efficient that dead cells disappear, often within minutes, without leaving a trace, and inflammation is absent even in the face of extensive apoptosis.

Clinicopathologic Correlations: Apoptosis in Health and Disease

Examples of Apoptosis

Cell death in many situations is known to be caused by apoptosis, and the selected examples listed illustrate the role of this death pathway in normal physiology and in disease.

Growth Factor Deprivation. Hormone-sensitive cells deprived of the relevant hormone, lymphocytes that are not stimulated by antigens and cytokines, and neurons deprived of nerve growth factor die by apoptosis. In all these situations, apoptosis is triggered by the intrinsic (mitochondrial) pathway and is attributable to decreased synthesis of BCL2 and BCL-XL and activation of BIM and other pro-apoptotic members of the BCL2 family.

DNA Damage. Exposure of cells to radiation or chemotherapeutic agents induces apoptosis by a mechanism that is initiated by DNA damage (genotoxic stress) and that involves the tumor-suppressor gene *TP53*. p53 protein accumulates in cells when DNA is damaged, and it arrests the cell cycle (at the G_1 phase) to allow time for repair (Chapter 7). However, if the damage is too great to be repaired successfully, p53 triggers apoptosis. When *TP*53 is mutated or absent (as it is in many cancers), cells with damaged DNA fail to undergo p53-mediated apoptosis and instead survive. In such cells, the DNA damage may result in mutations of various types that lead to neoplastic transformation (Chapter 7). Thus, p53 serves as a critical "life or death" switch following genotoxic stress. The mechanism by which p53 triggers the distal death effector machinery—the caspases—is complex but seems to involve its function as a DNA-binding transcription factor. Among the proteins whose production is stimulated by p53 are several pro-apoptotic members of the BCL2 family, notably BAX, BAK and some BH3-only proteins, mentioned earlier.

Protein Misfolding. Chaperones in the ER control the proper folding of newly synthesized proteins, and misfolded polypeptides are ubiquitinated and targeted for proteolysis in proteasomes (Chapter 1). If, however, unfolded or misfolded proteins accumulate in the ER because of inherited mutations or stresses, they trigger a number of cellular responses, collectively called the *unfolded protein response*. The unfolded protein response activates signaling pathways that increase the production of chaperones, enhance proteasomal degradation of abnormal proteins, and slow protein translation, thus reducing the load of misfolded proteins in the cell (Fig. 2-26). However, if this cytoprotective response is unable to cope with the accumulation of misfolded proteins, the cell activates caspases and induces apoptosis. This process is called *ER stress*. Intracellular accumulation of abnormally folded proteins, caused by genetic mutations, aging, or unknown environmental factors, is now recognized as a feature of a number of neurodegenerative diseases, including Alzheimer, Huntington, and Parkinson diseases (Chapter 28), and possibly type 2 diabetes. Deprivation of glucose and oxygen, and stress such as heat, also result in protein

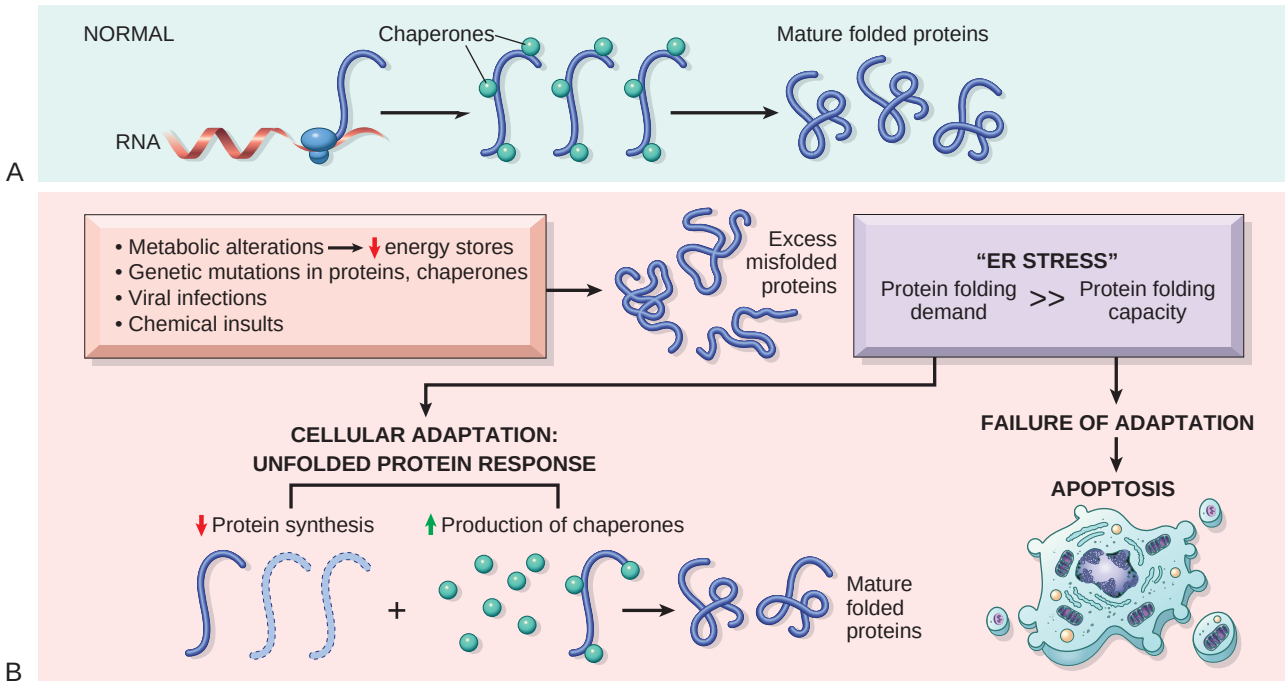

Figure 2-26 The unfolded protein response and endoplasmic reticulum (ER) stress. **A,** In healthy cells, newly synthesized proteins are folded with the help of chaperones and are then incorporated into the cell or secreted. **B,** Various external stresses or mutations induce a state called ER stress, in which the cell is unable to cope with the load of misfolded proteins. Accumulation of these proteins in the ER triggers the unfolded protein response, which tries to restore protein homeostasis; if this response is inadequate, the cell dies by apoptosis.