Chemicals induce cell injury by one of two general mechanisms:

- *Direct toxicity.* Some chemicals can injure cells directly by combining with critical molecular components. For example, in mercuric chloride poisoning, mercury binds to the sulfhydryl groups of cell membrane proteins, causing increased membrane permeability and inhibition of ion transport. In such instances, the greatest damage is usually to the cells that use, absorb, excrete, or concentrate the chemicals—in the case of mercuric chloride, the cells of the gastrointestinal tract and kidney (Chapter 9). *Cyanide* poisons mitochondrial cytochrome oxidase and thus inhibits oxidative phosphorylation. Many antineoplastic chemotherapeutic agents and antibiotics also induce cell damage by direct cytotoxic effects.
- *Conversion to toxic metabolites.* Most toxic chemicals are not biologically active in their native form but must be converted to reactive toxic metabolites, which then act on target molecules. This modification is usually accomplished by the cytochrome P-450 mixed-function oxidases in the smooth ER of the liver and other organs. The toxic metabolites cause membrane damage and cell injury mainly by formation of *free radicals* and subsequent lipid peroxidation; direct covalent binding to membrane proteins and lipids may also contribute. For instance, CCl_4, which was once widely used in the dry cleaning industry, is converted by cytochrome P-450 to the highly reactive free radical $^{\bullet}CCl_3$, which causes lipid peroxidation and damages many cellular structures. Acetaminophen, an analgesic drug, is also converted to a toxic product during detoxification in the liver, leading to cell injury. These and other examples of chemical injury are described in Chapter 9.

KEY CONCEPTS

Ischemic and Toxic Injury

- Mild Ischemia: Reduced oxidative phosphorylation →. reduced ATP generation → failure of Na pump → influx of sodium and water → organelle and cellular swelling (reversible)
- Severe/prolonged ischemia: severe swelling of mitochondria, calcium influx into mitochondria and into the cell with rupture of lysosomes and plasma membrane. Death by necrosis and apoptosis due the release of cytochrome c from mitochondria
- Reperfusions injury follows blood flow into ischemic area is caused by oxidative stress due to release of free radicals from leukocytes and endothelial cells. Blood brings calcium that overloads reversibly injured cells with consequent mitochondrial injury. Influx of leukocytes generates free radicals and cytokines. Local activation of complement by IgM antibodies deposited in ischemic tissues.
- Chemicals may cause injury directly or by conversion into toxic metabolites. The organs chiefly affected are those involved in absorption or excretion of chemicals or others such as liver where the chemicals are converted to toxic metabolites. Direct injury to critical organelles such as mitochondria or indirect injury from free radicals generated from the chemicals/toxins is involved.

Apoptosis

Apoptosis is a pathway of cell death that is induced by a tightly regulated suicide program in which cells destined to die activate intrinsic enzymes that degrade the cells' own nuclear DNA and nuclear and cytoplasmic proteins. Apoptotic cells break up into fragments, called *apoptotic bodies,* which contain portions of the cytoplasm and nucleus. The plasma membrane of the apoptotic cell and bodies remains intact, but its structure is altered in such a way that these become "tasty" targets for phagocytes. The dead cell and its fragments are rapidly devoured, before the contents have leaked out, and therefore cell death by this pathway does not elicit an inflammatory reaction in the host. The process was recognized in 1972 by the distinctive morphologic appearance of membrane-bound fragments derived from cells, and named after the Greek designation for "falling off." It was quickly appreciated that apoptosis was a unique mechanism of cell death, distinct from necrosis, which is characterized by loss of membrane integrity, enzymatic digestion of cells, leakage of cellular contents, and frequently a host reaction (Fig. 2-8 and Table 2-2). Because it is genetically regulated, apoptosis is sometimes referred to as *programmed cell death.* As already alluded to, certain forms of necrosis, called *necroptosis,* are also genetically programmed, but by a distinct set of genes.

Causes of Apoptosis

Apoptosis occurs normally both during development and throughout adulthood, and serves to remove unwanted, aged, or potentially harmful cells. It is also a pathologic event when diseased cells become damaged beyond repair and are eliminated.

Apoptosis in Physiologic Situations

Death by apoptosis is a normal phenomenon that serves to eliminate cells that are no longer needed, and to maintain a steady number of various cell populations in tissues. It is important in the following physiologic situations:

- *The destruction of cells during embryogenesis*, including implantation, organogenesis, developmental involution, and metamorphosis. The term *programmed cell death* was originally coined to denote death of specific cell types that was precisely regulated and occurred at defined times during the development of multicellular organisms. Apoptosis is a generic term for this pattern of cell death, regardless of the context, but it is often used interchangeably with programmed cell death. However, it is best to avoid this term to denote apoptosis, since in some cases necrosis may also be a form of programmed cell death
- *Involution of hormone-dependent tissues upon hormone withdrawal*, such as endometrial cell breakdown during the menstrual cycle, ovarian follicular atresia in menopause, the regression of the lactating breast after weaning, and prostatic atrophy after castration.
- *Cell loss in proliferating cell populations*, such as immature lymphocytes in the bone marrow and thymus and B