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# URINARY PORPHYRIN PROFILING

The following text and figures are extracted from  
*Laboratory Evaluations in Functional and Integrative Medicine*  
Richard S. Lord and James A. Bralley, editors  
Chapter 8, Toxicants and Detoxification



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## URINARY PORPHYRIN PROFILING

Heme is required at the active sites of oxygen-binding, oxygen utilizing and oxidizing systems, hemoglobin (and myoglobin), cytochromes and mitochondrial electron carriers, respectively. Heme is a macrocyclic, iron-sequestering molecule that is synthesized in most human tissues (predominantly liver and bone marrow) by a pathway with intermediates called porphyrinogens. The final phase of metal incorporation inserts iron, cobalt or magnesium into the protoporphyrin ring to produce heme, cobalamin and, in plants, chlorophyll, respectively. These complex organometallic structures are sometimes called the pigments of life.<sup>1</sup> Porphyrins are oxidized by-products that have escaped from the pathway. The spilling of porphyrins into urine

or more porphyrinogens, that leads to the corresponding rise of porphyrins in urine is called porphyria. The term porphyria may be reserved for primary conditions exhibiting specific clinical symptoms caused by an inherited defect in one or more of the heme biosynthetic enzymes.<sup>2</sup> Porphyrinopathy is an umbrella term for any disorder in porphyrin metabolism. For brevity in tables, the abbreviations Uro, Pre, and Copro may be used to designate uroporphyrinogen I and III, precoproporphyrin and coproporphyrin I and III, respectively.

**Table 8.5 Symptoms Associated with Porphyrinopathies**

Primary Complaints	Associated Symptoms	Condition Exacerbated by
Neurologic presentations: Abdominal pain; nausea; vomiting; constipation; seizures	Headaches; difficulty in concentration; personality changes; weakness; muscle and joint aches; unsteady gait, poor coordination; numbness, tingling of arms and legs; fluid retention; rapid heart rate; high blood pressure; increased sweating; intermittent fever	Low carbohydrate diets (skipped meals); intake of alcoholic beverages; medications, including sulfa-drug antibiotics, barbiturates, estrogen, birth control pills; exposure to toxic chemicals
Cutaneous presentations: Changes in skin pigmentation; changes in facial hair; fragile skin; rashes; blistering	Dark-colored urine (especially after its exposure to sunlight), and above symptoms may be present	Above factors, and skin symptoms made worse by exposure to sunlight. Copper or brass jewelry exacerbates reaction

generates porphyriurias. For example, iron deficiency causes a blockage near the end of the pathway where iron is incorporated resulting in elevated levels of erythrocyte protoporphyrin (EP) and serum zinc protoporphyrin (ZnPP or ZP).

