homeostasis. There are two principal pathways of cell death, *necrosis* and *apoptosis*. Nutrient deprivation triggers an adaptive cellular response called *autophagy* that may also culminate in cell death. A detailed discussion of these pathways of cell death follows later in the chapter.

Stresses of different types may induce changes in cells and tissues other than typical adaptations, cell injury, and death (Table 2-1). Metabolic derangements in cells and sublethal, chronic injury may be associated with *intracellular accumulations* of a number of substances, including proteins, lipids, and carbohydrates. Calcium is often deposited at sites of cell death, resulting in *pathologic calcification*. Finally, the normal process of *aging* is accompanied by characteristic morphologic and functional changes in cells.

This chapter discusses first how cells adapt to stresses, and then the causes, mechanisms, and consequences of the various forms of acute cell damage, including reversible cell injury, and cell death. We conclude with three other processes that affect cells and tissues: intracellular accumulations, pathologic calcification, and cell aging.

Adaptations of Cellular Growth and Differentiation

Adaptations are reversible changes in the size, number, phenotype, metabolic activity, or functions of cells in response to changes in their environment. Such adaptations may take several distinct forms.

Hypertrophy

Hypertrophy refers to an increase in the size of cells, that results in an increase in the size of the affected organ. The hypertrophied organ has no new cells, just larger cells. The increased size of the cells is due to the synthesis and assembly of additional intracellular structural components. Cells capable of division may respond to stress by undergoing both hyperplasia (described later) and hypertrophy, whereas in non dividing (e.g., myocardial fibers) increased tissue mass is due to hypertrophy. In many organs hypertrophy and hyperplasia may coexist and contribute to increased size.

Hypertrophy can be *physiologic* or *pathologic;* the former is caused by increased functional demand or by stimulation by hormones and growth factors. The striated muscle cells in the heart and skeletal muscles have only a limited capacity for division, and respond to increased metabolic demands mainly by undergoing hypertrophy. *The most common stimulus for hypertrophy of muscle is increased workload*. For example, the bulging muscles of bodybuilders engaged in "pumping iron" result from enlargement of individual muscle fibers in response to increased demand. In the heart, the stimulus for hypertrophy is usually chronic hemodynamic overload, resulting from either hypertension or faulty valves (Fig. 2-2). In both tissue types the muscle cells synthesize more proteins and the number of myofilaments increases. This increases the amount of force each myocyte can generate, and thus increases the strength and work capacity of the muscle as a whole.

The massive physiologic growth of the uterus during pregnancy is a good example of hormone-induced enlargement an organ that results mainly from hypertrophy of muscle fibers (Fig. 2-3). Uterine hypertrophy is stimulated by estrogenic hormones acting on smooth muscle through estrogen receptors, eventually resulting in increased synthesis of smooth muscle proteins and an increase in cell size.

Mechanisms of Hypertrophy

Hypertrophy is the result of increased production of cellular proteins. Much of our understanding of hypertrophy is based on studies of the heart. There is great interest in defining the molecular basis of hypertrophy since beyond a certain point, hypertrophy of the heart becomes maladaptive and can lead to heart failure, arrhythmias and

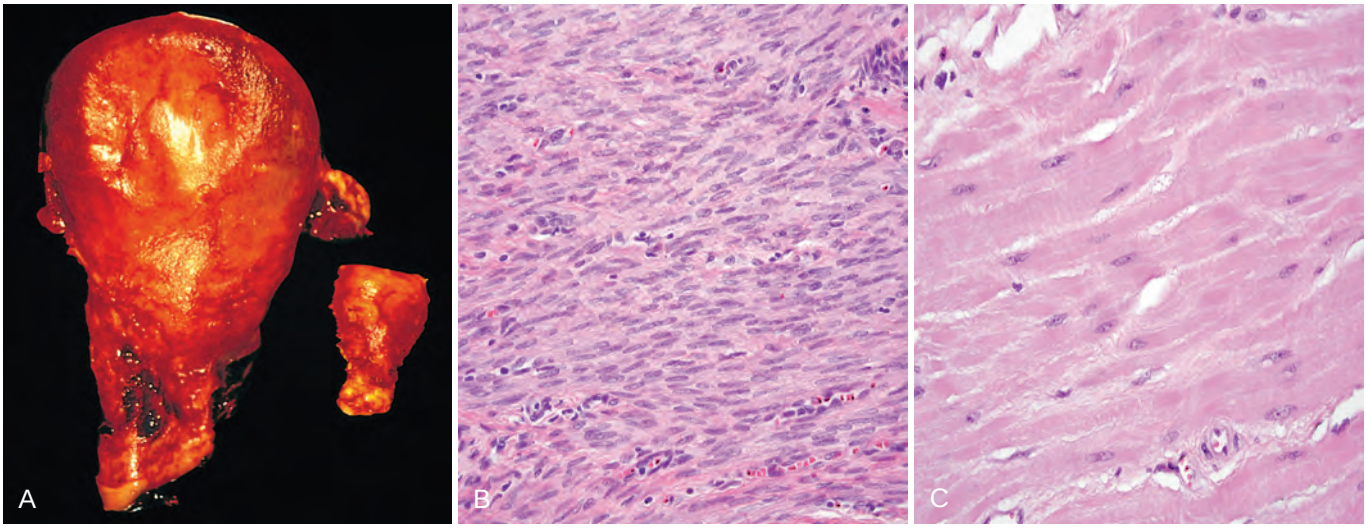

Figure 2-3 Physiologic hypertrophy of the uterus during pregnancy. **A,** Gross appearance of a normal uterus *(right)* and a gravid uterus (removed for postpartum bleeding) *(left).* **B,** Small spindle-shaped uterine smooth muscle cells from a normal uterus, compared with **C,** large plump cells from the gravid uterus, at the same magnification.