

Is Mercury Toxicity an Epidemic? (Part II)

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As promised in my last editorial (*IMCJ* 8.1:8-10) where I covered the symptoms and prevalence of mercury (Hg) toxicity, I am now addressing the forms of mercury, how to measure mercury body load, and ways to get this toxin out of the body.

Forms of Mercury

Mercury exposure comes in basically 3 forms: elemental, inorganic, and organic.

Elemental mercury comes from industrial exposure, old thermometers, sphygmomanometers, fluorescent bulbs, electrical switches, and other electrical equipment.

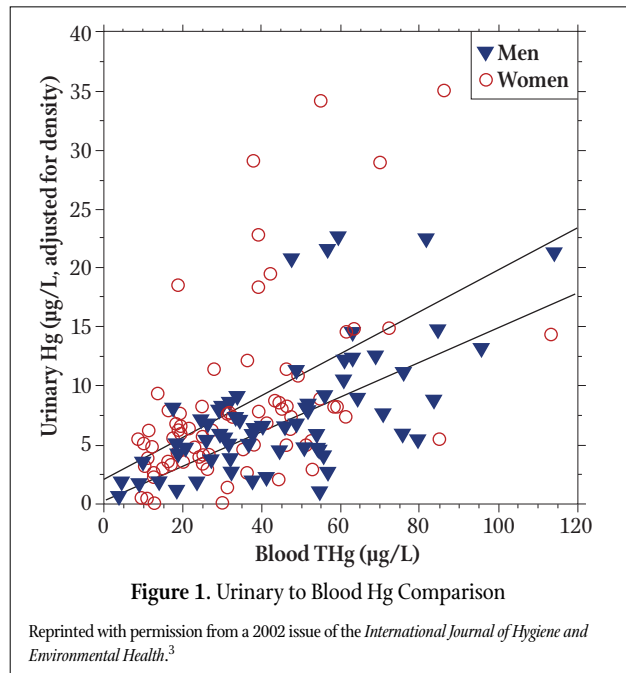
Inorganic mercury is the ionic form that is combined with an anion like chlorine, sulfur, or oxygen to make a powder or crystal. Some batteries contain inorganic mercury. In the past it was used in medicine as an antiseptic, in creams, and as a preservative. Unfortunately, some Ayurvedic products still use this form of mercury in their formulas. Many blanching skin creams used in third world countries are also contaminated with this kind of mercury.

Organic mercury is bound to an organic compound such as methyl or ethyl. Environmentally, it is produced by microscopic organisms in mercury-contaminated waters and soil. Methyl mercury (MM) can build up in fish, shellfish, and animals that eat fish. In another common form, dental amalgams, mercury leakage from the amalgams is methylated by mouth bacteria. The primary source of ethyl mercury is from thimerosal used in vaccinations, eye drops, etc, as an antimicrobial preservative. Thimerosal (sodium ethylmercurithiosalicylate) is 49% mercury by weight and rapidly converts to ethyl mercury in the body. (Those of us with gray hair may remember the merthiolate our mothers used for various childhood wounds—it was thimerosal.) Due to the autism controversy, the use of thimerosal in vaccines in the United States has been greatly reduced.

Laboratory Assessment of Mercury Load

Except when exposure is at high levels, which results in kidney deposition and damage, the mercury of clinical interest is in the brain. The only way to accurately assess amounts is with a brain biopsy—obviously not practical. This leaves us with hair, saliva, spinal fluid, serum, red blood count (RBC), urine, and stool tests. (Functional tests such as visual color discrimination are available as well,¹ but they do not discriminate the type of brain toxin causing the neurological damage.²) Unfortunately, none of these tests are reliable or sensitive measures of brain mercury. In addition, they do not correlate well with each other or with symptoms. This is one of the key reasons the issue of mercury toxicity is so controversial.

As an example, one study that correlated mercury levels in urine, saliva, and blood found only an R of 0.30 for urine and blood (see Figure 1). Pretty discouraging.



