Heavy-Metal Toxicity—With Emphasis on Mercury

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Metal toxicity is a major medical concern. Of particular concern are "heavy metals," which occur naturally in the earth's crust[1] and are defined in physiochemical terms as metals with a density at least 5 times as great as water. This definition translates into an approximate heavy-metal minimum density of 5, and—in addition to cadmium, lead, and mercury—the metals zinc, copper, iron, cobalt, nickel, tin, manganese, and molybdenum also qualify. Scientifically, then, some heavy metals are essential nutrients. Cadmium (with a density of 8), lead (10), and mercury (14) are strikingly high in density compared with such common essential minerals as magnesium, calcium, or potassium, which all have densities below 2.

Exposure to environmental contaminants comes through various routes, including natural sources (eg, groundwater, metal ores, and metal leaching from the soil), industrial processes, commercial products, and contaminated dietary supplements and food (eg, fish).[1] The risk for chronic toxicity depends on the frequency, intensity, and duration of contact with the contaminant along with the exposure route.[2] Toxicity risk also depends on the inherent toxic potential of the metal itself; thus, mercury, a nonessential metal, possesses more inherent toxic potential than copper, a metal essential for physiologic function. Metal toxicity affects all organ systems and can result in wide-ranging and nonspecific symptoms; however, the central nervous system (CNS) is especially susceptible to damage from metals (see Table 1 for examples of mercury toxicity).

Table 1. Symptoms of Mercury Poisoning[1,7-9,14]

Neurological	Non-Neurological
Ataxia	Alopecia totalis
Chorea	Autoimmunity
Blindness	Fatigue
Depression	Hypersalivation
Drowsiness	Keratosis
Excitability	Melanosis
Fearfulness/anxiety	Recurrent infections
Insomnia	Ulcers
Irritability	
Low Intelligence Quotient	
Memory loss	
Mental retardation	
Parasthesias	
Quarreling	
Restlessness	
Temper outbursts	
Tremors	

The Five Elements of Toxic Metal Exposure[2]

1. Source (eg, amalgam fillings, food such as fish, manufacturing processes)
2. Transport (eg, via air, water, soil, dust, plants, and animals)
3. Location (eg, playground, dental office, manufacturing plant)
4. Route (eg, oral, inhalation, dermal absorption)
5. Population (eg, extent of exposure among groups of people)

This article summarizes information on the most clinically important toxic metals—mercury, lead, cadmium, and arsenic—with a special emphasis on mercury. The ability for clinicians to assess risk for acute and chronic toxic metals exposure is essential to identifying the underlying cause for many different conditions.

Mercury

Mercury, named for the planet Mercury, was known to the ancient Chinese and has been discovered in Egyptian tombs dating back to 1500 BCE. It was also used to treat syphilis in the 15th-century European syphilis pandemic.[3]

There are 3 chemical forms of mercury—elemental (mercury without any additional atoms attached to it), organic, and inorganic (see Table 2.) These forms are interconvertible, and all can produce systemic toxicity.[3] At room temperature, inorganic mercury, once commonly available in thermometers, is a liquid and is released into the atmosphere as mercury vapor. Methylmercury (MeHg) results from methylation of inorganic mercury by microorganisms in soil and water,[4] by microorganisms in the mouth when mercury vapor is released from amalgam dental fillings,[5] and by nonenzymatic methylation (eg, by donation of a methyl group to mercury from methylcobalamin, a form of vitamin B12).[6]

Table 2. Forms of Inorganic and Organic Mercury

Inorganic	Organic
Mercuric chloride	Ethylmercury
Mercuric iodide	Methylmercury
Mercuric oxide	Merbromin
Mercuric sulfide	Merthiolate
Mercurous chloride	Phenylmercuric salts

Toxicokinetics of Mercury

All forms of mercury are toxic to humans. Their

effects are organ-specific and depend on the chemical form of the mercury and the exposure level, duration, and route.[4] Different forms of mercury deposit preferentially in different tissue compartments, which explains their different toxic profiles. Methylmercury (MeHg) is almost 100% absorbed across the intestines and also crosses the blood-brain barrier (BBB).[3,10,11] Inorganic mercury is also absorbed through the intestines and crosses the BBB, but much less so than MeHg.[3,10,11,12]

