Mercury: A metabolic perspective minus the fear

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• “...the Martians –dead! – slain by the putrefactive and disease bacteria against which their systems were unprepared; slain as the red weed was being slain; slain, after all man’s devices had failed, by the humblest things that God, in his wisdom, has put upon this earth.”

• “These germs of disease have taken toll of humanity since the beginning of things—taken toll of our prehuman ancestors since life began here. But by virtue of this natural selection of our kind we have developed resisting power; to no germs do we succumb without a struggle, and to many—those that cause putrefaction in dead matter, for instance—our frames are altogether immune.”
• “That they did not bury any of their dead, and the reckless slaughter they perpetrated, point also to an entire ignorance of the putrefactive process.”
• “For so it had come about, as indeed I and many men might have forseen had not terror and disaster blinded our minds.”
Obligatory, fear based introduction to mercury
Key points

• The issue of environment mercury did not start with dentists and the industrial revolution.

• Because the relationship between all life on earth and mercury has been so intimate, the laws of nature have allowed most all living beings to develop a fairly sophisticated detoxification system to efficiently deal with the mercury.

Key points

• While the anti-mercury militia (chelation, amalgam removal) has its place, we are best served when we facilitate the laws of nature through optimizing endogenous detoxification mechanisms via good nutrition, supplements, healthy lifestyle modifications and, of course, practical mercury avoidance measures.
Key points - amalgam

• The world would be best served if all amalgam placement ceased immediately – in most situations.

• We need to address patients who currently have several large amalgams with our hearts as well as our intellect – but minus the fear.

• “Respondents were 82% women and 95% Caucasian. Participants’ ages ranged from 20 to 82 years, with a mean age of 53 years.”
• “When asked to identify the severity of their condition, 7% identified their MCS as mild, 32% as moderate, 45% as severe, and 13% as totally disabling.”

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A look at the realities of large scale amalgam removal and replacement

• “Biological side-effects of composites may be caused by toxic or allergic reactions to various components of the materials. These components may be residual impurities from the manufacturing processes, chemicals formed during polymerization or degradation, e.g., formaldehyde, or chemicals released from the material because of incomplete polymerization, e.g. methacrylate.


A look at the realities of large scale amalgam removal and replacement

• “Also the risk of mucosal reactions to composites and the chemicals used for improved bonding to tooth substance should be considered.”

A look at the realities of large scale amalgam removal and replacement

• “The prevalence of gold sensitivity in individuals with gold dental restorations is approximately 33.8%. This is significantly greater than the 10.8% prevalence seen in individuals without gold dental appliances as well as greater than the 3-year rate from the Oregon Health Sciences University Contact Dermatitis Clinic.”


Controversies to be addressed

• Do we even have a mercury problem in this country?
• Who caused the mercury problem?
• Is there a direct relationship between levels of mercury in the body and the level of toxicity experienced by an individual?
• What form of mercury is most toxic?
• Can mercury levels in the body be ascertained via laboratory testing?
• What, specifically, is the best way to address elevated mercury levels in various patients?
What does mercury do that makes it so bad?


“The affinity of mercury for sulfur and sulphydryl groups is a general property of mercury and its compounds.”
Do we even have a mercury problem in this country?

The big picture
• “Between 2700 and 6000 tons of elemental mercury is released per year via natural means to the biosphere through degassing from the earth’s crust and oceans.”

• “Volcanoes can be an important natural source.”

• “Industrial wastes and the combustion of fossil fuels add up to an additional 2000-3000 tons of mercury to the environment.”

• “Levels of mercury vapor in the ambient atmosphere are so low that intake from this source is negligible.”
Mercury pollution -
More than just an issue of amalgam

• “Although the natural degassing of the earth’s crust is the major source of environmental Hg, man-made release of Hg from mining, smelting, industrial discharge, such as chloralkali plants and paper pulp industries, burning fossil fuels, and other activities significantly contributes to the total global burden.”


Mercury pollution -
More than just an issue of amalgam

• Hg and Hg salts can be found in dental amalgam, creams, ointments, antiseptics, paints, foods, diuretics, cosmetics, and fumigants. Additionally, free Hg is found in barometers, thermometers, medical instruments, and certain types of lamps.”

Mercury pollution -
More than just an issue of amalgam

• “Large amounts of the metal are used in the production of chlorine and sodium hydroxide (chloralkali industries). The largest portion of the metal is used in electrical and electronic equipment, instruments, and apparatus. Compounds of mercury are employed as catalysts, pigments, and fungicides.”


Why is mercury so popular in industry?

• “Mercury has been widely used in industrial processes because of its chemical and physical properties (for example, it conducts electricity, it responds to temperature and pressure changes, and it forms alloys with many metals.”

“Mercury toxicity depends on exposure route, frequency, dose level, nutritional status, industrial susceptibility, and genetic predisposition.”
What is the most important source of mercury clinically?

• It depends who you talk to!!

• “It’s the dentists’ fault!

• “No, it’s the airborne polluters’ fault!!”

• “No, it’s the vaccine producers’ fault!!”
What is the most important source of mercury clinically?

• “...the natural degassing of the earth’s crust is the major source of environmental Hg...”


What is the most important source of mercury clinically?

• “Inorganic mercury is, due to dental amalgam fillings, the principal source of mercury exposure in the general population.”

What is the most important source of mercury clinically?

• “The major source of non-occupational exposure is dietary intake of methylmercury, with fish and seafood the main culprits because of their propensity to concentrate mercury from water.”


Why the difference in opinion?

Hypothesis:

• Different researchers, all of whom being human, are not totally free of prejudice.
• Different researchers are examining different populations.
Evidence of the latter point

• “On the average, amalgam tooth fillings add 0.5-30 μg Hg/day to a dietary and environmental uptake of 1-6 (without fish) or 2-25 (with fish) μg Hg/day.”


Evidence of the latter point

• “Available data on Hg vapor emission show very large interindividual variation.”

Why the large variation?

• “It is generally believed that the dominant route of uptake of Hg from amalgam fillings is through pulmonary absorption of inhaled Hg vapor. A number of studies show that amalgam fillings continuously emit Hg vapor and that the emission increases as a result of chewing, toothbrushing, or with intake of hot beverages.”


Occupational versus chronic, low grade exposure
**Occupational vs chronic, low grade exposure**

- "Workers are mostly exposed from breathing air that contains mercury vapors, but may also be exposed to other inorganic mercury compounds in the workplace."
- "Occupations that have a greater potential for mercury exposure include manufacturers of electrical equipment or automotive parts that contain mercury, chemical processing plants that use mercury, metal processing, construction where building parts contain mercury (e.g., electrical switchers, thermometers) and the medical professions (medical, dental, or other health services) where equipment may contain mercury (e.g., some devices that measure blood pressure contain liquid mercury."
**Occupational vs chronic, low grade exposure**

- “Dentists and their assistants may be exposed to metallic mercury from breathing mercury vapor released from amalgam fillings and to a much lesser extent from skin contact with amalgam restorations.”
- “Family members of workers who have been exposed to mercury may also be exposed to mercury if the worker’s clothes are contaminated with mercury particles or liquid.”

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“…urinary concentrations in people with amalgams (about 2 to 4 µg of mercury per liter) are well below concentrations found in people who are occupationally exposed to mercury (20 to 50 µg of mercury per liter) unless they are also excessive chewers.”
The fate of atmospheric mercury

• “Mercury in the atmosphere has a complex fate. The mercury that is released into the air is mercury vapor or inorganic mercury. Mercury released into the atmosphere as a gas ultimately redeposits on the earth with precipitation. Once on the earth or in the waterways, it is incorporated into sludges or sediments, where it is methylated by microbial or abiotic processes into methylmercury.”