The most common mercury tests used in the research world assay serum, RBC, whole blood, stool, urine, and hair. Serum and RBC mercury are strong tests for recent exposures, but people with chronic exposure will often have normal levels because of upregulation of compensatory measures that mask the heavy body burden. RBC mercury testing assesses both inorganic and organic mercury, but it is likely to be a better test for inorganic forms, which are bound to hemoglobin to a large degree. RBC tests show exposure over the previous 90 days, so they will be sensitive to recent and prolonged exposures but not to distant ones. Stool testing is inconvenient and will underdetect those with impaired excretion mechanisms. Urine tests are effective for elemental mercury but poorly detect organic mercury, which is a far more common health risk. They will also be misleadingly low in those with kidney damage from, for example, mercury. Hair tests are problematic since levels appear dependent on mercury excretion mechanisms, which seem to be flawed in those with mercury toxicity.

Complementary and alternative medicine professionals have often used urine provocation testing with a chelation agent (usually DMPS, 2,3-dimercapto-1-propanesulfonic acid; or DMSA, meso-2,3-dimercaptosuccinic acid) to diagnose elevated

levels of mercury. Chelating agents will reliably increase urinary output of mercury but not in a consistent amount from person to person. Nonetheless, experienced clinicians find it correlates well with symptoms—but, unfortunately, there is apparently no peer-reviewed research published to evaluate this claim.

In summary, recent (within the past 90 days) and current exposure is reliably measured, probably most conveniently through whole blood levels. Whole blood is now generally the epidemiological standard for assessment of exposure to essentially all toxic metals. Quite a lot of information can be found from the Agency for Toxic Substances and Disease Registry (ATSDR), based in Atlanta, Georgia (www.ATSDR.cdc.gov). ATSDR is a federal public health agency of the US Department of Health and Human Services that is mandated to track toxic exposures and educate the public about their health effects. However, there is no gold standard for chronic or brain levels of mercury. The best protocol for measuring body load appears to be first morning urine to assess recent and current exposure, administering a DMSA/DMPs provocation, then collecting urine for 4 to 6 hours to determine body load.

At this time, I believe the best way to assess brain mercury levels is a combination of assessing symptoms according to the probability table in my last editorial and the urine challenge protocol described above. A person with many of the symptoms and an elevated challenge test is very probably suffering mercury toxicity, especially if a source of exposure is identified (as summarized above and discussed in more detail in my last editorial).

Mercury Transport and Storage in the Body

A growing number of studies suggest that mercury contributes to the etiology of neurodegenerative diseases such as Alzheimer's disease (AD).⁴ Autopsy shows that AD incidence correlates with both increased central nervous system (CNS) and blood mercury levels.⁵ In addition, concentration of mercury in the brain correlates with the number of dental amalgams—patients with amalgams have mercury levels 2 to 10 times higher than those without amalgams.⁶ Confusing the issue, however, is the observation that the neurotoxicity found in acute mercury exposure tends to affect the cerebellum and the speech and vision centers most, which is different from the damage seen in AD.

Elemental mercury vapor, such as may be present in the workplace, is readily absorbed through the lung tissue and is then taken up by several tissue types through passive diffusion. In particular, kidney tissue and RBCs act as important sinks. As mercury levels go up, the kidneys are damaged and their excretion of mercury becomes impaired.

Elemental mercury easily diffuses across the blood-brain barrier (BBB) but is usually quickly ionized in the lungs so the window for transport is relatively short. Nonetheless, ionized mercury still deposits in various tissues. Organic mercury also diffuses directly across the BBB while bound to cysteine, but levels in the blood are usually low because cysteine also binds to sulfur-containing proteins and molecules.

Methyl mercury (MM), typically from contaminated fish and dental amalgams, is absorbed well through the gut mucosa and

travels through the circulation largely in complex with cysteine or homocysteine. This cysteine-complexed molecule is a near mimic of methionine and so moves into cells through the same transporter. Once inside the cell, MM mostly transfers to glutathione (GSH), depleting the GSH supply and oxidizing into GSH-Hg.

Mercury Excretion

This GSH-bound Hg exits cells via GSH excretion channels. Circulating MM is sent into bile via liver GGT (gamma glutamyltransferase) and excreted into the stool. Fetuses and infants lack mature GGT function, making them most vulnerable to MM exposure. Although about 1% of the body burden of mercury is excreted every day through the bile, 95% of the cleared MM returns via enterohepatic circulation—one of the more odious complications of mercury toxicity, as the mercury keeps getting recycled.⁷

The protein metallothionein is particularly important in helping to eliminate mercury from tissues. Supplemental zinc can upregulate production of metallothionein and has been associated in animal studies with reduced acute toxicity. However, upregulation of metallothionein reduces bile clearance of mercury, suggesting that this treatment may not be useful other than for the acute phase of exposure.

