SECTION I

Pathophysiology: Background and Overview

CHAPTER 1

Introduction to Pathophysiology

CHAPTER OUTLINE

LEARNING OBJECTIVES

After studying this chapter, the student is expected to:

1. Explain the role of pathophysiology in the diagnosis and treatment of disease.
2. Use the terminology appropriate for pathophysiology.
3. Explain the importance of a patient's medical history.
4. Describe common cellular adaptations and possible reasons for the occurrence of each.
5. Identify precancerous cellular changes.
6. List the common causes of cell damage.
7. Describe the common types of cell necrosis and possible outcomes.

KEY TERMS

anaerobic
apoptosis
autopsy
biopsy
endogenous
exogenous
gangrene
homeostasis
hypoxia
iatrogenic
idiopathic
inflammation
ischemia
lysis
lysosomal
microorganisms
microscopic
morphologic
probability

What Is Pathophysiology and Why Study It?

Pathophysiology involves the study of *functional* or physiologic changes in the body that result from disease processes. This subject builds on knowledge of the normal structure and function of the human body. Disease development and the associated changes to normal anatomy and/or physiology may be obvious or may be hidden with its quiet beginning at the cellular level. As such, pathophysiology includes some aspects of *pathology*, the laboratory study of cell and tissue changes associated with disease.

Understanding Health and Disease

Disease may be defined as a deviation from the *normal* structure or function of any part, organ, system (or combination of these) or from a state of *wellness*. The World Health Organization includes physical, mental, and social well-being in its definition of health.

A state of health is difficult to define because the genetic differences among individuals as well as the many variations in life experiences and environmental influences create a variable base. The context in which health is measured is also a consideration. A person who is blind can be in good general health. Injury or surgery may create a temporary impairment in a specific area, but the person's overall health status is not altered.

Homeostasis is the maintenance of a relatively stable internal environment regardless of external changes. Disease develops when significant changes occur in the body, leading to a state in which **homeostasis** cannot be maintained without intervention. Under normal conditions homeostasis is maintained within the body with regard to such factors as blood pressure, body temperature, and fluid balance. As frequent minor changes occur in the body, the compensation mechanisms respond, and homeostasis is quickly restored. Usually the individual is not aware of these changes or the compensations taking place.

Steps to Heath (Box 1-1) are recommended to prevent disease.

When one is defining "normal" limits for health indicators such as blood pressure or pulse, the values used usually represent an *average* or a small *range*. These values represent what is expected in a typical individual but are not an absolute criterion. Among normal healthy individuals, the actual values may be adjusted for factors such as age, gender, genetics, environment, and activity level. Well-trained athletes often have a slower pulse or heart rate than the average person. Blood pressure usually increases slightly with age, even in healthy individuals. Also, small daily fluctuations in blood pressure occur as the body responds to minor changes in activity, body position, and even emotions. Therefore it is impossible to state a single normal value for blood pressure or pulse rate. It is also important to remember that any one indicator or lab value must be considered within the total assessment for the individual client.

BOX 1-1 Seven Steps to Health

1. Be a nonsmoker and avoid second-hand smoke.
2. Eat 5 to 10 servings of vegetables and fruit a day. Choose high-fiber, lower-fat foods. If you drink alcohol, limit your intake to one to two drinks a day.
3. Be physically active on a regular basis. This will also help you maintain a healthy body weight.
4. Protect yourself and your family from the sun.
5. Follow cancer screening guidelines.
6. Visit your doctor or dentist if you notice any change in your normal state of health.
7. Follow health and safety instructions at home and at work when using, storing, and disposing of hazardous materials.

Likewise, a discussion of a specific disease in a text presents a general description of the typical characteristics of that disease, but some differences in the clinical picture can be expected to occur in a specific individual, based on similar variables.

Concept and Scope of Pathophysiology and Evidenced-Based Practice

Pathophysiology requires the use of knowledge of basic anatomy and physiology and is based on a loss of or a change in normal structure and function. This basis also saves relearning many facts! Many disorders affecting a particular system or organ, for example the liver, display a set of common signs and symptoms directly related to that organ's normal structure and function. For example, when the liver is damaged, many clotting factors cannot be produced; therefore, excessive bleeding results. Jaundice, a yellow color in the skin, is another sign of liver disease, resulting from the liver's inability to excrete bilirubin. Also, basic pathophysiologic concepts related to the causative factors of a disease, such as the processes of inflammation or infection are common to many diseases. Inflammation in the liver causes swelling of the tissue and stretching of the liver capsule, resulting in pain, as does inflammation of the kidneys. This cause and effect relationship, defined by signs and symptoms, facilitates the study of a specific disease.

In this text, in order to provide a comprehensive overview of disease processes, the focus is on major diseases. Other disorders are included when appropriate to provide exposure to a broad range of diseases. The principles illustrated by these diseases can then be applied to other conditions encountered in practice. In addition, a general approach is used to describe diseases in which there may be several subtypes. For example, only one type of glomerulonephritis, a kidney disease, is described in the text, acute poststreptococcal glomerulonephritis, which represents the many forms of glomerulonephritis.

Prevention of disease has become a primary focus in health care. The known causes of and factors predisposing to specific diseases are being used in the development of more effective preventive programs, and it is important to continue efforts to detect additional significant factors and gather data to further decrease the incidence of certain diseases. The Centers for Disease Control and Prevention in the United States have a significant role in collection of data about all types of disease and provide evidence based recommendations for prevention. Prevention includes such activities as maintaining routine vaccination programs and encouraging participation in screening programs such as blood pressure clinics and vision screening (Box 1-2). As more community health programs develop, and with the increase in information available on the internet, health care workers are becoming more involved in responding to questions from many sources, and have an opportunity to promote appropriate preventive measures in their communities. A sound knowledge of pathophysiology is the basis for preventive teaching in your profession.

