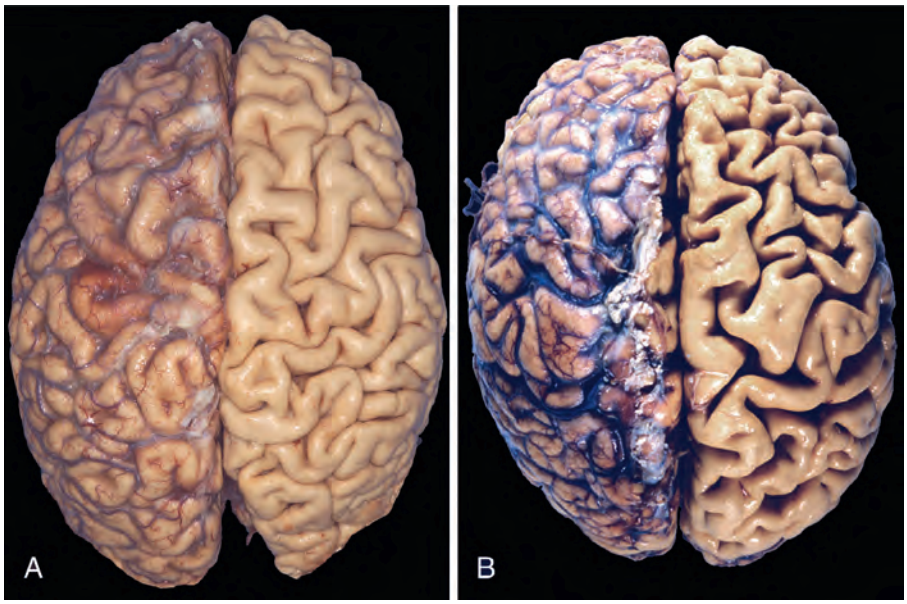

Figure 2-5 Atrophy. **A,** Normal brain of a young adult. **B,** Atrophy of the brain in an 82-year-old man with atherosclerotic cerebrovascular disease, resulting in reduced blood supply. Note that loss of brain substance narrows the gyri and widens the sulci. The meninges have been stripped from the right half of each specimen to reveal the surface of the brain.

suppression and lipid depletion, culminating in muscle atrophy.

- *Loss of endocrine stimulation.* Many hormone-responsive tissues, such as the breast and reproductive organs, are dependent on endocrine stimulation for normal metabolism and function. The loss of estrogen stimulation after menopause results in physiologic atrophy of the endometrium, vaginal epithelium, and breast.
- *Pressure.* Tissue compression for any length of time can cause atrophy. An enlarging benign tumor can cause atrophy in the surrounding uninvolved tissues. Atrophy in this setting is probably the result of ischemic changes caused by compromise of the blood supply by the pressure exerted by the expanding mass.

The fundamental cellular changes associated with atrophy are identical in all of these settings. The initial response is a decrease in cell size and organelles, which may reduce the metabolic needs of the cell sufficiently to permit its survival. In atrophic muscle, the cells contain fewer mitochondria and myofilaments and a reduced amount of rough endoplasmic reticulum (RER). By bringing into balance the cell's metabolic demands and the lower levels of blood supply, nutrition, or trophic stimulation, a new equilibrium is achieved. *Early in the process atrophic cells and tissues have diminished function, but cell death is minimal*. However, atrophy caused by gradually reduced blood supply may progress to the point at which cells are irreversibly injured and die, often by apoptosis. Cell death by apoptosis also contributes to the atrophy of endocrine organs after hormone withdrawal.

Mechanisms of Atrophy

Atrophy results from decreased protein synthesis and increased protein degradation in cells. Protein synthesis decreases because of reduced metabolic activity.

The degradation of cellular proteins occurs mainly by the ubiquitin-proteasome pathway. Nutrient deficiency and disuse may activate ubiquitin ligases, which attach the small peptide ubiquitin to cellular proteins and target these proteins for degradation in *proteasomes.* This pathway is also thought to be responsible for the accelerated proteolysis seen in a variety of catabolic conditions, including cancer cachexia. In many situations, atrophy is also accompanied by increased *autophagy*, marked by the appearance of increased numbers of *autophagic vacuoles*. Autophagy ("self-eating") is the process in which the starved cell eats its own components in an attempt to reduce nutrient demand to match the supply. Some of the cell debris within the autophagic vacuoles may resist digestion and persist in the cytoplasm as membrane-bound *residual bodies*. An example of residual bodies is *lipofuscin granules*, discussed later in the chapter. When present in sufficient amounts, they impart a brown discoloration to the tissue *(brown atrophy).* Autophagy is associated with various types of cell injury, and we will discuss it in more detail later.

Metaplasia

Metaplasia is a reversible change in which one differentiated cell type (epithelial or mesenchymal) is replaced by another cell type. It often represents an adaptive response in which one cell type that is sensitive to a particular stress is replaced by another cell type that is better able to withstand the adverse environment.

The most common epithelial metaplasia is *columnar to squamous* (Fig. 2-6), as occurs in the respiratory tract in response to chronic irritation. In the habitual cigarette smoker, the normal ciliated columnar epithelial cells of the trachea and bronchi are often replaced by stratified squamous epithelial cells. Stones in the excretory ducts of the salivary glands, pancreas, or bile ducts, which are normally lined by secretory columnar epithelium, may also lead to squamous metaplasia by stratified squamous epithelium. A deficiency of vitamin A (retinoic acid) induces squamous metaplasia in the respiratory epithelium (Chapter 9). In all