MeHg is considered the most toxic form of mercury[13] and has a half-life of 70 days in humans.[14] Transport mechanisms of MeHg result in systemic distribution, which explains its high rate of deposition in both hematopoietic and neural tissues.[4] MeHg in tissues binds to water-soluble sulfhydryl molecules (a compound that contains the functional group composed of a sulfur atom and a hydrogen atom, ie, -SH) such as L-cysteine, glutathione (GSH), hemoglobin, albumin, and other cysteine-containing polypeptides.[15,16] MeHg is transported across endothelium, through the blood-brain barrier and into cells via the L-type large neutral amino-acid transporters (LATs).[15,16] The MeHg-L-cysteine complex is a substrate of the LAT.[16]

Mercury vapor is lipid soluble and enters the blood from both lungs and oral mucosa.[14] Once in the body, mercury vapor traverses cell membranes, thereby entering the central nervous system, red blood cells, and placenta.[14] In contrast, mercurial salts and minerals are not readily transported or diffused into tissues, and therefore primarily affect renal function.[4]

Inorganic mercury granules have been detected in peripheral nerves and within the CNS of mice injected with inorganic mercury. In one study, mice were injected intraperitoneally (i.p.) with 0.2 ml of aqueous mercuric chloride ($HgCl_2$) of 0.05, 0.1, 0.2, 0.3, 0.4, 0.6, 1, and 2 μg $HgCl_2$/g body weight.[12] In rats injected with 0.2 μg $HgCl_2$/g body weight, mercury granules were detected in the cell bodies of large lateral motor neurons in the anterior horn of all spinal-cord levels and in the nuclei of the third, fourth, sixth, seventh, and twelfth cranial nerves. (Interestingly, mercury granules did not accumulate in cerebral cortical neurons, cerebellar neurons, astrocytes, ependymal cells, choroid plexus, or blood vessels.) Furthermore, retrograde, trans-synaptic transport of inorganic mercury has been described, as well as uptake of $HgCl_2$ by motor neurons, irrespective of the route of exposure (intraperitoneal injection, in drinking water, or inhaled as a vapor).[12]

Once mercury enters the body it binds to sulfur-containing molecules such as glutathione and cysteine. Mercury vapor absorbed through the lungs is converted to divalent mercury (Hg^{2+}) in tissues and excreted in bile as glutathione conjugates, which are then eliminated in feces.[17] MeHg is also eliminated via glutathione conjugation in the liver and then excreted in bile.[18] Inorganic mercury bound to glutathione or cysteine is also filtered through glomeruli and reabsorbed in the renal proximal tubule.[19]

Mercury Exposure

Exposure to mercury comes from a variety of sources, with 1 common source in the United States being silver-amalgam dental fillings. These weigh 1.5 to 2.0 grams each and contain approximately 50% elemental mercury[20] along with other metals such as silver, copper, and tin. It has been estimated that people with 1 to 4 amalgams fillings are exposed to 8 μg/day of elemental mercury, and those with 12 or more to 29 μg/day of elemental mercury.[20] Chewing food and gum, tooth brushing, and consuming hot beverages all release mercury vapor from the amalgams, which can then be absorbed.[20] Inorganic mercury vapor from amalgam fillings can be methylated by bacteria in the mouth, thereby increasing exposure and absorption of methylmercury.[5] It's commonly accepted that, over time, the amount of mercury vapor released decreases, which is why if amalgams are more than 10 years old, some dentists may decide not to remove them.

In contrast to inorganic mercury, the most frequent exposure to MeHg is via fish consumption.[21] Fish that have the highest levels of mercury are king mackerel, shark, swordfish, tilefish, and tuna.[22] In pregnant women, MeHg crosses the placenta and is found in higher concentrations in cord blood compared to maternal systemic circulation,[22] which prompted the U.S. Environmental Protection Agency (EPA) to draft specific guidelines for fish consumption for this population. The EPA recommends that women of childbearing age, pregnant women, nursing mothers, and children completely avoid eating these fish, while limiting fish that are lower in mercury (catfish, pollock, shrimp, salmon, and canned light tuna) to no more than 12 ounces per week.[23] (See Table 3.)

