Proposed:

INTEGRATIVE/ENVIRONMENTAL MEDICINE STANDARD OF CARE GUIDELINES FOR INCREASED TOTAL BODY BURDEN OF TOXIC METALS

Edited by Robban Sica, MD

Endorsed in 2004 by the American Board of Clinical Metal Toxicology, the American Association of Environmental Medicine, and the International College of Integrative Medicine.

Living in an industrialized society exposes all inhabitants to metals in the environment.[1] Some minerals are toxic to life in all but the tiniest of amounts, including lead, mercury, arsenic, cadmium, nickel, and aluminum. The increasing rates of cancer, vascular disease, dementia, and other diseases are directly related to the increase of toxic metals and other chemicals in our environment, as chronic, even low-grade, environmental exposures raise the body burden.

With the industrialization of the world, the environmental amounts of toxic metals have markedly increased. Lead, arsenic, mercury, cadmium and other toxic metals have been known to have adverse biological effects on humans since ancient times. Over the years, the nervous system, vascular system, and the immune system have been shown to be adversely effected by toxic metals. The extent of the problem has just been brought into focus during the past decade. The United Nations and the World Health Organization are very concerned about the effect of toxic metals.[2] A recent article in the NEJM concluded that there is an inverse association between blood lead levels and IQ scores.[3] The chief author, Richard L. Canfield, Ph.D., stated in a subsequent interview, "There is no safe level of lead".

The USA National Science Foundation's Institute of Medicine recently stated in a meeting in Washington, D.C. that children vaccinated with thimerosal (ethyl-mercury) containing vaccines had a 27 Times (2,700%) greater chance to develop autism than those vaccinated with vaccines not containing the thimerosal.[4] The USA Environmental Protection Agency and the Food and Drug Administration have released guidelines for restricting fish consumption based on the mercury content.[5] [6] [7] Peer reviewed medical journals, such as the New England Journal of Medicine, the Journal of the American Medical Association and others, have published multiple recent articles about lead and mercury, even low levels, affecting the entire vascular system[8] [9], leading to hypertension[10] [11] [12] , stroke, heart attack[13], cardiomyopathy[14] and renal failure.[15] [16] [17] [18] [19] [20] [21] Other journals have shown lead and other heavy metals as a partial causation of macular degeneration as well as decreased intelligence, reading disability[22], gout, thyroid diseases, and other physiologic problems.[23] [24] [25] [26] [27] Archives of Internal Medicine published a 2002 study demonstrating that morbidity and mortality at all ages is directly influenced by lead levels.[28]

Mercury in both organic and inorganic forms is neurotoxic.[29] Mercury has been shown to be related to autism, Alzheimer's disease, and cancer. Metallic mercury[30] is readily converted under physiological conditions to substantially more toxic biologically active forms (e.g. methylmercury, dimethylmercury, mercuric sulfides and other mercurial compounds, etc.) and constitutes is a major public health risk[31]. Biologically active mercury is considered by Nriagu and colleagues to be the most toxic of all the toxic minerals[32]. Primary non-occupational 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 bio-concentration in fish and fowl, 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 'mine able ore' if only this dust could be trapped before it reaches the Southern United States and Caribbean Basin[33]. 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 potential to mercury, arsenic is a potent metabolic, hormonal, immune and gene toxin[34 35]. Primary sources of arsenic exposure in humans are water, food, arsenical biocides and therapeutics. In aggregate, exposures to total arsenicals pose a significant human health risk above levels at or below 1 part per billion (ppb)[36]. 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 life-time. Toxicologists 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 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 solutions are available. (Examples of this approach are given in the book *Natural Capitalism*[37] and the report of the Department of Consumer Affairs of the State of California, titled *Clean Your Room*[38].)

With regard to lead, the evidence base of pervasive sub-acute toxicities is stronger and reviewed elsewhere.[39] Cadmium and nickel are also potent toxicants with similar mechanisms of action to arsenic[40 41], including cardiovascular risk[42]. Cadmium has been accepted by the International Agency for Research on Cancer as a Category 1 human carcinogen. Determination of immunotoxicity from toxic minerals such as mercury and arsenic depends upon mechanisms that are still being elucidated[43]. Excess iron impairs nitric oxide action, causes free radical damage, and contributes to endothelial dysfunction in cardiovascular disease.[44 45 46]

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[47]. The direct disease care cost induced by toxic minerals are calculated to be in excess of $100 Billion annually (HCFA, 2000; Princeton University, 2001).[48] The public health risk from toxic minerals is yet greater due to suspected but not extensively defined or replicated synergies of mineral toxicities[49].

ASSESSMENT OF THE TOTAL BODY BURDEN OF TOXIC METALS:

Blood levels of heavy metals are not representative of tissue levels and frequently fail to identify significantly toxic tissue levels, i.e. levels that are causing tissue damage.[50] Determination of blood metal

levels does not accurately reflect total body retention, but rather is more useful for assessment of recent or ongoing **exposure**, per the Agency for Toxic Substances and Disease Registry (ATSDR).[51] For instance, the relationship between blood lead levels and the quantity of lead excreted after EDTA chelation is nonlinear in that arithmetic increases in blood lead are associated with **exponential** increases in lead excretion, and in adults with past exposure, the correlation between blood lead and chelatable lead is poor.[52] [53]

Determining the total body burden of any given toxic metal is not a straightforward matter, as tissues levels vary significantly[54] and many factors complicate the assessment of a given individual. For example, the pituitary is known to significantly concentrate toxic metals; brain, kidney, liver, lung, thyroid, and thymus tissue tested far higher levels than blood; and the adverse effects may only be revealed by long-term morbidity and mortality studies, such as the one published in Archives of Internal Medicine.[55] The assumption that serum levels correlate with body burden has been clearly recognized as erroneous.[56] [57] There is no single test that adequately determines the total body burden of toxic metals. Metals are detoxified via the skin, hair, finger and toenails, stool and urine. However, all tests for mineral excesses and deficiencies have their limitations, including hair, random urine collection, blood (serum or intracellular-red cell), and fecal testing.

Perhaps the optimal test of tissue burden currently available may be tissue biopsies of heart muscle, quadriceps muscle, liver, kidney, brain, and other organs, examined using x-ray florescence guided by electronic microscope to assess intracellular levels, or x-ray fluorescence of bones such as the patella. However, these tests are obviously impractical and not widely available.

Blood levels of toxic metals show only recent or ongoing exposure still remaining in the blood. Thirty days after exposure there is little evidence of any remaining toxic metal in the serum as it has been deposited to other tissues and partially excreted. Random urine tests for toxic metals show only what is being detoxified via the kidneys from serum. Intracellular (red blood cell) mineral analysis is one form of a "tissue" analysis but is also most significant for recent exposure (four to six months about 63 days for Me-Hg). Hair analysis for toxic metals, while controversial, has been widely accepted and validated for epidemiological studies by the World Health Organization and the EPA[58] as being extremely useful and cost effective for identifying toxic metal *exposures* (when performed by laboratories with the appropriate expertise and quality control). Any of these tests may be used for screening, with the awareness that false negatives are common, in that other tissues may contain toxic levels not present in the sample screened. These samples should be carefully collected and processed according to the instructions provided by the laboratory running the test, especially urine specimens since the volatility of mercury, for instance, can lead to a false negative if not properly handled.

The most valid, readily available test to show the total body burden of toxic metals is the provoked urine test, where urine is collected and analyzed following administration of EDTA[59] [60] [61]or other chelating agents[62] [63]. (See Appendix 1) However, even a properly performed provoked urine specimen can significantly under-estimate the adverse effects on various individual tissues and or organs in the body. Measured levels may increase following several treatments with chelating agents, indicating mobilization of tissue stores of heavy metals. An unpublished study demonstrated an average 147-fold increase over baseline lead excretion in healthy individuals receiving 3 gm of Ca EDTA.[64]

As demonstrated, heavy metals can cause cellular damage and disease even in very small amounts. Given the growing evidence of correlation between heavy metal burden and disease states, **<u>any</u>** test showing heavy metals deserves to be treated, if only for preventative purposes. Ideal level of heavy metals in human tissue is zero, if we are to prevent the development of chronic illness. Arbitrary threshold values to define "toxic" level proposed by conventional occupational medicine are not useful and may be harmful if the

patient is left untreated. For example, urinary levels of mercury up to 50 ug/gm creatinine are considered to be within the "normal" range[65], despite the fact that neurological impairment has been reported for occupationally exposed subjects who had urinary mercury levels well below the W.H.O. standard. [66] [67]

Over the years, the recommended "reportable" blood levels for lead have been reduced repeatedly. As recently as 1990, the Connecticut Department of Health Services considered 25 mcg/dl as the "reportable" level[68]. While the CDC currently considers greater than 10 mcg/dl as a level of concern, it is commonly acknowledged that "lead can have neurological and other negative effects on health at much lower levels of exposure."[69] [70] However, the principle that there are no safe levels of environmental toxins such as heavy metals is becoming more widely accepted.[71] For instance, the NEJM study cited above[72], which examined the effects on IQ of low levels of lead, caused the chief investigator to come to the conclusion that there is NO SAFE LEVEL OF LEAD. A manuscript published in The Archives of Internal Medicine concludes that patients with lower levels of lead live longer with less morbidity and mortality from ALL diseases.[73] Bruce Fowler, PhD commented in a recent lecture [74] that the average American has a serum lead level of 3 mcg/dl. Longer-term studies have demonstrated the persistence of lead in the body over many years[75] and that "exposure to lead in childhood is associated with deficits in central nervous system functioning that persist into young adulthood."[76] Furthermore, synergistic effects of heavy metal combinations could be more damaging than a single toxin. [77]

One of the basic principles of integrative and environmental medicine is that every patient is unique, biochemically, genetically, and physiologically. Individual tolerance to a given level of a toxic metal varies considerably, based on presence of other antagonistic metals and chemicals, and genetically determined detoxification capabilities.[78] Some individuals may be more susceptible to toxic effects of a heavy metal or other chemical than others, for example: patients with autism, multiple chemical sensitivity, chronic fatigue syndrome, genetic deficiency of glutathione production, aberrant homocysteine metabolism, and other genomic variations. For example, impaired glutathione synthetase activity due to a DNA translational error would impair detoxification competence for toxic minerals like mercury and arsenic.[79] Acquired susceptibility, for example, impaired glutathione synthetase activity due to a RNA transcriptional error from haptenic binding and distortion of the mRNA complex or due to impaired and disordered protein synthesis due to low ATP production in the cellular mitochondria would have similar adverse effects[80]. When zinc, selenomethionine, and magnesium are marginal or deficient, metallothionein loses functionality[81]. 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 a vaccine injection with thimerosal (which typically contains 50-75 µg of mercury).[82] These individuals are not protected and are at relatively high risk. These individuals will most likely be symptomatic and require treatment at lower levels of toxic metals than a healthy individual.