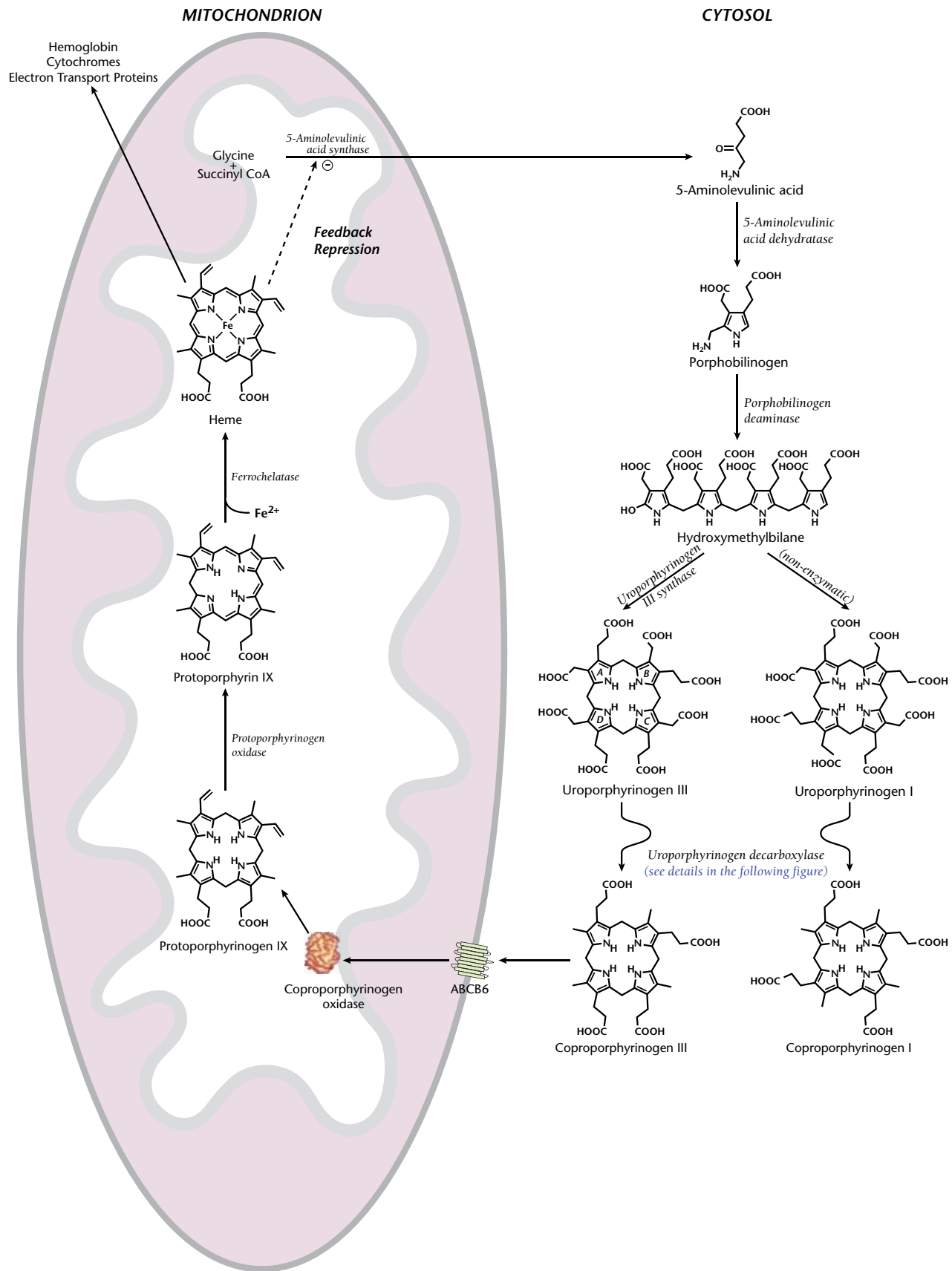
The porphyrin pathway involves eight enzymes in a sequence beginning and ending in the mitochondria, with four steps occurring in the cytosol. Glycine and succinyl-CoA are joined in the initial reaction of the sequence, producing delta-aminolevulinic acid (ALA). The porphyrin ring is formed in subsequent steps (Figure 8.8). Restriction of an enzyme activity following uroporphyrinogen creation produces back up of one

### Inherited Enzyme Defects

The utility of urinary porphyrins as a diagnostic tool is not new – its use has been documented in the medical literature since 1934, and review articles summarize the genetic and molecular aspects of the various clinical manifestations that are listed in Table 8.6.<sup>3,4</sup> Porphyrins, which can be inherited or acquired, are often diagnosed with the aid of information regarding the distribution profile of individual porphyrin intermediates in urine.<sup>5</sup> Porphyrins are particularly well suited as biomarkers for two reasons. First, the pathway is highly active, so any

**Table 8.6 Enzymatic Defects of Some Inherited Porphyrins**

Porphyrin	Enzymatic defect	Porphyria
Acute intermittent porphyria	Porphobilinogen deaminase	Uro
Congenital erythropoietic porphyria	Uroporphyrinogen cosynthetase	Uro, Copro
Porphyria cutanea tarda and hepatoerythropoietic porphyria	Uroporphyrinogen decarboxylase	Uro, Hepta
Hereditary coproporphyrin	Coproporphyrinogen	Copro
Variegate porphyria	Protoporphyrinogen	Copro
Protoporphyrin	Ferrochelatase	None (Fecal Proto)



disturbance tends to cause rapid and relatively large accumulations of intermediates. Second, the enzymes of the porphyrin-producing pathway are widely distributed in human tissues and some of them are highly sensitive to the presence of various toxins.

Up-regulation of the heme biosynthetic pathway is another mechanism by which porphyria can be precipitated. Table 8.7

<b>Table 8.7 – Conditions That Can Cause Porphyria</b>	
<b>Genetic Disorders</b>	
Hereditary hyperbilirubinemias	– Dubin–Johnson syndrome – Rotor’s syndrome
Bronze baby syndrome	
Erythrohepatic protoporphyria	
Hereditary tyrosinemia	
<b>Metabolic Disturbances</b>	
Diabetes mellitus	
Myocardial infarction	
Hematologic diseases	– Hemolytic, sideroachrestic, sideroblastic, aplastic anemias – Ineffective erythropoiesis (intramedullary hemolysis) – Pernicious anemia – Thalassemia – Leukemia – Erythroblastosis
Disturbance of iron metabolism	– Hemosiderosis – Idiopathic and secondary hemochromatosis – Iron deficiency anemia
<b>Diseases</b>	
Infectious diseases	– Mononucleosis – Acute poliomyelitis
Liver diseases	– Cirrhosis – Active chronic hepatitis – Toxic and infectious hepatitis – Fatty liver – Alcoholic liver syndromes – Drug injury – Cholestasis – Cholangitis – Biliary cirrhosis
Malignancies	– Hepatocellular tumors – Hepatic metastases – Pancreatic carcinoma – Lymphomatosis
<b>Other Conditions</b>	
Pregnancy	
Carbohydrate fasting	

