CHAPTER 2

Cell Injury, Adaptation, and Death

This chapter discusses the natural and pathologic life and death of cells and how they change with disease, covering biologic aging as well as distinguishing between mild and severe cell injury.

BACK TO BASICS
• The Origins of Cells and the Organization of Tissues
• The Nucleus
• The Cytoplasm
• The Cell Membrane
• The Cell Cycle
• Cellular Communication

BIOLOGIC AGING
• Cell Injury and Disease
  MILD CELL INJURY
  • Intracellular Accumulations
  • Adaptations of Cell Growth and Differentiation
  SEVERE CELL INJURY AND CELL DEATH

Learning Objectives

After studying this chapter you should be able to:
1. Offer a brief description of the basic organization of a cell and of the organization of tissues, organs, and organ systems
2. Explain how the genetic code is written into DNA
3. Explain the role of messenger RNA
4. Explain the role of mitochondria
5. Explain how DNA replicates during cell division (mitosis)
6. Differentiate between apoptosis and necrosis
7. Explain the relationship between injury and disease
8. Explain the relationship of genes and environment in the pathogenesis of disease
9. Name the most common cause of cell injury
10. Name one cell reaction resulting from mild acute cell injury and one resulting from mild chronic injury
11. List at least two causes of cell atrophy
12. Differentiate between hypertrophy and hyperplasia
13. Define dysplasia
14. Define metaplasia and offer an example
15. Name the consequence of severe, irreversible cell injury
16. Name the most common cause of necrosis and the most common type of necrosis
Modern understanding of the nature of disease began with the great 19th century German pathologist Rudolph Virchow (1821-1902), who introduced the concept of cellular pathology and argued that injured cells were the cause of all disease. Virchow’s observations finally put to rest the ancient belief that all illness was an affliction of the body at large caused by one of four “humors”—phlegm, blood, black bile, or yellow bile. Virchow understood that cells collect together to form tissues, tissues collect to form organs, and organs collect into systems that compose the body. Subsequent scientists discovered the anatomic and chemical constituents of the cell, demonstrating that all cells have three main elements—nucleus, cytoplasm, and cell membrane.

**The Origins of Cells and the Organization of Tissues**

Every cell is derived from one of three primitive embryologic tissues: ectoderm, endoderm, and mesoderm. Ectoderm differentiates into hair, nails, and epidermis—the superficial layer of skin—and into brain and nerves.
Endoderm differentiates into the internal lining (mucosa) of the intestinal and respiratory tracts and into the liver and pancreas. Mesoderm differentiates into the deep layer of skin (dermis), bone, skeletal muscle, blood vessels, smooth muscle—including the muscular wall of the gastrointestinal tract—pleura, peritoneum, pericardium, and the urinary system and gonads.

With the exception of skin, bone, muscle, and ductless glands (endocrine glands), all organs can be conceived of as hollow tubes surrounded by tissue. Even the brain and spinal cord are hollow, tubular structures. The ventricles and canals are in the center; however, the hollow space is small compared to total organ mass. Similarly, the liver and other ducted glands can be conceived of as a network of small, hollow tubes—ducts—to which a large number of specialized cells are attached.

Epithelium is a sheet of cells that covers a body surface or lines the hollow interior of an organ or its ducts. Epithelium rests on a basement membrane, a thin film of non-cellular tissue. There are two types of epithelial cells: columnar (tall and thin) and squamous (like fish scales; from Latin squama, for scale). Gland ducts (such as pancreatic or breast ducts) and the intestine are hollow tubes lined by a shoulder-to-shoulder layer of columnar epithelial cells. Conversely, squamous epithelial cells are layered, shingle-like to form the covering layer (epidermis) of skin, and they line the vagina, oral cavity, and esophagus.

The specialized cells of an organ form the parenchyma (e.g., hepatocytes in the liver, or neurons in the brain). Parenchymal cells are held together by a supporting network of stroma—fibrocytes and collagen and elastin fibers—whose purpose is to maintain structural integrity and to provide space through which blood vessels and nerves can travel.

**THE NUCLEUS**

The critical parts of a cell are illustrated in Figure 2-1. Every living cell has a nucleus, with the exception of red blood cells (RBC), which expel their nucleus upon entering the circulation in order to have maximum room for hemoglobin to carry oxygen. The nucleus is organized into a round mass floating in the middle of each cell.
cell and is composed of nuclear proteins, which are large molecules composed of multiple amino acids. The proteins of the nucleus are deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). DNA has two purposes: 1) to duplicate itself during cell division and 2) to code for proteins to be synthesized by elements of the cytoplasm. RNA carries DNA messages from the nucleus into the cytoplasm, the fluid part of the cell surrounding the nucleus.

DNA is constructed of building blocks known as nucleotide bases, small molecules that are strung together in a long chain. A gene is a segment of DNA with a specific task: to code for a protein to be made by a cell. Many genes are combined to form a chromosome (Fig. 2-2). There are 46 chromosomes, 23 from the ovum and 23 from the sperm. In humans this parental set of 23 is referred to as the haploid number. People with a normal haploid set from each parent are said to be genetically diploid, or euploid (chromosomally normal). Each gene governs production of a single protein or variations of that protein; these proteins in turn influence every molecular event in life. For example, a gene on chromosome 9 governs major blood group type, determining whether a person is blood type A, B, AB, or O (Chapter 8).

DNA is a very, very long molecule composed of sequences of four small molecules, the nucleotide bases: adenine (A), thymine (T), guanine (G), and cytosine (C). The sequence of these bases is the genetic code. A short sequence might be . . . AAACGTGCCATC . . . ; however, the actual code is thousands of bases long. Two strands of these molecules are twisted together like a rope to form the complete DNA molecule. As is illustrated in Figure 2-2, each nucleotide base has a “handshake” link with a matched companion base on the other strand of DNA—guanine (G) and cytosine (C) always link together, while thymine (T) is always matched to adenine (A) on the other side.