Table 3. EPA Weekly Fish Consumption Recommendation for Pregnant Women, Women Who May Become Pregnant, Nursing Mothers, and Children[23]

Completely avoid	Eat less than 6 ounces (1 average meal)	Eat less than 12 ounces (2 average meals)
King mackerel	Albacore ("white") tuna	Catfish
Shark	Any fish for which no local advisory is available	Pollock
Swordfish Tilefish		Salmon Shrimp
		Tuna, canned light

Concern is so high that when advisories about local fish stocks have not been issued, the EPA recommends these women and children consume no more than 6 ounces per week of fish caught from local waters, and consume no other fish that week.[23] Contamination of fish with mercury is a major public-health concern since many people worldwide rely on fish as their major protein source, and fish con-

sumption has increased as more people learn of the health benefits from the omega-3 series polyunsaturated fatty acids they contain.

Dietary Supplements and Metal Toxicity

Heavy-metal contamination in dietary supplements has become an increasing concern, ranging from lead and mercury to arsenic and more. No safe level of lead consumption has been established by the EPA, but "tolerable" levels for lead consumption have been set by the U.S. Food and Drug Administration (FDA). (See Tables 4-6.)

Table 4. United States Pharmacopoeia (USP) Limit for Nutritional Supplements

Lead	10 ppm
Arsenic	3 ppm
Cadmium	3 ppm
Mercury	3 ppm

Table 5. California Proposition 65 Daily Limits for Heavy Metal Consumption

Lead	0.5 mcg
Arsenic	10 mcg
Cadmium	4.1 mcg

Table 6. FDA Tolerable Daily Diet Lead Intake

Children <6yo	6 mcg
Pregnant women	25 mcg
Adults	75 mcg

In general, as you can see, the regulatory environment for defining toxic doses of metals is fragmented. Regardless, given the increased use of dietary supplements and the fact that many integrative medicine physicians prescribe them, clinicians should consider a series of recent studies, described below, that demonstrate contamination of dietary supplements with heavy metals. This is why *IMCJ* has focused so consistently on the need for quality assurance in dietary supplements. (See this and previous issues presenting articles on quality assurance by Rick Liva, ND.)

- A meta-analysis of 22 case reports, case series, and epidemiological research concluded that "heavy-metal (particularly lead) poisoning through traditional Chinese medicine use has been reported with some regularity."[9]
- A 2006 survey of Ayurvedic dietary supplements produced in South Asia and sold in 20 stores in the Boston area revealed that 20% of the dietary supplements (14 of 70 Ayurvedic supplements) contained heavy metals.[24] Of those with heavy metals, 13 contained lead at a median concentration of 40 μg/g (5–37,000 μg/g), 6 tested positive for arsenic at a median concentration of 430 μg/g (37–8,130 μg/g), and 6 contained mercury at a median concentration of 20,225 μg/g (28–104,000 μg/g). The EPA-established reference doses for oral chronic exposure of arsenic and mercury is 0.3 μg/kg per day,[24] which calculates to 15 μg per day for a 50-kg person.
- An earlier 2002 case report documented lead poisoning from Ayurvedic medicine in a 41-year-old male.[25] He complained of malaise, weakness, abdominal pain, and weight loss. His blood lead level was 78 μg/dL and its hemoglobin count anemic at 7.9 g/dL. He had traveled to India where he was treated with Ayurvedic medicine for oligospermia (decreased sperm number). Analysis of the dietary supplements he had used revealed high concentrations of lead—13,084 μg/g in one pill and 1,917 μg/g in another pill. It was estimated that over the course of his treatment he had ingested 1.26 g of lead.
- Another 2002 case report described arsenic toxicity in a 39-year-old woman taking the dietary supplement chitosan,[26] derived from chitin, a polysaccharide found in shellfish. Chitosan is believed to help people lose weight by blocking the absorption and storage of fat. The woman reported to the emergency room complaining of fatigue, headache, and weakness for the previous 6 months. She had been taking 6 capsules daily of the "fat blocker" pills for a year. A 24-hour urine collection revealed 186 μg/L arsenic (nL: 0–50 μg/L). Analysis of the pills revealed an arsenic concentration of 135.5 ng/g/capsule. Shellfish is a known reservoir of arsenic, and no other sources could be identified.