BOX 1-2 Primary, Secondary, and Tertiary Prevention

Primary Prevention

The goal is to protect healthy people from developing a disease or experiencing an injury in the first place. For example:

- Education about good nutrition, the importance of regular exercise, and the dangers of tobacco, alcohol, and other drugs
- Education and legislation about proper seatbelt and helmet use
- Regular exams and screening tests to monitor risk factors for illness
- Immunization against infectious disease
- Controlling potential hazards at home and in the workplace

Secondary Prevention

These interventions happen after an illness or serious risk factors have already been diagnosed. The goal is to halt or slow the progress of disease (if possible) in its earliest stages; in the case of injury, goals include limiting long-term disability and preventing re-injury. For example:

- Telling people to take daily, low-dose aspirin to prevent a first or second heart attack or stroke
- Recommending regular exams and screening tests in people with known risk factors for illness
- Providing suitably modified work for injured workers

Tertiary Prevention

This focuses on helping people manage complicated, long-term health problems such as diabetes, heart disease, cancer, and chronic musculoskeletal pain. The goals include preventing further physical deterioration and maximizing quality of life. For example:

- Cardiac or stroke rehabilitation programs
- Chronic pain management programs
- Patient support groups

From http://www.iwh.on.ca/wrmb/primary-secondary-and-tertiary-prevention.

While studying pathophysiology, the student becomes aware of the complexity of many diseases, the difficulties encountered in diagnosis and treatment, and the possible implications arising from a list of signs and symptoms or a prognosis. Sophisticated and expensive diagnostic tests are now available. The availability of these tests, however, also depends on the geographic location of individuals, including their access to large, well-equipped medical facilities. More limited resources may restrict the number of diagnostic tests available to an individual, or a long waiting period may be necessary before testing and treatment are available. When a student understands the pathophysiology, comprehension of the manifestations and potential complications of a disease, and its treatment, usually follows. A solid knowledge base enables health care professionals to meet these increased demands with appropriate information.

Individuals working in health care have found that many new scientific developments have raised ethical, legal, and social issues. For example, the recent explosion in genetic information and related technologies has raised many ethical concerns (see Chapter 21). In relatively new areas of research such as genetics, discussion and resolution of the legal and ethical issues lag far behind the scientific advances. Health research is most often funded by commercial sources (up to 80% according to some studies) and new breakthrough therapies are often announced before the start of any clinical trials. This causes increased hope and immediate demand for such treatments often as much as a decade before they become available. Understanding the research process and the time required for clinical trials of new therapies is crucial in answering questions about new therapies.

The research process in the health sciences is a lengthy three-stage process that aims to demonstrate both the safety and effectiveness of a new therapy. The first stage in this process is often referred to as "basic science" in which researchers work to identify a technology that will work to limit or prevent the disease process. This stage is carried out in the laboratory and often requires the use of animals or cell cultures. The second stage involves a small number of human subjects to determine if the therapy is safe for humans. The third stage only takes place if the results of the previous research are positive; the majority of therapies do not make it to this point. In the third stage of research a large number of patients with the disease or at risk for the disease are enrolled in clinical trials. These are usually *double blind studies* in which the research subject and the person administering the treatment do not know if the subject is receiving a standard, proven therapy or the therapy

being tested. The subject is identified by number only without the particular therapy administered. All results are recorded by the subject's identification number. The principal investigator is responsible for tracking data collected in trials with many patients often in several different health centers. The data are then analyzed to determine if the new therapy is more effective than the traditional therapy. In studies of vaccines or other preventive measures, data are collected about the occurrence of disease in both the control and the experimental group to determine if the new measure reduces the incidence of the specific disease. Research findings that demonstrate merit after this three-stage process are often referred to as "evidence-based research findings." The research data collected up to this point are then passed on to regulatory bodies such as the Food and Drug Administration for review. If the therapy is deemed safe and better than the standard therapy used in the past, the data will be approved for use for the specific disease identified in the research protocol.

Evidence-based research does not take into account cost, availability, or social and cultural factors that may influence use and acceptance of a therapy. These factors may be quite significant and affect the physician's or patient's acceptance of a therapy.

In some rare cases, stage three research trials will be stopped if there is a significant difference in the mortality rate for the experimental group versus the control group. Research on the first antiretroviral agent, AZT, was stopped 6 months early when the research showed a striking difference in survival rates. Those in the experimental group receiving AZT were outliving the control group in significant numbers. When the results were analyzed, trials stopped and all patients were given the option of receiving AZT.

Once a therapy is approved for use, it may show additional potential to treat a different disease. Such use is termed "off-label" use. For the manufacturer to advertise the drug or therapy for use in different diseases, it must go through stage three clinical trials in patients having the new disease. An example of this is research using the drug thalidomide to treat malignancies such as multiple myeloma.

THINK ABOUT 1-1

a. What is the purpose of a double blind research trial?
b. What is a placebo and why is it used in some studies?

Other issues may affect professional practice. Current technology provides an opportunity to prolong life through the use of various machines, many advances in surgery, and the use of organ transplants. Legal and ethical issues about fetal tissue transplants, stem cell therapies, experimental drugs or treatments, and genetic engineering continue to be difficult topics to address. In these developing areas, the primary goal is to reduce the incidence of disease and improve recovery rates. Concerns about new medical and health technologies include issues of access to therapy, costs, and relative risk versus benefits of new treatments. Questions have also been raised about the allocation of health care resources for new therapies such as heart transplants or in vitro fertilization (test-tube babies), which are very costly. A public health dilemma results because a choice must be made between a high-cost treatment for one person or a low-cost treatment for many people, given the limited resources available. In many cases evidence-based research is demonstrating little significant difference in outcomes for newer versus older technologies. A skilled and trained professional is essential in the use and interpretation of any technology. Clinical research funding is being directed to identifying treatments as well as preventive measures that are more effective on a cost-per-patient basis.

Many options other than traditional therapies are now available. Treatment by acupuncture or naturopathy may be preferred (see Chapter 3). These options may replace traditional therapies or may be used in conjunction with them. A patient may seek an alternative or complementary mode of treatment to supplement traditional care; thus knowledge of these complementary therapies is often needed. It is also recognized that such therapies and practices should be part of a health history for any client seeking care.

