- Inadequate removal of a normal substance secondary to defects in mechanisms of packaging and transport, as in fatty change (steatosis) in the liver (Chapter 18)
- Accumulation of an abnormal endogenous substance as a result of genetic or acquired defects in its folding, packaging, transport, or secretion, as with certain mutated forms of α_1-antitrypsin (Chapter 15)
- Failure to degrade a metabolite due to inherited enzyme deficiencies. The resulting disorders are called *storage diseases* (Chapter 5).
- Deposition and accumulation of an abnormal exogenous substance when the cell has neither the enzymatic machinery to degrade the substance nor the ability to transport it to other sites. Accumulation of carbon or silica particles is an example of this type of alteration (Chapter 15).

In many cases, if the overload can be controlled or stopped, the accumulation is reversible. In inherited storage diseases, accumulation is progressive, and the overload may cause cellular injury, leading in some instances to death of the tissue and the patient.

Lipids

All major classes of lipids can accumulate in cells: triglycerides, cholesterol/cholesterol esters, and phospholipids. Phospholipids are components of the myelin figures found in necrotic cells. In addition, abnormal complexes of lipids and carbohydrates accumulate in the lysosomal storage diseases (Chapter 5). Triglyceride and cholesterol accumulations are discussed here.

Steatosis (Fatty Change)

The terms steatosis and fatty change describe abnormal accumulations of triglycerides within parenchymal cells. Fatty change is often seen in the liver because it is the major organ involved in fat metabolism (Fig. 2-30), but it also occurs in heart, muscle, and kidney. The causes of steatosis include toxins, protein malnutrition, diabetes mellitus, obesity, and anoxia. *In developed nations, the most common causes of significant fatty change in the liver (fatty liver) are alcohol abuse and nonalcoholic fatty liver disease, which is often associated with diabetes and obesity.* Fatty liver is discussed in more detail in Chapter 18.

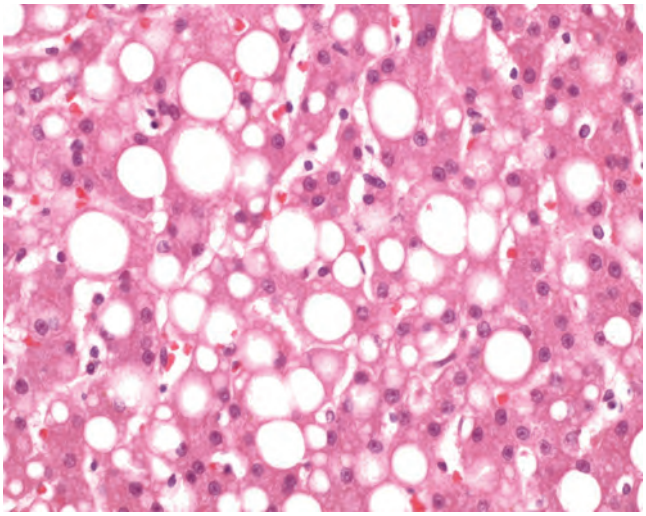

Figure 2-30 Fatty liver. High-power detail of fatty change of the liver. In most cells the well-preserved nucleus is squeezed into the displaced rim of cytoplasm about the fat vacuole. (Courtesy Dr. James Crawford, Department of Pathology, University of Florida School of Medicine, Gainesville, Fla.)

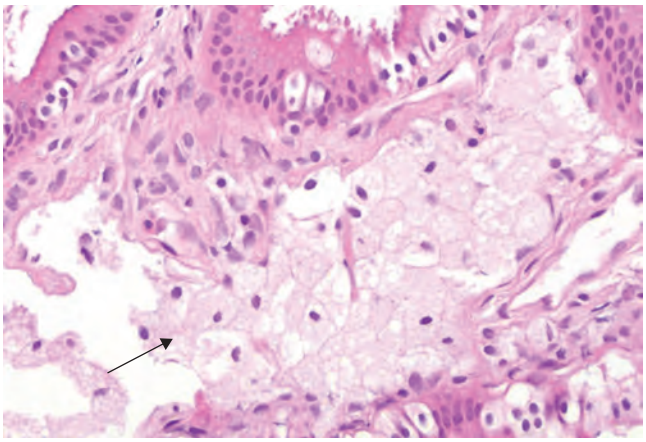

Figure 2-31 Cholesterolosis. Cholesterol-laden macrophages (foam cells, *arrow*) in a focus of gallbladder cholesterolosis. (Courtesy Dr. Matthew Yeh, Department of Pathology, University of Washington, Seattle, Wash.)

Cholesterol and Cholesterol Esters

The cellular metabolism of cholesterol (Chapter 5) is tightly regulated such that most cells use cholesterol for the synthesis of cell membranes without intracellular accumulation of cholesterol or cholesterol esters. Accumulations manifested histologically by intracellular vacuoles are seen in several pathologic processes.

- *Atherosclerosis.* **In atherosclerotic plaques, smooth muscle cells and macrophages within the intimal layer of the aorta and large arteries are filled with lipid vacuoles, most of which are made up of cholesterol and cholesterol esters.** Such cells have a foamy appearance (foam cells), and aggregates of them in the intima produce the yellow cholesterol-laden atheromas characteristic of this serious disorder. Some of these fat-laden cells may rupture, releasing lipids into the extracellular space. The mechanisms of cholesterol accumulation in atherosclerosis are discussed in detail in Chapter 11. The extracellular cholesterol esters may crystallize in the shape of long needles, producing quite distinctive clefts in tissue sections.
- *Xanthomas.* **Intracellular accumulation of cholesterol within macrophages is also characteristic of acquired and hereditary hyperlipidemic states.** Clusters of foamy cells are found in the subepithelial connective tissue of the skin and in tendons, producing tumorous masses known as xanthomas.
- *Cholesterolosis.* This refers to the focal accumulations of cholesterol-laden macrophages in the lamina propria of the gallbladder (Fig. 2-31). The mechanism of accumulation is unknown.
- *Niemann-Pick disease, type C.* This lysosomal storage disease is caused by mutations affecting an enzyme involved in cholesterol trafficking, resulting in cholesterol accumulation in multiple organs (Chapter 5).