The fate of atmospheric mercury

- "The plant and sedimentary materials are consumed by small fish and finally by humans. During the course of this progression a great increase in concentration occurs—known as bioaccumulation or bioconcentration. This increase can result in concentrations of mercury in fish tissues that are hundreds of thousands of times as high as the concentration of inorganic mercury in the water."


The fate of atmospheric mercury

- "It is this bioaccumulation that results in significant exposures through the aquatic food web. Inorganic mercury, which is less efficiently absorbed and more readily eliminated from the body than methylmercury, does not tend to bioaccumulate."

The fate of atmospheric mercury

• “Predators at the top of the aquatic food web generally have higher mercury concentrations than those lower in the food web.”


The fate of atmospheric mercury

• “In Minamata, Japan in 1953, neurologic manifestations including mental confusion, convulsions, and coma were reported in villagers who had eaten methylmercury-contaminated fish and shellfish (38% of them later died). Between 1953 and 1971, cerebral palsy, chorea, ataxia, tremors, seizures, and mental retardation were seen in the children of exposed mothers.”

The fate of atmospheric mercury

• “The infants had not eaten contaminated fish, so the neurologic symptoms must have resulted from toxicity in utero. In 1964, an epidemic similar to the one in Minamata occurred in Niigata, Japan. The source of methylmercury was traced to ingestion of fish contaminated by mercury from industrial discharge.”


The fate of atmospheric mercury

• “In 1971, a widespread epidemic with similar symptoms occurred in Iraq. The source was barley and wheat grain treated with methylmercury for defumigation and distributed in error among Iraqi farmers.”

Is environmental mercury a concern in the U.S.?

• “But some of the mercury in Massachusetts comes from incinerators and power plants in states to the west, which underlies the need for the EPA to adopt a national standard, said Gina McCarthy, an assistant secretary at the state’s Executive office of Environmental Affairs.”

Daily Hampshire Gazette, Sept. 19, 2000

‘We must do no less than clean the rain’
Sources of mercury and the forms of mercury involved


"Today...exposure of the general population comes from three major sources: fish consumption, dental amalgams, and vaccines. Each has its own characteristic form of mercury and a distinctive toxicologic profile and clinical symptoms."
The basic forms of mercury

• “Mercury exists as elemental (metallic) metal, inorganic mercury salts (mercurous or mercuric) and organic mercury compounds (aryl- or alkylmercury).”


Forms of mercury: Overview and history


Inorganic Mercury

- “In the case of metallic (liquid, elemental) mercury only the inhalation route has been proven to be biologically relevant in most instances.”
- “When taken orally, less than 0.01% is typically absorbed through the GI tract.”
- “Skin contact normally results in even less absorption in most instances.”
- “In sharp contrast, however, up to 80% of inhaled mercury vapor can be expected to be absorbed through the lungs into the blood.”
Organic Mercury

- “Unlike inorganic forms of mercury, organic mercurials are readily absorbed through the digestive tract (~95%).”
- “For organomercurials, blood is a good indicator of exposure, and urine is a poor indicator, due to differences in the pharmacokinetics of these compounds.”
- “Hair is also a suitable indicator of a history of organic mercury exposure, since incorporation into the hair follicle of both methylmercury and ethylmercury is a known route of elimination of these organomercurials from the body.”

- “Perhaps the earliest medical application may have been in ancient Egypt, where mercury compounds in ointments were used to treat infections.”
- “The skin sores from syphilis may have prompted the early application of mercury to combat this disease as it swept across Europe soon after the return of Christopher Columbus.”
- “Treatment included not only the application of mercury compounds but also the exposure of the person’s skin surfaces to mercury vapor.”
• “Paracelsus was one of the first advocates for the mercury treatment, which included skin exposure to the vapor.”
• “He soon realized, however, that a little too much mercury might kill the patient, hence his famous dictum ‘Dose makes the poison.’”
• “So it may be argued that mercury played a key role in establishing the basic guiding principle in modern toxicology and risk assessment.”


“Reports of Hg\textsuperscript{0} intoxication have been traced back to the writings of Hippocrates and Galen, and in western literature to Ulrich Ellenbog in 1524. The occupational use of Hg\textsuperscript{0} in Japan was reported as early as the eighth century.”
Elemental mercury

• “Elemental mercury vapor is absorbed readily by the lungs and transported through the blood to the brain and other tissues. It is oxidized, presumably in the red blood cells, to mercuric ions that combine with sulfhydryl groups on cell membranes and enzymes.”

**Elemental mercury**

- “Interestingly, metallic mercury is absorbed negligibly after oral ingestion. Unless regurgitation and aspiration occur, swallowing this element poses no health hazard”


**Elemental mercury**

- “When taken orally, metallic mercury is normally not very harmful. In a single case of ingestion of 204 g of metallic mercury, no signs of intoxication were observed.”

Elemental mercury

• “Occasional intoxication through enteral uptake of metallic mercury cannot be excluded, however. Altered gastrointestinal residence times due to the presence of diverticula or abscesses and the degree of dispersion of the mercury ingested may affect absorption.”


Physiology of elemental mercury

• “Inhaled mercury vapors have a high affinity for the central nervous system (CNS). After a single exposure to mercury vapor, ten times more mercury is retained in the brain than after intravenous injection of the same dose of mercuric salt.”

**Physiology of elemental mercury**

- “In the brain, most of the mercury is distributed to the gray matter, especially in the occipital and parietal cortical areas of the cerebral cortex, various nuclei in the brain stem, and the cortical area of the cerebellum. The average biological half-time of inhaled vapor in the whole body is about 60 days. The biological half-time for the mercury accumulated in the brain is probably much longer.”

  Chang, L.W. and Verity MA

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**Elimination of elemental mercury**

- “It is excreted primarily by the kidneys where it accumulates and induces the most damage. Long-term sequelae often include renal failure.”

Non-amalgam sources of elemental mercury

- “Common sources of metallic mercury exposure include mercury switches, thermostats, barometers, and thermometers. When this heavy metal is spilled onto upholstery and carpeting it may slowly volatilize over time, thereby resulting in toxic air concentrations, a common scenario for pediatric poisoning.”


Absorption of elemental mercury from amalgam

- “It is generally believed that the dominant route of uptake of Hg from amalgam fillings is through pulmonary absorption of inhaled Hg vapor. A number of studies show that amalgam fillings continuously emit Hg vapor and that the emission increases as a result of chewing, toothbrushing, or with intake of hot beverages.”

Absorption of elemental mercury from amalgam

- “Divalent Hg ions that are dissolved in the saliva and swallowed will be partly absorbed in the gastrointestinal tract; such absorption is about 15%.”


Absorption of elemental mercury from amalgam

- “Possible routes of uptake of mercury from fillings also include a direct absorption of mercury in the mucosa of the oral cavity and a migration of mercury through the dentin to the dental pulp and the adjacent bones.”

Absorption of elemental mercury from amalgam

- “In continued Swedish autopsy studies cases with no amalgam fillings showed a mean Hg concentration of 6.7 ng/g (2.4 to 12.2) in the occipital cortex, whereas cases with a moderate amount of amalgam fillings, i.e., an average of 21 tooth surfaces restored with amalgam, showed a mean concentration of 12.3 ng/g (4.8 to 28.7). There was a significant correlation between Hg concentration and number of amalgam surfaces.”


Absorption of elemental mercury from amalgam

- “It should be stressed that the individual variation in the release and uptake of Hg from fillings is very large.”

“The total amount of mercury released from dental amalgam depends upon the total number of fillings and surface areas of each filling, the chewing and eating habits of the person, and other chemical conditions in the mouth.”

“Estimates of the amounts of mercury released from dental amalgams range from 3 to 17 micrograms per day.”

