CHAPTER TWO
PATHOPHYSIOLOGY

CHAPTER OUTLINE AND OBJECTIVES

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➢ Describe cellular adaptations to disease.
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This chapter addresses the following competencies from the Athletic Training Educational Competencies, 4th ed.:

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<tr>
<th>Domain</th>
<th>Cognitive #</th>
<th>Psychomotor #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology of Injuries and Illnesses</td>
<td>1-6</td>
<td></td>
</tr>
<tr>
<td>Orthopedic Clinical Examination and Diagnosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Acute Care of Injuries and Illnesses</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>
Introduction

This chapter reviews normal physiology and introduces the concepts of pathophysiology, physiology related to disease. It will not replace formal study of normal cell structure and physiology. Basic physiology provides a basis for discussion in subsequent chapters. Many clinical and cellular pathophysiology textbooks are available for greater detail.2-7

Homeostasis.—Homeostasis is the control of biochemical equilibrium within the body through many processes that constantly regulate fluid, chemical, and energy balance in the cells, tissues, organs, and systems.2, 8 Normal function constantly disturbs and restores this biological balance. For example, blood glucose level rises after eating a meal. In response, cells in the pancreas release insulin, a hormone that helps to move glucose from the blood into the liver and muscles. Once blood glucose level has returned to normal, the pancreas stops releasing insulin to prevent blood glucose levels from becoming too low. These normal stimulus-response cycles are necessary to maintain health.

The healthy state can vary somewhat depending on the individual. Thus, “normal” values for chemical and functional indicators (e.g., blood test results and vital signs) are usually described as a range that depends on age, gender, and other factors. In addition, these values may exceed “normal” range in response to stress to maintain organ-system function. For instance, persons living at high altitude have more red blood cells as an adaptation to the lower concentration of atmospheric oxygen. This adaptation allows the blood to hold an adequate amount of oxygen.

Pathophysiology.—Many diseases disrupt homeostasis, causing deviation from the normal, balanced biochemical state. Pathophysiology describes the cellular mechanisms of disease and their functional systemic consequences.7 Signs and symptoms are a result of the functional systemic consequences of pathology. Understanding the normal physiology of the body's organ-systems assists in the discussion of the effects of disease. Study of physiology begins with the basic unit of the body's tissues: the cell.

The Cell.—All living cells contains many structures, including cytoplasm, a nucleus, lysosomes, mitochondria, and a cell membrane. Each structure serves a particular purpose (Table 2.1).8

Cells can be damaged by physical trauma, toxins, infection, genetic abnormalities, malnutrition, dehydration, or hypoxia, or combinations of these factors.2, 6 Cell damage impairs one or more cell structures, which affects tissue and organ function, which in turn affects function of the associated system or systems. Cells in other tissues and organs can be affected as the effects spread to surrounding tissues, thus disrupting homeostasis. Some effects of cell damage initiate responses that attempt to limit the disease process, to initiate cell repair, and to restore homeostasis.
Table 2.1. Cell structures and their functions.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleus</td>
<td>Contains genetic material of the cell (DNA and RNA)</td>
</tr>
<tr>
<td></td>
<td>Controls cell division and synthesis of protein</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>Provides internal fluid environment of the cell</td>
</tr>
<tr>
<td></td>
<td>Supports all internal cell structures</td>
</tr>
<tr>
<td>Lysosomes</td>
<td>Contains catabolic enzymes within the cell</td>
</tr>
<tr>
<td></td>
<td>Disposes cell waste and foreign substances</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>Converts carbohydrate, protein, and fat to ATP (energy)</td>
</tr>
<tr>
<td>Cell membrane</td>
<td>Consists of complex semipermeable phospholipid and protein structure</td>
</tr>
<tr>
<td></td>
<td>Provides physical border of the cell</td>
</tr>
<tr>
<td></td>
<td>Excludes or exchanges substances between the internal and external</td>
</tr>
<tr>
<td></td>
<td>environment of the cell</td>
</tr>
</tbody>
</table>

Once cell damage occurs, the cell either adapts or dies. Adaptation occurs if the cell can maintain function of the nucleus and begin repair. Extreme adaptation, however, may affect the normal function of the cell, leading to subsequent problems in the tissue or organ. Cells may also respond to environmental factors by adapting before cell damage occurs.

