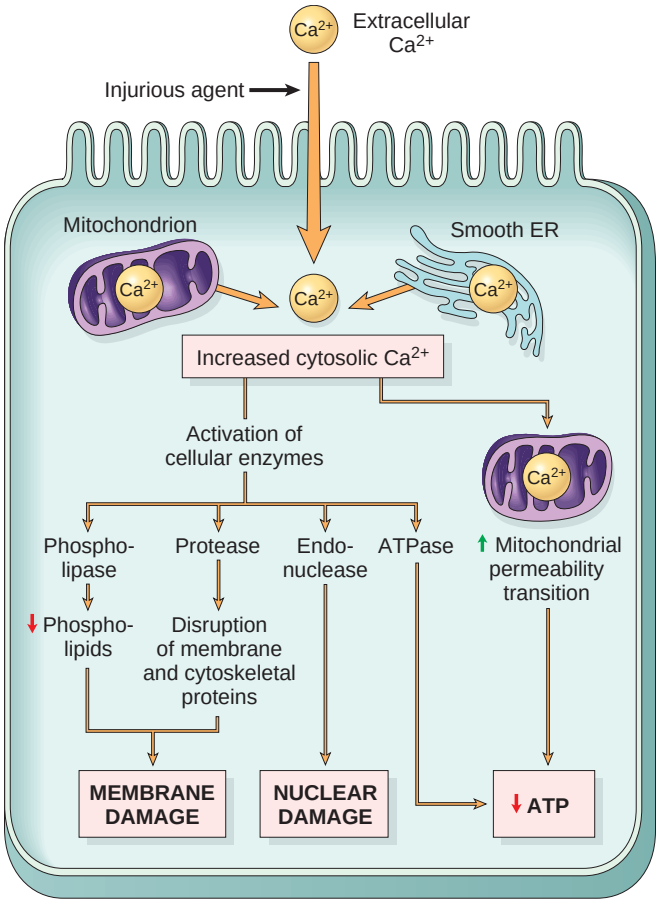

Figure 2-19 The role of increased cytosolic calcium in cell injury. ER, Endoplasmic reticulum.

and later due to increased influx across the plasma membrane (Fig. 2-19). Increased intracellular Ca^{2+} causes cell injury by several mechanisms.

- The accumulation of Ca^{2+} in mitochondria results in opening of the mitochondrial permeability transition pore and, as described earlier, failure of ATP generation.
- Increased cytosolic Ca^{2+} activates a number of enzymes with potentially deleterious effects on cells. These enzymes include *phospholipases* (which cause membrane damage), *proteases* (which break down both membrane and cytoskeletal proteins), *endonucleases* (which are responsible for DNA and chromatin fragmentation), and *ATPases* (thereby hastening ATP depletion).
- Increased intracellular Ca^{2+} levels also result in the induction of apoptosis, by direct activation of caspases and by increasing mitochondrial permeability.

Accumulation of Oxygen-Derived Free Radicals (Oxidative Stress)

Cell injury induced by free radicals, particularly reactive oxygen species, is an important mechanism of cell damage in many pathologic conditions, such as chemical and radiation injury, ischemia-reperfusion injury (induced by restoration of blood flow in ischemic tissue), cellular aging, and microbial killing by phagocytes. *Free radicals* are chemical species that have a single unpaired electron in an outer orbit. Unpaired electrons are highly reactive and "attack" and modify adjacent molecules, such as inorganic or organic chemicals—proteins, lipids, carbohydrates, nucleic acids—many of which are key components of cell membranes and nuclei. Some of these reactions are autocatalytic, whereby molecules that react with free radicals are themselves converted into free radicals, thus propagating the chain of damage.

Reactive oxygen species (ROS) are a type of oxygen-derived free radical whose role in cell injury is well established. ROS are produced normally in cells during mitochondrial respiration and energy generation, but they are degraded and removed by cellular defense systems. Thus, cells are able to maintain a steady state in which free radicals may be present transiently at low concentrations but do not cause damage. Increased production or decreased scavenging of ROS may lead to an excess of these free radicals, a condition called *oxidative stress*. Oxidative stress has been implicated in a wide variety of pathologic processes, including cell injury, cancer, aging, and some degenerative diseases such as Alzheimer disease. ROS are also produced in large amounts by activated leukocytes, particularly neutrophils and macrophages, during inflammatory reactions aimed at destroying microbes and cleaning up dead cells and other unwanted substances (Chapter 3).

The following section discusses the generation and removal of ROS, and how they contribute to cell injury. The properties of some of the most important free radicals are summarized in Table 2-3.

Generation of Free Radicals. Free radicals may be generated within cells in several ways (Fig. 2-20):

- *The reduction-oxidation reactions that occur during normal metabolic processes.* As a part of normal respiration, molecular O_2 is reduced by the transfer of four electrons to H_2 to generate two water molecules. This conversion is catalyzed by oxidative enzymes in the ER, cytosol, mitochondria, peroxisomes, and lysosomes. During this process small amounts of partially reduced intermediates are produced in which different numbers of electrons have been transferred from O_2; these include superoxide anion ($O_2^{\cdot-}$, one electron), hydrogen peroxide (H_2O_2, two electrons), and hydroxyl ions ($^{\cdot}OH$, three electrons).
- *Absorption of radiant energy* (e.g., ultraviolet light, x-rays). For example, ionizing radiation can hydrolyze water into $^{\cdot}OH$ and hydrogen (H) free radicals.
- Rapid bursts of ROS are produced in activated leukocytes during *inflammation*. This occurs in a precisely controlled reaction carried out by a plasma membrane multiprotein complex that uses NADPH oxidase for the redox reaction (Chapter 3). In addition, some intracellular oxidases (e.g., xanthine oxidase) generate $O_2^{\cdot-}$.
- *Enzymatic metabolism of exogenous chemicals or drugs* can generate free radicals that are not ROS but have similar effects (e.g., CCl_4 can generate $^{\cdot}CCl_3$, described later in the chapter).
- *Transition metals* such as iron and copper donate or accept free electrons during intracellular reactions and catalyze free radical formation, as in the Fenton reaction