The mercury from dental amalgam may contribute from 0 to more than 75% of your total daily mercury exposure, depending on the number of amalgam fillings you have, the amount of fish consumed, the levels of mercury (mostly as methylmercury) in those fish, and exposure from other less common sources such as mercury spills, religious practices, or herbal medicines that may contain mercury.”
Inorganic mercury

Inorganic mercury salts

- “Inorganic mercurials include ammoniated mercury, mercuric chloride, mercuric oxide, mercuric sulfide, mercurous chloride, mercuric iodide, and the phenylmercuric salts. These have been previously used as laxatives (mercurous chloride, calomel) and as anthelmintic agents.”

Inorganic mercury salts

- “Toxicity from laxative abuse is uncommon but may still occur. Most exposure today occurs with pesticides, antiseptics, and germicides. Cutaneous compounds for skin lightening, infected eczema or impetigo, psoriasis, and secondary syphilis may contain inorganic mercury compounds and are still available, particularly in developing countries.”


Inorganic mercury salts

- “Unlike elemental mercury, the inorganic salts are readily absorbed by the gut and are excreted through the kidneys and gastrointestinal system. Only about 10% of an ingested dose is absorbed, but the half-life is approximately 40 days. Mercury salts interfere with sulfhydryl-containing enzyme systems.”

**Inorganic mercury salts**

- “Chronic exposure to mercuric mercury is usually a consequence of occupational exposure where mercury, e.g., mercuric nitrate or oxide, enters the body either via inhalation (dusts of mercuric salt) or via dermal contact.”


**Inorganic mercury salts**

- The best-known example in this situation is the “Mad Hatter” syndrome, with characteristic neurological disturbances similar to those seen in mercury vapor poisoning; micromercurialism, erethism, tremor, personality and neuropsychological changes, and incoordination.”

Inorganic mercury salts

• “The primary target organ for mercuric salts is the kidney. Neurotoxicity for mercuric salts is not prominent.”


Inorganic mercury salts

• “Uptake of Hg in the form of Hg\textsuperscript{2+} is less likely to explain accumulation in the brain, as Hg\textsuperscript{2+} has a limited penetration of the blood-brain barrier.”

Methylmercury


“Mercury poisoning in children is most commonly the result of consumption of methylmercury-contaminated foods, primarily fish.”
**Organic mercury (Methylmercury)**

- “Mercury is dissipated in the environment largely by transport through the atmosphere, where it exists almost exclusively in the elemental form (Hg⁰), as a gas or adsorbed to the surface of small particles. This elemental mercury may then be oxidized to the more water-soluble divalent form (Hg²⁺) dissolved in raindrops, and deposited from the atmosphere.”


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**Organic mercury (Methylmercury)**

- “In soil and water, Hg²⁺ can be (1) reduced to gaseous Hg⁰, thereby returning mercury to the atmosphere, or (2) methylated by microorganisms. The resultant methylmercury unit CH₃Hg⁺ is kinetically remarkably inert towards decomposition, so it may persist in the environment or in an organism even though thermodynamic conditions strongly favor demethylation.”

Organic mercury (Methylmercury)

- “The electrically neutral methylmercury species, CH₃HgCl, (CH₃)₂Hg, etc. are quite lipophilic, and can thus readily pass biological membranes and be concentrated along ecological food chains – a process known as bioamplification. Any substance that is more soluble in the tissues of simple organisms than in the surrounding water will be a more concentrated component of the diet of the more complex species which feed on the simpler ones. Methylmercury has a very strong tendency for bioamplification, which is why the fish in Minamata Bay could attain such toxic levels.”


Source of mercury for methylation

- “Mercury is also released into the environment by oil burning, from its use as a fungicide (often applied to seeds), from outdoor paint (mercury was banned in indoor paint in 1990), and from processes involving chlorine manufacture and use. Waste mercury is released into the atmosphere by cremations (with estimates that a single crematorium releases more than 5,400 kg of mercury per year).”

Source of mercury for methylation

- "A significant amount of elemental mercury is also released into the environment from wastewater from dental offices. In King County, Washington, mercury contaminates the sludge from wastewater treatment sites, which is often sold as fertilizer. Gold mining in the Amazon Basin utilizes mercury to capture gold particles as amalgam, resulting in widespread mercury pollution in the Amazon River and its human and animal inhabitants."


Human methylmercury metabolism

- "After peroral intake, methylmercury is readily absorbed from the gastrointestinal tract. It is transported in the blood and evenly distributed to all tissues within 4 days. In blood, the major part is bound to hemoglobin in the red cells, and the remainder in the plasma proteins. The ratio between the levels in erythrocytes and in plasma is usually about 20:1. Species differences exist."

Human methylmercury metabolism

• “Methylmercury penetrates the blood-brain and placental barriers and accumulates in the brain and in the fetus. In the brain methylmercury is demethylated to inorganic mercury. The ratio between methylmercury and inorganic mercury depends on exposure time, and the time since the cessation of exposure.”


Absorption of methylmercury

• “Methylmercury is efficiently absorbed into the body (more than 95-percent absorption from food…”

Methylmercury and the blood brain barrier

• “Methylmercury crosses the blood brain barrier readily, and brain tissues have a high affinity towards methylmercury. Although methylmercury accumulates in the brain at a slower rate than in other organs (e.g., liver and kidney), methylmercury in the brain tissues is relatively stable and resists degradation to inorganic form.”


Methylmercury and the blood brain barrier

• “With time, the level of alkylmercury in the brain would eventually accumulate at least 3 to 6 times higher than that in blood to reach the threshold intoxication several weeks after exposure. Data from the Minamata episode suggest that overt neurological signs and symptoms of alkylmercury poisoning correlate with the brain mercury level of 10 ppm or more.”

Methylmercury elimination

- “Methylmercury is secreted into the bile and has an enterohepatic circulation. In the gut, a fraction of the methylmercury is demethylated by the intestinal microflora, and most of this inorganic mercury is excreted in the feces. Excretion of urine is limited.”


Methylmercury elimination

- “The daily elimination is about 1% of the body burden. The estimated biological half-time in blood and the whole body, described by a single compartment model, is about 40 to 70 days.”

Other methylmercury storage compartments

• “Methylmercury is present in the breast milk of lactating mothers who consume mainly a seafood diet.”


Other methylmercury storage compartments

• “Methylmercury also has a high affinity for growing hair. At time of hair formation, the concentration ratio of mercury in hair to that in the blood is about 250:1. Thus, when analyzed with appropriate methodology, the hair mercury may serve as a good index for the assessment of mercury exposure.”

Key symptom of methylmercury toxicity

- “Primary sensory neuropathy is probably one of the most sensitive indicators in methylmercury poisoning.”


Key factor in methylmercury deposition

- “The biological disposition of and effects of, inorganic and organic forms of mercury are largely determined by their high affinity for sulfhydryl groups, in particular glutathione (GSH)…”

How much fish do Americans eat?

- “EPA estimates that about 85% of people in the US eat fish or shellfish over the course of a month, with about 60% consuming fish four or more times a month or, on average, at least once a week.”


How much methylmercury is in fish?

- “Fortunately, the most commonly consumed fish species in the United States are comparatively low in methylmercury – shrimp, Alaskan pollock, most tuna, and salmon. In its Report to Congress, EPA estimated based on dietary surveys that the average concentration of methylmercury in fish and shellfish in the US was 0.12 ppm to 0.14 ppm mercury. In fact, the 10 most commonly consumed species usually contained less than 0.2 ppm mercury.”

Which fish are high in methylmercury?

• “Although the most popular species of fish are comparatively low in methylmercury, it is important to recognize that there are also fish species with considerably higher average concentrations. Shark and swordfish average approximately 1 ppm or higher.”


Which fish are high in methylmercury?

• Other species often in the range of 0.5 ppm and higher include various bass, king mackerel, orange roughy, pike, and porgy. Typically, large, predatory fish at the upper end of the aquatic food chain are high in mercury.”

Is farm-raised better?

• “Usually farm-raised fish are lower in mercury concentrations than comparable species and sizes of wild-caught fish.”


