Environmental Medicine, Part Three: Long-Term Effects of Chronic Low-Dose Mercury Exposure

Walter J. Crinnion, ND

Abstract

Mercury is ubiquitous in the environment, and in our mouths in the form of "silver" amalgams. Once introduced to the body through food or vapor, mercury is rapidly absorbed and accumulates in several tissues, leading to increased oxidative damage, mitochondrial dysfunction, and cell death. Mercury primarily affects neurological tissue, resulting in numerous neurological symptoms, and also affects the kidneys and the immune system. It causes increased production of free radicals and decreases the availability of antioxidants. It also has devastating effects on the glutathione content of the body, giving rise to the possibility of increased retention of other environmental toxins. Fortunately, effective tests are available to help distinguish those individuals who are excessively burdened with mercury, and to monitor them during treatment. Therapies for assisting the reduction of a mercury load include the use of 2,3-dimercaptosuccinic acid (DMSA) and 2,3-dimercapto-1-propanesulfonic acid (DMPS). Additional supplementation to assist in the removal of mercury and to reduce its adverse effects is discussed.
(*Altern Med Rev* 2000;5(3):209-223)

Methylmercury Sources

Mercury is ubiquitous in the environment due to constant off-gassing of mercury from the earth's crust. This mercury enters waterways, where it is methylated by algae and bacteria. Methylmercury makes its way through the food chain into fish and shellfish, and ultimately into humans. Additional mercury, released from industrial sources into the atmosphere, also is converted in waterways into methylmercury. Because of mercury contamination, 40 states now have warnings on some of their waterways. Warnings of unacceptably high mercury levels in fish have been issued for nearly 15 percent of the nation's lake acres and five percent of its river and stream miles. In the Pacific Northwest, the most recent finding of high mercury levels is in the sediment of the Spokane River in Washington State. The mercury contamination came from its headwaters – Lake Coeur d'Alene, in northern Idaho. The contamination of this lake with mercury, as well as zinc, lead, cadmium, arsenic, and antimony is believed to have come from more than a century of mining operations in northern Idaho's Silver Valley. The United States Geological Survey has estimated the bed of Lake Coeur d'Alene contains about 70 million metric tons of contaminated sediment.

In 1999, the U.S. Environmental Protection Agency (EPA) directed utilities to measure the amount of mercury released by coal-burning power plants. Mercury is also released into the

Walter Crinnion, ND. Healing Naturally. 11811 NE 128th St, Suite 202. Kirkland, WA 98034

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).[1] 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.[2] Fish absorb methylmercury from water passing over their gills and as they feed on aquatic organisms. Methylmercury accumulates in fish, and ultimately in humans as it travels up the food chain. Methylmercury binds tightly to fish proteins, and its presence in consumed fish is not appreciably reduced by cooking. The half-life of methylmercury in fish is two years, which is two-to-five times greater than the half-life of inorganic mercury.[3]

Nearly all fish contain trace amounts of methylmercury. Fish living in areas of high pollution, such as the Great Lakes, have higher levels of mercury and other pollutants. Methylmercury levels for most fish range from less that 0.01 ppm to 0.5 ppm. Usually only large predator fish, such as shark and swordfish, are found to contain tissue levels of methylmercury that reach the U.S. Food and Drug Administration (FDA) limit – 1 ppm – for human consumption. Certain species of very large tuna, typically sold as tuna steaks or sushi, can have levels of 1 ppm or greater. Canned tuna is usually composed of smaller species of tuna such as skipjack and albacore, which typically have much lower levels, averaging about 0.17 ppm. In the Seychelles Islands in the western Indian Ocean, the larger

fish – kingfish, becune, carangue, balo, and bonita – all exceeded the 1 ppm level. More than half of the dogtooth tuna recently sampled there also exceeded the FDA limit, with some sampled fish reaching levels of 3.3 and 4.4 ppm.[4] While the level of methylmercury in skipjack tuna from those waters ranged only from 0.02-0.44 ppm, the average concentration of methylmercury in most commercial fish is less than 0.3 ppm.[5] Sport fish from the Great Lakes average from a low of 0.11 ppm in Lake Michigan and 0.19 ppm in Lake Huron, to between 0.24-0.58 ppm in Lake Erie and 0.48-0.88 ppm in Lake St. Clair. Perch from Lake St. Clair had the high mark of 0.88 ppm, while those from Lake Erie averaged 0.24 ppm. In Lake Erie, the high mercury-containing fish were walleye, white bass, and smallmouth bass.[6] Whales also have a very high mercury content.

In the FDA's Total Diet Survey, mercury was found in 100 percent (16/16) of canned tuna samples (avg. 0.277 ppm), frozen cod/haddock fillets (avg. 0.132 ppm), canned mushrooms (avg. 0.0298 ppm), and shrimp (avg. 0.0281 ppm). Mercury was found in 15/16 samples of fish sticks (avg. 0.0254 ppm) and crisped rice cereal (avg. 0.0044 ppm).[7]

Methylmercury is efficiently absorbed into the body (more than 95-percent absorption from food) and crosses both the blood-brain barrier and the placental barrier. It is known to be a potent neurotoxin and teratogen.[8] Its biological half-life in humans is about 70 days.[9] Methylmercury is present in the breast milk of lactating mothers who consume a mainly seafood diet. The mercury concentration in the milk of these women ranges from 2.45 µg/liter in women of the Faroe Islands, who eat meat and blubber of the pilot whale,[10] to 3 µg/liter in Sweden[11] and 7.6 µg/liter in coastal Alaska (where they consume whale).[12]

Major methylmercury poisoning incidents occurred in Minamata Bay (1953-1960) and Niigata (1965) in Japan after industrial

dumping of mercury led to chronic mercury poisoning in people whose primary source of food was seafood from those waters.[13] Another poisoning episode occurred in Iraq in the fall and winter of 1971-1972. In this situation, wheat treated with alkyl mercury as a fungicide and intended for seed was instead ground into flour for bread. This contamination resulted in more than 6,000 individuals being hospitalized and 459 deaths.[14]

