Diagnostic and Treatment Protocols
for safer, effective mercury human biohazard management

Report of the:
Consensus Development Working Group of the
International College of Integrative Medicine

Review date: 14 March 2003
Release date:
Version: 21

Executive Summary / Abstract:

While metallic mercury is of low direct human toxicity[1], its ready conversion under physiological conditions to substantially more toxic biologically active forms (e.g. methylmercury, dimethylmercury, mercuric sulfides, and other mercurous / mercuric compounds, etc.) is a major public health risk[2]. Biologically active mercury is considered by Naraiju and colleagues to be the most toxic of all the toxic minerals[3]. Primary sources of mercury exposure in humans include: medications and devices (including amalgams and vaccines), metallic mercury, mercurial fungicides, water, and recreational exposures including from ceramic glazes. Dietary sources are important, especially due to bioconcentration in fish and fowl and in ruminants and game of toxic minerals the 'higher' up the food chain the dietary choices.

Some 300 tons annually are added to the American ecosystem from all industrial and consumer sources. An additional ~ one kiloton of mercury is derived from trans-Atlantic dust storms that contain enough mercury to qualify as 'mineable ore' if only this dust could be trapped before it reaches the southern United States and Caribbean Basin[4]. This last environmental burden was unknown until as recently as 1990. This illustrates how substantial sources of 'high-toxic effects compounds' can greatly enrich an environment in a toxicant without general awareness of the influx of that toxicant. These largely invisible depositions remain, in aggregate, just as potent as toxicants.

The addition of 1,300 tons of mercury to the ecosystem equals 1.18×10^{15} micrograms (μg). Given that toxicity of mercury is usually measured in micrograms, there are about a quadrillion toxic doses of mercury released into the environment each year. With a population of 300 million (or 3×10^8) in the United States, this equates to 3.93×10^7 μg (39,000,000 μg) per citizen per year.

Similar in toxic potency to mercury, arsenic, in biologically active forms, is a potent metabolic, hormonal, immune, and gene toxin[5]. Primary sources of arsenic exposure in humans are water, food, arsenical biocides, and therapeutics. In aggregate, exposures to total arsenicals pose a significant

---

[1] www.nlm.nih.gov/medlineplus/mercury.html.

[2] *Toxic Mineral Monographs*, ATSDR, CDC, USPHS, 1998-2002

[3] Nriagu JO, Pacyna, JM. Quantitative assessment of worldwide contamination of air, water, and soils by toxic metals. *Nature* 1988; 333(6169): 134-139.

[4] Seba D. Personal communications, 2000-2001.

[5] *Arsenic Monograph*, ATSDR, CDC, PHS, GOV, 2000

human health risk above levels at or below 1 part per billion (ppb)[6]. Cadmium and nickel are also potent toxicants with similar mechanisms of action[7]. This includes cardiovascular risk[8].

With regard to lead, the evidence base of pervasive subacute toxicities is stronger and reviewed elsewhere[9]. Living in an industrialized society exposes all inhabitants to metals in the environment. Some minerals are essential for life. These include potassium and sodium, calcium and magnesium, zinc and copper, chromium and vanadium, manganese and molybdenum, selenomethionine and iodides, *et. al.* Other minerals are toxic to life in all but the tiniest of amounts. These include lead, mercury, arsenic, cadmium, nickel, and aluminum.

Some minerals, like selenium in the proper, bioactive form, can form stable complexes with biologically active mercury or arsenic, thereby detoxifying them. These stable complexes are not easy to remove and may remain in the body for periods of years to decades. Their relatively low toxicity reduces the priority placed on their removal from the host.

The public health burden due to toxic minerals is an acquired and reversible health risk for at least 80 million Americans. The human cost is a reduction of 8.8 years of life for the average person due to the effects of these toxicants[10]. The direct disease care cost induced by toxic minerals are calculated to be in excess of $100 billion annually (HCFA, 2000; Princeton University, 2001)[11].

This means that we could fund the transition from our current reactive, detoxification focus to a proactive, intoxication prevention program out of savings from sick care costs not incurred. This, in turn, means substantial resources could be available for investment in economic growth rather than the payment for end stage, non-renewable health resources devoted to disease care. The public health risk from toxic minerals is yet greater due to suspected but not extensively defined or replicated synergies of mineral toxicities[12].

---

[6] EPA revised arsenic risk assessment. *Chemical & Engineering News* January 8, 2001.

[7] www.atsdr.cdc.gov/tfacts5.html

[8] Cohn SL, Goldman L. Preoperative risk evaluation and perioperative management of patients with coronary artery disease. *Med Clin North Am* 2003; 87: 111-136.

[9] Needleman HL. Childhood lead poisoning: The promise and abandonment of primary prevention. *Am J Public Health* 1998; 88: 1871-1877.

[10] www.atsdr.cdc.gov/HEC/CSEM/lead/references_cited.html

[11] www.healthbenchmarks.org/mercury/

[12] Jaffe R, Morris E. Medicine in Transition from Disease Treatment to Healthcare. *HSC Report 100-14* 2000, Sterling, VA.

The purpose of this report is three fold:

1. **Review the evaluated approaches to toxic metals' bioburden and hypersensitivity / "delayed allergy" determination. Protocols that can report data on safety, adverse events, patient compliance, and patient quality of life satisfaction are the primary sources for this report.**

2. **Summarize the safer, evaluated protocols for reduction of human toxic (mercury, arsenic, *et. al.*) mineral burden.**

3. **Present clinical experience on the risks and benefits of mitigation and bioremediation approaches in humans' toxic metal xenobiotic management.**

Mercury effects, sources, consequences, and mitigation

While direct effects of organic or biologically active (non-metallic) mercury are of concern, there are also biologically important interactions amongst toxic minerals, volatile organic chemicals (VOCs), and biocides (neuro-, immuno-, and hormonal toxicities). The synergies of toxicity amongst toxic minerals remains to be fully defined, especially in regard to autoimmune, cardiovascular, and cancer risks[13]. Further, possible synergies across categories of toxicants add an additional burden of concern that can not yet be quantified. It is, however, increasingly clear that lower levels of mercury and arsenic are more potent cancer promoters, hormone disrupters, and neuroimmuo toxicities than had previously been expected.

The EPA recommended, in 2001, a 10 ppb arsenic maximum acceptable level in drinking water. The Institute of Medicine of the United States National Academy of Sciences expert panel on arsenic recommends a drinking water standard of less than 1 ppb because the cancer promoting effects of even this level of arsenic in the water are deemed to be too high.

Arsenic, at 1 ppb in the drinking water, increases the risk of cancer by 1 in 1,000 in a lifetime. As toxicologists, we are used to thinking about risks in terms of excess cancers per million people. Thus 1 ppb arsenic in the drinking water over a lifetime increases the risk of cancer by 1,000 per 1,000,000 people. This is above the historically accepted, conservative Environmental Protection Agency (EPA) risk threshold of one (1) extra cancer per million population. To many physicians and scientists, even this level of risk is unacceptable given that cost effective 'mitigation at the source' solutions are available. Examples of this approach are given in the recent book *Natural Capitalism*[14]. Other examples are the report to the Department of Consumer Affairs of the State of California titled *Clean Your Room*[15].

There are also T-helper lymphocytes that are involved with delayed allergy reactions to haptenic[16] immunotoxins like mercury. Clinically, this can be

---

[13] Bernstam L, Nriagu JO. Molecular aspects of arsenic stress. *J Toxicol Environ Health B Crit Rev* 2000; 3(4): 293-322.

[14] Lovins A, Lovins H, Hawken P. *Natural Capitalism* 2000, Brown & Co.

[15] Jaffe R. *Clean Your Room*. Report to the Department of Consumer Affairs of the State of Caliornia, Richard Spohn, Director, 1983.

[16] Haptenic substances (or haptens) are small molecules which, while not large enough to be recognized as foreign by the body, bind to the body's own proteins. This bindings distorts the innate structure rendering them 'foreign' and immnunoreactive in the body.

functionally measured by a classic MELISA modification of thymidine incorporation or by the ELISA/ACT® LRA tests, which assay kinase activation prior to inducing thymidine incorporation. These technologies show us that even a tiny amount of internal or environmental exposure to a substance that induces an immunotoxic hypersensitivity burdens immune defense and induces deferral of immune repair.

As Casdorph reminds us, "our toxic metal time bomb's impact on human health and on our ecosystem has been compared in importance to the total radioactive waste in need of disposal[17] or the excess carbon dioxide production associated with enhanced greenhouse gas effects[18]. This is less surprising given the following:

1. **~ 1,000 fold increase in toxic minerals in our environment over the last 1,000 years.**

2. **Over half of the toxic mineral burden on the environment has been added within the last century.**

3. **Bioaccumulation in mammals, including humans, is typically 100,000 to 200,000,000 times that of the environment. This is largely due to most mammals ready uptake and impaired innate release (detoxification + excretion) mechanisms.**

Given what we now appreciate about. . .

