

***Metamatrix 2007 Teleconference Series***  
***Friday, September 7, 2007 1:00 PM EDT***

**Richard S. Lord, Ph.D.**  
**and**  
**Terry A. Pollock, M.S.**

***Interpreting Urinary Porphyrin Profiles***

***Synopsis:***

The recent flurry of interest in detecting mercury toxic impact has moved porphyrin profiling into a new level of recognition and clinical application. The work of Dr. James Woods has shown that mercury toxicity causes a specific pattern of elevations in urinary porphyrins. When this pattern is found, there is evidence that mercury may be the cause and that certain clinical presentations may be traced to the inhibition of porphyrin synthesis.

There are many other genetic and environmental factors that can impact the enzymes of the porphyrin pathway. Understanding the impact of these factors on the pathway helps to interpret the full range of abnormal patterns in urinary porphyrins. Biochemical background will be discussed and cases presented with differing degrees and types of porphyrias, including three autistic children with mercury toxicity and an 83-year-old retired dentist with refractory anemia.

***Teleconference Outline and Documentation***

***Porphyrin Pathway Biochemistry***

See Figure 1 for the pathway that is discussed in the teleconference. The intermediates called porphyrinogens are spontaneously oxidized to porphyrins when they appear in urine.

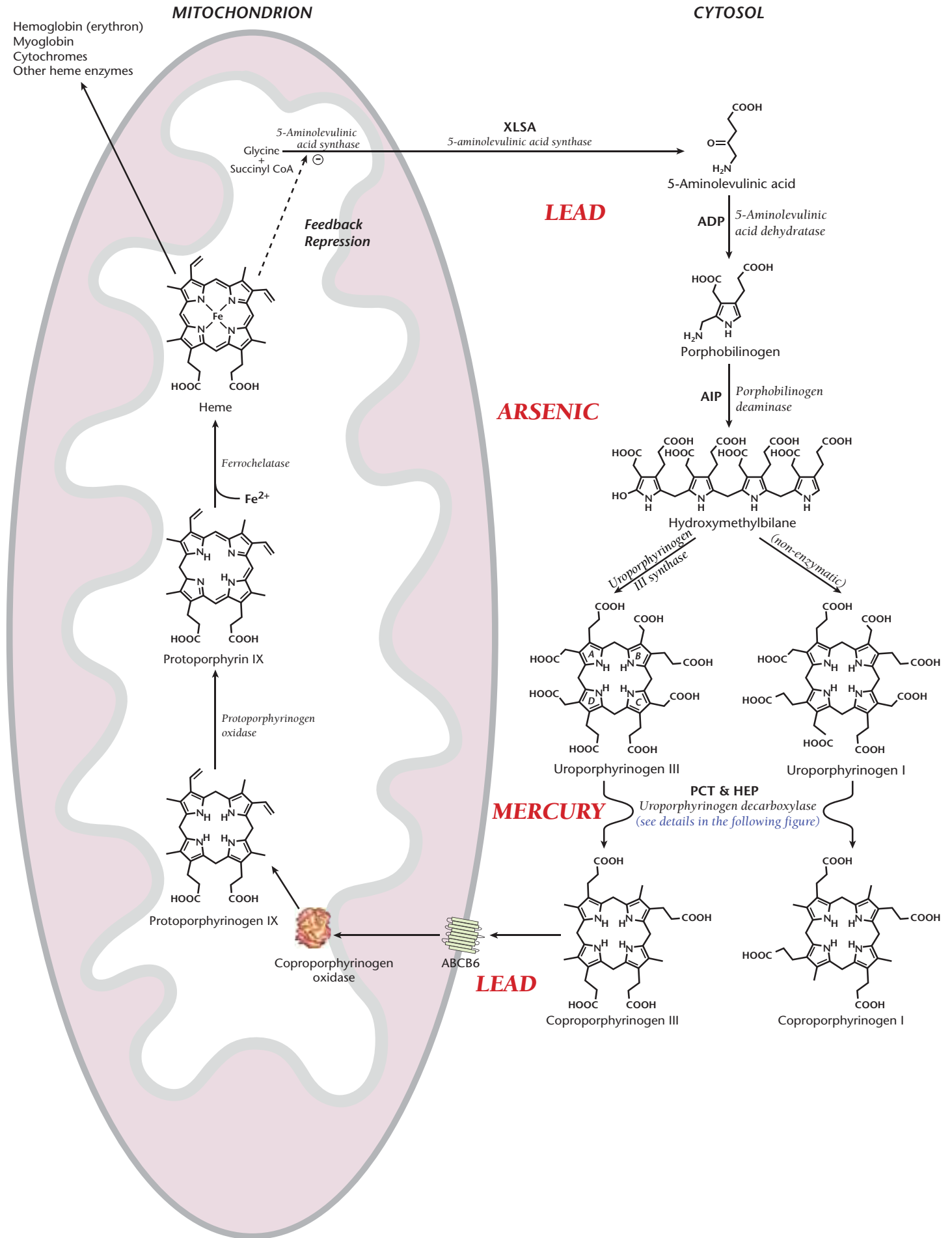
***Toxicant Involvement***

In addition to their involvement in mediating the expression of latent porphyrias, many drugs, xenobiotics and toxic metals may exert specific interferences that can be detected by the sensitivity of porphyrin testing. In addition to the mercury-specific effects shown in Figure 2, lead can cause coproporphyrin III elevation and arsenic interferes with uroporphyrinogen III synthase causing elevated levels of the coproporphyrin I/III ratio.

***Cases***

- Case 1 83-yr-old male with refractory anemia
- Case 2 71-yr-old female with dementia – Uro, hepta and mild penta elevations
- Case 3 3-yr-old autistic male with strong mercury pattern
- Case 4 10-yr-old autistic male with strong mercury pattern
- Case 5 3-yr-old autistic male with pattern suggesting mercury and lead