Elemental Mercury Sources

Silver "amalgam" dental fillings typically weigh between 1.5-2.0 g, with approximately 50 percent of the material being elemental mercury. When no chewing occurs, individuals with amalgam fillings on occlusal surfaces have been found to have oral levels of mercury vapor nine times greater than those without amalgams. Upon chewing, the same individuals had a six-fold increase in oral elemental mercury levels, resulting in a 54-times greater level of mercury vapor in their oral cavities than persons without amalgams.[15] Serial measurements of these individuals found mercury concentrations remained elevated during 30 minutes of continuous chewing, and then declined slowly over 90 minutes after chewing ceased.[16] Based on the relatively small size of the trial (35 subjects), the researchers concluded individuals with 1-4 occlusal amalgams would be exposed to an average daily dose of 8 μg elemental mercury; those with 12 or more occlusal amalgams were estimated to receive 29 μg per day, and the average of all 35 subjects was estimated at 20 μg per day. 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.[17] 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 tooth brushing[18] and after consuming hot drinks.[19]

Mercury vapor is highly lipid soluble and enters the blood from both the lungs and oral mucosa. It traverses cell membranes (including the blood-brain and placental barriers), rapidly partitions between plasma and red blood cells, and becomes widely distributed. As much as 40 percent of mercury vapor is excreted through the feces.[20] Once in the cell, elemental mercury is oxidized by catalase-hydrogen peroxide and becomes divalent Hg^{2+}, which then combines covalently with sulfhydryl groups in molecules such as hemoglobin, reduced glutathione, and cysteine residues in proteins. Thus, individuals exposed to mercury have been found to have lower levels of reduced glutathione.

Blood mercury concentrations have been positively correlated with the number and surface area of amalgam restorations, and are significantly higher in individuals with amalgams than those without.[22] Amalgams are also associated with higher urinary mercury output,[23] as well as higher levels in breast milk, although not hair.[24] When examining the association between mercury presence and breast milk it was found the total and inorganic mercury levels in blood and milk did correlate with the number of amalgam fillings. In this study, when seafood was not the main dietary staple, there was no association found between dietary methylmercury intake and milk levels. Exposure of the breastfed infant to mercury from the mother's amalgams was calculated up to 0.3μg/kg (one-half of the tolerable daily

Table 1. Factors that Increase Mercury Release from Amalgams.

Chewing (food or gum)
Brushing
Bruxism
Hot drinks
Drilling or polishing

intake for adults recommended by the World Health Organization).

Animal models have demonstrated that mercury from dental amalgams concentrates in the kidney, liver, gastrointestinal tract, and jaw.[25,26] The choroid plexus, an important part of the blood-brain barrier, acts as a sink for mercury and other heavy metals.[27] It has also been shown that mercury is selectively concentrated in the human brain in the medial basal nucleus, amygdala, and hippocampus regions (all of which are involved with memory function), in the granular layer of the cerebellum, and in sensory neurons of the dorsal root ganglia. Mercury has also been shown to be taken up by the retina[28] and in granule cells of layer IV in the visual cortex, which can cause a reversible impairment of color perception.[29]

Other Mercury Exposure Sources

Historically, mercury was used to treat syphilis and other infective diseases.[30] Mercury is still used today in some medicines as a preservative, being present in this form in various vaccinations.

Mercury poisoning has occurred from mercury in abandoned industrial sites. In Texarkana, Arkansas, teenagers found two pints of mercury in an abandoned neon sign plant, resulting in one hospitalization and seven homes being evacuated by the EPA.[31] A more serious incident occurred in New Jersey in 1995, where a five-story factory building used to manufacture mercury vapor lamps in the 1930s was converted into condominium apartments. When residents reported finding standing pools of mercury on the countertops and floors, local health agencies were contacted. Air mercury levels were found to range from 5 $\mu g/m^3$ to 888 $\mu g/m^3$ (over visible pools of mercury on the floor). Sixty-nine percent of the residents had urinary mercury levels greater than 20 $\mu g/l$.[32] Comparisons of urine at the time of evacuation from the building and 10 weeks later showed no significant differences.[33] Former residents with the highest urinary mercury levels exhibited the most errors on a test of fine motor function, and reported the most somatic and psychological symptoms.

In another residential poisoning, mercury vapor was spread by the use of the family vacuum cleaner, which had been used to clean up mercury from a broken thermometer. Continued use of the vacuum cleaner spread mercury droplets throughout the house. A two-year-old girl developed nephrotic syndrome and her three-year-old brother had significant neurological problems.[34] Mercury poisoning has also been found in persons living proximal to an inactive mercury mine in California,[35] and in individuals from several states using Crema de Belleza-Manning facial cream. This cream was found to contain 6-10 percent mercury, while the facial cream Nutrapeil Cremaning Plus was found to have 9.7 percent mercury.[36]

Adverse Effects on the Body
Cellular and Nutritional Alterations

Mercury has the ability to cause changes at the cellular level, which has been seen in platelets and erythrocytes. These cells have been used as surrogate markers for mercury damage of neurological tissue. The addition of methylmercury to whole blood can cause a dramatic dissolution of microtubules in platelets and red blood cells – an effect more pronounced in erythrocytes than platelets – which is consistent with the known sequestration of methylmercury in erythrocytes.[37] This effect on microtubules has also been found in the brain,[38] and results in disruption of the cell cycle. This disruption can cause apoptosis (programmed cell death) in both neuronal and non-neuronal cells.[39]

Mercury causes apoptosis in monocytes and decreases phagocytic activity.[40] In one study, the percentage of cells undergoing apoptosis was dependent on the

mercury content of the medium, regardless of the form of mercury. Methylmercury chloride exposure caused a decrease in the mitochondrial transmembrane potential within one hour of exposure, leading to altered mitochondrial function. Methylmercury can also cause increased lymphocyte apoptosis. This mechanism includes a depletion of glutathione (GSH) content, which predisposes the cell to oxidative damage, while activating death-signaling pathways.[41] On examination of synovial tissue, it was found that mercury (as well as cadmium and lead) caused a decrease in DNA content and an increase in collagenase-resistant protein formation,[42] leading to increased risk for reduced joint function and decreased ability to repair joint damage.