1. **the synergies of interaction among toxic metals,**

2. **how toxic metals deplete the body of primary defense and essential mineral transport capabilities,**

3. **the interactions among classes of biocides including solvents, lipophilic hormone mimic pesticides, and toxic minerals,**

4. **an epidemic of epidemics of autoimmune, cardiovascular, neoplastic, and psychoemotional disorders and their link to toxic metals. . .**

---

[17] Nriagu JO, Pacyna, JM Quantitative assessment of worldwide contamination of air, water, and soils by toxic metals. *Nature* 1988; 333(6169): 134-139.

[18] Boden TA, Marland G, Andres RJ. CO2 emission calculations and trends. *Govt Reports Announcements and Index*, Issue 17, 1996.

the geometric rise in chronic illness likely linked to or potentiated by toxic metals' effects is now clear.[19]

[19] See ATSDR/CDC/USPHS monographs on specific toxic metals.

This report addresses three principle issues:

1. **Review the evaluated approaches to toxic metals' bioburden and hypersensitivity / "delayed allergy" determination. Protocols that can report data on safety, adverse events, patient compliance, and patient quality of life satisfaction are the primary sources for this report.**

2. **Summarize the safer, evaluated protocols for reduction of human toxic (mercury, arsenic, *et. al.*) mineral burden.**

3. **Present clinical experience on the risks and benefits of mitigation and bioremediation approaches in humans' toxic metal xenobiotic management. Guzelian *et.al.* showed that cholestyramine resin would tightly and effectively bind kepone[20]. Jaffe applied this to heptachlor in Hawaii[21]. More recently, Shoemaker has applied this strategy clinically to reduce xenobiotic neurotoxins[22].**

Other review articles have recently summarized general aspects of toxic metal effects on human and other animal systems[23]. When available, information about relative cost, predictive value, and suitability for various population cohorts is presented here.

N.B.: **These are meant to be:**

1. **Guidelines or suggested treatment protocols for clinical care.**
2. **A basis for competent, professional, individualized, evidence-based care.**
3. **A basis for national standards of practice for the integrative and comprehensive medical community in regard to diagnosis and biologic therapy.**

Bioaccumulation of mercury, arsenic, or other toxic mineral is a function of intake and output balance, *i.e.*,

Intake - Output = Residual [in body]

---

[20] Boylan JJ, Egle JL, Guzelian PS. Cholestyramine: Use as a new therapeutic approach for chlordecone (kepone) poisoning. *Science* 1978; 199 (4331): 893-895 and NEJM 1978; 298(5): 243-248.

[21] Jaffe R. Heptachlor binding by cholestyramine. *Report to the Board of Agriculture of Hawaii* 1981.

[22] Shoemaker R. Possible estuary-associated syndrome: Symptoms, vision, and treatment. *Environ Health Perspect* 2001; 109 (5): 539-545.

[23] WHO Working group. Mercury – environmental aspects. *Environmental Health Criteria (WHO)* 1989, 86p.

The integral of this simple 'input / output' model, over time, determines the status of the individual with regard to the toxic mineral (such as mercury or arsenic) in terms of their individual body burden.

For example, if…

1. **Intake (high) – output (low) = Increase in toxic burden**
2. **Intake (high) – output (high) = Steady state, high-risk state**
3. **Intake (low) – output (high) = Decrease in toxic burden**
4. **Intake (low) – output (low) = Low exposure**
5. **Intake (low) – output (high) = Body burden reduction [this is the clinical goal state]**

Determination of immunotoxicity from toxic minerals such as mercury and arsenic depends upon mechanisms that are still being elucidated[24]. Among the mechanisms proposed for the development of such immunotoxicity are:

1. **Loss of homeostasis leads to a sensitizing state. Host tolerance in the individual's immune defense and repair systems may progressively be lost. At the time of distress for the individual, exposure to a sensitizing substance such as mercury or arsenic can lead, by haptenic mechanisms[25], to development of delayed allergies / DTH of the Gel and Coombs Types II, III, and IV[26].**

2. **Chemical reactions form mercury or arsenic covalent links with selenium, sulfur, or other chemically reactive and available substances that trap and safely carry out of the body. Ascorbate (vitamin C) is the principle physiologic example of this detoxifying action[27].**
   • Healthy people increase their selenium in proportion to mercury. This allows for the formation of a covalent bond between mercury and selenium (mercuric selenide).
   • In contrast, typical individuals in the population are not fully healthy as assessed by the Cornell Medical Index or similar standardized

---

[24] HazDat: ATSDR's hazardous substance release / health effects database. http://atsdr1.atsdr.cdc.gov:8080/hazdat.htm#A3.1

[25] Jaffe R. Autoimmunity: Clinical relevance of biological response modifiers in diagnosis, treatment, and testing. *Intl J Integ Med, Part I* 2000; 2(2): 16-22 and *Part II* 2000; 2(4): 58-65.

[26] Gel PG, Coombs RR, Lachman PJ. *Clinical Aspects of Immunology*. Blackwell Pub, Oxford, UK, 1975, 1399-1404.

[27] Risher JF, DeRosa CT, Jones DE, Murray HE. Summary report for the expert panel review of the toxicological profile for mercury. *Tox Indust Health* 1999; 15(5): 483-516.

assessment of an individual's signs of symptoms of ill health.
• When selenium, ascorbate, glutathione, and other innate detoxifying agents are marginal or deficient, compounds with an available sulfur become preferred by mercury or other toxic minerals.
• Protein sulfhydryls may be sacrificed when available detoxifying sulfhydryl pools are depleted. These proteins are primarily cellular enzyme catalysts or important transport proteins such as the metallothioneins.
• This serves as a back-up system that reduces mercury's toxicity. The sulfur that reacts in compromised hosts is often a cysteine molecule at the active site will be impaired or poisoned[28]. Free sulfur compounds include cysteine, cystine, N-acetyl-cysteine, d-penicillamine, N-acetyl-d-penicillamine, allicin, allyproylsulfides, and allysulfides.

- ✓ **Bioaccumulation of mercury and other toxic minerals has additional physiologic effects. These compounds are:**
  • Hormone disrupters,
  • Neurochemical aberrant nerve impulses,
  • Teratogenic effects on the developing fetus, and,
  • Immune dysregulation.
  All these effects have been observed as actions of mercury and other toxic minerals.

3. **Genetic susceptibility, for example, impaired glutathione synthetase activity due to a DNA translational error, would impair detoxification competence for toxic minerals like mercury and arsenic[29].**

4. **Acquired or pseudogenetic susceptibility, for example, impaired glutathione synthetase activity due to a RNA transcriptional error due to haptenic binding and distortion of the mRNA complex or due to impaired and disordered protein synthesis due to low ATP production in the cell's mitochondrial power house battery[30].**

Evaluation of a patient suspected of heavy metal toxicity and/or heavy metal sensitivity should be based on:

---

[28] Pfeiffer C. *Mental and Elemental Nutrients*. Keats Pub., New Canaan, Ct., 1983 .

[29] Great Lakes College of Clinical Medicine. *A Useful Tool: Mercury: A Risk Realized* March 21-22, 2001, Baltimore, MD

[30] Makani S, Gollapudi S, Yel L, Chiplunkar S, Gupta S. Biochemical and molecular basis of thimerosal-induced apoptosis in T cells: A major role of mitochondrial pathway. *Genes Immun* 2002; 3(5): 270-278.

1. **Determining the body burden of the toxic minerals (and relevant nutritional minerals) on an appropriately provoked specimen. This may follow screening assessments using such analytes as hair, nails, skin, stool, and tissue. In addition, unprovoked urine, may be employed as a pre-provocative testing screening assessment.**

2. **Compounds such as dimercaptosuccinic acid (DMSA), dimethylpropionylsulfide (DMPS), d-penicillamine (d-pen), and ethylene diamine diacetic acid (EDTA) are examples of mineral binding or chelating compounds that may be used for provocative testing. These chelating compounds have been standardized. These compounds have been evaluated for use as challenge agents using commonly employed protocols for determination of body toxic and / or nutritional mineral content. Combinations of chelators for either provocation or treatment have recently been proposed based on clinical experience. Examples of best outcomes protocols are included in the appendices of this report for each provocative compound.**

Further, the timing of detoxification is best accomplished when host systems for sequestration and rapid elimination of toxin are facilitated. For example, removal of mercury-containing amalgams (if needed) should follow a systematic program to enhance dietary intake of foods such as garlic, onions, and/or ginger that block uptake and bind (thereby detoxifying) toxic minerals and other sources of biologically active sulfur compounds to accomplish the same effects by including intensive supplementation as needed. In addition, the following are synergistically helpful in reducing body burdens of toxic minerals including mercury and arsenic:

1. **Supplementation with ascorbate to tissue and cell sufficiency ('saturation'),**

2. **Reduced glutathione and related sulfur compounds,**

3. **Soluble magnesium and zinc sources,**

4. **Sulfur derived from ginger, garlic, and onions. Brassica vegetables such as broccoli as well as eggs are additional sources of biologically active sulfur, all of which help to enhance mercury and toxic minerals binding and excretion.**

These compounds work best when the individual is in a homeostatically balanced lifestyle.

