(URO synthase) catalyzes the rearrangement and rapid cyclization of HMB to form the asymmetric, physiologic, octacarboxylate porphyrinogen, uroporphyrinogen (URO'gen) III.

The fifth enzyme in the pathway, uroporphyrinogen decarboxylase (URO decarboxylase), catalyzes the sequential removal of the four carboxyl groups from the acetic acid side chains of URO'gen III to form coproporphyrinogen (COPRO'gen) III, a tetracarboxylate porphyrinogen. This compound then enters the mitochondrion via a specific transporter, ABCB6, where COPRO oxidase, the sixth enzyme, catalyzes the decarboxylation of two of the four propionic acid groups to form the two vinyl groups of protoporphyrinogen (PROTO'gen) IX, a decarboxylate porphyrinogen. Next, PROTO oxidase oxidizes PROTO gen to protoporphyrin IX by the removal of six hydrogen atoms. The product of the reaction is a porphyrin (oxidized form), in contrast to the preceding tetrapyrrole intermediates, which are porphyrinogens (reduced forms). Finally, ferrous iron is inserted into protoporphyrin to form heme, a reaction catalyzed by the eighth enzyme in the pathway, ferrochelatase (also known as heme synthetase or protoheme ferrolyase).

REGULATION OF HEME BIOSYNTHESIS

Regulation of heme synthesis differs in the two major heme-forming tissues, the liver and erythron. In the liver, the concentration of "free" heme regulates the synthesis and mitochondrial translocation of the housekeeping form of ALA synthase 1. Heme represses the synthesis of the ALA synthase 1 mRNA and interferes with the transport of the enzyme from the cytosol into mitochondria. Hepatic ALA synthase 1 is increased by many of the same chemicals that induce the cytochrome P450 enzymes in the endoplasmic reticulum of the liver. Because most of the heme in the liver is used for the synthesis of cytochrome P450 enzymes, hepatic ALA synthase 1 and the cytochrome P450s are regulated in a coordinated fashion, and many drugs that induce hepatic ALA synthase 1 also induce the CYP genes. The other hepatic heme biosynthetic enzymes are presumably expressed at constant levels, although their relative activities and kinetic properties differ. For example, normal individuals have high activities of ALA dehydratase, but low activities of HMB synthase, the latter being the second rate-limiting step in the pathway.

In the erythron, novel regulatory mechanisms allow for the production of the very large amounts of heme needed for hemoglobin synthesis. The response to stimuli for hemoglobin synthesis occurs during cell differentiation, leading to an increase in cell number. In contrast, the erythroid-specific ALA synthase 2 is expressed at higher levels than the housekeeping enzyme, and erythroid-specific control mechanisms regulate other pathway enzymes as well as iron transport into erythroid cells. Separate erythroid-specific and nonerythroid or "housekeeping" transcripts are known for the first four enzymes in the pathway. As noted above, housekeeping and erythroid-specific ALA synthases are encoded by genes on different chromosomes, but for each of the next three genes in the pathway, both erythroid and nonerythroid transcripts are transcribed by alternative promoters from their single respective genes (Table 430-2).

CLASSIFICATION OF THE PORPHYRIAS

As mentioned above, the porphyrias can be classified as either *hepatic* or *erythropoietic*, depending on whether the heme biosynthetic intermediates that accumulate arise initially from the liver or developing erythrocytes, or as *acute* or *cutaneous*, based on their clinical manifestations. Table 430-1 lists the porphyrias, their principal symptoms, and major biochemical abnormalities. Four of the five hepatic porphyrias—AIP, HCP, VP, and ADP—present during adult life with acute attacks of neurologic manifestations and elevated levels of one or both of the porphyrin precursors, ALA and PBG, and are thus classified as *acute porphyrias*. Patients with ADP have presented in infancy and adolescence. The fifth hepatic disorder, PCT, presents with blistering skin lesions. HCP and VP also may have cutaneous manifestations similar to PCT.