Methylmercury content of fish based on geography

• “Freshwater fish can be found with concentrations greater than 0.5 ppm if they swim in contaminated waters. Fishing advisories based on mercury contamination have been issued by 40 states, with 10 states advising limitations on fish consumption from all water bodies.”

Methylmercury content of fish based on geography

• “Five coastal states have advisories to limit consumption of marine fish. Data from the Northeast states collected in the mid-1990s showed average mercury concentrations > 0.5 ppm in 20% to 100% of fish samples of some species depending on location. In Wisconsin, the most commonly sought-after game species, walleye, averaged approximately 0.5 ppm, with individual values > 3 ppm, in a 1998 study.”


Clinical management of methylmercury toxicity

Treatment - Gut Microflora - Underlying concepts

• “Methylmercury is unusual among toxic heavy metal compounds in that it is rapidly and almost completely absorbed from the mammalian gut.”

Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Underlying concepts

• “…a considerable amount of methylmercury is secreted into the bile…”


Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Underlying concepts

• “It has been recognized that enterohepatic circulation of methylmercury plays an important role in its retention and toxicity…”

Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Underlying concepts

• “Conversion of MeHg to the poorly absorbed mercuric form could interrupt the enterohepatic cycle and hence increase Hg excretion in feces.”


Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Underlying concepts

• “The main route of excretion is via the faeces in man and laboratory animals. In rats and mice given MeHg, the majority (50-90%) of the mercury in faeces is in the mercuric form. Therefore demethylation of methylmercury would appear to be a rate-determining step in the excretion of the organomercurial from the body.”

Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Underlying concepts

• “The cumulative body-burden of mercury after methylmercury exposure is determined not only by the quantity taken in, but also, critically, by its rate of elimination.”


Clinical management of methylmercury toxicity
Treatment-Gut Microflora

• “…the observation that antibiotic treatment of mice leads to almost complete retention of a dose of MeHg (half-time of mercury elimination greater than 100 days) would suggest that non-bacterial demethylation does not play a significant role in determining the body-burden of mercury after MeHg exposure.”

Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Demethylation

• “MeHg-induced behavioral signs of neurotoxicity and the severity of the histopathological lesions in the cerebellum were much greater in antibiotic-treated rats than in their conventional flora counterparts.”


Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Demethylation

• “Treatment of the mice with antibiotics decreased both the rate of mercury excretion and the proportion of mercuric mercury found, and at the same time abolished the dietary differences in mercury excretion, demonstrating that the diets per se were not directly affecting MeHg metabolism.”

Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Demethylation

• “Large variations have been reported in rates of elimination of Hg in human populations exposed to MeHg. It is conceivable that this variation may be related to the wide variation in composition of gut flora among individuals.”


Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Demethylation

• Furthermore, if the major differences in gut flora that have been observed in populations in different geographic areas are reflected in their MeHg demethylation rates, it is possible that there are interindividual as well as inter-regional differences in susceptibility to MeHg poisoning.”

Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Methylation

• “The bacterial methylation of mercuric mercury converts the metal from a form poorly absorbed from the gut to one which is virtually completely absorbed and so, potentially, should increase the uptake of mercury from an oral dose or mercuric mercury.”


Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Methylation

• “The highest levels of methylating activity were seen among streptococci, E. coli, yeasts, and staphylococci. Only a small proportion of the obligate anaerobes and lactobacilli formed MeHg.”

Clinical management of methylmercury toxicity
Treatment-Gut Microflora-Methylation

• Rowland also notes that, generally, the amounts of mercuric mercury ingested by most individuals is so small that methylation mediated by gut microflora will probably have no real toxicologic significance. However, if your history reveals that the patient works in a chloralkali plant, for example, where the presence of mercuric mercury is quite high, this type of bacterial activity could be of tremendous importance in creating the symptoms the patient presents.
Mercury and vaccines

• How much mercury is in thimerosal?

“[It] is composed of 49.6% mercury by weight in the form of ethylmercury.”

• “Mercury in the thiomerosal molecule is in the form of ethyl mercury (CH₃CH₂-Hg⁺), for which there is limited toxicologic information.”
• “Thus, health risks from thiomerosal vaccines were based on the assumption that ethyl mercury is toxicologically similar to its close chemical relative, methyl mercury (CH₃-Hg⁺), about which much is known. However...there are reasons to believe that this assumption is not necessarily correct for all aspects of the disposition and toxicity of ethyl mercury compounds, including thiomerosal.”

• “In the late 1880s, diethyl mercury was first used in the treatment of syphilis, a practice soon abandoned because of the toxic properties of this agent.”
• “...early in the twentieth century, the fungicidal properties of the short-chain alkyl mercury compounds led to commercial application in agriculture.”
• “For example, they are especially effective in plant root disease in wheat caused by Tellettia Triticia.”
• “In fact, many different organic mercury compounds were being used to prevent seed-borne diseases of cereal by 1914.”
• “…two outbreaks occurred in rural Iraq in 1956 and 1960 from the misuse of the fungicide ethyl mercury toluene sulfanilamide.”
  “The farmers’ families prepared homemade bread directly from the treated grain instead of planting it.”
• “Hundreds of cases of severe poisoning occurred, many of which had a fatal outcome.”
• “Cases of ethyl mercury poisoning have occurred in China as recently in the 1970s. The exposure pathway was the same as in Iraq: The farmers consumed rice treated with ethyl mercury chloride.”

• “Ethyl mercury in the form of thiomerosal has found wide application in medicine as a disinfectant.”
• “Thiomerosal contains the ethyl mercury radical attached to the sulfur atom of the thiol group of salicylic acid.”
• “Generally, mercuric ions bind tightly but reversibly to thiol ligands.”
• “It is likely, therefore, that the ethyl mercury cation will dissociate from the ethiosalicylic acid moiety immediately after injection to bind to the surrounding thiol ligands present in great excess in tissue proteins.”

• Unlike methylmercury, ethylmercury breaks down to inorganic mercury fairly quickly:
• “A significant fraction of the total mercury in both gray and white matter of the brain was in the form of inorganic mercury of the order of 30-40%.”
• “The kidney cortex has the highest percentage. These findings are confirmed by studies on experimental animals.”
• “Blood and tissue levels, including the brain, were higher in animals doses with ethyl mercury compared with an equivalent dose of a methyl mercury compound.”
• “The high tissue levels of inorganic mercury seen in both humans and animals indicate that ethyl mercury breaks down to inorganic mercury more rapidly than methyl mercury.”

Is there a direct relationship between levels of mercury in the body and the level of toxicity experienced by any individual?
“Humans are highly diverse and, as a result, variability in response to environmental toxicants should be expected.”

“Past efforts to address response variability have tended to divide humans into those who are ‘susceptible’ and those who are ‘normal’ in their responses.”

“A more accurate view of human response to contaminants recognizes a continuum extending from the most resistant to the most susceptible individuals.”

Mechanisms of mercury toxicity and elimination

• “The biological disposition of and effects of inorganic and organic forms of mercury are largely determined by their high affinity for sulfhydryl groups, in particular glutathione (GSH)…”

Mechanisms of mercury toxicity and elimination

• “Once mercury gains access to the circulatory system, the three primary tissues or organ systems that determine the status of mercury are the blood, liver, and kidneys.”


Mechanisms of mercury toxicity and elimination

• “In each of these compartments, GSH status appears to be an important determinant in the disposition of mercury.”

Mechanisms of mercury toxicity and elimination

• “Due to the presence of the free sulfhydryl group on the cysteinyl residue, GSH has a great propensity for forming complexes with ions of metals that have strong electrophilic characteristics, such as mercury.”


Mechanisms of mercury toxicity and elimination

• “Mercury decreases GSH levels in the body, which occurs by several mechanisms. Mercury binds irreversibly to GSH, causing the loss of up to two GSH molecules per molecule of mercury. The GSH-Hg-GSH complex is excreted via the bile into the feces.”

