Type IX GSD (Liver Phosphorylase Kinase Deficiency) Defects of PhK cause a heterogeneous group of glycogenoses. The PhK enzyme complex consists of four subunits (α, β, γ, and δ). Each subunit is encoded by different genes (X chromosome as well as autosomes) that are differentially expressed in various tissues. PhK deficiency can be divided into several subtypes on the basis of the gene/subunit involved, the tissues primarily affected, and the mode of inheritance. The most common subtype is X-linked liver PhK deficiency, which is also one of the most common liver glycogenoses. PhK activity may also be deficient in erythrocytes and leukocytes but is normal in muscle. Typically, a child between the ages of 1 year and 5 years presents with growth retardation and hepatomegaly. Children tend eventually to exhibit normal growth patterns initiated by a delayed growth spurt during puberty. Liver fibrosis has been identified in some patients, including children. Levels of cholesterol, triglycerides, and liver enzymes are mildly elevated. Fasting ketosis is another feature of the disease. Lactic and uric acid levels are usually normal. Hypoglycemia is typically mild; however, phenotypic variability is being increasingly recognized, with significant involvement in some cases of the X-linked form. The accumulated glycogen in liver (β particles, rosette form) has a frayed or burst appearance and is less compact than the glycogen seen in type I or type III GSD. Hepatomegaly and abnormal blood chemistries gradually return to normal with age. Most adults reach a normal final height and are practically asymptomatic, despite persistent PhK deficiency. The prognosis is usually good, and adult patients have minimal hepatomegaly. Some patients have significant ketosis and progressive liver disease that can advance to fibrosis and liver failure. It is recommended that adult patients be monitored for hepatic complications with regular CT or MRI scans.

Treatment is symptom based. A high-carbohydrate diet and frequent feedings are effective in preventing hypoglycemia. Some patients require no specific treatment. Recent studies have shown that instituting a treatment regimen of cornstarch and protein feedings early, even in seemingly stable patients, may prevent long-term complications. Blood ketones and glucose should be evaluated during times of stress.

Other subtypes of type IX GSD include an autosomal recessive form of liver and muscle PhK deficiency, an autosomal recessive form of liver PhK deficiency that often develops into liver cirrhosis, a muscle-specific PhK deficiency that causes cramps and myoglobinuria with exercise, and a cardiac-specific PhK deficiency that is lethal during infancy because of massive glycogen deposition in the myocardium. The finding of PhK deficiency in the cardiac-specific PhK deficiency may be a secondary phenomenon, as a subset of these patients have mutations in PRKAG2.

Other Liver Glycogenoses with Hepatomegaly and Hypoglycemia These disorders include hepatic phosphorylase deficiency (Hers disease, type VI) and hepatic glycogenosis with renal Fanconi syndrome (type XI). Patients with GSD type VI can have growth retardation, hyperlipidemia, and hyperketosis in addition to hepatomegaly and hypoglycemia. Some patients have a benign clinical course. GSD XI is caused by defects in the facilitative glucose transporter 2 (GLUT-2), which transports glucose and galactose in and out of hepatocytes, pancreatic cells, and the basolateral membranes of intestinal and renal epithelial cells. The disease is characterized by proximal renal tubular dysfunction, impaired glucose and galactose utilization, and accumulation of glycogen in liver and kidney.

SELECTED MUSCLE GLYCOGENOSES

DISORDERS WITH MUSCLE-ENERGY IMPAIRMENT

Type V GSD (Muscle Phosphorylase Deficiency, McArdle Disease) Type V GSD is an autosomal recessive disorder caused by deficiency of muscle phosphorylase. McArdle disease is a prototypical muscle-energy disorder as the enzyme deficiency limits ATP generation by glycogenolysis and results in glycogen accumulation.