It seems the take-home message is that, regardless of which definition of toxicity you use from Tables 4-6, people are being exposed to excessively high levels of toxic heavy metals.

Prior to purchasing a dietary supplement, clinicians should protect themselves by verifying that the ingredients in the formula have been tested for purity. The best way to do this is by using *IMCJ*'s supplier quality-assurance certification tool. It is available at *IMCJ*'s website, www.imjournal.com. When there, click on "Quality Assurance" in the left lower side bar, then click on "Manufacturer Certification and Quality Assurance Self-Audit Form." It provides a way for clinicians to ensure the quality and safety of dietary supplements by requesting manufacturers answer a series of questions and provide documentation regarding their manufacturing and quality-control procedures.

Mechanisms of Metals Toxicity

Metals generate many of their deleterious effects through the formation of free radicals, resulting in DNA damage, lipid peroxidation, depletion of protein sulfhydryls (eg, glutathione), and other effects.[27] These reactive radicals include a wide range of chemical species, including oxygen, carbon, and sulfur radicals originating from the superoxide radical, hydrogen peroxide, and lipid peroxides, and also from chelates of amino acids, peptides,

and proteins complexed with the toxic metals.[27] (For more information on free radicals see: Neustadt J. "Antioxidants: Redefining their roles." *IMCJ* 5.6:22-26.)

Mitochondrial Damage

One major mechanism for metals toxicity appears to be direct and indirect damage to mitochondria via depletion of glutathione, an endogenous thiol-containing (SH-) antioxidant, which results in excessive free radical generation and mitochondrial damage.[28] Anecdotally, Dr Neustadt, in his clinic, frequently observes an elevation of urinary pyroglutamate, an organic acid that is a specific marker for glutathione depletion in patients with confirmed mercury toxicity.[29] Not surprisingly, these patients also complain of fatigue, a hallmark symptom of mitochondrial damage.

Mercury can accumulate in mitochondria and causes granular inclusions, which are visible with a scanning electron micrograph.[30] Oxidative stress occurs in vitro and in vivo from both organic and inorganic mercury via their high affinity for binding thiols (sulfur-containing molecules) and the depletion of mitochondrial glutathione.[27]

The central nervous system is particularly sensitive to damage by MeHg-induced glutathione depletion. In one study, ex vivo human neurons, astrocytes, and neuroblastoma cells were exposed for 24 hours to various levels of MeHg. The LC_{50} (concentration at which 50% of the cells died) was 6.5, 8.1, and 6.9 μM, respectively.[28] A second ex vivo study of mouse neurons and astrocytes confirmed the lower LC_{50} concentration for neurons,[31] and another vivo rat-brain study demonstrated mitochondrial respiratory-chain damage.[32]

An in vitro, dose-response study of glutathione depletion and the LC_{50} of human neurons, astrocytes, and neuroblastoma cells exposed to MeHg showed an indirect relationship between GSH depletion and cell death and a direct relationship between length of MeHg exposure and cell damage.[28] Cell were exposed to 6.5, 8.1, and 6.9 μM MeHg for 7 days. After 24 hours of exposure to MeHg, the LC_{50} for neurons, astrocytes and neuroblastoma cells was 6.5 (4.9–8.6), 8.1 (7.2–9.1), and 6.9 (6.4–7.5) μM, respectively; after 48 hours it was 3.7 (3.2–4.3), 7.4 (6.9–7.9), and 5.5 (5.0–6.0) μM, respectively; after 72 hours it was 2.9 (2.4–3.5), 7.0 (6.2–7.9), and 2.2 (0.5–8.9) μM, respectively; and after 7 days of exposure to MeHg it was 2.4 (1.5–3.6) and 4.4 (1.0–19.5) μM, respectively (toxicity of neuroblastoma cells after 7 days of exposure was not determined). Addition of buthionine sulfoximine (BSO), a glutathione-depleting agent, prior to MeHg exposure significantly increased the cytotoxicity of MeHg in all cell lines ($P<.001$). In contrast, pre-incubation with 1 mM GSH for 24 hours, followed by 10 μM MeHg, resulted in protection of all cell lines from gross damage detected by phase-contrast microscopy.

