involvement traditionally has been divided into three categories: (1) Hurler disease (MPS I H) for severe deficiency with neurodegeneration, (2) Scheie disease (MPS I S) for later-onset disease without neurologic involvement and with relatively less severe disease in other organ systems, and (3) Hurler-Scheie syndrome (MPS I H/S) for patients intermediate between these extremes. MPS I H/S is characterized by severe somatic disease, usually without overt neurologic deterioration.

MPS I often presents in infancy or early childhood as chronic rhinitis, clouding of the corneas, and hepatosplenomegaly. As the disease progresses, nearly every organ system can be affected. In the more severe forms, cardiac and respiratory diseases become life-threatening in childhood. Skeletal disease can be quite severe, resulting in very limited mobility.

There are two current treatments for the MPS I diseases. Hematopoietic stem cell transplantation (HSCT) is the standard treatment for patients presenting at <2 years of age who appear to have or are at risk for neurologic degeneration. HSCT results in stabilization of CNS disease and reverses hepatosplenomegaly. It also beneficially affects cardiac and respiratory disease. HSCT does not eliminate corneal disease or result in the resolution of progressive skeletal disease. Enzyme therapy effectively addresses hepatosplenomegaly and alleviates cardiac and respiratory disease. The enzyme does not effectively penetrate the CNS and does not directly affect CNS disease. Enzyme therapy and HSCT appear to have similar effects on visceral signs and symptoms. Enzyme therapy poses a lower risk of life-threatening complications and may therefore be advantageous for patients who have attenuated manifestations without CNS disease. A combination of enzyme therapy and HSCT has been used, with enzyme therapy initiated prior to transplantation in an attempt to reduce the disease burden. The experience with this approach is not well documented, but it appears to have advantages over HSCT alone.

Enzyme therapy for Maroteaux-Lamy disease (MPS VI) has received U.S. Food and Drug Administration (FDA) approval. This very rare autosomal recessive disorder is characterized by hepatosplenomegaly, bone disease, heart disease, and respiratory compromise similar to those seen in MPS I; however, MPS VI is due to deficiency of arylsulfatase B and is not associated with neurologic degeneration.

Hunter disease (MPS II) is an X-linked disorder due to deficiency in iduronate sulfate sulfatase and has manifestations similar to those of MPS I, including neurologic degeneration. There is no corneal clouding or other eye disease. Like MPS I, MPS II is clinically variable, with CNS and non-CNS variants. HSCT has not been successful in treating CNS disease associated with MPS II. The FDA and the European Medicines Agency (EMA) have approved enzyme therapy for the visceral manifestations of MPS II.

### POMPE DISEASE

Acid maltase (acid α-glucosidase, GAA) deficiency, also called Pompe disease, is the only glycogen LSD. The classic severe infantile form presents with hypotonia, myocardiopathy, and hepatosplenomegaly. This variant is rapidly progressive and generally results in death in the first year of life. However, as with other LSDs, there are early- and late-onset forms of this disorder. The late-onset variants may be as common as 1 in 40,000; patients typically present with a slowly progressive myopathy that may resemble limb-girdle muscular dystrophy. Respiratory insufficiency may be the presenting sign or may develop with advancing disease. In late stages of the disease, patients may require mechanical ventilation, report swallowing difficulties, and experience loss of bowel and bladder control. Myocardiopathy is not usually seen in late-onset variants of Pompe disease.

The FDA and EMA have approved enzyme therapy for Pompe disease. This treatment clearly prolongs life in the infantile form, consistently resulting in improved cardiac function. Respiratory function is also improved in most treated infants. Some infants demonstrate marked improvement in motor functions, while others have minor changes in muscle tone or strength. Prevention of deterioration has been shown with GAA enzyme therapy in the late-onset forms. Early intervention with GAA enzyme therapy in such patients may limit or prevent deterioration, but very advanced disease will have significant irreversible components.