Nutritional Imbalances. Nutritional imbalances continue to be major causes of cell injury. Protein-calorie deficiencies cause an appalling number of deaths, chiefly among underprivileged populations. Deficiencies of specific vitamins are found throughout the world (Chapter 9). Nutritional problems can be self-imposed, as in anorexia nervosa (self-induced starvation). Ironically, nutritional excesses have also become important causes of cell injury. Excess of cholesterol predisposes to atherosclerosis; obesity is associated with increased incidence of several important diseases, such as diabetes and cancer. Atherosclerosis is virtually endemic in the United States, and obesity is rampant. In addition to the problems of undernutrition and overnutrition, the composition of the diet makes a significant contribution to a number of diseases.

Morphologic Alterations in Cell Injury

It is useful to describe the basic alterations that occur in damaged cells before discussing the biochemical mechanisms that bring about these changes. All stresses and noxious influences exert their effects first at the molecular or biochemical level. There is a time lag between the stress and the morphologic changes of cell injury or death; the duration of this delay may vary with the sensitivity of the methods used to detect these changes (Fig. 2-7). With histochemical or ultrastructural techniques, changes may be seen in minutes to hours after injury; however, it may take considerably longer (hours to days) before changes can be seen by light microscopy or on gross examination. As would be expected, the morphologic manifestations of necrosis take more time to develop than those of reversible damage. For example, in ischemia of the myocardium, cell swelling is a reversible morphologic change that may occur in a matter of minutes, and may progress to irreversibility within an hour or two. Unmistakable light microscopic changes of cell death, however, may not be seen until 4 to 12 hours after onset of ischemia.

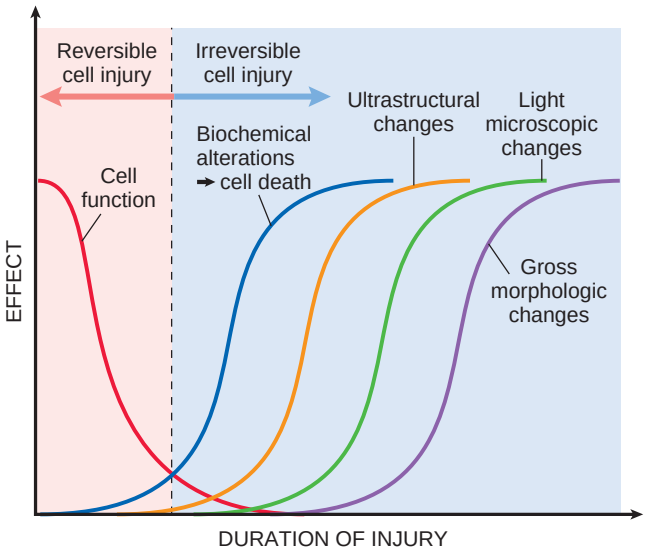

Figure 2-7 Sequential development of biochemical and morphologic changes in cell injury. Cells may become rapidly nonfunctional after the onset of injury, although they may still be viable, with potentially reversible damage; a longer duration of injury may lead to irreversible injury and cell death. Note that irreversible biochemical alterations may cause cell death, and typically this precedes ultrastructural, light microscopic, and grossly visible morphologic changes.

Table 2-2 Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis → karyorrhexis → karyolysis	Fragmentation into nucleosome-size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage

The sequential morphologic changes in cell injury progressing to cell death are illustrated in Figure 2-8. Reversible injury is characterized by generalized swelling of the cell and its organelles, blebbing of the plasma membrane, detachment of ribosomes from the ER, and clumping of nuclear chromatin. These morphologic changes are associated with decreased generation of ATP, loss of cell membrane integrity, defects in protein synthesis, cytoskeletal damage, and DNA damage. Within limits, the cell can repair these derangements and, if the injurious stimulus abates, will return to normalcy. Persistent or excessive injury, however, causes cells to pass the rather nebulous "point of no return" into irreversible injury and *cell death*. Different injurious stimuli may induce death by necrosis or apoptosis (Fig. 2-8 and Table 2-2). Severe mitochondrial damage with depletion of ATP and rupture of lysosomal and plasma membranes are typically associated with necrosis. Necrosis occurs in many commonly encountered injuries, such as those following ischemia, exposure to toxins, various infections, and trauma. Apoptosis has many unique features (see later).

Reversible Injury

Two features of reversible cell injury can be recognized under the light microscope: *cellular swelling* and *fatty change*. Cellular swelling appears whenever cells are incapable of maintaining ionic and fluid homeostasis and is the result of failure of energy-dependent ion pumps in the plasma membrane. Fatty change occurs in hypoxic injury and various forms of toxic or metabolic injury. It is manifested by the appearance of lipid vacuoles in the cytoplasm. It is seen mainly in cells involved in and dependent on fat metabolism, such as hepatocytes and myocardial cells. The mechanisms of fatty change are discussed later in the chapter.