Beginning the Process: A Medical History

Many individuals in the health professions will be contributing to, completing, or updating a patient's medical or health history (see Ready Reference 6 for an example). This information is essential to identify any impact health care activities might have on a patient's condition, or how a patient's illness might complicate care. The assessment includes questions on current and prior illnesses, allergies, hospitalizations, and treatment. Current health status is particularly important, and should include specific difficulties and any type of therapy or drugs, prescription, nonprescription, and herbal items, including food supplements.

A basic form is usually provided for the patient to fill out, and then completed by the health professional asking appropriate follow-up questions to clarify the patient's current condition and identify any potential problems. Knowledge of pathophysiology is essential to developing useful questions, understanding the implications of this information, and deciding on the necessary precautions or modifications required to prevent complications. For example, a patient with severe respiratory problems or congestive heart failure would have difficulty breathing in a supine position. Reducing stress may be important for a patient with high blood pressure. Prophylactic medication may be necessary for some patients to prevent infection or excessive bleeding. In some cases, additional problems or undesirable effects of medications may be detected.

New Developments and Trends

Constant updating of information and knowledge is required by both students and practitioners. Developments in all areas of health care are occurring at a very rapid rate primarily due to changes in technologies. New causes of disease and more detail regarding the pathophysiology of a disorder are uncovered, diagnostic tests are improved, and more effective drugs are formulated. Technology has greatly altered many aspects of health care.

Extensive research projects continue in efforts to prevent, control, or cure many disorders. For example, research indicated that most cases of cervical cancer resulted from infection by human papillomavirus (HPV). The next step involved development of a vaccine effective against the most common strains of the virus. In clinical trials, use of the vaccine showed a reduction in the number of women developing cervical cancer. This vaccine is now available to young women to prevent cervical cancer in later years. It does not provide 100% prevention and other health prevention behaviors, such as routine screening, need to be maintained, but the number of actual cases of cervical cancer and the cost of treatment are expected to decline dramatically in the coming decades.

It is essential for the student and practitioner to continually check for new information, employing reliable, accurate resources such as professional web sites, journals, or seminars. It is anticipated that many changes in health care will occur in the near future as electronic devices are more frequently used. For example, sensors implanted under the skin may measure blood glucose levels in diabetic patients or release the amount of insulin appropriate to the patient's needs. The increased costs associated with technological advances then are balanced against the costs of hospitalization or chronic care.

Reports from health professionals are gathered by the World Health Organization (WHO), United States Public Health Service, the Centers for Disease Control and Prevention (CDC), and state and local authorities, as well as agencies in countries around the world. These data are organized and published, leading to new research efforts, tracking new or deadly diseases or in some cases, signaling a warning about predisposing conditions or current treatments. Awareness of deviations from the expected outcomes is a responsibility of those working in health care. Keeping up with new discoveries may sometimes feel like "information overload," but it is a critical part of professional practice.

APPLY YOUR KNOWLEDGE 1-1

Using the heart and the lungs, show how you can apply your prior knowledge of anatomy and physiology to your study of pathophysiology. (Hint: Change part of the normal structure and predict the resulting loss of function.)

Basic Terminology of Pathophysiology

Understanding basic terminology is the essential first step in learning a new subject. Second, a review of past learning in normal anatomy and physiology, along with the associated proper names and terms, is needed in the study of pathophysiology. Selected anatomical terms may be reviewed in Ready References 1 and 2 in the appendices at the back of the text. A firm foundation in anatomy and physiology is particularly important when a disease affects several organs or systems in the body. For example, kidney disease often affects cardiovascular function through the renin, angiotensin, and aldosterone mechanisms. The significance of these effects on another system can be more easily understood and remembered when prior knowledge of normal physiology can be quickly applied to the altered function.

A disease or abnormal condition usually involves changes at the organ or system (*gross*) level as well as at the cellular, or **microscopic**, level. Pathophysiology focuses on the effects of abnormalities at the organ level, but cellular changes are usually integral to a full understanding of these effects. Pathology laboratory studies, which are particularly useful in establishing the *cause* of a disease, examine tissue specimens from **biopsy** procedures (excision of very small amounts of living tissue), surgical specimens, or examination after death (**autopsy**). Analysis of body fluids is another essential diagnostic tool in a pathology laboratory. As indicated, the pathophysiologic changes at a particular site also include evidence of the basic cause of disease, whether it is an infection, a neoplasm, or a genetic defect.

The Disease Process

Following are a few terms frequently used in the discussion of disease processes. Not all of these terms are necessarily used when describing any one disorder.

- *Diagnosis* refers to the identification of a specific disease through evaluation of signs and symptoms, laboratory tests (see front inside cover and Ready Reference 5 in the Appendix) or other tools. More than one factor is usually required to verify a diagnosis. For example, a diagnosis of diabetes mellitus could be confirmed by a blood test following consideration of the patient's signs and a fractured leg bone is indicated by pain, swelling, perhaps the position of the leg, but it is confirmed by x-ray.
- *Etiology* concerns the causative factors in a particular disease. There may be one or several causative factors.

Etiologic agents include congenital defects, inherited or genetic disorders, microorganisms such as viruses or bacteria, immunologic dysfunction, metabolic derangements, degenerative changes, malignancy, burns and other trauma, environmental factors, and nutritional deficiencies.

Causes of Disease

When the cause of a disease is unknown, it is termed **idiopathic**. In some cases, a treatment, a procedure, or an error may cause a disease, which is then described as **iatrogenic**. Examples of iatrogenic disease are a bladder infection following catheterization, or bone marrow damage caused by a prescribed drug. In some cases, a difficult decision must be made about a treatment that does involve an additional serious risk, with careful assessment of the benefits versus the risks of a specific treatment. For example, certain forms of chemotherapy and radiation used in the treatment of cancer may cause other serious complications for the patient. In these situations, an informed choice must be made by the client and practitioner.

