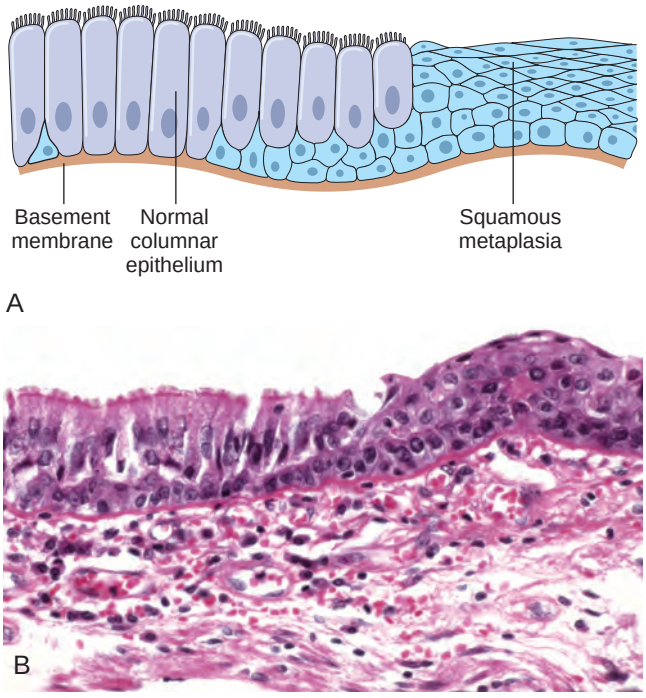

Figure 2-6 Metaplasia of columnar to squamous epithelium. **A,** Schematic diagram. **B,** Metaplasia of columnar epithelium *(left)* to squamous epithelium *(right)* in a bronchus.

these instances the more rugged stratified squamous epithelium is able to survive under circumstances in which the more fragile specialized columnar epithelium might have succumbed. However, the change to metaplastic squamous cells comes with a price. In the respiratory tract, for example, although the epithelial lining becomes tough, important mechanisms of protection against infection—mucus secretion and the ciliary action of the columnar epithelium—are lost. Thus, epithelial metaplasia is a double-edged sword and, in most circumstances, represents an undesirable change. Moreover, *the influences that predispose to metaplasia, if persistent, can initiate malignant transformation in metaplastic epithelium*. Thus, a common form of cancer in the respiratory tract is composed of squamous cells, which can arise in areas where the normal columnar epithelium has been replaced by squamous epithelium.

Metaplasia from squamous to columnar type may also occur, as in *Barrett esophagus*, in which the esophageal squamous epithelium is replaced by intestinal-like columnar cells under the influence of refluxed gastric acid. Cancers may arise in these areas; these are typically glandular (adenocarcinomas) (Chapter 17).

Connective tissue metaplasia is the formation of cartilage, bone, or adipose tissue (mesenchymal tissues) in tissues that normally do not contain these elements. For example, bone formation in muscle, designated *myositis ossificans*, occasionally occurs after intramuscular hemorrhage. This type of metaplasia is less clearly seen as an adaptive response, and may be a result of cell or tissue injury.

Mechanisms of Metaplasia

Metaplasia does not result from a change in the phenotype of an already differentiated cell type; instead it is the result of a reprogramming of stem cells that are known to exist in normal tissues, or of undifferentiated mesenchymal cells present in connective tissue. In a metaplastic change, these precursor cells differentiate along a new pathway. The differentiation of stem cells to a particular lineage is brought about by signals generated by cytokines, growth factors, and extracellular matrix components in the cells' environment. These external stimuli promote the expression of genes that drive cells toward a specific differentiation pathway. A direct link between transcription factor dysregulation and metaplasia is seen with vitamin A (retinoic acid) deficiency or excess, both of which may cause metaplasia. Retinoic acid regulates gene transcription directly through nuclear retinoid receptors (Chapter 9), which can influence the differentiation of progenitors derived from tissue stem cells. How other external stresses cause metaplasia is unknown, but it is clear that they too somehow alter the activity of transcription factors that regulate differentiation.

KEY CONCEPTS

Cellular Adaptations to Stress

- **Hypertrophy**: increased cell and organ size, often in response to increased workload; induced by growth factors produced in response to mechanical stress or other stimuli; occurs in tissues incapable of cell division
- **Hyperplasia**: increased cell numbers in response to hormones and other growth factors; occurs in tissues whose cells are able to divide or contain abundant tissue stem cells
- **Atrophy**: decreased cell and organ size, as a result of decreased nutrient supply or disuse; associated with decreased synthesis of cellular building blocks and increased breakdown of cellular organelles
- **Metaplasia**: change in phenotype of differentiated cells, often in response to chronic irritation, that makes cells better able to withstand the stress; usually induced by altered differentiation pathway of tissue stem cells; may result in reduced functions or increased propensity for malignant transformation

Overview of Cell Injury and Cell Death

As stated at the beginning of the chapter, cell injury results when cells are stressed so severely that they are no longer able to adapt or when cells are exposed to inherently damaging agents or suffer from intrinsic abnormalities. Injury may progress through a reversible stage and culminate in cell death (Fig. 2-1).

- *Reversible cell injury.* In early stages or mild forms of injury, the functional and morphologic changes are reversible if the damaging stimulus is removed. The hallmarks of reversible injury are reduced oxidative phosphorylation with resultant depletion of energy stores in the form of adenosine triphosphate (ATP), and cellular swelling caused by changes in ion concentrations and water influx. In addition, various intracellular organelles, such as mitochondria and the cytoskeleton, may show alterations.