Mercury is bound by selenium in the body, which can actually counteract mercuric chloride and methylmercury toxicity.[43,44] This appears to result in a reduced amount of available selenium, which compounds the oxidative burden on the body. Mercury decreases GSH levels in the body,[21] 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. Part of the irreversible loss of GSH is due to the inhibition of GSH reductase by mercury,[45] 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. Since mercury promotes formation of hydrogen peroxide, lipid peroxides, and hydroxyl radicals, it is evident that

mercury sets up a scenario for a serious imbalance in the oxidative/antioxidant ratio of the body.[46] Mercury's heavy oxidative toll on the body has been postulated to be a cause of increased rates of fatal myocardial infarctions and other forms of cardiovascular disease.[47] These interactions clearly show an increased need for selenium, glutathione, and vitamin E (which have been shown to reduce methylmercury toxicity).[42,48]

Mercury-Induced Neurotoxicity

Mercury in both organic and inorganic forms is neurotoxic. Methylmercury accumulates in the brain and becomes associated with mitochondria, endoplasmic reticulum, golgi complex, nuclear envelopes, and lysosomes. In nerve fibers methylmercury is localized primarily in myelin sheaths, where it leads to demyelination, and in mitochondria.[49] Pathologic examination of patients with methylmercury poisoning indicates the cerebellar cortex is prominently affected, with granule cells being more susceptible than Purkinje cells. Typically, glial cells are spared direct damage, although reactive gliosis may occur. Toxicity from mercury probably does not result from action on a single target. Instead, because of its highly reactive nature, a complex series of many unrelated (and some interrelated) effects may occur more or less simultaneously, initiating a sequence of additional events that ultimately lead to cell death.

The adverse affect of mercury on GSH has secondary effects on the levels of Na^+, K^+ and Mg^{++} ATPases, all of which are dependent on sulfhydryl compounds. These enzymes, all

Table 2. Neurotoxicty of Mercury.

Myelinopathies
Granule cells in cerebellar cortex
Neuronal swelling
Destruction of astrocytes
Inhibits uptake and release of
 dopamine, serotonin, norepinephrine

critical for proper functioning of nervous and other tissues, are all inhibited by various mercurial compounds.[50] Injection of GSH in animals exposed to methylmercury resulted in the recovery of N^+, K^+, and Mg^{++} ATPases.[51] In the absence of nutrients to counteract this action, the inhibition of these ATPases results in neurotoxic swelling and destruction of astrocytes.[52] Astrocytes are the primary cells responsible for homeostatic control of synaptic pH, Na/K, and glutamate. Mercury is also known to inhibit synaptic uptake of dopamine,[53] serotonin,[54] and norepinephrine.[55] Mercury apparently has a higher binding affinity for serotonin binding sites. Mercury has also been reported to cause an increase in evoked acetylcholine release followed by a sudden and complete blockade.[56] Prolonged exposure to methylmercury results in an up-regulation of muscarinic cholinergic receptors in the hippocampus and cerebellum, and on circulating lymphocytes.[57] It also affects the release of neurotransmitters from presynaptic nerve terminals. This may be due to its ability to change the intracellular concentration of Ca^{2+} by disrupting regulation of Ca^{2+} from intracellular pools and increasing the permeability of plasma membranes to Ca^{2+}.[58] While there is undoubtedly much more to learn about the specific mechanisms of mercury-induced neurotoxicity, the symptoms are fairly clear.

The widespread pollution of Minamata Bay in Japan by methylmercury in the 1950s has provided researchers with a clear picture of methylmercury-induced neurotoxicity. Known as Minamata Disease, the neurotoxic signs include ataxia, speech impairment, constriction of visual fields, hypoesthesia, dysarthria, hearing impairment, and sensory

Table 3. Psychological Symptoms of Mercury Overload.

Irritability
Excitability
Temper outbursts
Quarreling
Fearfulness/anxiety
Restlessness
Depression
Insomnia

disturbances. These neurological problems persisted and were found in other areas of Japan as the mercury contamination spread.[59] Follow-up studies in the Minamata area 40 years after the spill and 30 years since a fishing ban was enacted revealed continued problems. In 1995, male residents of fishing villages in the area reported significantly higher prevalences than "town-resident-controls" for the following complaints: stiffness, dysesthesia, hand tremor, dizziness, loss of pain sensation, cramping, atrophy of the upper arm musculature, arthralgia, insomnia, and lumbago. Female residents of the fishing villages had significantly higher incidences of leg tremor, tinnitus, loss of touch sensation, leg muscular atrophy, and muscular weakness.[60]

Amazonian children exposed to methylmercury from gold mining activity have also been studied for methylmercury's neurotoxic effects. In the villages studied, more than 80 percent of the children had hair mercury levels above 10 µg/g (a level above which adverse effects on brain development are likely to occur). Neuropsychological tests of motor function, attention, and visuospatial performance in these children showed decrements associated with hair mercury concentrations.[61]

Neurotoxicity is not related only to methylmercury, as a study of 98 dentists and 54 non-dentist controls revealed. The dentists, with an average of 5.5 years of exposure to amalgams, performed significantly worse on all of the following neurobehavioral tests: motor speed (finger tapping), visual scanning (trail making), visuomotor coordination and concentration (digit symbol), verbal memory, visual memory, and visuomotor coordination

speed.[62] The dentists' performance on each of these tests diminished as their total exposure increased (amount of daily exposure and years of exposure).

Mercury is also implicated in Alzheimer's disease and other chronic neurological complaints. In 1988, Alzheimer's cadaver studies reported mercury was found in much higher levels in the nucleus basalis of Meynert than in controls (40 ppb vs. 10 ppb).[63] Subsequent studies have shown elevated mercury throughout the brain in individuals with Alzheimer's.[64] Furthermore, when rats were exposed to elemental mercury vapor at the same levels as documented in the oral cavity of humans with amalgams, lesions similar to those seen in Alzheimer's disease have occurred.[65] The same lesions have been demonstrated when rat brains were exposed to EDTA-mercury complex.[66]

While amyotrophic lateral sclerosis (ALS) has been associated in some instances with possible cadmium exposure, a published case history revealed a diagnosed case of ALS recovering after amalgam removal. The individual in question had 34 amalgam fillings. After the first removal her ALS symptoms were exacerbated, but improvement was noted fairly soon after all amalgam fillings were removed. Upon returning to the neurology clinic five months later, she exhibited no evidence of the motor neuron disorder.[67]