- *Predisposing factors* encompass the tendencies that promote development of a disease in an individual. A predisposing factor indicates a *high risk* for the disease but not certain development. Predisposing or high-risk factors may include age, gender, inherited factors, occupational exposure, or certain dietary practices. For example, insufficient calcium intake predisposes to osteoporosis. Exposure to asbestos is known to increase the risk of developing cancer. A high dietary intake of cholesterol and saturated fats, cigarette smoking, obesity, and a sedentary lifestyle are factors that increase the risk of heart attacks. By promoting avoidance of predisposing factors, the number of individuals developing the disorder could be greatly reduced.
- Prophylaxis measures designed to preserve health (as of an individual or society) and prevent the spread of disease. Prophylactic treatment for myocardial infarction for high-risk patients is a baby aspirin daily.
- *Prevention* of disease is closely linked to etiology and predisposing factors for a specific disease. Preventive measures include vaccinations, dietary or lifestyle modifications, removal of harmful materials in the environment, and cessation of potentially harmful activities such as smoking. The health professional can provide appropriate and reliable information about the activities that support the client's needs and allow him or her to make better decisions about his or her personal health.

Characteristics of Disease

In describing the characteristics of a particular disease, certain terms are standard:

- *Pathogenesis* refers to the development of the disease or the sequence of events involved in the tissue changes related to the specific disease process.
- The *onset* of a disease may be *sudden* and obvious or *acute*; for example, gastroenteritis with vomiting, cramps, and diarrhea; or the onset may be *insidious*, best described as a gradual progression with only vague or very mild signs. Hepatitis may manifest quietly in this way. There may be several stages in the development of a single disease.
- An *acute* disease indicates a short-term illness that develops very quickly with marked signs such as high fever or severe pain; for example, acute appendicitis.
- A *chronic* disease is often a milder condition developing gradually, such as rheumatoid arthritis, but it persists for a long time and usually causes more permanent tissue damage. Often a chronic disease is marked by intermittent acute episodes.
- A *subclinical* state exists in some conditions in which pathologic changes occur, but no obvious manifestations are exhibited by the patient, perhaps because of the great reserve capacity of some organs. For example, kidney damage may progress to an advanced stage of renal failure before symptoms are manifested.
- An initial *latent* or "silent" stage, in which no clinical signs are evident, characterizes some diseases. In infectious diseases this stage may be referred to as the *incubation* period, which is the time between exposure to the microorganism and the onset of signs or symptoms; it may last for a day or so or may be prolonged, perhaps for days or weeks. Often the disease agent may be communicable during this incubation period.
- The *prodromal* period comprises the time in the early development of a disease when one is aware of a change in the body, but the signs are nonspecific; for example, fatigue, loss of appetite, or headache. A sense of feeling threatened often develops in the early stage of infections. Laboratory tests are negative during the prodromal period; thus it is difficult to confirm a diagnosis.
- The *manifestations* of a disease are the clinical evidence or effects, the signs and symptoms, of disease. These manifestations, such as redness and swelling, may be *local*, or found at the site of the problem. Or signs and symptoms may be *systemic*, meaning they are general indicators of illness, such as fever.
- *Signs* are objective indicators of disease that are obvious to someone other than the affected individual. Examples of a sign are a fever or a skin rash.
- *Symptoms* are subjective feelings, such as pain or nausea. Both signs and symptoms are significant in diagnosing a particular problem.
- *Lesion* is the term used to describe a specific local change in the tissue. Such a change may be microscopic, as when liver cells are examined for pathologic change, or highly visible, such as a blister or pimple observed on the skin.
- A *syndrome* is a collection of signs and symptoms, often affecting more than one organ, that usually occur together in response to a certain condition.
- *Diagnostic* tests are laboratory tests that assist in the diagnosis of a specific disease. The appropriate tests are ordered on the basis of the patient's manifestations and medical history, the clinical examination, and the patient's answers to specific questions. These tests may also be used for monitoring the response to treatment or the progress of the disease. Such tests may involve chemical analysis of body fluids such as blood, examination of tissues and cells from specimens (e.g., biopsies or body secretions), identification of microorganisms in body fluids or tissue specimens, or radiologic examination of the body. It is important that medical laboratories have a Quality Assurance (QA) program in place to ensure accurate test results. Also, it is often helpful for a patient to have any future or repeated tests done by the same laboratory to provide a more accurate comparison of results.
- *Remissions* and *exacerbations* may mark the *course* or progress of a disease. During a remission, the manifestations of the disease subside, whereas during an exacerbation the signs increase. Rheumatoid arthritis typically has periods of remission when pain and swelling are minimal, alternating with acute periods when swelling and pain are severe.
- A *precipitating* factor is a condition that triggers an acute episode, such as a seizure in an individual with a seizure disorder. Note that a precipitating factor differs from a predisposing factor. For example, a patient may be predisposed to coronary artery disease and angina because of a high-cholesterol diet. An angina attack can be precipitated by shoveling snow on a very cold day.
- *Complications* are new secondary or additional problems that arise after the original disease begins. For example, following a heart attack, a person may develop congestive heart failure, a complication.
- *Therapy* or therapeutic interventions are treatment measures used to promote recovery or slow the progress of a disease. These measures may include surgery, drugs, physiotherapy, alternative therapies or behavior modification (see Chapter 3).
- *Sequelae* describe the potential unwanted outcomes of the primary condition, such as paralysis following recovery from a stroke.
- *Convalescence* or *rehabilitation* is the period of recovery and return to the normal healthy state; it may last for several days or months.

Disease Prognosis

Prognosis defines the **probability** or likelihood for recovery or other outcomes. The probability figures used in prognosis are based on average outcomes, and there may be considerable variation among affected individuals. It is important to consider the basis of the statistics used to form such conclusions. How big was the clinical group? How long was the study? It is very difficult to state a prognosis for diseases that affect a very small group of clients or in which outcomes vary unpredictably.

