Evaluation of Toxic Metal Exposure and Net Retention

David Quig, PhD
Disclosure

David Quig is employed by Doctor’s Data, Inc.
Chronic Metal Retention

- “Low-level exposures are associated with long-term effects not previously recognized” (NIEHS)
- Knowledge of adverse effects are based primarily on independent studies of a single toxicant (C.D.C)
- Metals can elicit independent, additive or synergistic toxic effects (C.D.C)
- MRLs for exposures have not considered that humans bioaccumulate metals (C.D.C.)

"Individuals vary considerably in their sensitivity to metals, and susceptibility to toxic effects varies with age, gender, pregnancy status, nutritional status and genetics." (C.D.C.)

Single Nucleotide Polymorphisms (SNPs) (aberrant methionine metabolism, MTHFR, CBS, MTR, etc.)

Basic Toxicology

#1: Remove the source(s) of exposure!
### Red Blood Cell Elements: Exposure

#### Red Blood Cell Elements

**LAB#:**
**PATIENT:**
**SEX:** Female
**AGE:** 66

#### Potentially Toxic Elements

<table>
<thead>
<tr>
<th>Toxic Elements</th>
<th>Result $\mu g/g$</th>
<th>Reference Range</th>
<th>95th</th>
<th>99th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>0.007</td>
<td>&lt; 0.010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.001</td>
<td>&lt; 0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>0.023</td>
<td>&lt; 0.050</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury</td>
<td>0.049</td>
<td>&lt; 0.010</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thallium</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0005</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The table shows the results of toxic elements in the red blood cell elements, with reference ranges and percentile values. The element **Hg** (Mercury) is highlighted, indicating a potentially significant exposure level.
The Source of Hg Exposure

- “Facial Renovate” lightening cream
- Hg content:
  13,300 µg / gm
  (commercial fish < 0.5 ppm)

Quig D and Wilson J (2009) unpublished
Exposure ≠ Toxicity!

Exposure

Assimilation

Retention

Toxicity
Assessment of Exposure: Hair

- Excretory tissue binds *circulating* metals
- Hair *concentrates* metals cumulatively.
- Hair Me-Hg 200-300X > than blood Hg
- Useful for recent/ongoing EXPOSURE
- Cannot be used to diagnose metal toxicity
- NO direct indication of net retention

**Exposure: Hair Mercury**

- W.H.O. endorsed screening test for woman of child bearing years- exposure to MeHg (fish)
- Maternal MeHg highly correlated with adverse developmental effects on fetus / children.
- “The concentration of Hg in hair correlates with the severity of clinical symptoms.” *
- Several nationally recognized labs have been offering hair analysis for Hg, Pb and As for years.

*www.mayomedicallaboratories.com/interpretive-guide* [Accessed 3/14/12]  
*www.aruplab.com/* [Accessed 3/10/14]  
Pharmacol (2007) **49**: 17-24  
Env Hlth Perspect(2006) **114**: 302-6
**Arsenic Exposure: Hair**

- American family spent 3 months in Ecuador
- Consumed chicken every day (Roxarsone)
- Net retention?

### POTENTIALLY TOXIC ELEMENTS

<table>
<thead>
<tr>
<th>TOXIC ELEMENTS</th>
<th>RESULT $\mu$g/g</th>
<th>REFERENCE RANGE</th>
<th>68$^{th}$</th>
<th>95$^{th}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>9.8</td>
<td>&lt; 7.0</td>
<td></td>
<td>8X</td>
</tr>
<tr>
<td>Antimony</td>
<td>0.074</td>
<td>&lt; 0.066</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic</td>
<td>0.64</td>
<td>&lt; 0.080</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluminum</td>
<td>4.0</td>
<td>&lt; 7.0</td>
<td></td>
<td>8.3X</td>
</tr>
<tr>
<td>Antimony</td>
<td>0.021</td>
<td>&lt; 0.050</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic</td>
<td>0.50</td>
<td>&lt; 0.060</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aluminum</td>
<td>3.1</td>
<td>&lt; 8.0</td>
<td></td>
<td>5.3X</td>
</tr>
<tr>
<td>Antimony</td>
<td>0.015</td>
<td>&lt; 0.066</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic</td>
<td>0.42</td>
<td>&lt; 0.080</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Assessment of Exposure: **Blood**

