Exposure to Toxic Metals

Metals Adversely Affect Every Organ System

- Neurotoxic (ASD, ADHD, PD, Alzhiemers)
- Cardiovascular Disease
- Dysregulation of Immune System
- Compromise Gastrointestinal Integrity
- Nephrotoxic
- Carcinogenic

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**Environmental Toxins**

- **W.H.O.** 30-40% of childhood illnesses associated with environmental toxins

- **C.D.C.** “The epidemic of epidemics of CVD and immunological and neurological disease is likely associated with environmental toxins”

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**General Mechanisms for Toxicity of Metals**

- **Pro-oxidative** (lipid peroxides, R-OH)
- **Inhibit antioxidative enzymes**
  - SOD (Cu, Zn, Mn), GSH-px (Se)
- **Deplete glutathione** (GSH)
  - Direct binding/irreversible excretion
  - Inhibit GSH synthetase/reductase
- **Disrupt protein metabolism and ion homeostasis**
Glutathione

- γ-glutamylcysteinylglycine (SH)
- **Intracellular Protective Functions**
  - Antioxidant (redox state)
  - Conjugation of metals and chemicals
  - Activation of immune function
  - Inhibit replication of retroviruses


Depletion of GSH with:

- Metal Toxicity
- Chemical toxicity
- CVD
- Diabetes
- Cancer
- Neurological diseases
- **Extreme** exercise
- Aging
- Radiation Exposure
- Chronic stress
- Anxiety
- Chronic fatigue
- Autism
- Drugs

RBC Total Glutathione

- Find “source” of oxidative stress
- Support intracellular GSH (e.g., whey protein, oral liposomal GSH, iv GSH, N-AC)

Oxidative Damage to DNA:
8-OH-2’-deoxyguanosine (8OHdG)

3X > oxidized DNA than average
First AM urine void or 24 hr.

DNA Oxidative Damage and Environmental As
- 10-12 yo students, 2 schools (n ≥ 50 each)
- School A: adjacent to, and downwind of 8 power plants, B: upwind, suburban areas

<table>
<thead>
<tr>
<th></th>
<th>School A</th>
<th>School B</th>
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</thead>
<tbody>
<tr>
<td>As (µg/gm)</td>
<td>21 (4)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>8-OHdG (ng/gm)</td>
<td>19 (2)</td>
<td>8 (1)</td>
</tr>
</tbody>
</table>

Env. Hlth. Persp. (2005)113: 1186-90
**Oxidative Stress, Metals Exposure**

- 50 yo male, hypertension
- RBC GSH = 652 (900 - 1,900 μmoles/L)
- 8-OHdG = 26.1 (< 8.5 ng/mg cr)
- **Blood Metals**
  - Cd = 8.2 (< 4 μg/L)  Hg = 3.6 (< 2 μg/L)  Pb = 2.7 (< 2 μg/L)
- Smoker, 18 amalgams