The main route for mercury clearance from the brain appears to be transport of the GSH-bound Hg across the BBB.⁶ This slow process probably explains the very long mercury half life in the brain of 1 year.

Mercury Removal

Since mercury concentration in the CNS cannot be directly measured prior to autopsy and symptoms correlate so poorly with existing measures, definitive conclusions about clinical management are not possible. While some clinicians and proprietary interests make absolute statements about the advantages of one treatment over another, their observations are based on limited and inconsistent evidence. Nonetheless, the existing research, while not definitive, does give guidance for management of acute and chronic mercury exposure.

The first task, obviously, is to identify and eliminate the source—amalgams, contaminated fish, industry, air, etc. Also to be considered are household goods such as fluorescent lights, old thermometers, and Ayurvedic medicines to which mercury is intentionally added. A growing risk of mercury exposure will be fluorescent lights as incandescent bulbs are being replaced by high-efficiency bulbs. As Congress has mandated that incandescent bulbs no longer be sold after 2012, we are likely to see more exposure as their replacements break. A very disturbing recent study found mercury in high-fructose corn syrup.⁸ The most highly contaminated samples found 25 µg of mercury per can of soft drink, the equivalent of eating 2 ounces of fish without the benefits of fish's omega 3 fatty acids. Yet another reason to guide our patients away from processed foods.

Amalgams are a common source of mercury—especially in those with multiple different metal fillings (eg, gold in some teeth and mercury amalgams in others). The problem with multiple metals is that they have different electrical potentials, thus

they form an electrical current that increases the dissolution rate of the mercury. Great care must be taken in mercury amalgam removal. According to a recent study, by using standard removal techniques, blood mercury levels increase by 50% for the subsequent 18 months measured!⁹ A growing number of dentists now specialize in removing amalgams with minimal mercury release (for more information, see the International Academy of Oral Medicine and Toxicology website: www.iaomt.org).

Once a person has developed a significant body burden, the primary clinical goal is to get mercury out of the brain. There are basically 3 strategies:

1. Decrease the mercury in the blood so the gradient for leaving the brain is less steep.
2. Stimulate the brain to excrete mercury more rapidly.
3. Use agents that cross the blood-brain barrier (without carrying mercury with them), bind to mercury in the brain, cross back out of the brain, and are then excreted in the urine or stools.

DMSA and DMPS Chelation

Although the term “chelation” is widely (and erroneously) used to describe agents that bind to metals and clear them from the body, its technical definition is more specific. According to *Wikipedia*, “Chelation is the binding or complexation of a bi- or multidentate ligand. These ligands, which are often organic compounds, are called chelants, chelators, chelating agents, or sequestering agents. Chelating agents form multiple bonds with a single metal ion.”¹⁰ Although the term is often misused, I do not think this means much clinically, and so I will continue the common use here.

For acute and elemental mercury exposure, “chelating” agents such as DMSA and DMPS—which compete with cysteine for binding MM—are effective in reducing non-CNS mercury levels. They are primarily used intravenously, although DMSA is also used orally. Almost all of the research is on intravenous (IV) use of these drugs. Animal research shows that outside the central nervous system DMSA and DMPS appear very similar in mercury chelation efficacy. However, different dose and administration models make direct comparison difficult. During acute exposure, both appear effective in binding and removing circulating mercury and preventing deposition in organs (including the brain). Be warned: DMSA and DMPS also simultaneously chelate copper and zinc.¹¹

Since DMSA and DMPS are large and polar molecules, they cannot cross the BBB. While this likely prevents them from depositing circulating mercury into the brain, it likely also prohibits their removal of mercury already stored in central nervous tissue. However, early animal research found that, on dissection, the brains of animals treated with DMSA/DMPS had lower Hg levels.¹² This literature has since been used to justify DMSA and DMPS for human treatment. Unfortunately, the early animal research was flawed as the dissection techniques allowed contamination of the brain with non-CNS blood (where mercury levels are several times higher than in the brain). Once proper bloodless techniques were used, the research showed no brain-lowering effects—suggesting that DMSA and DMPS do not

reduce CNS concentrations of mercury in the brain.¹³⁻¹⁵

Another complicating factor with the research is the conflation of chelation therapy during exposure versus chelation after exposure. Chelation during exposure will result in lower brain mercury levels since there is less circulating Hg to enter the brain.