summarizes various conditions that generate porphyria by altering the overall activity of the pathway. Elevations from these factors can be mistaken for genetic or toxicant-mediated porphyria. Calculation of ratios of key intermediates like precoproporphyrin to uroporphyrinogen can identify the presence of specific inhibitions caused by toxicants while minimizing possible effects of creatinine variability when overnight urine is utilized. Increases in the ratio, indicate true abnormal intermediate accumulation independent of overall pathway fluctuations. Active porphyria occurs when ALA overproduction coincides with inhibition of one or more of the porphyrin pathway enzymes. In other words, the blockage is apparent as elevations of specific intermediates relative to others when the pathway is accelerated. It is estimated that among cases of inherited porphyrinogenic enzyme deficiencies, as many as 90% are healthy throughout adulthood until their porphyria is triggered mid-life by toxic chemicals or drugs, an acute illness or worsening chronic condition, or a major dietary change. <sup>6</sup>

**Environmental Toxicant Effects**

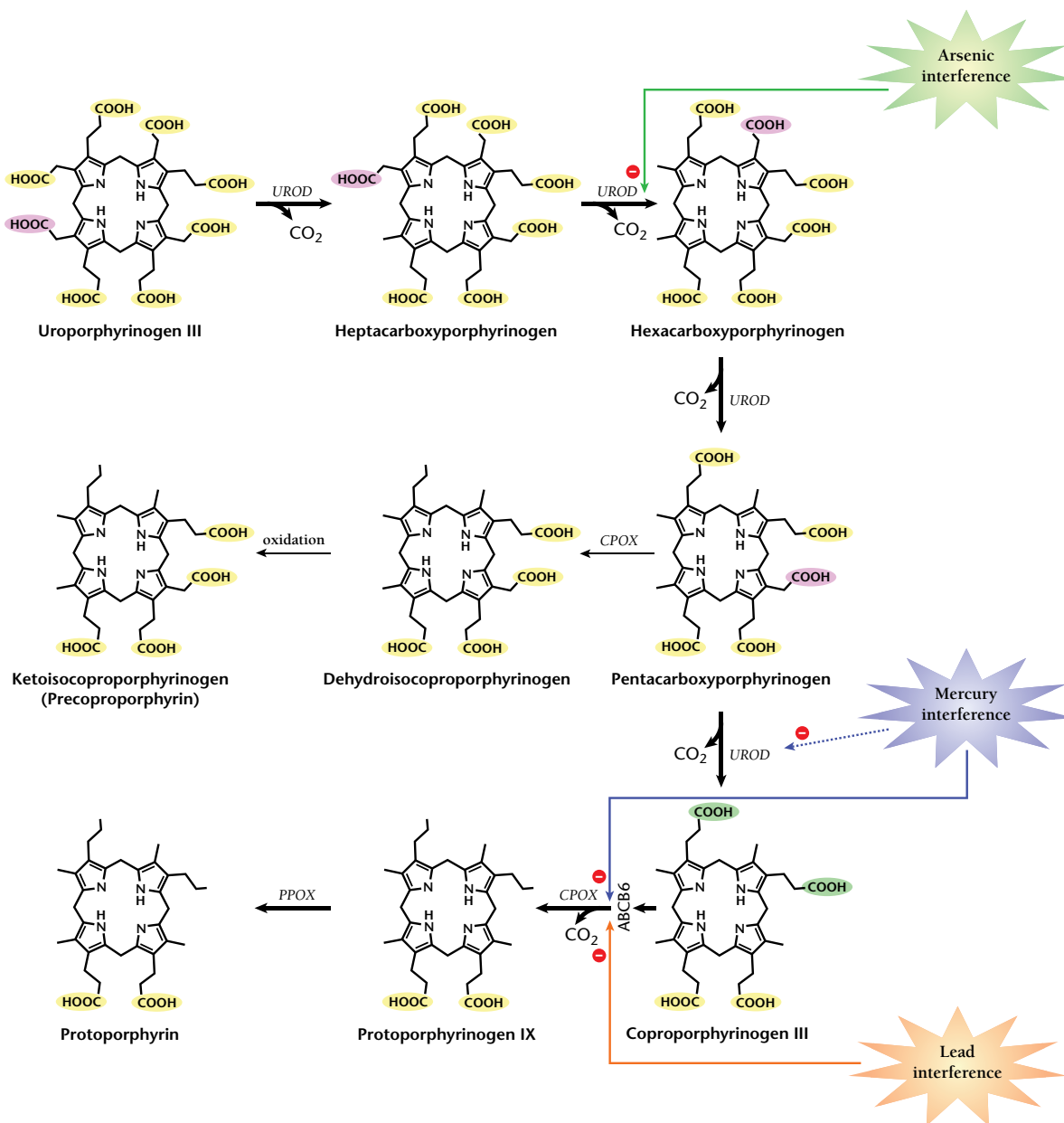
Porphyrins measured in urine serve as biomarkers of toxin effects. Toxic chemicals can affect human biochemistry at any level of exposure. Fortunately the body has mechanisms for transforming, eliminating or compartmentalizing the many toxic chemicals encountered over a lifetime. Nonetheless these “safety” mechanisms may be inadequate in the modern industrialized society, especially for susceptible people such as the elderly, children, individuals with poor nutritional habits, and others who are physiologically stressed. <sup>7,8</sup> Recognizing and identifying offending chemicals can present a difficult challenge for the clinician. Many chemicals exert their effect at such low concentrations that they escape direct detection except by very sophisticated laboratory methods. Compartmentalization in tissues, especially brain, that are difficult to access makes routine direct concentration measurements impractical. Elevated porphyrins in urine serve as such biomarkers to verify the clinical observations of symptomatic effects of toxicity. Current analytical advances make routine profiling of the multiple intermediates a powerful tool for assessing toxic effects of heavy metals and some xenobiotics.

