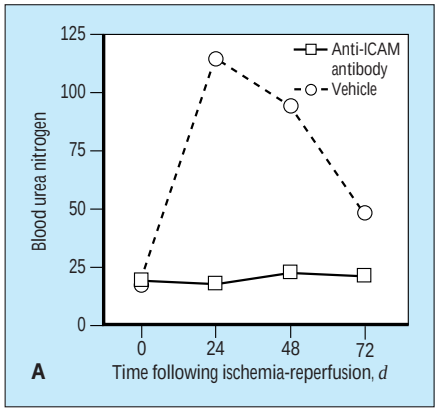
B. LEUKOCYTE ADHESION MOLECULES AND THEIR LIGANDS POTENTIALLY IMPORTANT IN ACUTE RENAL FAILURE

Major Families	Cell Distribution
Selectins	
L-selectin	Leukocytes
P-selectin	Endothelial cells
E-selectin	Endothelial cells
Carbohydrate ligands for selectins	
Sulphated polysaccharides	Endothelium
Oligosaccharides	Leukocytes
Integrins	
CD11a/CD18	Leukocytes
CD11b/CD18	Leukocytes
Immunoglobulin G–like ligands for integrins	
Intracellular adhesion molecules (ICAM)	Endothelial cells

FIGURE 14-29 *(Continued)*

B. Selectin-mediated leukocyte-endothelial interaction results in the rolling of leukocytes along the endothelium and facilitates the firm adhesion and immobilization of leukocytes. Immobilization of leukocytes to endothelium is mediated by the β_2-integrin adhesion molecules on leukocytes and their ICAM ligands on endothelial cells. Immobilization of leukocytes is necessary for diapedesis of leukocytes between endothelial cells into parenchymal tissue. Leukocytes release proteases, elastases, and reactive oxygen radicals that induce tissue injury. Activated leukocytes also elaborate cytokines such as interleukin 1 and tumor necrosis factor which attract additional leukocytes to the site, causing further injury.



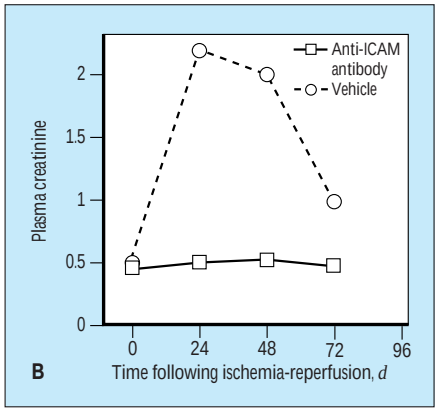


FIGURE 14-31

Neutralizing anti–ICAM antibody ameliorates the course of ischemic renal failure with blood urea nitrogen, **A**, and plasma creatinine, **B**. Rats subjected to 30 minutes of bilateral renal ischemia or a sham-operation were divided into three groups that received either anti-ICAM antibody or its vehicle. Plasma creatinine levels are shown at 24, 48, and 72 hours. ICAM antibody ameliorates the severity of renal failure at all three time points. (*Adapted from* Kelly *et al*. [24]; with permission.)

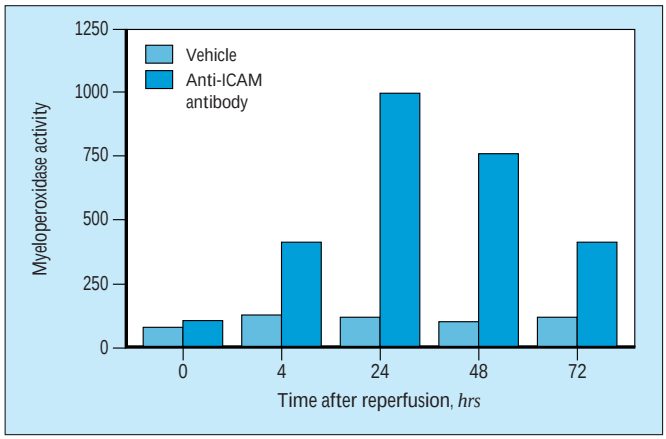


FIGURE 14-32

Neutralizing anti-ICAM-1 antibody reduces myeloperoxidase activity in rat kidneys exposed to 30 minutes of ischemia. Myeloperoxidase is an enzyme specific to leukocytes. Anti-ICAM antibody reduced myeloperoxidase activity (and by inference the number of leukocytes) in renal tissue after 30 minutes of ischemia. (*Adapted from* Kelly *et al*. [24]; with permission.)