DNA sends its commands to the cytoplasm by synthesizing RNA. RNA is composed of the same nucleotide bases as DNA, with one exception: in RNA uracil (U) replaces the thymine (T) found in DNA. Furthermore, RNA is a single molecular strand, not a twisted double strand like DNA. There are several types of RNA, one active in the nucleus, the others active in the cytoplasm. As is illustrated in Figure 2-3, DNA synthesizes RNA and transcribes its code into it. This initial RNA is messenger RNA (mRNA), which carries the code across the nuclear membrane and into the cytoplasm, where it requires the help of transfer RNA (tRNA) to pass the code to ribosomes composed of ribosomal RNA (rRNA), which are where proteins are made.

**THE CYTOPLASM**

Elements of the cytoplasm are illustrated in Figure 2-1. The fluid component of cytoplasm is the cytosol, com-
RNA synthesis. DNA synthesizes RNA by transcribing its code to messenger RNA (mRNA). Notice that RNA is only a single strand of bases coded from a single strand of DNA.

MITOCHONDRIA AND THE HISTORY OF HUMANKIND

Among the more interesting facts about mitochondria is that they have their own DNA, mitochondrial DNA (mDNA), which is completely independent of nuclear DNA and, stranger still, it is inherited from the mother only—human eggs are full of mitochondria; sperm have only a few. After fertilization of the egg, paternal mitochondria are destroyed. The result is that we get our all of our mDNA from our mother. She got it from her mother, who got it from hers—and so on back in time. This unique fact has helped answer one of the most fundamental human questions: “Who am I?”

The immediate answer depends on knowing your ancestors, but with the passage of each generation the trail becomes murkier and is soon lost a few generations back. DNA analysis (Chapter 7) of families and ethnic groups has been helpful in clarifying relationships and extending genealogical trees. The analysis depends on the regularity of innocent mutations of mDNA that occur in every person, which produce a unique “fingerprint” that is passed along to subsequent generations.

But of the grander question “Who are we?”, mitochondrial DNA provides strong scientific evidence suggesting modern humans (Homo sapiens) appeared first on the east African plains between 100,000 and 200,000 years ago. Mutations (changes of DNA base sequences) occur in mitochondrial DNA as they do in nuclear DNA; and they occur at a very regular rate, so that it is possible to calculate the theoretical date at which all of the sequences merge into one “mitochondrial Eve.” It was about 175,000 years ago. Modern humans began their worldwide spread by crossing the Red Sea from Africa into the Middle East about 50,000 years ago.
posed mainly of water, in which are floating small structures—cytoplasmic organelles. The main organelles are mitochondria (see Basics in Brief 2-1), ribosomes, endoplasmic reticulum, the Golgi apparatus, and lysosomes. Also, some cells have specialized cytoplasmic organelles; for example, glandular cells contain secretory vacuoles, and muscle cells contain contractile protein filaments.

Mitochondria produce the energy required for all metabolic processes. They are shaped somewhat like elongated, intracellular bacteria. Mitochondria are formed of an external membrane with many internal folds, and they are packed with enzymes that consume oxygen and chemical foodstuffs (glucose, fatty acids, and amino acids) to create the chemical energy that powers metabolism. In the process, carbon dioxide, water, and heat are produced. The latter accounts for body temperature.

Ribosomes are tiny granules composed of ribosomal RNA (rRNA). As is illustrated in Figure 2-4, ribosomes manufacture amino acids and string them together to form proteins. Each amino acid component of a protein is coded by sequential sets of three nucleotide bases (that is, by a particular sequence of A, C, T, or G). The DNA code for the amino acid methionine is TAC, and for glycine the code is CCG. Therefore, a protein con-

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**Figure 2-4 Protein synthesis.** In the nucleus, the genetic code from DNA is transcribed into messenger RNA (mRNA), which carries the code to ribosomes, where the code is translated into amino acids. The amino acids are joined together in a particular sequence to form a specific protein, which is then used internally or exported from the cell into interstitial fluid.
taining methionine attached to glycine would originate with the DNA base sequence TACCCG. In this way a protein composed of a long string of amino acids is originally coded by a long set of DNA bases, transferred by matching sequences of messenger RNA, which carries the code to ribosomes that use it to synthesize protein.

The endoplasmic reticulum is a folded network of membranes that connect with the nucleus on one side and the cytoplasmic membrane on the other. Rough (granular) endoplasmic reticulum (RER) has ribosomes attached to its surface. RER accepts messenger RNA from the nucleus and delivers packets of synthesized proteins into either the cytoplasm or into the extracellular space (the interstitial fluid) for further distribution to nearby cells or into blood. For example, insulin is synthesized by the rough endoplasmic reticulum of the beta cells of the pancreatic islets of Langerhans (Chapter 17) and is secreted into blood for distribution throughout the body as a key ingredient in cellular glucose metabolism. One of the two main types of diabetes is caused by a deficiency of cellular insulin synthesis.

Smooth endoplasmic reticulum (SER) has a number of complex functions, the two most important of which are synthesis of steroids and the metabolic breakdown of drugs and other molecules. Liver cells have a large amount of SER because they degrade and excrete drugs and products of metabolism in other parts of the body.

The Golgi apparatus is a hollow metabolic cytoplasmic organelle somewhat like a balloon collapsed upon itself into multiple folds. It accepts packets of protein from the endoplasmic reticulum, biochemically modifies them, stuffs them into packets, and releases them into the cytoplasm. These free-floating, intracellular packets may 1) remain in the cytoplasm as packets of enzymes (lysosomes) or storage vesicles; 2) be incorporated into the cell membrane; or 3) be expelled from the cell into the extracellular space. For example, lipoproteins (Chapter 12) are formed in the Golgi complex of liver cells and are expelled from the cell and absorbed into blood.