- *Morbidity* indicates the disease rates within a group; this term is sometimes used to indicate the functional impairment that certain conditions such as stroke cause within a population.
- *Mortality* figures indicate the relative number of deaths resulting from a particular disease.
- *Epidemiology* is the science of tracking the pattern or occurrence of disease. Epidemiologic records include data on the transmission and distribution of diseases and are particularly important in the control of infectious diseases and environmentally related diseases. Data may be presented in graphs, tables, or on maps to provide a visible pattern. For example, epidemiologic information is used to determine the components of the influenza vaccine to be administered each year based on the currently active strains and geographic movement of the influenza virus. Major data collection centers are the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, and Ottawa, Canada. Notification and reporting of disease is required to provide data for epidemiologic studies and prevent occurrence of diseases.
- *Epidemics* occur when there are a higher than expected number of cases of an infectious disease within a given area, whereas *pandemics* involve higher numbers of cases in many regions of the globe (Fig. 1-1). Influenza may occur sporadically as well as in epidemic or pandemic outbreaks.
- The *occurrence* of a disease is tracked by recording two factors, the incidence and the prevalence. The *incidence* of a disease indicates the number of new cases in a given population noted within a stated time period (see Fig. 1-1). A significant increase or decrease in incidence of a specific disease may be analyzed to determine the responsible factors. *Prevalence* refers to the number of new and old or existing cases within a specific population and time period. Note that prevalence is always a larger figure than incidence.
- *Communicable* diseases are infections that can be spread from one person to another. Some of these must be reported to health authorities.
- *Notifiable* or *reportable* diseases must be reported by the physician to certain designated authorities. The authority varies with the local jurisdiction. The specific diseases required to be reported may change over time. The requirement of reporting is intended to prevent further spread of the disease and maintain public health. Such infections as measles, severe acute respiratory syndrome (SARS), and human immunodeficiency virus (HIV) or acquired

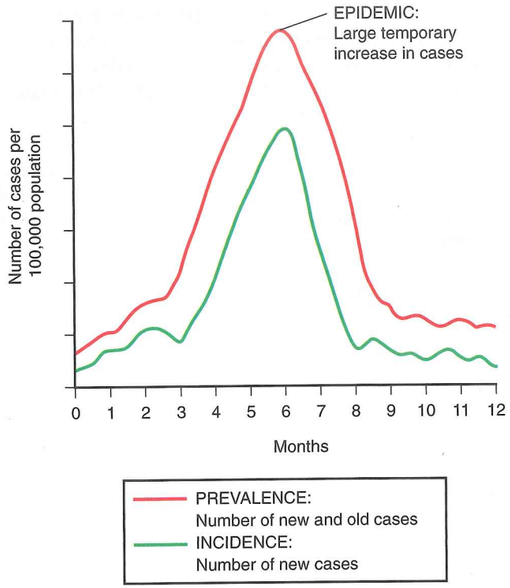

FIGURE 1-1 Graph illustrating the occurrence of disease.

immunodeficiency syndrome (AIDS) may be included in some jurisdictions.

- An *autopsy* or *postmortem examination* may be performed after death to determine the exact cause of death, or determine the course of the illness and effectiveness of treatment. An autopsy is an examination of all or part of the body by a pathologist. It includes gross and microscopic examination of tissues, organs, and fluids, and can include a variety of tests depending on individual circumstances.

THINK ABOUT 1-2

Rheumatoid arthritis is defined as a chronic systemic disorder with remissions and exacerbations, resulting in permanent joint damage. Describe this disease in terms of manifestations, etiology, predisposing factors, pathogenesis, and treatments.

Introduction to Cellular Changes

The cells have mechanisms by which they can adapt their growth and differentiation to altered conditions in the body. Some minor alterations, such as increases in breast and uterine tissue during pregnancy, are normal adaptations to change in the body. Tissues are frequently modified as a response to hormonal stimulation or environmental stimuli such as irritation. Frequently such changes are reversible after the stimulus is removed. However, disease may develop when cell structure and function change and homeostasis cannot be maintained as a result. Irreversible changes in a cell signal a change in DNA structure or function. (See Fig. 21-2 for an illustration of DNA, the controlling nuclear material in a cell.) Abnormal changes are not necessarily a precursor to permanent tissue damage or the development of tumors or cancer, but it is important to determine the cause and monitor any abnormality to reduce the risk of serious consequences. Cells may be damaged or destroyed by changes in metabolic processes, reduced levels of adenosine triphosphate (ATP), altered pH in the cells, or damage to the cell membrane and receptors.

Terms Used for Common Cellular Adaptations

- *Atrophy* refers to a *decrease* in the *size* of cells, resulting in a reduced tissue mass (Fig. 1-2). Common causes include reduced use of the tissue, insufficient nutrition, decreased neurologic or hormonal stimulation, and aging. An example is the shrinkage of skeletal muscle that occurs when a limb is immobilized in a cast for several weeks.
- *Hypertrophy* refers to an *increase* in the *size* of individual cells, resulting in an enlarged tissue mass. This increase may be caused by additional work by the tissue, as demonstrated by an enlarged heart muscle resulting from increased demands (see Fig. 12-23). A common example of hypertrophy is the effect of consistent exercise on skeletal muscle, leading to an enlarged muscle mass. Excessive hormonal stimulation may also stimulate cell growth.
- *Hyperplasia* is defined as an increased *number* of cells resulting in an enlarged tissue mass. In some cases, hypertrophy and hyperplasia occur simultaneously, as in the uterine enlargement that occurs during pregnancy. Hyperplasia may be a compensatory mechanism to meet increased demands, or it may be pathologic when there is a hormonal imbalance. In certain instances there may be an increased risk of cancer when hyperplasia occurs.
- *Metaplasia* occurs when one mature cell type is replaced by a different mature cell type. This change may result from a deficit of vitamin A. Sometimes, metaplasia may be an adaptive mechanism that provides a more resistant tissue; for instance, when stratified squamous epithelium replaces ciliated columnar epithelium in the respiratory tracts of cigarette smokers. Although the new cells present a stronger barrier, they result in decreased defenses for the lungs because cilia are no longer present as a defense mechanism for the simpler squamous cells in the mucosa.
- *Dysplasia* is the term applied to tissue in which the cells vary in size and shape, large nuclei are frequently present, and the rate of mitosis is increased. This situation may result from chronic irritation