# Interpreting Urinary Porphyrin Profiles

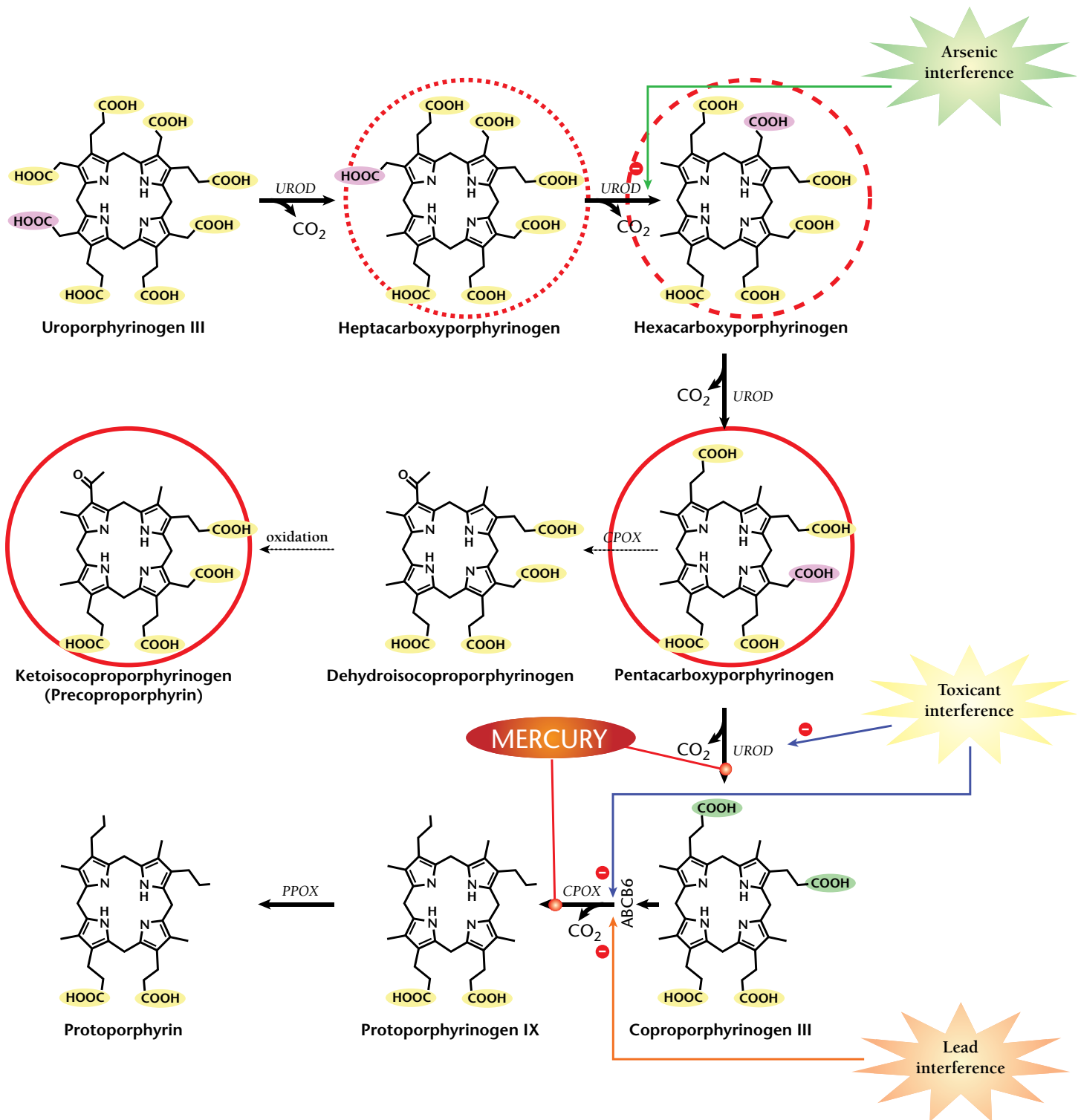


**Figure 1 The Porphyrin Pathway and Associated Genetic Porphyrrias**

Heme synthesis starts and ends in the mitochondrial matrix, but the ring-forming and decarboxylation steps are performed by cytosolic enzymes. Ring closure of hydroxymethylbilane produces a macrocycle with twenty carbon atoms and four nitrogen atoms. Eight carboxylic acid groups extend from the macrocyclic ring of uroporphyrinogens I and III that differ only in the positions of one pair of acetate and propionate groups. Stepwise decarboxylations produce compounds with 7, 6, 5 or 4 acid groups causing a large change in polarity that prepares the ring for resting in the binding sites of heme proteins. Ultimately, insertion of iron results in stable, organometallic structure that participates in metabolism as coenzymes and oxygen carriers. The decarboxylase enzymes are points of toxin interference in the pathway. Heme is exported from mitochondria for incorporation into cellular hemoproteins. As free heme levels increase feedback regulation on 5-aminolevulinic acid synthase occurs, particularly in liver, slowing the flow of products.