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**Basic Toxicology**

```
+---+---+---+
|   | Exposure | Assimilation |
+---+---+---+
    |         | Retention    |
    +---+---+---+
        |         | Toxicity     |
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**Chronic Metal Toxicity**

- Exposure → Assimilation → Retention → Toxicity
- NOT generally accepted as requiring treatment

“**Sub clinical metal toxicity**”
**Chronic Metal Toxicity**

- “Sub-clinical” metal toxicity = **sub-threshold**
- For a given **individual**, toxicity is exhibited when the level of **net retention** exceeds physiological tolerance.

**Net Retention**

- Relative rates of **assimilation** and **excretion**.
- Excretion is **highly variable** and determined by protein expression (GSH, MT), nutritional status, antibiotic use, lifestyle, and **total toxic load**.

**Assessment of Exposure: Hair**

- Excretory tissue that binds **circulating** metals
- **Concentrates** metals cumulatively
- Hair Me-Hg 200-300X > than blood Hg
- Useful for recent/ongoing **EXPOSURE**

Arch Environ Hlth (1980)  atsdr.cdc.gov/HAV/hairanalysis/6.2htm
Public Hair Metals: Machinist / Welder

<table>
<thead>
<tr>
<th>TOXIC ELEMENTS</th>
<th>RESULT</th>
<th>REFERENCE RANGE</th>
<th>PERCENTILE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>0.41</td>
<td>&lt; 1.00</td>
<td></td>
</tr>
<tr>
<td>Chromium</td>
<td>0.01</td>
<td>&lt; 0.20</td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td>0.01</td>
<td>&lt; 0.20</td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>0.01</td>
<td>&lt; 0.35</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.01</td>
<td>&lt; 1.00</td>
<td></td>
</tr>
<tr>
<td>Manganese</td>
<td>&lt; 0.00</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Nickel</td>
<td>0.01</td>
<td>&lt; 0.50</td>
<td></td>
</tr>
<tr>
<td>Tin</td>
<td>0.09</td>
<td>&lt; 0.50</td>
<td></td>
</tr>
<tr>
<td>Tinctorius</td>
<td>0.06</td>
<td>&lt; 0.50</td>
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</tr>
<tr>
<td>Total Pb</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Assessment of Exposure: Blood

- Recent or ongoing **exposure**
- Toxicokinetic models; shortest T\(^{1/2}\)
- **NO** indication of net retention
- “Standard of care” is still blood Pb


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Fish 3X / week

Unprovoked Urine: As Exposure

- Organic As+5 rapidly excreted w/in 48 hrs. of consumption of shellfish
- PREVENT ALARMISM!
  Do pre- and post urinalysis initially, and abstain from fish and shellfish a week prior to provocative challenges.

Unprovoked 1st AM Urine

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**For Your Quiver**

The measurement of lead excreted in urine following an injection of Ca-Na₂-EDTA has been used to detect elevated body burden of lead in adults (2,3,4,5) and children (6,7), and is considered to be a reliable measure of the potentially toxic fraction of the lead body burden (8).

www.atsdr.cdc.gov/toxprofiles/tp13.html#

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**Assessment of Retention**

- The precedent has been set, assess the net retention of metals using EDTA, DMPS or DMSA
- Pre- vs. Post-provocation urinary metals
  - (1) objective assessment of body burden
  - (2) legal/medical board considerations
- Monitor efficacy with identical challenges after 5-10 treatments

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**Pharmacological Provocations**

- Extracellular, aqueous compartments
- Do NOT appreciably cross a healthy BBB
- Ca-EDTA, DMPS & DMSA provocations do not directly reflect retention in the CNS
- Significant kidney “flush”


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**Evaluations Prior to Provocation**

- Blood chemistries (e.g. CBC w/ differential, creatinine, BUN, liver enzymes)
- Oral DMSA / DMPS
  - GI symptoms → Comprehensive Stool Analysis

**DOCUMENT Assessment of Kidney Function!**

- Many toxic metals are nephrotoxic
- Agent-metal complexes excreted primarily through the kidneys
- Avoid acute renal failure!

**Assessment of Glomerular Filtration**

- Serum creatinine (Cockcroft-Gault Equation)
- Elderly and others with very low muscle mass, serum creatinine alone inadequate/insensitive for detection of compromised GF
- Creatinine clearance: timed urine (6 h), and blood draw

FDA Status of Agents

- **Ca-Na$_2$-EDTA**: FDA approved in the 50s (Pb)

Ca-Na$_2$-EDTA

- Ca-Na$_2$-EDTA: slow infusion/fast drip
- 50 mg/kg, not to exceed 3 gm
- $T_{1/2}$ about 30-45 minutes
- 6 hr. urine collection

DMSA

- **Chemet**: FDA approved for Pb “poisoning” in children in 1990
  2,3-meso-dimercaptosuccinic acid

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**DMSA General**

- Does **NOT** ↑ brain Pb or Hg levels
- ↓ brain Pb and Hg levels (animal studies)
- Increases urinary Pb, Hg and As in humans, **NOT** Al, U or Tl


**Clinical Pharmacology: DMSA**

- Oral: 20-25% absorbed, $T^{1/2a}$ ~ 4 hrs.
- Peak plasma ~ 3 hrs., rate urinary excretion ~ 4 hrs.
- Urinary excretion: **90%** as **mixed disulfides** with 2 cysteines (1:2)


**DMSA Challenge**

- **20-30** mg DMSA/kg BW as oral bolus on empty stomach (≤ 2 gms)
- With hold food about 2 hrs.
- Encourage ~ 0.5L fluid over next few hrs.
- Collect all urine for 6 hrs.


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**DMPS**