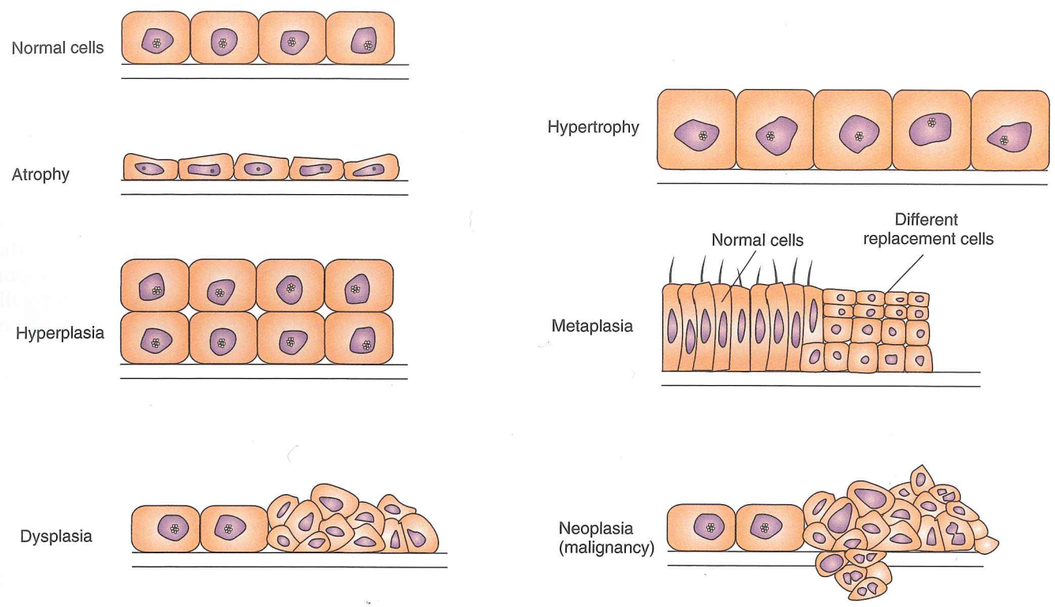

FIGURE 1-2 Abnormal cellular growth patterns.

infection, or it may be a precancerous change. Detection of dysplasia is the basis of routine screening tests for atypical cells such as the Pap smear (Papanicolaou test on cervical cells).

- *Anaplasia* refers to cells that are undifferentiated with variable nuclear and cell structures and numerous mitotic figures. Anaplasia is characteristic of cancer and is the basis for grading the aggressiveness of a tumor.
- Neoplasia means "new growth," and a neoplasm is commonly called a tumor. Tumors are of two types, benign and malignant (see Figs. 20-1 and 20-2). Malignant neoplasms are referred to as *cancer*. Benign tumors do not necessarily become malignant. Benign tumors are usually considered less serious because they do not spread and are not life threatening unless they are found in certain locations, such as the brain, where they can cause pressure problems. The characteristics of each tumor depend on the specific type of cell from which the tumor arises, resulting in a unique appearance and growth pattern. Neoplasms are discussed further in Chapter 20.

THINK ABOUT 1-3

Differentiate among hypertrophy, hyperplasia, anaplasia, and dysplasia.

Cell Damage and Necrosis

Apoptosis refers to programmed cell death, a normal occurrence in the body, which may increase when cell development is abnormal, cell numbers are excessive, or cells are injured or aged. Cells self-destruct, appearing to digest themselves enzymatically, and then disintegrate into fragments.

There are many ways of injuring cells in the body, including:

- **Ischemia**, a decreased supply of oxygenated blood to a tissue or organ, due to circulatory obstruction
- Physical agents, excessive heat or cold, or radiation exposure
- Mechanical damage such as pressure or tearing of tissue
- Chemical toxins
- Microorganisms such as bacteria, viruses, and parasites
- Abnormal metabolites accumulating in cells
- Nutritional deficits
- Imbalance of fluids or electrolytes

The most common cause of injury is ischemia or reduced blood supply to the tissue, which results in insufficient oxygen and reduced cellular metabolism. Decreased oxygen in the tissue may occur locally because of a blocked artery or systemically because of respiratory impairment. Cells with a high demand for oxygen, such as those of the brain, heart, and kidney, are quickly affected by **hypoxia**(reduced oxygen in the tissue). A severe oxygen deficit interferes with energy (ATP)

production in the cell, leading to loss of the sodium pump at the cell membrane as well as loss of other cell functions. An increase in sodium ions inside the cell leads to swelling of the cell and eventually to rupture of the cell membrane. At the same time, in the absence of oxygen, **anaerobic** metabolism occurs in the cell, leading to a decrease in pH from build of lactic acid and further metabolic impairment. A deficit of other essential nutrients such as vitamins may also damage cells because normal metabolic processes cannot take place.

Another cause of cellular damage is physical injury related to thermal (heat) or mechanical pressures. These may impair blood supply to the cells or affect metabolic processes in the cells. Radiation exposure may damage cells by interfering with their blood supply or directly altering their chemical constituents, creating toxic materials inside the cells or changing DNA. Chemicals from both the environment (**exogenous**) and inside the body (**endogenous**) may damage cells, either by altering cell membrane permeability or producing other reactive chemicals, known as free radicals, which continue to damage cell components. Infectious diseases cause cell injury through the actions of **microorganisms** (living organisms too small to be seen with the naked eye) such as bacteria and viruses. Some genetic defects or inborn errors of metabolism can lead to abnormal metabolic processes. Altered metabolism leads to accumulation of toxic intermediary compounds inside the cells that ultimately destroy them.

