized by the tissues so that maintaining constant values requires matching supply to consumption. The rates of supply and consumption also have units and numerical values. As [Figure 1.1.5](#) shows, the circulatory system unites all organs of the body by virtue of their perfusion with a common fluid, the blood. Maintenance of this flow requires pressure differences that also have units and magnitudes. Understanding the flows and forces that keep the blood moving and keep its composition relatively constant requires a quantitative approach.

SUMMARY

Physiology is the integrated study of the normal function of the human body. Like many complicated things, the body can be viewed as a set of subcomponents that interact by linking the output of one component to the input of another. These subcomponents are the organ systems. These include the cardiovascular system, the respiratory system, the renal system, the gastrointestinal system, the neuroendocrine system, the musculoskeletal

system, the integument, and the reproductive system. Understanding how the body works as a whole requires us to make a model, either implicit or explicit, that explains the integration of the structures that make up organ systems, and the integration of the organ systems that produces the overall system behavior. Explanation requires that cause and effect in the model faithfully predicts cause and effect in the real system. Understanding can occur on different hierarchical levels of integration: the systems level, the organ level, the cell level, and the subcellular level. Each level seeks to explain behavior at that level on the basis of the components that make up that level. This is reductionism, the explanation of the behavior of a complicated object on the basis of its parts. We say that we understand something when we can explain function in terms of the parts one level below and we can show how behavior at that level contributes to behavior one level above.

Aristotle identified four classes of causality: the material cause, the efficient cause, the formal cause, and the final cause. Explanation of something on the basis of the final cause is called teleology. Although science presumes that each component of living things obeys physical law alone, systems produce emergent properties that we seem to be unable to predict. These emergent properties belong to the system as a whole rather than to individual parts within it.

Evolution is one cause of the human form and function, but it aids us only a little in understanding how physiological systems work.

In the hierarchy of levels of organization, cells are the fundamental unit of life. The various cells of the body show a remarkable diversity of form and function, but they all carry the complete genome, with the exception of erythrocytes and reproductive cells. The diversity of form arises from the use of only parts of the genome for each type of cell.

The overriding principle of human physiology is homeostasis, meaning the maintenance of a constant internal environment. Our internal environment is the extracellular fluid that bathes all cells in the body. A combination of internal control systems and external behavior maintains homeostasis. In the final analysis, our life depends on inputs from the environment and so our behavior (feeding, drinking, and temperature control) is crucial to our survival. Internal regulation of the internal environment relies primarily on negative feedback control, in which controlled parameters feed into a sensor that compares the value of the controlled parameter to the desired set point or reference levels. Variation from the set point results in the activation of effector mechanisms that increase or decrease the controlled parameter so that it more closely approximates the set-point level. Anticipatory control also contributes to homeostasis without allowing wide swings in the values of controlled parameters. Some important physiological events, such as puberty, menstruation, pregnancy, parturition, menopause, and the sleep/wake cycle, are not homeostatic. Instead, they incorporate switches between one physiological state and another.

These control systems contribute to the robust control of bodily functions that enable homeostasis under harsh environmental conditions.

REVIEW QUESTIONS

1. What argument does holism make against reductionism?
2. Give some examples of emergent properties
3. What is a cell? Why is it considered to be a fundamental unit of organization of life?
4. Contrast genotype with phenotype
5. What is homeostasis? Why is it central to physiology?
6. What is the internal environment in large multicellular animals such as ourselves?
7. What would constitute proof for the theory of evolution? Do you think science has provided it? Why or why not?
8. From Einstein's equation $E = mc^2$, you have learned in physics that mass and energy are interconvertible. Why can we say that mass and energy are conserved in physiological systems? What does it mean to say that living things "transform" matter and energy?
9. Describe the hierarchical organization of the body.
10. Give examples of signaling at the organism level and cellular level.