Lysosomes are packets of lytic (digestive) enzymes surrounded by a membrane. They originate from the Golgi complex and may remain in the cell, either to destroy foreign material ingested by the cell or to metabolize foodstuff molecules for further cell metabolism. Lysosome activity is exemplified by neutrophils, a type of white blood cell that accumulates quickly in injured tissue (Chapter 3). Neutrophil cytoplasm contains lysosomes, which by conventional microscopy are a neutral (pale) tan, hence the name. Neutrophils are phagocytes (they ingest things) that swallow bacteria and foreign material to kill or digest it.

**THE CELL MEMBRANE**

The plasma membrane (cell membrane) is illustrated in Figure 2-5. It forms the outer surface of the cell and controls interaction between the cell and its environment. Just as skin separates and protects the body’s inner parts from the environment, the cell membrane keeps cell cytoplasm separated from the interstitial fluid. Rupture of the membrane usually results in cell death (necrosis). Because most of the cytoplasm and interstitial fluid is composed of water, the membrane is composed mainly of lipids (lipid means “fat soluble”), which allow limited passive diffusion of small molecules. Large molecules require active transport, controlled by membrane proteins that act as channels through which some proteins leave the cell. Additional proteins lie on the outer surface of the cell membrane and act as receptors, latching onto molecules that regulate cell activity. Other surface proteins are enzymes that speed up reactions on the cell surface.

In addition to the molecular-scale (microscopic) activities described above, the cell membrane engages in larger-scale (macroscopic) actions. Phagocytosis and exocytosis are bulk transfer mechanisms. Phagocytosis (Fig. 2-1) is the ingestion of bacteria and similarly large bits of outside material through the membrane and into cytoplasm. Exocytosis is the reverse—passage of packets of material from the cytoplasm into the extracellular fluid. Material expelled by exocytosis can be the remains of ingested material or substances synthesized in the cell.

A cell membrane may contain specialized structures. Microvilli are tiny, closely packed, short, hair-like projections of cell membrane on cells that need increased surface area for absorptive purposes—the internal margin of intestinal epithelial cells is an example. Cilia are much larger than microvilli and are long hair-like structures that project from the cell membrane and sway together with cilia of nearby cells in waves to move material from one point to another in hollow organs. Cilia of cells lining the bronchi and trachea move mucus and inhaled particles up the tracheobronchial tree, where they can be coughed out or swallowed; and cilia in the fallopian tube move ova (fertilized or unfertilized) down the tube to the uterine cavity.

**THE CELL CYCLE**

Mitosis see Basics in Brief 2-2 is the division of one cell into two identical daughter cells. During mitosis chromosomes line up single-file around the equator of the parent cell. The two strands of DNA unravel, and one strand goes to each daughter cell. Figure 2-6 illus-
Figure 2-5 The plasma membrane. This membrane consists primarily of phospholipid molecules oriented so that the lipid segment is in the center of the membrane, and the phosphate (water-soluble) segment faces interstitial fluid on the outside and cytoplasm on the inside. The membrane also contains proteins, carbohydrates, and cholesterol, which serve special functions.

**BASICS IN BRIEF 2-2**

**MITOSIS VERSUS MEIOSIS**

Mitosis is cell division of the type that occurs in somatic (non-germ) cells, the cells that compose every organ in the body except some of the cells in the gonads. In mitosis every chromosome (all 46 of them) divides, half going into one cell, half into the other, so that each new cell contains 46 chromosomes.

Meiosis is cell division of the type that occurs only in ovarian and testicular germ cells (the precursor cells of ova and sperm). In meiosis chromosomes line up in matched pairs and one of each goes into the new cells. For example, both number 21 chromosomes line up side by side—one entire chromosome destined for one offspring ovum or sperm, the other destined for the other. Ova and sperm, therefore, contain 23 chromosomes, not 46. Thus, when one ovum and one sperm combine fertilization the new conceptus has a normal complement of 46 chromosomes.
Figure 2-6 DNA replication. A. DNA before division. B. DNA begins to unravel, with each strand attracting new nucleotide bases. C. Cell division continues as new nucleotide bases attach to each strand to form a coil of new DNA. D. Cell division is complete. Each new cell contains an exact copy of the parent chromosome’s DNA.
trates the process. After unraveling, the nucleotide bases in each strand capture a partner base in the “chemical soup” of the cytoplasm—glycine (G) grabs onto a cytosine (C) molecule, and adenine (A) to a new thymine (T), and so on. These newly captured nucleotides then link sideways to one another to form a new strand of DNA identical to the strand lost to the new daughter cell. The result is a newly formed DNA chain with two intertwined strands of nucleotide bases. The original DNA molecule has thus become two; one in each new daughter cell. The DNA in each daughter cell is identical to the DNA of the parent cell, which ensures perpetuation of the original genetic code from one generation of cells to another.

Cell reproduction is either promoted or restrained by pro- or anti-growth genes. Anti-growth genes synthesize growth inhibition proteins and are called tumor suppressor genes because unsuppressed cell growth may grow uncontrollably into a tumor. A very important tumor suppressor is the p53 gene. Over 50% of all cancers contain an ineffective, mutated (abnormal) p53 gene, which fails to suppress cell growth. Conversely, some genes that stimulate cell growth (proto-oncogenes) are capable of mutation into genes (oncogenes) that promote uncontrolled cell overgrowth and the formation of tumors.