Cell damage usually occurs in two stages. In general, the *initial* cell damage causes an alteration in a metabolic reaction, which leads to a *loss of function* of the cell. If the factor causing the damage is removed quickly, the cell may be able to recover and return to its normal state, and the damage is said to be reversible. As the amount of damage increases, detectable **morphologic** or structural changes occur in the nucleus and the cell as well. Cell death may take on a variety of forms. Generally these involve cellular swelling and rupture if the cell membrane is affected or accumulations of lipid inside the cell if metabolic derangements are present. If the noxious factor remains, the damage becomes irreversible and the cell dies.

Following cell death, the nucleus of the cell disintegrates. The cells undergo **lysis** or dissolution, releasing destructive **lysosomal** enzymes into the tissue, which cause **inflammation** (swelling, redness, and pain) as well as damage to nearby cells and reduced function (see Chapter 5). If a large number of cells have died, inflammation can be extensive, causing the destruction of additional cells. The enzymes released from the dead cells can diffuse into the blood, providing helpful clues in blood tests that indicate the type of cells damaged. Diagnostic tests for specific enzymes present in the blood may determine the site and source of the problem, for example, a heart attack, in which part of the heart muscle is destroyed.

Necrosis is the term used when a group of cells die. The process of cell death varies with the cause of the damage (Fig. 1-3).

- *Liquefaction necrosis* refers to the process by which dead cells liquefy under the influence of certain cell enzymes. This process occurs when brain tissue dies or in certain bacterial infections in which a cavity or ulcer may develop in the infected area.
- *Coagulative necrosis* occurs when the cell proteins are altered or denatured (similar to the coagulation that occurs when cooking eggs), and the cells retain some form for a time after death. This process typically occurs in a myocardial infarction (heart attack) when a lack of oxygen causes cell death.
- *Fat necrosis* occurs when fatty tissue is broken down into fatty acids in the presence of infection or certain enzymes (see Fig. 1-3C). These compounds may increase inflammation.
- *Caseous necrosis* is a form of coagulation necrosis in which a thick, yellowish, "cheesy" substance forms. Tuberculosis (TB) offers an interesting example of caseous necrosis (Fig. 1-4). When tuberculosis develops, the first stage is characterized by development of a granuloma, a small solid mass of macrophages and lymphocytes, often covered by connective tissue, which forms in some types of chronic inflammation (see Chapter 5). With TB, caseous necrosis can be seen inside this mass. The granuloma associated with tuberculosis is called a Ghon focus or complex, and it usually heals like a scar, containing the infection. If the infection continues to develop, this area may undergo liquefaction necrosis, forming a cavity. (See Chapter 13 for more details on tuberculosis.)
- *Infarction* is the term applied to an area of dead cells resulting from lack of oxygen (see Fig. 12-16B). When a large number of cells in an area die, the functional loss can be significant. For example, when part of the heart muscle is infarcted or dies, that area can no longer contract to pump blood (see Chapter 12). After tissue dies, it is eventually replaced either by tissue regenerated from nearby similar cells or connective tissue or scar tissue that fills the gap. Myocardial or heart muscle cells do not undergo mitosis; therefore scar tissue must replace the dead tissue.

Gangrene refers to an area of necrotic tissue that has been invaded by bacteria (see Fig. 1-3D). Necrotic tissue can provide a good medium for infection by microorganisms. Such an infection frequently occurs after an infarction in the intestines or in a limb in which blood supply is deficient and bacteria are normally present. Depending on its location, gangrene may be described as wet or dry. Gangrene may cause the buildup of gases within tissue and further reduce blood supply. Gangrenous tissue frequently must be removed surgically (e.g., by amputation) to prevent the spread of infection to other parts of the body.