METAL TOXICOLOGY AND TREATMENT:

The Environmental Protection Agency[83], the Centers for Disease Control's Agency for Toxic Substances and Disease Registry (ATSDR)[84], OSHA/NIOSH[85], and more recently the National Institutes of Health[86] have been tracking various aspects of metal toxicology and have issued alerts regarding toxicity of various metals and occupational safety and health guidelines. Under pressure from the international community and new scientific knowledge, such as preventing dialysis for a minimum of two years by repeated intravenous lead detoxification[87], the realization that low doses of toxic metals leading to an increased body burden[88] are a significant contributing cause of many disease states is finally becoming recognized.

Patient Selection for use of chelating agents:

While some cases clearly qualify for the diagnosis of heavy metal toxicity from the viewpoint of history, occupation, signs and symptoms, and lab data, integrative physicians should consider treatment for patients when, in their professional judgment, the level of heavy metal found utilizing any of the tests discussed reveals a greater level of toxic metal(s) than is in the best interest of their patient.

Integrative physicians may also base their clinical decisions on the patient's stated health goals, which may vary from increasing longevity[89] to improved cognitive and physical impairment to the prevention of heart and other diseases. A well-educated patient, knowledgeable about the dangers of heavy metal toxicity and the increased, unavoidable exposures in our modern society is certainly within their rights to request and receive assessment for heavy metals and treatment with chelating agents as a preventive measure. (This is analogous to plastic surgeons who undertake invasive surgical procedures at the request of their patients.)

From a preventive standpoint, there are no safe levels of heavy metals.[90] Since patients with lower levels of lead live longer with less morbidity and mortality from all diseases[91], to achieve our goals of preventing disease we should consider lowering the body burden of heavy metals in all patients. Swiss researchers found a marked decrease in cancer incidence in patients who had received chelation therapy.[92] Authors of the 1995 study on lead and reading disability concluded that "chelation of the 1.4% of the United States preschoolers whose blood lead levels are 2.21 mumol/L (25 mcg/dL) or higher could prevent more than 45,000 cases of reading disability and save more than $900 million per year in overall costs when the costs of remedial education are considered."[93] Belgian scientists confirmed that aluminum and iron accumulate in the brain with aging and recommend long term chelation to prevent and treat a number of aging-related neurodegenerative diseases.[94]

The issue then is to identify those in the population where more aggressive treatment is needed and warranted. The physician should have a high index of suspicion. Certainly any patient with any of the symptoms of intoxication (a partial list in Appendix 3) with heavy metals deserves a provoked urine test and treatment, if indicated. The mounting evidence of the connection between cardiovascular, renal, hypertensive, and neurological disease and heavy metal body burden also justifies testing and treatment of heavy metal toxicity in patients suffering from any of these conditions.

PATIENT EDUCATION: MITIGATION AND ABATEMENT OF EXPOSURES

As integrative and environmental physicians, we should ideally educate ALL patients in our practices about the issues and dangers of heavy metal toxicity and chemical exposures as a preventive strategy. This includes, but is not limited to:

- recommendations for air and water filtrations systems
- drinking bottled water
- eating organic foods whenever possible
- reducing fish intake, using only purified fish oil supplements
- using integrated pest management and natural lawn care instead of pesticides around the home
- replacement/avoidance of new of silver amalgam dental fillings[95] [96]
- avoidance of thimerosal containing immunizations, including flu vaccine
- minimizing exposure to common sources of toxins from the environment, work place, hobbies

Parents should be counseled to ask their pediatricians for thimerosal-free vaccines for their children. Furthermore, patient educational materials (such as Appendix 3) should be distributed to all patients but especially given to and discussed with any patient who has been diagnosed with elevated levels of heavy

metals and all patients who may have occupational exposure or any signs or symptoms of heavy metal toxicity. For environmental testing of air, water, or soil, the patient should be referred to environmental testing services and environmental consultants for abatement of household exposures. For current occupational exposures, the employer (and possibly OSHA or the EPA) should be notified and abatement measures requested. If these measures cannot be accomplished, the patient may need to find alternative employment to halt ongoing exposures. Patients with mercury toxicity should be referred to an appropriately trained dentist for amalgam removal and replacement with safer dental materials. 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 composed mostly of patients who had improper or premature amalgam removal[97].)

TREATMENT WITH CHELATING AGENTS:

In order to lower body burden, treatment must be aimed at increasing output, once the individual is in a homeostatically balanced lifestyle, that is, has eliminated or reduced exposures where possible. In addition, change in diet and, if necessary, supplementation of certain nutrients and foods that are synergistically helpful in reducing body burdens of toxic minerals, including mercury and arsenic. (Sample Protocols for the use of chelating agents AND nutritional supplementation to reduce body burdens of are included in Appendix 2.)

The decision of which chelating agent to use for a particular patient ultimately must be made by the treating physician, in accordance with his or her determination as to which approach is best suited to that patient. There are several factors that are important to consider in the selection of which treatment agent[98] to prescribe:

1. affinity of the chelating agent for the specific metal(s)
2. nutritional status, particularly regarding amino acids and essential minerals
3. condition of the patient and ability to tolerate treatment
4. allergies to medication
5. co-morbidity
6. clinical response

Confirmatory, repeat testing is encouraged at 3-6 months intervals, following the initiation of therapy. It is not unusual for the levels of toxic metals to increase from the initial test as body stores are mobilized. Often, additional toxic metals will appear in urine as the major source of toxicity is removed and metals of lesser affinity are chelated and excreted. Essential nutritional mineral deficits may be revealed and need to be addressed. It is cost effective to engage these elements of comprehensive and integrative care. Reduction in morbidity can be linked to the reduction of biologically active toxic minerals and the enhancement of antioxidant stores in the patient.

HOW LONG IS TREATMENT NECESSARY?

Treatment is recommended until the levels of toxic metals have dropped below the reference range level and the patient has become asymptomatic. Therefore, testing should be repeated every 6-12 months for 1-3 years in order to capture any re-poisoning of the tissues. Total elimination of ALL lead from the body is not necessary (or maybe even possible) to see clinical benefits, however, preventively a strong case can be made for the greatest possible reduction of body burden of toxic metals, given the documented adverse health effects.

Years ago, Harvard researcher Harriet Hardy published studies that demonstrated that ulnar nerve paralysis that had been present for years in a lead worker responded within weeks to chelation. However, published studies in the American Journal of Kidney Disease [99] has shown that the major STORES of lead are in bone[100] and that EDTA does not begin to significantly lower bone lead level unless chelation is continued long enough for total bone remodeling to occur, that is 7 or more years in younger people and longer in the elderly. If the extra cellular fluid and plasma levels of virtually any toxic metal are kept low enough for a long enough time, all tissues, including brain cells will have a greater likelihood to significantly download their toxic levels of all metals. This article also comments that chelation agents do not have access to total bone lead deposits and the skeleton remains a source for re-poisoning the other tissues. Therefore, even in patients whose urine lead levels drop to zero following treatment, lead can redistribute to soft tissues from bone. Such patients therefore need monitoring and possibly treatment for several years.

INTEGRATIVE MEDICINE:

Since David Eisenberg's original article in the New England Journal of Medicine [101] documenting the number of patients seeking Complementary and Alternative Medicine (CAM) practices[102], huge changes have and are occurring in medicine. Over two thirds of the medical schools now have some introductory courses to CAM and many now refer to the integration of the best of traditional and non-traditional medicine as Integrative Medicine. While occupational medicine has focused on acute exposures to heavy metals particularly in occupational settings, environmental medicine's emphasis has been on the chronic low-level exposure to and RETENTION of metals which can lead to chronic disease, appreciating the increasing environmental load of these toxins.

The Institute of Medicine in a report entitled, "Crossing the Quality Chasm: A New Health Care System for the 21st Century", dated Apr., 2001, stated that the current health care system must be replaced and that CAM as well as **prevention** must be part of the new system. It also stated that safety, effectiveness, patient centeredness, efficiency, timeliness of care, and the equality of delivery of care must be part of the evolution into the new system.

Appendix 1: [103]

PROTOCOL FOR DETERMINING MINERAL STATUS BY PROVOCATION OF URINE EXCRETION WITH CHELATING AGENT OR AGENTS[104]

Purpose: Determine the body's burden of mobilizable, potentially toxic minerals. Nutritional divalent mineral status may also be assessed, if desired.

Compounds such as dimercaptosuccinic acid (DMSA), dimethylpropionylsulfide (DMPS), d-Penicillamine (D-Pen), and ethylene diamine diacetic acid (EDTA)[105] are examples of mineral binding or chelating compounds that may be used for provocative testing. 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 metal-binding agents for either provocation or treatment have recently been proposed based on clinical experience.

