Proteins

Intracellular accumulations of proteins usually appear as rounded, eosinophilic droplets, vacuoles, or aggregates in the cytoplasm. By electron microscopy they can be amorphous, fibrillar, or crystalline in appearance. In some disorders, such as certain forms of amyloidosis, abnormal proteins deposit primarily in extracellular spaces (Chapter 6).

Excesses of proteins within the cells sufficient to cause morphologically visible accumulation have diverse causes.

- *Reabsorption droplets in proximal renal tubules* are seen in renal diseases associated with protein loss in the urine (proteinuria). In the kidney small amounts of protein filtered through the glomerulus are normally reabsorbed by pinocytosis in the proximal tubule. In disorders with heavy protein leakage across the glomerular filter there is increased reabsorption of the protein into vesicles, and the protein appears as pink hyaline droplets within the cytoplasm of the tubular cell (Fig. 2-32). The process is reversible; if the proteinuria diminishes, the protein droplets are metabolized and disappear.
- The proteins that accumulate may be normal secreted proteins that are produced in excessive amounts, as occurs in certain plasma cells engaged in active synthesis of immunoglobulins. The ER becomes hugely distended, producing large, homogeneous eosinophilic inclusions called *Russell bodies*.
- *Defective intracellular transport and secretion of critical proteins.* In α_1-antitrypsin deficiency, mutations in the protein significantly slow folding, resulting in the buildup of partially folded intermediates, which aggregate in the ER of the liver and are not secreted. The resultant deficiency of the circulating enzyme causes emphysema (Chapter 15). In many of these diseases the pathology results not only from loss of protein function but also ER stress caused by the misfolded proteins, culminating in apoptotic death of cells (discussed earlier).
- *Accumulation of cytoskeletal proteins.* There are several types of cytoskeletal proteins, including microtubules (20 to 25 nm in diameter), thin actin filaments (6 to 8 nm), thick myosin filaments (15 nm), and intermediate filaments (10 nm). Intermediate filaments, which provide a flexible intracellular scaffold that organizes the cytoplasm and resists forces applied to the cell, are divided into five classes: keratin filaments (characteristic of epithelial cells), neurofilaments (neurons), desmin filaments (muscle cells), vimentin filaments (connective tissue cells), and glial filaments (astrocytes). Accumulations of keratin filaments and neurofilaments are associated with certain types of cell injury. Alcoholic hyaline is an eosinophilic cytoplasmic inclusion in liver cells that is characteristic of alcoholic liver disease, and is composed predominantly of *keratin* intermediate filaments (Chapter 18). The *neurofibrillary tangle* found in the brain in Alzheimer disease contains neurofilaments and other proteins (Chapter 28).
- *Aggregation of abnormal proteins.* Abnormal or misfolded proteins may deposit in tissues and interfere with normal functions. The deposits can be intracellular, extracellular, or both, and the aggregates may either directly or indirectly cause the pathologic changes. Certain forms of *amyloidosis* (Chapter 6) fall in this category of diseases. These disorders are sometimes called *proteinopathies* or *protein-aggregation diseases*.

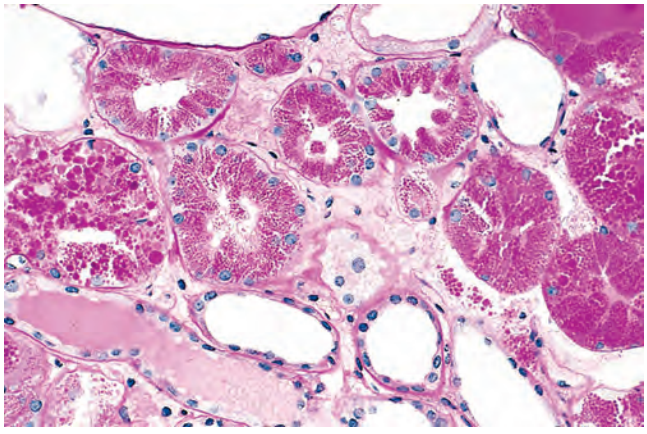

Figure 2-32 Protein reabsorption droplets in the renal tubular epithelium. (Courtesy Dr. Helmut Rennke, Department of Pathology, Brigham and Women's Hospital, Boston, Mass.)

Hyaline Change

The term hyaline usually refers to an alteration within cells or in the extracellular space that gives a homogeneous, glassy, pink appearance in routine histologic sections stained with hematoxylin and eosin. It is widely used as a descriptive histologic term rather than a specific marker for cell injury. This morphologic change is produced by a variety of alterations and does not represent a specific pattern of accumulation. Intracellular accumulations of protein, described earlier (reabsorption droplets, Russell bodies, alcoholic hyaline), are examples of intracellular hyaline deposits.

Extracellular hyaline has been more difficult to analyze. Collagenous fibrous tissue in old scars may appear hyalinized, but the biochemical basis of this change is not clear. In long-standing hypertension and diabetes mellitus, the walls of arterioles, especially in the kidney, become hyalinized, resulting from extravasated plasma protein and deposition of basement membrane material.

Glycogen

Glycogen is a readily available energy source stored in the cytoplasm of healthy cells. Excessive intracellular deposits of glycogen are seen in patients with an abnormality in either glucose or glycogen metabolism. Whatever the clinical setting, the glycogen masses appear as clear vacuoles within the cytoplasm. Glycogen dissolves in aqueous fixatives; thus, it is most readily identified when tissues are fixed in absolute alcohol. Staining with Best carmine or the PAS reaction imparts a rose-to-violet color to the glycogen, and diastase digestion of a parallel section before staining serves as a further control by hydrolyzing the glycogen.

Diabetes mellitus is the prime example of a disorder of glucose metabolism. In this disease glycogen is found