

- **Cell death.** With continuing damage the injury becomes irreversible, at which time the cell cannot recover and it dies. *Historically, two principal types of cell death, necrosis and apoptosis, which differ in their morphology, mechanisms, and roles in physiology and disease, have been recognized.*
 - Necrosis has been considered an “accidental” and unregulated form of cell death resulting from damage to cell membranes and loss of ion homeostasis. When damage to membranes is severe, lysosomal enzymes enter the cytoplasm and digest the cell giving rise to a set of morphologic changes described as necrosis. Cellular contents also leak through the damaged plasma membrane into the extracellular space, where they elicit a host reaction (inflammation). Necrosis is the pathway of cell death in many commonly encountered injuries, such as those resulting from ischemia, exposure to toxins, various infections, and trauma.
 - In contrast to necrosis, when the cell’s DNA or proteins are damaged beyond repair, the cell kills itself by *apoptosis*, a form of cell death that is characterized by nuclear dissolution, fragmentation of the cell without complete loss of membrane integrity, and rapid removal of the cellular debris. Because cellular contents do not leak out, unlike in necrosis, there is no inflammatory reaction. Mechanistically, apoptosis is known to be a highly regulated process driven by a series of genetic pathways. It is hence also sometimes called “programmed cell death.”
 - *Whereas necrosis is always a pathologic process, apoptosis serves many normal functions and is not necessarily associated with cell injury.* Despite the distinctive morphologic manifestations of necrosis and apoptosis, it is now clear that the mechanistic distinction between necrosis and apoptosis is not as clear cut as previously imagined. In some cases necrosis is also regulated by a series of signaling pathways, albeit largely distinct from those that are involved in apoptosis. In other words, in some cases necrosis, like apoptosis, is also a form of programmed cell death. In recognition of this similarity, this form of necrosis has been called *necroptosis* as will be discussed later. Despite some potential overlap of mechanisms, it is still useful to discuss necrosis and apoptosis, the two principal pathways of cell death, separately because of the differing circumstances in which they develop.

The morphologic features, mechanisms, and significance of these death pathways are discussed in more detail later in the chapter. We will discuss first the causes of cell injury.

Causes of Cell Injury

The causes of cell injury range from the physical violence of an automobile accident to subtle cellular abnormalities, such as a mutation causing lack of a vital enzyme that impairs normal metabolic function. Most injurious stimuli can be grouped into the following broad categories.

Oxygen Deprivation. *Hypoxia* is a deficiency of oxygen, which causes cell injury by reducing aerobic oxidative

respiration. Hypoxia is an extremely important and common cause of cell injury and cell death. *Causes of hypoxia* include reduced blood flow (*ischemia*), inadequate oxygenation of the blood due to cardiorespiratory failure, and decreased oxygen-carrying capacity of the blood, as in anemia or carbon monoxide poisoning (producing a stable carbon monoxyhemoglobin that blocks oxygen carriage) or after severe blood loss. Depending on the severity of the hypoxic state, cells may adapt, undergo injury, or die. For example, if an artery is narrowed, the tissue supplied by that vessel may initially shrink in size (atrophy), whereas more severe or sudden hypoxia induces injury and cell death.

Physical Agents. Physical agents capable of causing cell injury include mechanical trauma, extremes of temperature (burns and deep cold), sudden changes in atmospheric pressure, radiation, and electric shock (Chapter 9).

Chemical Agents and Drugs. The list of chemicals that may produce cell injury defies compilation. Simple chemicals such as glucose or salt in hypertonic concentrations may cause cell injury directly or by deranging electrolyte balance in cells. Even oxygen at high concentrations is toxic. Trace amounts of *poisons*, such as arsenic, cyanide, or mercuric salts, may damage sufficient numbers of cells within minutes or hours to cause death. Other potentially injurious substances are our daily companions: environmental and air pollutants, insecticides, and herbicides; industrial and occupational hazards, such as carbon monoxide and asbestos; recreational drugs such as alcohol; and the ever-increasing variety of therapeutic drugs. Many of these are discussed further in Chapter 9.

Infectious Agents. These agents range from the submicroscopic viruses to tapeworms several feet in length. In between are the rickettsiae, bacteria, fungi, and higher forms of parasites. The ways by which these biologic agents cause injury are diverse (Chapter 8).

Immunologic Reactions. The immune system serves an essential function in defense against infectious pathogens, but immune reactions may also cause cell injury. Injurious reactions to endogenous self antigens are responsible for several autoimmune diseases (Chapter 6). Immune reactions to many external agents, such as viruses and environmental substances, are also important causes of cell and tissue injury (Chapters 3 and 6).

Genetic Derangements. As described in Chapter 5, genetic abnormalities as obvious as an extra chromosome, as in Down syndrome, or as subtle as a single base pair substitution leading to an amino acid substitution, as in sickle cell anemia, may produce highly characteristic clinical phenotypes ranging from congenital malformations to anemias. Genetic defects may cause cell injury because of deficiency of functional proteins, such as enzyme defects in inborn errors of metabolism, or accumulation of damaged DNA or misfolded proteins, both of which trigger cell death when they are beyond repair. DNA sequence variants that are common in human populations (polymorphisms) can also influence the susceptibility of cells to injury by chemicals and other environmental insults.