SAMPLE IV PROTOCOL FOR PROVOKED URINE TEST:[106]

Method:

1. Collect a 24º urine sample or a spot collection prior to administering chelating agent to determine baseline values, to provide information about recent exposure versus net retention. (Optional but has become recommended more often in recent years. especially important if arsenic toxicity is suspected. For example, urinary arsenic as high as 1500mcg/gm creatinine for an individual who consumed a large amount of shellfish within 48 hrs. of the urine collection. Arsenobetaine and arsenocholine, from shellfish, are rather nontoxic and readily excreted.)
2. Have the patient void before starting the IV.
3. Administer one of the following intravenous chelating agents:
    a. DMPS is administered at 3 mg/Kg with a maximum of 250 milligrams given as a 15 to 20 minute slow IV push.[107]
    b. DMPS followed by a 3 hour infusion of 1.5 grams of EDTA to facilitate heavy metal provocation. Note: Do not mix other chelating agents with DMPS in the same injection.
    c. There are clinical reports of enhanced mercury mobilization when 0.5 grams of l-glutathione is infused as a bolus just prior to the DMPS infusion. DMPS may also be preceded by an infusion of ascorbic acid 10-25 gm over 1 hour.
    d. EDTA 3 hour infusion of 3.0 grams according to ABCMT protocol (with ascorbic acid**).**
4. Collect either 24 hour urine sample or a 6 hour urine sample, beginning with the next voided sample, collecting all urine for the designated time period.
5. Keep the sample refrigerated, process according to laboratory instructions, and send to the laboratory for analysis. Due to the short half-life of both DMPS and EDTA in the body, a six hour collection will capture 95% of the excreted chelated metals and has better patient compliance.

SAMPLE ORAL PROTOCOL FOR PROVOKED URINE TEST

Method:

1. Collect a 24º or spot urine sample prior to administering chelating agent to determine baseline values. (Optional; see above.)
2. Do not use oral vitamins and mineral supplementation during the day(s) the patient is taking chelating agents.
3. Administer one of the following chelating agents:

a. Administer 20-30 mg DMSA/kg body weight on an empty stomach as a single oral bolus dose. It is important to test for acute reaction with about 100 mg DMSA prior to such a challenge.
b. DMPS 300 mg as a single oral bolus dose.[108]
c. A short 3-day course of d-penicillamine or Acetyl-d-penicillamine is prescribed. For a typical 70 Kg adult, based on 30 mg/Kg body weight, prescribe d-penicillamine or N-Acetyl-d-penicillamine 500 mg. (Two 250 mg capsules) with each meal and before bed (total of 2 grams each day) for <u>just</u> three days. If weight is under 100 pounds or over 300 pounds, calculation of dose is recommended. For a 100-pound adult weighing 45.5 Kg., a daily dose of 1,590 mg. (~1,500 mg.) is recommended. This would most easily be achieved by giving two 250 mg. capsules with breakfast, dinner, and at bedtime. By comparison, a 350-pound person weighs 160 Kg. At 30 mg/Kg, this calculates to a daily dose of 4,800 mg. (~4,750 mg.), requiring five 250 mg. capsules with each of three meals plus four 250 mg. capsules at bedtime.

4. Collect a urine specimen for analysis:
    a. 6 hour for DMSA or DMPS.
    b. 24 hour for D-penicillamine on the 2nd day.
        i. Beginning with the second morning urine, collect in a heavy metal-free container (usually provided by the doctor or the laboratory) all urine output for the next day including the first morning urine on the next day (a full 24-hour cycle).
    c. It is 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. Keep the urine refrigerated during the collection period.
    d. 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 *indirectly estimated* in this way. **Note:** If d-Penicillamine is used, third-day collection may not be as comparable with the standardized second-day collection results.
    e. 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.

Appendix 2:

The average physician has little or no training or experience in the use of chelating agents. The American Board of Clinical Metal Toxicology, or ABCMT (originally founded in 1982 as the American Board of Chelation Therapy), and its sister organization the International Board of Clinical Metal Toxicology, have provided training programs and tested the knowledge and competence of physicians to identify metal toxicological effects on health and to safely detoxify metals in the clinical setting.[109] Over the last forty years, these physicians have documented the marked clinical relief of symptoms in these patients following the clinical metal detoxification, utilizing the protocols outlined.[110]

BACKGROUND AND SAMPLE PROTOCOLS FOR USE OF CHELATING AGENTS:[111] [112]

EDTA

EDTA (ethylene diamine tetra acetic acid)[113] is a poly amine carboxylic acid, originally developed for industrial uses to keep metal ions such as calcium or magnesium from interfering with chemical processes. Its use as a treatment for heavy metal toxicity was discovered in the 1950's. EDTA forms stable chelate complexes with a wide range of metal ions. While the FDA has approved EDTA for treatment of lead toxicity, EDTA is useful for the chelation of other toxic metals as well.[114] EDTA's affinity for calcium is relatively low, yet the FDA has also approved EDTA for treatment of hypercalcemia as well as ventricular arrhythmias associated with digitalis toxicity. It is perfectly acceptable for physicians to use approved medications for off-label use. "The FDA has also recognized that the FD&C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may choose to prescribe it for uses or in treatment regimens or patient populations that are not included in the approved labeling. The FDA also observes that accepted medical practice includes drug use that is not in the approved labeling."[115]

There is significant scientific evidence and many anecdotal reports that indicate that intravenous EDTA might be effective for treating and preventing cardio-vascular diseases[116] [117] [118] [119] [120] [121] [122] [123] as well as other diseases.[124] [125] Several possible mechanisms for cardiovascular improvement post-chelation therapy that postulated,[126] including reduction in free radical activity[127] by EDTA directly or as a result of reduction of iron, lead and other heavy metals that cause free radical damage to the endothelium.[128] [129] [130] [131] [132] [133] [134]

ABCMT Treatment Protocol:
ABCMT has been working with the leading organizations supporting CAM since its inception, including The National Institutes of Health that now houses the National Center for Complementary and Alternative Medicine. One of NCCAM's key current research projects is the Trial to Assess Chelation Therapy (TACT) which is studying chelation therapy for recent myocardial infarctions.[135] The National Institutes of Health and several institutional review boards have determined that it is safe to use intravenous EDTA for the treatment of circulatory problems, according to this protocol[136], and does not cause renal toxicity.

A standard basic protocol[137], administered over 1.5 to 3 hours, consists of:

Sterile water	250-500cc
Na2 EDTA	1.5 - 3 grams*
Magnesium (chloride or sulfate)	2 grams
Heparin	2500 -5000 iu
Ascorbate	7 - 10 grams
potassium chloride	2-5 meq

Pyridoxine	100 -250 mg**
Thiamine	100 mg**
Sodium bicarbonate	840 mg
Pantothenic acid	250 mg**

The protocol may be adjusted according to the patient circumstances. For instance, some physicians choose to add a small dose of procaine 100 mg or lidocaine 2% to minimize burning at the infusion site. The osmolarity of this solution is iso-osmolar to slightly hyper-osmolar. Osmolarity should be recalculated if the protocol is significantly altered.

*While this is the dose most often used, the dose of EDTA for a given patient can be determined by as follows:

- 50 mg/kg lean body weight times (creatinine clearance/100).
- Creatinine Clearance may be calculated by the Modified Cockroft-Gault Equation:
  Creatinine Clearance (ml/min) = (140 – age in years) /serum creatinine (mg/dl)
- Lean Body mass is calculated as:
  Males: 50 kg plus 2.3 kg for each inch of height over 5 feet.
  Females: 45.5 kg plus 2.3 kg for each inch of height over 5 feet.

**B complex 1 cc may be substituted and B 12 1 cc may be added.

DMPS:

DMPS (2,3 DiMercaptopropane-l-sulfonic acid; Dimaval; DMPS-Heyl) is a chelating agent from the group of vicinal dithiols. It is in the same chemical family as: DMSA (Dimercaptosuccinic acid) and BAL (Dimercaptovaline; British Anti-Lewisite). Synthesized in Russia in the mid 1950s, it has been extensively use there and throughout Europe in the treatment of acute and chronic, sub-clinical heavy metal toxicity. Heyltex Corporation, the German maker of DMPS, filed an IND in the United States that was subsequently withdrawn, leaving the status of DMPS ambiguous. DMPS is approved for human use in Europe and it has long been on the FDA's 'bulk compounding list', making it legal for use through compounding pharmacies.

DMPS shows low toxicity and is generally well tolerated. Most adverse reactions are allergic. These can include itching, nausea, dizziness, fever, weakness, fatigue, and rashes ± urticaria, possible leucopenia and transient elevation in liver enzymes (transaminases).[138] Periodic evaluation of liver enzyme levels is suggested during prolonged treatment. Pretreatment with vitamin B12 1,000 mcg IM reduces these effects, particularly rashes at the injection site. Four cases of Stevens-Johnson syndrome have been reported; anaphylaxis is not known.

Treatment Protocol:

1. Parenteral Administration:
   a. Parenteral administration is 3 mg/Kg (maximum of 250 mg) slow IV push. DMPS is available in 5 cc vials of 50 mg/cc.
   b. DMPS is the preferred mercury provocative agent by many clinicians.
   c. Since DMPS does enter saliva, there has been some concern about 'pulling' mercury from existing oral amalgams; however, it is general clinical experience that DMPS infusions can be safely administered regardless of the amalgam status of the individual.

d. To treat chronic metal toxicity, DMPS is usually administered every two to four weeks at the calculated dose. Frequency depends upon the individual's over-all health and the amount of metal mobilized in the challenge specimen.
e. To enhanced metal mobilization and improve reactivity of DMPS, l-glutathione 0.5 gm can be mixed with the DMPS infusion. In sensitive patients, DMPS may also be preceded by an infusion of ascorbic acid 10-25 gm over 1 hour, which may reduce fatigue from the metal mobilization.
f. Alternatively, in accordance with the pharmacokinetic data, DMPS may be administered orally, as recommended by HeylTech, using 100-200 mg DMPS three times per day for 3-5 days with about 7-10 days between treatment cycles.

