lingual weakness, gastrointestinal dysmotility, and incontinence due to poor sphincter tone are now being recognized as part of the clinical spectrum. Individuals with advanced disease often require some form of ventilation and are dependent on a walking aid or wheelchair.

Laboratory findings include elevated levels of serum CK, aspartate aminotransferase, and lactate dehydrogenase. Levels of urine glucose tetrasaccharide (Hex4), a breakdown product of glycogen, are elevated, especially on the severe end of the disease spectrum. In infants, chest x-ray shows massive cardiomegaly, and electrocardiographic findings include a high-voltage QRS complex and a shortened PR interval. Muscle biopsy shows vacuoles that stain positive for glycogen; the muscle acid phosphatase level is increased, presumably from a compensatory increase of lysosomal enzymes. Electromyography reveals myopathic features, with irritability of muscle fibers and pseudomyotonic discharges. Serum CK is not always elevated in adults, and, depending on the muscle biopsied or tested, muscle histology or electromyography may not be abnormal. The affected muscle should be examined.

DIAGNOSIS The confirmatory step for a diagnosis of Pompe disease is enzyme assay demonstrating deficient acid α-glucosidase or a gene sequence with two pathogenic mutations in the GAA gene. Enzyme activity can be measured in muscle, cultured skin fibroblasts, or blood. Deficiency is usually more severe in the infantile form. Early diagnosis is the key to treatment efficacy.

GSD Mimicking Hypertrophic Cardiomyopathy Deficiency of LAMP2—also called Danon's disease—or of the protein kinase, AMP-activated gamma 2 noncatalytic subunit (PRKAG2), results in the accumulation of glycogen in the heart and skeletal muscle. LAMP2 deficiency is X-linked, whereas PRKAG2 deficiency is autosomal dominant. Clinically, both subsets of patients present primarily with hypertrophic cardiomyopathy. Their electrophysiologic abnormalities, particularly ventricular preexcitation and conduction defects, can distinguish them from patients with hypertrophic cardiomyopathy resulting from defects in sarcomere-protein genes. In patients with LAMP2 deficiency, mental delays are common and the onset of cardiac symptoms, including chest pain, palpitation, syncope, and cardiac arrest, can occur between the ages of 8 and 15 years—i.e., earlier than the average age of 33 years for patients with PRKAG2 deficiency. Patients as young as 9 years old have presented with PRKAG2 deficiency. A rapidly fatal congenital form of PRKAG2 presents in early infancy with severe hypertrophic cardiomyopathy and Wolff-Parkinson-White syndrome. In these patients, levels of PhK have been found to be low. The prognosis for LAMP2 deficiency is poor, with progressive end-stage heart failure early in adulthood. By contrast, except in the fatal congenital form, long-term survival is possible for patients with cardiomyopathy due to PRKAG2 mutations. Some patients may require the implantation of a pacemaker and aggressive control of arrhythmias. Congestive heart failure has been documented in patients with PRKAG2 deficiency.

TREATMENT GLYCOGEN STORAGE DISEASE MIMICKING HYPERTROPHIC CARDIOMYOPATHY

Heart transplantation has been suggested as a preventive measure for LAMP2 deficiency and noncongenital PRKAG2 deficiency.

SELECTED DISORDERS OF GALACTOSE METABOLISM

"Classic" *galactosemia* is caused by galactose 1-phosphate uridyltransferase (GALT) deficiency. It is a serious disease with an incidence of 1 in 60,000 and an early onset of symptoms. The newborn infant normally receives up to 40% of caloric intake as lactose (glucose + galactose). Without the transferase, the infant is unable to metabolize galactose 1-phosphate (Fig. 433e-1), which consequently accumulates, resulting in injury to parenchymal cells of the kidney, liver, and brain. After the first feeding, infants can present with vomiting, diarrhea, hypotonia, jaundice, and hepatomegaly. Patients with galactosemia are at increased risk for *Escherichia coli* neonatal sepsis; the onset of sepsis often precedes the diagnosis of galactosemia.