Confirmatory, follow-up testing is encouraged at 3-6 months following the initiation of therapy. In many cases, otherwise unexpected additional toxicants or essential nutritional mineral deficits will be revealed. It is cost effective to engage these elements of comprehensive and integrative care. This reduction in morbidity can be linked to the reduction of biologically active toxic minerals and the enhancement of antioxidant, anti-toxic stores in the person.

Dr. William Walsh of the Pfeiffer Treatment Center, Wheaton, Illinois, reports a link between the above basic science genetic and phenotypic data, suggesting a hereditary or xenobiotic pseudogenetic predisposition to mercury toxicity and / or T lymphocyte hypersensitivity (DTH). This emerging data makes thimerisol exposure at times of distress or impaired detoxification particularly troublesome.

Under normal circumstances, there is a large concentration of the protein metallothionein waiting in your intestines, as a sentinel, to interact with the mercury or other toxic mineral and detoxify it before it enters the body.

Each metallothionein molecule has binding sites for seven atoms of zinc plus variable amounts of selenomethionine and glutathione. Basically, it is a linear protein of 61 amino acids. Being loaded with minerals is like priming the pump. Twenty of those amino acids or about one-third of all amino acids are cysteine and cystine, which can form powerful sulfidryl double bonds. Its job is toxic mineral detoxification. It is in high concentration in the gastrointestinal (GI) tract and in the liver, but it is present in every cell in the body. It thereby protects the GI tract from all of the nasty things that toxic minerals like mercury can do. However, its production is elective. Metallothionein production occurs only when the body is healthy and in homeostatic equilibrium. In states of hormonal, neurochemical, or immune distress, metallothionein production can be substantially downregulated.

"If you take somebody whose metallothionein system is not working, however, the mercury form covalent links to other, active sulfhydryl groups. The sulfhydryl groups in active site of certain enzymes in the GI tract include the enzymes that breakdown casein from cow's milk and gluten from wheat and other grains. A metallothionein disorder, therefore, is often associated with major digestive and / or dysbiosis problems in the GI tract. Most typically, wheat and casein intolerances and other delayed T cell mediated allergic hypersensitivities occur. These individuals are also prone to intestinal inflammation and enteropathy."

"Metallothionein is primarily a family of four proteins (metallothioneins 1,2,3, and 4). Metallothioneins 1 and 2 are ubiquitous and present in every cell in the body. Metallothioneins are there to carry out innate antioxidant functions and/or to deliver zinc wherever it is needed." It is interesting to note that in Professor

Ulf Lindh's nuclear microscopy studies, patients who had mercury inside their leukocytes also had abnormally low concentrations of zinc in the nucleus."

If you look at a population of adults who have amalgams, many people show little adverse effects. Similarly, most children who receive vaccinations containing thimerosal (mercury) go through this experience without many notable adverse effects. Perhaps these are the individuals with adequate ascorbate and glutathione, magnesium, zinc, selenomethionine, and sulfur from dietary sources (including breast milk from mothers whose anti-toxic levels are high). These individuals are protected and at relatively low risk. When zinc, selenomethionine, and magnesium are marginal or deficient, metallothionein looses functionality[31]. Such individuals are sensitive and/or at high risk of toxic metals' effects. On the other hand, certain individuals are dramatically affected by the mercury from their amalgams, or they are seriously affected by an injection of thimerosal (which typically contains 50-75 μg of mercury). These individuals are not protected and are at relatively high risk. The at-risk group correlates with deficits in anti-toxics.

Metallothionein is also responsible for homeostasis between copper and zinc. These trace elements, in turn, are related to production of specific hormones, cytokines, and neurotransmitters. For example, in order for the zinc or copper requiring enzyme catalysts to convert the right amount of dopamine into norepinephrine, copper to zinc balance and sufficiency are required.

Walsh and colleagues have used the plasma zinc / copper ratio as an indicator of properly functioning metallothionein. They use it as an indicator of "toxic-coping ability". If you have a population of:

1. Obsessive-compulsive (OC) individuals, the ratio between plasma zinc and serum copper will be around 0.8.
2. The healthy range, based on nearly 100,000 individuals, is about 1.0.
3. Walsh *et. al.* have examined 5,700 individuals with attention-deficit disorder and the ratio is 1.17.
4. For children who exhibit violent behavior, the ratio is 1.4.

Walsh suggests that impaired homeostasis for copper and zinc correlates with poor metallothionein function. The detailed influence of supplementation on normalizing these ratios and their impact on function and performance is, as yet, unspecified.

The Swedish experience is the most rigorous and extensive regarding toxicity from dental materials, particularly mercury amalgam. Certain factors may be responsible for this leadership including:

---

[31] Maret W, Heffron G, Hill HA, Djuicic, D, Jiang, LJ, Vallee, BL. The ATP/metallothionein interaction: NMR and STM. *Biochemistry* 2002; 41(5): 1689-1694.

1. First is the presence of a nuclear accelerator available to Lindh who conducted research using nuclear microscopy in biomedical analysis[32]. Neutrophil (granulocyte) mercury in patients with mercury amalgams who were sick and compared to controls (people with mercury amalgams who were not sick).

   The results showed that the patients who had amalgams and who were sick had detectable mercury in their cells and that the controls did not show bioaccumulation of mercury. In addition, the concentrations of other elements such as magnesium, calcium, manganese, iron, and zinc were more than one standard deviation different between the patients and the controls. Furthermore, examination of elements in the nucleus showed a maldistribution of zinc, which correlated with the presence of mercury in the nucleus of the neutrophils. There is a typical zinc distribution in the nucleus of the neutrophil granulocyte. In contrast to this normal situation, the patients who had mercury showed an abnormal distribution and an invasion of mercury. When mercury had entered parts of the nucleus, the zinc in those areas seems to be decreased.

   In other words, the availability of nuclear microscopy enabled Lindh and colleagues to clearly demonstrate the presence of mercury above the detection limit in the cells of patients who had amalgams and who were sick, and the absence of mercury above this level in the cells of controls who also had amalgams.

2. Stejskal's research agrees that T lymphocytes play a role in all types of allergic and autoimmune reactions[33]. This makes them evident candidates as markers for metal-induced sensitivity. After contact with an antigen, T and B lymphocytes that are antigen-specific for that substance correlate with inflammatory reactions that lead to cell damage when repair is delayed or blocked. Repeated exposure with the same or a chemically

---

[32] Nuclear microscopy or PIXE is an advanced analytical tool, which allows for the measurement of trace elements in small objects, such as the nucleus of the neutrophil granulocyte (with a detection limit of 0.5 microgram/gram dry substance). This is done by bombarding the cells and their organelles with protons (hydrogen atoms). Because each trace element has its own characteristic emission fingerprint, it is then possible to determine the amounts of a particular element in the various regions of the cell. This was based on the earlier work of Jaffe, Smith, and Costa.

[33] Stejskal VD, Danersrund A, Lindvall A, Hudecek R, Nordman V, Yaqob A, Mayer W, Bieger W, Lindh U. Metal-specific lymphocytes: biomarkers of sensitivity in man. *Neuroendocrinol Lett* 1999; 20: 289-298.

similar cross-reacting antigen will immediately induce a faster, secondary immunological reaction initiated by the memory cells. Cytokine release will activate other cell types, and the result is either beneficial for the body when repair is facilitated or, in the case of repair deficient autoimmune diseases, a pathological consequence.

Human lymphocytes can be stimulated *in vitro* with various foreign substances called mitogens[34]. The lymphocyte stimulation test has been used for 30 years as routine analysis for evaluation of cellular immunity and clinical immunology, as well as for diagnoses of allergic reactions to medicines, metals, and other substances. Specific stimulation is based on the fact that every person's immune system remembers the antigen that it has previously been programmed to remember. Such a reaction gives rise to memory cells, which circulate in the bloodstream and defend the individual against foreign substances including:

A. Xenobiotics and other synthetic small molecules (mostly haptens)
B. Partially digested, immunoreactive food remnants
C. Pathogens including bacteria, parasites, viruses, or anything recognized by an individual as foreign to their immune system.