2. Oral Administration:
    a. Oral uptake of DMPS is typically 40-60% of the given dose.
    b. Oral doses are 2.5-3.5 times those for parenteral administration (7.5-10 mg/Kg) for challenge purposes.
3. DMPS does bind avidly to zinc and copper. Patients treated with DMPS should be appropriately supplemented with zinc and copper to avoid acquired deficiencies.

DMSA:

DMSA (Dimercaptosuccinic acid, Chemet™, Captomer™, succimer) is a metal-complexing DMSA is not a true chelator by definition:does't form a cyclic ring around the entrapped metal] agent from the group of vicinal dithiols. It is in the same chemical family as: DMPS (2,3 DiMercaptopropane-l-sulfonic acid; Dimaval; DMPS-Heyl) and BAL (Dimercaptovaline; British Anti-Lewisite). It has been used since the 1950's as an antidote for lead poisoning. DMSA has been approved by the FDA for lead toxicity in children, however, with similar affinities to DMPS, it is a useful detoxification agent for other heavy metals as well, especially methylmercury.[139] Administered orally, DMSA mobilizes mercury and lead from soft tissues stores[140] [141] and may be necessary to use following DMPS or EDTA in order to remove toxic levels from these compartments.

Treatment Protocol:

1. The dose of DMSA is calculated at the rate of 10 mg/kg per day.
2. Intermittent Administration: Give DMSA at the rate of 10 mg/kg per day for three (3) consecutive days in three (3) divided doses. For the average adult, this dose is 200 mg three times a day.
    a. Do not use oral vitamins and mineral supplementation during the days the patient takes DMSA.
    b. Give oral vitamin and mineral supplementation during the next 11 days between DMSA cycles, especially molybdenum, zinc, and copper which may be depleted.
3. An alternative protocol is to give 100 to 500 mg (depending on body weight and condition) every 2 to 3 days qhs. This is especially useful if a patient gets too fatigued by the three day protocol. Small frequent doses, rather than widely separate doses is preferable to prevent metal redistribution.
    a. For a very sensitive patient, 50 mg. over a 4-6 hour period for a couple of days followed by a break may be better tolerated.
4. Complete 8 to 12 weeks of treatment (or 5 to 10 cycles) and then re-test the urine, using the same chelating agent previously used, in order to best compare results.
5. Repeat treatment if there is still significant toxic metal in a provoke urine sample.
6. If DMSA is compounded, it is optimal to 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.

D-PENICILLAMINE

D-Penicillamine (Cupramine™, D-Pen™, dimethylcysteine, mercaptovaline) was found to bind copper in the urine of patients with Wilson's disease[142] for which it has remained the treatment of choice for almost half a century. Walsh has reported the safe and successful use of d-penicillamine in pregnant women, infants, the elderly and the infirm. In animal studies, lead in bone seems to be effectively mobilized by d-penicillamine than lead in soft tissues[143] [144]. Clinical benefits of d-penicillamine are described by Sachs[145] *et al* and Vitale[146] *et al* yet not by Marcus[147] (who administered d-penicillamine while the study subjects continued to live in lead exposed environments, stressing the importance of mitigation of environmental exposures). Penicillamine also mobilizes and facilitates excretion of toxic minerals[148] including mercury[149],[150],[151],[152],[153],[154],[155],[156] arsenic[157], [158], [159], [160], [161], [162] cadmium[163],[164],[165] and nickel[166]. While inconsistent reports of efficacy have been published, these may reflect lack of attention to sufficient reducing substance (ascorbate) to enhance toxic mineral mobilization and excretion while maintaining the more effective reduced form of d-penicillamine, rather than the disulfide form. An additional factor that reduces toxic mineral mobilization is metabolic cellular acidosis. Correction of magnesium buffering deficit aids directly (by displacement) and indirectly (by correcting cellular acidosis) enhanced toxic mineral mobilization.

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/kg per day and may respond to a decrease in dosage[167].

When given daily and for prolonged periods (not recommended) adverse blood and skin effects seem to be idiosyncratic hypersensitivity reactions and are not dose related. Reversible leukopenia or mild thrombocytopenia is reported in less than 10% of children in one study[168], but not with similar dosages in two other larger series[169]. This may have resulted from interaction between d-penicillamine and pyridoxine (B-6)[170]. Supplemental B-6 is now routinely recommended as part of d-penicillamine *therapy* (not necessary for provocation protocol). Eosinophilia has been noted in one-fifth of children treated daily for an extended duration[171]. Angioedema, urticaria, or maculopapular eruptions that require discontinuation of drug therapy are reported at a rate of 0.5-1%[172]. Still less commonly reported reactions are proteinuria, microscopic hematuria, and urinary incontinence[173]. 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 likely when it is given in the pulsed manner recommended here.

Treatment Protocol:

The recommended dose and duration of therapy with d-penicillamine have been empirically derived.

1. Doses have ranged from 100 mg/kg per day in earlier studies to 20 to 40 mg/kg per day, more recently. Far fewer side effects are reported at the lower dosage range and with pulsed therapy.
2. For reducing body burden of heavy metals, pulse therapy with d-penicillamine is recommended. For most adults, the dose (30 mg/kg/d) calculates to 500 mg 4 times a day, given twice a week (e.g., Monday and Thursday)
3. Give supplemental calcium, magnesium, and zinc particularly on the non-penicillamine days to replace these minerals.
4. Continue treatment for 4 to 12 weeks, then repeat provoked urine toxic test.

ADDITIONAL RECOMMENDATIONS TO ENHANCE CHELATION FOR HEAVY METALS:[174]

1. 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 should be followed by a systematic program with enhanced dietary intake of foods such as garlic, onions and/or garlic that block uptake and bind (thereby detoxifying) toxic minerals.
2. Nutritional supplementation may be given orally or intravenously, as indicated by the above treatment protocols and the following recommendations and the nutritional status of the patient. Certain nutrients facilitate heavy metal excretion, such as ascorbate[175], r-GSH and other antioxidants including taurine, ALA, N-AC and melatonin, by improving the redox state of a chronically oxidatively stressed cell and enabling normal endogenous detoxification mechanisms.
    a. Free sulfur compounds serves as a back-up system that reduces toxicity of mercury and other heavy metals.[176] Biologically active sulfur compounds include:
        i. Reduced glutathione and related sulfur compounds, such as cysteine, cystine (found in undenatured whey protein), N-acetyl-cysteine, allicin (from garlic), allyproylsulfides, and allyallysulfides.
            1. Caution is indicated with regards to N-acetyl cysteine supplementation. Studies on rats demonstrated increased glutathione levels by 75%, increased urinary methylmercury 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. There is no effect of N-acetyl-l-cysteine in promoting the excretion of inorganic mercury.
            2. A safer, more effective option is undenatured whey protein containing large amount of cystine, which crosses the blood brain barrier in that inert (relative to metal binding) form and is cleaved to cysteine in the brain, thereby raising levels of glutathione.)[177]
        ii. Chelating agents, d-Penicillamine and N-acetyl-d-Penicillamine, are also sulfur based compounds.
        iii. Sulfur derived from ginger, garlic, and onions. Brassica vegetables such as broccoli and eggs are additional sources of biologically active sulfur all of which help to enhance mercury and toxic minerals binding and excretion.
        iv. Lipoic acid (alpha lipoic acid, ALA, thioctic acid) is an oxidized disulfide molecule, similar to DMSA. The utility of ALA lies in the fact that it is fat loving. Thus ALA can get into hydrophobic protein pockets and does bind to inorganic mercury. It does, however, have the potential of causing redistribution and enhancing the movement of mercury into the brain. (While one study by Gregus *et.al.* showed an immediate or marked increase in the biliary excretion of mercury with a concomitant marked decrease in the biliary excretion of methylmercury, copper, and cadmium and they found 77 % increased mercury in the heart, ~200 % in the brain, and a plasma copper increase of almost 400 %.) 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. When selenium, ascorbate and glutathione other innate detoxifying agents are marginal or deficient, compounds with an available sulfur become preferred by mercury or other toxic mineral. 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. Supplementation with MSM or other sulfur compound can prevent the destruction of sulfhydryls needed for detoxification.

b. Therapeutic doses of antioxidants are beneficial to prevent oxidative damage from mobilized heavy metals. This includes:
    i. Supplementation with buffered ascorbate (vitamin C) to tissue and cell sufficiency ('saturation').
        1. Oral dose can be based on ascorbate calibration to determine physiological ascorbate need[178].
        2. 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 baseline.[179]
    ii. Flavonoid / flavanol combinations (such as quercetin dihydrate and OPC) potentiate the benefits of buffered ascorbate.
    iii. Natural vitamins E (mixed tocopherols) 400-600 IU/day with tocotrienols
c. Omega 3 essential fatty acids, especially DHA and CLA, purified to remove mercury and fat soluble toxins
d. A balanced, high-potency, high-activity B complex including PABA
e. Trace Minerals: A comprehensive mineral supplement is recommended since mineral deficits are pervasive in the population.
    i. Bioavailable magnesium, selenium, and zinc sources. Healthy people increase their selenium in proportion to mercury. This allows for the formation of a covalent bond between mercury and selenium (mercuric selenide).
    ii. Adequate Zinc is critical to formation of functional metallothionein molecules.
    iii. 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. Selenomethionine is the most active mineral form for combining with and inactivating toxic minerals.
    iv. Minerals such as potassium, calcium, magnesium, and zinc as ascorbate, aspartate, citrates, glycinate, malate, fumarate, and succinate or other fully soluble mineral salts displace the toxic minerals and replace minerals excreted by chelating agents.
    v. Magnesium deficit, as the second most prevalent mineral inside mammalian cells, is a major contributor to cellular acidosis[180] and must be prevented.