**Table 1 Genetic Porphyrrias**

Enzyme	Disease	Onset & Incidence	Symptoms	Associated Factors
5-Aminolevulinic acid synthase	X-Linked sideroblastic anemia ( <b>XLSA</b> )	2nd or 3rd decade	Pallor, shortness of breath, fatigue, weakness	Progressive iron accumulation and toxicity (sideroblast); B6 & folate responsive; chelation of iron
5-Aminolevulinic acid dehydratase	Aminolevulinic acid dehydratase deficiency porphyrria ( <b>ADP</b> )	Highly variable	Neuropathy and abdominal pain (adult) or failure to thrive (infants)	
Porphobilinogen deaminase	Acute intermittent porphyrria ( <b>AIP</b> )	High degree of clinical latency; high prevalence (210/100K) in US psychiatric population; more common in women	Intermittent neurologic and visceral symptoms (abdominal pain)	Any exposure that increases demand for hepatic cytochrome synthesis (see list of drugs)
Uroporphyrinogen III synthase	Chronic erythropoietic porphyrria ( <b>CEP</b> )	Cutaneous lesions (adult); severe hemolytic anemia (in utero)	Anemia; photosensitivity due to accumulation of non-physiologic and pathogenic isomers, Uroporphyrin I and Coproporphyrin I	
Uroporphyrinogen decarboxylase	Porphyria cutanea tarda ( <b>PCT</b> )	Most common porphyrria; estimates vary from 2-5/M (UK) to 1/5000 (Check)	Blistering skin lesions on sun-exposed areas	Abnormal liver enzymes Ethanol, estrogens, smoking, many drugs; well documented outbreak of hexachlorobenzene-induced porphyrrias from insecticide treatment of wheat
Uroporphyrinogen decarboxylase	Hepatoerythropoietic porphyrria ( <b>HEP</b> )	Usually in infancy or childhood	Red urine, blistering skin, sclerodermoid skin changes, anemia	Avoid sunlight; oral charcoal
Coproporphyrinogen oxidase	Hereditary coproporphyrria ( <b>HCT</b> )		Like AIP	Similar to AIP
Protoporphyrinogen oxidase	Variete porphyrria ( <b>VP</b> )	1.3/100K (Finland) to 3/1000 (white S. Africans)	Neurologic or cutaneous or both (therefore "variegate")	Drugs, hormones, nutritional factors as in AIP
Ferrochelatase	Erythropoietic protoporphyria ( <b>EPP</b> )		Itching, painful erythema and swelling can develop within minutes of sun exposure	Protoporphyrin accumulates in plasma, RBC, bile and feces (not urine)



**Figure 2: Mercury Interferences With Decarboxylation Reactions**

The normal heme-forming pathway involves six decarboxylation steps, four of which are carried out by a single enzyme, uroporphyrinogen decarboxylase (UROD). Carboxyl groups are shaded yellow and the groups that are cleaved by UROD and CPOX are shaded brown and green, respectively. Binding of mercury 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), yielding the abnormal product, ketoisocoporphyrinogen that is thought to account for the chromatographic peak called precoporphyrin. Depending on how severely elevated penta- become, accompanying elevation of hexa- and hepta- are possible. Blocking of CPOX by mercury produces simultaneous elevation of coproporphyrin III.