Mental health symptoms are also quite common with mercury toxicity. Evidence linking mercury exposure to psychological disorders has been accumulating for 60 years. The recognized psychological symptoms of mercury toxicity include irritability, excitability, temper outburst, quarreling, fearfulness, restlessness, depression, and in some cases insomnia. In a study of individuals with amalgam fillings who had them removed, the majority noted psychological improvement. The greatest improvements were found in anger outbursts, depression, irritability, and fatigue.[68] None of these manifestations are surprising when mercury's inhibitory effect on serotonin is considered. The association of mercury to depression has stimulated a number of interesting questions; such as whether mercury toxicity was to blame for Sir Isaac Newton's health problems of 1692-93,[69] and might it have contributed to the depression and apparent suicide of the explorer Meriwether Lewis.[30]

Renal Toxicity

Kidney injury is a characteristic consequence of acute poisoning from inorganic mercury. Albuminuria is a classic sequelae, and may be of either glomerular or tubular origin. In rabbits, rats, and mice, multiple exposures to inorganic mercury induce the production of antibodies against the glomerular basement membrane, deposition of immune complexes in the mesangium and glomerular basement membrane, and glomerulonephritis.[70-73] Further studies have shown mercury induces a nephropathy that at the lowest effective doses is restricted primarily to the S3 segment of the proximal tubule. With greater doses of mercury the lesions move to include the S2 and S1 segments as well.[74] This nephropathy is apparently due to a selective induction of apoptosis of the renal proximal tubular cells,[75] presumably by the same method of mercury-induced apoptosis in other cell lines. Studies in sheep have identified renal tubular reabsorption of inulin to be impaired following amalgam placement.[76] In a small human study, no increased albuminuria was found in healthy male students with amalgams,[77] but a study of natural gas workers exposed to mercury vapor revealed minor kidney changes without the presence of neurological changes.[78] Mercury has also been associated with potassium-wasting nephropathy,[79] including one case in the author's practice.[80]

Table 4. Mercury Immunotoxicity.

Autoimmunity
Decreased cellular immune function
Apoptosis of monocytes and lymphocytes
Decreased phagocytosis
Decreased production of TNF alpha, IL-1
Increased release of ACTH and cortisol

Immunotoxicity

As mentioned earlier, mercury increases apoptosis of both monocytes and lymphocytes, and reduces the phagocytic ability of monocytes. It has been demonstrated that workers occupationally exposed to mercury vapor exhibited diminished capacity to produce both TNF alpha and IL-1.[81] A number of investigators have reported mercury compounds are capable of immune activation, leading to autoimmunity, while simultaneously reducing the cellular immune response, leading to increased infection,[70-73,82-85] which is the classic appearance of immunotoxicity.[86] Simultaneous with immune alterations are changes in the hypothalamic-pituitary-adrenal axis, as exhibited by increased levels of ACTH and corticosterone.[87] The increase in corticosterone levels could add to the immunosuppressiveness already present. Not only can mercury cause aberrant responses in both the cellular and humoral immune systems, it may also cause bacteria to become resistant to antibiotics. In a primate study, within five weeks of receiving amalgam fillings the intestinal bacteria of the primates became resistant to penicillin, streptomycin, kanamycin, chloramphenicol, and tetracycline.[88]

Testing

Several methods for assessing mercury contamination have been used, including hair, urine, and blood. Methylmercury shows up very well in the hair, which has been the primary testing measurement of Amazonian children[61] and people from the Minamata Bay area.[89] Some methylmercury studies use a combination of urine and hair, both of which appear to be sensitive markers that correlate significantly with each other.[90] Elemental mercury (from amalgams) does not show up well in the hair.[24] In fact, other hair mercury studies have shown hair mercury levels are 79-94 percent methylmercury, leaving only 6-21 percent as elemental mercury.[89] 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 the hair test. Since mercury binds tightly to selenium and sulfur, it has been suggested that low mercury and high sulfur and/or selenium on hair testing indicates a body burden of elemental mercury.[91] Elemental mercury from amalgams shows up best in the plasma and urine.[92] While 24-hour urine samples are generally used in such studies, in males no diurnal variations are found in mercury excretion, and the first morning urine shows strong correlation with the twenty-four hour sample.[93] Women do exhibit a diurnal pattern in urinary mercury excretion, leaving the 24-hour sample as the best way to measure mercury.

While an unprovoked 24-hour urine test for mercury can be very illuminating, a urine test following a provocative challenge with 2,3-dimercaptosuccinic acid (DMSA) or 2,3-dimercapto-1-propanesulfonic acid (DMPS) can reveal even more. This can be especially revealing if the provoked test is done following the unprovoked one. The author has found this method to be quite effective at revealing heavy metal (not just mercury) burdens in chronically ill individuals. However, neither provoked nor unprovoked tests may show the whole picture of heavy metal load. In a study of 18 subjects, all of whom previously had amalgam fillings and who exhibited symptoms of mercury overload, the four

Provocative Urine Testing for Mercury and Other Heavy Metals

While there is NO test that can show total mercury or heavy metal burden in an individual the provocative urine test is quite beneficial at revealing who has heavy metals in their tissues. The best method is to utilize the following protocol.

1. Run a non-provoked 24-hr toxic metal UA to determine the number of heavy metals being cleared on a random day and whether any of them are above the lab's range.
2. Run a creatinine clearance test to ensure there is sufficient kidney function. Some of the heavy metals can be damaging to the kidney and precautions should be taken.
3. DMSA/DMPS "sensitivity testing" to ensure that the individual is not reactive to these sulfur-containing compounds.

If the above look all right, proceed to
4. Flushing dose of DMSA or DMPS. The DMPS is generally given in its full body weight dose of 3 mg/kg IV. DMSA can be given to an adult at a dose of 500 mg tid for three days with the urine being collected on the third day (while taking the capsules).
5. Repeat the 24-hr toxic metal UA.

who still had amalgam fillings showed urine mercury levels within the normal range. Those who had amalgam removal showed elevated urine levels. When the four had their amalgams removed, their urine output increased to elevated levels over time. The researchers hypothesized that some persons with amalgams exhibit a "retention toxicity,"[94] where they fail to dump mercury in the urine even while they are mercury-burdened. The same researchers hypothesized a large fraction of the total body mercury burden may be present in the bone, as is found with lead.