3. Dietary Recommendations:
    a. An alkalinizing diet is recommended as to correct correcting cellular acidosis, thereby enhancing toxic mineral mobilization. A high-fiber diet with 80% of food intake that is alkaline-forming when metabolized. Check first morning urine pH to assess net acid excess (NAE) and clinically evaluate metabolic acidosis.
    b. Increased insoluble dietary fiber: To facilitate bile flow and avoid constipation, so toxic metals can be excreted in the feces. (Adequate intake of ascorbate and sufficient magnesium are also important.)
    c. Adequate herbal tea, mineral water, or spring water (eight ounce glasses each day) helps to 'wash out' these toxins.
    d. Increased intake of Sulfhydryl-rich foods such as garlic, ginger, and onions; eggs; and brassica vegetables (*e.g.*, broccoli, cabbage, etc.), fresh ginger tea.
    e. Chlorophyl-rich food such as chlorella, sodium alginate, and alfalfa have been promoted as chelating agents. However, informal studies done by Quig at the Southwest College of Naturopathic Medicine failed to show any positive effect of chlorella or sodium alginate on urine or fecal excretion of mercury.

Appendix 3:

Example of an Ideal Integrative Evaluation and Treatment Program of Patients for clinical signs, symptoms, or adverse health effects of toxic metals[181]

1. History and clinical presentation.
    a. Questionnaire to be completed before initial visit. Ask patient to include copies of any personal health diary(s)
    b. Case history to include:
        i. Time and context of onset of conditions, character over time
        ii. Relationship to dental procedure or other toxic exposures
        iii. Occupational, hobby, and/or environmental exposures to toxic minerals and immuno-toxins, including cosmetic and jewelry exposures
        iv. 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, etc. However,
            1. Many people have an excess of heavy metals without an obvious exposure
            2. Some people are much more sensitive to lower levels of heavy metals than others
        v. Diet evaluation
    c. Written consent from the patient to obtain 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 reports that are relevant to the person's current situation.
    d. Comprehensive Office Visit with physician (including physical exam with attention to dental work) and allied healthcare practitioners, such as nurse, physician assistant, nutrition educator
    e. Laboratory tests (ordered as indicated by treating physician):
        i. Chemistry/lipid screen (including evaluation of liver and kidney function), insulin, HDL, apolipoprotein A1, B 100, E
        ii. CBC with differential and platelet
        iii. CRP or other inflammatory markers
        iv. Trace element screening tests and provocative urine for toxic metals
        v. Antioxidant status profile and homocysteine
        vi. Hypersensitivity (ELISA/ACT LRA or biocompatibility) tests for heavy metals
2. Revisit with the doctor
    a. Discussion of test results.
    b. Discussion of treatment options and Treatment plan development
    c. Enteral and parenteral nutrition, including special diet and supplementation protocols as needed.
    d. Patient education and plan implementation
    e. Appropriate written informed consent (as applicable)
3. Treatment
    a. Depending on the metals found, the amount of metals, and the age and health factors of the patient, different chelating agents can be prescribed.
    b. It is helpful to periodically repeat the challenge test to help determine how many treatments might be required or whether the chelation compound or mode of delivery should be changed.
    c. Periodic kidney or liver function tests are recommended.
    d. The patient's symptoms should be monitored as well.
    e. Monitoring for depletion of minerals when using broad spectrum chelating agents with mineral analysis, if indicated.

f. All physicians who prescribe chelating agents should be trained thoroughly in their use and preferably certified by ABCMT examination.

4. Follow up physician visits at one month, three months, and six months, and then as needed until treatment objectives are accomplished. (Note: Individual educational, acupuncture, nutritional and dental schedules vary.) Annual visits are encouraged with repeat provocative urine tests in patients with heavy metal toxicity.

Example of Patient Education Materials:

"Heavy Metal Sources, Occupational Exposures, and Symptoms"

Listed below are common sources of exposure, both occupational and in every day life of the most common and most toxic of the heavy metals. While some of these sources are historical, it is important to remember that heavy metals often accumulate in bone, brain, connective tissue, muscle (including heart muscle), fat, kidneys, and other tissues. They are not efficiently excreted by the body. Therefore, even exposures from the distant past may be relevant as well as small daily doses over years of exposure. The list of signs and symptoms is not intended to be exclusive as chronic toxicity may cause a variety of the symptoms listed and other diseases as well.

ALUMINUM

The toxicity of aluminum has long been a disputed subject. Although many scientists did not previously consider aluminum to pose a significant health risk, recent evidence seriously questions this conclusion. Research now suggests that aluminum may interfere with normal body functioning at levels lower than previously assumed and there have been increasing reports of aluminum toxicity from environmental exposure.

SOURCES

- Antacids (certain brands: check labels)
- Aluminum cooking vessels
- Baking powder (contains aluminum sulfate)
- Deodorants and antiperspirants
- Aluminum dust from industrial aluminum manufacturing
- Building construction materials
- Household and industrial utensils
- Insulated cables and wiring
- Packaging materials (e.g. cooking with or wrapping food in aluminum foil)
- Fine aluminum powder used in bronze paint
- Aluminum cans
- Drinking water (alum used to kill bacteria)
- Soil (naturally occurring ores)
- Coal burning power plants
- Plants, including those used as food
- Beer
- Milk and milk products (from equipment)
- Alum used in food processing, such as pickles and maraschino cherries
- Medicinal aluminum compounds used externally to treat dermatitis, wounds, and burns
- Nasal spray (alum)
- Toothpaste
- Ceramics (made from A1203 clay)
- Dental amalgams
- Cigarette filters and Tobacco smoke
- Automotive exhausts
- Pesticides
- Animal feed
- F D & C color additives
- Vanilla powder
- Table salt and seasonings
- Bleached flour
- American cheese
- Fumigant residues in foods (aluminum phosphide)
- Kaopectate and other medications containing Kaolin (aluminum silicate)
- Feldspar and mica
- Mcintyre aluminum powder (used in prophylaxis of silicosis)
- Aluminum silicate paste (arthritis treatment)
- Sutures with wound-healing coatings containing aluminum
- Aluminum chelates of polysaccharide
- sulfuric acid esters for peptic ulcer treatment
- Aluminum nicotinate (hypercholesterolemia treatment)

OCCUPATIONAL EXPOSURES

- Manufacturing of aluminum abrasives
- Treating bauxite ore to obtain alumina
- Production of aluminum sulfate (alum) from bauxite ore
- Manufacturing of aluminum products
- Aluminum alloy manufacturing
- Paper industry
- Glass industry
- Textile industry (waterproofing)
- Use of aluminum abrasives in many industrial operations
- Manufacturing of aluminum metal powders
- Synthetic leather manufacturing
- Aluminum welding
- Porcelain industry
- Explosives manufacturing
- Pyrotechnical devices manufacturing and use

SIGNS AND SYMPTOMS

- Aluminum pneumoconiosis (inhalation of AI dust) and pneumothorax
- pulmonary fibrosis with emphysema
- dyspnea
- right-sided cardiac hypertrophy
- Shaver's disease: cough, substernal pain, weakness, fatigue, bilateral lacelike shadowing on lung x-ray
- Phosphate binding in GI tract
- aching muscles
- rickets
- osteoporosis
- Skin reactions (from AI antiperspirants)
- miliaria (acute inflammation of sweat glands)
- Encephalopathy
- Senile dementia (Alzheimer's Disease)
- Nephritis
- Hepatic dysfunction
- Gastric distress
- GI inflammation, colitis
- flatulence and acid eructation (belching)
- Hyperactivity in children
- Psychosis in children

ARSENIC

Arsenic is a common environmental contaminant derived from natural and anthropogenic sources. Both oral ingestion and inhalation of arsenic are modes of intoxication. Arsenical toxicity is highly dependent on the chemical form, oxidation state, and route of exposure. Natural concentrations of arsenic in foodstuffs are usually rapidly absorbed but also quickly excreted. Absorbed arsenic is transported by the blood to the kidneys, liver, spleen, skin, hair, and nails in that order. Some arsenic may remain in tissues long after it has disappeared from the blood, urine and feces.

SOURCES

- Rat poisons
- Insecticide residues on fruits and vegetables (eg. Apple orchards)
- Herbicide residues on cottonseed products
- Wine (if arsenical insecticides used in vineyards)
- Drinking water
- Well water
- Seafood
- Some kelp supplements
- Seawater
- Feed additives (poultry and livestock)
- Coal burning
- Air polluted by arsenic dust from industrial plants
- Wood preservatives
- Pressure treated lumber
- Wallpaper dye and plaster (containing volatile arsenicals)
- Paris green (arsenic containing pigment formerly used in ornaments, toys, curtains, carpets)
- Some household detergents
- Colored chalk
- Automobile exhaust

OCCUPATIONAL EXPOSURES

- Smelter workers
- Chemical workers handling inorganic arsenic
- Vintners working with arsenical insecticides
- Sheep dip workers using sodium arsenite
- Gold miners (associated arsenic ores)
- Processors of taconite (low grade iron ore)
- Acetylene workers
- Alloy makers
- Aniline color workers
- Bleaching powder makers

- Boiler operators
- Book binders
- Bronze makers
- Colored candle makers
- Canners
- Ceramic enamel workers
- Painters
- Paper hangers
- Petroleum refinery workers
- Plumbers
- Solderers
- Tree sprayers
- Wood preservative makers
- Hide preservers
- Taxidermists
- Weed sprayers
- Forestry workers

SIGNS AND SYMPTOMS

- Headache
- Drowsiness, fatigue, chronic fatigue syndrome
- Confusion
- Brittle nails
- Follicular dermatitis
- Hoarse voice
- Raynaud's syndrome (poor circulation to extremities)
- Weakness and muscular atrophy
- Palmar and plantar keratoses
- Pigmented spots on trunk
- Atypical (precancerous) keratoses on hands, feet, and trunk
- Squamous cell carcinoma of skin
- "Mees lines" (transverse white ridges or parallel lines on nails)
- Erythromelalgia (burning pain, redness, swelling of hands and feet)
- Hemiplegia
- Sensory changes (paresthesias, hyperesthesias, neuralgias, myalgia)
- Garlic odor on breath and perspiration
- Goiter
- Heart failure
- Hypertension
- Hepatomegaly and jaundice

CADMIUM

Cadmium is toxic to every body system whether ingested, injected, or inhaled and tends to accumulate in body tissues. Consequently there is concern about the increase in environmental cadmium that has occurred as a result of its increasing industrial use. Inhaled cadmium is usually better absorbed than ingested cadmium. Once absorbed, the elimination rate is generally very slow. The toxicity of cadmium, however, is significantly influenced by dietary intake of other elements such as zinc, copper, and selenium.