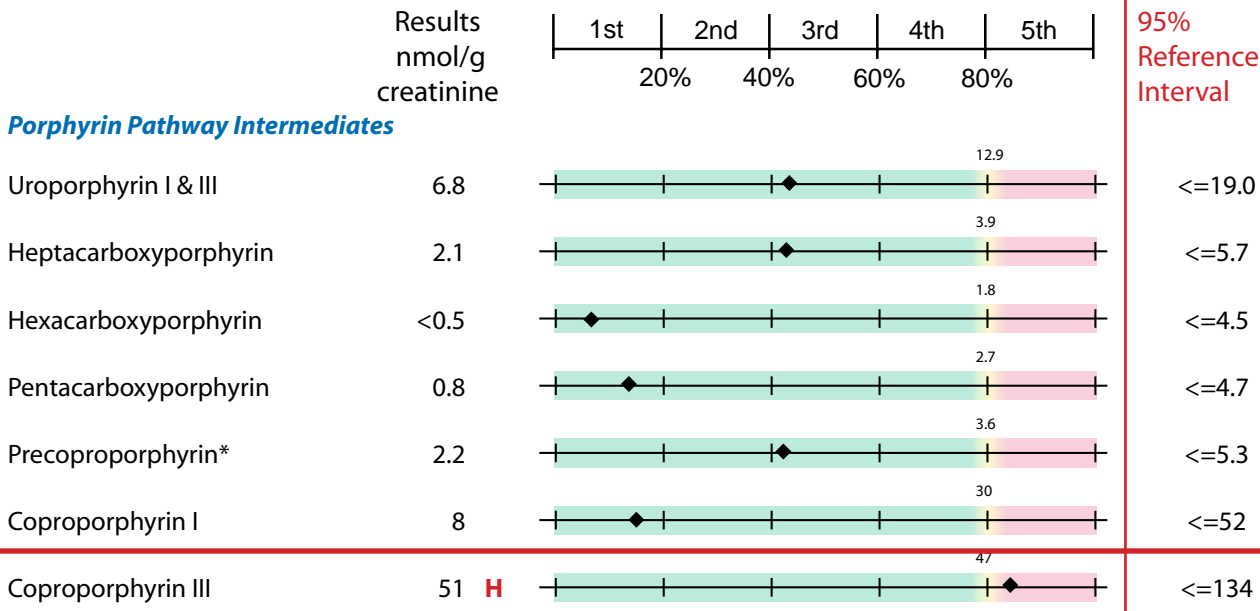
## Cases

### 0060 Porphyrin Profile - Urine

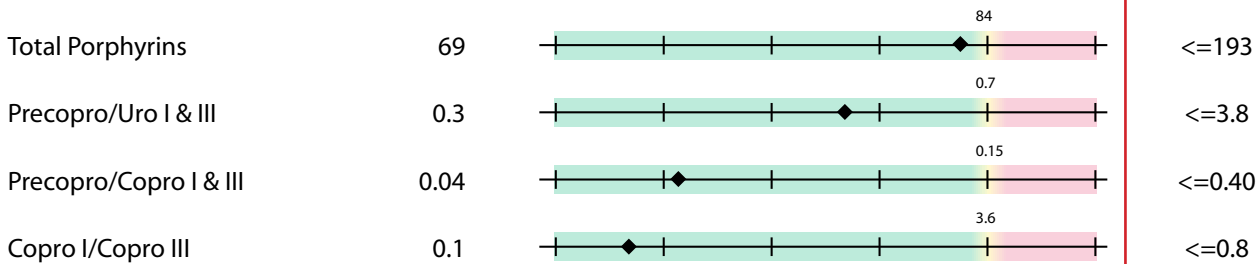
Methodology: Liquid Chromatography/Mass Spectroscopy

#### Porphyryns Profile - Urine

#### Percentile Ranking by Quintile



#### Calculated Values



creatinine = 36 mg/dL

### Case 1: 83-yr-old with refractory anemia

The question raised here is whether the refractory anemia is causing a general down-regulation of porphyrin synthesis. That would present as a left-shifting of the intermediates on the profile, so a residual mercury effect on coproporphyrin III looks less significant than it would be if the porphyrin pathway were fully functional.

