prior to transplantation. After transplantation, her elevated urinary ALA and BPG levels returned to normal in 24 h, and she did not experience acute neurologic attacks for more than 3 years after transplant. Two AIP patients had combined liver and kidney transplants secondary to uncontrolled acute porphyria attacks, chronic peripheral neuropathy, and renal failure requiring dialysis. Both patients had a marked improvement with no attacks and normal urinary PBG levels after transplantation, as well as improvement of their neuropathic manifestations. More recently, a group from the United Kingdom reported their experience with liver transplantation in 10 AIP patients with recurrent attacks that were refractory to medical management and impaired quality of life. Patients had a complete biochemical and symptomatic resolution after transplant. The investigators reported a high rate of hepatic artery thrombosis in their series. Clearly, liver transplantation is a high-risk procedure and should be considered as a last resort in patients with severe recurrent attacks. Recently, liver-directed gene therapy has proven successful in the prevention of drug-induced biochemical attacks in a murine model of human AIP, and clinical trials of AAV-*HMBS* gene transfer have been initiated. In addition, preclinical studies of a hepatic-targeted RNA interference (RNAi) therapy directed to inhibit the markedly elevated hepatic *ALAS1* mRNA in the AIP mouse model prevented induced biochemical attacks and rapidly reduced the *ALAS1* mRNA during an ongoing attack.

PORPHYRIA CUTANEA TARDA (PCT)

PCT, the most common of the porphyrias, can be either sporadic (type 1) or familial (type 2) and can also develop after exposure to halogenated aromatic hydrocarbons. Hepatic URO decarboxylase is deficient in all types of PCT, and for clinical symptoms to manifest, this enzyme deficiency must be substantial (~20% of normal activity or less); it is currently attributed to generation of an URO decarboxylase inhibitor in the liver, which forms uroporphomethene in the presence of iron and under conditions of oxidative stress. The majority of PCT patients (~80%) have no *UROD* mutations and are said to have sporadic (type 1) disease. PCT patients heterozygous for *UROD* mutations have familial (type 2) PCT. In these patients, inheritance of a *UROD* mutation from one parent results in half-normal enzyme activity in liver and all other tissues, which is a significant predisposing factor, but is insufficient by itself to cause symptomatic PCT. As discussed below, other genetic and environmental factors contribute to susceptibility for both types of PCT. Because penetrance of the genetic trait is low, many patients with familial (type 2) PCT have no family history of the disease. HEP is an autosomal recessive form of porphyria that results from the marked systemic deficiency of URO decarboxylase activity with clinical symptoms in childhood.

Clinical Features Blistering skin lesions that appear most commonly on the backs of the hands are the major clinical feature (Fig. 430-3). These rupture and crust over, leaving areas of atrophy and scarring. Lesions may also occur on the forearms, face, legs, and feet. Skin friability and small white papules termed milia are common, especially on the backs of the hands and fingers. Hypertrichosis and hyperpigmentation, especially of the face, are especially troublesome in women. Occasionally, the skin over sun-exposed areas becomes severely thickened, with scarring and calcification that resembles systemic sclerosis. Neurologic features are absent.

A number of susceptibility factors, in addition to inherited *UROD* mutations in type 2 PCT, can be recognized clinically and can affect management. These include hepatitis C, HIV, excess alcohol, elevated iron levels, and estrogens. The importance of excess hepatic iron as a precipitating factor is underscored by the finding that the incidence of the common hemochromatosis-causing mutations, hemochromatosis gene (*HFE*) mutations C282Y and H63D, are increased in patients with types 1 and 2 PCT (Chap. 428). Excess alcohol is a long-recognized contributor, as is estrogen use in women. HIV is probably an independent but less common risk factor that, like hepatitis C, does not cause PCT in isolation. Multiple susceptibility factors that appear to act synergistically can be identified in the individual PCT patient. Patients