Cells differ in their ability to proliferate. Some cells (labile cells) reproduce continuously; some (stable cells) are quiet and reproduce very slowly until stimulated (by injury, for example); and others (permanent cells) never divide—they must last a lifetime. Cells of the epidermis and epithelial cells lining the GI tract are labile cells, and they divide continuously and are renewed every few days, a feature that ensures a constant supply of fresh cells to face the harshness of the outside environment and intestinal lumen. Liver, kidney, and pancreas cells, stable cells, divide slowly but can reproduce rapidly in response to injury. Brain and muscle cells are permanent cells and cannot reproduce.

**CELLULAR COMMUNICATION**

Normal function requires that cells influence one another. As is illustrated in Figure 2-7, influence is communicated by chemicals known as hormones. There are three varieties of hormones: autocrine, paracrine, and endocrine. Autocrine hormones act on the cell that produced them; paracrine hormones diffuse through interstitial fluid to act on nearby cells; and endocrine hormones are transported by blood to act on cells at a distant site.

Hormones are essential in the maintenance of cells, tissues, organs, and organ systems in a balanced, steady state of equilibrium known as homeostasis, a word derived from Greek *homoios* (steady) and *stasis* (state). External events may upset this equilibrium or move it to a faster or slower rate for some period of time, during which a new steady state may exist for a while; for example, running increases the heart rate. However, such deviations are temporary and cannot be maintained indefinitely without injury. If demand exceeds adaptive capacity, an injurious imbalance may occur. For example, if blood sugar rises, the pancreas secretes insulin into blood to reduce it by enabling cells to use more. However, if the patient is diabetic and lacks enough functioning beta cells in the islets of Langerhans, demand for insulin may exceed the ability of the pancreas to respond, and diabetic acidosis or coma may occur.
**Biologic Aging**

We all labour against our own cure, for death is the cure of all diseases.

*SIR THOMAS BROWNE (1605–1682), ENGLISH PHYSICIAN AND AUTHOR*

Cells age and die like every other living thing. It is a normal, physiologic process distinct from disease. Natural, physiologic, planned cell death is **apoptosis**—a programmed commitment to die. Many cells, mainly the rapidly proliferating labile cells of the epidermis and gastrointestinal epithelium, are genetically programmed to commit “suicide” after a few days. Cell death caused by disease is **necrosis**. Cell death, caused by either apoptosis or necrosis, releases cell substances into blood, where their concentration can be measured by laboratory tests.

It is also clear that as cells age they, like we, function with less efficiency. Just as a 70-year-old person cannot run as far or as fast as a teenager can, old cells do not function as well as young ones do. Old cells burn energy less efficiently and do not make DNA and proteins as well as young ones can. Cell nuclei, mitochondria, and other cell parts become deformed and less functional in old cells. As a result we and our cells adapt less effectively to environmental stress. For example, as we age our heat muscle loses some of its contractile power, our kidneys are less efficient at filtering waste, and nerve conduction (reflexes, for example) is slower. Interestingly, modern medicine has improved the average life span of humans, but the maximum life span has not changed. It has been about 100 years for centuries.

How cells age is not completely clear, but genes play an important role. In tissue culture normal cells do not continue to divide much beyond 50 doublings (generations). However, cancer cells, which have abnormal DNA, divide endlessly. An interesting feature of DNA that appears to play an important role in cell aging is the **telomere**, a cap of nucleotide bases on the end of each strand of DNA that does not reproduce with each cell division. Instead, it loses a few nucleotide bases with each cell replication. Telomeres are, in effect, genetic debit cards preloaded with a certain number of ticks. Reproduction stops when the account is emptied, and the cell dies.

That genes are important in aging is also clear from the study of patients with **progeria** and **Werner syndrome**. Both are rare genetic diseases associated with early aging and short life span. Early in life these patients develop gray hair, cataracts, atherosclerosis, diabetes, wrinkled skin, and other attributes of old age, and they die very young.

**Cell Injury and Disease**

All disease occurs because of injury. Severe injury causes cell death (necrosis). Mild injury or stress, however, induces cells to alter and adapt without dying. Cellular adaptations may occur in cells pushed to physiologic extremes by unusual physiologic demand. Regardless of the cause, cell adaptations return to normal once the stress or injury is relieved. The process of cell injury or stress and reactions to it are depicted in Figure 2-8.

→ All disease is caused by injury.

Injury may occur at the molecular level or any level above it—at the level of cells, tissues, or organs. Cancer is an example of injury that arises at the molecular level.
injured DNA is the root cause of cancer. However, injury is not confined to the level of molecules and cells, as anyone with a broken bone can testify. Our genes influence how we react to injury. Some people are more predisposed than others to develop severe disease from a given injury. Genes may be thought of as the soil in which the seed of injury is planted; some soil is fertile to certain seeds and less fertile to others. Some persons (very few) can eat all the cheeseburgers they want and not develop high cholesterol (Chapter 12), but others (most of us) cannot remain healthy and eat a lot of fatty foods because our cholesterol rises and we develop atherosclerosis. Genes account for much of the difference between those who develop atherosclerosis and those who do not.

Disease may result from the injury itself or from the repair process that follows. Fatal hemorrhage from a gunshot wound is disease resulting directly from injury. On the other hand, the new blood vessel growth and scar formation that occurs as the body tries to repair an injured cornea can impair vision long after the original injury is resolved.

Cells can be injured in several ways:

- **Inadequate oxygenation** (hypoxia): Hypoxia is the most common cause of cell injury and is usually caused by insufficient arterial blood flow (ischemia). Ischemia usually affects a local block of tissue supplied by a single artery. However, generalized hypoxia may be produced by lung disease, some kinds of poison, and other conditions. Hypoxia initiates a series of chemical and acid-base imbalances that may be reversible if blood flow or oxygenation is restored; however, prolonged hypoxia produces cell death.

