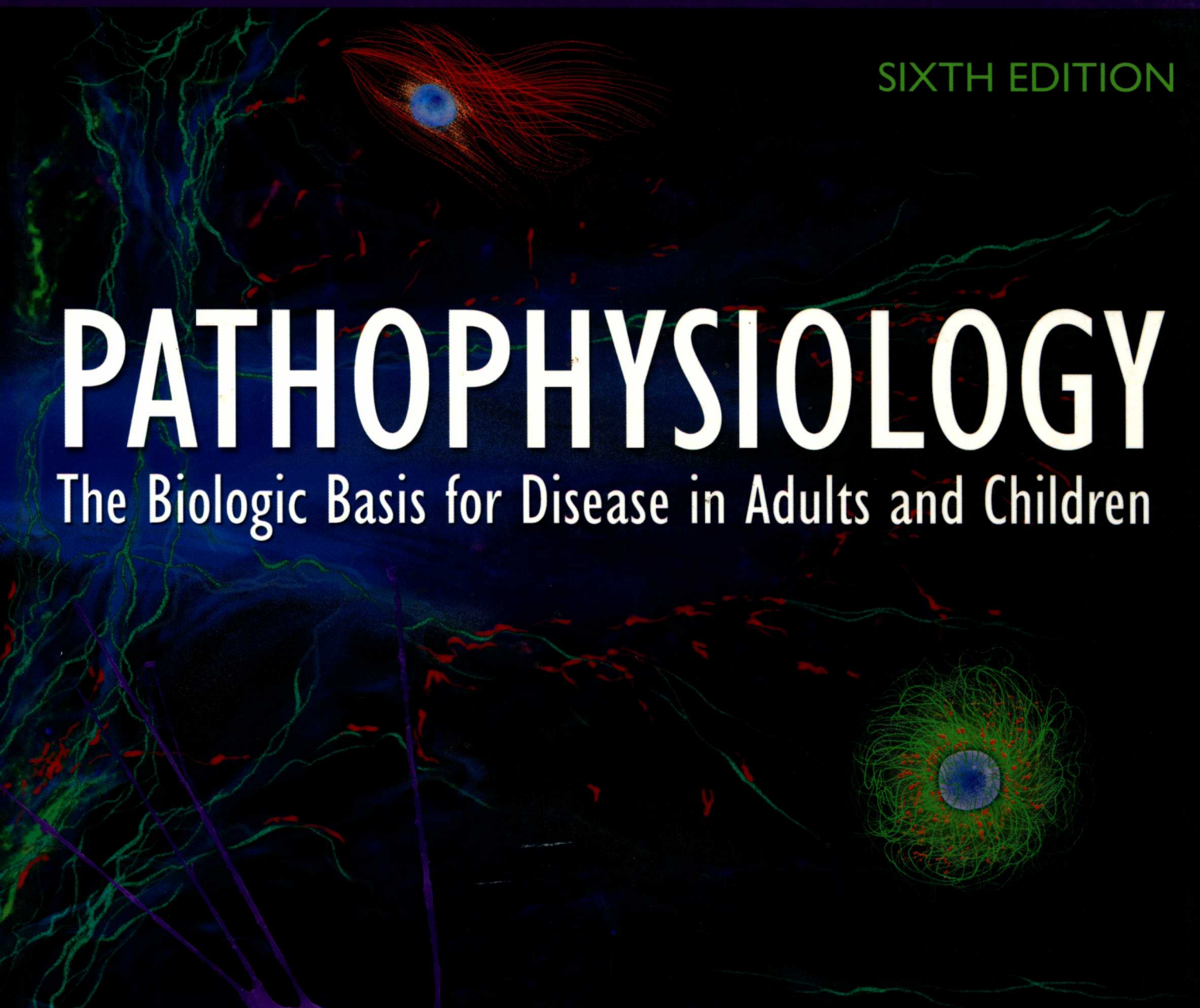
STUDY GUIDE

SIXTH EDITION

PATHOPHYSIOLOGY

The Biologic Basis for Disease in Adults and Children



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Preface

The study of pathophysiology is complex, ever expanding, and challenging. It requires correlation between normal and abnormal anatomy and physiology and the processes resulting in the manifestations of disease.

This study guide is designed for students as an adjunct to *Pathophysiology: The Biologic Basis for Disease in Adults and Children* by Kathryn L. McCance and Sue E. Huether. It is intended to facilitate an understanding of the consequences of pathologic processes on the structure and function of the human body.

The guide has 47 chapters, and each follows the organization of the textbook. The guide's chapters have two different formats—one for normal anatomy and physiology and another for anatomic and physiologic alterations.

For the normal anatomy and physiology chapters, it is assumed that the student possesses knowledge of anatomy and physiology; therefore no supplemental narrative is provided.

- These chapters have prerequisite knowledge objectives that direct review of information, principles, and concepts that are essential for understanding the specific diseases that follow in the next chapter.
- Each chapter has a practice examination to give students an opportunity to assess their understanding of normality.

The alterations chapters direct the learner's study of abnormal anatomy and physiology. Their information is not intended to be all inclusive.