- Recent or ongoing *exposure* (BPb $T^{1/2} \sim 27$ days)
- **Whole blood** Pb is the *Standard of Care* regarding potential issues with lead exposure / **toxicity**
- Red Blood Cells - 99% of blood Pb; 95% of MeHg
- Serum - not acceptable (exception - inorganic Hg)
- **NO indication of net retention**

ATSDR/CDC Toxicological Profile for Lead (2007 update)  
**Clinical Guidelines for Blood Lead (CDC-based, not ACAM)**

<table>
<thead>
<tr>
<th>Age (yrs.)</th>
<th>Reference Values&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Critical Values&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6</td>
<td>&lt; 0-4 ug/dL</td>
<td>≥ 20&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>≥ 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7-15</td>
<td>&lt; 0-9 ug/dL</td>
<td>≥ 20</td>
</tr>
<tr>
<td>≥ 16</td>
<td></td>
<td>≥ 70</td>
</tr>
</tbody>
</table>

<sup>1</sup> “Elevated blood lead”  
<sup>2</sup> “Medical management”  
<sup>3</sup> *Chelation indicated when BPb is > 45 ug/dL (adult)*

[Accessed 3/29/14]

www.mayomedicallaboratories.com

**Blood Reference Values: Hg and Cd**

- **Blood Total Mercury** (all ages)
  
  $< 10 \text{ ug/L} \quad \text{* (95}^{\text{th}} \text{ percentile} = \sim 5 \text{ ug/L, adults)}**

  “significant exposure”$* > 50 \text{ ug/L (organic-Hg)}$

  $> 200 \text{ ug/L (inorganic)}$

- **Blood Cadmium** (all ages)
  
  $< 5 \text{ ug/L} \quad \text{* (95}^{\text{th}} \text{ percentile} \sim 1.5 \text{ ug/L, adults)}**

  Acute **toxicity**$* > 50 \text{ ug/L}$

  

  **NHANES IV (2009), updated tables 2/12 cdc.gov/exposure report
Limitation of Blood Lead

“The concentration of lead in blood reflects mainly the exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of lead in bone.” (CDC)

- Bone Pb- about 95% of total body Pb in adults
- Blood Pb rebounds ~2 weeks after a single chelation
- **NO indication of net retention**

ATSDR/CDC Toxicological Profile for Lead (2007 update)

Net Retention

- **Metal toxicity** - accepted, *requires medical intervention* (e.g. if repeat blood Pb levels ≥ 45 mg/dL)
- **Bioacumulation/Body Burden** acknowledged (C.D.C.)*, but “chelation is useless and dangerous” (ACMT)**
- **Reality** For a given *individual*, **toxic effects** are elicited when the level of **retention** exceeds physiological tolerance. (typically vague and multiple diverse symptoms)


*ATSDR/CDC Toxicological Profile for Lead (2007 update)*

**ACMT** [www.acmt.net](http://www.acmt.net) [Accessed 8/18/09]
“Measurement of urine lead **before** and **after** chelation has been used as an indicator of significant lead **exposure.**” [retention/body burden]

“However, blood lead analysis has the strongest correlation with **toxicity**”

www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/60246
[Accessed 3/29/14]
The Basis of Provocation Testing

- Nonlinear relationship between blood Pb and post DMSA or Ca-EDTA urine Pb (NIEHS)*
- Post DMSA urine Pb- good indicator of the “bioavailable” Pb burden
- Better predictor of Pb-related neuromuscular symptoms than blood Pb

Int Arch Occup Environ Hlth (2000)73:298-304
## Urinary Hg Before and After Provocation with DMPS

<table>
<thead>
<tr>
<th>Group</th>
<th>Before (mg Hg/6h ± SE)</th>
<th>After (mg Hg/6h ± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental techs</td>
<td>5 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Dentists</td>
<td>3 (1)</td>
<td>0.8 (0.2)</td>
</tr>
<tr>
<td>Controls</td>
<td>0.8 (0.2)</td>
<td></td>
</tr>
</tbody>
</table>

*(P < 0.001)*

### Urinary Hg Before and After Provocation with DMPS

(300 mg DMPS po)

<table>
<thead>
<tr>
<th>Group</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental techs (10)</td>
<td>5 (1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>424 (85)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dentists (5)</td>
<td>3 (1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>162 (51)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Controls (13)</td>
<td>0.8 (0.2)</td>
<td>27 (3)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

“Urinary Hg excretion rises in everyone after a chelation challenge.”