Other types of white blood cells are monocytes and macrophages. These cells perform various functions such as presentation of antigens to lymphocytes and removal of toxic substances; thus they are termed "scavenger" or dendritic cells. They are short lived with a typical life span of 8-12 hours in the body. Tests that employ changes in short lived granulocytes are not using contemporary technology for functional immune system predictive response. At best they are looking 'through a glass darkly' and over interpreting aggregate particle changes as lymphocyte-specific changes, which they probably are not.

The possibility to diagnose allergy with the help of lymphocyte stimulation tests rests on the fact that, in the case of low molecular weight substances (haptens), antigen-specific memory cells are present in patients with allergy symptoms, but not in healthy exposed individuals. Further, since memory cells circulate through the body, the sensitization or allergy is always a systemic phenomenon. The term local allergy often used in the case of oral mucosal changes indicates ignorance of basic immunological principles.

---

[34] Also known as response antigens, under conditions where stimulated response is induced by an adjuvant such as croton oil or Freund's adjuvant (immune non-specific upregulating booster for attaining higher monospecific antigen responses from mitogens).

The majority of the lymphocytes that operate in cell-mediated reactions are T-lymphocytes. T-lymphocytes play a key role in the development of all types of allergic and autoimmune disorders. The identification of the antigenic structures (epitopes) involved in allergy and autoimmunity is a 'hot field' in current research. The term allergy was originally designed as a divergent immune reaction.

Autoimmunity describes a condition when lymphocytes will attack the body's own cells. One hypothesis proposed as an explanation for the autoimmune process is that metals bind to the sulfhydryl groups on proteins and alter their three-dimensional structure. The immune system recognizes the altered proteins as foreign, and an autoimmune process starts, often with condition-specific imbalances in Th1 and Th2 populations of lymphocytes.

The majority of metals that are used in dentistry belong to the transition group in the periodic table. A general characteristic of these elements is that they have an uncompleted electron shell, either in the natural or oxidative state. Since electrons always exist in pairs, transition metals form strong complexes with both organic and inorganic ligands. The memory cells are long lived and can be detected in the blood of sensitive individuals, prior to the appearance of objectively documented clinical symptoms.

Metals can affect the immune system in several ways. In the oral cavity, high concentrations of metal ions may suppress the immune response and result in immunosuppression. This could explain why the oral mucosa contains only a low number of cells with the capability to present antigen to T-lymphocytes. This may also be why mucosal changes adjacent to metal fillings are rarely seen. Higher concentrations of metals can also up-regulate immune reactions (so-called the polyclonal or non-specific stimulation) and such responses are seen in individuals with intact immunity. In contrast, in some hereditarily predisposed individuals, metals may act as haptenic allergens. To be able to use the conventional lymphocyte stimulation test for diagnosis of metal-induced allergy, it was necessary to modify the test in such a way that only the antigen-specific reaction was measured. This was achieved by reducing the concentrations of the metals added to cultures. Since antigen-specific memory cells in the blood are relatively few, the number of lymphocytes in the metal cultures was increased, and the number of other cells that could affect the lymphocyte proliferation negatively was reduced. This version of the lymphocyte stimulation test is called MELISA, which stands for memory lymphocyte immunostimulation assay. Another advanced

lymphocyte response assay is the ELISA/ACT LRA tests system.

In short, MELISA or ELISA/ACT LRA enables individuals who are immunoreactive to mercury and other metals to be identified. Furthermore, after the removal of amalgam and replacement with nonmetal composites or the systematic reduction in immunoreactive exposures, the lymphocyte stimulation test often reverts to non-reactive. This 'resetting' of immune responses typically takes 6-18 months. These changes parallel the decrease in concentrations of mercury inside the neutrophil granulocyte. The dental research in this regard in Sweden is documented particularly by Hudecek, a capable biological dentist. Following dental metal removal, his data showed that 76 % of patients reported long-term health improvement, 22% reported unchanged health, and 2 % reported a worsening of symptoms.

Recently Lindvall reported that at one to two years following amalgam removal, about a quarter of patients had completely recovered from their chronic autoimmune or immune dysfunction syndromes; half were substantially improved; one-fifth showed no change; and one-twentieth (5%) were worse off than before. This latter group was mostly patients who had improper or premature amalgam removal[35].

[35] Lindh U, Hudecek R, Danesrund A, Ericksson S, Lindvall A. Removal of dental amalgam and other metal alloys supported by antioxidant therapy alleviates symptoms and improves quality of life in patients with amalgam-associated ill health. *Neuroendocrinol Lett* 2002; 23: 459-482.

Appendix 1: Protocols for determining toxic mineral status by provocation into the urine

A. **DMSA protocol (based on Gerz, Rozema, and Waters)**
B. **D-penicillamine protocol (based on Jaffe)**

Appendix 1A: DMSA / DMPS protocol (based on Gerz, Rozema, and Waters) for determining toxic mineral status by provocation into the urine

Note: The urine challenge test for mercury is with DMPS only. Do not mix with other chelating agents with DMPS.

Provocation:
Collect a 24º urine sample prior to DMPS challenge to determine baseline values. DMPS is administered at 3 mg./Kgm. with a maximum of 250 mg. given as a 15- to 20-minute slow IV push. The second 24-hour urine sample is then collected and sent to the laboratory for analysis.

Comparison is made between the first and second sample to determine the need for active treatment. Treatment with DMSA for mercury toxicity, if indicated from provocation:

1. **Give DMSA at the rate of 10 mg./Kgm. per for 3 consecutive days in 3 divided doses. We request that the compounding pharmacist on the case use magnesium aspartate as the "filler" in the capsule with the DMSA. Adequate magnesium is known to block uptake of mercury and to facilitate correction of magnesium deficits.**
2. **Do not use oral vitamins and mineral supplementation during the days the patient takes DMSA.**
3. **Give oral vitamin and mineral supplementation during the next 11 days between DMSA dosages.**
4. **Do 8 to 12 weeks of treatment (36 to 54 capsules of DMSA) and then re-challenge with DMPS as above.**

Repeat this program depending on how much mercury is still burdening the body.

DMSA Patient Information Sheet: Date_____

DMSA chelation program for: _____

Chart # _____

Use DMSA _____milligrams taken 3 times a day for 3 days.
Then use your vitamins and minerals regularly for the next 11 days:
This means 3 days of DMSA only and 11 days of vitamins / minerals.
Repeat the program every 2 weeks for 12-16 weeks. Then come to our office to repeat the challenge test to see how much mercury you still have left.

Appendix 1D: Penicillamine protocol (based on Jaffe) for determining toxic and nutritional mineral status by provocation into the urine

Purpose: Determine the body's burden of mobilizable, potentially toxic minerals.

Nutritional divalent mineral status may also be assessed.

Method: A short (3-day) course of d-penicillamine [Cupramine™, D-Pen™, dimethylcysteine, mercaptovaline] *or* Acetyl-d-penicillamine is prescribed.

Specimen for analysis: Collect a **24° urine** on the **2nd day**.

Protocol:

- ✓ Take 500 mg. (two (2) capsules of 250 mg. each) of d-penicillamine or N-Acetyl-d-penicillamine with each meal and before bed for just three (3) days. This is a total of 2 grams each day for three (3) days for a typical 70 Kgm. adult. This is based on 30 mg./Kgm. body weight. If the weight is under 100 pounds or over 300 pounds, a calculation of the dose is recommended.
  * For example, a 100-pound adult weighs 45.5 Kgms. A daily dose of 1,590 mg. (~1,500 mg.) is recommended. This would most easily be achieved by giving two (2) x 250 mg. capsules with breakfast, dinner, and at bedtime [two (2) capsules TID].
  * By comparison, a 350-pound person weighs 160 Kgm. At 30 mg./Kgm., this calculates to a daily dose of 4,800 mg. (~4,750 mg.). This means taking five (5) x 250 mg. capsules with each of three (3) meals plus four (4) x 250 mg. capsules at bedtime.
- **Starting** on the **morning of the second day**, collect in a heavy, metal-free container (usually provided by the doctor or the laboratory) all urine output for the next day (a full 24-hour cycle). It is quite important to collect **ALL** the urine.
- If a urine sample is missed, the collection is incomplete. Start over with a new provocation one week later. Urine collected in an incomplete sample may be poured out and the same collection container reused. Take the entire urine collection to the laboratory as soon as possible after completion. **The total volume is an important part of the information to be sent to the analytic lab.** It is desirable, although not necessary, to keep the urine refrigerated during the collection period. **Note:** A third-day collection can not be compared with the standardized second-day collection results.

