lymphocytes in germinal centers that fail to express useful antigen receptors (Chapter 6), and epithelial cells in intestinal crypts, so as to maintain a constant number *(homeostasis)*.

- *Elimination of potentially harmful self-reactive lymphocytes*, either before or after they have completed their maturation, so as to prevent reactions against one's own tissues (Chapter 6).
- Death of host cells that have served their useful purpose, such as neutrophils in an *acute inflammatory response*, and lymphocytes at the end of an *immune response*. In these situations cells undergo apoptosis because they are deprived of necessary survival signals, such as growth factors.

Apoptosis in Pathologic Conditions

Apoptosis eliminates cells that are injured beyond repair without eliciting a host reaction, thus limiting collateral tissue damage. Death by apoptosis is responsible for loss of cells in a variety of pathologic states:

- *DNA damage*. Radiation, cytotoxic anticancer drugs, and hypoxia can damage DNA, either directly or via production of free radicals. If repair mechanisms cannot cope with the injury, the cell triggers intrinsic mechanisms that induce apoptosis. In these situations elimination of the cell may be a better alternative than risking mutations in the damaged DNA, which may result in malignant transformation.
- *Accumulation of misfolded proteins*. Improperly folded proteins may arise because of mutations in the genes encoding these proteins or because of extrinsic factors, such as damage caused by free radicals. Excessive accumulation of these proteins in the ER leads to a condition called *ER stress*, which culminates in apoptotic cell death. Apoptosis caused by the accumulation of misfolded proteins has been invoked as the basis of several degenerative diseases of the central nervous system and other organs.
- *Cell death in certain infections*, particularly viral infections, in which loss of infected cells is largely due to apoptosis that may be induced by the virus (as in adenovirus and HIV infections) or by the host immune response (as in viral hepatitis). An important host response to viruses consists of cytotoxic T lymphocytes specific for viral proteins, which induce apoptosis of infected cells in an attempt to eliminate reservoirs of infection. During this process there can be significant tissue damage. The same T-cell–mediated mechanism is responsible for cell death in *tumors* and cellular rejection of *transplants*.
- *Pathologic atrophy in parenchymal organs after duct obstruction*, such as occurs in the pancreas, parotid gland, and kidney.

Morphologic and Biochemical Changes in Apoptosis

Before discussing the mechanisms of apoptosis, the morphologic and biochemical characteristics of this process are described.

MORPHOLOGY

The following morphologic features, some best seen with the electron microscope, characterize cells undergoing apoptosis (Fig. 2-22, and see Fig. 2-8).

Cell shrinkage. The cell is smaller in size, the cytoplasm is dense (Fig. 2-22*A*), and the organelles, although relatively normal, are more tightly packed. (Recall that in other forms of cell injury, an early feature is cell swelling, not shrinkage.)

Chromatin condensation. This is the most characteristic feature of apoptosis. The chromatin aggregates peripherally, under the nuclear membrane, into dense masses of various shapes and sizes (Fig. 2-22*B*). The nucleus itself may break up, producing two or more fragments.

Formation of cytoplasmic blebs and apoptotic bodies. The apoptotic cell first shows extensive surface blebbing, then undergoes fragmentation into membrane-bound apoptotic bodies composed of cytoplasm and tightly packed organelles, with or without nuclear fragments (Fig. 2-22*C*).

Phagocytosis of apoptotic cells or cell bodies, usually by macrophages. The apoptotic bodies are rapidly ingested by phagocytes and degraded by the phagocyte's lysosomal enzymes.

Plasma membranes are thought to remain intact during apoptosis, until the last stages, when they become permeable to normally retained solutes.

On histologic examination, in tissues stained with hematoxylin and eosin, the apoptotic cell appears as a round or oval mass of intensely eosinophilic cytoplasm with fragments of dense nuclear chromatin (Fig. 2-22*A*). Because the cell shrinkage and formation of apoptotic bodies are rapid and the pieces are quickly phagocytosed, considerable apoptosis may occur in tissues before it becomes apparent in histologic sections. In addition, apoptosis—in contrast to necrosis—does not elicit inflammation, making it more difficult to detect histologically.

Mechanisms of Apoptosis

Apoptosis results from the activation of enzymes called *caspases* (so named because they are cysteine proteases that cleave proteins after aspartic residues). Like many proteases, caspases exist as inactive proenzymes, or zymogens, and must undergo enzymatic cleavage to become active. The presence of cleaved, active caspases is a marker for cells undergoing apoptosis (Fig. 2-22*C*). The process of apoptosis may be divided into an *initiation phase,* during which some caspases become catalytically active, and an *execution phase,* during which other caspases trigger the degradation of critical cellular components. The activation of caspases depends on a finely tuned balance between production of pro-apoptotic and anti-apoptotic proteins.

Two distinct pathways converge on caspase activation: the mitochondrial pathway and the death receptor pathway (Fig 2-23). Although these pathways can intersect, they are generally induced under different conditions, involve different molecules, and serve distinct roles in physiology and disease.

The Intrinsic (Mitochondrial) Pathway of Apoptosis

The mitochondrial pathway is the major mechanism of apoptosis in all mammalian cells. It results from increased permeability of the mitochondrial outer membrane with consequent release of death-inducing (pro-apoptotic)