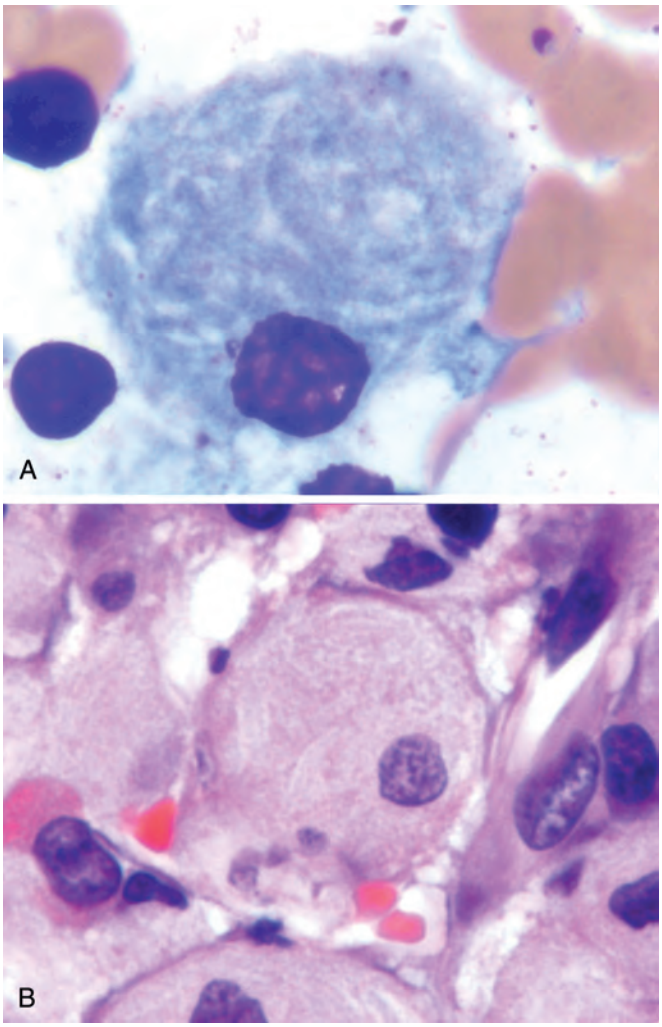

Figure 5-13 Gaucher disease involving the bone marrow. Gaucher cells (**A,** Wright stain; **B,** Hematoxylin and eosin) are plump macrophages that characteristically have the appearance in the cytoplasm of crumpled tissue paper due to accumulation of glucocerebroside. (Courtesy of Dr. John Anastasi, Department of Pathology, University of Chicago, Chicago, IL.)

neurons appear shriveled and are progressively destroyed. It is suspected that the lipids that accumulate in the phagocytic cells around blood vessels secrete cytokines that damage nearby neurons.

Clinical Features. The clinical course of Gaucher disease depends on the clinical subtype. In type I, symptoms and signs first appear in adult life and are related to splenomegaly or bone involvement. Most commonly there is pancytopenia or thrombocytopenia secondary to hypersplenism. Pathologic fractures and bone pain occur if there has been extensive expansion of the marrow space. Although the disease is progressive in the adult, it is compatible with long life. In types II and III, central nervous system dysfunction, convulsions, and progressive mental deterioration dominate, although organs such as the liver, spleen, and lymph nodes are also affected. The diagnosis of homozygotes can be made by measurement of glucocerebrosidase activity in peripheral blood leukocytes or in extracts of cultured skin fibroblasts. In principle, heterozygotes can be identified by detection of mutations. However, because more than 150 mutations in the glucocerebroside gene can cause Gaucher disease, currently it is not possible to use a single genetic test. However, with rapid advances in next generation sequencing (discussed later), it is likely that a comprehensive molecular diagnostic test for carriers will soon be developed.

Replacement therapy with recombinant enzymes is the mainstay for treatment of Gaucher disease; it is effective, and those with type I disease can expect normal life expectancy with this form of treatment. However, such therapy is extremely expensive. Because the fundamental defect resides in mononuclear phagocytic cells originating from marrow stem cells, allogeneic hematopoietic stem cell transplantation can be curative. Other work is directed toward correction of the enzyme defect by transfer of the normal glucocerebrosidase gene into the patient's hematopoietic stem cells. Substrate reduction therapy with inhibitors of glucosylceramide synthetase is also being evaluated.

Mucopolysaccharidoses (MPS)

The MPSs are a group of closely related syndromes that result from genetically determined deficiencies of enzymes involved in the degradation of mucopolysaccharides (glycosaminoglycans). Chemically, mucopolysaccharides are long-chain complex carbohydrates that are linked with proteins to form proteoglycans. They are abundant in the ground substance of connective tissue. The glycosaminoglycans that accumulate in MPSs are dermatan sulfate, heparan sulfate, keratan sulfate, and chondroitin sulfate. The enzymes involved in the degradation of these molecules cleave terminal sugars from the polysaccharide chains disposed along a polypeptide or core protein. In the absence of enzymes, these chains accumulate within lysosomes in various tissues and organs of the body.

Several clinical variants of MPS, classified numerically from MPS I to MPS VII, have been described, each resulting from the deficiency of one specific enzyme. All the MPSs except one are inherited as autosomal recessive traits; the exception, *Hunter syndrome*, is an X-linked recessive trait. Within a given group (e.g., MPS I, characterized by a deficiency of α-l-iduronidase), subgroups exist that result from different mutant alleles at the same genetic locus. Thus, the severity of enzyme deficiency and the clinical picture even within subgroups are often different.

In general, MPSs are progressive disorders, characterized by *coarse facial features*, *clouding of the cornea*, *joint stiffness*, and *mental retardation*. Urinary excretion of the accumulated mucopolysaccharides is often increased.

MORPHOLOGY

The accumulated **mucopolysaccharides are generally found in mononuclear phagocytic cells, endothelial cells, intimal smooth muscle cells, and fibroblasts** throughout the body. Common sites of involvement are thus the spleen, liver, bone marrow, lymph nodes, blood vessels, and heart.

Microscopically, affected cells are distended and have apparent clearing of the cytoplasm to create so-called balloon cells.