Cells adapt in several ways. First, they can shrink and become less active in response to decreased metabolic demands, a process called atrophy, or grow and become more active in response to increased demands, called hypertrophy. Atrophy is generally caused by disuse due to injury or immobilization or impaired cellular metabolism, such as malnutrition. Hypertrophy, conversely, increases cell size to meet increased metabolic or physical demands, such as weight lifting. Aging is a type of atrophic cellular adaptation caused by multiple factors, including cell damage caused by exposure to metabolic and external toxins over a lifetime.

Cells may also adapt by changing in number, type, or morphology (structure). Hyperplasia is an increase in the number of cells in a tissue without a change in the rate of cell division or cell function. This occurs as an adaptation to chronic increased metabolic demands, genetic abnormalities, or hormonal imbalances. Metaplasia is a replacement of cells of one type with another type, often in response to physical or chemical irritants. These “new” cells do not display changes in rate of division or function, but may change the relative proportion of one cell type to another within a particular tissue.

When cells adapt by changing to an abnormal cell type, increasing the rate of division, and increasing in number, the process is called dysplasia. Dysplasia can be caused by chronic irritation or a malfunction in DNA replication. Formation of neoplasms, or tumors, involve dysplasia. Malignant (severely invasive) dysplasia produces neoplasms in a process called cancer (rapid proliferation of undifferentiated,
non-specific cell types). Cell death, or necrosis, occurs when cell resources cannot meet the metabolic (i.e., oxygen and energy) demands of the nucleus. A large number of dead cells impairs organ function and disables the associated body system. Cell necrosis can lead to disease or death of the organism.

Most normal cellular adaptations, such as callus formation (hyperplasia) or menstruation (hyperplasia and metaplasia), are temporary physiological responses that are part of homeostasis. Other adaptations or cell damage produce general chemical and physical responses to repair tissue structure or function. An example of such a general response is inflammation, as discussed below. Other normal and abnormal effects are caused by tissue-specific adaptations, such as the hypertrophy of muscle when regularly exposed to loads or the atrophy of muscle when it loses its neural control. The general and specific effects may impair organ function, thus becoming pathology and causing signs and symptoms.

**Tissue healing.**—Damaged tissue is capable of healing in one of two ways. First, functional organ and tissue cells may be regenerated, essentially rebuilding the injured tissue. Second, the functional cells may be replaced by connective tissue, which is a process called scarring. Scarred tissue restores structural integrity of the organ, but does not function like the original tissue. If a significant amount of scarring occurs, the function of the organ may be permanently impaired. Scarring occurs in tissues and organs that cannot regenerate their functional cells.

Regardless of method, tissue healing generally progresses in three stages: inflammatory, proliferative, and remodeling. Each stage takes a different amount of time depending on the tissue (Table 2.2). The inflammatory phase begins at the moment of tissue injury. The inflammatory phase includes hemostasis, a vascular response, and a cellular response. Hemostasis involves an immediate vasoconstriction and activation of platelets. This immediate response is an effort to control blood loss. After a period of vasoconstriction, the vessels dilate and become more permeable. This permeability allows plasma and other blood compounds to exit the vessel and enter the damaged tissue, causing edema. Some of these compounds also signal the cellular response. In the cellular response, various types of white blood cells move into the area to clear it of bacteria and dead cells. Some of these cells also release growth factors that stimulate cell growth and revascularization, as well as attracting cells called fibroblasts that function in the proliferative stage. The inflammatory phase typically lasts only days after injury, but can be prolonged if the source of damage is not removed.

