diagnostic even when the levels of urinary ALA and PBG have returned to normal or near normal. The various porphyrias that cause blistering skin lesions are differentiated by measuring porphyrins in urine, feces, and plasma. These porphyrias also should be confirmed at the DNA level by the demonstration of the causative gene mutation(s). It is often difficult to diagnose or "rule out" porphyria in patients who have had suggestive symptoms months or years in the past, and in relatives of patients with acute porphyrias, because porphyrin precursors and porphyrins may be normal. In those situations, detection of the specific gene mutation in the index case can make the diagnosis and facilitate the diagnosis and genetic counseling of at-risk relatives. Consultation with a specialist laboratory and physician will assist in selecting the heme biosynthetic gene or genes to be sequenced.

THE HEPATIC PORPHYRIAS

Markedly elevated plasma and urinary concentrations of the porphyrin precursors, ALA and/or PBG, which originate from the liver, are especially evident during attacks of neurologic manifestations of the four acute porphyrias—ADP, AIP, HCP, and VP. In PCT, excess porphyrins also accumulate initially in the liver and cause chronic blistering of sun-exposed areas of the skin.

ALA DEHYDRATASE-DEFICIENT PORPHYRIA (ADP)

ADP is a rare autosomal recessive acute hepatic porphyria caused by a severe deficiency of ALA dehydratase activity. To date, there are only a few documented cases, some in children or young adults, in which specific gene mutations have been identified. These affected homozygotes had <10% of normal ALA dehydratase activity in erythrocytes, but their clinically asymptomatic parents and heterozygous relatives had about half-normal levels of activity and did not excrete increased levels of ALA. The frequency of ADP is unknown, but the frequency of heterozygous individuals with <50% normal ALA dehydratase activity was ~2% in a screening study in Sweden. Because there are multiple causes for deficient ALA dehydratase activity, it is important to confirm the diagnosis of ADP by mutation analysis.

Clinical Features The clinical presentation depends on the amount of residual ALA dehydratase activity. Four of the documented patients were male adolescents with symptoms resembling those of AIP, including abdominal pain and neuropathy. One patient was an infant with more severe disease, including failure to thrive beginning at birth. The earlier age of onset and more severe manifestations in this patient reflect a more significant deficiency of ALA dehydratase activity. Another patient developed an acute motor polyneuropathy at age 63 that was associated with a myeloproliferative disorder. He was heterozygous for an *ALAD* mutation that presumably was present in erythroblasts that underwent clonal expansion due to the bone marrow malignancy.

Diagnosis All patients had significantly elevated levels of plasma and urinary ALA and urinary coproporphyrin (COPRO) III; ALAD activities in erythrocytes were <10% of normal. Hereditary tyrosinemia type 1 (fumarylacetoacetase deficiency) and lead intoxication should be considered in the differential diagnosis because either succinylacetone (which accumulates in hereditary tyrosinemia and is structurally similar to ALA) or lead can inhibit ALA dehydratase, increase urinary excretion of ALA and COPRO III, and cause manifestations that resemble those of the acute porphyrias. Heterozygotes are clinically asymptomatic and do not excrete increased levels of ALA but can be detected by demonstration of intermediate levels of erythrocyte ALA dehydratase activity or a specific mutation in the *ALAD* gene. To date, molecular studies of ADP patients have identified nine point mutations, two splice-site mutations, and a two-base deletion in the *ALAD* gene (Human Gene Mutation Database; *www.hgmd.org*). The parents in each case were not consanguineous, and the index cases had inherited a different *ALAD* mutation from each parent. Prenatal diagnosis of this disorder is possible by determination of ALA dehydratase activity and/or gene mutations in cultured chorionic villi or amniocytes.

TREATMENT **ALA-DEHYDRATASE DEFICIENT PORPHYRIA**

The treatment of ADP acute attacks is similar to that of AIP (see below). The severely affected infant referred to above was supported by hyperalimentation and periodic blood transfusions but did not respond to intravenous hemin and died after liver transplantation.

ACUTE INTERMITTENT PORPHYRIA (AIP)

This hepatic porphyria is an autosomal dominant condition resulting from the half-normal level of HMB synthase activity. The disease is widespread but is especially common in Scandinavia and Great Britain. Clinical expression is highly variable, and activation of the disease is often related to environmental or hormonal factors, such as drugs, diet, and steroid hormones. Attacks can be prevented by avoiding known precipitating factors. Rare homozygous dominant AIP also has been described in children (see below).

Clinical Features Induction of the rate-limiting hepatic enzyme ALA synthase in heterozygotes who have half-normal HMB synthase activity is thought to underlie the acute attacks in AIP. The disorder remains latent (or asymptomatic) in the great majority of those who are heterozygous for *HMBS* mutations, and this is almost always the case prior to puberty. In patients with no history of acute symptoms, porphyrin precursor excretion is usually normal, suggesting that half-normal hepatic HMB synthase activity is sufficient and that hepatic ALA synthase activity is not increased. However, under conditions where heme synthesis is increased in the liver, half-normal HMB synthase activity may become limiting, and ALA, PBG, and other heme pathway intermediates may accumulate and be excreted in the urine. Common precipitating factors include endogenous and exogenous steroids, porphyrinogenic drugs, alcohol ingestion, and low-calorie diets, usually instituted for weight loss.

The fact that AIP is almost always latent before puberty suggests that adult levels of steroid hormones are important for clinical expression. Symptoms are more common in women, suggesting a role for estrogens or progestins. Premenstrual attacks are probably due to endogenous progesterone. Acute porphyrias are sometimes exacerbated by exogenous steroids, including oral contraceptive preparations containing progestins. Surprisingly, pregnancy is usually well tolerated, suggesting that beneficial metabolic changes may ameliorate the effects of high levels of progesterone. Table 430-4 provides a partial list of the major drugs that are harmful in AIP (and also in HCP and VP). Extensive lists of unsafe and safe drugs are available on websites sponsored by the American Porphyria Foundation (*www.porphyriafoundation.com*) and the European Porphyria Initiative (*www.porphyria-europe.org*), and at the Drug Database for Acute Porphyrias website (*www.drugs-porphyria.com*). Reduced intake of calories and carbohydrate, as may occur with illness or attempts to lose weight, can also increase porphyrin precursor excretion and induce attacks of porphyria. Increased carbohydrate intake may ameliorate attacks. Studies in a knockout AIP mouse model indicate that the hepatic *ALAS1* gene is regulated by the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α). Hepatic PGC-1α is induced by fasting, which in turn activates *ALAS1* transcription, resulting in increased heme biosynthesis. This finding suggests an important link between nutritional status and the attacks in acute porphyrias. Attacks also can be provoked by infections, surgery, and ethanol.

Because the neurovisceral symptoms rarely occur before puberty and are often nonspecific, a high index of suspicion is required to make the diagnosis. The disease can be disabling but is rarely fatal. Abdominal pain, the most common symptom, is usually steady and poorly localized but may be cramping. Ileus, abdominal distention, and decreased bowel sounds are common. However, increased bowel sounds and diarrhea may occur. Abdominal tenderness, fever, and leukocytosis are usually absent or mild because the symptoms are neurologic rather than inflammatory. Nausea; vomiting; constipation; tachycardia; hypertension; mental symptoms; pain in the limbs, head, neck, or chest; muscle weakness; sensory loss; dysuria; and urinary