also leak metabolites that are vital for the reconstitution of ATP, thus further depleting energy stores.

- *Injury to lysosomal membranes* results in leakage of their enzymes into the cytoplasm and activation of the acid hydrolases in the acidic intracellular pH of the injured cell. Lysosomes contain RNases, DNases, proteases, phosphatases, and glucosidases. Activation of these enzymes leads to enzymatic digestion of proteins, RNA, DNA, and glycogen, and the cells die by necrosis.

Damage to DNA and Proteins

Cells have mechanisms that repair damage to DNA, but if DNA damage is too severe to be corrected (e.g., after exposure to DNA damaging drugs, radiation, or oxidative stress), the cell initiates a suicide program that results in death by apoptosis. A similar reaction is triggered by improperly folded proteins, which may be the result of inherited mutations or acquired triggers such as free radicals. Because these mechanisms of cell injury typically cause apoptosis, they are discussed later in the chapter.

Reversible vs Irreversible Injury. Before concluding the discussion of the mechanisms of cell injury, it is useful to consider the possible events that determine when reversible injury becomes irreversible and progresses to cell death. The clinical relevance of this question is obvious—if we can answer it, we may be able to devise strategies for preventing cell injury from having permanent deleterious consequences. However, the molecular mechanisms connecting most forms of cell injury to ultimate cell death have proved elusive, for several reasons. The "point of no return," at which the damage becomes irreversible, is still largely undefined, and there are no reliable morphologic or biochemical correlates of irreversibility. *Two phenomena consistently characterize irreversibility—the inability to reverse mitochondrial dysfunction* (lack of oxidative phosphorylation and ATP generation) even after resolution of the original injury, and *profound disturbances in membrane function*. As mentioned earlier, injury to lysosomal membranes results in the enzymatic dissolution of the injured cell that is characteristic of necrosis.

Leakage of intracellular proteins through the damaged cell membrane and ultimately into the circulation provides a means of detecting tissue-specific cellular injury and necrosis using blood serum samples. Cardiac muscle, for example, contains a specific isoform of the enzyme creatine kinase and of the contractile protein troponin; liver (and specifically bile duct epithelium) contains an isoform of the enzyme alkaline phosphatase; and hepatocytes contain transaminases. Irreversible injury and cell death in these tissues are reflected in increased levels of such proteins in the blood, and measurement of these biomarkers is used clinically to assess damage to these tissues.

KEY CONCEPTS

Mechanisms of Cell Injury

- ATP depletion: failure of energy-dependent functions → reversible injury → necrosis
- Mitochondrial damage: ATP depletion → failure of energy-dependent cellular functions → ultimately, necrosis; under some conditions, leakage of mitochondrial proteins that cause apoptosis
- Influx of calcium: activation of enzymes that damage cellular components and may also trigger apoptosis
- Accumulation of reactive oxygen species: covalent modification of cellular proteins, lipids, nucleic acids
- Increased permeability of cellular membranes: may affect plasma membrane, lysosomal membranes, mitochondrial membranes; typically culminates in necrosis
- Accumulation of damaged DNA and misfolded proteins: triggers apoptosis

Clinicopathologic Correlations: Selected Examples of Cell Injury and Necrosis

Having briefly reviewed the causes, morphology, and mechanisms of cell injury and necrotic cell death, we now describe some common and clinically significant forms of cell injury that typically culminate in necrosis. These examples illustrate many of the mechanisms and sequence of events in cell injury described earlier.

Ischemic and Hypoxic Injury

Ischemia is the most common type of cell injury in clinical medicine and it results from hypoxia induced by reduced blood flow, most commonly due to a mechanical arterial obstruction. It can also be caused by reduced venous drainage. In contrast to hypoxia, during which energy production by anaerobic glycolysis can continue, ischemia compromises the delivery of substrates for glycolysis. Thus, in ischemic tissues, not only is aerobic metabolism compromised but anaerobic energy generation also stops after glycolytic substrates are exhausted, or glycolysis is inhibited by the accumulation of metabolites that would otherwise be washed out by flowing blood. For this reason, *ischemia tends to cause more rapid and severe cell and tissue injury than does hypoxia in the absence of ischemia.*

Mechanisms of Ischemic Cell Injury

The sequence of events following hypoxia or ischemia reflects many of the biochemical alterations in cell injury described earlier and summarized here. As the oxygen tension within the cell falls, there is loss of oxidative phosphorylation and decreased generation of ATP. The depletion of ATP results in failure of the sodium pump, leading to efflux of potassium, influx of sodium and water, and cell swelling. There is also influx of $Ca2^{+}$, with its many deleterious effects. There is progressive loss of glycogen and decreased protein synthesis. The functional consequences may be severe at this stage. For instance, heart muscle ceases to contract within 60 seconds of coronary artery occlusion. Note, however, that loss of contractility does not mean cell death. If hypoxia continues, worsening ATP depletion causes further deterioration. The cytoskeleton disperses, resulting in the loss of ultrastructural features such as microvilli and the formation of "blebs" at the cell surface (Figs. 2-9 and 2-10). "Myelin figures," derived from degenerating cellular membranes, may be seen within the cytoplasm (in autophagic vacuoles) or extracellularly. They