The proliferative stage serves to close the tissue wound. Fibroblasts secrete collagen, a complex protein that binds to itself and other structures to create a scar. This tissue becomes vascularized and new tissue cells begin to form at the periphery of the injured region, if possible. Collagen continues to be secreted until the wound is closed, sometimes persisting for several weeks. The deposition of collagen stimulates the third stage of tissue healing: remodeling.
Table 2.2. Stages of healing, associated time frames, and treatment by tissue type.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Stage</th>
<th>Time</th>
<th>Treatment or action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligament</td>
<td>Inflammatory</td>
<td>48 to 72 hours</td>
<td>protect; splint in approximation</td>
</tr>
<tr>
<td></td>
<td>Proliferative</td>
<td>6 to 8 weeks</td>
<td>active mobilization within limits &amp; activity</td>
</tr>
<tr>
<td></td>
<td>Remodeling</td>
<td>12 to 30 months</td>
<td>activity as tolerated</td>
</tr>
<tr>
<td>Tendon</td>
<td>Inflammatory</td>
<td>48 to 72 hours</td>
<td>protect; splint in approximation</td>
</tr>
<tr>
<td></td>
<td>Proliferative</td>
<td>4 to 6 weeks</td>
<td>active and passive mobilization within limits</td>
</tr>
<tr>
<td></td>
<td>Remodeling</td>
<td>12 to 20 weeks</td>
<td>strengthening &amp; activity as tolerated</td>
</tr>
<tr>
<td>Muscle</td>
<td>Inflammatory</td>
<td>48 to 72 hours</td>
<td>protect; gentle passive or active-assisted mobilization</td>
</tr>
<tr>
<td></td>
<td>Proliferative</td>
<td>4 to 8 weeks</td>
<td>active muscle recruitment, passive mobilization</td>
</tr>
<tr>
<td></td>
<td>Remodeling</td>
<td>12 weeks</td>
<td>strengthening and accommodation to load</td>
</tr>
<tr>
<td>Bone</td>
<td>Inflammatory</td>
<td>48 to 72 hours</td>
<td>strict immobilization or surgical fixation; approximation is critical</td>
</tr>
<tr>
<td></td>
<td>Proliferative</td>
<td>3 to 6 weeks*</td>
<td>continue immobilization or fixation until union (or longer), then begin gentle</td>
</tr>
<tr>
<td></td>
<td>Remodeling</td>
<td>6 to 24 weeks†</td>
<td>after consolidation, begin load-bearing activity as tolerated</td>
</tr>
<tr>
<td>Articular Cartilage</td>
<td>Inflammatory</td>
<td>48 to 72 hours</td>
<td>Weight-bearing as tolerated; maintain muscular function.</td>
</tr>
<tr>
<td></td>
<td>Proliferative</td>
<td>6 months</td>
<td>Controlled weight-bearing activity to stimulate fibrocartilage.</td>
</tr>
<tr>
<td></td>
<td>Remodeling</td>
<td>2 years</td>
<td>Activity as tolerated.</td>
</tr>
<tr>
<td>Nerve</td>
<td>Inflammatory</td>
<td>2 to 7 days</td>
<td>medical evaluation; splinting may be needed to stabilize</td>
</tr>
<tr>
<td></td>
<td>Proliferative</td>
<td>1 inch per month</td>
<td>monitor; periodic sensory and motor testing</td>
</tr>
<tr>
<td></td>
<td>Remodeling</td>
<td>up to 1 year</td>
<td>return to normal use; may need strengthening or other therapy</td>
</tr>
</tbody>
</table>

*Time for union, not for callus formation or consolidation. The lower extremity generally takes twice as long as the upper extremity.
†Time for hard callus formation and consolidation; lower extremity bones generally take twice as long.
The remodeling stage overlaps with the proliferative stage: some tissue remodeling occurs while collagen is still being deposited to heal the damage. Remodeling involves the simultaneous breakdown and continued deposition of collagen bonds. This allows the final collagen structure to form in response to forces experienced by the tissue during this stage. The remodeling stage stops when the structure is restored, although the tissue strength does not return to its normal, uninjured state. In tissues that are able to regenerate, remodeling involves the creation of the new tissue and restoration of organ function. The remodeling stage continues for months, until the integrity and function of the tissue and organ is restored.