- **Direct physical action**. Mechanical force disrupts organ tissues on a large scale, altering their structure; hemorrhage and ischemia are major consequences. Ingested acids or alkalis may so profoundly alter blood pH that death ensues. Acids, alkalis, or heat may cause necrosis of skin, cornea, or mucosal surfaces. Low temperature may freeze cell water in skin (frostbite), from which cell necrosis occurs when ice crystals rupture cell membranes. Low body temperature may cause cardiac arrest subsequent to slowing of the heart's intrinsic pacemaker.

- **Ionizing radiation**: Ionizing radiation is radiation strong enough to break (ionize) water (H₂O) into H⁺ (hydrogen ion) and OH⁻ (hydroxyl ion). In acute radiation injury the hydroxyl ion attaches to DNA and prevents cell reproduction. For brain cells (permanent cells, which do not divide) and liver cells (stable cells, which divide slowly) this is of little consequence; however, for the bone marrow and gastrointestinal epithelium (rapidly dividing labile cells, which must be replaced daily), it is a disaster. In acute radiation injury, intestinal lining cells stop reproducing, and the lining sloughs away. The white blood cell count falls dramatically because white blood cells live only a few days and must be replaced daily. Loss of intestinal epithelium and decreased white blood cell count leave the body vulnerable to infection. Chronic radiation injury causes DNA mutations that may result in neoplasia.

- **Toxic molecular injury**: Virtually any natural or synthetic molecule can cause injury. Depending on the chemical, injury may occur in different organs and by different mechanisms. For example, heavy metals such as mercury and lead cause direct toxic injury to enzymes necessary for cell health. The effect of most
toxic molecules is dose related; fatal overdose of heroin is an example.

- **Microbes**: Bacteria often produce toxins that interfere with cell protein synthesis or cell oxygen utilization. For example, *Staphylococcus aureus* growing on unrefrigerated food produces a toxin that may cause food poisoning. The ingested toxin damages intestinal epithelial cells. The cell wall of some bacteria contains substances that are released into blood when the bacteria die. Typically these toxins cause vascular collapse (shock) or widespread blood clotting inside of blood vessels (Chapter 5). Viruses invade cells and kill from within: They disrupt the cell or nuclear membrane or incite an immune system (Chapter 8) response that, while aimed at the virus, kills the cell.

- **Inflammatory and immune reactions**: Inflammation and immune reactions are the result of cell injury, but they may in turn cause injury themselves. The neutrophils of acute inflammation (Chapter 3) release digestive enzymes designed to neutralize foreign agents, but they also digest nearby tissue. Immune reactions injure cells directly by several mechanisms, discussed in Chapter 8. A common example is an autoimmune disease such as rheumatoid arthritis, in which the immune system is fooled into believing that the body’s own cells (joint cells, in the case of rheumatoid arthritis) are foreign and must be attacked.

- **Nutritional imbalance**: Too much or too little nutrition can cause disease. Obesity is an epidemic in the developed world. About 65% of Americans are overweight, and about half of these are frankly obese. Obesity is associated with cardiovascular disease, cancer, diabetes, and dozens of other ills. Excess intake of animal fat leads to atherosclerosis. Conversely, cells may not receive enough energy (calories) or building blocks (protein). Protein-calorie deficiency is a major cause of illness and death worldwide. Specific vitamin and mineral deficiencies may induce cell injury by interfering with metabolic reactions necessary for cell health. Nutritional disease is discussed in Chapter 10.

- **Genetic defects**: There are two main types of genetic defects: mutations and cytogenetic abnormalities. A mutation is a permanent change in DNA represented by an abnormal sequence of nucleotide bases. Cytogenetic disease is large-scale change in chromosomes and is characterized by extra or missing whole chromosomes or parts of chromosomes. Genetic diseases are discussed in detail in Chapter 7.

- **Aging**: Cell aging is a progressive, mild injury that ultimately leads to cell death directly or renders cells less able to withstand other injury.

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**Mild Cell Injury**

Normally the cell membrane maintains intracellular sodium at a lower concentration than in the extracellular fluid, a job that requires expenditure of energy. Injury that is mild and lasts for a few minutes or hours may damage this mechanism and allow intracellular sodium to rise, which attracts water and causes the cytoplasm to swell. The result is hydropic change (vacuolar degeneration), as can be seen in Figure 2-9. Substances other than water can also accumulate in cells.

**INTRACELLULAR ACCUMULATIONS**

Not all intracellular accumulations are attributable to cell injury. Some are the result of phagocytosis (ingestion of solid material by a cell), and others occur in normal physiology. Accumulations owing to injury usually occur in association with mild injury lasting at least a few weeks.

- **Fat**: The kidney (Fig. 2-10) and the liver often react to stress by accumulating fat. Most fat accumulates as triglyceride, which appears as clear cytoplasmic globules (Fig. 2-11). Injured liver cells are particularly apt to accumulate fat. Chronic alcoholism (Chapter 16) is notable for causing marked fat accumulation in the liver because alcohol (ethanol) interferes with triglyceride metabolism.

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**Figure 2-9** Hydropic change in liver cells. This microscopic study is from a patient with toxic liver injury. Injured hepatocytes are enlarged and filled with water. (Reprinted with permission from Rubin E. Pathology. 4th ed. Philadelphia. Lippincott, Williams and Wilkins, 2005.)
• **Cholesterol**: The most extensive and most damaging intracellular accumulation is cholesterol, deposited in the cells of arteries in atherosclerosis (Chapter 12). Cholesterol first appears in macrophages and smooth muscle cells in the arterial wall and later accumulates into large, extracellular pools in the arterial wall.

