by intracellular hepatic proteins may be one avenue that leads to such a reduction of heme. ALA synthetase activity is increased by carbohydrate deprivation, but the mechanism is unknown. The preponderance of several of the hepatic porphyrias among women, the onset of the disease after puberty, and the phenomenon of premenstrual and menstrual exacerbation of disease all suggest that circulating estrogens play a role in the course of the disease.

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Several conditions most likely represent acquired lesions of porphyrin production. Lead inhibits ALA dehydratase, which leads to increased ALA, but not excess PBG, excretion in the urine. Abdominal pain, peripheral neuropathy, and lesions of the central nervous system occur; lead-induced lesions in the porphyrin pathway may contribute to these symptoms, but their precise role is unclear. Chronic liver disease, hemolysis, hepatic neoplasms, and some medications are associated with increased coproporphyrin excretion.

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Acute Intermittent Porphyria

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The autosomal dominant pattern of inheritance of AIP results in only about 50 percent of normal activity of the enzyme PBG deaminase (formerly called uroporphyrinogen I synthetase).

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Investigation of the pathology of this disease in 92 affected families revealed that 97 percent (89 families) had diminished erythrocyte PBG deaminase activity; CRIM was expressed by 12 percent of this group (11 families). Studies of these CRIM-positive variants showed either a decrease in the kinetic properties and stability of PBG deaminase or enhanced binding or defective release of substrate by the enzyme. The remaining three percent of affected families had normal erythrocyte PBG deaminase levels. (ref 3) An explanation for some of these exceptional cases of AIP is that both the hepatocyte and the erythrocyte PBG deaminase are derived from a 10 kb gene containing 15 exons, but the messenger RNA (mRNA) is spliced differently in the two tissues, causing heme synthesis to be regulated differently. (ref 6, 12) Whereas the hepatic enzyme is translated from exons 1 and 3 through 15, the erythrocytic process splices off exon 1, translating its enzyme from exons 2 through 15. In the hepatocyte, a G•A mutation at the first intron immediately proximal to the splicing site prevents transcription of exon 1, disabling the hepatic enzyme and reducing PBG deaminase activity by 50 percent. In the erythrocyte, transcription starts at exon 2, which is situated 2.8 kb downstream from the mutation, and thus has no adverse effect on expression of the enzyme. Conversely, isolated erythrocyte PBG deaminase deficiency may occur in persons with normal hepatic enzyme function. In this