**Inflammation.**—Every tissue of the body responds to cellular injury or infection with inflammation. The inflammatory response may be limited only to the affected tissue, producing localized symptoms, or be generalized, causing “systemic” symptoms (see Table 1.7). Consequently, diseases of many organ-systems cause similar systemic signs and symptoms.

*Acute inflammation.*—Damaged cells release chemicals (e.g., histamine, bradykinin, prostaglandin) that cause local capillaries to dilate and become more permeable. This reaction increases blood flow to the area and allows proteins and plasma fluid to enter the interstitial space, the space between cells. Proteins in the blood interact with fibrin and begin to form a collagen clot at the damaged site. The chemicals released by the damaged cells also attract leukocytes from the blood. Some leukocytes act as phagocytes and others prolong the inflammatory response. Phagocytes dissolve and absorb damaged cell structures, invading microbes, and foreign debris.

As inflammation continues, excess interstitial fluid causes tissue pressure to rise relative to pressure in the nearby capillaries. Blood flow in the area consequently decreases, producing ischemic damage in otherwise healthy cells and increasing tissue damage. This secondary tissue damage is greatest near the site of primary cell injury.

These mechanisms cause the characteristic signs and symptoms of inflammation. *Pain* results from tissue damage (primary and secondary), the inflammatory chemicals, and ischemia. *Swelling*, *erythema* (redness), and *heat* are effects of increased regional blood flow and plasma fluid in the interstitial space. *Ecchymosis* (dark red, blue, or black discoloration) from red blood cells in the tissues may occur. Pain causes local muscle *spasm* to guard the damaged tissue, thus causing loss of movement and function. The acute phase of inflammation somewhat depends on the extent of cellular damage, but generally lasts from 48 to 72 hours.

*Chronic inflammation.*—Chronic inflammation, which also can occur in any tissue, is usually a result of long-term chemical irritation or mechanical stress. Chronic inflammation is destructive to the cells and tissues because the chemical action and leukocyte activity is prolonged. In addition, chronic inflammation produces more fibrin and collagen to protect the undamaged tissue or isolate the offending substance. Thus, chronic inflammation can prevent or inhibit tissue healing.

The signs and symptoms of chronic inflammation are the same as acute inflammation, but less intense. Chronic inflammation produces aching pain, pitting edema, mild to moderate
muscle spasms, and increased local tissue temperature. Chronic inflammation persists until the
cause of cellular damage is removed.

**Infection.**—The response to infection is essentially a specialized inflammatory response.
Cell damage caused by the infectious organism causes inflammation. In addition, activation of
the immune system can also stimulate a generalized inflammatory response. This response is
more widespread than occurs with a local tissue wound. Activated leukocytes in the blood affect
neurons in the medulla, which causes an increase in body temperature. Involuntary shivering
(“chills”), widespread vasoconstriction, and lying down and flexing the body all occur to
increase body temperature to a “new” level. This process is called *fever*.

The presence of fever significantly increases metabolic demands. This causes *hyperpnea*
(rapid respiration) and *tachycardia* (rapid heart rate) as well as breakdown (*catabolism*) of
muscle and other tissues, except fat, to obtain energy. The effects of fever are unusual fatigue,
*malaise* (“feeling bad”), weakness, and loss of appetite. Once the microorganism has been
eliminated, the fever “breaks.” To reduce body temperature, the person exhibits *diaphoresis*
(sweating), *lethargy* (extreme drowsiness), and extension of the body in supine. In addition,
appetite returns to replace energy stores that were drained during the course of the fever. The
duration of fever depends on the virulence (aggressiveness) of the infection.