• **Protein**: Protein accumulations can occur in cells. An important feature of normal proteins is that they are long molecules that must be folded into correct shape for normal function. Microscopically visible cytoplasmic accumulations of misfolded or otherwise abnormal proteins occur in a variety of diseases.

• Alpha-1 antitrypsin deficiency is a heritable disorder (Chapter 14) associated with protein clumps in hepatocytes.

• **Glycogen**: Glycogen is a long chain of glucose molecules formed and stored in liver and muscle as a glucose reserve. Glycogen synthesis is regulated by blood glucose concentration. For example, patients with diabetes (Chapter 17); have high blood glucose levels, and, as a consequence, hepatocytes and kidney cells in people with diabetes are often stuffed with glycogen.

• **Pigments**: The most widely occurring cell pigment accumulation is lipofuscin, a “wear-and-tear,” golden brown substance most notable in brain neurons and myocardial muscle cells, both of which are permanent, non-reproducing cells, and in hepatocytes, which are slow-dividing, stable cells. Melanin is a dark-brown compound that gives skin its color (Chapter 24). It is synthesized by melanocytes in the epidermis and deposited in the cytoplasm of cells in the basal layer of the epidermis. Inhaled carbon particles from cigarette smoke or polluted air are ingested by macrophages of bronchial lymph nodes (Fig. 2-12) and remain permanently with little damage. Hemosiderin and ferritin are brownish pigmented normal iron-storage compounds important in iron and hemoglobin metabolism (Chapter 11).
ADAPTATIONS OF CELL GROWTH AND DIFFERENTIATION

In addition to hydropic degeneration and intracellular accumulations, cellular response to persistent stress or chronic mild injury may include a change in size (atrophy or hypertrophy), an increase in number (hyperplasia), or alteration into another type of cell (metaplasia).

**Atrophy** is decreased size and function of a cell. It is an adaptive response to decreased demand or to increased stress; the cell shuts down its metabolic processes to conserve energy. Cells atrophy for several reasons:

- **Reduced functional demand.** For example, muscle atrophy occurs in a limb encased in a cast.
- **Inadequate blood supply** (ischemia). For example, atherosclerosis of the renal artery can impair blood flow enough to cause atrophy of a kidney.
- **Absent or reduced neural or hormonal support.** For example, skeletal muscle cells must be continually stimulated by intact nerves; interruption of nerve supply leads to muscle atrophy (Chapter 23). Other cells require hormonal support, as do thyroid and adrenal glands, which atrophy if they do not receive hormonal support from the pituitary gland.
- **Chronic inflammation associated with chronic injury.** For example, chronic inflammation of the stomach lining is associated with a condition known as *chronic atrophic gastritis* (Chapter 15), which causes the lining to become atrophic and very thin.

**Hypertrophy** is the opposite of atrophy—an increased size and functional capacity of a cell. It can be caused by:

- **Hormonal stimulation.** Cells depend on hormonal support. Too little and they wither; too much and they enlarge and become overactive. For example, following delivery, women's breasts enlarge and become temporarily hyperfunctional in order to produce milk, a change induced by secretion of prolactin (a hormone) from the pituitary.
- **Increased functional demand.** Increased functional demand stresses cells and causes them to enlarge and increase their activity. For example, a heart under the constant strain of high blood pressure increases in size because the individual cardiac muscle cells increase in size (Fig. 2-13).

**Hyperplasia** is the enlargement of a tissue or organ owing to an increase in the number of cells, as opposed to an increase in the cell size. It is cause by:

- **Hormonal stimulation.** For example, the increase of estrogen in female puberty causes an increase in the number of endometrial cells.
- **Increased functional demand.** For example, low atmospheric oxygen stimulates bone marrow production of RBC to carry oxygen. It is for this reason that people living at high altitude have increased numbers of circulating red blood cells (RBC).
- **Chronic stress or injury.** For example, the stress of exceptionally high blood pressure (Chapter 12) on small arteries in the kidney causes cells in the arterial

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**Figure 2-13 Hypertrophy.** A. Normal left ventricle. B. Hypertrophic left ventricle in a patient with severe, chronic hypertension. Ventricular wall is markedly thickened as a result of the increased size of individual muscle cells.
wall to divide and accumulate in layers, an effect called “onionskin” hyperplasia, illustrated in Figure 2-14.

As a rule, tissues whose cells are capable of dividing enlarge by undergoing both hyperplasia and hypertrophy. But tissues composed only of permanent cells (which cannot divide) can respond to increased demand only by cell enlargement (hypertrophy). Heart muscle is an example: All enlarged hearts occur because the size, not the number, of cardiac muscle cells increases.

Dysplasia a premalignant change of cells discussed in more detail in Chapter 6. Dysplasia typically occurs in previously normal epithelium, which features an orderly arrangement of cells of uniform size, shape, and appearance. In dysplastic epithelium this bland appearance is replaced by a disorderly overgrowth of cells with enlarged, dark, irregular nuclei. Dysplasia is a milepost on the way to malignancy; however, it is reversible and not yet malignant.

As is illustrated in Figure 2-15, metaplasia is a reversible change of one cell type into another. It is most common in epithelium, because epithelial cells are short-lived and are always being replenished from special cells (stem cells) that reside all along the basement membrane (see Case Study 2-1 at the end of this chapter). Normally epithelial stem cells mature into the usual cell type, but when injured or stressed they mature into a different type of cell more suitable to existing conditions. For example, the normal endocervix is lined by tall, columnar, mucinous cells, but when chronically inflamed it changes into squamous epithelium, a simpler, more durable epithelium better suited to defend against the agents causing the chronic inflammation. Metaplastic epithelium usually reverts to normal when the injury stops.