Mechanisms of Cell Death: Necrosis and Apoptosis

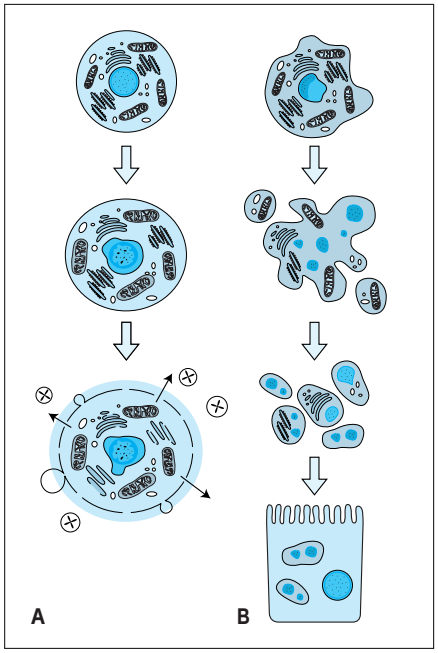


FIGURE 14-33

Apoptosis and necrosis: two distinct morphologic forms of cell death. **A**, Necrosis. Cells undergoing necrosis become swollen and enlarged. The mitochondria become markedly abnormal. The main morphoplogic features of mitochondrial injury include swelling and flattening of the folds of the inner mitochondrial membrane (the christae). The cell plasma membrane loses its integrity and allows the escape of cytosolic contents including lyzosomal proteases that cause injury and inflammation of the surrounding tissues. **B**, Apoptosis. In contrast to necrosis, apoptosis is associated with a progressive decrease in cell size and maintenance of a functionally and structurally intact plasma membrane. The decrease in cell size is due to both a loss of cytosolic volume and a decrease in the size of the nucleus. The most characteristic and specific morphologic feature of apoptosis is condensation of nuclear chromatin. Initially the chromatin condenses against the nuclear membrane. Then the nuclear membrane disappears, and the condensed chromatin fragments into many pieces. The plasma membrane undergoes a process of "budding," which progresses to fragmentation of the cell itself. Multiple plasma membrane–bound fragments of condensed DNA called apoptotic bodies are formed as a result of cell fragmentation. The apoptotic cells and apoptotic bodies are rapidly phagocytosed by neighboring epithelial cells as well as professional phagocytes such as macrophages. The rapid phagocytosis of apoptotic bodies with intact plasma membranes ensures that apoptosis does not cause any surrounding inflammatory reaction.

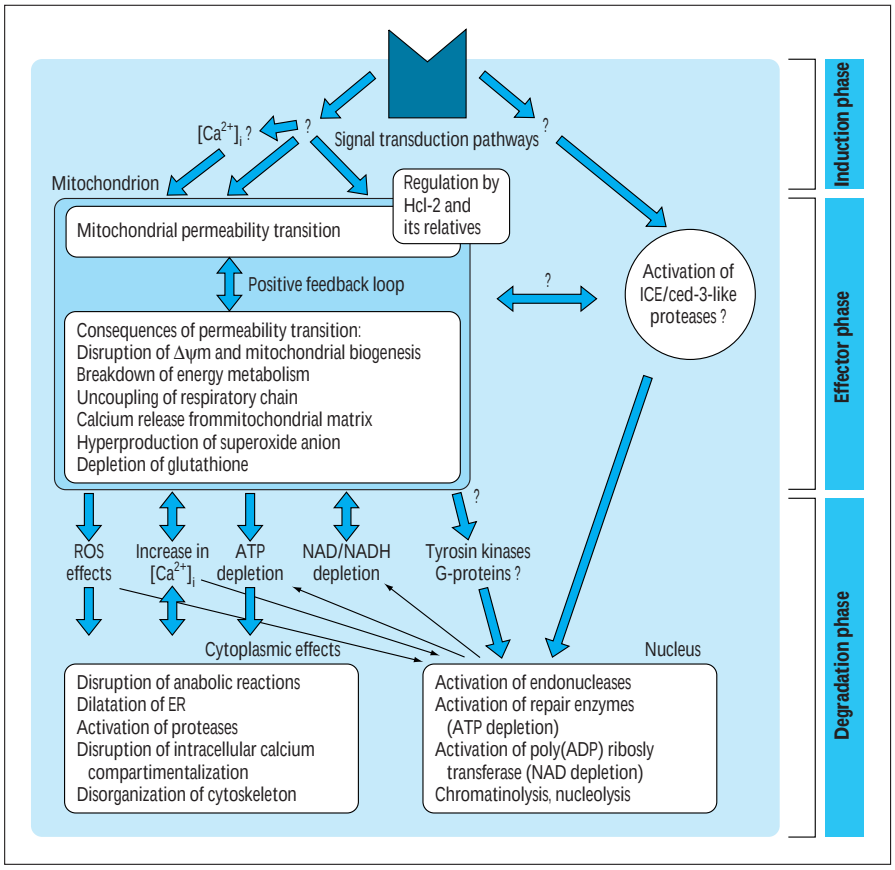


FIGURE 14-34

Hypothetical schema of cellular events triggering apoptotic cell death. (*From* Kroemer *et al*. [25]; with permission.)