**Cellular Physiology and Pathophysiology:**
**Response to Cell Damage**

**Bone.**—
*Normal morphology and physiology.*—Bone provides a framework for the body, levers
for muscle, and protection for internal organs (heart, lungs, kidneys, liver, spleen, brain, spinal
cord). Mature bone cells are called *osteocytes*, which are produced by *osteoblasts* and resorbed
by *osteoclasts*. Bone tissue is being constantly resorbed and rebuilt, maintaining a balance in
homeostasis. When this balance is disrupted by pathology, bone mass and density can be
affected. For example, in the disease process of osteoporosis more bone is resorbed than is
rebuilt, resulting in an overall decrease in bone mass and density (a sign called osteopenia) and,
consequently, a structural weakening of the bone. There are also diseases that cause the bone to
lose its mineral content, which affects the mechanical properties of bone, or cause an excess
building of bone. In each of these types of conditions, the normal homeostatic process has been
interrupted, which leads to deformity or injury to the affected bones.

Each bone is covered by *periosteum*, an innervated and vascular structure that provides
nutrition to the cortical (compact) bone. Cancellous bone has its own blood supply and contains
the bone marrow. Bone marrow is either yellow (fatty) or red. The red marrow, a critical organ,
produces blood cells. In children, most bones contain red marrow, whereas adults have red
marrow only in the flat bones (cranium, ribs, pelvis, vertebrae). Bones articulate to form joints.
Joint surfaces are covered with articular cartilage, which decreases the friction between the
opposing bones. Articular cartilage is avascular, has no nervous supply, and has very few
*chondrocytes* (living cartilage cells) within its tissue.
Pathological processes.—Fracture is physical damage to the structure of a bone and can occur across an entire bone, involving both cortical and cancellous bone, or occur only in the cortical bone (e.g., greenstick and stress fractures). A fracture that penetrates the skin, called a compound (open) fracture, is particularly prone to infection because the bone and other deep tissues are exposed to the environment. Bone infection causes osteomyelitis, an inflammation of bone and bone marrow (see Chapter 4), which destroys normal bone cells and deforms the bone. Many genetic and metabolic abnormalities of bone, such as osteogenesis imperfecta and osteoporosis, can produce severe deformity and disability. Toxic damage, such as exposure to high-dosage radiation, is another possible source of pathology. Articular cartilage can be damaged by physical trauma (osteochondritis dissecans), inflammation (osteoarthritis, rheumatoid arthritis), or infection.

Response to disease or injury.—Fractured bone can heal, given the appropriate environment: alignment and approximation of bone ends, stability, sterility, and nutrition. In fractured bone, the inflammatory stage includes bleeding (hematoma formation) and muscle guarding. The proliferative stage begins as the hematoma resolves and a fibrin clot forms; osteoblast activity increases to produce new bone cells. Fibrocartilage forms around the fracture, and is then gradually replaced by a bony callus, or mass of osteocytes in various stages of formation. Once the bony callus is complete, the bone is stable and can bear weight. This process takes approximately 4 to 6 weeks in children and 8 to 12 weeks in adults. The remodeling stage lasts for 1 to 2 years following the fracture as the bone remodels in response to the demands placed upon it.

Bone infections heal by a similar mechanism after the infection is eliminated, which often involves surgical resection and stabilization. Some genetic and metabolic bone disorders, such as osteogenesis imperfecta or osteoporosis (see Chapter 9), may not allow bone to heal completely.

Articular cartilage has no blood supply. When damaged, it is either replaced by fibrocartilage, which not as smooth, or not replaced at all. Since articular cartilage also has no nerve supply, pain does not occur unless the underlying (subchondral) bone or synovial tissue is involved. Articular cartilage injuries are relatively permanent, although function can be preserved with replacement by fibrocartilage. Articular cartilage injuries are usually accompanied by subtle joint instability and synovial (joint capsule) inflammation, a clinical syndrome known as arthritis. Significant damage to the articular cartilage, subchondral bone, and synovium may require surgical replacement with an artificial joint.