Currently, a single laboratory is utilizing fecal testing on heavy metals. Since the primary route of excretion for heavy metals is the bowel, this form of testing makes sense. It is also an easy method for testing young children, as gathering a sample is fairly easy. This laboratory currently reports that a high mercury content in the fecal sample is indicative of a high mercury output on a provocative urine test.[91]

Treatment

Proper treatment for heavy metal overload follows a three-part treatment outline: avoidance of further exposure; nutritional supplementation, to reduce toxin-induced damage and stimulate toxin excretion; and cleansing, to clear toxins from the body.

Avoidance

To properly avoid further exposure to mercury, one must know their main sources of exposure. Fortunately, this is fairly easily accomplished with mercury by looking at amalgam presence and fish intake. It is recommended that persons with mercury overload from amalgams find a dentist who is properly trained in amalgam removal and have this procedure done. Proper precautions for this procedure include the use of an oral dam and an alternative air source for the person having the amalgams removed. These two precautions will prevent further mercury exposure from occurring during the procedure.

Often, amalgam removal will cause a transient rise in plasma mercury levels (less pronounced in those in whom a dam is used), with a significant decrease in mercury excretion being noted 100 days after removal.[95] In a study of 1800 individuals who underwent amalgam removal and replacement with biocompatible composites, 21 percent showed no change in common mercury-related symptoms, 48 percent noted reduction of symptoms, and 31 percent achieved total elimination of these adverse symptoms.[96] While some symptoms could clearly be of an origin other than mercury toxicity, it is quite possible the symptoms could be lessened or eliminated by removing mercury which had already left the fillings and was deposited in the tissues.

Supplementation

The purpose of supplementation in this situation is to attempt to counterbalance adverse effects of mercury on the tissues and to aid in elimination of mercury from the body. As previously mentioned, mercury can be devastating to the oxidant/antioxidant balance in the body, dramatically shifting to a greatly increased pro-oxidant state. Selenium and vitamin E both help reduce mercury toxicity; however, in doing so, mercury decreases the availability of these nutrients to other tissues. Supplementation with these and other antioxidants are highly recommended. Since detoxification of mercury depletes glutathione, supplements that increase glutathione levels should also be employed, including, whey protein, vitamin C, milk thistle, selenium, and N-acetylcysteine. These are all highly necessary in any case of toxin overload. While some have suggested intravenous vitamin C may be of benefit in chelating mercury from the body, this has not been shown to be the case. In a study of 28 subjects, IV ascorbic acid failed to significantly increase mercury excretion.[97] Alpha lipoic acid is helpful in cases of mercury-induced neuropathy and has the ability to mobilize heavy metals. Thus, it might also be beneficial for those with mercury overload.

Reduction of Heavy Metal Burden (cleansing)

The sulfur-containing compounds DMSA, DMPS, and N-acetylcysteine (NAC) have all been used to effectively reduce the body burden of mercury. DMSA was first utilized as a treatment for heavy metal toxicity in 1965.[98] It has since demonstrated its effectiveness in successfully mobilizing lead, mercury, cadmium, and arsenic.[99,100] The optimum dose utilized by these researchers was 30 mg/kg/day, taken in three divided doses for five days at a time. This dose actually showed greater clearing of lead than EDTA did, given at a dose of 50 mg/kg/day. Both will increase urinary output of these four heavy metals, with no nephrotoxicity being noted. DMPS may be of benefit in reducing the nephrotoxicity of mercuric chloride.[101] When these three agents were tested, along with potassium citrate (5 g), DMPS (orally given at a dose of 10 mg/kg – intravenously it is dosed at 3 mg/kg), DMSA (30 mg/kg), and NAC (30 mg/kg), their effects on mercury excretion were comparable.[102] When given alone, DMSA caused an increase in urinary mercury excretion of 163 percent, DMPS 135 percent, NAC 13 percent, and potassium citrate 83 percent. When given with potassium citrate the urinary mercury excretion increased to 163 percent for both DMPS and NAC. It is generally recommended that these agents be given in several day courses repeatedly, with rest periods in between. Repeat urine testing every fifth round of these compounds is desirable, to monitor effectiveness of the therapy and to know if more rounds are needed.

DMSA and DMPS have similar affinities for heavy metals, although in the author's experience DMSA is more effective at mobilizing lead. DMSA was also found to have no effect on the elimination of iron or calcium, although both DMSA and DMPS will increase the excretion of copper and zinc.[103] In addition, these chelators have affinity for

manganese and molybdenum. It may be prudent to provide these nutrients before, during, or after the use of these agents, to prevent nutrient depletion. Zinc supplementation may also be warranted, for extra protection of the kidneys from mobilized arsenic, cadmium, and mercury, as it will stimulate the production of metallothionien (see excellent review on this topic by Quig,D, *Altern Med Rev* Aug. 1998). The author has found that although these compounds do not chelate magnesium, their use will increase urinary magnesium excretion, which is already elevated in many heavy-metal-burdened individuals. Magnesium supplementation is necessary in these individuals.

It must be kept in mind that the usual primary route of excretion for mercury is the bowels. Increased symptoms can occur when mobilizing metals, especially if there is hepatic reuptake from the bowels. In order to minimize reuptake of these compounds (and therefore reduction in adverse symptoms) it is prudent to utilize psyllium fiber as a binding agent. Bowel cleansing via colonic irrigations has also demonstrated effectiveness in reducing symptoms from heavy metal movement, in the author's practice.

Often patients will experience fatigue, irritability, anger, depression, insomnia, or anxiety during mercury cleansing. If DMSA is used, the person may experience gas, diarrhea, bloating, and GI discomfort, simply from the sulfur content of DMSA. When adverse symptoms occur while using DMSA, they can often be quickly decreased by the reduction or cessation of DMSA dosing.

Conclusion

Mercury is ubiquitous in our environment, and in our mouths in the form of "silver" amalgams. It is rapidly absorbed in the body and accumulates in several tissues, leading to increased oxidative damage, mitochondrial dysfunction, and cell death. It primarily affects neurological tissue, the kidneys, and the immune system. Mercury also has devastating effects on the glutathione content of the body, giving rise to the possibility of increased retention of other environmental toxins. Blood, urine, and fecal tests are available to quantify the mercury burden. Subsequently, sulfur-containing compounds and other nutritional supplementation can help reduce the load.

References

1. Maloney SR, Phillips CA, Mills A. Mercury in the hair of crematoria workers. *Lancet* 1998;352:1602.

2. Lebel J, Mergler D, Lucotte M. Evidence of early nervous system dysfunction in Amazonian populations exposed to low-levels of methylmercury. *Neurotoxicology* 1996;17:157-167.