\*Precoproporphyrin is reported as response/g creatinine

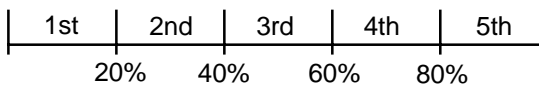
**0060 Porphyrin Profile - Urine**

Methodology: Liquid Chromatography/Mass Spectroscopy

**Porphyrins Profile - Urine**

**Percentile Ranking by Quintile**

Results  
nmol/g  
creatinine



95%  
Reference  
Interval

**Porphyrin Pathway Intermediates**

Substrate	Results nmol/g creatinine	Percentile Ranking	95% Reference Interval
<b>Uroporphyrin I &amp; III</b>	23.4 <b>H</b>	12.5	<=19.0
<b>Heptacarboxyporphyrin</b>	7.1 <b>H</b>	3.9	<=5.7
Hexacarboxyporphyrin	<0.5	1.8	<=4.5
Pentacarboxyporphyrin	4.4 <b>H</b>	2.7	<=4.7
Precoproporphyrin*	1.0	3.6	<=5.3
Coproporphyrin I	40 <b>H</b>	30	<=52
Coproporphyrin III	120 <b>H</b>	47	<=134
<b>Calculated Values</b>			
Total Porphyrins	195 <b>H</b>	84	<=193
Precopro/Uro I & III	0.0	0.7	<=3.8
Precopro/Copro I & III	0.01	0.15	<=0.40
Copro I/Copro III	0.3	3.6	<=0.8

**Hg**

creatinine = 36 mg/dL

**Case 2: 71-yr-old F with dementia – Uro, hepta, mild penta**

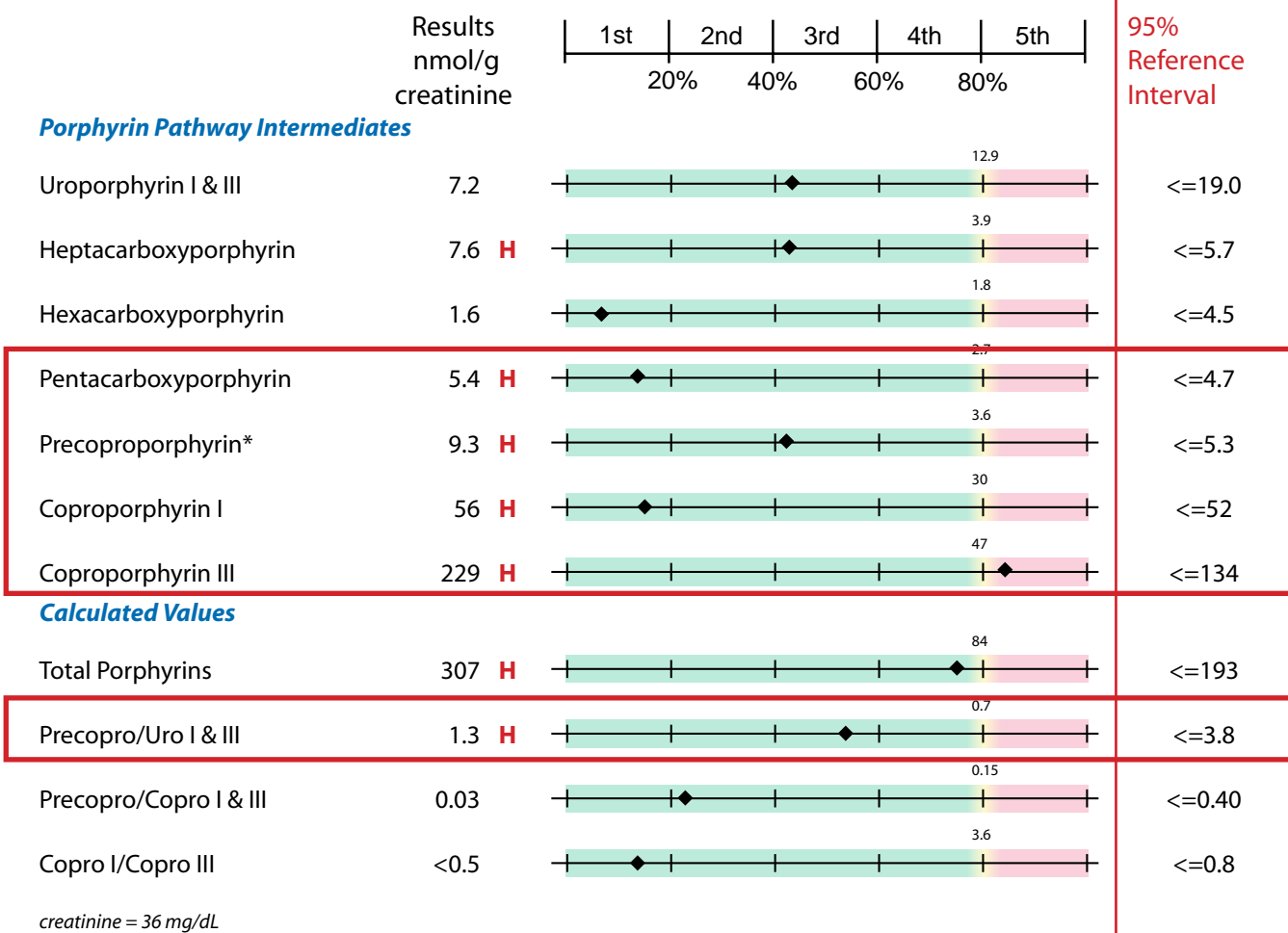
The elevation of uroporphyrin I & III is so severe as to suggest toxic buildup as found in genetic porphyrias such as acute intermittent porphyria or porphyria cutanea tarda. There is elevation of the mercury-specific pentacarboxyporphyrin and coproporphyrin III.

