followed at 6- to 12-month intervals for early detection of recurrences, which are treated by additional phlebotomy.

An alternative when phlebotomy is contraindicated or poorly tolerated is a low-dose regimen of chloroquine or hydroxychloroquine, both of which complex with the excess porphyrins and promote their excretion. Small doses (e.g., 125 mg chloroquine phosphate twice weekly) should be given, because standard doses can induce transient, sometimes marked increases in photosensitivity and hepatocellular damage. Recent studies indicate that low-dose hydroxychloroquine is as safe and effective as phlebotomy in PCT. Hepatic imaging can diagnose or exclude complicating hepatocellular carcinoma. Treatment of PCT in patients with end-stage renal disease is facilitated by administration of erythropoietin.

HEREDITARY COPROPORPHYRIA (HCP)

HCP is an autosomal dominant hepatic porphyria that results from the half-normal activity of COPRO oxidase. The disease presents with acute attacks, as in AIP. Cutaneous photosensitivity also may occur, but much less commonly than in VP. HCP patients may have acute attacks and cutaneous photosensitivity together or separately. HCP is less common than AIP and VP. Homozygous dominant HCP and harderoporphyria, a biochemically distinguishable variant of HCP, present with clinical symptoms in children (see below).

Clinical Features HCP is influenced by the same factors that cause attacks in AIP. The disease is latent before puberty, and symptoms, which are virtually identical to those of AIP, are more common in women. HCP is generally less severe than AIP. Blistering skin lesions are identical to PCT and VP and begin in childhood in rare homozygous cases.

Diagnosis COPRO III is markedly increased in the urine and feces in symptomatic patients, and often persists, especially in feces, when there are no symptoms. Urinary ALA and PBG levels are increased (but less than in AIP) during acute attacks, but may revert to normal more quickly than in AIP when symptoms resolve. Plasma porphyrins are usually normal or only slightly increased, but they may be higher in cases with skin lesions. The diagnosis of HCP is readily confirmed by increased fecal porphyrins consisting almost entirely of COPRO III, which distinguishes it from other porphyrias.

Although the diagnosis can be confirmed by measuring COPRO oxidase activity, the assays for this mitochondrial enzyme are not widely available and require cells other than erythrocytes. To date, over 64 mutations have been identified in the *CPOX* gene, 67% of which are missense or nonsense (Human Gene Mutation Database; *www.hgmd.org*). Detection of a *CPOX* mutation in a symptomatic individual permits the identification of asymptomatic family members.

TREATMENT HEREDITARY COPROPORPHYRIA

Neurologic symptoms are treated as in AIP (see above). Phlebotomy and chloroquine are not effective for the cutaneous lesions.

VARIEGATE PORPHYRIA (VP)

VP is an autosomal dominant hepatic porphyria that results from the deficient activity of PROTO oxidase, the seventh enzyme in the heme biosynthetic pathway, and can present with neurologic symptoms, photosensitivity, or both. VP is particularly common in South Africa, where 3 of every 1000 whites have the disorder. Most are descendants of a couple who emigrated from Holland to South Africa in 1688. In other countries, VP is less common than AIP. Rare cases of homozygous dominant VP, presenting in childhood with cutaneous symptoms, also have been reported.

Clinical Features VP can present with skin photosensitivity, acute neurovisceral crises, or both. In two large studies of VP patients, 59% had only skin lesions, 20% had only acute attacks, and 22% had both. Acute attacks are identical to those in AIP and are precipitated by the same factors as AIP (see above). Blistering skin manifestations are similar to those in PCT, but are more difficult to treat and usually are of longer duration. Homozygous VP is associated with photosensitivity, neurologic symptoms, and developmental disturbances, including growth retardation, in infancy or childhood; all cases had increased erythrocyte levels of zinc protoporphyrin, a characteristic finding in all homozygous porphyrias so far described.

Diagnosis Urinary ALA and PBG levels are increased during acute attacks, but may return to normal more quickly than in AIP. Increases in fecal protoporphyrin and COPRO III and in urinary COPRO III are more persistent. Plasma porphyrin levels also are increased, particularly when there are cutaneous lesions. VP can be distinguished rapidly from all other porphyrias by examining the fluorescence emission spectrum of porphyrins in plasma since VP has a unique fluorescence peak at neutral pH.

Assays of PROTO oxidase activity in cultured fibroblasts or lymphocytes are not widely available. Over 174 mutations have been identified in the *PPOX* gene from unrelated VP patients (Human Gene Mutation Database; *www.hgmd.org*). The missense mutation R59W is the common mutation in most South Africans with VP of Dutch descent. Five missense mutations were common in English and French VP patients; however, most mutations have been found in only one or two families.

TREATMENT VARIEGATE PORPHYRIA

Acute attacks are treated as in AIP, and hemin should be started early in most cases. Other than avoiding sun exposure, there are few effective measures for treating the skin lesions. β-Carotene, phlebotomy, and chloroquine are not helpful.

THE ERYTHROPOIETIC PORPHYRIAS

In the erythropoietic porphyrias, excess porphyrins from bone marrow erythrocyte precursors are transported via the plasma to the skin and lead to cutaneous photosensitivity.

X-LINKED SIDEROBLASTIC ANEMIA (XLSA)

XLSA results from the deficient activity of the erythroid form of ALA synthase (ALA synthase 2) and is associated with ineffective erythropoiesis, weakness, and pallor.

Clinical Features Typically, males with XLSA develop refractory hemolytic anemia, pallor, and weakness during infancy. They have secondary hypersplenism, become iron overloaded, and can develop hemosiderosis. The severity depends on the level of residual erythroid ALA synthase activity and on the responsiveness of the specific mutation to pyridoxal 5′-phosphate supplementation (see below). Peripheral blood smears reveal a hypochromic, microcytic anemia with striking anisocytosis, poikilocytosis, and polychromasia; the leukocytes and platelets appear normal. Hemoglobin content is reduced, and the mean corpuscular volume and mean corpuscular hemoglobin concentration are decreased. Patients with milder, late-onset disease have been reported recently.

Diagnosis Bone marrow examination reveals hypercellularity with a left shift and megaloblastic erythropoiesis with an abnormal maturation. A variety of Prussian blue-staining sideroblasts are observed. Levels of urinary porphyrin precursors and of both urinary and fecal porphyrins are normal. The activity of erythroid ALA synthase 2 is decreased in bone marrow, but this enzyme is difficult to measure in the presence of the normal ALA synthase 1 housekeeping enzyme. Definitive diagnosis requires the demonstration of mutations in the erythroid *ALAS2* gene.

TREATMENT X-LINKED SIDEROBLASTIC ANEMIA

The severe anemia may respond to pyridoxine supplementation. This cofactor is essential for ALA synthase activity, and mutations in the pyridoxine binding site of the enzyme have been found in