3. Stopford W, Goldwater LJ. Methylmercury in the environment: a review of current understanding. *Environ Health Perspect* 1975;12:115-118.

4. Matthews AD. Mercury content of commercially important fish of the Seychelles, and hair mercury levels of a selected part of the population. *Environ Res* 1983;30:305-312.

5. Mercury in fish: cause for concern? *U.S. Food and Drug Administration, FDA Consumer.* September 1994, Revised May 1995.

6. Tollefson L, Cordle F. Methylmercury in fish: a review of residue levels, fish consumption and regulatory action in the United States. *Environ Health Perspect* 1986;68:203-208.

7. Gunderson EL. FDA Total Diet Study, April 1982-April 1986. Dietary intake of pesticides, selected elements and other chemicals. Distributed by: Association of Official Analytical Chemists. Arlington, VA.

8. Clarkson TW, Hursh JB, Sager PR, Syversen JP. Mercury. In: Clarkson TW, Friber L, Nordberg GF, Sager PR, eds. *Biological Monitoring of Toxic Metals.* New York: Plenum Press; 1988:199-246.

9. Miettinen JK. Absorption and elimination of dietary mercury(2+) ion and methylmercury in man. In: Miller MW, Clarkson TW, eds. *Mercury, Mercurials, and Mercaptans. Proceedings 4th International Conference on Environmental Toxicology*. New York: Plenum Press; 1973.

10. Grandjean P, Weihe P, Needham LL, et al. Relation of a seafood diet to mercury, selenium, arsenic and polychlorinated biphenyl and other organochlorine concentrations in human milk. *Environ Res* 1995;71:29-38.

11. Skerfving S. Mercury in women exposed to methylmercury through fish consumption, and in their newborn babies and breast milk. *Bull Environ Contam Toxicol* 1988;41:475-482.

12. Galster WA. Mercury in Alaskan Eskimo mothers and infants. *Environ Health Perspect* 1976;15:135-140.

13. Watanabe C, Satho H. Evaluation of our understanding of methylmercury as health threat. *Environ Health Res* 1996;104:367-378.

14. Clarkson TW, Amin-Zaki L, Al-Tikriti SK. An outbreak of methylmercury poisoning due to consumption of contaminated grain. *Fed Proc* 1976;35:2395-2399.

15. Vimy MJ, Lorsheider FL. Intra-oral air mercury released from dental amalgams. *J Dent Res* 1985;64:1069-1071.

16. Vimy MF, Lorsheider FL. Serial measurements of intra-oral air mercury: estimation of daily dose from dental amalgams. *J Dent Res* 1985;64:1072-1075.

17. Barregard L, Sallsten G, Jarvholm B. People with high mercury uptake from their own dental amalgam fillings. *Occup Environ Med* 1995;52:124-128.

18. Patterson JE, Weissberg B, Dennison PJ. Mercury in human breath from dental amalgam. *Bull Environ Contam Toxicol* 1985;34:459-468.

19. Anthony H, Birtwistle S, Eaton K, Maberly J, eds. *Environmental Medicine in Practice.* Southhamptom: BSAENM Publications; 1997:204-208.

20. Engqvist A, Colmsjo A, Skare I. Speciation of mercury excreted in feces from individuals with amalgam fillings. *Arch Environ Health* 1998;53:205-213.

21. De Souza Queiroz ML, Pena SC, Salles TSI, et al. Abnormal antioxidant system in erythrocytes of mercury exposed workers. *Human & Exp Toxicol* 1998;17:225-230.

22. Abraham JE, Svare CW, Frank CW. The effect of dental amalgam restorations on blood mercury levels. *J Dent Res* 1984;63:71-73.

23. Trepka MJ, Heinrich J, Krause C, et al. Factors affecting internal mercury burdens among East German children. *Arch Environ Health* 1997;52:134-138.

24. Oskarsson A, Schutz A, Skerfving S, et al. Total and inorganic mercury in breast milk and blood in relation to fish consumption and amalgam fillings in lactating women. *Arch Environ Health* 1996;51:234-241.

25. Hahn LJ, Kloiber R, Leininger RW, et al. Whole body imaging of the distribution of mercury released from dental fillings into monkey tissue. *FASEB J* 1990;4:3256-3260.

26. Hahn LJ, Kloiber R, Vimy MJ, et al. Dental "silver" tooth fillings: a source of mercury exposure revealed by whole-body image scan and tissue analysis. *FASEB J* 1989;3:2641-2646.

27. Zheng W, Perry DF, Nelson DL, Aposhian HV. Choroid plexus protects cerebrospinal fluid against toxic metals. *FASEB J* 1991;5:2188-2189.

28. Stortebecker P. *Mercury Poisoning from Dental Amalgam, A Hazard to Human Brain*. Stockholm: Stortebecker Foundation for Research; 1985:24.

29. Cavalleri A, Gobba F. Reversible color vision loss in occupational exposure to metallic mercury. *Environ Res* 1998;77:173-177.

30. Barth G, ed. *The Lewis and Clark Expedition, Selections from the Journals Arranged by Topic.* New York: Bedford St. Martins; 1998:158-162.

31. Kissel KP. Teens fall ill after taking, playing with mercury. *The Seattle Times*: January 15, 1998.

32. Orloff KG, Ulirsch G, Wilder L, et al. Human exposure to elemental mercury in a contaminated residential building. *Arch Environ Health* 1997;52:169-172.

33. Fiedler N, Udasin I, Gochfeld M, et al. Neuropsychological and stress evaluation of residential mercury exposure. *Environ Health Perspect* 1999;107:343-347.

34. Bonhomme C, Gladyszaczak-Kohler J, Cadou A, et al. Mercury poisoning by vacuum-cleaner aerosol. *Lancet* 1996;347:115.

35. Harnly M, Seidel S, Rojas P, et al. Biological monitoring for mercury within a community with soil and fish contamination. *Environ Health Perspect* 1997;105:424-429.

36. Mercury poisoning cases traced to face cream. *Epi Trends*. Washington State Department of Health 1996;1:4.

37. Durham HD, Minotti S, Caporicci E. Sensitivity of platelet microtubules to disassembly by methylmercury. *J Toxicol Environ Health* 1997;48:57-69.