Mechanisms of mercury toxicity and elimination

• Part of the irreversible loss of GSH is due to the inhibition of GSH reductase by mercury, which is used to ‘recycle’ oxidized GSH and return GSH to the pool of available antioxidants. At the same time, mercury also inhibits GSH synthetase, so a lesser amount of new GSH is created.”


Mechanisms of mercury toxicity and elimination

• “In spite of the focus on handling mercury by the kidneys because of the nephropathy induced by mercury, the liver and intestines are the primary organ involved in the early elimination of mercury, with fecal excretion greatly exceeding urinary excretion. Hence, translocation of mercury, presumably in the form of various mercury complexes, to the liver and intestines is quantitatively the major route of mercury interorgan flux.”

Mechanisms of mercury toxicity and elimination

• “Metals that tend to remain longer in the plasma fraction of blood appear to be more likely to be handled by a greater extent by the kidneys.”


Mechanisms of mercury toxicity and elimination

• It appears that mercury ends up in the kidneys only after first line protective mechanisms found in the liver, intestine, and erythrocytes have either failed or have been overwhelmed. Therefore, one of our primary clinical goals from a preventive standpoint is to do what we do with virtually every other patient, improve liver and gut function.
Mechanisms of mercury toxicity and elimination - The role of erythrocytes

• “Complexes of GSH with inorganic or organic mercury may be handled by erythrocytes…”


Mechanisms of mercury toxicity and elimination - The role of erythrocytes

• “Since mature erythrocytes have the capability to synthesize GSH de novo and have significant activity levels of GSH peroxidase and GSH S-transferase, erythrocytes can be viewed as a first line of defense against blood borne oxidants and reactive electrophiles.”

Mechanisms of mercury toxicity and elimination - The role of erythrocytes

- “Once GSH in erythrocytes acts on these potential toxicants, the cells transport GSSG or the thioether conjugate into plasma for translocation to other tissues, particularly the liver, kidneys, and intestines, for further metabolism or excretion.”


Mechanisms of mercury toxicity and elimination - Liver importance

- “Although the liver is a primary site of the excretion of mercury, little hepatotoxicity is generally observed in vivo. This suggests that the mercury that is taken up by hepatocytes for transport across the sinusoidal plasma membrane does not interact significantly with hepatocellular thiols or macromolecules.”

Mechanisms of mercury toxicity and elimination - Liver importance

• Rather, the mercury that is taken up by the hepatocyte must be efficiently delivered into the bile across the canalicular plasma membrane for excretion into the intestine.”


Mechanisms of mercury toxicity and elimination - Liver importance

• “Because of the predominance of GSH in the cell and the existence of specific plasma membrane transport systems, GSH appears to play a central role in the hepatic disposition of both organic and inorganic mercury.”

**Mechanisms of mercury toxicity and elimination - Kidney susceptibility**

- “Of all the organs in the body of a mammal, the kidneys are the primary site for accumulation of mercury after exposure to inorganic or elemental mercury. Organic forms of mercury also accumulate in the kidneys of mammals to a significant degree, but to a lesser extent than inorganic or elemental forms of mercury.”


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**Mechanisms of mercury toxicity and elimination - Impact on sulfur metabolism**

- “It has been established that through alterations in intracellular thiol metabolism, mercury can promote oxidative stress, lipid peroxidation, mitochondrial dysfunction, and changes in heme metabolism.”

Mechanisms of mercury toxicity and elimination
Kidney and sulfur metabolism

• “In all these various renal systems, a threshold effect is generally observed, in that no cellular necrosis (death) is observed up to a certain dose. Above that dose, however, cellular death progresses rapidly, and in some systems an all-or-none response is observed. This does not mean that subtoxic doses of mercury do not have biochemical or physiological effects.”


Mechanisms of mercury toxicity and elimination
Kidney and sulfur metabolism

• “One possible explanation for the threshold effect and the subsequent steep dose-response curve is that endogenous ligands, such as glutathione, bind mercury and may act as a buffer to prevent functional changes from occurring. Above a certain dose or concentration of mercury, the buffer becomes depleted, and mercuric or mercurous ions can bind more readily to critical nucleophilic groups in the cell, thereby causing functional impairment.”

Research that suggests a lack of correlation between mercury body burden and toxic responses:

Presence of amalgams


- “The presence of amalgam fillings was the most significant predictor of high urine mercury in children.”
- “Our results support those of previous studies indicating that the concentration of Hg found in urine of adult and children subjects with no occupational exposure is mainly dependent on the presence of amalgam fillings.”
"The evidence presented here confirms previous findings that children with amalgam fillings have an increased exposure to mercury, although no inference can be drawn about possible adverse health effects."

• “...it is well known that exposure to high concentrations of organic mercury (notably methyl mercury) via fish and seafood consumption, such as those found in the Minimata Bay episode, is associated with neuropsychologic deficits in children.”

• “Those findings, however, were not confirmed in more recent studies in the Faroe Islands in the lowest exposure groups (which are likely to reflect levels found in U.S. children).”

• “The mean urinary mercury concentration was 1.7 µg/g creatinine (range 0.09-17.8); the mean total number of amalgam surfaces was 10.6 (range, 0-46) and the mean number of occlusal amalgam surfaces was 6.1 (range 0-19).”

• “No measure of exposure was significantly associated with the scores on any neuropsychologic test in analyses that adjusted for the sampling design and other covariates.”

• “In a sample of healthy working adults, mercury exposure derived from dental amalgam restorations was not associated with any detectable deficits in cognitive or fine motor functioning.”
Research that suggests a lack of correlation between mercury body burden and toxic responses:

**Urinary challenge testing**
• “Self-reported healthy individuals volunteered to undergo an oral chelation test using dimercaptosuccinic acid (DMSA) at a dose of 30 mg/kg by weight. Urinary mercury : creatinine ratios were measured predose and 3 h post-dose.”

• “Urinary mercury : creatinine ratios were similar to levels previously reported in individuals with symptoms that could have been attributed to mercury toxicity. One volunteer suffered a serious reaction to DMSA.”

“**The oral chelation test using DMSA may lead to misleading diagnostic advice regarding potential mercury toxicity and can be associated with serious side effects.**”
Research that suggests a lack of correlation between mercury body burden and toxic responses:

Mercury removal and elimination of signs and symptoms

As you will see, research on this relationship is very inconsistent and conflicting.

- “The efficacy of the chelating agents…to complex mercury and temporarily facilitate the elimination of that metal in the urine is well established. However, while the use of chelation is increasing for known or suspected heavy metal exposure, there is a paucity of controlled studies showing that this procedure actually improves the long-term outcome of the patient.”

- “In fact, a number of studies found no clear clinical benefit from DMSA treatment of humans documented to have been poisoned, or suspected to have been poisoned, by elemental mercury vapor.”

- “The use of chelating agents is even more questionable in cases where symptoms and/or clinical signs of severe mercury intoxication are absent and where urine and/or blood levels are within the normal background range.”
Trace elements in persons with dental amalgam
The role of a chelating agent

Paul Johan Hol


“All groups in our study showed higher urinary Hg excretion after DMPS administration but the test was still not able to differentiate between patients with and those without complaints self-related to their amalgam fillings.”

Why is there a lack of correlation between body mercury levels, toxic responses, and results of eliminative therapies
Endogenous detoxification!!

• “By increasing the protein content of the diet (from 10% to 20%) or by adding cystine or a combination of cystine and selenium, the toxicity of methylmercury is reduced when methylmercury is added to the diet in an amount of 25 ppm. Not only the level of protein in the diet, but also its source influenced the mercury toxicity, since the survival of rats fed a diet containing 20% protein as fish protein concentrate was higher than the survival of those fed a 20% casein diet.”