The pancreas has also been studied for its susceptibility to mercury poisoning. In one study, ex vivo mouse pancreatic beta-cells were exposed to 2 and 5 μM MeHg.[33] Compared to control cells, both levels of MeHg exposure significantly increased free-radical generation ($P<.05$), decreased mitochondrial membrane potential ($P<.05$), and inhibited insulin secretion (percentage change not reported, $P<.05$). This indicates a possible etiologic role for mercury toxicity in the pathogenesis of diabetes. Free-radical production and the insulin response to MeHg, however, were reversed when the cells were treated with 0.5 mM *N*-acetylcysteine (NAC). Two ex vivo studies with NAC have shown an increase in intracellular glutathione and a decrease in reactive oxygen species formation in MeHg-treated neurons, astrocytes, and neuroblastoma cells.[28,31]

Inorganic mercury also impairs kidney function through depletion of glutathione, generation of free radicals, and mitochondrial damage. Rat kidney mitochondria treated with Hg^{2+} (as $HgCl_2$, 1.5 mg/kg i.p.) doubled hydrogen peroxide (H_2O_2) for 6 hours afterwards, which occurred at the ubiquinone (coenzyme Q10)-cytochrome B region of the mitochondrial respiratory chain in vivo. Concomitant with this increase in H_2O_2 production, glutathione was depleted by more than 50%, and thiobarbiturate reactive substances (TBARS, an indicator of mitochondrial lipid peroxidation) increased 68%.[34]

Other metals also damage cellular energy production pathways. Arsenic inhibits pyruvate dehydrogenase (PDH) activity.[27] PDH catalyzes the transformation of pyruvate to acetyl-coenzyme A, a post-glycolysis intermediate, to generate energy as adenosine triphosphate.[35] Additionally, arsenic decreases mitochondrial energy production by directly blocking the Krebs cycle enzymes isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, succinate dehydrogenase, NADH-dehydrogenase, and cytochrome C oxidase.[36]

Endocrine Disruption

Another documented effect of mercury is that it can increase catecholamine (epinephrine, norepinephrine) levels by inhibiting the enzyme catechol-*O*-methyltransferase through inactivation of its coenzyme *S*-adenosylmethionine (SAMe).[1] This can cause hypertension, sweating, and tachycardia that may be indistinguishable from pheochromocytoma. A suite of personality changes resulting from mercury toxicity is called erethism, and includes memory loss, drowsiness, withdrawal, lethargy, depression, and irritability.[1]

Other Metals

Pathology generated by other metals, such as cadmium and arsenic, can also involve mitochondrial damage, free-radical generation and decreased endogenous antioxidants. Cadmium inhibits the antioxidant manganese superoxide dismutase (MnSOD) in hepatocyte mitochondria, depletes glutathione through generation of free radicals, causes lipid peroxidation, and directly causes uncoupling of mitochondrial respiratory-chain activity.[27,37] Cadmium exposure is also associated with increased risk for osteoporosis and fracture.[38] Arsenic, which is also conjugated with glutathione and excreted in bile,[39] results in decreased glu-

tathione, increased free radicals, and mitochondrial damage.[40] Furthermore, occupational exposure to lead that results in plasma levels of 40 μg lead/100 ml blood reduces sperm concentration in men, while occupational exposure to mercury is associated with decreased testosterone.[41]

Risk Assessment

Since metal toxicity masquerades as other conditions, and since chronic exposure to metals, especially to mercury, is common, metal toxicity should be on the list of rule-outs for many presenting symptoms. A series of simple questions can help discern a patient's risk (see Table 7). Combining these questions with knowledge of the patient's symptoms can help clinicians determine if additional testing is warranted to rule out heavy-metal toxicity.