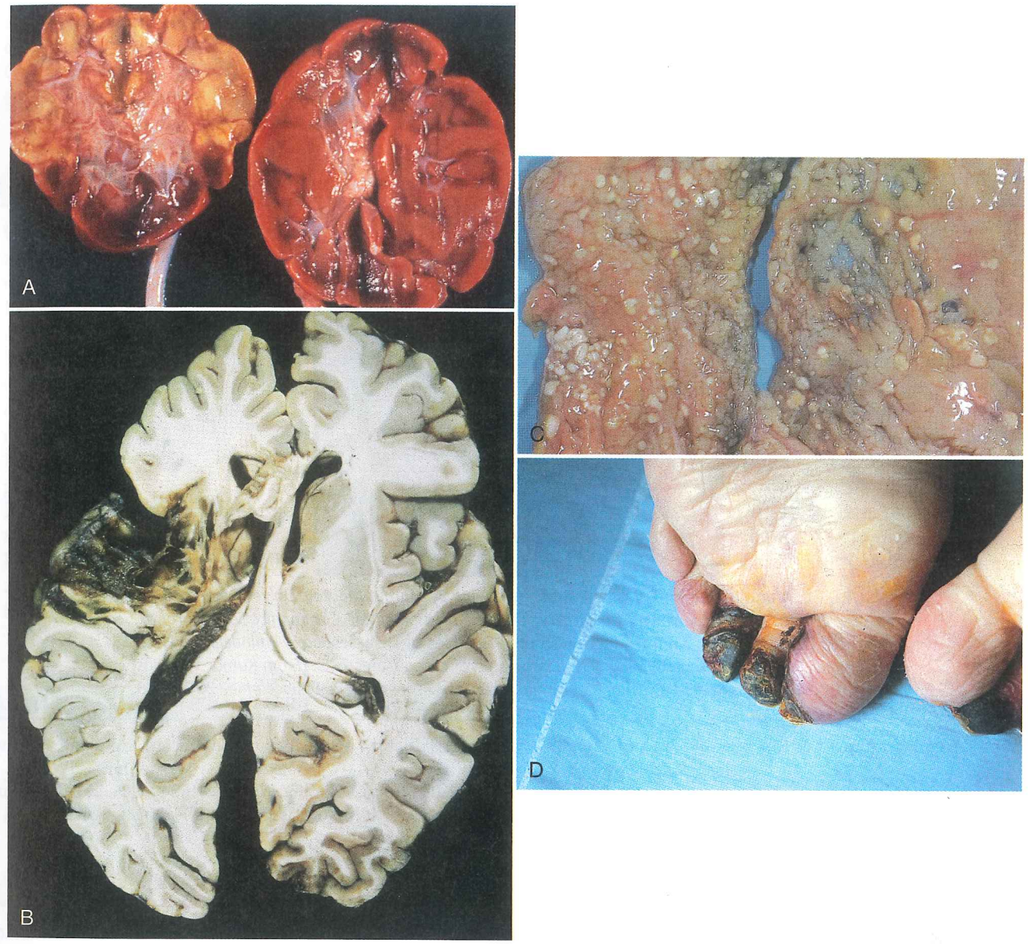

FIGURE 1-3 **A**, Coagulative necrosis of the kidney caused by ischemia. The necrotic area is pale yellow, in contrast to the normal reddish-brown tissue. **B**, Liquefaction necrosis following infarction in the brain, leading to destruction of tissue and cystic infarct. **C**, Fat necrosis in the mesentery. The areas of white chalky deposits represent calcium soap formation at sites of lipid breakdown. **D**, Dry gangrene of the toe. *(A, D From Damjanov I:* Pathology for the Health Professions, *ed 3, Philadelphia, 2006, WB Saunders. B, C From Kumar V, Abbas AK, Fausto M:* Robbins and Cotran Pathologic Basis of Disease, *ed 7, Philadelphia, 2005, WB Saunders.)*

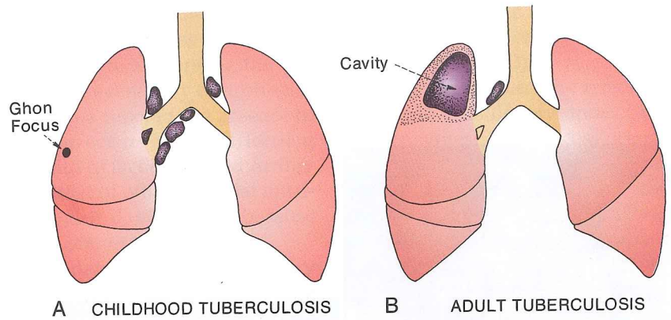

FIGURE 1-4 A and B, Pulmonary tuberculosis. *(Drawing by Margot Mackay, University of Toronto Faculty of Medicine, Department of Surgery, Division of Biomedical Communications, Toronto. Reprinted from Walter JB:* An Introduction to the Principles of Diseases, *ed 3, Philadelphia, 1992, WB Saunders.)* **C,** A tuberculous lung with a large area of caseous necrosis. *(From Kumar V, Abbas AK, Fausto M:* Robbins and Cotran Pathologic Basis of Disease, *ed 7, Philadelphia, 2005, WB Saunders.)*

THINK ABOUT 1-4

Describe the different types of necrosis and identify conditions in which amputation may be necessary.

Specific types of cells die at different rates. *Brain* cells die quickly (4-5 minutes) when deprived of oxygen, whereas *heart muscle* can survive for approximately 30 minutes. Formerly death of the body (*somatic death*) was assumed to occur when heart action and respiration ceased. Now because cardiac and respiratory function can be maintained artificially, the diagnosis of death is more complex. Currently *brain death* provides the criteria for somatic death. A diagnosis of brain death is made following a set protocol of tests and examinations including a lack of responses to stimuli, EEG changes, and decreased perfusion in the brain (see Chapter 14).

CHAPTER SUMMARY

- Disease is defined as a deviation from the individual's normal state of physical, mental, and social well-being, leading to a loss of homeostasis in the body. Pathophysiology is the study of the structural and functional changes related to disease processes.
- Effects of a specific disease depend on the organ or tissue affected and the cause of the disease; for example, infection or malignant tumor.
- Disease prevention campaigns or screening programs for early diagnosis are based on factors such as causes, predisposing factors, and incidence of specific disease.
- Health professionals need to be aware of the new information, diagnostic tests, and therapies that are constantly emerging. The allocation of resources for health care and the ethical issues related to new technologies are concerns.
- The discussion of disease processes includes such topics as occurrence, diagnosis, or the identification of a disease; etiology or the cause of disease; pathologic changes in the tissues or organs, or signs and symptoms of disease; and prognosis, or the probable outcomes.
- Cell and tissue changes such as atrophy and hypertrophy are frequently linked to changes in demand or use of the tissue. Metaplasia often occurs as an adaptive change, replacing the normal cell with a more resistant cell. Dysplasia and anaplasia are connected to malignant changes.
- Cell damage for any reason may be reversible, causing temporary loss of function. Severe damage to a cell causes necrosis and loss of function.
- Causes of cell damage include ischemia or lack of oxygen, toxic substances, changes in pH, or microorganisms such as bacteria and viruses.

STUDY QUESTIONS

1. Choose a specific disease and prepare an appropriate list of six terms that you could use to describe this disease, and define each of the terms.
2. Define and give an example of:
   a. etiology
   b. incidence
   c. precipitating factor
   d. complication
   e. prognosis
   f. iatrogenic
   g. sequelae
3. Differentiate between the terms *metaplasia* and *malignant neoplasm*.
4. Describe the changes in a cell that lead to:
   a. loss of function
   b. necrosis
5. Define:
   a. apoptosis
   b. gangrene
6. What preventive practices can be used to reduce disease?
7. CJ is having surgery next week to remove a malignant breast tumor, following discovery of a lump in the breast and a biopsy. Her mother and aunt have had breast cancer. CJ is taking medication for high blood pressure.

   Match the significant information in the preceding question to the appropriate term: diagnosis, medical history, etiology, prognosis, benign neoplasm, iatrogenic, signs, complication, treatment, cancer, examination of living tissue. Some terms may not be used or may be used more than once.

ADDITIONAL RESOURCES

Dorland's Illustrated Medical Dictionary, ed 29, Philadelphia, 2009, WB Saunders.

Kumar V, Abbas AK, Fausto M: *Robbins and Cotran Pathologic Basis of Disease*, ed 7, Philadelphia, 2007, WB Saunders.

Mosby's Medical, Nursing & Allied Health Dictionary, ed 6, St Louis, 2009, Mosby.