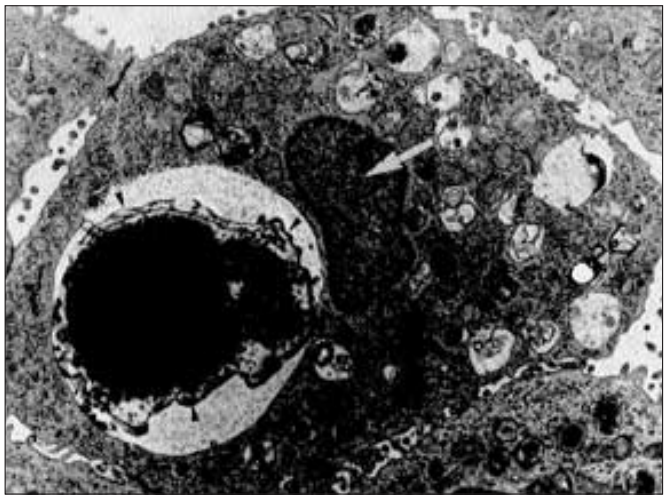


FIGURE 14-35

Phagocytosis of an apoptotic body by a renal tubular epithelial cell. Epithelial cells dying by apoptosis are not only phagocytosed by macrophages and leukocytes but by neighbouring epithelial cells as well. This electron micrograph shows a normal-looking epithelial cell containing an apoptotic body within a lyzosome. The nucleus of an epithelial cell that has ingested the apoptotic body is normal (*white arrow*). The wall of the lyzosome containing the apoptotic body (*black arrow*) is clearly visible. The apoptotic body consists of condensed chromatin surrounded by plasma membrane (*black arrowheads*).

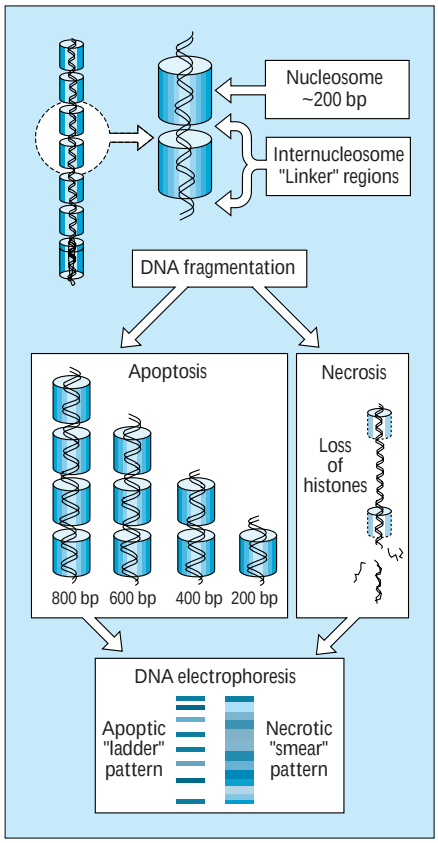


FIGURE 14-36

DNA fragmentation in apoptosis vs necrosis. DNA is made up of nucleosomal units. Each nucleosome of DNA is about 200 base pairs in size and is surrounded by histones. Between nucleosomes are small stretches of DNA that are not surrounded by histones and are called linker regions. During apoptosis, early activation of endonuclease(s) causes double-strand breaks in DNA between nucleosomes. No fragmentation occurs in nucleosomes because the DNA is "protected" by the histones. Because of the size of nucleosomes, the DNA is fragmented during apoptosis into multiples of 200 base pair pieces (*eg*, 200, 400, 600, 800). When the DNA of apoptotic cells is electrophoresed, a characteristic ladder pattern is found.

In contrast, necrosis is associated with the early release of lyzosomal proteases, which cause proteolysis of nuclear histones, leaving "naked" stretches of DNA not protected by histones. Activation of endonucleases during necrosis therefore cause DNA cleavage at multiple sites into double- and single-stranded DNA fragments of varying size. Electrophoresis of DNA from necrotic cells results in a smear pattern.