Severe Cell Injury and Cell Death

As discussed above, necrosis is the pathologic death of cells and is one of the most common of pathologic findings in disease. It is to be distinguished from apoptosis, the programmed, normal death of cells. Necrosis usually occurs in blocks of cells forming a collective mass fed with blood from a single artery. For example, a heart attack is the death of a group of heart muscle cells fed by a single blocked coronary artery. Similarly, an abscess is a group of liquefied cells killed by localized bacterial infection. However, in certain circumstances selected groups of cells die because they are of a certain type in a certain organ. For example, in patients in shock from blood loss, kidney blood flow falls dramatically because blood vessels to the kidney and other abdominal organs constrict in order to conserve blood for the brain, heart, and lungs. In this circumstance, certain kidney cells are vulnerable to necrosis because they are metabolically very active and require more oxygen than does the remainder of the kidney.

Apoptosis is normal, physiologic, planned cell death. Necrosis is pathologic cell death.
There are four types of necrosis:

- **Coagulative necrosis** is the most common type and is a gel-like change in blocks of freshly dead cells in which cell anatomy remains visible. The word *coagulate* derives from the most common use of the word *coagulate*—to convert fluid into a soft, solid mass, as when blood coagulates from fluid into a jelly-like consistency. In this case, the intracellular and extracellular fluid of the dead tissue is temporarily converted into a gel. The hallmark of coagulative necrosis is that the cells die in place, without anatomic disruption, so tissue architecture is preserved. Microscopic study reveals a ghostly outline of cells and tissues, as is seen in Figure 2-16. As discussed above, ischemia (insufficient arterial blood flow) is the most common cause of coagulative necrosis.

- An **infarct** is the ischemic death of a group of cells fed by an artery. *It is the most common cause of coagulative necrosis.* In an infarct, cells die and remain undisrupted and unrepaired for some time because the repair process (Chapter 4) must creep in from nearby living tissue that has a normal blood supply. For example, a heart attack is caused by blockage of a coronary artery, which deprives cardiac muscle tissue of oxygen; the dead muscle shows coagulative necrosis and remains a ghostly image of itself until the repair process can clean up the site. Figure 2-17 shows a liver with numerous infarcts and coagulative necrosis that resulted from occlusion of multiple small hepatic arteries.

- **Liquefactive necrosis** is cell death in which the dead tissue dissolves into fluid. Liquefaction occurs because dead cells are disrupted (not left intact as in coagulative necrosis) and dissolved by the injury at a rate faster than the repair process (Chapter 4) can clean it up. The most frequent type of liquefactive necrosis is an abscess produced by bacterial infection.

- **Caseous necrosis** is a special type of necrosis caused by tuberculosis infection. Caseous means cheesy and the dead tissue is off-white, soft, pasty, and clumpy, like some varieties of cheese. All cellular detail is obliterated.

**Figure 2-16 Coagulative necrosis.** This microscopic study shows kidney tissue. A. Normal renal glomerulus and tubules. B. Coagulative necrosis. “Ghost” outline of normal anatomy remains visible in the dead tissue.

**Figure 2-17 Infarction.** This is a liver with multiple infarcts that occurred after embolic thrombi from the heart occluded hepatic arteries. The light-colored blocks of necrotic liver tissue showed coagulative necrosis on microscopic examination.
In addition, fat necrosis, a specialized necrosis of fatty tissue, is usually found in retroperitoneal fat around the pancreas in cases of pancreatitis (Chapter 17). Sometimes fat necrosis occurs in subcutaneous or breast fat as a result of trauma. Triglycerides from disrupted fat cells are digested, and free fatty acids are released and precipitated as calcium soaps, which accumulate around the edges of the dead fat. The associated calcium deposits are microscopically distinctive and may be large enough to be visible on radiographic exam. On mammograms, calcium in fat necrosis can mimic calcium deposits in breast cancer (Fig. 2-18).

Fat necrosis is not the only cause of tissue calcium deposits. The calcium deposits in fat necrosis are but one type of dystrophic calcification, a type of calcification that may occur in any inflamed or necrotic tissue, particularly in cases of chronic injury and scarring. To the naked eye, calcium deposits appear as gritty white flecks, often visible on radiographic study.

CASE STUDY 2-1 “THIS HEARTBURN IS KILLING ME”

**TOPICS**
Metaplasia  
Dysplasia  
Barrett metaplasia of the esophagus

**THE CASE**
**Setting:** Your job is to do initial interviews on new patients and see some regular patients on follow-up visits in the office of a gastroenterologist on the faculty of a medical school. Today you are accompanying the gastroenterologist to a “difficult case” presentation in the department conference room, where he is to present the case of a patient you know well because he was one the first patients you saw on your first day at work a little over a year ago. While waiting for the conference to begin, you study the chart.

**Clinical history:** Rod B. is a 42-year-old man who was referred from his primary care physician with a diagnosis of “severe heartburn.” The physician had been treating him with limited success for several years and referred him for consultation when the problem became more severe. The first entry in his chart is your handwritten quote of his main complaint, “This heartburn is killing me.”

The chart is thick and crammed with notes, imaging reports, and lab results about the problem, which subsequent workup by the gastroenterologist proved to be caused by stomach acid refluxing upward into the lower esophagus (gastroesophageal reflux disease). Direct examination of his esophagus with a flexible endoscope revealed that the lower end of his esophagus was inflamed and showed evidence of Barrett metaplasia, which the gastroenterologist explained to you is a change of the lining cells of the lower esophagus from flat squamous cells, which normally are not bathed in acid, to tall, columnar mucus cells identical to those in the stomach, which tolerate acid much better. A variety of oral medicines helped relieve some of the symptoms, but altogether the results have been disappointing, and the gastroenterologist is seeking other opinions about how to proceed.