Connective Tissue, Epithelium, and Endothelium.—

Normal morphology and physiology.—Connective tissue consists of collagen and elastin. Connective tissue attaches body structures, such as organs, bones, and muscles, to one another. A higher proportion of collagen indicates relatively greater tensile strength but less flexibility, whereas the opposite is true for a higher proportion of elastin. Connective tissue, although highly vascular and innervated, usually has only a few living cells interspersed in the tissue. There are several types of connective tissue.
Epithelium lines the interior and exterior surfaces of the body, including the skin, the gastrointestinal tract, and the pulmonary system. Epithelium provides a barrier to the external environment. Endothelium lines the cardiovascular system, including the heart, arteries, veins, and lymphatics. Endothelium regulates the exchange of substances, including nutrients, metabolic waste products, gases, infectious microorganisms, and toxins, between the blood and other organs. Both epithelium and endothelium have several specialized cell subtypes and exist in various cell thicknesses throughout the body. The rate of replication for these cells is very high. Thus, as function of homeostasis, relatively "new" cells are constantly replacing "older" cells that may have been exposed to potentially toxic, infectious, or damaging substances. By constantly replacing cells that have been exposed to the environment, the body can protect itself by always presenting fresh cells as the first line of defense against potential pathogens.

Pathological processes.—Physical damage or infection cause cell damage in connective tissue. Metabolic diseases are also relatively common in connective tissue (e.g., rheumatoid arthritis, gout, vasculitis), causing chronic inflammation, tissue destruction, and scarring. Epithelium and endothelium are prone to cancer and toxic damage due to their constant exposure to the environment (indirectly through the blood in the case of endothelium). Damage to epithelium or endothelium cells also causes changes in tissue permeability. Once permeability is change, either allowing substances that normally do not enter the cell in or keeping substances that normally move into the cell from doing so. This disruption in normal cellular exchange affects the function of the cell and the underlying organ, thus disrupting homeostasis.

Response to injury or disease.—Connective, epithelial, and endothelial tissues follow the typical tissue healing stages outlined above. Connective tissue heals with collagen only. Hence, any tissue that has elastin as a primary component loses flexibility after injury and healing. This effect may also interfere with normal organ function. For instance, scarring in the abdomen following surgery can sometimes cause a stricture, or narrowing of the intestinal passageway, thus restricting the passage of food. Similarly, scarring in the connective tissues of the thorax may restrict chest expansion or gas exchange in the lungs.

Collagen scar tissue usually provides the same tensile strength as the original connective tissue within six to eight weeks, provided the optimal healing environment (nutrients and oxygen from the blood) is present and the tissue is protected from reinjury. Remodeling of the collagen tissue to arrange fiber alignment consistent with the original structure, however, may take six to twelve months. Since collagen aligns along lines of consistent tissue stretch, thus providing higher tensile strength, appropriate functional demands should be placed on the tissue through this period. Again, the elastic qualities of the tissue are not restored by the remodeled collagen.

Injured epithelium and endothelium can be replaced with normal cells provided the damage does not extend through all cell layers and the genetic mechanism is not affected. The healing process takes a few days to close the wound, a few weeks to return to full strength, and several months to remodel completely. Function of the resulting scar is dependent on the extent of the injury. A larger injury, resulting in a larger scar, will have a greater impairment of tissue function. If all cell layers are damaged, the tissue is replaced by nonfunctional collagen scar (metaplasia). If the DNA replication mechanism is affected, a cancerous lesion forms (dysplasia). Replacement of living cells with inflexible collagen not only leads to possible
restrictions or obstructions, as noted above, but also causes the tissue to be nonpermeable, preventing normal cellular exchange. Cancerous changes can also cause obstructions and interfere with normal tissue function.

**Muscle and Nerve.—**

*Normal morphology and physiology.*—Muscle tissue has three types: skeletal, cardiac, and smooth (Table 2.3). The principle function of muscle is contraction, which moves the skeleton, circulates the blood, or moves food through the bowels. Nerve cells transmit electrical signals that are initiated by external or internal stimuli. These signals control the movement, cognitive, and regulatory systems of the body. Nerve cells within the brain and associated structures are highly specialized, whereas the structure of nerve cells in the peripheral nervous system tend to be very similar to one another. All nerve cells contain a cell body, dendrites (projections that receive signals from other cells), and axons (projections that send signals to other cells). Chemical processes form the electrical impulses within (primarily sodium ion exchanges) and between (via neurotransmitters) cells.