Because of short-term effects on other minerals, this specimen should *not* be used for calcium or other mineral balance studies. The specimen ***may*** also be used to check kidney function and to analyze for most hormones, neurotransmitter metabolites, etc.

This short course of d-penicillamine avoids the rare but important side effects of longer-term therapeutic doses of the drug as discussed in the *Physicians Desk Reference* (*PDR*). Of course, if you note any adverse response, discontinue taking the medication until otherwise instructed by your health professional.

Interpretation and substantiation of d-penicillamine protocol:

- Each laboratory has an applicable reference range for each mineral assayed. Elevation above the range reported by that laboratory is indicative of increased tissue stores of that heavy metal. Tissue status of nutritional minerals may also be assessed in this way. Typical d-penicillamine provocation reference ranges are included in the table at the end of this document.

- For modest amounts of provoked toxic minerals:

  Follow an '**alkaline way diet'** combined with therapeutic amounts of antioxidants plus minerals (potassium, calcium, magnesium, and zinc as their ascorbates, aspartates, citrates, glycinates, or other fully soluble, non-allergenic mineral salts) to displace the toxic minerals. Adequate herbal tea, mineral water, or spring water (eight (8) or more 8-ounce glasses each day) helps to 'wash out' these toxins. A repeat provocative heavy metal test after 30-60 days is recommended to confirm the reduction in available heavy metals.

  For more than modest amounts of provoked toxic minerals:

  Use d-penicillamine twice a week (*e.g.*, Monday and Thursday) for 30-60 days at 7.5 mg./Kgm. taken QID (500 mg./QID for most adults) with supplemental calcium, magnesium, and zinc particularly on the non-Penicillamine days to replace these minerals (which d-penicillamine will chelate along with the other divalent [double charged] minerals along with toxic or heavy metals). Therapeutic doses of antioxidants are beneficial as well as described. This includes:

A. **Buffered ascorbate** based on ascorbate calibration to determine physiological ascorbate need[36]. **Flavanoid / flavanol combinations** (such as quercetin dihydrate and soluble OPC) potentiate the benefits of buffered ascorbate. Their need increases in proportion to buffered ascorbate need as noted in the ascorbate calibration document.
B. **Natural vitamins E** (mixed tocopherols) 200-600 I.U./day with tocotrienols (polycosanols).

---

[36] Jaffe R. Determination of ascorbate physiologic need by calibration. *Health Studies Collegium Document 111*. Contact Client Services at 800-525-7372 for reprints.

C. A balanced, high-potency, **high-activity B complex including PABA**.
D. A **comprehensive micromineral supplement** is recommended since micromineral deficits are pervasive. Selenomethionine is the most active mineral form for combining with and inactivating toxic minerals.
E. Sulfhydryl-rich foods such as **garlic, ginger, and onions; eggs; and brassica vegetables** (*e.g.*, broccoli, cabbage, etc.). Make fresh ginger tea (with raw honey to taste) a staple beverage. A thumb-size piece of fresh ginger, finely chopped and steeped in hot water for five minutes, contains over 5,000 mcg. of toxic mineral-trapping sulfhydryl compounds. Ginger tea may be made up ahead of time and may be drunk cool or cold if preferred.
F. Probiotics (10-20 Bn./day) containing multiple human-cultured strains.

- D-penicillamine was found to bind copper in the urine of patients with Wilson's disease[37] for which it has remained the treatment of choice for almost half a century.

- In animal studies, lead in bone seems to be even more effectively mobilized by d-penicillamine than lead in soft tissues[38,39]. However, $CaNa_2EDTA$ is reported to be a more effective lead chelator than d-penicillamine *in vitro* in tissue culture[40]. Questions have been raised about the safety of using any agent for low-level toxic mineral detoxification because some animal studies report that lead may redistribute into soft tissues such as the choroid plexus or the loop of Henle after $CaNa_2EDTA$ therapy[41]. Concerns of this type have been raised about all oral chelators although less in regard to d-penicillamine than any other substance.

---

[37] Walshe JM. Penicillamine, a new oral therapy for Wilson's disease. *Am J Med* 1956;21:487-495.

[38] Russell JC, Griffin TB, McChesney EW, Coulston F. Metabolism of airborne particulate lead in continuously exposed rats: Effect of Penicillamine on mobilization. *Ecotoxicol Environ Safety* 1978;2:49-53.

[39] Hammond PB. The effects of D-Penicillamine on the tissue distribution and excretion of lead. *Toxicol Appl Pharmacol* 1973;26:241-246.

[40] Rosen JF, Markowitz ME. D-Penicillamine: Its actions on lead transport in bone organ culture. *Pediatr Res* 1980;14:330-335.

[41] Klaassen CD. Heavy metals and heavy metal antagonists. *In*: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *The Pharmacological Basis of Therapeutics* 7th ed. New York: MacMillan Publishing Co; 1985:1605-1627.

- Clinical benefits of d-penicillamine are described by Sachs[42] *et al* and Vitale[43] *et al* yet not by Marcus[44] who administered d-penicillamine while the study subjects continued to live in lead-exposed environs. This may well explain the less dramatic decline in blood lead levels in the Marcus study. In Chisholm's study, children removed from further exposure and treated with d-penicillamine showed more rapid decline in blood lead levels and in the reversal of hematologic toxicity than the decline in toxicities resulting *solely* from eliminating the lead exposure sources[45]. In contrast, the study by Rogan[46] *et al* did not confirm these findings. This study has been criticized as flawed in method because the environment of the children studies was not mitigated for continued toxic mineral exposure during the study period[47].

- The toxicity of d-penicillamine has been described based on its use for several indications in both adults and children. Toxicity of the racemic mixture used years ago to treat chronic arthritis in adults may account for the severity of some of these symptoms and should never be used. In children, nausea and vomiting appear more often at doses exceeding **60** mg./Kgm. per day and may respond to a decrease in dosage[48]. This protocol uses 30 mg./Kgm. doses for just three (3) days for provocation.

- When given daily and for prolonged periods (which we never recommend) adverse blood and skin effects seem to be idiosyncratic hypersensitivity reactions and are not dose related. Reversible leukopenia or mild

---

[42] Sachs HK, Blanksma LA, Murray EF, O'Connell MJ. Ambulatory treatment of lead poisoning: Report of 1155 cases. *Pediatrics* 1970;46:389-396.

[43] Vitale LF, Rosalinas-Bailon A, Folland D, Brennan JF, McCormick B. Oral Penicillamine therapy for chronic lead poisoning in children. *J Pediatr* 1973;83:1041-1045.

[44] Marcus SM. Experience with D-Penicillamine in treating lead poisoning. *Vet Hum Toxicol* 1982;24:18-20.

[45] Chisholm JJ Jr. Chelation therapy in children with subclinical plumbism. *Pediatrics* 1974;53:441-443.

[46] Rogan WJ, Dietrich KN, Ware JH, Dockery DW, Salganik M, Radcliffe J, Jones R L, Ragan NB, Chisholm JJ, Rhoads GG. The effect of chelation therapy with Succimer on neuropsychological development in children exposed to lead (The treatment of lead-exposed children trial group). *N Engl J Med* 2001; 344:1421-1426.

[47] Shannon M, Woolf A, Binns H, Mandelbaum DE, Rogan WJ, Shaffer TR, Dietrich KN. Chelation therapy in children exposed to lead the treatment of lead-exposed children trial investigators. *N Engl J Med* 2001; 345:1212-1213.

[48] Sachs HK, Blanksma LA, Murray EF, O'Connell MJ. Ambulatory treatment of lead poisoning: Report of 1155 cases. *Pediatrics* 1970;46:389-396.

thrombocytopenia is reported in less than 10% of children in one study[49], but not with similar dosages in two other larger series[50]. This may have resulted from interaction between d-penicillamine and pyridoxine (B-6)[51]. Supplemental B-6 is now routinely recommended as part of d-penicillamine *therapy* (not provocation). Eosinophilia (defined as >18% eosinophils) has been noted in one-fifth of children treated daily for an extended duration[52]. Angioedema, urticaria, or maculopapular eruptions that require discontinuation of drug therapy are reported at a rate of 0.5-1%[53]. Still less commonly reported reactions are proteinuria, microscopic hematuria, and urinary incontinence[54]. All of these relate to increased tissue permeability due to inhibition of connective tissue cross links when d-penicillamine is given on a continuing daily basis and not when it is given in the pulsed manner recommended here.

- Food or ferrous sulfate[55] may reduce the peak level of d-penicillamine in blood by a third or more[56]. Antacids or functional hypochlorhydria[57] decrease d-penicillamine absorption by as much as two-thirds[58]. As with all amino acids, peak blood levels are achieved when the amino acid is given on an empty stomach. For provocation and for therapy, **mean** rather than **peak** blood levels are more important. Thus, taking the d-penicillamine with food is acceptable. Compliance with this regimen is high.