Details of the decarboxylation steps in heme biosynthesis are shown in Figure 8.9. Porphyrinogens (precursors to porphyrins) are easily oxidized to porphyrins by free toxic metals non-enzymatic catalysis. However, enzyme-specific effects result from binding of toxins to specific sites on the enzymes that carry out the porphyrin biosynthesis. In rats, chronic low-level exposure to methyl mercury was associated with characteristic urinary porphyrin changes, which included highly elevated levels of the coproporphyrin and pentacarboxyporphyrin intermediates, not

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found in urine of unexposed animals. These distinct changes increased in a dose- and time-related fashion, and reverted to normal levels once exposure was removed.<sup>9</sup> In human studies, a comparable change in the urinary porphyrin profile was also observed among dentists with occupational exposure to mercury.<sup>10</sup> Urinary porphyrin profiles were also shown to correlate significantly with mercury body burden and with specific neurobehavioral deficits associated with low level (mean levels of 36 mcg/L) mercury exposure.<sup>11</sup> Urinary mercury levels greater than 20 mcg/ml produced urinary porphyrin elevations (esp. precop-

roporphyrin) comparable to those found in rats with specific low level mercury exposure.<sup>10,12</sup> Ongoing validation studies of dental practitioners with low-level occupational mercury exposure have continued to demonstrate the predicted urinary porphyrin profile change (elevated urinary pentacarboxyporphyrin, precoproporphyrin and coproporphyrin) among subjects.<sup>12</sup> A final fulfillment of proof that the porphyria is not only characteristic of mercury exposure but, in fact, caused by the toxic effects of mercury has come by demonstration of sequential induction and removal of porphyria by exposure followed by mobiliza-