- These chapters have limited, but essential (1) foundational knowledge objectives featuring Memory Checks and (2) learning objectives with concise selective narrative, flow charts, and tables to help students better comprehend the information to be learned.
- Each chapter has a practice examination requiring factual and conceptual knowledge related to disease mechanisms.
- Each chapter has one or two case studies linking fact and concept to reality.

The objectives for all chapters are referenced to corresponding pages in McCance and Huether's textbook. These authors' philosophy that students need to grasp basic laws and principles to understand how alterations occur led them to develop an understandable and conceptually integrated textbook. I enjoyed working with Elsevier, particularly Sandra Clark, Charlene Ketchum, and Joy Moore. All of Elsevier's staff ensured that my efforts were developed into a creative, professional, and pleasing style for student learners.

I wish to dedicate my efforts during the preparation of this study guide to eager students who make teaching pleasurable and inspire me to search for truth and a better way to convey it to students.

Clayton F. Parkinson

Contents

1 Cellular Biology

PREREQUISITE KNOWLEDGE OBJECTIVES

After reviewing the primary text where referenced, the learner will be able to do the following:

1. **Identify the eight major cellular functions.**
   Review text page 2.
2. **Identify the location of the three principal parts of a typical eukaryotic cell.**
   Refer to Figure 1-1.
3. **Describe the function of the nucleus and the cytoplasmic organelles.**
   Review text pages 2 and 4 through 10; refer to Figures 1-2 through 1-9.
4. **Describe the structure and composition of the plasma membrane.**
   Review text pages 10 through 13 and 15; refer to Figures 1-10 through 1-13.
5. **Categorize plasma membrane functions.**
   Refer to Tables 1-1 and 1-2.
6. **Describe the mechanisms that bind cells together.**
   Review text pages 15, 16, and 18; refer to Figures 1-14 and 1-15.
7. **Describe the primary modes of chemical signaling.**
   Review text pages 18 through 20; refer to Figures 1-16 through 1-21 and Tables 1-3 and 1-4.
8. **Describe cellular metabolism and the transfer of energy to drive other cellular processes.**
   Review text pages 21 through 25; refer to Figures 1-22 through 1-24.
9. **Classify cellular transport as active or passive; give examples of each.**
   Refer to Figures 1-25 through 1-29 and Table 1-5.
10. **Contrast macromolecular transport by endocytosis and exocytosis with micromolecular transport by potocytosis.**
    Review text pages 30 through 32; refer to Figures 1-30 and 1-31.
11. **Describe the changes in the plasma membrane that result in an action potential.**
    Review text pages 32 and 33; refer to Figure 1-32.
12. **Identify the phases of mitosis and cytokinesis; give examples of growth factors.**
    Refer to Figure 1-33 and Table 1-6.
13. **Identify two mechanisms for tissue formation.**
    Review text pages 35 and 36; refer to Figure 1-34.
14. **Identify the location and a major function of each of the following types of tissue: epithelial, connective, muscle, and nervous.**
    Review the tissue summary on text page 43; refer to Tables 1-7 through 1-9.

PRACTICE EXAMINATION

Multiple Choice

Circle the correct answer(s) for each question.

1. Which are principal parts of a eukaryotic cell?
   a. Fat, carbohydrate, and protein
   b. Minerals and water
   c. Organelles
   d. Phospholipids and protein
2. Caveolae:
   a. serve as repositories for some receptors.
   b. provide a route for transport into a cell.
   c. relay signals into cells.
   d. a and b are correct.
   e. a, b, and c are correct.
3. A vault is:
   a. an organelle.
   b. barrel-shaped.
   c. believed to transport mRNA to ribosomes.
   d. a and b are correct.
   e. a, b, and c are correct.
4. For a cell to engage in active transport processes, it requires:
   a. an expenditure of energy.
   b. appropriate fuel.
   c. ATP.
   d. All of the above are correct.
5. Which of the following is *inconsistent* with the others?
   a. Diffusion
   b. Osmosis
   c. Hydrostatic pressure
   d. Phagocytosis