• “A higher protein level (20% vs. 10%) reduced and delayed the onset of toxic signs, and fish protein concentrate was more effective in this respect than was casein. This effect of fish protein concentrate was presumably due to its selenium content, since fish protein concentrate contained about 4 ppm of selenium. It was also shown that 0.4% cystine and 0.6 ppm selenium were about the optimum levels for reducing visible toxic signs produced when diets contained about 25 ppm of mercury from methylmercury chloride.”
• “Mercury concentrations in the kidney were considerably lower when diets contained cystine, selenium, and fish protein concentrate. The protective effect of cystine and selenium may be exerted through a reduction in mercury deposition in the kidney, and hence a delay in the onset of kidney failure caused by continued exposure to high intakes of mercury.”

• “Another possible explanation is that cystine provides additional sulfur-binding sites in proteins that complex with mercury. At least a partial effect of cystine in these studies may also have been via an increased rate of conversion of methylmercury to inorganic mercury, which is less toxic. Norseth and Clarkson showed that inorganic mercury was released from methylmercury chloride when placed in a buffered solution containing 0.1 M cysteine. No inorganic mercury was released when cysteine was absent.”

- "The small amount of MeHg consumed with each exposure and spreading the exposure over a longer time period may alter the way the human body handles it. Clarkson (1995) has suggested that the liver may excrete or detoxify small amounts, but may be unable to handle larger amounts."

- "Exposure to MeHg in conjunction with other components of fish such as selenium and amino acids may also influence its potential toxicity in other ways. Selenium may decrease any potentially toxic effects and amino acids may compete with MeHg transport into the brain."
Is the best way to deal with mercury body burden always elimination from the body as quickly as possible?

Selenium:
Possibly the most important “X factor” that explains why mercury levels do not correlate with symptomatology
• “Regarding the concern about mercury contamination, the National Oceanic and Atmospheric Administration (NOAA) statement advises: ‘Women will not put their baby at risk if they avoid eating shark, swordfish, tilefish, king mackerel, tuna steaks and whale meat until after they have delivered and stopped breast feeding.’ For good measure, women planning to become pregnant should avoid these fish for six months beforehand.”


• “The recommendations have a 10-fold safety margin built in for precaution, which some scientists think is scaring people away from seafood. ‘This margin might make people continue depriving their families and their children of the benefits of consuming seafood,’ William E. M. Lands, a retired Professor of Biochemistry at the University of Michigan and the University of Illinois, and an expert in the field of the metabolism of fats, phospholipids, and prostaglandins, told Reuters Health.”
• Evidence presented at the conference showed that selenium, another element present in ocean fish, neutralizes the effects of mercury acquired from foods. ‘This very important, but little analyzed, point helps us understand how people from the Seychelles Islands can eat fish 12 times per week and show no toxic signs,’ Lands said. ‘The subtle toxic signs seen in places like the Faroe Islands now seem attributable to mercury being ingested in mammalian meats (pilot whale) that have much lower selenium than mercury.’
• ‘Not eating seafood is more harmful than eating it,’ Lands concluded. ‘The benefits of eating seafood far outweighs the risks of the little bit of mercury that are in the seafood.’

Selenium and the brain
• “It becomes more and more apparent that the essential trace element Se plays a critical role in the maintenance of proper functioning of the nervous system.”

• “Furthermore, insufficient brain Se levels have potentially detrimental effects on brain function and may exacerbate neuronal loss and dysfunction subsequent to endogenous or exogenous stimuli, trauma and other neurodegenerative conditions.”

• “Selenium is a potent protective agent for neurons through the expression of selenoproteins, which are mostly involved in regulation of redox status under physiological conditions and in antioxidant defense.”
• “The co-administration of methylmercury and selenium is known to depress methylmercury toxicity. Furthermore, the level of selenium in human hair has been found to negatively correlate with the level of mercury in brain tissue. Methylmercury forms a bismethylmercury selenide complex. Selenium in foods (especially fish) may also complex with methylmercury and, therefore, may potentially reduce the bioavailability of methylmercury.”

“Mercury selenide precipitates have extremely low solubility, ranging from $10^{-58}$ to $10^{-65}$, thus they are thought to be metabolically inert.”

“It is reasonable then to assume that not only does selenium have an effect on mercury’s bioavailability, but mercury may also have an effect on selenium bioavailability.”

“...a part of the neurobehavioral toxicity of MeHg may result from Se deficiency in the brain.”

“...the effects of MeHg on ‘endogenous’ Se might contribute to the neurotoxicity of MeHg in fetus/neonates.”

• “Their research confirmed the neurological deficits reported from MeHg poisoning incidents in Japan. However, they found no adverse associations from consuming fish containing typical mercury levels. Additionally, their studies of both prenatal and postnatal measures of MeHg exposure from fish consumption in Seychellois children have been associated with beneficial effects.”

• “Their results, however, contrast with those found in studies being carried out in the Faroe Islands, which reported adverse associations from prenatal MeHg exposure. There are several differences between these studies and the populations in general. However, the most intriguing distinction may be the source of the MeHg exposure.”
• “The diet consumed by the Faroe Islanders includes whale whereas the Seychelles Islanders diet does not. Whale is known to contain PCBs as well as possibly other toxins not typically found in fish. Additionally, the amount of MeHg in some types of whale meat analyzed has been reported to be exceedingly high. The concentration of mercury present in whale rises continually with age and can exceed the selenium content. This is seen in high-end predator whales such as pilot whales rather than filter feeders such as bowhead whales. Mercury concentrations in samples of pilot whale have been 5000 times greater than the Japanese government’s limit for mercury contamination of 0.4 ppm.”

“**In contrast to whales, methyl mercury concentrations in fish rise with age, but as their mercury contents increase, so do their selenium concentrations. To our knowledge, there are no reports of mercury exceeding selenium concentrations in any ocean fish.**”
• “Friedman et al studied the protective effect of freeze-dried swordfish on methylmercury toxicity in rats. The rats that were experimentally administered methyl mercury and fed a swordfish diet showed no signs of neurotoxic effects characteristic of mercury poisoning, while rats not fed swordfish did. Analysis of the swordfish showed selenium concentrations were at least twice as high as the mercury levels. The authors suggested that the excess selenium protected the rats from the effects of the administered methyl mercury.”

• “Several studies suggest an important role of selenium in the bioaccumulation of mercury in fish. Paulsson and Lindbergh reported selenium supplementation to lake waters in Sweden resulted in a 75%-85% reduction in mercury levels of fish when measured over a three-year period.”
• “Southworth et al reported that the elimination of selenium-rich discharges of fly ash to Rogers Quarry in Tennessee in 1989 caused a steady increase in mercury concentrations. The aqueous selenium concentrations decreased from 25 to <2 μg/L. The mean selenium concentrations in bass declined from 3 to 1 mg/kg over the first 5 years and remained at 1-1.5 mg/kg for the last three years of the study. During this time, the mean mercury concentrations in bass rose from 0.02 to 0.61 mg/kg.”

• “Although several population studies have suggested an association between high fish intake and reduced coronary heart disease (CHD), men in eastern Finland who consume large amounts of freshwater fish have an exceptionally high CHD mortality. Salonen et al studied the relationship between mercury intake from fish and CHD in Finland. The authors hypothesized that the high mercury levels from fish contributed to increased incidence of CHD. Before soil supplementation, Finland had the lowest selenium levels throughout Europe.”
The authors suggested that mercury might contribute to CHD risk by complexing to selenium and reducing its bioavailability for glutathione peroxidase, thus promoting lipid peroxidation. They further suggest that the lack of a similar correlation between CHD and fish consumption in other population studies was owing to high intakes of selenium.


“Thus, our results suggest that the nutritional status of Se should be taken into account when the neurobehavioral effects of perinatal MeHg are evaluated.”