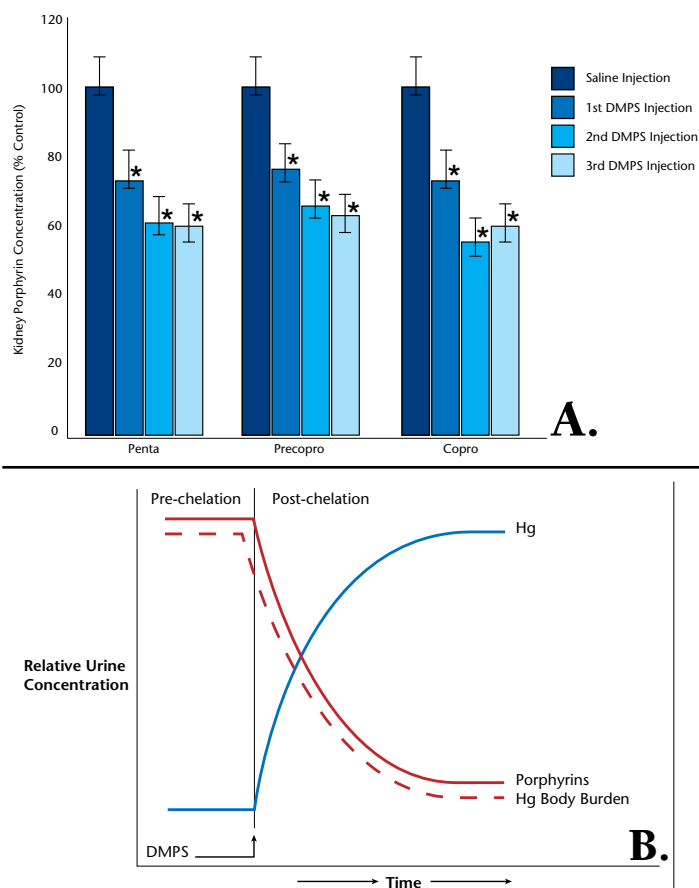


**Figure 8.9 Toxic Metal Interferences in Porphyrin Pathway Decarboxylation Reactions**

The normal heme-forming pathway involves six decarboxylation steps, four of which are carried out by a single enzyme, uroporphyrinogen decarboxylase (UROD). Binding of toxicants causes the creation of an altered binding site that causes slowing of the conversion of pentacarboxyporphyrinogen to coproporphyrinogen. Accumulating pentacarboxyporphyrinogen may be acted upon by coproporphyrinogen oxidase (CPOX) and oxidized, yielding the abnormal product, ketoisocoproporphyrinogen that is thought to account for the chromatographic peak called the precoproporphyrin. Carboxyl groups are shaded yellow and the groups that are cleaved by UROD and CPOX are shaded purple and green, respectively.

tion with the metal chelator DMPS.<sup>13</sup> The data from this study is reproduced in Figures 8.10.

Since the conversion of uroporphyrinogen to coproporphyrinogen III involves four decarboxylation reactions catalyzed by the same enzyme, it is initially curious that toxins affect only the fourth reaction. The explanation seems to lie in the fact that uroporphyrinogen decarboxylase is a complex dimeric protein containing two active sites. The dimeric structure allows for alteration as carboxyl group removal decreases substrate polarity.<sup>14</sup> This allows the rationale for slowing of the final decarboxylation of pentacarboxyporphyrin by toxins without affecting the previous three decarboxylation.<sup>15</sup> Thus the distinctive pattern of mercury poisoning can appear in porphyrin profiles. Laboratory Figanalysis of urine, from a mercury-toxic patient by high performance liquid chromatography, shows an abnormal compound



**Figure 8.10 Porphyrin Changes with Consecutive DMPS Injections**

In mercury-exposed rats, urinary levels of pentacarboxyporphyrin, precoproporphyrin and coproporphyrin are elevated. The data shown in Fig. A reveal how kidney levels of these porphyrins are lowered with removal of mercury by 3 consecutive DMPS injections (100 mg/kg, ip) at 72 hour intervals. The porphyrin levels are displayed as a percentage of pre-chelation saline injection concentrations. \* Indicates a significantly different result ( $p < 0.05$ ). Based on such data from animal and human studies, the hypothetical relationship depicted in Fig. B was proposed. The presence of mercury produces elevated porphyrin levels and its removal is indirectly related to lowering of the characteristic porphyrinuria.

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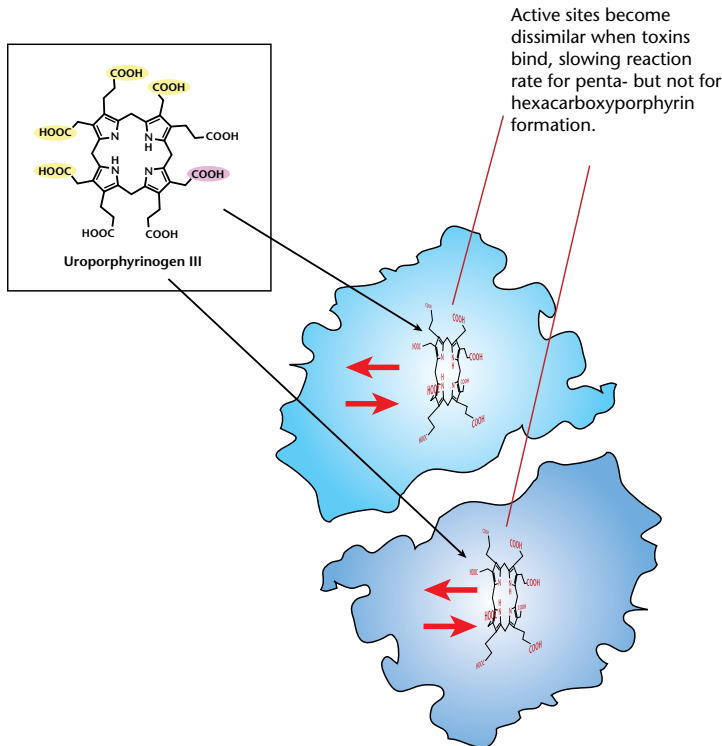
that is called precarboxyporphyrin because it emerges shortly ahead of carboxyporphyrin. This compound is thought to be the ketoisocoproporphyrin by-product shown in Figure 8.9, although no definitive structural confirmation studies are available at the time of writing this book. Further back up of intermediates can produce elevations of penta- and hexacarboxyporphyrins. The mechanism for toxic metal interference is thought to involve active site discrimination on the uroporphyrinogen decarboxylase enzyme as illustrated in Figure 8.11.<sup>9</sup>