SOURCES

- Drinking water
- Soft water, causing uptake of Cadmium from galvanized pipes
- Soft drinks from vending machines with Cadmium piping
- Refined wheat flour (increased Cadmium: Zinc ratio)
- Batteries (nickel-cadmium)
- Evaporated milk
- Many processed foods
- Oysters, kidney, liver
- Rice (irrigated by Cadmium - contaminated water)
- Cigarette smoke and Tobacco
- Super-phosphate fertilizers
- Cadmium alloys (e.g. dental prosthetics)
- Ceramics
- Paint pigments (yellow tint)
- Electroplating
- Cadmium vapor lamps
- Tools rust-proofed with cadmium
- Marine hardware rust-proofed with cadmium
- Welding metal, Solders, bolts
- Silver polish
- Polyvinyl plastics
- Soil: Fungicides and Pesticides
- Sewage sludge and effluents
- Copper refineries
- Dust in urban streets, homes, businesses, and schools
- Rubber carpet backing
- Black rubber: rubber tires
- Burning of motor oil
- Plastic tapes
- Black polythylene

OCCUPATIONAL EXPOSURES

- Nickel-cadmium battery manufacturing
- Zinc or polymetallic ore smelting
- Paint manufacture using cadmium pigments
- Painting with cadmium pigments
- Jewelry making
- Cadmium alloy manufacturing
- Ceramic making using cadmium
- Electroplating metals with cadmium and Process engraving
- Cadmium vapor lamp manufacturing
- Rustproofing tools, marine hardware, etc.
- Tool & die workers, Soldering
- Tetraethyl lead manufacturing (uses diethyl cadmium)
- Fungicide manufacturing

SIGNS AND SYMPTOMS

- Fatigue, chronic fatigue syndrome
- Hypertension (possibly related to increased concentration of Cadmium in renal parenchyma)
- Iron deficiency anemia
- Emphysema
- osteomalacia in parous women over 40 years of age with dietary deficiencies
- liver damage
- Anosmia (loss of sense of smell)
- Yellow coloring of teeth
- Reduced birthweight in newborns
- Renal colic (with passage of calculi)
- Nephrocalcinosis
- Hypercalcuria
- Pain in lower back and legs
- Pain in sternum
- "Milkman's syndrome" (lines of pseudofracture in scapula, femur, ileum)
- Hypophosphatemia
- Possible rheumatoid arthritis
- Decreased production of active Vitamin D
- Decreased pulmonary function
- Proteinuria, glucosuria, and aminoaciduria
- Possible prostatic cancer (in workers exposed to Cadmium oxide)
- Possible carcinogenesis
- Increased mortality

COPPER

Although copper is an essential element, there are situations in which the possibility of human copper toxicity requires consideration. Wilson's Disease (an in- born error of human metabolism) represents a special case of copper toxicosis. Large amounts of copper accumulate in the liver, kidney, and brain of those with this disease. Copper can be absorbed by the lungs, skin, uterus, and gastrointestinal tract. The toxic effects of copper are related to the adequacy of other elements, such as zinc. Soil copper is high in certain Northeastern states, such as Connecticut.

SOURCES

- Drinking water
- Copper plumbing and piping Surface and ground water
- Animal and industrial waste Fungicides and insecticides Sewage sludge
- Oysters, liver, nuts, and chocolate
- Vinegar, carbonated beverages, or citrus juices if prolonged contact with copper
- Beer (from copper piping and brew kettles) Refrigerator ice makers
- Hemodialysis
- Copper intrauterine contraceptive devices (IUD)
- Copper in dental prosthesis
- Milk (accumulates copper from heated copper rollers during pasteurization)
- Industrial emissions
- Swimming pools (fungicide)
- Copper cookware
- Vitamin-mineral supplements

OCCUPATIONAL EXPOSURES

- Jewelry manufacturing
- Riveting of copper parts
- Metal fumes
- Copper smelter and refinery workers
- Vineyard workers (copper sulfate used to prevent mildew)
- Copper miners
- Copper piping manufacturing
- Plumbers

- Copper utensil manufacturing

SIGNS AND SYMPTOMS

Accidental poisoning (acute):

- vomiting
- hematuria
- diarrhea
- oliguria
- jaundice
- hypotension
- impaired liver function
- coma
- hemoglobinuria
- death

Copper metal fume fever:

- chills
- dryness of mouth and throat
- fever
- headache
- aching muscles
- digestive disorders

- Arthritis
- Scleroderma
- Eczema
- Schizophrenia
- Post partum psychosis
- Autism
- Fatigue
- Graying hair
- Menstrual irregularities
- Gingivitis (caused by Copper containing dental work)
- Nasal irritation
- Bitter taste
- Anemia (iron-deficiency)
- Atherosclerosis

LEAD

Lead has long been known as a toxic element. At one time it was felt that the only significant sources that increased lead ingestion were due to plaster, paint, or industrial exposure. Although this is probably true for acute lead poisoning, it is not true for chronic lead toxicity. The increasing prevalence of lead as an environmental contaminant has lead to sub-clinical exposures which often result in subtle, yet significant, adverse health effects. Although lead gasoline additives were banned in the early 1970's which eliminated a degree of environmental exposure, statistics showed that the average urban adult continued to inhale 20-40 ug. of inorganic lead per day even into the late 1980's. Lead may enter the body through ingestion, inhalation, or skin eruption. Adults normally absorb 5.10% of ingested lead while children may readily absorb up to 50%. Inhaled lead is absorbed at 25 - 100% depending on the lead particle size. Tolerance to lead varies with age forms, and sources of lead, and the composition of the diet being consumed.

SOURCES

- Atmospheric lead
- motor vehicle exhausts (persists in soil)
- lead smelters
- coal burning
- refining lead scrap
- burning materials containing lead
- Dust and dirt
- Leaded house paint (still present in older homes)
- Sanding, sandblasting or chipping paint
- Drinking water
- Lead plumbing
- Vegetation grown on lead contaminated soils, eg. by roadside
- Canned fruit and fruit juice
- Canned evaporated milk
- Milk from animals grazing on contaminated pastures
- Bone meal
- Organ meats, especially liver
- Lead-arsenate pesticides
- Wine (leaded caps)
- Rainwater / Snow
- Improperly glazed pottery Painted glassware Pencils (paint)
- Toothpaste
- Newsprint
- Colored printed materials
- Eating utensils
- Curtain weights
- Putty
- Car batteries
- Cigarette smoke, ash, Tobacco
- Lead shot / bullets
- Mascara

- Painted children's toys
- PVC containers
- Canned pet food
- Hair dyes (progressive darkeners)

OCCUPATIONAL EXPOSURES

- Galvanizers
- Battery makers
- Garage mechanic
- Blacksmiths
- Glass makers/ polishers
- Bookbinders
- Bottle cap makers
- Glost kiln workers
- Brass founders
- Gold refiners
- Flower makers (artificial)
- Actors
- Acid finishers
- Brass polishers
- Gun barrel browners
- Braziers
- Incandescent lamp makers
- Brick burners
- Ink makers
- Brick makers
- Insecticide makers / users
- Bronzers
- Brushmakers
- Cable makers
- Cable splicers
- Jewelers
- Canners
- Junk metal refiners
- Cartridge makers
- Labelers (paint can)
- Chemical equipment makers
- Lacquer makers
- Chlorinated Paraffin makers
- Lead burners
- Chippers
- Lead counterweight makers
- Cigar makers
- Lead flooring makers
- Crop dusters
- Lead foil makers
- Cutlery makers
- Lead mill workers
- Foundry workers
- Decorators (pottery)
- Lead miners
- Demolition workers
- Lead pipe makers
- Dental technicians
- Lead salt makers
- Diamond polishers
- Lead shield makers
- Dye makers
- Lead smelters
- Dyers
- Lead stearate makers
- Electronic circuit or device makers
- Lead workers
- Electroplaters
- Linoleum makers
- Electrotypers
- Linotypers
- Embroidery workers
- Linseed oil boilers
- Emery wheel makers
- Lithotransfer workers
- Enamel burners
- Enamelers / Enamel makers
- Match makers
- Explosives makers
- Metal grinders / cutters / polishers
- Metal refiners /burners
- Farmers
- Metal File cutters
- Firemen
- Metal refinishers /Metallizers
- Semiconductor workers
- Mirror silverers
- Service station attendants
- Musical instrument makers
- Sheet metal workers
- Nitric acid workers
- Shellac makers
- Nitroglycerin makers
- Ship dismantlers
- Painters
- Shoe stainers
- Paint makers
- Shot makers
- Paint pigment makers
- Silk weighters
- Paper hangers
- Slushers (porcelain enameling)
- Patent leather makers
- Solderers / Solder makers
- Pearl makers (imitation)
- Pharmaceutical makers
- Steel engravers
- Photography workers
- Pipe fitters
- Tannery workers
- Plastic workers
- Television picture tube makers
- Plumbers
- Printers
- Textile makers
- Policemen
- Tile makers
- Pottery glaze mixers
- Tinners
- Pottery glaze dippers
- Type founders / setters
- Pottery workers
- Putty makers
- Vanadium compound makers
- Pyroxylin-plastic workers Varnish makers
- Riveters
- Toll booth attendants
- Roofers
- Wallpaper printers
- Rubber buffers
- Welders
- Rubber mill workers / reclaimers
- Wood stainers
- Scrap metal workers
- Zinc smelter chargers