The gastroenterologist presents the case to the assembled physicians, residents, and others in the conference room. After a lengthy discussion about different medicines and possible surgery, the group agrees that the patient needs a biopsy of the lower esophageal mucosa in the area of metaplasia because there is an increased risk for esophageal cancer in patients with Barrett metaplasia.

Several weeks later a biopsy is obtained through an endoscope. The diagnosis on the pathology report is, “Severe chronic esophagitis, with gastric (Barrett) metaplasia. Moderate dysplasia is present in the metaplastic epithelium. No malignancy is present.”
**DISCUSSION**

Metaplasia is a reversible change of one cell type into another. Dysplasia is a reversible, premalignant change of epithelium, which can progress to cancer. In this instance esophageal squamous epithelium was being flooded by gastric acid regurgitated upward from the stomach, which stimulated esophageal epithelial stem cells to mature into gastric-type mucus cells that were resistant to the effect of gastric acid. The injury was long standing and severe, enough to cause precancerous change.

Dysplasia is a well-known risk of Barrett metaplasia. Dysplasia is a mile-post on the road to malignancy, but it is not fully malignant, nor is it irreversible. However, if the chronic injury and dysplasia persist, the dysplastic epithelium can become frankly malignant, invade and spread widely.

This patient needed vigorous treatment, perhaps including surgery, to stop the acid reflux into his esophagus and remove or destroy the dysplastic epithelium.

**POINTS TO REMEMBER**

- Chronic injury can cause cells to change from one type to another.
- Chronic injury can cause cells to change from benign to malignant.
- Barrett metaplasia is a premalignant condition.

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**Objectives Recap**

1. Offer a brief description of the basic organization of a cell and of the organization of tissues, organs, and organ systems: A cell consists of a nucleus that is surrounded by cytoplasm, which is contained within a cell membrane. The nucleus is composed of DNA, which is organized into the genetic code, and which controls all cell activity. The cytoplasm carries out the metabolic instructions of nuclear DNA. Cells are organized into tissues, which are organized into organs, which are organized into organ systems.

2. Explain how the genetic code is written into DNA: The code is a long sequence of four specialized molecules, the DNA bases—adenine (A), thymine (T), guanine (G), and cytosine (C). The order in which these molecules occur is the genetic code.

3. Explain the role of messenger RNA: Messenger RNA (mRNA) carries a copy of the genetic code from DNA in the nucleus to ribosomes in the cytoplasm, where the code is used to synthesize the protein coded by the DNA.

4. Explain the role of mitochondria: Mitochondria produce the energy required for metabolic processes.

5. Explain how DNA replicates during cell division (mitosis): During mitosis chromosomes line up single-file around the equator of the parent cell; one strand of DNA goes to one daughter cell; the other strand to the second daughter cell. To do this DNA unravels from the end into two strands like a frayed rope—one strand destined for each new daughter cell. Bases in each unraveled strand create a “handshake” with complementary bases from the “chemical soup” of the cytoplasm to form a second, new strand of DNA—glycine (G) forms a loose bond across to a new cytosine (C), and adenine (A) to a new thymine (T), and so on. These handshakes steady the new ATCG (base) sequences so that they can bind laterally up and down the chain to form a new helix intertwined with the other to form a new DNA molecule.

6. Differentiate between apoptosis and necrosis: Apoptosis is natural, physiologic, programmed cell death; necrosis is pathologic death of cells because of injury.

7. Explain the relationship between injury and disease: All disease is caused by injury.

8. Explain the relationship of genes and environment in the pathogenesis of disease: Genes influence how we react to injury. Some people are more disposed, others less disposed, to develop severe disease from a given injury.

9. Name the most common cause of cell injury: Hypoxia; usually secondary to ischemia (low blood flow).

10. Name one cell reaction resulting from mild acute cell injury and one resulting from mild chronic injury: Acute mild injury—hydropic (vacuolar) change; chronic mild injury—intracellular accumulations of fat, cholesterol, protein, glycogen or pigments.

11. List at least two causes of cell atrophy: Reduced functional demand, inadequate blood supply, lack of hormonal or neural support, chronic injury, cell aging.

12. Differentiate between hypertrophy and hyperplasia: Hypertrophy is tissue enlargement resulting from an increase in the size of individual cells. Hyperplasia is tissue enlargement resulting from increased number of cells.
13. **Define dysplasia:** Dysplasia is a premalignant change of cells typically seen in epithelium, in which the orderly arrangement of normal cells is replaced by a disorderly overgrowth of cells with enlarged, dark, irregular nuclei.

14. **Define metaplasia and offer an example:** Metaplasia is the change of one cell type into another following stress or chronic mild injury; for example, the change of endocervical glandular epithelium into squamous epithelium as a result of chronic inflammation of the cervix (cervicitis).

15. **Name the consequence of severe, irreversible cell injury:** Necrosis.

16. **Name the most common cause of necrosis and the most common type of necrosis:** Coagulative necrosis is the most common type of necrosis; it is most often caused by ischemia (inadequate blood flow).

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**Typical Test Questions**

1. Which of the following is composed of nucleotide bases?
   - A. DNA
   - B. mRNA
   - C. tRNA
   - D. rRNA
   - E. All of the above

2. Which of the following is characteristic of apoptosis?
   - A. It is reversible
   - B. It is natural
   - C. It is caused by injury
   - D. It features fat accumulation in cells

3. Which of the following is the most common cause of cell injury?
   - A. Physical action
   - B. Toxic molecular injury
   - C. Ionizing irradiation
   - D. Hypoxia

4. True or false? Hemosiderin is a normal iron storage molecule that may accumulate in cells.

5. True or false? Hypertrophy is increased number of cells.

6. True or false? Metaplasia is a reversible change of cell type.