A recent finding of heme transporters that regulate movement of coproporphyrin III into the mitochondria offers an alternative point of toxic interference to explain the porphyrias associated with toxic elements.<sup>16</sup> Inhibition of the transporter would tend to raise levels of coproporphyrin III and precursors. The preferential elevation of copro I relative to copro III by arsenic as shown in Table 8.9 suggests that both copro III and I should be measured. This perturbation points to involvement of uroporphyrinogen decarboxylase because the elevation of copro I over III indicates a block in the formation rather than the disposition of copro III. Such a block would cause more spilling of uro into the non-productive pathway to copro I.

Chronic exposure to toxic metals, including lead, mercury, arsenic, aluminum, and cadmium often results in organ-specific accumulation that compromises target organ physiology. Heavy metals damage many aspects of metabolism. Similarly, chronic exposure to organic chemicals such as herbicides, pesticides, and industrial and manufacturing by-products can have deleterious impact on the body's biochemistry which results in the decline of cellular function.<sup>17</sup> A well-studied incident of hexachlorobenzene-induced porphyrinuria occurred due to ingestion of wheat that had been preserved with the chlorinated hydrocarbon intending that it would be used for crop planting.<sup>18,19</sup> Polychlorinated phenyls (e.g. dioxin, PCBs),<sup>20</sup> and many drugs (Table 8.11)<sup>21</sup> may induce porphyrinuria.<sup>22</sup> Whatever the cause, when porphyrins accumulate they induce oxidative cellular damage and contribute to lowered hemoglobin. Chronological listings of reports showing porphyrias associated with mercury and arsenic are provided in Tables 8.8 and 8.9, respectively. Table 8.10 provides a summary of the most common patterns associated with specific environmental toxins.

### Clinical Applications

Attacks of neuropsychiatric symptoms that occur in acute porphyrias may be due to a toxic surplus of 5-aminolevulinic acid or deficiency of vital hemoproteins resulting from impaired synthesis of heme. Accumulation of phototoxic porphyrins produces the solar hypersensitivity found in cutaneous porphyrias.<sup>1</sup>



**Figure 8.11 Uroporphyrin Decarboxylase Active Dimer**

The blue shaded form represents the silhouette of the enzyme uroporphyrin decarboxylase. The crystallographic three-dimensional structural detail has been determined for this enzyme, showing that the active form is a dimer with the two active sites facing toward the center. The inset shows the structure of uroporphyrinogen III (Uro) with the first three leaving carboxyl groups shaded in yellow and the final one in purple. Two molecules of Uro are shown in oblique view at the active sites and the red arrows indicate dissociation and re-association as the substrate is altered. As carboxyl groups are removed, the sequentially-created intermediates must shift their positions. Toxicants like heavy metals may bind to the enzyme in ways that alter the affinity for specific intermediates.

In these conditions, the most affected heme precursors are frequently found at levels more than several-fold greater than laboratory upper limits during symptomatic porphyrias. Milder presentations are found in most environmental toxin-induced porphyriurias. It has been suggested that chronic, mild porphyria may be an etiologic factor in multiple chemical sensitivities, Persian Gulf War syndrome, chronic fatigue and conditions associated with silicone breast implants, although direct evidence for such causation is lacking.<sup>36</sup>

Mounting evidence implicates mercury as a specific risk factor for regressive autism.<sup>37</sup> Arguments for potential interactions such as interference with the function of methionine synthase in the brain have been proposed.<sup>38</sup> However, mercury exposure levels from thimerosal-preserved immunizations or maternal transfer are relatively low, making demonstration of metabolic toxicity difficult. Examination of patterns for urinary excretion of pentacarboxyporphyrin, precoproporphyrin and coproporphyrin has revealed significantly higher occurrences in autistic children compared with controls.<sup>24</sup> These results have been confirmed

**Table 8.8 Reports Showing Porphyria Associated with Mercury Toxicity**

Year	Principal Finding	Reference
1991	Dose response increases of penta, precopro and copro in rats (24 hr)	9
1995	Higher levels of penta, precopro and copro in dentists (spot conc. and ng/mg creat.)	11
1996	Higher levels of penta, precopro and copro in dentists correlated with higher urinary mercury and neurological effects	12
2001	Rats dosed with mercury show declining penta, precopro and copro with sequential dosing with DMPS	13
2001	Editorial discussion of rationale for extrapolation of rat studies to humans	23
2006	Higher copro and precopro in autistics (but not aspergers) and lowering with DMSA treatment	24
2006	Higher copro (not penta, precopro not measured) in autism and ASD	25
2007	In rats, total porphyrins (colorimetric) increased with Hg exposure, but not when Se-Met was coadministered	26