6. Which of the following can transport substances against or up the concentration gradient?
   a. Active transport
   b. Osmosis
   c. Dialysis
   d. Facilitated diffusion
   e. None of the above is correct.
7. Imagine that you have an aqueous (water) solution A and an aqueous solution B separated by a membrane that is permeable to the solvent but is not permeable to the solute. If solution A is isotonic to human blood and solution B is hypotonic to human blood, then:
   a. net diffusion of the solute will occur from side B to side A.
   b. net diffusion of the solute will occur from side A to side B.
   c. net osmosis will occur from side B to side A.
   d. net osmosis will occur from side A to side B.
8. Which statement is true about cytoplasm?
   a. It is located outside the nucleus.
   b. It provides support for organelles.
   c. It is mostly water.
   d. All of the above are true.
   e. Only a and b are true.
9. Ribosomes:
   a. are found on smooth endoplasmic reticulum.
   b. are the sites for cellular protein synthesis.
   c. are synthesized in the cytosol.
   d. are made of the protein clathrin.
   e. conduct nerve impulses.
10. Activities occurring in the cytosol include:
    a. intermediary metabolism.
    b. ribosomal protein synthesis.
    c. conversion of glucose to glycogen.
    d. a and b are correct.
    e. a, b, and c are correct.
11. Ligands that bind with membrane receptors include which of the following?
    a. Hormones
    b. Antigens
    c. Neurotransmitters
    d. Drugs
    e. Infectious agents
12. The products from the metabolism of glucose include which of the following?
    a. Kilocalories
    b. CO_2
    c. H_2O
    d. ATP
13. Identify the correct alphabetical sequence of events for initiation and conduction of a nerve impulse.
    a. Sodium moves into cell.
    b. Potassium leaves cell.
    c. Sodium permeability changes.
    d. Resting potential is reestablished.
    e. Potassium permeability changes.
14. Potocytosis:
    a. involves the cellular uptake of small molecules.
    b. opens and closes caveolae.
    c. does not form a membrane-enclosed vesicle.
    d. a and b are correct.
    e. a, b, and c are correct.
15. Cell junctions:
    a. coordinate activities of cells within tissues.
    b. are an impermeable part of the plasma membrane.
    c. hold cells together.
    d. a and c are correct.
    e. b and c are correct.
16. Cells respond to external stimuli by activation of a variety of signal transduction pathways. Signaling molecules cause all of the following *except*:
    a. acceleration/initiation of intracellular protein kinases.
    b. arrest of cellular growth.
    c. apoptosis.
    d. conversion of an intracellular signal into an extracellular response.

Matching

Match the term with its descriptor.

_____ 17. Signal recognition particles

_____ 18. Metaphase

_____ 19. Mitochondria

_____ 20. Gating

_____ 21. Rafts

_____ 22. Paracrine signaling

a. 75% to 90% H_2O, lipids, and protein

b. RNA stored within the nucleus

c. compartmentalizes cellular activity

d. attach to and detach from ribosomes

e. "generation plant" for ATP

f. enables uninjured cells to seal themselves away from injured cells

g. chromatid pair alignment

h. hook cells together

i. acts on nearby cells

j. help organize membrane components

Match the location with its tissue type.

_____ 23. Lines kidney tubules

_____ 24. Lines urinary bladder

_____ 25. Lines upper respiratory tract

a. simple squamous

b. simple cuboidal

c. simple columnar, ciliated

d. stratified squamous

e. transitional

2 Altered Cellular and Tissue Biology

FOUNDATIONAL KNOWLEDGE OBJECTIVES

After reviewing the primary text where referenced, the learner will be able to do the following:

a. Describe processes of cellular intake and output.

Review text pages 25 through 32.

MEMORY CHECK!

- The intact, normally functioning plasma membrane is selectively permeable to substances; this means that it allows some substances to pass and excludes others. Water and small, uncharged substances move through pores of the lipid bilayer via passive transport, which requires no expenditure of energy. This process is driven by the forces of osmosis, hydrostatic pressure, and diffusion. Larger molecules and molecular complexes are moved into the cell via active transport, which requires the expenditure of energy, or ATP, by the cell. In active transport, materials move from areas of low concentration to areas of high concentration. The largest molecules and fluids are ingested through endocytosis and expulsed through exocytosis after cellular synthesis of smaller building blocks. When the plasma membrane is injured, it becomes permeable to virtually everything, and substances move into and out of the cells in an unrestricted manner. Notably, such substances may affect (1) the nucleus and its genetic information, or (2) the cytoplasmic organelles and their varied functions; when either of these happens, there is altered cellular physiology and pathology.

b. Identify the relationship among homeostasis, stress, and disease.

MEMORY CHECK!

- Homeostasis is the concept of a dynamic steady state and a turnover of bodily substances that maintains physiologic parameters within narrow limits. Stressors cause reactions that alter this dynamic steady state. Deviations from normal values, which are normally maintained by homeostasis, cause disease.

LEARNING OBJECTIVES

After studying this chapter, the learner will be able to do the following:

1. Describe the cellular adaptations that occur during atrophy, hypertrophy, hyperplasia, dysplasia, and metaplasia and identify conditions under which each can occur.

Study text pages 47 through 50; refer to Figures 2-1 through 2-6 and Table 2-1.

When confronted with stresses that disrupt normal structure and function, the cell undergoes adaptive changes that permit survival and maintain function. An adapted cell is neither normal nor injured—it is somewhere between these two states. These changes may lead to atrophy, hypertrophy, hyperplasia, metaplasia, or dysplasia. These adaptive responses occur in response to need and an appropriate stimulus. Once the need is no longer present, the adaptive response ceases.

Cellular atrophy decreases the cell substance and results in cell shrinkage. The size of all of the structural components of the cell usually decreases as the cell atrophies. Causes of atrophy include disuse, denervation, lack of endocrine stimulation, decreased nutrition, and ischemia. Disuse atrophy is seen in muscles that are not used. Denervation atrophy occurs in the muscles of paralyzed limbs. Lack of endocrine stimulation causes changes that may occur in reproductive structures during menopause. During prolonged periods of malnutrition,

the body may undergo a generalized wasting of tissue mass. Ischemia reduces blood flow and delivery of oxygen and nutrients to tissues.