Although the minimal published human research studies have not noted this, there have been a few anecdotal reports of excessive toxicity associated with DMPS, including potential Stevens-Johnson syndrome (for more information, see www.dmpsbackfire.com).

In summary, considerable research shows that DMPS and DMSA are effective in lowering body burden of mercury, especially when concurrent with exposure. There does not appear to be any strong evidence at this time that either one directly diminishes brain mercury. However, by lowering body burden a reasonable assumption is that this makes the normal brain mercury excretion processes more effective.

Oral Agents

The oral chelation agent that has been shown most effective in decreasing mercury in the CNS is N-acetylcysteine (NAC).^{16,17} Its mechanism of action appears to be upregulation of brain glutathione, thus increasing GSH's binding to mercury and transport across the BBB as GSH-Hg. As might be expected, this is a slow process. Despite this binding ability, glutathione, chemically very similar to NAC, can have either no effect or actually increase CNS and kidney concentrations of mercury, most likely by binding with Hg in the blood.

Alpha-lipoic acid (ALA), another over-the-counter nutrient with a high affinity for mercury, crosses the blood-brain barrier more efficiently than do other chelating agents. However, preliminary study has not shown that ALA can reduce brain concentrations of mercury and it has been speculated that ALA could actually work in reverse—pulling peripheral mercury across the BBB into the brain, potentially increasing CNS toxicity.

The table on page 11 summarizes the research on most agents that have been tested for the removal of mercury; they are listed in the order of minerals, nutrients, and then synthetic compounds.

Finally, to prevent the enterohepatic recirculation described above from occurring, increasing dietary fiber decreases MM recirculation while antibiotics increase it.¹⁸

Recommendations

Obviously, this brief review cannot do justice to the thousands of published studies on mercury toxicity. Surprisingly, despite the huge number of studies, the clinician is left with far too many unanswered questions.

Assessment

There is no definitive test for brain mercury burden. At best, it can be inferred from symptoms and indirect tests. At this time, I suggest using whole blood mercury for screening. However, if the blood mercury levels are normal but the patient is still exhibiting signs and symptoms of mercury toxicity (as outlined in my editorial last issue), then utilize a DMPS urine challenge test.

Table 1. Agents Used in the Treatment of Mercury Toxicity*		
†Molecule	Type	†Role in the Treatment of Hg Toxicity
Zn	Mineral	Induces production of the metal-binding protein metallothionein, which, in turn, is thought to be neuroprotective on exposure to Hg vapor. However, may not be indicated for long-term use as increased metallothionein levels decrease bile excretion of mercury.
Se	Mineral	Shown to affect the distribution and reduce the toxicity of Hg in animals. However, there is evidence of negative interactions with the dithiol chelation agents DMPS and DMSA in animals with Hg toxicity.
NAC	Exogenous thiol	Known to boost GSH levels in all tissues including the brain. GSH has been shown to increase biliary excretion of methyl Hg and increase brain excretion of Hg. Early research suggested NAC could transport Hg into the brain, but later research has found only a lowering effect of mercury in the brain.
GSH	Endogenous thiol	Involved in biliary excretion of methyl-Hg. Intracellular GSH plays a role in protecting cells. However, has also been shown to be involved in renal uptake of both inorganic Hg and methyl Hg.
ALA	Exogenous disulfide	Metabolized intracellularly to DHLA (a dithiol). Shown to have protective effects against mercury toxicity in several mammalian species. Dose size and frequency appear to be important, with inappropriate dosing seemingly increasing toxicity. Can access all tissues of the body including the brain, suggesting potential to carry Hg into (rather than from) the brain.
DMPS	Synthetic dithiol	Binds tightly to inorganic Hg molecules. Due to its low molecular weight, it is readily filtered by the kidneys and excreted via the urine. Does not chelate mercury in the brain.
DMSA	Synthetic dithiol	Binds tightly to inorganic Hg molecules. Due to its low molecular weight, it is readily filtered by the kidneys and excreted via the urine. Does not chelate mercury in the brain.
*Table is modified with permission from a 2007 issue of <i>Toxicology</i> . ¹¹		
†Key: Hg=mercury; Zn=zinc; Se=selenium; NAC=N-acetylcysteine; GSH=glutathione; ALA=alpha-lipoic acid; DHLA=dihydro-lipoic acid; DMPS=Na 2,3-dimercaptopropanesulfate; DMSA= <i>meso</i> -2,3-dimercaptosuccinic acid; G6PD=glucose 6-phosphate dehydrogenase.		