• “In summary, studying the pathology of mercury toxicity may require a more insightful question than simply, ‘How much mercury is consumed?’ The more appropriate question may be, ‘Is a sufficient amount of free selenium available in the cell to create the necessary selenoenzymes or is too much selenium lost by binding to mercury?’”
“In this regard, the sensitivity to mercury-induced neurotoxicity may be due to the balance of mercury and selenium.”

• “Selenium’s involvement is apparent throughout the mercury cycle, influencing its transport, biogeochemical exposure, bioavailability, toxicological consequences, and remediation. Therefore, measuring the amount of mercury present in the environment or food sources may provide an inadequate reflection of the potential for health risks if the protective effects of selenium are not also considered.”

- “It is well known that Se is an antagonist that moderates the toxic effects of many heavy metals such as arsenic, cadmium, Hg, and lead in organisms.”
- “Burk et al. suggested that the Hg-Se-protein complex plays a role in restraining the acute toxicity of inorganic Hg by binding Hg to prevent it from reaching the target tissues. Recent *in vitro* studies suggest that Se and Hg could form Hg-Se complexes in a reducing environment and that this 1:1 complex is then bound with plasma selenoprotein P (SeP).”
“Thus, we propose that selenoproteins may have two important roles in protecting against mercury toxicity. First, they may bind more Hg through their highly reactive selenol group, and second, their antioxidative properties help compromise the reactive oxygen species induced by Hg in vivo.”

Selenium and amalgams

- “Individuals with amalgam excreted less selenium (36.4 microg, median value) over 24 hours than those without amalgam (45.5 microg).”
- “The blood selenium concentrations were statistically significantly lower in subjects who claimed symptoms of mercury amalgam illness, than in healthy subjects with amalgam. This difference was more evident between the individuals with more than 35 amalgam surfaces.”

- “The use of the selenium containing toothpaste resulted in all cases, in significantly lower amounts of mercury vapour.”
- “When the amalgam surfaces were brushed with the conventional toothpaste, an increase of the released vapour was noted.”
Mercury, selenium, and other nutrients

• “The susceptibility of a tissue to damage would be a function of the methylmercury concentration, the rate at which hemolytic breakdown occurred, and the capacity of the tissue to defend against peroxidative damage, as determined by levels of glutathione peroxidase, vitamin E, and other substances.”

The best way to remove mercury
Boyd Haley, Ph.D.
• “The following is my opinion on the use of natural materials and compounds that may be safely used to remove mercury from the body. It is totally based on the science known about how the mammalian body removes toxic mercury.”

• “I do not present any opinion on EDTA, DMSA, DMPS, or BAL or other manufactured chelators. It is my opinion they should be used only after the use of natural compounds has failed.”

• “Using the adage “First, do no harm” I think that supplementing the body’s metabolic system that is active and needed for natural removal of mercury is the best approach. This is not as much “chelation therapy” as “anti-oxidative stress therapy” and is based on the supplementation that enhances the production of materials normally used to remove heavy metals.”
Boyd Haley’s protocol

- Vitamin C
- Lipoic acid
- IV glutathione
- Melatonin
- Vitamin B12
- Selenium
- Sulfurized amino acids

Boyd Haley’s thoughts on selenium

- “Se2+ forms a very tight bond with Hg2+ and forming HgSe (similar to HgS, mercury sulfide or cinnabar the ore where mercury is mined from) would greatly reduce the toxicity of mercury.”
- “However, it may also interfere with the removal of mercury from the body as HgSe would not be removed by GSH or lipoic acid.”
- “One should also consider that any patient who is mercury toxic should also be selenium deficient as the mercury would remove the selenium from bioavailability.”
Boyd Haley’s thoughts on chelation

• “After the patient is showing improvement it may be advantageous to use DMPS or DMSA to enhance the removal of mercury. I am not totally against their use but I do not think they will represent the best or safest way to approach removal of mercury from a very sick patient due to their own toxicity as British Anti-Lewisite agents.”

Boyd Haley’s thoughts on chelation

• “Also, they do not effectively enter cells nor cross the blood brain barrier as do natural compounds. However, in the hands of a good physician they may prove very helpful. It is when the pills of DMPS and DMSA are given to the lay-person for them to decide how to use on a daily basis that I feel they can become dangerous.”
“…especially in chronic toxicity, the presence of vitamin E and selenium might allow for a sustained decomposition of alkylmetals by stabilizing microsomal cytochrome P450 systems involved in alkylmetal metabolism.”

DMSA/DMPS
Is DMSA/DMPS a valid tool for **diagnosis** of *mercury body burden*?

Maybe
Is DMSA/DMPS a valid tool for diagnosis of mercury related symptoms?
According to much research, *No!!*
Is DMSA/DMPS a valid tool for treatment of mercury body burden?

Yes!!
Is DMSA/DMPS a valid tool for treatment of mercury related symptoms?

According to much research, No!!
• “…while the use of chelation is increasing for known or suspected heavy metal exposure, there is a paucity of controlled studies showing that this procedure actually improves the long-term outcome of the patient. In fact, a number of studies found no clear clinical benefit from DMSA treatment of humans documented to have been poisoned, or suspected to have been poisoned, by elemental mercury vapor.”
• “The use of chelating agents is even more questionable in cases where symptoms and/or clinical signs of severe mercury intoxication are absent and where urine and/or blood levels are within the normal background range. In addition to being unnecessary and financially burdensome, inappropriate use of chelators may present untoward danger to the patient and may also bind other divalent mineral cations essential for normal physiologic function.”
However, what happens when DMSA/DMPS is combined with nutritional therapies?

• “All patients who experienced a reduction in mercury levels reported improved overall health, increased energy, and decreased symptoms. Chronic candidiasis…resolved as a possible result of the mercury extraction and other appropriate treatment protocols. Symptoms of depression and allergies were markedly reduced.”

Could adverse effects be the reason for all of the conflicting findings?
• “Delta-aminolevulinate dehydratase (delta-ALA-D) is a sulfhydryl-containing enzyme that catalyzes the asymmetric condensation of two delta-aminolevulinic acids molecules yielding porphobilinogen, a heme precursor.”

• “Consequently, delta-ALA-D inhibition can impair heme biosynthesis and can result in accumulation of delta-ALA, which may disturb aerobic metabolism and also have some pro-oxidant activity.”
Which parts of the body does DMSA/DMPS favor concerning mercury removal?

“…mercury in certain tissues (e.g., the brain) is known to be essentially impossible to remove using DMSA and DMPS [although this may be due to a lack of access to the brain, rather than the effectiveness (or lack of it) of DMSA and DMPS].”

• “The purpose of this study was to test the hypothesis that DMPS, DMSA, glutathione, vitamin C, or lipoic acid, alone or in combination, would decrease brain mercury in rats exposed to elemental mercury vapor. Our results clearly indicated that none of these agents did so.”

Fact or Fallacy:
Before chelating with DMSA or DMPS all amalgams should be removed. If this is not done, these compounds will leach mercury from amalgams, which will, in turn, be reabsorbed.
• “Ideally intravenous DMPS should never be used in patients who still have amalgam fillings in place...DMPS appears in the saliva and may mobilize significant amounts of mercury from the surface of the fillings and precipitate seizures, cardiac arrhythmias, or severe fatigue.”


• “…investigators have done this diagnostically, as a one-time dose, without complications.”


• “However, orally administered chelating agents forming hydrophilic metal complexes may efficiently reduce intestinal metal uptake and local toxicity at early times after oral intoxication.”