Hypertrophy increases the amount of functioning mass by increasing cell size; this allows the cell to achieve an equilibrium between demand and function. Hypertrophy usually is seen in cardiac and skeletal muscle tissue. These tissues cannot adapt to increased workload by mitotic division to form more cells. The increase in cell components is related to an increased rate of protein synthesis. However, the extent of hypertrophy may be related to limitations in blood flow. Hypertrophy may be either physiologic or pathologic. In myocardial hypertrophy, initial enlargement is caused by dilation of the cardiac chambers in response to valvular disease or hypertension. This adaptation is short-lived and is followed by increased synthesis of cardiac muscle proteins that allows cardiac muscle fibers to do more work. Ultimately, advanced hypertrophy becomes pathologic and can lead to heart failure.

Hyperplasia is an increase in the number of cells of a tissue or an organ. It occurs in tissues in which cells are capable of mitotic division. Hyperplasia is a controlled response to an appropriate stimulus, and it ceases after the stimulus has been removed. Breast and uterine enlargement during pregnancy are examples of a *physiologic* hyperplasia that is hormonally regulated. A *pathologic* hyperplasia occurs when the endometrium enlarges because of excessive estrogen production; in this situation, the abnormally thickened uterine layer may bleed excessively and frequently. *Compensatory* hyperplasia enables certain organs, like the liver, to regenerate after a loss of substance.

Dysplasia (atypical hyperplasia) is deranged cell growth that results in cells that vary in size, shape, and appearance at maturity. Minor degrees of dysplasia occur in association with chronic irritation or inflammation in the uterine cervix, oral cavity, gallbladder, and respiratory passages. Dysplasia is potentially reversible after the irritating cause has been removed. In females, atypical hyperplasia changes may progress to breast neoplastic disease. Importantly, dysplasia does not indicate cancer and may not progress to cancer.

Metaplasia is a reversible conversion from one adult cell type to another adult cell type. It allows for replacement with cells that are better able to tolerate environmental stresses. In metaplasia, one type of cell may be converted to another type of cell within its tissue class (i.e., an epithelial cell cannot change to a connective tissue cell). An example of metaplasia is the substitution of stratified squamous epithelial cells for ciliated columnar epithelial cells in the airways of the person who is a habitual cigarette smoker.

2. Identify the mechanism of cellular injury for the following causes.

Hypoxia (study text pages 52 through 55; refer to Figures 2-8 through 2-10 and Tables 2-2 through 2-5); **chemicals** (study text pages 56, 57, and 59 through 62; refer to Figures 2-11 through 2-13 and Table 2-6); **unintentional and intentional injuries** (study text pages 62 through 69; refer to Figures 2-14 through 2-21); **infectious agents** (study text page 69); **immunologic and inflammatory responses** (study text page 69); **genetic factors** (study text page 69); **nutritional imbalances** (study text page 69; refer to Figure 2-22 and Table 2-7); and **physical trauma** (study text pages 71 through 76; refer to Figure 2-23 and Tables 2-8 and 2-9).

Hypoxia deprives the cell of oxygen and interrupts oxidative metabolism and the generation of ATP. As the levels of ATP decline, there is (1) decreased sodium pump activity, and (2) increased glycolysis. One of the earliest effects of reduced ATP is acute cellular swelling caused by failure of the sodium-potassium membrane pump. With impaired function of this pump, intracellular potassium levels decrease, and sodium and water accumulate within the cell. As fluid and ions move into the cell, there is dilation of the endoplasmic reticulum, increased membrane permeability, and decreased mitochondrial function as extracellular calcium accumulates in the mitochondria; all of these lead to decreased protein synthesis, lytic enzyme release, and cellular lysis.

If the oxygen supply is not restored, there is continued loss of essential enzymes, proteins, and ribonucleic acid through the very permeable membrane of the cell. Increased glycolysis decreases the pH, which leads to protein denaturation, nuclear chromatin clumping, and lysosomal swelling with enzyme release and cellular digestion. Hypoxia can result from inadequate oxygen in the air, respiratory disease, decreased blood flow due to circulatory disease, anemia, or inability of the cells to use oxygen.

Restoration of oxygen can cause **reperfusion (reoxygenation) injury.** Reperfusion is a cause of injury in tissue transplantation and in myocardial, hepatic, intestinal, cerebral, renal, and other ischemic syndromes. During reperfusion with oxygen, xanthine oxidase is produced, which makes massive amounts of superoxide, hydrogen peroxide, and the free radical nitric oxide.

Free radicals and reactive oxygen species (ROS), which overwhelm endogenous antioxidant systems, cause membrane damage and mitochondrial overload. A free radical is an atom or group of atoms with an unpaired electron; the unpaired electron makes the atom or group unstable. To gain stability, the radical gives up an electron to another molecule or steals an electron. These radicals can bond with proteins, lipids, and carbohydrates, which are key molecules in membranes and nucleic acids. These reactive species cause injury by (1) lipid peroxidation, which destroys unsaturated fatty acids; (2) fragmentation of polypeptide chains within proteins; and (3) alteration of DNA by breakage of single strands. Free radicals are difficult to control, and they initiate chain reactions. Free radicals may be initiated within cells by the absorption of ultraviolet light or x-rays, oxidative reactions that occur during normal metabolism, and enzymatic metabolism of exogenous chemicals or drugs.