## 0060 Porphyrin Profile - Urine

Methodology: Liquid Chromatography/Mass Spectroscopy

### Porphyryns Profile - Urine

#### Percentile Ranking by Quintile



### Case 3: A 3-yr-old autistic male with strong pattern indicating mercury toxicity

This report shows the full pattern of mercury interference, with Precopro, Penta, Copro III and Precopro/ Uro I&III ratio elevations.

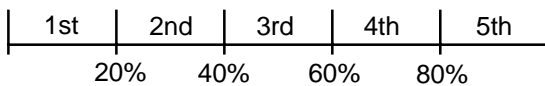
## 0060 Porphyrin Profile - Urine

Methodology: Liquid Chromatography/Mass Spectroscopy

### Porphyrins Profile - Urine

#### Percentile Ranking by Quintile

Results  
nmol/g  
creatinine



95%  
Reference  
Interval

#### Porphyrin Pathway Intermediates

Substance	Results (nmol/g creatinine)	Percentile Ranking	95% Reference Interval
Uroporphyrin I & III	14.7 H	~45th	<=19.0
Heptacarboxyporphyrin	4.5 H	~45th	<=5.7
Hexacarboxyporphyrin	2.4 H	~15th	<=4.5
Pentacarboxyporphyrin	17.3 H	~25th	<=4.7
Precoproporphyrin*	2.0	~45th	<=5.3
Coproporphyrin I	59 H	~25th	<=52
Coproporphyrin III	219 H	~85th	<=134

#### Calculated Values

Total Porphyrins	317 H	~85th	<=193
Precopro/Uro I & III	0.1	~45th	<=3.8
Precopro/Copro I & III	0.01	~25th	<=0.40
Copro I/Copro III	0.3	~25th	<=0.8

