Under the electron microscope, the clear cytoplasm can be resolved as numerous minute vacuoles. These are swollen lysosomes containing a finely granular periodic acid–Schiff–positive material that can be identified biochemically as mucopolysaccharide. Similar lysosomal changes are found in the neurons of those syndromes characterized by central nervous system involvement. In addition, however, some of the lysosomes in neurons are replaced by lamellated zebra bodies similar to those seen in Niemann-Pick disease. **Hepatosplenomegaly, skeletal deformities, valvular lesions, and subendothelial arterial deposits, particularly in the coronary arteries, and lesions in the brain are common threads that run through all of the MPSs.** In many of the more protracted syndromes, coronary subendothelial lesions lead to myocardial ischemia. Thus, myocardial infarction and cardiac decompensation are important causes of death.

Clinical Features. Of the seven recognized variants, only two well-characterized syndromes are described briefly here. *Hurler syndrome*, also called MPS I-H, results from a deficiency of α-l-iduronidase. It is one of the most severe forms of MPS. Affected children appear normal at birth but develop hepatosplenomegaly by age 6 to 24 months. Their growth is retarded, and, as in other forms of MPS, they develop coarse facial features and skeletal deformities. Death occurs by age 6 to 10 years and is often due to cardiovascular complications. *Hunter syndrome*, also called MPS II, differs from Hurler syndrome in mode of inheritance (X-linked), absence of corneal clouding, and milder clinical course.

KEY CONCEPTS

Lysosomal Storage Diseases

Inherited mutations leading to defective lysosomal enzyme functions gives rise to accumulation and storage of complex substrates in the lysosomes and defects in autophagy resulting in cellular injury.

- **Tay-Sachs disease** is caused by an inability to metabolize G_{M2} gangliosides due to lack of the α subunit of lysosomal hexosaminidase. G_{M2} gangliosides accumulate in the central nervous system and cause severe mental retardation, blindness, motor weakness, and death by 2 to 3 years of age.
- **Niemann-Pick disease types A and B** are caused by a deficiency of sphingomyelinase. In the more severe type A variant, accumulation of sphingomyelin in the nervous system results in neuronal damage. Lipid also is stored in phagocytes within the liver, spleen, bone marrow, and lymph nodes, causing their enlargement. In type B, neuronal damage is not present.
- **Niemann-Pick disease type C** is caused by a defect in cholesterol transport and resultant accumulation of cholesterol and gangliosides in the nervous system. Affected children most commonly exhibit ataxia, dysarthria, and psychomotor regression.
- **Gaucher disease** results from lack of the lysosomal enzyme glucocerebrosidase and accumulation of glucocerebroside in mononuclear phagocytic cells. In the most common, type I variant, affected phagocytes become enlarged (Gaucher cells) and accumulate in liver, spleen, and bone marrow, causing hepatosplenomegaly and bone erosion. Types II and III are characterized by variable neuronal involvement.
- **Mucopolysaccharidoses** result in accumulation of mucopolysaccharides in many tissues including liver, spleen, heart, blood vessels, brain, cornea, and joints. Affected patients in all forms have coarse facial features. Manifestations of Hurler syndrome include corneal clouding, coronary arterial and valvular deposits, and death in childhood. Hunter syndrome is associated with a milder clinical course.

Glycogen Storage Diseases (Glycogenoses)

The glycogen storage diseases result from a hereditary deficiency of one of the enzymes involved in the synthesis or sequential degradation of glycogen. Depending on the tissue or organ distribution of the specific enzyme in the normal state, glycogen storage in these disorders may be limited to a few tissues, may be more widespread while not affecting all tissues, or may be systemic in distribution.

The significance of a specific enzyme deficiency is best understood from the perspective of the normal metabolism of glycogen (Fig. 5-14). Glycogen is a storage form of glucose. Glycogen synthesis begins with the conversion of glucose to glucose-6-phosphate by the action of a hexokinase (glucokinase). A phosphoglucomutase then transforms the glucose-6-phosphate to glucose-1-phosphate, which, in turn, is converted to uridine diphosphoglucose. A highly branched, large polymer is then built (molecular weight as high as 100 million), containing as many as 10,000 glucose molecules linked together by α-1,4-glucoside bonds. The glycogen chain and branches continue to be elongated by the addition of glucose molecules mediated by glycogen synthetases. During degradation, distinct phosphorylases in the liver and muscle split glucose-1-phosphate from the glycogen until about four glucose residues remain on each branch, leaving a branched oligosaccharide called *limit dextrin.* This can be further degraded only by the debranching enzyme. In addition to these major pathways, glycogen is also degraded in the lysosomes by acid maltase. If the lysosomes are deficient in this enzyme, the glycogen contained within them is not accessible to degradation by cytoplasmic enzymes such as phosphorylases.

On the basis of specific enzyme deficiencies and the resultant clinical pictures, glycogenoses have traditionally been divided into a dozen or so syndromes designated by roman numerals, and the list continues to grow. On the basis of pathophysiology glycogenoses can be divided into three major subgroups (Table 5-7):

- *Hepatic forms.* The liver is a key player in glycogen metabolism. It contains enzymes that synthesize glycogen for storage and ultimately break it down into free glucose, which is then released into the blood. An inherited deficiency of hepatic enzymes that are involved in glycogen degradation therefore leads not only to the storage of glycogen in the liver but also to a reduction in blood glucose concentrations (hypoglycemia) (Fig. 5-15). Deficiency of the enzyme glucose-6-phosphatase