Toxic chemical agents can injure the cell membrane and cell structures, block enzymatic pathways, coagulate cell proteins, and disrupt the osmotic and ionic balance of

any cell. Chemicals may injure cells during the process of metabolism or elimination. Carbon tetrachloride, for example, causes little damage until it is metabolized by liver enzymes to a highly reactive free radical, and then it is extremely toxic to liver cells. Carbon monoxide has a special affinity for the hemoglobin molecule, and it reduces the ability of this molecule to carry oxygen.

Lead likely acts on the central nervous system by interference with neurotransmitters; this may cause hyperactive behavior. Manifestations of brain involvement include convulsions and delirium. Peripheral nerve involvement may cause wrist, finger, and foot paralysis. Lead inhibits enzymes that are involved in hemoglobin synthesis; anemia is seen in lead toxicity.

Alcohol (ethanol) is the favorite mood-altering drug in the United States. Liver and nutritional disorders are serious consequences of alcohol abuse. The hepatic changes, which are initiated by ethanol conversion to acetaldehyde, include deposition of fat, enlargement of the liver, interruption of transport of proteins and their secretions, increase in intracellular water, depression of fatty acid oxidation, increased membrane rigidity, and acute liver cell necrosis. In the central nervous system, alcohol is a depressant that initially affects subcortical structures. Consequently, motor and intellectual activities become disoriented. At high blood alcohol levels, respiratory medullary centers become depressed. **Fetal alcohol syndrome (FAS)** caused by prenatal alcohol exposure can lead to growth retardation, cognitive impairment, facial anomalies, and ocular disturbances.

Unintentional and intentional injuries are important health problems in the United States, and death from these causes is more common in men than in women and in blacks and other racial groups than in whites. Injuries by **blunt force** result in tearing, shearing, or crushing of tissues; the most common blunt force injuries are caused by falls and vehicle accidents. A **contusion** is bleeding into the skin or underlying tissues as a consequence of a blow; when blood is contained in an enclosed space, it is called a **hematoma.** An **abrasion** results from the removal of the superficial layers of the skin caused by friction between the skin and an injuring object. A **laceration** occurs when the tensile strength of the skin or tissue is exceeded and a tear or rip results. An **incised wound** is a cut that is longer than it is deep, and a **stab wound** is deeper than it is long. A **gunshot wound** may be penetrating (bullet remains in the body) or perforating (bullet exits the body). **Asphyxial injuries** are caused when cells fail to receive or use oxygen, and they occur as a result of suffocation, strangulation, chemical exposure, or drowning.

Infectious agents produce injury by invading and destroying cells, producing toxins, or inducing hypersensitivity reactions. (Infection is discussed in Chapter 9.)

Immunologic and inflammatory injury are important causes of cellular injury. Cellular membranes are injured by direct contact with cellular and chemical components of the immune and inflammatory responses. Such mediators are lymphocytes and macrophages and chemicals such as histamine, antibodies, lymphokines, complement, and proteases. Complement, which is a serum protein, is responsible for many of the membrane alterations that occur during immunologic injury. Membrane alterations are associated with the rapid leakage of potassium out of the cell and the rapid influx of water. Antibodies can interfere with membrane function by binding to and occupying receptor molecules on the plasma membrane. (Later chapters deal with these injurious consequences and with hypersensitivity and autoimmune disease.)

Genetic disorders may alter the cell's nucleus and the plasma membrane's structure, shape, receptors, or transport mechanisms. (Mechanisms that cause genetic abnormalities are discussed in Chapters 4 and 5.)

Nutritional imbalances are important because cells require adequate amounts of proteins, carbohydrates, lipids, vitamins, and minerals to function normally. If inadequate or excessive amounts of nutrients are consumed and transported, pathophysiologic cellular effects can develop.

Proteins are the major structural units of the cell, and they participate in many enzymatic and hormonal functions. With lowered plasma proteins, particularly albumin, fluids move into the interstitium and produce edema. Children with protein malnutrition are very susceptible to and often die from infectious diseases.

Glucose is the major carbohydrate obtained from the breakdown of starch. Hyperglycemia (excessive glucose in the blood), if caused by excessive carbohydrate intake, may lead to obesity. Deficiencies of glucose result from starvation or from inadequate use, as in diabetes. In both of these conditions, the body compensates by metabolizing lipids to obtain cellular energy. In lipid deficiency, the body compensates by mobilizing fatty acids from adipose tissue; this causes an increase in the production and circulation of acidic ketone bodies. Severe increases in ketone bodies can cause coma or death. Hyperlipidemia, which is an increase in lipoproteins in the blood, results in deposits of fat in the heart, liver, and muscle.

Vitamins are involved in many reactions, including metabolism of visual pigments (vitamin A), calcium and phosphate metabolism (vitamin D), prothrombin synthesis (vitamin K), and antioxidation reactions (vitamin E). Vitamin B affects amino acid transfer reactions; flavin adenine dinucleotide (FAD), FMN, and nicotinamide adenine dinucleotide (NAD) help transfer electrons. Deficiencies in vitamin C cause poor wound healing and scurvy. Vitamin D deficiency causes rickets and problems with healing of fractures. Folate deficiency is associated with plasma and membrane changes of the red blood cell, and it is particularly a problem in individuals with severe liver dysfunction. Vitamin deficiencies are associated with several other disease states, including cancer.