<table>
<thead>
<tr>
<th>Type</th>
<th>Body System</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striated</td>
<td>Musculoskeletal</td>
<td>Movement of the bones and body through space</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Heart</td>
<td>Maintain blood flow to body</td>
</tr>
<tr>
<td>Smooth</td>
<td>Vascular and gastrointestinal</td>
<td>Movement of blood and food through the respective system</td>
</tr>
</tbody>
</table>

*Pathological processes.*—Skeletal muscle is most commonly affected by physical trauma (contusion or strain) or infection (e.g., tetanus), although genetic and metabolic diseases also occur (e.g., muscular dystrophy, myasthenia gravis). In contrast, cardiac and smooth muscle are more commonly affected by metabolic states (such as ischemia) and infection. Toxins can also affect the various types of muscle, nervous tissue, or the neuromuscular junction, and interrupt function. Interruption of muscle function is a loss of contraction; depending on the muscle type and location, the effect can be disabling (e.g., skeletal muscle) or even fatal (cardiac muscle).

Nerve cells are fragile and are easily damaged by physical trauma, toxins, infections, and metabolic imbalances. Many pathological processes directly or indirectly affect the nervous system. Thus, signs of nervous system impairment are often early indications of systemic disease. In addition, some diseases affect the biochemical mechanisms that propagate electrical impulse. In such instances, cell structure is maintained although cell function is impaired. Loss of neural function implies a loss of the ability to propagate the electrical signal; the location and type of nerve determines the functional effects of nerve injury.

*Response to injury or disease.*—The response of muscle cells to damage is similar to that of connective tissue. Damaged cells and tissue are replaced by collagen tissue rather than normal contractile muscle. Depending on severity and extent of injury, a large noncontractile scar within a muscle can be disabling. If a relatively small proportion of skeletal muscle tissue is damaged,
however, resistance training of the remaining muscle tissue can compensate for the loss of functional motor units. If a significant proportion of the smooth muscle of internal organs or cardiac muscle is damaged, however, severe impairment or complete loss of function occurs in the associated organ. Irreversible damage to muscle of internal organs, particularly the heart, can be fatal.

Unfortunately, damage to the cell body of a nerve cell is permanent. A nerve cell can neither be replaced nor regenerated, resulting in permanent loss of the functions associated with that nerve cell. Damage to any portion of the nerve cell (dendrite, axon, or body) in the central nervous system (brain and spinal cord) is also permanent. If an axon is damaged in the peripheral nervous system, however, it can regenerate provided the myelin (a lipoprotein) sheath surrounding the axon is preserved and aligned. The axon first degenerates distal to the point of injury (a process called wallerian degeneration) and then regenerates inside the myelin sheath at a rate of approximately one quarter-inch per month.

Specialized Cells and Tissues.

Normal morphology and physiology.—Cells of the blood, gastrointestinal system, liver, kidneys, and endocrine glands are highly specialized to perform specific tasks (Table 2.4). Most of the functions are integral to larger systems or to homeostasis in general. Thus, abnormal function in one of the systems usually (eventually) affects one or more of the other systems. Pathology in these organs often produce the systemic signs reviewed in Table 1.7, which reflect the interaction of these systems clinically.