38. Falconer MM, Vaillant A, Reuhl KR, et al. The molecular basis of microtubule stability in neurons. *Neurotoxicology* 1994;15:109-122.

39. Miura K, Koide N, Himeno S, et al. The involvement of microtubular disruption in methylmercury-induced apoptosis in neuronal and nonneuronal cell lines. *Toxicol Appl Phamacol* 1999;160:279-288.

40. InSug O, Datar S, Koch CJ, et al. Mercuric compounds inhibit human monocyte function by inducing apoptosis: evidence for formation of reactive oxygen species, development of mitochondrial membrane permeability transition and loss of reductive reserve. *Toxicology* 1997;124:211-224.

41. Shenker BJ, Guo TL, Shapiro IM. Low-level methylmercury exposure causes human T-cells to undergo apoptosis: evidence of mitochondrial dysfunction. *Environ Res* 1998;77:149-159.

42. Goldberg RL, Kaplan SR, Fuller GC. Effect of heavy metals on human rheumatoid synovial cell proliferation and collagen synthesis. *Biochem Pharmacol* 1983;32:2763-2766.

43. Ganther HE. Modification of methylmercury toxicity and metabolism by selenium and vitamin E: possible mechanisms. *Environ Health Perspect* 1978;25:71-76.

44. Ganther HE. Selenium: relation to decreased toxicity of methylmercury in diets containing tuna. *Science* 1972;175:1122.

45. Zalups RK, Lash LH. Interactions between glutathione and mercury in the kidney, liver and blood. In: Chang LW, ed. *Toxicology of Metals*. Boca Raton: CRC Press; 1996:145-163.

46. Miller OM, Lund BO, Woods JS. Reactivity of Hg(II) with superoxide: evidence for the catalytic dismutation of superoxide by Hg(II). *J Biochem Toxicol* 1991;6:293-298.

47. Salonen JT, Seppanen K, Nyyssonen K, et al. Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men. *Circulation* 1995;91:645-655.

48. Welsh SO, Soares JH Jr. The protective effect of vitamin E and selenium against methylmercury toxicity in the Japanese quail. *Nutr Rep Int* 1976;13:43.

49. Chang LW. Neurotoxic effects of mercury. A review. *Environ Res* 1977;14:329-373.

50. Magour S, Maser H, Grein H. The effect of mercury and methylmercury on brain microsomal Na+, K+ ATPase after partial delipidisation with Lubrol. *Pharmacol Toxicol* 1987;60:184-186.

51. Bapu C, Rao P, Sood PP. Restoration of methylmercury inhibited adenosine triphosphatases during vitamin and monothiol therapy. *J Environ Path Toxicol Oncol* 1998;17:75-80.

52. Aschner M, Eberle NB, Miller K, Kimelberg HK. Interactions of methylmercury with rat primary astrocyte cultures: inhibition of rubidium and glutamate uptake and induction of swelling. *Brain Res* 1990;530:245-250.

53. Rajanna B, Hobson M, Harris L, et al. Effects of cadmium and mercury on Na+, K+ ATPases and the uptake of 3H-dopamine in rat brain synaptosomes. *Arch Int Physiol Biochem* 1990;98:291-296.

54. Oudar P, Caillard L, Fillon G. In vitro effects of organic and inorganic mercury on the serotonergic system. *Pharmacol Toxicol* 1989;65:245-248.

55. Rajanna B, Hobson M. Influence of mercury on uptake of dopamine and norepinephrine by rat brain synaptosomes. *Toxicol Lett* 1985;27:7-14.

56. Cooper GP, Manalis RS. Influence of heavy metals on synaptic transmission: a review. *Neurotoxicology* 1983;4:69-83.

57. Coccini T, Randine G, Candura SM, et al. Low-level exposure to methylmercury modifies muscarinic cholinergic receptor binding characteristics in rat brain and lymphocytes: physiologic implication and new opportunities in biological monitoring. *Environ Health Perspect* 2000;108:29-33.

58. Atchison WD, Hare MF. Mechanisms of methylmercury-induced neurotoxicity. *FASEB J* 1994;8:622-629.

59. Ninomiya T, Ohmori H, Hashimoto K, et al. Expansion of methylmercury poisoning outside of Minamata: an epidemiological study on chronic methylmercury poisoning outside Minamata. *Environ Res* 1995;70:47-50.

60. Fukuda Y, Ushinjima K, Kitano T, et al. An analysis of subjective complaints in a population living in a methylmercury-polluted area. *Environ Res* 1999;81:100-107.

61. Grandjean P, White RF, Nielsen A, et al. Methylmercury neurotoxicity in Amazonian children downstream from gold mining. *Environ Health Perspect* 1999;107:587-591.

62. Ngim CH, Foo SC, Boey KW, Jeyaratnam J. Chronic neurobehavioral effects of elemental mercury in dentists. *Br J Indust Med* 1992;49:782-790.

63. Thompson CM, Markesbery WR, Ehmann WD, et al. Regional brain trace-element studies in Alzheimer's disease. *Neurotoxicology* 1988;9:1-8.

64. Cornett CR, Markesbery WR, Ehmann WD. Imbalances of trace elements related to oxidative damage in Alzheimer's disease brain. *Neurotoxicology* 1998;19:339-346.

65. Pendergrass JC, Haley BE, Vimy MJ, et al. Mercury vapor inhalation inhibits binding of GTP to tubulin in rat brain: similarity to a molecular lesion in Alzheimer's disease brain. *Neurotoxicity* 1997;18:315-324.

66. Pendergrass JC, Haley BE. Mercury-EDTA complex specifically blocks brain beta-tubulin-GTP interactions: similarity to observations in Alzheimer's disease. In: Friberg LT, Scrauzer GN, eds. *Status Quo and Perspectives of Amalgam and other Dental Materials.* Stuttgart: Georg Thieme Verlag; 1995:98-105.

67. Redhe O, Pleva J. Recovery form Amyotrophic Lateral Sclerosis and from allergy after removal of dental amalgam filling. *Int J Risk Safety Med* 1994;4:229-236.

68. Siblerud RL. The relationship between mercury from dental amalgam and mental health. *Am J Psychotherapy* 1989;43:575-587.