Treatment

While the protocol for acute exposure and reducing total body burden is well documented, there is no documented intervention strategy for quickly lowering brain levels of mercury. Therefore, any recommendations at this time will be controversial. My best assessment, given the available evidence and talking with experienced clinicians, is as follows:

1. Identify and remove potential sources of Hg exposure, especially industrial, mercury amalgams, contaminated fish, and high-fructose corn syrup. Be sure to warn patients about broken florescent light bulbs.
2. For acute exposure, use IV DMSA/DMPS until blood levels return to 1/10 the minimum toxicity level.‡
3. For chronic long-term exposure or high body burden,
 - a. treat with oral NAC, 600 mg 3x/day, and
 - b. increase dietary fiber
4. If symptomatic, in addition to the above, perform the following:
 - a. Treat with IV DMSA/DMPS. Experienced clinicians typically treat once a month and report 6 to 12 treatments necessary for optimal results.
 - b. Use blood testing and symptoms to monitor treatment progress. Test kidney function regularly.
 - c. Monitor and maintain healthy nutritional mineral levels, especially zinc and selenium, as several will become depleted.

In This Issue

We are pleased to present to you the abstracts for The North American Research Conference on Complementary and Integrative Medicine, produced by the Consortium of Academic Health Centers for Integrative Medicine (CAHCIM) and scheduled for May 12-15, 2009. You will find these in the back of the journal.

Since day 1 of *IMCJ*, I have been most interested in interventions that combine conventional and natural medicine. While there are times that drugs are necessary, in my experience, expert use of natural therapies and/or medicines can increase efficacy, decrease toxicity, and even decrease drug dosages needed to achieve the desired clinical result. In “Modulation of Neurogenic Inflammation in Osteoarthritis Patients Undergoing a Combined Treatment of Mud Packs, Thermal Baths, and Acetaminophen: A Preliminary Study,” Simona Bellometti, MD, Antonella Roveri, MD, Tommaso Tassoni, Plinio Richelmi, and Mattia Zaccarin provide us original research showing how such integration can work to the patient’s benefit.

Alan Gaby, MD, provides us a useful review of natural approaches for Ménière’s disease. As usual, a common underlying problem is the insulin resistance that has become so prevalent. Also of key importance are nutrients such as chromium, magnesium, and flavonoids, and the vitamins niacin, thiamine, E, and D.

One of my continuing frustrations has been the limited objective research on some botanicals with a long tradition of

‡Various mercury tests use different measuring methodologies, so it is very difficult to compare levels between tests. Thus, I do not list a minimum toxicity level.

folk use. Dandelion (*Taraxacum officinale* and *T. mongolicum*) is a prime example. Eric Yarnell, RH (AHG), ND, and Kathy Abascal, JD, RH (AHG), provide us a review of the current information available on this useful botanical.

In his column on quality assurance, Rick Liva, ND, RPh, gives us a detailed discussion about the types of quality control testing manufacturers should do. Of particular interest are several disturbing examples he provides of recent results he found when testing raw materials.

The Green Medicine Tip from Joel Kreisberg, DC, discusses bacterial resistance from antibiotic overuse. The use of antibiotics in livestock significantly impacts the type and quantities of bacteria in the environment as well as in the human gut. Interesting research resulting from the ban of certain antibiotics in European livestock documents the change in concentrations of these bacteria in humans. For example, after stopping the use of avoparcin in livestock, prevalence of vancomycin-resistant enterococci in human excrement was significantly lower overseas.

The Obama reign begins and is the focus of John Weeks' column. With his 25 years' experience in the public affairs of integrative medicine, he provides welcomed insights.

After reading this issue's BackTalk by Bill Benda, MD, all I can say is thank you! Again. As so often in the past, Bill makes a critical point that is personally meaningful. If we don't practice what we preach, what are we, truly?



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