**Table 8.9 Reports Showing Porphyria Associated with Arsenic Toxicity**

Year	Principal Finding	Reference
1994	Uro, copro I (high I/III ratio)	27
1999	Uro, Copro III and high I/III ratio (humans)	28
2001	ALA (As (III) in rats and guinea pigs)	29
2002	Uro, copro I, copro III, proto IV (As(V) in rats)	30
2002	Uro and penta (As (III) in humans)	31
2002	Copro I, III and proto IV (rat and human)	32
2004	Copro I and III (mice)	33
2006	Copro I and, later, III (mice)	34
2006	Copro I and high I/III ratio (in geese)	35

**Table 8.10 Environmental Toxin-induced Porphyrinurias\***

Environmental toxin	Urinary porphyrin elevation (or as noted)
Arsenic	Uroporphyrins Coproporphyrin I High Copro I/III ratio
Mercury	Precoproporphyrin Pentacarboxyporphyrin Coproporphyrin (total)
Lead	Aminolevulinic acid (ALA) Coproporphyrin III Coproporphyrin I (sometimes) Zinc protoporphyrin
Hexachlorobenzene	Uroporphyrins
Methyl chloride	Coproporphyrins
Dioxin	Uroporphyrins
Polyvinylchloride	Coproporphyrins
Polybrominated biphenyl	Coproporphyrins (Uroporphyrins)
* Rule out use of ethanol, estrogens, oral contraceptives, antibiotics, sedatives, analgesics, dietary brewer's yeast, and rule out pregnancy, liver disease, malignancies and pernicious or iron deficiency anemias.	

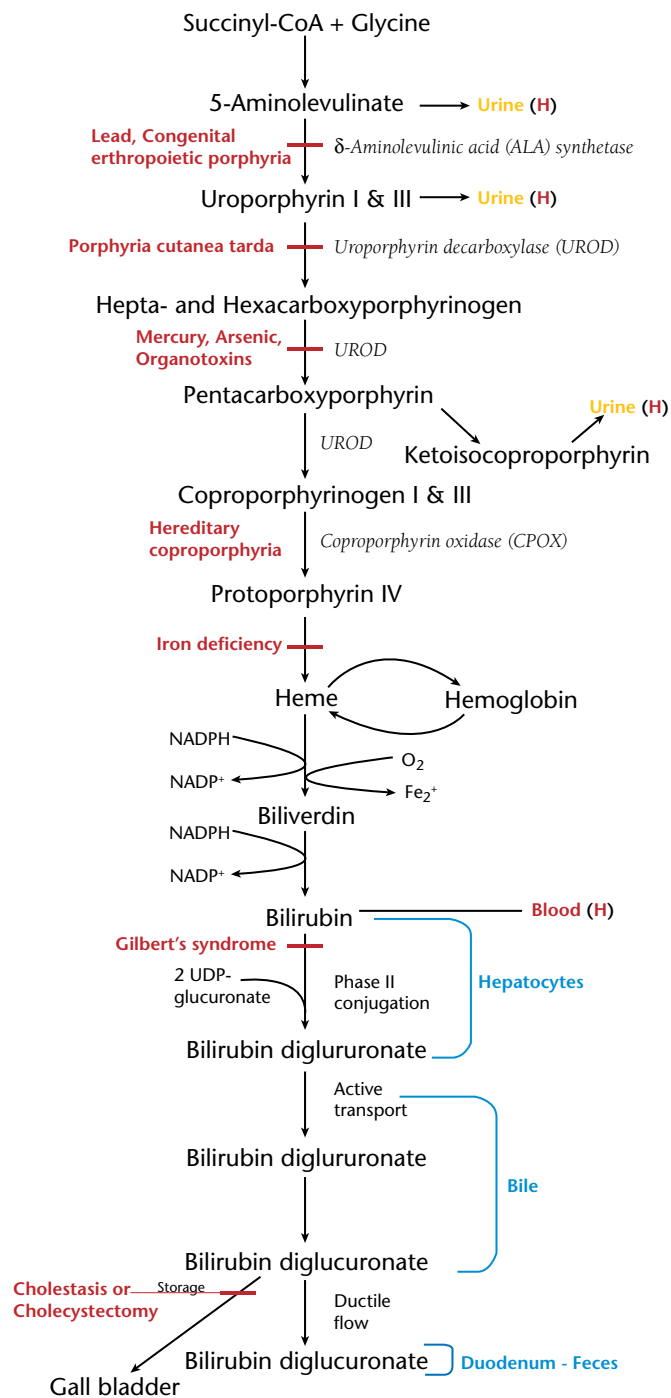
in a second study using data from a separate laboratory.<sup>25</sup> Such studies give evidence implicating mercury as a contributing factor in regressive autism and related childhood developmental disorders. The finding of porphyrinuria indicative of the mercury effect in an autistic child, especially when verified by direct measurement of mercury, is evidence justifying further clinical action to reduce body burden of mercury.