CLINICAL AND LABORATORY FINDINGS Usually, symptoms first develop in adulthood and involve exercise intolerance with muscle cramps. Two types of activity tend to cause symptoms: (1) brief exercise of great intensity, such as sprinting or carrying heavy loads; and (2) less intense but sustained activity, such as climbing stairs or walking uphill. Most patients can engage in moderate exercise, such as walking on level ground, for long periods. Patients often exhibit the "second-wind" phenomenon, in which, after a short break from the initiation of strenuous physical effort, they are able to continue the activity without pain. Although most patients experience episodic muscle pain and cramping as a result of exercise, 35% report permanent pain that seriously affects sleep and other activities. About half of patients report burgundy-colored urine after exercise; this coloration results from myoglobinuria secondary to rhabdomyolysis. Intense myoglobinuria after vigorous exercise can lead to renal failure. Clinical heterogeneity is uncommon; however, there are cases with symptom onset as late as the eighth decade and cases that present early with hypotonia, generalized muscle weakness, and progressive respiratory insufficiency, which is often fatal.

Although cardiac involvement is not usually associated with muscle phosphorylase deficiency, hypertrophic cardiomyopathy has been observed in an adult patient with GSD V. In rare cases, electromyographic findings may suggest inflammatory myopathy, a diagnosis that may be confused with polymyositis. These patients may be at risk for statin-induced myopathy and rhabdomyolysis.

During rest, the serum CK level is usually elevated; after exercise, the CK level increases even more. Exercise also increases levels of blood ammonia, inosine, hypoxanthine, and uric acid; these abnormalities reflect residues of accelerated muscle purine nucleotide recycling as a result of insufficient ATP production. NADH is underproduced during physical exertion.

DIAGNOSIS Lack of an increase in blood lactate and exaggerated blood ammonia elevations after an ischemic exercise test are indicative of a muscle glycogenosis and suggest a defect in the conversion of glycogen or glucose to lactate. This abnormal exercise response, however, can also occur with other defects in glycogenolysis or glycolysis, such as deficiencies of muscle phosphofructokinase or debranching enzyme (when the test is done after fasting). The cycle test detects the hallmark heart rate observed during the second-wind phenomenon. A definitive diagnosis is made by enzymatic assay in muscle tissue or by mutation analysis of the myophosphorylase gene.

DISORDERS WITH PROGRESSIVE SKELETAL MUSCLE MYOPATHY AND/OR CARDIOMYOPATHY

Pompe Disease, Type II GSD (Acid α-1,4 Glucosidase Deficiency) Pompe disease is an autosomal recessive disorder caused by a deficiency of lysosomal acid α-1,4 glucosidase, an enzyme responsible for the degradation of glycogen in the lysosomes. This disease is characterized by the accumulation of glycogen in the lysosomes as opposed to accumulation in cytoplasm (as in the other glycogenoses).

CLINICAL AND LABORATORY FINDINGS The disorder encompasses a range of phenotypes. Each includes myopathy but differs in the age of onset, extent of organ involvement, and clinical severity. The most severe is the infantile form, with cardiomegaly, hypotonia, and death before the age of 1 year. Infants may appear normal at birth but soon develop generalized muscle weakness with feeding difficulties, macroglossia, hepatomegaly, and congestive heart failure due to hypertrophic cardiomyopathy.

The late-onset form (juvenile/late-childhood or adult form) is characterized by skeletal muscle manifestations, usually with minimal or no cardiac involvement, and a more slowly progressive course. The juvenile form typically presents as delayed motor milestones (if age of onset is early enough) and difficulty in walking. With disease progression, patients often develop swallowing difficulties, proximal muscle weakness, and respiratory muscle involvement. Death may occur before the end of the second decade.

Adults typically present between the second and seventh decades with slowly progressive myopathy without overt cardiac involvement. The clinical picture is dominated by slowly progressive proximal limb girdle muscle weakness. The pelvic girdle, paraspinal muscles, and diaphragm are most seriously affected. Respiratory symptoms include somnolence, morning headache, orthopnea, and exertional dyspnea. In rare instances, patients present with respiratory insufficiency as the initial symptom. Basilar artery aneurysms and dilation of the ascending aorta have been observed in patients with Pompe disease. Ptosis,