COMMON NONOCCUPATIONAL LEAD EXPOSURES INCLUDE:

- Ceramics, pottery and related hobbies
- Ceramics from other countries

- Stained glass work
- Electronics /related hobbies involving soldering
- Firing ranges
- Hunting (especially those who cast their own bullets)
- Eating or drinking from improperly fired lead-glazed ceramic tableware
- Eating lead-bearing paint
- Burning battery casings
- Consuming illicitly distilled whiskey
- Extensive work with motor fuels
- Painting with lead-containing paints
- Home plumbing repairs (lead pipe systems)
- Exterminating
- Extensive auto driving (especially in cities)

SIGNS AND SYMPTOMS

- Headache
- Depression
- Change in personality
- Insomnia and/or drowsiness
- Fatigue, chronic fatigue syndrome
- Nervousness, Anxiety
- Irritability
- Dizziness
- Confusion / disorientation
- Neurological deficits
- Muscle weakness and wasting
- Saturnine gout
- Aching muscles and bones
- Abdominal pain
- Loss of appetite
- Loss of weight
- Constipation
- Hypertension
- Kidney function defects
- Reproductive defects:
    - decreased fertility in men
    - spontaneous abortion in women
- Adrenal gland function impairment
- Iron deficiency anemia
- Blue-black lead lines near base of teeth

SYMPTOMS MORE COMMON IN CHILDREN:

- Hyperactivity (ADD/ADHD)
- Temper tantrums
- Withdrawal
- Frequent crying for no apparent reason
- Fearfulness
- Refusal to play
- Other emotional or behavioral problems
- Drowsiness /fatigue
- Learning disabilities
- Speech disturbances
- Perceptual motor dysfunctions
- Mental retardation
- Seizures or convulsions
- Ataxia
- Encephalopathy

MERCURY

Mercury, long known as a toxic element, has evoked increasing concern in recent years due to its use in industry and agriculture and the burning of fossil fuels. Methylmercury compounds and elemental mercury vapor are the two forms most likely to be involved in human exposures. In addition, the conversion of elemental mercury and mercury compounds by bacteria (in the intestinal tract) to the more toxic methylmercury also poses potential threats to human health. Ingested methylmercury is readily absorbed through the gastrointestinal tract and inhaled mercury vapor is easily retained by the pulmonary system. Skin absorption of mercury also occurs from touching or playing with elemental mercury.

SOURCES

- Mercury-silver amalgam (dental fillings)
- Consumption of grain seeds treated with methylmercury fungicides (esp. wheat)
- Fish, shellfish, and marine mammals
- Kelp and other seaweeds
- Medical sources:

    - Thimerosal (preservative in injectable pharmaceuticals)
    - Vaccinations / immunizations
    - Mercuric chloride (used in histology labs)

- Many common over the counter health medications including:
    - Antiseptics/first aid preparations
    - Psoriasis medications
    - Fungicides
    - Calomel (body powders and talc)
    - laxatives (containing calomel)
    - Acne preparations
    - Skin lightening /Bleaching creams
    - Ear preparations
    - Nasal sprays (Afrin, Neo-Synephrine, and others)
    - Throat lozenges
    - Hemorrhoid Ointments, suppositories (Lanacaine, Preparation H, and others)
    - Hair tonic
    - Mercurochrome and thimerosal (Merthiolate)
    - Veterinary preparations (BagBalm and others)
- Mercury containing cosmetics/mascara (especially waterproof)
- Contact lens solutions and other eye drops such as Murine, Allerest, and others
- Organic mercurials (historical use as diuretics)
- Broken thermometers and barometers
- Playing with elemental mercury
- Latex and solvent-thinned paints: mercury used as a fungicide (discontinued in 1992)
- Anti-fouling paint for boats
- Wood preservatives (ethyl mercury chloride)
- Sanding, sandblasting or chipping paint
- Air polluted by industrial mercury vapor
- Mercury polluted industrial water
- Clothing worn by mercury workers
- Fabric softeners
- Floor waxes and polishes
- Air conditioner filters
- Wood preservatives
- Cinnabar (used in jewelry)
- Cinnabar, yellow, vermillion pigments
- Batteries with mercury cells
- Gardening Chemicals:
    - Fungicides for use on lawns, trees, shrubs
    - Herbicides
    - Insecticides
- Tanning leather
- Felt
- Adhesives
- Photoengraving
- Photographic solutions
- Tatooing
- lab and industrial equipment using metallic mercury
- Sewage sludge used as fertilizer contaminates soil

- Sewage disposal (may release 1000's of tons of Hg annually world wide)

OCCUPATIONAL EXPOSURES

- Bactericide makers
- Battery makers, mercury
- Boiler makers
- Mirror makers
- Bronzers
- Neon light makers
- Paint makers
- Paper makers
- Carbon brush makers
- Percussion cap makers / loaders
- Caustic soda makers
- Pesticide workers
- Ceramic workers
- Photographers
- Chlorine makers
- Pressure gage makers
- Calibration instrument makers
- Dental amalgam makers
- Dentists
- Seed handlers
- Direct current meter workers
- Silver extractors
- Disinfectant makers
- Switch makers, mercury
- Disinfectors
- Tannery workers
- Drug makers
- Embalmers, Taxidermists
- Dye makers
- Textile printers
- Mercury workers, miners, refiners
- Electric apparatus makers
- Thermometer, Barometer, Manometer makers
- Electroplaters
- Vinyl chloride manufacturing
- Wood preservative workers
- Explosives makers
- Farmers
- Fingerprint detectors
- Fireworks makers
- Fish cannery workers
- Fungicide makers
- Fur preservers, processors
- Gold extractors
- Histology technicians
- Ink makers
- Insecticide makers
- Investment casting workers
- Jewelers
- Laboratory workers, chemical
- Lampmakers (fluorescent)

SIGNS AND SYMPTOMS

ELEMENTAL MERCURY EXPOSURE:

- Insomnia
- Drowsiness
- Shyness
- Depression
- Change in personality
- Nervousness
- Loss of weight
- Dizziness
- Loss of appetite
- Memory Loss
- Neuropathy
- Tremors
- Lack of self-control
- Irritability
- Anxiety
- Tachycardia
- Arrhythmias
- Hypertension
- Thyroid problems
- Hallucinations
- Loss of self-confidence
- Manic depression
- Fatigue, chronic fatigue syndrome
- Fibromyalgia

ORGANIC MERCURY EXPOSURE:

- fatigue
- headache
- forgetfulness
- numbness and tingling of the lips and feet
- Parasthesias/neuropathy
- muscle weakness progressing to paralysis
- loss of vision
- hearing difficulty
- speech disorders memory loss
- In-coordination, ataxia
- emotional instability
- dermatitis
- renal damage
- general brain dysfunction
- autism
- coma
- death

NICKEL

Nickel can be a toxic element in man. It can interact by four routes of entry into the body. These are oral ingestion, inhalation, parenteral administration, and percutaneous absorption. Nickel or nickel salts are relatively nontoxic when taken orally. Nickel toxicity from parenteral administration has only been observed experimentally. Cutaneous absorption may manifest as nickel dermatitis and is relatively common. The inhalation of nickel carbonyl causes the most serious type of nickel toxicity, although it usually occurs only in occupational workers due to an industrial accident.

SOURCES

- Tobacco smoke
- Contamination of air, drinking water, soil and vegetation by industrial nickel
- Testing of nuclear devices (radionuclide Ni-631)
- Exhausts of automobiles and trucks
- Burning of coal and oil for power generation
- Burning of fuel oil for space heating
- Wear of automobile tires and brake linings
- Superphosphate fertilizers
- Stainless steel cookware (Nickel absorbed by acid foods)
- Dissolved nickel from food-processing equipment
- Hydrogenated fats and oils
- Baking powder
- Dental fillings
- Nickel-cadmium batteries

SOURCES OF CONTACT FOR ALLERGIC INDIVIDUALS:

- Nickel jewelry
- Nickel coins
- Clothing fasteners
- Tools
- Cooking utensils
- Stainless steel kitchens
- Detergents
- Prostheses
- Medical appliances
- Metal chairs
- Thimbles
- Needles
- Scissors
- Zippers
- Bobby pins
- Fountain pens

OCCUPATIONAL EXPOSURES

- Nickel mining, refining
- Nickel electroplating
- Nickel alloy makers
- Nickel cadmium battery workers
- Che[182]mical industry
- Manufacture of items listed above
- Electronics and computer industry
- Food processing
- Nickel waste disposal / recycling
- Ceramics industry workers
- Duplicating machine workers
- Dyers
- Ink makers Jewelers
- Spark plug makers
- Rubber workers
- Plastics industry
- Coin manufacturers
- Automotive parts makers

SIGNS AND SYMPTOMS

- Nickel dermatitis ("nickel itch"): itching, burning, rash on fingers, wrist, forearms, earlobes, or other exposed area. The reaction is largely allergic in nature.
- Pulmonary cancer (from nickel in tobacco smoke)
- **Acute toxicity:**
  - Dyspnea
  - cyanosis
  - tachypnea
  - fatigue/apathy
  - headache
  - fever
  - anorexia
  - vomiting
  - insomnia
  - diarrhea

References:

[1] Maden, EF, Sexton, MJ, Smith, DR, Fowler, BA, *Lead*, Heavy Metals in the Environment. B. Sarkar, Ed. Marcel Dekker (New York), pp. 409-456 (2002).

[2] http://www.who.int/pcs/chem_fd_site/descr.html

[3] Canfield, et al, *Exposure to Lead in Children – How Low is Low Enough?* NEJM, 2003, 348; 16: 1517-1526, April 17 2003.