- **The recommended dose and duration of therapy with d-penicillamine have been empirically derived.** Doses have ranged from 100 mg./Kgm. per day

---

[49] Shannon M, Graef J, Lovejoy FH Jr. Efficacy and toxicity of D-Penicillamine in low-level lead poisoning. *J Pediatr* 1988;112:799-804.

[50] Bartsocas CS, Grunt JA, Boylen GW Jr, Brandt IK. Oral D-Penicillamine and intramuscular BAL + EDTA in the treatment of lead accumulation. *Acta Paediatr Scand* 1971;60:553-558. Also, Chisholm, *ibid*.

[51] Rothschild B. Pyridoxine deficiency. *Arch Intern Med* 1982;142:840.

[52] Vitale, *op. cit.* and Marcus, *op. cit.*

[53] Holt GA. *Food & Drug Interactions*. Chicago: Precept Press, 1998, 203.

[54] Shannon, *op. cit.* and Chisholm, *op. cit.*

[55] Harkness JAL, Blake DR. Penicillamine nephropathy and iron. *Lancet* 1982;ii:1368–9.

[56] Osman MA, Patel RB, Schuna A, Sundstrom WR, Welling PG. Reduction in oral Penicillamine absorption by food, antacid, and ferrous sulfate. *Clin Pharmacol Ther* 1983;33:465-470.

[57] Threlkeld DS, ed. Miscellaneous Products, Penicillamine. In Facts and Comparisons Drug Information. St. Louis, MO: *Facts and Comparisons* Aug 1996, 714–716b.

[58] Ifan A, Welling PG. Pharmacokinetics of oral 500 mg. Penicillamine: Effect of antacids on absorption. *Biopharm Drug Dispos* 1986;7:401-405.

(in earlier studies) to 20 to 40 mg./Kgm. per day (more recently). Far fewer side effects are reported at the lower dosage range. The duration of the pulse therapy herein recommended is typically on Monday and Thursday for 4 to 12 weeks, depending on the pretreatment provoked urine toxic mineral concentration. When used in this pulsed way, d-penicillamine has become a first line treatment of choice over the several decades of its increasingly widespread use.

- Finally, Penicillamine has the added virtue of serving as a source for nitric oxide (NO), which facilitates cellular communication and improved vascular compliance.

Mineral value ranges for nutritional and toxic minerals in 2nd day 24º urine after d-penicillamine provocation, 7.5 mg./Kgm. QID for three days [N=200]

Mineral Element	Reference Range µg/mg. Creatinine	Reference Range mg./24º Sample
Nutritional		
Calcium	310 - 620	400 - 900
Magnesium	250 - 550	350 - 700
Zinc	0.8 - 1.3	1.1 - 1.5
Copper	0.04 - 0.06	0.06 - 0.08
Iron	0.20 - 0.30	0.24 - 0.36
Manganese	0.005- 0.007	0.006- 0.008
Molybdenum	0.11 - 0.14	0.13 - 0.19
Boron	4.1 - 5.6	5.8 - 6.7
Chromium	0.19 - 0.30	0.21 - 0.33
Cobalt	0.04 - 0.06	0.05 - 0.07
Selenium	0.25 - 0.31	0.24 - 0.35
Vanadium	0.02 - 0.03	0.03 - 0.04

Note: Values lower than the reference range in provoked specimens suggest deficiency of the above needed essential minerals. Adequacy of supplemental intake to replenish deficits can be monitored by repeat d-penicillamine provocation every three months.

Toxic		
Lead	< 20	< 25
Mercury	< 7	< 9
Arsenic	<120	<175
Nickel	< 16	< 25
Cadmium	< 4	< 6

Summary of suggested treatment guide to reduce total toxic mineral tissue burden (TTMTB)

1. An '**alkaline way**,' energized, high-fiber diet with 80% of what is eaten being alkaline forming when metabolized.
2. **Ginger tea** (with raw honey to taste) as a beverage of choice. May be taken warm, cool, or cold.
3. Adequate **PERQUE Potent C Guard** based on the ascorbate calibration protocol.
4. **PERQUE Pain Guard** **1-4 tabs** **QID**
5. **PERQUE2 Life Guard** **2 tabs** **TID**
6. **PERQUE Digesta Guard** **3 caps** **BID**
7. **PERQUE Magnesium Plus Guard** **2 caps** **BID**
8. **PERQUE Choline Citrate** **1 tsp.** **BID** (in juice or water) taken along with Mg Plus Guard

The above supplements are given together to gain the cumulative benefit of the following detoxification mechanisms:

Enhanced antioxidant levels in:
A. Flowing blood
B. Metabolically and hormonally active cells
C. The blood brain barrier and the choroid plexus
D. The enterocytes in the digestive tract
E. Brain cells
F. Immune active cells and systems
G. Healthy skin look and function

9. In addition, if substantial total toxic mineral tissue burdens are documented, oral pulse therapy (two (2) days per week) with d-penicillamine is recommended. Use 7.5 mg./Kgm. QID on the two (2) days each week for three (3) months. After three (3) months, retest the urine by the d-penicillamine provocation test to determine residual toxic mineral being eliminated as well as comparison of nutritional mineral status. For example, are they assimilating what is being given? Do they have particularly high need for particular minerals for their unique metabolic type or metabolic condition?

- **Appendix 2. Nutrients that may be helpful in reducing body burden and detoxifying from toxic minerals.**

    C. Ascorbate (all l-ascorbate; all reduced; multi-mineral buffered)
    D. Glutathione (99+% reduced)
    E. Lipoic acid
    F. Insoluble dietary fiber
    G. Minerals such as magnesium and zinc
    H. Tocopherols (vitamins E) and Tocotrienols
    I. L-Cysteine or N-Acetyl-cysteine
    J. Chlorophyl-rich food such as chlorella and/or alfalfa (certified toxic mineral free)
    K. Sulfhydryl-rich foods such as garlic, ginger, and onions; eggs and brassica vegetables (*e.g.*, broccoli, cabbage, *etc.*)
    L. Selenium in the selenomethionine (active) form
    M. Omega 3 essential fatty acids (EFAs) especially DHA and CLA
    N. Krebs' 'energy salts' citrate, malate, fumarate, and succinate

Note: Optimum and therapeutic intake are substantially different from and not predicted by Daily Value (DV) or Recommended Daily Intake (RDI). Further, safer forms of nutrients are always recommended.

Dr. David Quig's summary of the literature on toxic metals' detoxification is the basis for this section of this report.

In regard to detoxification, N-acetyl cysteine given intra-peritoneally to rats, prior to injection of mercuric chloride, increased glutathione levels by 75%, increased urinary mercury excretion, and decreased the renal accumulation of mercury. However, if you co-infuse cysteine with methylmercury, it causes a marked *acceleration* of methylmercury uptake into the rat brain. This does not happen with cysteine and inorganic mercury. Methylmercury-complex mimics methionine, and perhaps the brain does not know the difference in terms of transport and deposition.

In one experiment, methylmercury was injected into mice. The mice were then given 10 mg./Kgm. of N-acetyl-l-cysteine. This resulted in a five- to ten-fold increase in the excretion of methylmercury in the urine. It also decreased mercury in all tissues compared to the controls. This, however, is in response to acute poisoning. Studies are not available for chronic exposure. In this type of acute exposure experiment, however, a high percentage of the mercury was very likely still in the plasma when N-acetyl cysteine was given.

This is very different from pulling mercury out of the cell. That is more complicated than just binding to mercury in a fluid compartment and sending it

out through the kidneys. In contrast to the situation with methylmercury, there is no effect of N-acetyl-l-cysteine in promoting the excretion of inorganic mercury. N-acetyl-l-cysteine in humans is only absorbed to the extent of only 5-10%. There is also a significant amount of de-acetylation that occurs in the intestines.

Alpha lipoic acid (ALA) is an oxidized disulfide molecule. To the untrained chemist, its structure resembles that of DMSA. It has 2 sulfhydryl groups. However, one of those groups is oxidized and is an integral component of the pyruvate dehydrogenase complex. This complex is the rate-limiting step going into the Krebs' cycle. Very low levels of ALA, therefore, can remove the inhibition and/or activate pyruvate dehydrogenase complex. This may be responsible for the beneficial effect of ALA in autistic children. It may have nothing to do with the removal of mercury. Low levels may be indicated to stimulate the activity of the pyruvate dehydrogenase complex.