69. Lieb J, Hershman D. Isaac Newton: mercury poisoning or manic depression. *Lancet* 1983;1479-1480.

70. Bigazzi PE. Lessons from animal models: The scope of mercury-induced autoimmunity. *Clin Immunol Immunopathol* 1992;65:81-84.

71. Druet P, Druet E, Potdevin F, Sapin C. Immune type glomerulonephritis induced by HgCl2 in Brown-Norway rat. *Ann Immunol (Inst Pasteur)* 1978;129C:777-792.

72. Enestrom S, Hultman P. Immune-mediated glomerular nephritis induced by mercuric chloride in mice. *Experientia* 1984;40:1234-1240.

73. Enestrom S, Hultman P. Dose-response studies in murine mercury-induced autoimmunity and immune-complex disease. *Toxicol Appl Pharmacol* 1992;113:199-208.

74. Diamond G, Zalups RK. Understanding renal toxicity of heavy metals. *Toxicol Pathol* 1998;26:92-103.

75. Homma-Takeda S, Takenaka Y, Kumagai Y, Shimojo N. Selective induction of apoptosis of renal tubular cells caused by inorganic mercury in vivo. *Environ Toxicol Pharmacol* 1999;7:179-187.

76. Boyd ND, Benediktsoon H, Vimy MJ, et al. Mercury from dental "silver" tooth fillings impairs sheep kidney function. *Am J Physiol* 1991;261:R1010-R1014.

77. Herrstrom P, Schutz A, Raihle G, et al. Dental amalgam, low-dose exposure to mercury, and urinary proteins in young Swedish men. *Arch Environ Health* 1995;50:103-110.

78. Boogaard PJ, Houtsma AJ, Journee HL, Van Sittert NJ. Effects of exposure to elemental mercury on nervous system and the kidneys in workers producing natural gas. *Arch Environ Health* 1996;5:108-115.

79. Szylman P, Benzakin A, Szjnader Y, Taitelman U. Potassium-wasting nephropathy in an outbreak of chronic organic mercurial intoxication. *Am J Nephrol* 1995;15:514-520.

80. Crinnion WJ. Unpublished research. Healing Naturally, Kirkland, WA 1999.

81. Langworth S, Elinder CG, Sundqvist KG. Minor effects of low exposure to inorganic mercury on the human immune system. *Scan J Work Environ Health* 1993;19:405-413.

82. Blakley BR, Sisodia CS, Mukkur TK. The effect of methylmercury, tetraethyl lead, and sodium arsenite on the humoral immunity response in mice. *Toxicol Appl Pharmacol* 1980;52:245-254.

83. Dieter MP, Luster MI, Boorman GA, et al. Immunological and biochemical responses in mice treated with mercuric chloride. *Toxicol Appl Pharmacol* 1983;68:218-228.

84. Nordlind K. Inhibition of lymphoid-cell DNA synthesis by metal allergens at various concentrations. Effect on short-time cultured non-adherent cell compared to non-separated cells. *Int Arch Allergy Appl Immunol* 1983;70:191-192.

85. Nakatsuru S, Oohashi J, Nozaki H, et al. Effect of mercurials on lymphocyte functions in vitro. *Toxicology* 1985;36:297-305.

86. Vojdani A. Personal communication.

87. Ortega HG, Lopez M, Takaki A, et al. Neuroimmunological effects of exposure to methylmercury forms in the Sprague-Dawley rat. Activation of the hypothalamic-pituitary-adrenal axis and lymphocyte responsiveness. *Toxicol Indust Health* 1997;13:57-66.

88. Kolata G. New suspect in bacterial resistance: amalgam. *The New York Times:* April 24, 1993.

89. Harada M, Nakanishi J, Kunuma S, et al. The present mercury contents of scalp hair and clinical symptoms in inhabitants of the Minamata area. *Environ Res* 1998;77:160-164.

90. Abe T, Ohtsuka R, Hongo T, et al. High hair and urinary mercury levels of fish eaters in the nonpolluted environment of Papua New Guinea. *Arch Environ Health* 1995;50:367-373.

91. Quig D. Doctors Data Lab, Personal Communication.

92. Halbach S, Kremers L, Willruth H, et al. Compartmental transfer of mercury released from amalgam. *Hum Exp Toxicol* 1997;16:667-672.

93. Cianciola ME, Echeverria D, Martin MD, et al. Epidemiologic assessment of measures used to indicate low-level exposure to mercury vapor. *J Toxicol Environ Health* 1997;52:19-33.

94. Ely JT, Fudenberg HH, Muirhead RJ, et al. Urine mercury in micromercurialism: a bimodal distribution and its diagnostic implications. Unpublished.

95. Halbach S, Kremers L, Willruth H, Mehl A, Welzl G, Wack FX, Hickel R, Greim H. Systemic transfer of mercury from amalgam fillings before and after cessation of emission. *Environ Res* 1998;77:115-123.

96. Lichtenberg H. Symptoms before and after proper amalagam removal in relation to serum-globulin reaction to metals. *J Orthomolec Med* 1996:11:195-204.

97. Dirks MJ, Davis DR, Cheraskin E, Jackson JA. Mercury excretion and intravenous ascorbic acid. *Arch Environ Health* 1994;49:49-52.

98. Ting KS, Liang YI, Shi J, Chen W, Gu T. Chelate stability of sodium dimercaptosuccinate on the intoxication from many metals. *Chinese Med J* 1965;64:1072-1075.

99. Graziano JH, Lolacono NJ, Meyer P. Dose-response study of oral 2,3-dimercaptosuccinic acid in children with elevated blood lead concentrations. *J. Pediatr* 1988;113:751-757.

100. Graziano JH. Role of 2,3-dimercaptosuccininc acid in the treatment of heavy metal poisoning. *Med Toxicol* 1986;1:155-162.

101. Zalups RK, Cernichiari E. 2,3-dimercapto-1-propanesulfonic acid (DMPS) as a rescue agent for the nephropathy induced by mercuric chloride. *The Toxicologist* 1990;10:271(abstract only).

102. Hibberd AR, Howard MA, Hunnisett AG. Mercury from dental amalgam fillings: studies on oral chelating agents for assessing and reducing mercury burdens in humans. *J Nutr Environ Med* 1998;8:219-231.

103. Aposhian HV. DMSA and DMPS-water soluble antidotes for heavy metal poisoning. *Ann Rev Pharmacol Toxicol* 1983;23:193-215.