Table 7. Metals Toxicity Risk-Assessment Questionnaire

Question	Answers that increase risk
Has the patient knowingly been exposed to metals?	Yes
What is the patient's occupation?	Dentist, welder, shipbuilder, etc.
How frequently does the patient eat tuna, swordfish or shark?	More than twice weekly
Does the patient have mercury-amalgam fillings?	Yes
If the patient is taking any dietary supplements, do they have verified proof they are free of contaminants?	No
Is the patient taking any Ayurvedic or traditional Chinese medicine dietary supplements?	Yes
Do patients experience a metallic taste in their mouth *and* have not recently been taking medications documented to cause metallic taste?	Yes
Do they have a history of smoking (since cigarettes are particularly high in cadmium) [42]?	Yes

Diagnosing Metal Toxicity

Diagnosis of metal toxicity can be made via serum, blood, and urine or hair analysis. However, be aware that different forms of mercury do not deposit equally in all these sites. According to Walter Crinnion, ND, who published an excellent series of articles in *Alternative Medicine Review* (2000) reviewing environmental-toxin exposure and treatments, MeHg shows up well in the hair, while elemental mercury does not.[14] Mercury in hair is 79–94% MeHg, leaving only 6–21% as elemental mercury.[14] Instead, elemental mercury shows up best in plasma and urine. Since MeHg also concentrates intracellularly, a red blood cell, intracellular, toxic-metals analysis can be a cost-effective way of detecting MeHg toxicity.

While 24-hour urine testing may be used to diagnose metal toxicity, the current clinical standard is a combination of 6-hour unprovoked and provoked urine tests. Use a chelating agent, such as 2,3-dimercaptosuccinic acid (DMSA) or 2,3-dimercapto-1-propanesulfonic acid (DMPS). (A chelator is a molecule designed to circulate through the body that binds to metals and carries those metals out of the body through the urine.) Urine is then collected for 6 hours after administration of the oral or intravenous DMSA- or DMPS-challenge protocol and sent to a lab for evaluation. Since recent fish consumption can elevate metals in the urine, it is important that patients eliminate fish from their diet for a week prior to the test.

While there currently is no accepted standard for diagnosing toxicity based on a comparison of metals in the unprovoked and provoked urine specimen, some clinicians utilize a multiple of 4. That is, if the provoked metals are 4 times greater than the unprovoked, treatment is considered. It is important, however, to correlate symptoms with test results, and this is where clinical experience is invaluable. It is imperative that the clinician rule out more proximal causes of symptoms, since treatment regimens to reduce heavy-metal toxicity can be long and expensive.

Treatment of Metal Toxicity

Treatment has three goals: 1) eliminate or minimize exposure to the toxic metal (eg, recommending patients reduce or eliminate consumption of king mackerel, shark, swordfish, tilefish, and tuna), 2) decrease the body burden of heavy metals by increasing excretion of toxic metals through urine and feces, and 3) protect organs during detoxification from potential adverse effects of the heavy metals. Since a major cause of chronic mercury exposure comes from amalgam fillings, finding a "biological dentist"—one who does safe mercury extraction—is important. Extracting mercury from teeth releases mercury vapors. Dentists who perform this procedure should use a dental dam and suction device to protect the patient from inhaling mercury vapors during extraction.

Therapeutic elimination of metals from the body utilizes a combination of strong and weak chelators. Given its strong affinity for lead, mercury, cadmium, and arsenic, as well as its low toxicity, chelation with oral DMSA is the currently accepted standard. For additional information on safety, testing, and treatment protocols using DMSA, refer to the DMSA monograph published by *Alternative Medicine Review*.[43]

Mobilizing metals for excretion by the kidneys can put a burden on organs through which the metals are passing. Prior to provocative testing or treatment, it's recommended that a serum creatinine be obtained to ensure proper kidney function. Chelation therapy can also cause transient bone marrow suppression, and therefore a complete blood