The erythropoietic porphyrias—CEP, EPP, and the recently described XLP—are characterized by elevations of porphyrins in bone marrow and erythrocytes and present with cutaneous photosensitivity. The skin lesions in CEP resemble PCT but are usually much more severe, whereas EPP and XLP cause a more immediate, painful, and nonblistering type of photosensitivity. EPP is the most common porphyria to cause symptoms before puberty. Around 20% of EPP patients develop minor abnormalities of liver function, with up to about 5% developing hepatic complications that can become life-threatening. XLP has a clinical presentation similar to EPP causing photosensitivity and liver disease.

DIAGNOSIS OF PORPHYRIA

A few specific and sensitive first-line laboratory tests should be used whenever symptoms or signs suggest the diagnosis of porphyria (Table 430-3). If a first-line test is significantly abnormal, more comprehensive testing should follow to establish the type of porphyria, including the specific causative gene mutation.

Acute Porphyrias An acute porphyria should be suspected in patients with neurovisceral symptoms after puberty, such as abdominal pain, and when the initial clinical evaluation does not suggest another cause. The urinary porphyrin precursors (ALA and PBG) should be measured (Fig. 430-2). Urinary PBG is virtually always increased during acute attacks of AIP, HCP, and VP and is not substantially increased in any other medical condition. Therefore, this measurement is both sensitive and specific. A method for rapid, in-house testing for urinary PBG, such as the Trace PBG kit (Thermo Scientific), can be used. Results from spot (single-void) urine specimens are highly informative because very substantial increases in PBG are expected during acute attacks of porphyria. A 24-h collection can unnecessarily delay diagnosis. The same spot urine specimen should be saved for quantitative determination of ALA, PBG, and creatinine, in order to confirm the qualitative PBG result and also to detect patients with ADP. Urinary porphyrins may remain increased longer than porphyrin precursors in HCP and VP. Therefore, it is useful to measure total urinary porphyrins in the same sample, keeping in mind that urinary porphyrin increases are often nonspecific. Measurement of urinary porphyrins alone should be avoided for screening, because these may be increased in disorders other than porphyrias, such as chronic liver disease, and misdiagnoses of porphyria can result from minimal increases in urinary porphyrins that have no diagnostic significance. Measurement of erythrocyte HMB synthase is not useful as a first-line test. Moreover, the enzyme activity is not decreased in all AIP patients, a borderline low normal value is not diagnostic, and the enzyme is not deficient in other acute porphyrias.

Cutaneous Porphyrias Blistering skin lesions due to porphyria are virtually always accompanied by increases in total plasma porphyrins. A fluorometric method is preferred, because the porphyrins in plasma in VP are mostly covalently linked to plasma proteins and may be less readily detected by high-performance liquid chromatography (HPLC). The normal range for plasma porphyrins is somewhat increased in patients with end-stage renal disease.

Although a total plasma porphyrin determination will usually detect EPP and XLP, an erythrocyte protoporphyrin determination is more sensitive. Increases in erythrocyte protoporphyrin occur in many other conditions. Therefore, the diagnosis of EPP must be confirmed by showing a predominant increase in free protoporphyrin rather than zinc protoporphyrin. In XLP, both free and zinc protoporphyrin are markedly increased in approximately equal proportions. Interpretation of laboratory reports can be difficult, because the term *free erythrocyte protoporphyrin* sometimes actually represents zinc protoporphyrin.

More extensive testing is justified when an initial test is positive. A substantial increase in PBG may be due to AIP, HCP, or VP. These acute porphyrias can be distinguished by measuring urinary porphyrins (using the same spot urine sample), fecal porphyrins, and plasma porphyrins. Assays for COPRO oxidase or PROTO oxidase are not widely available. More specifically, mutation analysis by sequencing the genes encoding HMB synthase, COPRO oxidase, and PROTO oxidase will detect almost all disease-causing mutations, and will be