Injurious physical agents include temperature extremes, changes in atmospheric pressure, radiation, illumination, mechanical factors, noise, and prolonged vibration. Physical injury is often environmental.

The **temperature extremes** of chilling or freezing of cells cause hypothermic injury directly by creating high intracellular sodium concentrations. This results from the

formation and dissolution of ice crystals. Indirect forms of injury like vasoconstriction paralyze vasomotor control, and vasodilation follows, with increased membrane permeability; this causes cellular and tissue swelling. Hyperthermic injury from excessive heat varies depending on the nature, intensity, and duration of the heat. Burns cause extensive loss of fluids and plasma proteins. Also, intense heat damages temperature-sensitive enzymes and the vascular endothelium and causes coagulation of the blood vessels.

Sudden increases or decreases in **atmospheric pressure** cause blast injury. In air blast or explosive injuries, tissue injury is caused by compressed waves of air against the body. The pressure changes may collapse the thorax, rupture solid internal organs, or cause widespread hemorrhage. In increased pressure caused by immersion blast, water pressure is applied suddenly to the body, and the body is forced up out of the water. The positive pressure compresses the abdomen and ruptures hollow internal organs such as the spleen, kidneys, and liver. With sudden decreases in pressure, carbon dioxide and nitrogen normally dissolved in the blood leave solution and form tiny bubbles (gas emboli) that obstruct blood vessels; this is seen in rapidly ascending deep sea divers and underwater workers. At low atmospheric pressure (above 15,000 feet), there is a decrease in available oxygen; this causes hypoxic injury. The compensatory vasoconstriction shunts the blood from the peripheral circulation to the visceral organs, including the lungs. The combination of increases in pulmonary blood flow and systemic hypoxia causes pulmonary edema, which is also known as interstitial water excess.

Ionizing radiation is any form of radiation capable of removing orbital electrons from atoms. Ionizing radiation is emitted by x-rays, gamma rays, and the process of radioactive decay. Radiant energy from sunlight can also injure cells. DNA is the most vulnerable target of radiation, particularly the bonds within the DNA molecule. Irradiation during mitosis produces chromosome aberrations, and membrane molecules and enzymes are also damaged by radiation. Radiosensitivity depends on the rate of mitosis and cellular maturity. The more numerous the mitotic figures, the greater is the sensitivity; more maturity equals less sensitivity. Particularly vulnerable cells are embryonic germ cells, which are precursors of ova and sperm. Throughout life, cells of the bone marrow, intestinal mucosa, testicular seminiferous epithelium, and ovarian follicles are susceptible to injury, because they are always undergoing mitosis.

Exposure to x-radiation and gamma radiation is most strongly correlated with leukemia and cancers of the thyroid, breast, and lung. Radiation exposure in children may increase the incidence of lymphomas and melanomas. Radiation exposure is significantly related to cardiovascular disease, hypertension, and elevated cholesterol levels. Studies of late effects in survivors of atomic bombs reveal elevated levels of mediators of inflammation and immune globulins.

The harmful effects of **illumination** in fluorescent lighting include eye strain, obscured vision, and possible cataract formation. Emission of ultraviolet radiation from halogen lamps is thought to be in the range of wavelengths responsible for inducing melanoma, which is a malignant skin growth.

Mechanical injury is caused by physical impact or irritation (e.g., a head injury when a worker is struck by a falling object). Most mechanical stresses, however, are subtle, and they can cause accumulative injuries and disorders over time. Mechanical stimulation of body tissues and cells is constant. When the forces exceed thresholds, injury results. The structural responses to deformation and strain mostly involve the cell membrane. Disruption of cell membranes, or **mechanoporation,** are central to progression of mechanical injury.

Noise is sound that has the potential for inflicting bodily harm. Noise trauma can be caused by acute loud noise or by the cumulative effects of various intensities, frequencies, and durations of noise.

Acoustic trauma is instantaneous damage and can rupture the eardrum, displace the ossicles of the middle ear, or damage the organ of Corti in the inner ear. Structural changes associated with prolonged exposure to loud sounds include intracellular changes in the sensory cells, swelling of the auditory nerve endings, and cochlear blood flow impairment. Noise-induced hearing loss is gradual and painless. Symptoms of noise-induced hearing loss include inability to hear soft sounds and tinnitus.

3. **Identify the various cellular accumulations and their causes and subsequent injuries.**
   Study text pages 76 through 79 and 81; refer to Figures 2-24 through 2-28. See Table on page 9.
4. **Identify systemic manifestations and causes of cellular injury.**
   Refer to Table 2-10. See Table on page 9.
5. **Identify the major types of cellular necrosis, and cite examples of the tissues involved in each type. Compare necrosis to apoptosis.**
   Study text pages 81 through 85; refer to Figures 2-29 through 2-36.