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosa</td>
<td>Gastrointestinal</td>
<td>Absorb nutrients, secrete mucus for protection and enzymes for digestion</td>
</tr>
<tr>
<td>Acinar</td>
<td>Exocrine pancreas</td>
<td>Secrete digestive enzymes</td>
</tr>
<tr>
<td>Islet</td>
<td>Endocrine pancreas</td>
<td>Alpha-cells secrete glucagon, Beta-cells secrete insulin</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Liver</td>
<td>Secrete bile, store carbohydrate, form urea, metabolism of cholesterol, lipids, and many drugs and toxins</td>
</tr>
<tr>
<td>Renal</td>
<td>Kidney</td>
<td>Regulate fluid, form urine</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Endocrine glands</td>
<td>Secrete regulatory specific hormones</td>
</tr>
</tbody>
</table>

Pathological processes.—Pathology of gastrointestinal, liver, or kidney cells can be caused by infection, metabolic or genetic changes, or toxicity. Direct physical trauma, which is perhaps most common in young people and people who participate in sports, can disrupt tissues and interfere with organ function. Blood cells can also be affected by infection, metabolic changes, or toxicity, and can be indirectly affected by trauma to other tissues. Substantial tissue trauma may cause a loss of large amounts of blood from the vascular system, called hemorrhage. Hemorrhage has serious and potentially fatal consequences as organs become progressively deprived of bloodborne nutrients and oxygen, a process known as shock (see Chapter 5).

The signs of shock reflect the homeostatic effort to maintain blood pressure in the vascular system and blood flow to the internal organs. These signs include pallor (pale skin) and
cool (“clammy”) skin as a result of peripheral vasoconstriction in an effort to preserve blood flow to the internal organs, hypotension (low blood pressure) as a result of low blood volume within the vascular system, and tachycardia (increased heart rate) in an effort to maintain blood flow to the organs of the body. Shock can also be caused by a response to heart failure (decreasing systemic blood flow) or widespread peripheral vasodilation (in response to autonomic nervous system action, systemic infection, or anaphylaxis).

Endocrine glands are rarely affected by trauma, but physical damage may occur with major injuries and diseases in surrounding organs. More commonly, genetic factors induce abnormal function or tumor development. Environmental factors also potentially affect endocrine function through toxicity. Tumors in the endocrine glands can either reduce or increase secretion of specific hormones, thus upsetting metabolic homeostasis. In addition, since hormones affect multiple organs, signs and symptoms are produced in several systems.

Response to injury or disease.—The tissues of the gastrointestinal organs, liver, and kidneys are highly vascularized and display a typical tissue healing response in reaction to cellular damage. The inflammatory response produces clinical signs that are specific to the functions of the affected organ or organs (see Chapters 7 and 8). Many of these cells have a limited ability to regenerate, but if chronic cell damage and inflammation persists, the damage becomes permanent and cells are replaced by scar tissue. With repeated, prolonged, or severe damage, the organs can no longer function properly, and may restrict blood flow to surrounding healthy cells, thus propagating cell damage. Examples of this type of pathology include cirrhosis of the liver, chronic renal failure, and inflammatory bowel disease.

Blood cells.—The presence of infection (septicemia) or a toxin in the blood causes a vigorous inflammatory response throughout the body. The high fever produced in such a condition can destroy other tissues, posing a serious threat to homeostasis and life. The blood can also be affected by genetic diseases, including sickle cell anemia (misshapen red blood cells; see Chapter 5) and leukemia (proliferation of immature blood cells; see Chapter 13). These diseases also cause a mild or moderate general inflammatory response.

Summary

Pathophysiology refers to the biological process of disease. The mechanism called homeostasis responds to the changing internal and external environment to maintain chemical, fluid, and energy balances in the body. Many pathological processes upset this equilibrium. Virtually all pathological processes can be expressed in terms of their effect on individual cells, and the cellular effects on organ function. Cells can be damaged by physical, infective, metabolic, genetic, or environmental factors, causing them to either adapt or die. When enough cells die, organ functions are affected. Inflammation and infection are general responses to cell damage. Each cell and tissue type also produces specific responses. Signs and symptoms are these general and specific responses to cell damage.
Online Resources

Online pathophysiology textbook www.mfi.ku.dk/ppaulev/content.htm.

Medline Plus (medical dictionary and encyclopedia, plus descriptions of over 700 medical conditions) medlineplus.gov.

References