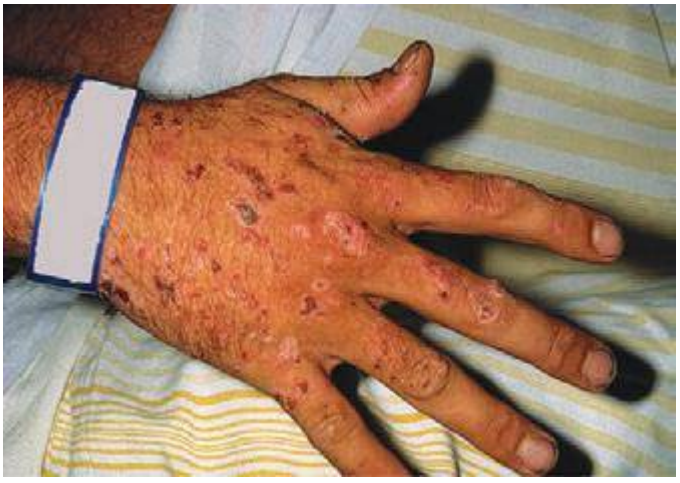

FIGURE 430-3 Typical cutaneous lesions in a patient with porphyria cutanea tarda. Chronic, crusted lesions resulting from blistering due to photosensitivity on the dorsum of the hand of a patient with porphyria cutanea tarda. *(Courtesy of Dr. Karl E. Anderson; with permission.)*

with PCT characteristically have chronic liver disease and sometimes cirrhosis and are at risk for hepatocellular carcinoma. Various chemicals can also induce PCT; an epidemic of PCT occurred in eastern Turkey in the 1950s as a consequence of wheat contaminated with the fungicide hexachlorobenzene. PCT also occurs after exposure to other chemicals, including di- and trichlorophenols and 2,3,7,8-tetrachlorodibenzo-(*p*)-dioxin (TCDD, dioxin).

Diagnosis Porphyrins are increased in the liver, plasma, urine, and stool. The urinary ALA level may be slightly increased, but the PBG level is normal. Urinary porphyrins consist mostly of uroporphyins and heptacarboxylate porphyrin, with lesser amounts of coproporphyrin and hexa- and pentacarboxylate porphyrins. Plasma porphyrins are also increased, and fluorometric scanning of diluted plasma at neutral pH can rapidly distinguish VP and PCT (Table 430-3). Isocoproporphyrins, which are increased in feces and sometimes in plasma and urine, are diagnostic for hepatic URO decarboxylase deficiency.

Type 2 PCT and HEP can be distinguished from type 1 by finding decreased URO decarboxylase in erythrocytes. URO decarboxylase activity in liver, erythrocytes, and cultured skin fibroblasts in type 2 PCT is approximately 50% of normal in affected individuals and in family members with latent disease. In HEP, the URO decarboxylase activity is markedly deficient, with typical levels of 3–10% of normal. Over 121 mutations have been identified in the *UROD* gene (Human Gene Mutation Database; *www.hgmd.org*). Of the mutations listed in the database, ~65% are missense or nonsense and ~10% are splice-site mutations. Most *UROD* mutations have been identified in only one or two families.

TREATMENT PORPHYRIA CUTANEA TARDA

Alcohol, estrogens, iron supplements, and, if possible, any drugs that may exacerbate the disease should be discontinued, but this step does not always lead to improvement. A complete response can almost always be achieved by the standard therapy, repeated phlebotomy, to reduce hepatic iron. A unit (450 mL) of blood can be removed every 1–2 weeks. The aim is to gradually reduce excess hepatic iron until the serum ferritin level reaches the lower limits of normal. Because iron overload is not marked in most cases, remission may occur after only five or six phlebotomies; however, PCT patients with hemochromatosis may require more treatments to bring their iron levels down to the normal range. To document improvement in PCT, it is most convenient to follow the total plasma porphyrin concentration, which becomes normal some time after the target ferritin level is reached. Hemoglobin levels or hematocrits and serum ferritin should be followed closely to prevent development of iron deficiency and anemia. After remission, continued phlebotomy may not be needed. Plasma porphyrin levels are