Widespread newborn screening for galactosemia has identified these infants early and allowed them to be placed on dietary restriction. Elimination of galactose from the diet reverses growth failure as well as renal and hepatic dysfunction, improving the prognosis. However, on long-term follow-up, some patients still have ovarian failure manifesting as primary or secondary amenorrhea as well as developmental delays and learning disabilities that increase in severity with age. Of women with classic galactosemia, 80–90% or more report hypergonadotropic hypogonadism. While most female patients are infertile when they reach childbearing age, a few have given birth. Several mutations appear to be protective, particularly the p.Ser135Leu mutation, which is more common in the African-American population. Methods for fertility preservation, such as cryopreservation, are still in the experimental stages. In addition, most patients have speech disorders, and a smaller proportion demonstrate poor growth and impaired motor function and balance (with or without overt ataxia). Adults on dairy-free diets have developed cataracts, tremors, and low bone density. The treatment of galactosemia to prevent long-term complications remains a challenge.

Deficiency of *galactokinase* (Fig. 433e-1) causes cataracts. Deficiency of *uridine diphosphate galactose 4-epimerase* can be benign when the enzyme deficiency is limited to blood cells but can be as severe as classic galactosemia when the enzyme deficiency is generalized.

SELECTED DISORDERS OF FRUCTOSE METABOLISM

Fructokinase deficiency, or essential fructosemia (Fig. 433e-1), causes a benign condition that is usually an incidental finding made through the detection of fructose as a reducing substance in the urine.

Deficiency of *fructose 1,6-bisphosphate aldolase* (aldolase B; hereditary fructose intolerance) is a serious disease in infants. These patients are healthy and asymptomatic until fructose or sucrose (table sugar) is ingested (usually from fruit, sweetened cereal, or sucrose-containing formula). Clinical manifestations may include jaundice, hepatomegaly, vomiting, lethargy, irritability, and convulsions. The incidence of celiac disease is higher among patients with hereditary fructose intolerance (>10%) than in the general population (1–3%). Laboratory findings show prolonged clotting time, hypoalbuminemia, elevation of bilirubin and aminotransferase levels, and proximal renal tubular dysfunction. If the disease is not diagnosed and intake of the noxious sugar continues, hypoglycemic episodes recur, and liver and kidney failure progresses, eventually leading to death. Treatment requires the elimination of all sources of sucrose, fructose, and sorbitol from the diet. Through this treatment, liver and kidney dysfunction improve, and catch-up growth is common; intellectual development is usually unimpaired. Over time, the patient's symptoms become milder, even after fructose ingestion, and the long-term prognosis is good.

Fructose 1,6-diphosphatase deficiency is characterized by childhood life-threatening episodes of acidosis, hypoglycemia, hyperventilation, convulsions, and coma. These episodes are triggered by febrile infections and gastroenteritis when oral food intake decreases. Laboratory findings show low blood glucose levels, high lactate and uric acid levels, and metabolic acidosis. Unlike hereditary fructose intolerance, this deficiency usually is not associated with an aversion to sweets, and renal tubular and liver functions are normal. Treatment of acute attacks requires the correction of hypoglycemia and acidosis by IV infusion. Later, avoidance of fasting and elimination of fructose and sucrose from the diet prevent further episodes. A slowly released carbohydrate such as cornstarch is useful for the long-term prevention of hypoglycemia. The prognosis is good, as patients who survive childhood develop normally.

GLOBAL CONSIDERATIONS

The GSDs and other inherited disorders of carbohydrate metabolism, although rare, have been reported in most ethnic populations. The prevalent genetic mutations for each disease may vary in different ethnic populations, but clinical symptoms are remarkably similar and treatment guidelines apply to all populations. The practice of newborn screening should be considered worldwide to intercept the rapid progression of many of these disorders.