Necrosis is local cell death, and it involves the process of cellular self-digestion known as autodigestion or autolysis. As necrosis progresses, most organelles are disrupted, and **karyolysis**, which is the nuclear dissolution from the action of hydrolytic enzymes, becomes evident. **Pyknosis** is a process wherein the nucleus shrinks and becomes a small, dense mass of genetic material. **Karyorrhexis** is nuclear fragmentation into smaller particles or "nuclear dust." There are four major types of necrosis: coagulative, liquefactive, caseous, and fat. Gangrenous necrosis is not a distinctive type of cell death; rather, it refers to large areas of tissue death.

Coagulative necrosis occurs primarily in the kidneys, heart, and adrenal glands and usually results from hypoxia caused by severe ischemia. Protein denaturation causes coagulation. An increased intracellular level of calcium may be a critical event in coagulation necrosis.

Liquefactive necrosis is common after ischemic injury to neurons and glial cells in the brain. Because brain cells are rich in digestive hydrolytic enzymes and

Cellular Accumulations

Accumulation	Causes	Injury
H_2O	Reduced ATP and ATPase, sodium accumulates in cell, extracellular H_2O shifts into cell	Cellular swelling, vacuolation, hydropic degeneration
Lipids, carbohydrates	Imbalance in production, utilization, or mobilization of lipid or carbohydrates	Vacuolation, displaced nucleus and organelles; leads to fibrosis and scarring
Glycogen	Genetic disorders, diabetes mellitus	Cytoplasmic vacuolation
Proteins	Enzymes digesting cellular organelles, renal disorders, plasma cell tumor	Disrupted function and intracellular communication, displaced cellular organelles
Pigments	Exogenous particle ingestion, UV light stimulating melanin production, malignancy, loss of hormonal feedback, genetic defects, bruising and hemorrhaging increasing hemosiderin, liver dysfunction	Membrane injury
Calcium	Altered membrane permeability, influx of extracellular calcium, excretion of H^+ leading to more OH^- that precipitates Ca^{++}, endocrine disturbances	Hardening of cellular structure; interferes with function
Urate	Absence of enzymes	Crystal deposition, inflammation

Systemic Manifestations of Cellular Injury

Manifestation	Cause
Fever	Endogenous pyrogens released by inflammatory response
Increased heart rate	Fever raises the metabolic rate
Pain	Bradykinins released, obstructive pressures
Extracellular fluid (blood) enzymes*	Released from injured cells or tissues

*Specific enzymes, such as creatine kinase (CK), lactic dehydrogenase (LDH), or amylase, are released from injured hearts, kidneys, skeletal muscles, among others.

lipids, the brain cells are digested by their own hydrolases. The brain tissue becomes soft and liquefies, and is walled off from healthy tissue to form cysts. Liquefactive necrosis can also result from bacterial infections. Here, the hydrolases are released from the lysosomes of phagocytic neutrophils that are attracted to the infected area to kill the bacteria; these hydrolases also destroy brain tissue. The accumulation of pus is present in liquefaction necrosis.

Caseous necrosis is commonly seen in tuberculous pulmonary infection and is a combination of coagulative and liquefactive necrosis. The necrotic debris is not digested completely by hydrolases, so tissues appear soft and granular and resemble clumped cheese. A granulomatous inflammatory wall may enclose the central areas of caseous necrosis.

Fat necrosis, found in the breast, pancreas, and other abdominal structures, is a specific cellular dissolution caused by lipases. Lipases break down triglycerides and release free fatty acids that then combine with calcium, magnesium, and sodium ions to create soaps (a process known as saponification). The necrotic tissue appears opaque and chalk white.

Gangrenous necrosis refers to the death of tissue, usually in considerable mass and with putrefaction. It results from severe hypoxic injury subsequent to arteriosclerosis or blockage of major arteries followed by bacterial invasion. Dry gangrene is usually due to a coagulative necrosis, and wet gangrene develops when neutrophils invade the site and cause liquefactive necrosis. Gas gangrene, which is a special type of gangrene, is caused by the bacterial infection of injured tissue by a species of *Clostridium.* These anaerobic bacteria produce hydrolytic enzymes and toxins that destroy connective tissue and the cellular membrane; bubbles of gas likely form in muscle cells.

Apoptosis is an important, distinct type of cell death that differs from necrosis. It is an active process of cellular self-destruction in both normal and pathologic tissue changes. Apoptosis likely plays a role in the deletion of cells during embryonic development and in endocrine-dependent tissues that are undergoing atrophic change. It may occur spontaneously in malignant tumors and in normal, rapidly proliferating cells treated with cancer chemotherapeutic agents and ionizing radiation. The progression of apoptosis depends on specific signaling

molecules that interplay among subcellular compartments. Proteases, in response to signals, cleave key proteins in the cell, thereby killing the cell quickly and neatly. Unlike necrosis, apoptosis affects scattered, single cells and results in shrinkage of a cell; whereas in necrosis, cells swell and lyse.

6. Describe theories of aging.

Study text pages 87 through 90; refer to Figure 2-37 and Table 2-11.

There are two general theories of aging: (1) aging is caused by the accumulations of injurious events, which are sometimes called damage-accumulation theories; or (2) aging is the result of a genetically controlled developmental program. In support of these two categories, three mechanisms of aging have emerged: (1) genetic, environmental, and behavioral factors produce cellular aging change; (2) changes in regulatory mechanisms, especially in the cells of the endocrine, immune, and central nervous systems, are responsible for aging; and (3) degenerative extracellular and vascular alterations cause aging.

