number of LSDs. The first was enzyme replacement therapy (ET) for Gaucher disease; this has been followed by additional ETs, but subsequent developments have included modified enzyme infusion, substrate inhibition, hematopoietic stem cell transplant (HSCT), pharmacologic chaperone therapy (which uses a small molecule to stabilize enzyme produced by the mutated gene and allows it to function), intrathecal enzyme delivery, and gene therapy. The technical ability to intervene for most LSDs now exists but with highly variable impact. Significant additional research is needed to reach the goals of long-term survival with good function and quality of life.

SELECTED DISORDERS

■ TAY-SACHS DISEASE

About 1 in 30 Ashkenazi Jews is a carrier for Tay-Sachs disease (total hexosaminidase A [Hex A] deficiency), resulting from α-chain gene mutations. The infantile form is a neurodegenerative disease that results in death in infancy. It is characterized by macrocephaly, loss of motor skills, increased startle reaction, and a macular cherry red spot. The juvenile-onset form presents as ataxia and dementia, with death by age 10–15 years. The adult-onset disorder is characterized by clumsiness in childhood; progressive motor weakness in adolescence; and additional spinocerebellar and lower-motor-neuron signs and dysarthria in adulthood; intelligence declines slowly, and psychiatric disorders are common. Screening for Tay-Sachs disease carriers is recommended in the Ashkenazi Jewish population. Sandhoff disease, due to a deficiency in both Hex A and Hex B resulting from defective β-chains, is phenotypically similar to Tay-Sachs disease with the addition of hepatosplenomegaly and bony dysplasias.

■ FABRY DISEASE

Fabry disease, an X-linked disorder and likely the most prevalent LSD, results from mutations in *GALA*, which encodes α-galactosidase A. The estimated prevalence of hemizygous males ranges from 1 in 40,000 to 1 in 3500 in selected populations.