several responsive patients. Cofactor supplementation may make it possible to eliminate or reduce the frequency of transfusion. Unresponsive patients may be transfusion-dependent and require chelation therapy.

CONGENITAL ERYTHROPOIETIC PORPHYRIA (CEP)

CEP, also known as Günther's disease, is an autosomal recessive disorder. It is due to the markedly deficient, but not absent, activity of URO synthase and the resultant accumulation of URO I and COPRO I isomers. CEP is associated with hemolytic anemia and cutaneous lesions.

Clinical Features Severe cutaneous photosensitivity typically begins in early infancy. The skin over light-exposed areas is friable, and bullae and vesicles are prone to rupture and infection. Skin thickening, focal hypo- and hyperpigmentation, and hypertrichosis of the face and extremities are characteristic. Secondary infection of the cutaneous lesions can lead to disfigurement of the face and hands. Porphyrins are deposited in teeth and in bones. As a result, the teeth are brownish and fluoresce on exposure to long-wave ultraviolet light. Hemolysis is probably due to the marked increase in erythrocyte porphyrins and leads to splenomegaly. Adults with a milder later-onset form of the disease also have been described.

Diagnosis URO and COPRO (mostly type I isomers) accumulate in the bone marrow, erythrocytes, plasma, urine, and feces. The predominant porphyrin in feces is COPRO I. The diagnosis of CEP can be confirmed by demonstration of markedly deficient URO synthase activity and/or by the identification of specific mutations in the *UROS* gene. The disease can be detected in utero by measuring porphyrins in amniotic fluid and URO synthase activity in cultured amniotic cells or chorionic villi, or by the detection of the family's specific gene mutations. Molecular analyses of the mutant alleles from unrelated patients have revealed the presence of over 48 mutations in the *UROS* gene, including four in the erythroid-specific promoter of the *UROS* gene. Genotype/phenotype correlations can predict the severity of the disease. The CEP phenotype may be modulated by sequence variations in the erythroid specific ALA synthase 2, mutation of which typically causes XLP. One mutation (p.ArgR216WTrp) in *GATA1*, encoding the X-linked erythroid-specific transcription factor GATA binding protein 1 (*GATA1*), has been identified in an individual with CEP, thrombocytopenia, and β thalassemia.

TREATMENT CONGENITAL ERYTHROPOIETIC PORPHYRIA

Severe cases often require transfusions for anemia. Chronic transfusions of sufficient blood to suppress erythropoiesis are effective in reducing porphyrin production but result in iron overload. Splenectomy may reduce hemolysis and decrease transfusion requirements. Protection from sunlight and from minor skin trauma is important. β-Carotene may be of some value. Complicating bacterial infections should be treated promptly. Recently, bone marrow and cord blood transplantation has proven curative in several transfusion-dependent children, providing the rationale for stem cell gene therapy.

ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

EPP is an inherited disorder resulting from the deficient activity of ferrochelatase (FECH), the last enzyme in the heme biosynthetic pathway. EPP is the most common erythropoietic porphyria in children and, after PCT, the second most common porphyria in adults. EPP patients have FECH activities as low as 15–25% of normal in lymphocytes and cultured fibroblasts. Protoporphyrin accumulates in bone marrow reticulocytes and then appears in plasma, is taken up in the liver, and is excreted in bile and feces. Protoporphyrin transported to the vessels in the skin causes the nonblistering photosensitivity. In most symptomatic patients (~90%) with this autosomal recessive disorder, a mutation in one *FECH* allele is inherited with a relatively common (~10% of normal whites) intronic 3 (IVS3) alteration (IVS3–48T>C) that results in the low expression of the normal enzyme. In about 10% of EPP families, two *FECH* mutations have been found. Recently, deletion mutations in exon 11 of the *ALAS2* gene have been described, causing XLP that is clinically indistinguishable from EPP. The deletion of the C-terminal amino acids of ALAS2 results in its increased activity and the accumulation of protoporphyrin. XLP accounts for approximately 2–10% of cases with the EPP phenotype in Europe and North America.

Clinical Features Skin photosensitivity, which differs from that in other porphyrias, usually begins in childhood and consists of pain, redness, and itching occurring within minutes of sunlight exposure (Fig. 430-4). Photosensitivity is associated with substantial elevations in erythrocyte protoporphyrin and occurs only in patients with genotypes that result in ferrochelatase activities below ~35% of normal. Vesicular lesions are uncommon. Redness, swelling, burning, and itching can develop shortly after sun exposure and resemble angioedema. Pain symptoms may seem out of proportion to the visible skin involvement. Sparse vesicles and bullae occur in ~10% of cases. Chronic skin changes may include lichenification, leathery pseudovesicles, labial grooving, and nail changes. Severe scarring is rare, as are pigment changes, friability, and hirsutism. Unless hepatic or other complications develop, protoporphyrin levels and symptoms of photosensitivity remain remarkably stable over many years in most patients. Factors that exacerbate the hepatic porphyrias play little or no role in EPP.

The primary source of excess protoporphyrin is the bone marrow reticulocytes. Erythrocyte protoporphyrin is free (not complexed with zinc) and is mostly bound to hemoglobin. In plasma, protoporphyrin is bound to albumin. Hemolysis and anemia are usually absent or mild.

Although EPP is an erythropoietic porphyria, up to 20% of EPP patients may have minor abnormalities of liver function, and in about 5% of these patients the accumulation of protoporphyrins causes chronic liver disease that can progress to liver failure and death. Protoporphyrin is insoluble, and excess amounts form crystalline structures in liver cells (Fig. 430-4) and can decrease hepatic bile flow. Studies in the mouse model of EPP have shown that the bile duct epithelium may be damaged by toxic bile, leading to biliary fibrosis. Thus, rapidly progressive liver disease appears to be related to the cholestatic effects of protoporphyrins and is associated with increasing hepatic protoporphyrin levels due to impaired hepatobiliary excretion and increased photosensitivity. The hepatic complications also are often characterized by increasing levels of protoporphyrins in erythrocytes and plasma as well as severe abdominal and back pains, especially in the right upper quadrant. Gallstones

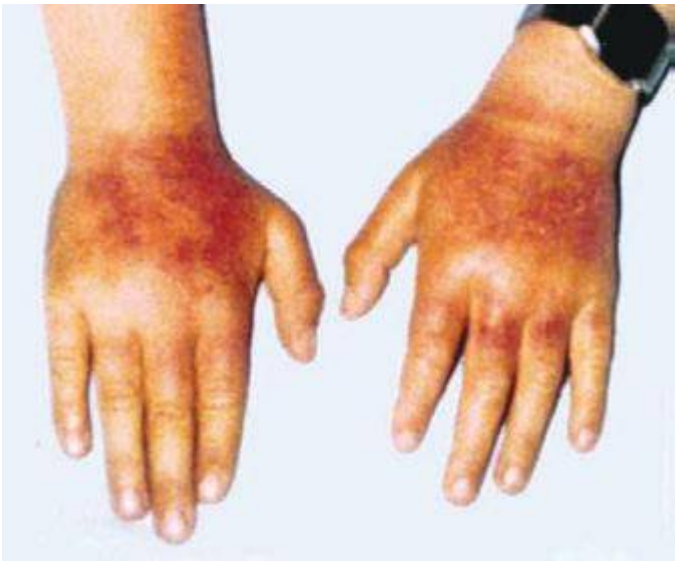

FIGURE 430-4 **Erythema and edema of the hands** due to acute photosensitivity in a 10-year-old boy with erythropoietic protoporphyria. *(From P Poblette-Gutierrez et al: Eur J Dermatol 16:230, 2006.)*