Regardless of injurious environmental factors, some believe that each cell may have a finite life span during which it can replicate. Fibroblasts have been demonstrated to be limited to 40 to 60 cell doublings. Alternatively, an intrinsic program within the human genome progressively slows or shuts down mitosis.

Alterations of cellular control mechanisms include increased hormonal degradations, decreased hormonal synthesis and secretion, and decreased receptors for hormones and neuromodulators. This suggests that a genetic program for aging is encoded in the brain and relayed through hormonal and neural agents because of shared, common receptors within these systems.

Immune function declines with age and the number of autoantibodies that attack body tissues increases with age; these observations implicate the immune system in the aging process.

A degenerative extracellular change that affects the aging process is collagen cross-linking, which makes collagen more rigid and results in decreased cell permeability to nutrients. Free radicals of oxygen are believed to damage tissues during aging. These reactive species not only permanently damage cells but also may lead to cell death. Damage accumulates over time and reduces the body's ability to maintain a steady state.

Frailty is a wasting syndrome of aging. The syndrome invokes decreased protein synthesis, muscular mass and strength decline, and neuroendocrine and immune dysfunction.

7. Characterize somatic death and its manifestations.

Study text page 90.

Somatic death is death of the entire organism. Unlike the changes that follow cellular death in a viable body, somatic death is diffuse and does not involve components of the inflammatory response, which is a vascular response to injury. The most notable manifestations of somatic death are complete cessation of respiration and circulation, skin surface usually becoming pale and yellowish, and body temperature falling gradually until, after 24 hours, body temperature equals that of the environment. Within 6 hours after death, depletion of ATP interferes with ATP-dependent detachment of the contractile proteins, and muscle stiffening, or rigor mortis, develops. Within 12 to 14 hours, rigor mortis usually affects the entire body. Rigor mortis gradually diminishes as the body becomes flaccid because of the release of enzymes and lytic dissolution.

PRACTICE EXAMINATION

Multiple Choice

Circle the correct answer(s) for each question.

1. A deranged cellular growth observable in uterine cervical epithelium is:
   a. atrophy.
   b. hyperplasia.
   c. hypertrophy.
   d. dysplasia.
   e. metaplasia.
2. What is the consequence when a cell is forced into anaerobic glycolysis?
   a. Insufficient glucose production
   b. Excessive pyruvic acid retention
   c. Increased lactic acid production
   d. Excessive CO_2 production
3. What is the probable cause of cellular swelling during the early stages of cell injury?
   a. Fat inclusion
   b. Loss of genetic integrity
   c. Hydrolytic enzyme activation
   d. Na^+, K^+ pump fails to remove intracellular Na^+
4. Calcification:
   a. alters membrane permeability.
   b. is the result of low calcium levels in the blood.
   c. is caused by UV light.
   d. is caused by hypoparathyroidism.
5. Cellular swelling is:
   a. reversible.
   b. evident early in all types of cellular injury.
   c. associated with hyperkalemia.
   d. extracellular movement of fluid.
6. Which of the following is irreversible?
   a. Karyolysis
   b. Fatty infiltration
   c. Hydropic degeneration
   d. Glycogen formation
7. Aging:
   a. likely involves autoantibodies.
   b. does not have a genetic relationship.
   c. results from damage accumulation.
   d. decreases hormonal degradation.
8. In the theories of aging, cross-linking implies that:
   a. the life span and number of times a cell can replicate are programmed.
   b. the number of cell doublings is limited.
   c. there is oxygen toxicity.
   d. cell permeability decreases.

Matching

Match the descriptor with its appropriate condition.

_____ 9. Caused by tuberculosis infection

_____ 10. Rigidity of muscles after somatic death

_____ 11. Increased tissue mass because of increased cell numbers

_____ 12. Results from lysosomal release of hydrolytic enzymes

_____ 13. Replacement of one cell type with another, more suitable type

a. liquefactive necrosis

b. rigor mortis

c. caseous necrosis

d. hyperplasia

e. metaplasia

f. cellular swelling

g. coagulation necrosis

Match the circumstance with the appropriate condition.

_____ 14. Disruption of cell membranes

_____ 15. Pancreatic necrosis

_____ 16. Coagulative and liquefactive necrosis

_____ 17. Tissue death

_____ 18. Normal and pathologic cellular self-destruction

a. fatty necrosis

b. gangrene

c. mechanoporation

d. caseous necrosis

e. apoptosis

f. algor mortis

g. hypertrophy

Match the consequence with its cause.

_____ 19. Lipid peroxidation

_____ 20. Neurotransmitter interference

_____ 21. Asphyxiation

_____ 22. Depressed fatty acid oxidation

_____ 23. Depressed protein synthesis

a. carbon monoxide

b. oxygen-derived free radicals

c. ethanol

d. lead

e. detached ribosomes

f. increased lactate

g. lysosomal edema

Fill in the Blanks

Supply the correct response for each statement.

24. During reperfusion with oxygen, _____ is produced, which creates superoxides, hydrogen peroxide, and free radicals.

25. Specific enzymes such as _____ are released into extracellular fluids during muscular injury.