There is a paper by Gregus *et. al.,* which focuses on ALA and mercury detoxification. Rats were given metal salts, either mercuric chloride or methylmercuric chloride, intravenously, and within one minute, in a separate vein, they received an infusion of 8-62 mg./Kgm. of ALA. There was an immediate or marked increase (12 to 37 times baseline) in the biliary excretion of mercury. However, there was a marked decrease in the biliary excretion of methylmercury, copper, and cadmium. If the injection of ALA was delayed for 24 hours, there was a marked decrease in the biliary excretion of mercury, to a level of 40 % above baseline. If they looked at the tissues three hours after putting the animals through this regimen, they found the following increases:

- 77 % in the heart,
- ~200 % in the brain, and
- a plasma copper increase of almost 400%.

The utility of ALA lies in the fact that it is fat loving. Thus ALA can get into hydrophobic protein pockets. It does bind to inorganic mercury, and it has a half-life on the order of two hours in the body. It does, however, have the potential of causing a redistribution and enhancing the movement of mercury into the brain. There is absolutely no evidence to support the use of ALA as a singular therapy for long-term detoxification: Neither as to its efficacy nor as to its safety.

Mercury combines readily with selenium to form a complex. However, this complex is retained within the body. Selenium does not directly promote the excretion of mercury. It may inactivate the mercury, however, by forming a covalent bond. Humans exposed to mercury in industrial accidents have a decreased excretion of selenium. High-dosed selenium treated animals have a greater survival rate when exposed to lethal levels of mercury. The selenium seems to make the mercury inactive. This mercury-selenium-complex is not

chelatable. Pharmaceutical agents such as DMSA and DMPS primarily mobilize mercury through the kidneys. Natural agents such as sulfur-rich foods, ascorbate, glutathione, alpha lipoic acid, and N-acetyl cysteine mobilize mercury, primarily through increased biliary excretion into the feces as well as some loss through urine and sweat.

Adequate intracellular levels of reduced glutathione during mercury detoxification are helpful. Intravenous or tissue-calibrated vitamin C is most effective as shown by Alton Meister, among others. We want to facilitate bile flow and avoid constipation, so toxic metals can be excreted in the feces. Thus adequate insoluble dietary fiber, adequate intake of ascorbate, and sufficient magnesium are each important.

With regard to seaweed-derived, alginate-binding mercury in the gut, a small clinical trial done by Quig showed absolutely no effect of sodium alginate in promoting the excretion of mercury. However, there is evidence in the literature that sodium alginate does promote the excretion of lead and strontium.

Intravenous vitamin C, at a dose of 50 grams in humans, resulted in a significant increase in the fecal excretion of mercury (400 %), and a 150 % increase in the excretion of lead, at 24 hours, when compared to the baseline. This is a reasonable alternative to pharmaceutical chelating agents.

Quig also did a study to test the claim that chlorella promotes the excretion of mercury. While chlorella has been used to spray the walls of caves, in order to pull the mercury out, no formal studies in humans have been reported. An informal chlorella study was performed at the Southwest College of Naturopathic Medicine. Medical students were used as subjects. They consumed no fish or seafood for five days prior to nor during the trial. Stool specimens were collected prior to supplementation and after three and seven days. The chlorella dose was 8-10 grams per day [N=8]. The results showed no effect of the high dose of chlorella on the fecal or urinary excretion of mercury. The side effects approached 100 %, and nearly every subject complained of gas, bloating, and diarrhea. The subjects did in fact have a greater than average intestinal mercury excretion. Each subject had from 8 to 10 amalgam fillings. Therefore, they should have had some mercury in their intestines.

Recent publications suggest that gene deletions of the glutathione S-transferases M1 and T1 are associated with thimerosal sensitization. A second publication suggests that glutathione S-transferases M1 gene deletion may also be associated with susceptibility to certain forms of schizophrenia. Therefore, it seems reasonable that a genetic defect in glutathione S transferases may predispose an individual to mercury sensitivity and/or toxicity. It remains to be determined if this is a genetic or pseudogenetic (xenobiotically acquired) condition.

Appendix 3A. Clinical protocol for Removal of Incompatible Dental Material (RID) *modified from* Dr. Anders Lindvall, Dept Clinical Metal Biology (DCMB), University Hospital, Uppsala, Sweden.

I. Patient referral from a 1º care office or hospital clinic
[after negative diagnostic for relevant diseases]
A. Contact with the patient by mail.
B. Pre-treatment questionnaire to be completed before admittance.
C. Written consent from the patient for history and prior data.

II. Requests hospital records + relevant health care data
e.g., dental records and X-ray

III. Visit with a doctor treatment facility

A. Case history and routine physical examination.

B. Determination of the time of onset of the disease, its characteristics over time, and its relationship in time, if any, with dental treatment and signs and symptoms of disease progression.

C. Evaluation of other circumstances that may be relevant, e.g. occupational exposure to allergens or toxins, possible side effects from drugs, allergies to common allergens including emissions from building materials, metal sensitization from ear rings, buttons etc.

IV. Visit with a dentist at DCMB:

A. Dental examination and oral status.

B. Summary of dental history with reference to X-ray examinations from other clinics.

C. Listing of materials in crowns, fillings, root canals, screws, posts, and dentures.

V. Blood examinations:

A. Patient fasting and peripheral venous blood
[samples drawn 8-10 AM without tourniquet]

B. Routine tests
1. Chem22,
2. sedimentation rate,
3. CBC with differential, platelet count, and size.

C. Trace elements (plasma, optional, by ICP-MS)

D. Toxic mineral hypersensitivity by LRA
[ELISA/ACT LRA or MELISA]

E. Lumbar puncture (CSF, optional)
[cell count, albumin ratio, protein electrophoresis, B12, homocysteine, methyl malonic acid, and trace elements]

VI. Revisit with the doctor
A. Information on test results
B. Treatment plan development
C. Patient education and plan implementation

VII. Removal/replacement of incompatible dental material (RID)
A. Prescription of antioxidants to protect during procedures
[Selenium, vitamin B-complex, C and E. . .]
B. Referral to co-operating dental clinic for RID procedures

VIII. Dental treatment if hypersensitivities are significant:
A. Revisit with the doctor to review treatment plan
B. Medical evaluation of patient-specific RID-measures needed
C. Analysis of type and severity of symptoms.
D. Suggested course of action.
E. IV-C [5-150 grams QD, BIT or TID as needed]
F. Patient written request for continued care

IX. Follow up contact, exam, tests, and questionnaire [12 months]
A. Evaluation of follow up-data and clinical status.
B. Information to the patient with suggested follow-up

X. Repeat follow-up annually as possible

XI. Closure of case

XII. Final verification of data before data bank entry

XIII. Check data entry into data bank.

Appendix 3B. The Health Studies Collegium Protocol for
• Toxic Mineral body burden and hypersensitivity determination by d-penicillamine provocation and by ELISA/ACT LRA Assays
• Safer clinical detoxification

1. **Evaluation of person for clinical signs or symptoms of toxic mineral adverse health effects**

2. **Written recommendation of diagnostic options (see Appendix 1)**

3. **Mail questionnaire and demographics to person for return within 7 days**
   N.B.: Contact patient on 8th day if forms not returned by then

4. **Person has videotaped informed consent discussion**

5. **Requests copies of all available records**
   - **medical office,**
   - **dental office x-rays and information about all materials used and dates of use,**
   - **hospital and/or**
   - **laboratory (s)**
   - **personal health diary(s)**

   that are relevant to the person's current situation.

6. **Visit with comprehensive care**
   - **physician**
   - **dentist**
   - **nurse practitioner / physician assistant**
   - **nutrition educator / community pharmacist**

7. **Case history to include:**
   - **time and context of onset of conditions,**
   - **character over time**
   - **relationship to dental procesured or other toxic exposures**
   - **occupational, hobby, and/or environmental exposures to toxic minerals and other immunotoxins**
   - **cosmetic and jewelry exposures**
   - **physical exam, and**
   - **initial battery of tests:**
     1. **SMAC with insulin, HDL, apolipoprotein A1, apolipoprotein B100**
     2. **CBC with differential and platelet size**
     3. **CRP or other inflammatory marker**
     4. **Provocative urine for toxic and nutritional minerals**
     5. **Antioxidant profile and homocysteine**

6. Hypersensitivity (ELISA/ACT LRA) tests for heavy metals (and other items as needed)

8. **Follow-up primary care visits at**
   - **One month**
   - **Three months**
   - **Six months**

   then as needed

   Note: Individual educational, acupuncture, nutritional and dental schedules vary.

9. **Enteral and parental nutrition, including special diet and supplementation protocols as needed**

Appendix 3C. Dr. Michael Godfrey's toxic metal protocol[59].

