are thought to result from unmasking of phosphatide groups, promoting the uptake and intercalation of water between the lamellar stacks of membranes. At this time the mitochondria are usually swollen, as a result of loss of volume control in these organelles; the ER remains dilated; and the entire cell is markedly swollen, with increased concentrations of water, sodium, and chloride and a decreased concentration of potassium. *If oxygen is restored, all of these disturbances are reversible.*

If ischemia persists, irreversible injury and necrosis ensue. Irreversible injury is associated morphologically with severe swelling of mitochondria, extensive damage to plasma membranes (giving rise to myelin figures) and swelling of lysosomes (Fig. 2-10C). Large, flocculent, amorphous densities develop in the mitochondrial matrix. In the myocardium, these are indications of irreversible injury and can be seen as early as 30 to 40 minutes after ischemia. Massive influx of calcium into the cell then occurs, particularly if the ischemic zone is reperfused. Death is mainly by necrosis, but apoptosis also contributes; the apoptotic pathway is probably activated by release of pro-apoptotic molecules from leaky mitochondria. The cell's components are progressively degraded, and there is widespread leakage of cellular enzymes into the extracellular space and, conversely, entry of extracellular macromolecules from the interstitial space into the dying cells. Finally, the dead cells may become replaced by large masses composed of phospholipids in the form of myelin figures. These are then either phagocytosed by leukocytes or degraded further into fatty acids. Calcification of such fatty acid residues may occur, with the formation of calcium soaps.

As mentioned before, leakage of intracellular enzymes and other proteins across the abnormally permeable plasma membrane and into the blood provides important clinical indicators of cell death. For example, elevated serum levels of cardiac muscle creatine kinase MB and troponin are early signs of myocardial infarction, and may be seen before the infarct is detectable morphologically (Chapter 12).

Mammalian cells have developed protective responses to deal with hypoxic stress. The best-defined of these is induction of a transcription factor called *hypoxia-inducible factor-1*, which promotes new blood vessel formation, stimulates cell survival pathways, and enhances anaerobic glycolysis. It remains to be seen if understanding of such oxygen-sensing mechanisms will lead to new strategies for preventing or treating ischemic and hypoxic cell injury.

Despite many investigations in experimental models there are still no reliable therapeutic approaches for reducing the injurious consequences of ischemia in clinical situations. The strategy that is perhaps the most useful in ischemic (and traumatic) brain and spinal cord injury is the transient induction of hypothermia (reducing the core body temperature to 92°F). This treatment reduces the metabolic demands of the stressed cells, decreases cell swelling, suppresses the formation of free radicals, and inhibits the host inflammatory response. All of these may contribute to decreased cell and tissue injury.

Ischemia-Reperfusion Injury

Restoration of blood flow to ischemic tissues can promote recovery of cells if they are reversibly injured, but can also paradoxically exacerbate the injury and cause cell death. As a consequence, reperfused tissues may sustain loss of cells in addition to the cells that are irreversibly damaged at the end of ischemia. This process, called *ischemia-reperfusion injury*, is clinically important because it contributes to tissue damage during myocardial and cerebral infarction and following therapies to restore blood flow (Chapters 12 and 28).

How does reperfusion injury occur? The likely answer is that new damaging processes are set in motion during reperfusion, causing the death of cells that might have recovered otherwise. Several mechanisms have been proposed:

- *Oxidative stress.* New damage may be initiated during reoxygenation by increased generation of *reactive oxygen and nitrogen species.* These free radicals may be produced in reperfused tissue as a result of incomplete reduction of oxygen by damaged mitochondria, or because of the action of oxidases in leukocytes, endothelial cells, or parenchymal cells. Cellular antioxidant defense mechanisms may be compromised by ischemia, favoring the accumulation of free radicals.
- *Intracellular calcium overload.* As mentioned earlier, intracellular and mitochondrial calcium overload begins during acute ischemia; it is exacerbated during reperfusion due to influx of calcium resulting from cell membrane damage and ROS mediated injury to sarcoplasmic reticulum. Calcium overload favors opening of the mitochondrial permeability transition pore with resultant depletion of ATP. This in turn causes further cell injury.
- *Inflammation*. Ischemic injury is associated with inflammation as a result of "dangers signals" released from dead cells, cytokines secreted by resident immune cells such as macrophages, and increased expression of adhesion molecules by hypoxic parenchymal and endothelial cells, all of which act to recruit circulating neutrophils to reperfused tissue. The inflammation causes additional tissue injury (Chapter 3). The importance of neutrophil influx in reperfusion injury has been demonstrated experimentally by the salutary effects of treatment with antibodies that block cytokines or adhesion molecules and thereby reduce neutrophil extravasation.
- Activation of the *complement system* may contribute to ischemia-reperfusion injury. Some IgM antibodies have a propensity to deposit in ischemic tissues, for unknown reasons, and when blood flow is resumed, complement proteins bind to the deposited antibodies, are activated, and cause more cell injury and inflammation.

Chemical (Toxic) Injury

Chemical injury remains a frequent problem in clinical medicine and is a major limitation to drug therapy. Because many drugs are metabolized in the liver, this organ is a frequent target of drug toxicity. In fact, toxic liver injury is perhaps the most frequent reason for terminating the therapeutic use or development of a drug. The mechanisms by which chemicals, certain drugs, and toxins produce injury are described in greater detail in Chapter 9 in the discussion of environmental diseases. Here the major pathways of chemically induced injury with selected examples are described.

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