• “Also orally administered dimercaptosuccinic acid (DMSA) reduced the intestinal uptake and toxicity of oral Cd$^{2+}$. Chelation of Ni$^{2+}$ with EDTA and Hg$^{2+}$ with DMSA or dimercaptoproprionic sulfonate (DMPS) reduced intestinal uptake. Accordingly, oral administration of chelating agents may in some cases offer both reduction of local toxicity and prevention of intestinal metal uptake.” (Andersen & Aaseth)

Fact or Fallacy: DMPS and DMSA cause increased mercury uptake into the brain
• “DMPS and DMSA do not mobilize heavy metals to the brain.”
  Nogueira CW et al. 2,3-dimercaptopropane-1-sulfonic acid and meso-2,3-dimercaptosuccinic acid increase mercury- and cadmium-induced inhibition of delta-aminolevulinate dehydratase. Toxicology. 2003;184(2-3):85-95.

• “DMPS does not redistribute arsenic, lead, or inorganic mercury to the brain…”
  (Anderson & Aaseth)

• “…DMSA chelation decreases the brain deposition of lead and methylmercury.”
  (Anderson & Aaseth)

Other diagnostic modalities: RBCs, Plasma, Hair, Urine
Whole Blood

• “In the blood, more than 90% of MeHg is bound to haemoglobin in the red blood cells (RBC), while IHg is more evenly distributed between RBC and plasma. Therefore, total Hg in RBC is also sometimes used as a proxy measure of MeHg exposure and total Hg in plasma is used as a proxy measure of IHg exposure (Hg²⁺ and Hg⁰).”
Plasma

- “Using total mercury concentrations in plasma as a measure of inorganic mercury exposure can lead to significant exposure misclassifications.”

RBCs

- “It can be concluded that IHg in RBC is partly emanating from inorganic Hg exposure, mainly Hg⁰ via amalgam, and partly from MeHg exposure via fish, which has demethylated to IHg in the body…”
- “”Most of the Hg found in RBC is in the form of MeHg with small inter-individual variations.”
Hair

• “Our data strongly indicates that the small fraction of IHg in hair (about 9%), with relatively small inter-individual variations (CV about 15%) is a result of MeHg exposure and demethylation of MeHg in blood or hair follicles (and in the analysis), rather than a result of IHg exposure.”

Hair

• “IHg in hair was positively correlated with fish intake, but not with dental amalgam fillings. It was also highly correlated with Hg0 in blood, RBC, and plasma.”
• “…it should be borne in mind that artificial waving and other hair treatments may reduce Hg concentrations within the hair strand.”
Hair

• “The concentrations of total Hg in hair (H-THg) is often used as a measure of MeHg exposure, assuming that > 80% of Hg in hair is in the form of MeHg. Mercury is incorporated in hair during formation in the hair follicle, and mercury in hair is associated with the concentration of MeHg in blood.”

Mercury vapor - Use of hair for diagnosis

“Elemental mercury (from amalgams) does not show up well in the hair. In fact, other hair mercury studies have shown hair mercury levels are 79-94 percent methylmercury, leaving only 6-21 percent as elemental mercury. With such a low affinity of elemental mercury for the hair, one may have a significant amount of elemental mercury and exhibit no presence of such on hair test.”

Mercury vapor - Use of hair for diagnosis

- Individual cases have been published showing urinary mercury excretion to be 23-60 μg/Hg/day (25-54 μg/g creatinine) indicating a daily intake as high as 100 μg. In these individuals, bruxism and gum chewing were noted as probable causes of the high mercury output, which fell back to normal levels with amalgam removal. Higher levels of mercury release from dental amalgams have also been found with toothbrushing and after consuming hot drinks.”

Crinnion, W.J.

Mercury vapor from amalgams

- “Elemental mercury from amalgams shows up best in the plasma and urine.”


**Urine**

- “The total Hg concentration in urine is used as a measure of IHg exposure as MeHg is excreted primarily via the bile (as glutathione complex) and faeces (about 90%: as IHg) and only to a limited extent (about 10%) in urine (as IHg).”
Urine

• “Our data shows that IHg in urine reflects the IHg exposure as nearly all Hg in urine (>98%) was IHg and as IHg in urine did not reflect fish consumption or the OHg concentration in various media.”
Porphyrin testing is the best way via laboratory testing to determine if the mercury body burden is contributing to my patient’s chief complaint.
• “Porphyrs, derivatives of the heme synthesis pathway, afford an independent measure of adverse exposure. Heme manufacture takes place most prominently in the liver, kidney and erythroid cells.”
• “Synthesis proceeds in two steps from succinyl-CoA + glycine to uroporphyrinogen and in a further series of steps via pentacarboxyporphyrinogen and coproporphyrinogen to heme.”

• “Excess porphyrinogen metabolites are excreted in the urine as oxidized porphyrins, particularly uroporphyrin and corroporphyrin, reflecting the most abundant molecules in the rat kidney cortex.”
• “Excess urinary porphyrin excretion or porphyrinuria results from blockade of key enzymatic steps in conditions including genetic deficiencies in heme manufacture enzymes, hepatic, renal and erythroid disease and also by toxic inhibition of heme synthesis enzymes.”
“In both experimental animals and humans exposed to heavy metals, porphyrins are exported at elevated levels into urine.”

Fig. 1. Pathway of heme synthesis, major urinary metabolites, and inhibition by heavy metals. Porphyrinogens appear in urine as porphyrin derivatives (right): urinary pentac-, precoprop-, and coproporphyrin are indicators of inhibition of UROD (uroporphyrinogen decarboxylase) and/or CPOX (coproporphyrinogen oxidase); urinary uroporphyrin is not reported to alter with inhibition of these enzymatic steps. 7-carboxy, 6-carboxy; 7CXP, 6CXP; hepta- and hexa-carboxyporphyrinogens and -carboxyporphyrins, respectively.
“In terms of specificity, the unique change in the porphyrin excretion pattern, characterized by elevated levels of five- and four-carboxyl porphyrins, as well as by the expression of the atypical porphyrin, precoproporphyrin, is, to our knowledge, unique to mercury exposure. This pattern is different from that which characterizes any of the known forms of inherited porphyria, and also differs distinctly from those elicited by exposure to other metals.”
• “The biochemical etiology of changes in five- and four-carboxyl porphyrins observed during mercury exposure has previously been shown to occur as a result of mercuric ion (Hg2+) (or CH3Hg+-) directed impairment of the specific heme pathway enzymes, uroporphyrinogen decarboxylase and coproporphyrinogen oxidase…”

“Changes in urinary porphyrin concentrations...vary directly in proportion to the dose of mercury administered.”
• “Since the change in the urinary porphyrin excretion pattern is unique to mercury exposure and occurs in subtoxic, as well as potentially toxic mercury levels, the urinary porphyrin profile method could be employed in the clinical setting to indicate whether a biological response to mercury has occurred, or to monitor the effectiveness of treatment regimens for facilitating mercury clearance.”

Porphyrin testing as a marker for DMSA chelation

Case report:

Lead toxicity with elevations of coproporphyrin & pentacarboxyporphyrin

- “Both compounds were restored to normal levels following two courses of meso 2,3-dimercaptosuccinic acid…”
- “Blood lead decreased from 384 to 24 micrograms/dL, urine lead from 1286 to 188 micrograms/L and urine coproporphyrin III from 5712 to 25 micrograms/L.”
**Brady chelation protocol**

- DMSA: 500 mg M-W-F x 3 weeks, 1 wk wash-out, repeat 3-5 cycles.
- Wait one month and repeat entire cycle as needed and conduct serial laboratory analysis for follow-up assessment.

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**Porphyrin testing and autism**

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“Excess urinary porphyrin, in addition to being a marker of toxicity, could play a contributory role in the behavioral manifestation of autistic disorder. Porphyrinuria is accompanied by elevated blood levels both of porphyrins and the precursor molecule 5-aminolevulinic acid ($\delta$ALA).”
• “These metabolites target benzodiazepine receptors in the brain and have been associated with neurologic disturbances, epilepsy and autism. Excess of these metabolites could contribute to the brain and behavior disturbances in some subjects with autism.”

Some parting thoughts
Thank you!!