Table 8. Metal-Chelation-Protocol Patient Instructions

Oral DMSA Chelation Instructions
Days 1-5: Have patient take 2 DMSA capsules (250 mg each) 3 times daily (total is 6 capsules/1500 mg each day) for 5 days.
Days 6-19: They should then take 1 DMSA capsule (250 mg) every 12 hours for an additional 14 days. This completes 1 DMSA cycle, a total of 19 days.
Days 20-33: Next, the patient should take 14 days off—ie, no additional DMSA should be taken for the next 14 days; however, from days 5 through14, they should take a multivitamin/mineral formula.
Days 34-52: After 14 days off DMSA, repeat steps 1 and 2, above. Once completed, the patient will have finished 2 DMSA cycles. (Note: For 2 cycles, approximately 3 bottles of oral DMSA 250-mg capsules are required at 60 pills/bottle.)
After the second DMSA cycle is finished, a toxic-metals retest is needed. As before, this requires 2 brief appointments.
Day 53: Have patient complete a blood draw (to check kidney and liver functions and to perform a complete blood count [CBC]). When the patient comes in for the blood draw, a urine-collection container should be provided. An unprovoked urine specimen should be collected for 6 hours.
Day 54: This appointment is to administer the chelating agent and to provide a second urine-collection container in which the provoked urine specimen will be collected. Again, urine should be collected for 6 hours. The patient should then ship the 2 vials of urine to a laboratory for analysis.
*Note: It is important that the patient empty his/her bladder prior to administering the chelating agent, and to consume 1 liter of water during both 6-hour urine collections to flush metals through the kidneys and excrete them in the urine.
Further actions: Based on results of the follow-up heavy-metal testing, oral DMSA may be continued. Six to 10 cycles may be required to bring toxic-metal levels down enough to discontinue therapy.
Additional instructions: The patient should daily consume throughout the treatment program: 1. Large quantities of pure water (half the body weight in ounces of water) to facilitate excretion of heavy-metal poisons in urine; 2. 30 g of dietary fiber to facilitate excrection of heavy-metal poisons in feces; 3. Vitamin C powder to bowel tolerance; 4. 600 mg α-lipoic acid (taken as 300 mg twice daily); 5. 40 g whey-protein powder (taken as 20 g twice daily); 6. 500 mg silymarin (standardized to contain 80% silymarin and taken as 250 mg twice daily).

count is indicated prior to initiating chelation treatments and periodically during treatment. Multiple animal experiments have shown that metals toxicity can be attenuated using sulfur donors such as *N*-acetylcysteine, garlic (*Allium sativum*), and antioxidants. In an ex vivo study of African green monkey kidney cells, cadmium-induced generation of free radicals and mitochondrial damage was attenuated by treatment with 10–40 μg/mL diallyl tetrasulfide, an extract from garlic.[44] This inhibition is likely due to the high sulfur content of the garlic extract. Whey-protein powder, which increases glutathione, is also a logical addition to any metal-detoxification protocol.[45]

Additionally, since a major route of excretion is in bile, choleretic herbs such as artichoke (*Cynara scolymus*) leaf, dandelion (*Taraxacum officinale*) root, and burdock (*Arctium lappa*) root, in addition to a high-fiber diet and colon hydrotherapy, may also be helpful. During chelation, silymarin, a hepatoprotective complex of flavolignans from milk thistle (*Silybum marianum*), is also frequently prescribed. (For more information, see the botanical medicine article about milk thistle on p. 20) Like whey-protein powder, milk thistle increases glutathione. Patient instructions for a metals-elimination protocol are provided in Table 8.

Conclusion

Metals are ubiquitous in our environment, and exposure to them is inevitable. However, not all people accumulate toxic levels of metals or exhibit symptoms of metal toxicity, suggesting that genetics play a role in their potential to damage health. Metal toxicity creates multisystem dysfunction, which appears to be mediated primarily through mitochondrial damage from glutathione depletion. Accurate screening can increase the likelihood that patients with potential metal toxicity are identified. The most accurate screening method for assessing chronic-metals exposure and metals load in the body is a provoked urine test.

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