*J Pharmacol Exp Ther (1995)272:264-74*  
Ruha A-M presentation at ACMT Conference on Use and Misuse of Chelation  
[www.acmt.net/2012](http://www.acmt.net/2012) [Accessed 5/22/2012]
“Urine Hg Increases in Everyone After DMPS”

- 27 yom immigrant from India
- Visit with CAM doc for persistent, major acne
- Previously treated with Ayurvedic herbs in India
- Post DMPS urine Hg = 5,850 ug/gm

Quig, unpublished observation (2013)
“No Diagnostic Value of Provocations?”

• “No randomized, controlled studies comparing use of a challenge test in subjects with metal poisoning to those without metal poisoning”*

• One cannot diagnose “metal toxicity” from provocation test results (ACMT).*

• Bioaccumulation with potential TOXIC EFFECTS is NOT accepted as “METAL TOXICITY.”

*Ruha A-M presentation at ACMT Conference on Use and Misuse of Chelation
www.acmt.net/2012 [Accessed 5/22/2012]
Net Retention: Provocation Testing

- **Pre-Specimen**: 1\textsuperscript{st} AM void or timed collection as close to provocation as possible
- **Post-Specimen**: Empty bladder, administer agent then collect all urine for 6 hours.
- Difference between pre- and post provides an *estimate* of bioaccumulation (net retention).
- Urine metals *should be* expressed per gm creatinine to eliminate dilution volume effects.

Unprovoked Urine: Arsenic Exposure

- **Organic** As species are excreted w/in 48 hrs. of consumption of *shellfish*. (arsenobetaine, arsenuocholine ~ 500X < toxic than inorganic As)

- **PREVENT ALARMISM!**

  Abstain from fish and shellfish for a week prior to provocative challenges. Do **pre-** and **post** urinalysis (initially).

# Unprovoked 1st AM Urine

## POTENTIALLY TOXIC METALS

<table>
<thead>
<tr>
<th>METALS</th>
<th>RESULT µg/g CREAT</th>
<th>REFERENCE RANGE</th>
<th>WITHIN REFERENCE RANGE</th>
<th>ELEVATED</th>
<th>VERY ELEVATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>&lt; dl</td>
<td>&lt; 60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antimony</td>
<td>&lt; dl</td>
<td>&lt; 1.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic</td>
<td>1930</td>
<td>&lt; 130</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beryllium</td>
<td>&lt; dl</td>
<td>&lt; 0.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bismuth</td>
<td>&lt; dl</td>
<td>&lt; 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.4</td>
<td>&lt; 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>0.5</td>
<td>&lt; 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mercury</td>
<td>&lt; dl</td>
<td>&lt; 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nickel</td>
<td>9.5</td>
<td>&lt; 15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As = 1,930 µg/gm

“All you can eat shrimp fest”
Prior to Provocation Testing

• Informed consent
• $\text{eGFR}$ (documentation, “continuous variable”)*
• Blood chemistries (e.g. CBC w/ differential, liver enzymes, BUN )
• Patients should be well hydrated
• Avoid supplemental zinc (Ca-EDTA) and selenium**
  (Se + DMPS/DMSA markedly ↓ provoked UHg)

Provocation Test: Inherent Limitations

- Agents are restricted to extracellular, aqueous compartments.
- Ca-EDTA, DMSA & DMPS do **NOT** appreciably cross a healthy blood brain barrier.
- Provocations do not **directly** reflect element retention in the CNS.
- **Significant kidney “flush”**

Interpretation of Provocation Test Results

- Provocation testing is valid when done correctly and can serve as a *component* of *diagnostic judgement*.
- Consider results *in context* with amounts of all elements excreted, physical exam, symptoms, *complete occupational/environmental exposure history*, and other findings.
- One cannot diagnose “*metal toxicity*” against unprovoked urine reference values (ACMT).*

*American College of Medical Toxicology  [www.acmt.net](http://www.acmt.net) [Accessed 8/2009]*
“Scientifically acceptable normal reference values for post-challenge urine metal testing have not been established”*

Too many variables- genetics, nutritional status, total toxicant load (additive/synergistic effects), agent / dose, etc.