Diagnosis:

1. **History and clinical presentation**.
   - The physician has to have a high index of suspicion.
   - Patient fills out a 5-page questionnaire.
2. **Electro-dermal-skin-testing** (EDST) is used to help confirm Hg and other possible heavy metal problems and to assess bio-compatibility of proposed dental restorative materials. The MORA device is particularly useful in this regard, as it is able to invert the signal and thus test crude materials instead of just homeopathics. Accuracy is probably 80% +/- but much quicker, cheaper, non-invasive, and better than guessing. Otherwise, the patient is instructed on the most currently bio-compatible materials. At least EDST will determine whether there is any fluoride sensitivity and that the patient is thus potentially intolerant to all flouride-containing materials.
3. **Hair mineral assay**. Partly to determine the presence of any missed heavy metals and more importantly, to determine nutrient deficiencies, so that a personalized replacement program can be started.
4. **Provocative test**: 5ml DMPS IV to confirm Hg status. This is optional due to cost. However, this test may have future use especially in medico-legal claims. It is also useful as public relations; *i.e.* most of my patients are female and rely on their partner to pay their bills.

Treatment:

- **Amalgam removal**, preferably after a minimum of 10 days of supplementation. Done in quadrants, according to Huggins protocol with staggered sessions, i.e. none on a 7-day cycle e.g. Monday through Thurs – Tuesday through Friday, over 2 or more weeks. Ideally, all is completed within 4-6 weeks. Ideally, teeth need to be tested with dentimeter/amalgameter for +ve or -ve readings and the highest -ve quadrant removed first. There is little objective evidence to support this theory, but as Hal Huggins has observed, the benefits of sequential removal in many hundreds of patients, I follow his example. It makes no difference for the dentist who is removing all the amalgam in any case.

- **IV C (Ascorbate)** is strongly recommended during amalgam removal, typically at 25Gm to 40Gm . Ideally, ascorbate dose is 0.7G/Kgm body weight.

---

[59] Godfrey M. Dental Amalgam and Health Experience: Exploring Health Outcomes and Issues for People Medically Diagnosed with Mercury Poisoning. *Bulletin, No. 97* December, 1999, New Zealand Psychological Society.

- **Supplementation**: Oral mixed (buffered) ascorbates with bioflavonoids made up by a compounding pharmacist sweetened with stevia and tasting like orange juice. Dose: minimum 2 grams ascorbate powder in water twice a day, but increasing levels to bowel tolerance is recommended.

Supplements are continued for at least 3 months after all amalgam is out:

1. **Chlorella** may be given if the patient has read about it, but otherwise I stick to my "tried and true" program. Concerns have been raised about a possible source of traces of unwanted heavy metals from fumigation in transit. Since many commercial chlorella preparations are contaminated with mercury or other toxic metals, if this agent is used, a certified, toxic mineral-free source is recommended.
2. **Garlic**, **ginger and onions** are recommended as a good sources of sulphur.
3. **DMSA** is usually given in small doses, so as to minimize the risk of any adverse effects, *i.e.,* at 250 mg. twice a week for several months. The jury is still out regarding dosages. It appears that it may be best to give it in small frequent doses for at least a couple of days, with a break, and then another short course, rather than widely separate doses that could risk simply allowing some to come out of a safe storage depot and be redeposited into a target organ before it is excreted. Thus a Hg-toxic or sensitive person could be instructed to take 50 mg. over a 4-6 hour period. If tolerated, the dose may be increased to 100 mg. parenterally over 4-6 hours for 2-3 days, with a 4-day break, then repeating the sequence as needed.

Urine Hg levels could be monitored at intervals to assess progress. Analytically we are still 'flying by the seat of our pants' in New Zealand with regard to scientific monitoring, due, in large part to the additional costs. Most patients have little money, having frequently spent it all over the years in a futile search for help from numerous medical specialists who have done unhelpful tests, before saying that there is nothing wrong with their specialized bit of the body.

Homeopathics:

1. **Amalgam according to EDST,** but otherwise start with amalgam 6x 8 hourly for 2-3 weeks, combined with liver and kidney drainage. Follow according to EDST with 12x for 2-3 weeks. Then 30c if appropriate single dose continuing with drainage. Review in 3-4 weeks for possible repeat 30c before going to 100c single dose. Occasionally will need to have longer period at lower potencies *e.g.* 12x.
2. **Drainage remedies**. I use the Futureplex range: A5, E4or5, N1 (depending on EDST), together with other complex remedies "mix 'n match" with 1ml of each in a 30ml dropper bottle filled up with 40 proof alcohol. (I have an excellent source of 200 % absolute alcohol at $2/L from a dairy factory (made from whey) that I dilute down with filtered water).

3. Each **patient** is **treated individually** depending on response. However, some German MDs I know give their patients a regimented course at each amalgam potency for 2 weeks i.e. 6x, 8x, 10x, 12x, 15x, 30c, then 100c, 200c, IM as single remedies at monthly intervals. Homeopathic amalgam must **never** be given before amalgam removal as patient likely to be made much worse due to mobilization of Hg, whilst a large source is still present.

Homoeopathy is not easy but may be quite effective at removing the "resonance" of Hg, *etc*. The resonance of a toxic substance can be as bad as the crude substance. Bienveniste has shown that the resonance of caffeine, adrenaline, and nicotine can be "read" using EDST and then transmitted via e-mail, downloaded, and imprinted into water, which then has the same effect on living subjects as the real thing. His research was presented at Cambridge University in February, 1998 and various academic meetings since.

Dr. Michael Godfrey's protocol has been independently evaluated by Linda Jones of Massey University.

Appendix 4. Internet resources of interest

1. Mercury Websites: Illinois Department of Public Health and EPA: Mercury Spills
   http://www.idph.state.il.us/envhealth/factsheets/mercuryspills.htm
   http://www.idph.state.il.us/envhealth/factsheets/mercuryspills.htm
   http://www.epa.gov/grtlakes/bnsdocs/hgsbook/index.html
   http://www.epa.gov/grtlakes/bnsdocs/hgsbook/index.html

2. Wisconsin Mercury Sourcebook
   Information on some sources of mercury & their reduction / elimination in home, school, & workplace.
   http://www.mercury-k12.org/>http://www.mercury-k12.org/

3. Mercury in Schools; Focuses on mercury problems in schools
   http://www.ehs.berkeley.edu/pubs/flashpoint/6Spr96html/minmerc.html
   http://www.ehs.berkeley.edu/pubs/flashpoint/6Spr96html/minmerc.html

4. U of California-Berkeley fact sheet on why, due to high cleanup costs, minimizing mercury use is needed.
   http://www.epa.gov/pbt/hgaction.htm>http://www.epa.gov/pbt/hgaction.htm

5. USEPA action plan for mercury reduction.
   New Jersey Dept. of Health & Sr. Services Guide for the Safe Clean-up of Mercury Spills at Home
   http://www.state.nj.us/health/eoh/survweb/merchome.pdf

6. Controlling Metallic Mercury Exposure in the Workplace -- A Guide for Employers (2 parts)
   http://www.state.nj.us/health/eoh/survweb/mercpt1.pdf
   http://www.state.nj.us/health/eoh/survweb/mercpt2.pdf

7. Information for People Exposed to Mercury at Work, Home, and in the Community
   http://www.state.nj.us/health/eoh/survweb/mercury.htm

8. EPA - Mercury - Emergency Spill & Release Facts
   http://www.epa.gov/oerrpage/superfund/tools/merc/index.htm
9. Agency for Toxic Substances and Disease Registry Media Advisory: ATSDR MERCURY UPDATE
   http://www.atsdr.cdc.gov/press/ma990419.html

10. ATSDR - National Alert: A Warning About Continuing Patterns of Metallic Mercury Exposure
   http://www.atsdr.cdc.gov/alerts/970626.html

11. OSHA/NIOSH - OCCUPATIONAL SAFETY AND HEALTH GUIDELINE FOR MERCURY VAPOR
   http://www.osha-slc.gov/SLTC/healthguidelines/mercuryvapor/recognition.html

12. California - Hazard Evaluation System and Information Service - Mercury Fact Sheet
   http://www.ohb.org/merc.htm>http://www.ohb.org/merc.htm

13. Toxicity, Mercury by Barry Diner, M.D., Cornell University, New York Hospital and Barry Brenner, M.D., Ph.D., Department of Emergency Medicine, The Brooklyn Hospital Center
   http://www.emedicine.com/emerg/topic813.htm
14. MMWR, June 16, 1995 / 44(23);436-437,443. Mercury Exposure in a Residential Florida, 1994
   http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/00037313.htm

15. Mercury, elemental; CASRN 7439-97-6 (03/01/97) - EPA/IRIS Health assessment information
   http://www.epa.gov/iris/irisdat/0370.DAT

16. Mercury Poisoning Project - ritualistic use of mercury
   http://www.geocities.com/awendroff/