- **DMPS**: Not FDA approved, available from compounding pharmacies
  - 2,3-dimercaptopropane-1-sulfonic acid

\[
\text{H} - \text{C} - \text{C} - \text{S} - \text{O}_3^- \cdot \text{Na}^+
\]

(Informed consent!)

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**Urinary Hg Before and After DMPS Challenge**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
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</thead>
<tbody>
<tr>
<td>Dental techs (10)</td>
<td>5 ± 1</td>
<td>424 ± 85</td>
</tr>
<tr>
<td>Dentists (5)</td>
<td>3 ± 1</td>
<td>162 ± 52</td>
</tr>
<tr>
<td>Controls (13)</td>
<td>1 ± 0.2</td>
<td>27 ± 3</td>
</tr>
</tbody>
</table>

(J Pharmacol Exp Ther (1995)272:264-74)

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**DMPS Challenges**

- **IV**: 3-5 mg/kg (250 mg max), **slow** push (5-10 min.)
- **Oral**: 10 mg/kg BW (5 mg/kg children), empty stomach (empty bladder)
- With hold food about 2 hrs.
- Encourage ~ 0.5L fluid over next few hrs.
- Collect all urine for 6 hrs.
**Inexplicable Neuropathy**

- 59 yo home maker, husband accountant
- Progressive, elusive peripheral neuropathy
- Doc checked for metal neurotoxic metal burden

40 mg/kg glycine (oral)
DMSA (10 mg/kg)

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### Urine Toxic Metals

**Pre-provocation**

<table>
<thead>
<tr>
<th>Metals</th>
<th>Result (ng/mL)</th>
<th>Reference Range</th>
<th>Elevated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum</td>
<td>0.2</td>
<td>0.0 – 1.0</td>
<td></td>
</tr>
<tr>
<td>Antimony</td>
<td>8.0</td>
<td>8.0 – 10.0</td>
<td></td>
</tr>
<tr>
<td>Arsenic</td>
<td>20</td>
<td>10 – 100</td>
<td></td>
</tr>
<tr>
<td>Barium</td>
<td>0.0</td>
<td>0.0 – 0.6</td>
<td></td>
</tr>
<tr>
<td>Bismuth</td>
<td>8.0</td>
<td>8.0 – 20.0</td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>6.0</td>
<td>6.0 – 7.0</td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>5.0</td>
<td>5.0 – 10.0</td>
<td></td>
</tr>
<tr>
<td>Mercury</td>
<td>0.8</td>
<td>0.8 – 1.1</td>
<td></td>
</tr>
<tr>
<td>Nickel</td>
<td>10</td>
<td>10 – 100</td>
<td></td>
</tr>
<tr>
<td>Platinum</td>
<td>0.0</td>
<td>0.0 – 1.5</td>
<td></td>
</tr>
<tr>
<td>Ruthenium</td>
<td>0.1</td>
<td>0.1 – 0.2</td>
<td></td>
</tr>
<tr>
<td>Tungsten</td>
<td>0.5</td>
<td>0.5 – 0.7</td>
<td></td>
</tr>
<tr>
<td>Uranium</td>
<td>0.5</td>
<td>0.5 – 1.2</td>
<td></td>
</tr>
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</table>

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### Urine Toxic Metals

**Oral glycine, 10 mg/kg DMSA**

<table>
<thead>
<tr>
<th>Metals</th>
<th>Result (ng/mL)</th>
<th>Reference Range</th>
<th>Elevated</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Antimony</td>
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<td>0.0 – 1.5</td>
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<tr>
<td>Arsenic</td>
<td>0.02</td>
<td>0.0 – 1.5</td>
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<tr>
<td>Barium</td>
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<td>0.00 – 0.6</td>
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</tr>
<tr>
<td>Bismuth</td>
<td>0.02</td>
<td>0.02 – 0.4</td>
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<tr>
<td>Cadmium</td>
<td>0.00</td>
<td>0.00 – 0.6</td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>0.8</td>
<td>0.8 – 10.0</td>
<td></td>
</tr>
<tr>
<td>Mercury</td>
<td>0.00</td>
<td>0.00 – 1.5</td>
<td></td>
</tr>
<tr>
<td>Nickel</td>
<td>0.00</td>
<td>0.00 – 1.5</td>
<td></td>
</tr>
<tr>
<td>Platinum</td>
<td>0.00</td>
<td>0.00 – 0.6</td>
<td></td>
</tr>
<tr>
<td>Ruthenium</td>
<td>0.00</td>
<td>0.00 – 0.6</td>
<td></td>
</tr>
<tr>
<td>Tungsten</td>
<td>0.00</td>
<td>0.00 – 0.6</td>
<td></td>
</tr>
<tr>
<td>Uranium</td>
<td>0.00</td>
<td>0.00 – 0.6</td>
<td></td>
</tr>
</tbody>
</table>
**Glycine : Assisting Agent**

- 40 mg/kg glycine orally ~ about 2 hrs. before provocation test
- **Use in CONJUNCTION** with agents (logK- Hg: 9-13, Al: 8-10, Pb & Sb: 8-9)
- **Not** to be used alone

Quig, Townsend Letter, June 2007

**Summary: Lab Tests**

- **Exposure** (very recent or ongoing)
  - Blood and unprovoked urine
  - Hair (longer temporal window)
  - Elevated RBC GSH (induced)
- **Net retention**
  - Comparison of pre and post provoked urine
  - Low RBC GSH (depleted)
  - oxidized DNA damage (urine 8-OHdG)

**Take Home Messages**

- Assess status of liver & glomerular filtration.
- Apply pharmacokinetic **facts**.
- Do **pre** (1st AM) and **post** provocation urinalysis initially
- Remove **source(s)** of ongoing exposure.
- Monitor efficacy of detoxification:
  - Repeat challenge after 5-10 treatments

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<table>
<thead>
<tr>
<th>Metal</th>
<th>1st Choice</th>
<th>2nd Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hg, MeHg</td>
<td>DMPS or DMSA</td>
<td></td>
</tr>
<tr>
<td>Pb</td>
<td>DMSA/EDTA</td>
<td>DMPS</td>
</tr>
<tr>
<td>As</td>
<td>DMPS/EDTA</td>
<td>DMSA</td>
</tr>
<tr>
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<td>EDTA</td>
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<tr>
<td>Pt, Ti</td>
<td>DMPS</td>
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<tr>
<td>Fe, Al</td>
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<td>DFO</td>
</tr>
<tr>
<td>Ti</td>
<td>Prussian Blue</td>
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