creatinine = 36 mg/dL

**Pb**

### Case 4: A 10-yr-old autistic male with strong mercury pattern, but normal precopro

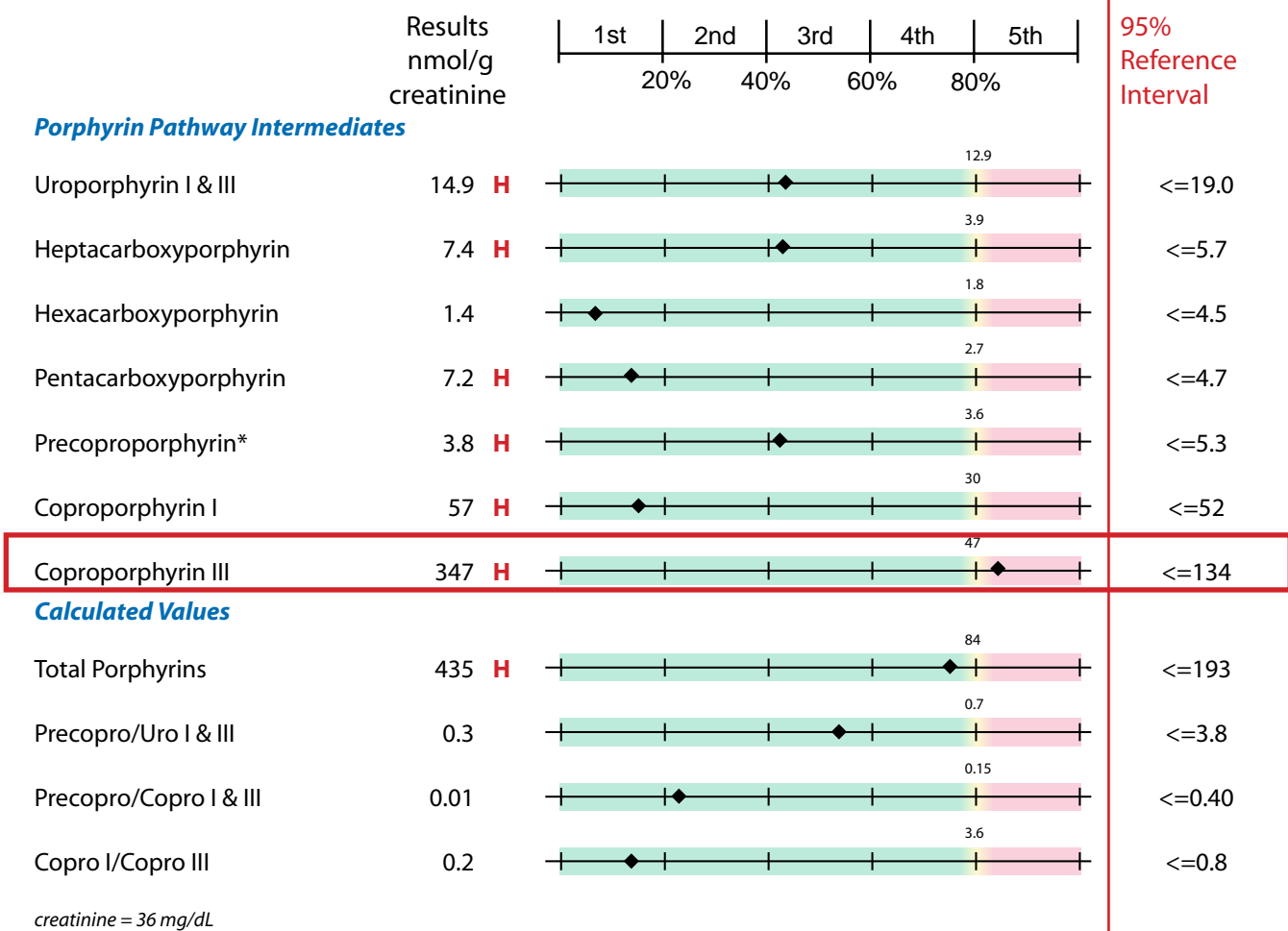
Hair analysis shows elevated Pb with low Hg. Has progressed behaviorally on supplementation, including B12 injections, since testing. Porphyrin pattern shows lead effect on CPOX causing suppression of Penta conversion to Precopro.

## 0060 Porphyrin Profile - Urine

Methodology: Liquid Chromatography/Mass Spectroscopy

### Porphyryns Profile - Urine

#### Percentile Ranking by Quintile



### Case 5: A 3-yr-old autistic male with a pattern suggesting mercury and lead effects

Here the full mercury pattern is present with coproporphyrin III so high as to suggest additive effects of lead or genetic porphyria. Note that Uro I&III is barely in the 5th quintile, indicating lack of strong induction of the pathway as a cause of the downstream elevations. Thus, even though the Precopro/Uro ratio is not elevated, the specific involvement of mercury is strongly indicated.