*Am. College of Medical Toxicology [www.acmt.net](http://www.acmt.net) ACMT Conference, Atlanta, 2/29/12
# Urine Toxic Metals: Retention

## Results

<table>
<thead>
<tr>
<th></th>
<th>Unprovoked (Exposure)</th>
<th>Post DMSA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lead</strong></td>
<td>0.4</td>
<td>&lt; 2</td>
</tr>
<tr>
<td><strong>Mercury</strong></td>
<td>2.3</td>
<td>&lt; 3</td>
</tr>
</tbody>
</table>

Compare Pre and Post RESULTS
Provocation Testing is Useful for Monitoring Metal Depuration Therapy

- Urine lead analysis is useful for monitoring chelation.\(^1,2\)
- Follow up provocations should be performed IDENTICALLY to monitor elimination of toxic elements. (agent, dose, route of administration, collection time)
- Documentation- Progress notes for assessment of changes in symptoms and findings (e.g. GFR) associated with metal decorporation.\(^3\)

Monitor Therapy: Post vs. Post

Initial Post Ca-Na$_2$-EDTA

Follow up Post Ca-Na$_2$-EDTA
Take Home Messages: Provocation Testing

- Check whole blood toxic elements (*standard of care* for metal exposure/toxicity)
- Provocation testing is valid when done correctly and can serve as a **component** of diagnostic judgment.
- Assess status of liver & glomerular filtration prior to provocation testing.
**Provocation Testing (cont’d)**

- **Pre-** and **post** provocation urinalysis *initially*.
- Cannot **DIAGNOSE metal toxicity** from provocation test results.
- Provocation testing is very useful for **monitoring** the efficacy of toxic element depuration therapy.
**Urine Porphyrins: Heme Biosynthesis and Toxicants**

- **Porphyrinogens** - normal intermediates in heme synthesis
- **Porphyrias** are inherited or acquired (toxicants).
- Toxicants can inhibit specific decarboxylase enzymes and oxidized **porphyrins** are excreted (8-4 carboxyl groups)
- **Toxic effects** - Urinary porphyrin profiles have been well established for Hg, Pb and As (extensive exposure)
- Urine porphyrins are inherently **much higher in children** (must use age-specific reference values)*


Mercury-Associated Porphyrin Profile

- ↑ levels of pentacarboxyl, copro-III and precopropophyrin
- MeHg-fed rats- dose, duration, urine Hg. Decreased with administration of DMPS (also dentists, Hg⁰ exposure)
- Dentists- Correlated with UHg and neurological deficits, Most extreme w/ CPOX4 genetic polymorphism
- Correlated w/ severity of ASD and oxidative stress; lower plasma cysteine, rGSH, and sulfate (single study, n=14)*
- Porphyrin analysis alone does NOT replace provocation testing for metal retention

Interpretation of Porphyrin Results

Excretion of porphyrins is affected by:

- Hepatic, renal and erythroid diseases
- **Pharmaceuticals** - mood stabilizers, antidepressants, anti-epileptics (Depokine™, Convulex™), antibiotics, sedatives, analgesics, ethanol, estrogen
- **Nutrient deficiencies** - Zn, Fe (anemia)
- **Chemicals** - e.g. PCBs, hexachlorobenzene, PVCs, dioxins
- **Bottom line** - May not see a clear-cut, metal-specific porphyrin profile (additive or synergistic effects*)

Lab Tests for Metal Toxicology

• **Metal Poisoning / Acute Toxicity**
  Blood metal concentration
  Urine porphyrins-adjunctive (possibly chronic exposure)

• **Exposure** (recent or ongoing)
  Blood and unprovoked urine
  Hair (longer temporal “window”)

• **Net Retention** (estimation)
  Pre- and Post-Provocation urine elements
  “Potential toxic effects of bioaccumulation”