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Tables 3 and 4 Prepared for SCIENTIFIC AMERICAN Medicine by Mark G. Perlroth, M.D., and Robert Hagberg, M.S.

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Figure Captions

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Figure 1. Biochemistry of Porphyrias. The initial and rate-limiting step in the synthesis of heme is the synthesis of ë-aminolevulinic acid (ALA) from glycine and succinyl-CoA. This step is catalyzed by the intramitochondrial enzyme ALA synthetase. The next step, which takes place in the cytosol, consists of the condensation of two molecules of ALA by the enzyme ALA dehydratase to form the pyrrole ring porphobilinogen (PBG). PBG contains two carboxyl residues, acetate (-CH2COOH) and propionate (-CH2CH2COOH), and is water soluble. Condensation of four molecules of PBG by the enzyme PBG deaminase and the coenzyme uroporphyrinogen III cosynthetase yields uroporphyrinogen III, an asymmetric tetrapyrrole that contains four propionate and four acetate groups. Uroporphyrinogen I synthetase (but not uroporphyrinogen III cosynthetase) also catalyzes formation of uroporphyrinogen I, which can subsequently form coproporphyrinogen I. In addition, all of the porphyrinogen intermediates can oxidize to their corresponding porphyrins. However, only uroporphyrinogen III is a precursor of heme. Partial decarboxylation of uroporphyrinogen III by the enzyme uroporphyrinogen decarboxylase yields coproporphyrinogen III, which contains four carboxyl groups. Coproporphyrinogen III reenters the mitochondrion and is oxidized by coproporphyrinogen oxidase to form protoporphyrinogen IX, with a loss of two more propionate residues. The enzyme protoporphyrinogen oxidase catalyzes further oxidation of the molecule, with a loss of six hydrogen atoms, to form protoporphyrin IX. Finally, the insertion of Fe[2+] by the mitochondrial enzyme ferrochelatase completes the synthesis of heme. The proximity in the mitochondrion of heme (the end product) and ALA synthetase (the inducible rate-limiting enzyme) facilitates regulation of porphyrin synthesis. Heme inhibits ALA synthetase activity directly and also acts to repress synthesis of the enzyme. The porphyrias are caused by inherited defects in specific enzymes in the heme synthetic pathway. The porphyria associated with each defective step is shown in blue. A partial blockage at any step in the pathway, when combined with certain endogenous or exogenous factors, results in an overproduction of precursor

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s or of products normally produced only in small amounts and is associated with overt clinical disease.

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