Changes in the urinary porphyrins (i.e. porphyrinuria) coincident with provocation (e.g. fasting) or therapeutic intervention (e.g. medications, chelation therapy) are suggestive of some type of porphyrinopathy. If the patient's response upon provocation can be duplicated then the possibility of a diagnosis of porphyria should be investigated. Urinary porphyrin elevations of three or more times the upper limit of the reference range may indicate that organ accumulation of porphyrins is reaching pathological levels. In such cases, a comprehensive genetic porphyria work-up and toxin body burden testing is warranted. For out-of-range results that are lower than three times the upper limit, the rationale for further porphyria testing is predicated upon the availability of corroborating clinical and/or biochemical data such as complaints, family and patient medical history. Female sex hormone use can raise levels<sup>39</sup>, and consumption of brewer's yeast has been reported to cause a pseudoporphyria.<sup>40</sup> Drugs that can affect test measurements include aminosalicic acid, birth

control pills, barbiturates, chloral hydrate, chlorpropamide, ethyl alcohol, griseofulvin, morphine, phenazopyridine, procaine, and sulfonamides.<sup>41</sup> A more extensive list is shown in Table 8.11.

Figure 8.12 represents some of the multiple genetic, nutritional and toxicant influences on the porphyrin biosynthesis and degradation pathways. In patients with multiple exposures and compromised nutrient status, the pattern of porphyrinuria may not allow exclusive assignment of single toxicant effects because of overlapping interferences. Use of porphyrin tests as biomarkers of chemical toxicity is useful in combination with other laboratory tests (e.g. blood, urine or hair analysis in cases of suspected metal toxicity). The clinician should realize that there are many conditions unrelated to primary or toxicant-induced porphyria that can cause porphyrinuria. When considering a urinary porphyrin result, the clinician should be mindful that the distribution of normal urinary porphyrin values, representing healthy individuals, overlaps significantly with values representing those who have suffered from porphyria at one time or another. An observed porphyria may be the result of a chemical insult to a pathway enzyme combined with a stressor like iron deficiency that modifies heme pathway activity.<sup>15</sup> Patients testing mildly positive on the urinary porphyrins test should be followed up with more specific testing such as toxic element testing of chelation challenged urine for a differential diagnosis. Tests that assay toxic metals directly in biological samples are essential for confirming whether the toxicity symptoms are caused by a metal. When a significant toxic element metabolic impact is seen in the porphyrin pathway, other functional tests may show abnormalities related to the metabolic perturbations of the toxicant on metabolic pathways governed by enzymes sensitive to toxic effects of the element. For example, oxidative stress markers may show elevations and citric acid cycle enzymes<sup>42</sup> or electron transport system proteins may be affected.<sup>43, 44</sup>

<b>Table 8.11 Some Drugs That Cause or Exacerbate Porphyria</b>
• Antipyrine
• Amidopyrine
• Aminogluthethimide
• Barbiturates
• Carbamazepine
• Carbromal
• Chloropropamide
• Chloral hydrate
• Danazol
• Dapsone
• Diclofenac
• Diphenylhydrantoin
• Ergot preparations
• Ethanol (acute)
• Ethchlorvynol
• Ethinamate
• Glutethimide
• Griseofulvin
• Isopropylmeprobamate
• Mephenytoin
• Meprobamate
• Methylprylon
• N-butylscopolammaonium bromide
• Nitrous oxide
• Novobiocin
• Phenylbutazone
• Primadone
• Pyrazolone preparations
• Succinimides
• Sulfonamide antibiotics
• Sulfonylmethane
• Sulfonmethane
• Synthetic estrogens, progestins
• Tolazamide
• Tolbutamide
• Trimethadone
• Valproic acid



**Figure 8.12 Interferences in the Pathway for Heme Formation and Degradation**

From the initial reactions of the biosynthetic pathway to the final steps of elimination, the intense activity to form and clear heme presents numerous opportunities for interferences due to toxins, nutrient deficiency, genetic weaknesses or iatrogenic interventions. The intermediates that pass into urine can serve as markers of exposure to environmental toxins, while those that accumulate can become endotoxins. When the sum of interferences slows the rate of heme production below that required to maintain total body oxygen transport, anemia results, and free iron oxidative challenge may occur. When the degradation reactions or secretory systems are blocked, failure of clearance can cause symptoms bilirubin elevations.

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