[4] Testimony from the Immunization Safety Review Committee, (ISRC), for the National Institute of Medicine, (NOM), under the US National Academy of Sciences, (NAS): http://www.universityofhealth.net/PR/3304PRUSNOMHearing.htm http://www.iom.edu/subpage.asp?id=18065 www.uninformedconsent.com http://www.autismcanada.org/News/Weldon.pdf.

[5] *Mercury in fish: cause for concern.* US Food and Drug Administration, FDA Consumer. Sept 1994, Revised May 1995.

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

[7] www.cfsan.fda.gov/`dms/mehg703b.html www.fda.gov/oc/opacom/mehgadvisory1011.html www.fda.gov/bbs/topics/ANSWERS/2003/ANS01270.html www.fda.gov/oc/opacom/mehgadvisory1208.html www.cfsan.gov/`frf/sea-mehg.html

[8] Tomera, J, Harakal, C. *Mecury and lead induced contraction of aortic smooth muscle in vitro. Arch Int Pharmacodyn, 1986, 283(2);295-302.*

[9] Perry, H, et al. *In vitro production and inhibition of aortic vasoconstriction by mercuric, cadmium and other metal ions.* Proc Exp Biol Med, 1967, 124; 485-490.

[10] Perry, H. *Hypertension and tissue levels following intravenous Cadmium, mercury, and zinc.* Amer J Physiol, 1971, 220;808-811.

[11] Nash, et al, *Blood Lead, Blood Pressure, and Hypertension in Perimenopausal and Postmenopausal Women.* JAMA, March 26, 2003, Vol. 289, No. 12, *1523-1532*.

[12] Hu, H. *Poorly controlled hypertension in a painter with chronic lead toxicity.* Environ Health Perspect 2001 Jan;109(1):95-9.

[13] Guallar, et al. *Mercury, fish oils, and the risk of myocardial infarction.* NEJM 2002,347:22, 1747-54.

[14] Frustaci, A, et al. *Marked elevation of myocardial trace elements in idiopathic cardiomyopathy compared with secondary cardiac dysfunction*. J Am College Cardiology, 1999(33):1578-83.

[15] Lin, et al, *Environmental Lead Exposure and Progression of Chronic Renal Diseases in Patients without Diabetes. NEJM 348(4)277-86. Jan.23, 2003.*

[16] Kim R, et al. *A longitudinal study of low-level lead exposure and impairment of renal function: the Normative Aging Study*. JAMA, 1996, 275: 1177-81.

[17] JBC 200: 275: 12175-12184.

[18] Lin, et al. *Improving kidney function in patients with mild lead burden.* Arch Int Med 2001, Jan 22;161(2):264-71.

[19] *Increase Body Lead Burden- Cause or Consequence of Chronic Renal Insufficiency.* NEJM 2003 Jan 23; 348(4):345-47.

[20] Bolger, PM, Schwartz, BA. *Mercury and health.* NEJM2002, 347:22, 1735-36.

[21] Perazella, M. *Lead and the kidney: nephropathy, hypertension, and gout.* Connecticut Medicine, 1986:Vol 60, No 9, pp 521-526.

[22] Glotzer, DE, Freedberg, KA, Bauchner, H. *Management of childhood lead poisoning: clinical impact and cost effectiveness. IMed Decis Making 15(1):13-24, Jan-Mar. 1995.*

[23] Lin, et al. *Environmental lead exposure and urate excretion in the general population.* Am J Med 2002 Nov: 113(7):563-8.

[24] Landrigan, PJ. Mount Sinai School of Medicine, NY. *Toxicity of lead at low dose.* Brit J Indust Med 1989:46:593-6.

[25] JAMA, Apr 2, 2003, Vol 289, No 13, pg 1667-1674

[26] Brucker-Davis, F. Effects of Environmental synthetic chemicals on thyroid function. *Thyroid*, Vol.8, 1998, 827-856.

[27] Howdeshell, K. A model of the development of the brain as a construct of the thyroid system. *Env Health Pers*, Vol. 110, Supplement 3, June 2002.
[28] Lustberg, M, Silbergeld E. *Blood Lead Levels and Mortality,* Archives of Internal Medicine, 2002 Nov 25 162 (21) 2443-9.
[29] Crinnion, WJ. *Environmental Medicine, Part Three: Long-term effects of chronic low-dose mercury exposure.* Al Med Rev, Vol 5, No 3, 2000.
[30] www.nlm.nih.gov/medlineplus/mercury.html.
[31] Toxic Mineral Monographs, ATSDR, CDC, USPHS, 1998-2002
[32] Nriagu JO, Pacyna, JM Quantitative assessment of worldwide contamination of air, water, and soils by toxic metals, *Nature*, 1988; 333(6169): 134-139.
[33] Seba, D. Personal communications 2000-2001.
[34] Arsenic Monograph, ATSDR, CDC, PHS, GOV, 2000
[35] Wang L. Arsenic pollution disrupts hormones. *Science New*, March 17, 2001, 159(11):164.
[36] EPA revised Arsenic risk assessment, Chemical & Engineering News, January 8, 2001.
[37] Lovins A, Lovins H, Hawken P. Natural Capitalism, Brown & Co., 2000.
[38] Jaffe R Clean Your Room. Report to the Department of Consumer Affairs of the State of California, Richard Spohn, Director, 1983.
[39] Needleman, HL. Childhood lead poisoning: the promise and abandonment of primary prevention. Am J Public Health 1998; 88: 1871-1877.
[40] www.atsdr.cdc.gov/tfacts5.html
[41] Johnson, MD etal. Cadmium mimics th in vivo effects of estrogen in the uterus and mammary gland. *Nature Medicine* 2003, 9(8): 1081-84.
[42] Cohn SL, Goldman L. Preoperative risk evaluation and perioperative management of patients with coronary artery disease. Med Clin North Am, 2003; 87: 111-136.
[43] HazDat: ATSDR's hazardous substance release / health effects database. http://atsdr1.atsdr.cdc.gov:8080/hazdat.htm#A3.1
[44] Circulation, 2001, 103: 2788-2804. Duffy, et al, Evans Dept. of Medicine and Whitaker Cardiology Institute, Boston Univ. School of Medicine.
[45] Circulation. 1992.
[46] Horowitz, LD, Rosenthal, EA, *Iron mediated cardiovascular injury. Vasc Med 4(2):93-99.1999.*
[47] www.atsdr.cdc.gov/HEC/CSEM/lead/references_cited.html
[48] www.healthbenchmarks.org/mercury/
[49] Jaffe R, Morris E. Medicine in Transition from Disease Treatment to Healthcare. HSC Report 100-14, 2000, Sterling, VA.
[50] Muir, M. *Current controversies in the Diagnosis and Treatment of heavy metal toxicity.* Alt Comp Therapies, June 1997, pp.170-178.
[51] *Toxicological profile for lead.* ATSDR, CDC, Atlanta, GA: U.S. Department of Health and Human Service, Public Health Service, 1993; p.36.
[52] Goyer, R. *Chelation of toxic metals: Current interests*. Env Hlth Perspect. (1995) 103:988-989.
[53] Goyer RA, Cherian MG, Jones MM et al. Role of chelating agents for prevention, intervention, and treatment of exposures to toxic metals. Env Hlth Perspect. (1995)11:1048-1052
[54] Howie, RA, Smith H. *Mercury in human tissue.* Forensic Sci: 7:90-96, 1967.
[55] *Blood Lead Levels and Mortality,* Archives of Internal Medicine, 2002 Nov 25 162 (21) 2443-9.
[56] Cecil Textbook of Medicine, 18th Edition, Chapter 542: Trace Metal Poisoning. Pages 2386-87.
[57] Vitale, LF et al. *Blood Lead – An inadequate Measure of Occupational Exposure.* J Occup Med, Vol 17, No 3, Mar 1975.
[58] EPA Document # 609 498 499, Aug 1979.
[59] Sokas, R, et al. *Shortened Forms of Provocative Lead Chelation.* J Occup Med, Vol 30, No 5, May 1988.
[60] Markowitz, ME, Rosen, JF. *Assessment of lead stores in children: Validation of an 8 hour CaNa2EDTA provocative test.* J Pediatics. March 1984: 337-341.
[61] Rempel, D. *The lead exposed worker.* JAMA, July 28, 1989: Vol 262, No 4, pp. 532-534.
[62] Godfrey, M, Campbell, N. *Confirmation of mercury retention and toxicity using DMPS.* J Adv Med. Vol 7, No1, Spring 1994.
[63] Cecil Textbook of Medicine, 18th Edition, Chapter 542: Trace Metal Poisoning. Pages 2386-87.
[64] Quig, Filedei and Whitaker, Study in preparation for publication.

[65] World Health Organization (WHO). Inorganic mercury. Environmental Health Criteria 118. Geneva: World Health Organization, International Program on Chemical safety. 1991.
[66] Echeverria D, Heyer NJ, Martin MD et al. Behavioral effects of low-level exposure to Hg^0 among dentists. Neurotox. Teratol. 1995; 17; 161-168.
[67] Langworth S, Almkvist O, Soderman E et al. Effects of occupational exposure to mercury vapour on the central nervous system. Brit. J. Indust. Med. 1992:49; 545-555.
[68] State of Connecticut Dept. of Health Services, *Lead Poisoning Fact Sheet*. AVB/10-90.
[69] Morse, T, Grey, M, Storey, E, Keta-Bib, E. Occupational Disease in Connecticut, 2001. Connecticut Medicine, Vol 68, NO 3, pp 131-138.
[70] *Blood lead levels in young children-United States and selected states, 1996-1999.* Morbidity and Mortality Weekly Report, CDC, NIH, Dec 22, 2000, Vol 49, no 50.
[71] http://www.ewg.org/reports/bodyburden/toc.php.
[72] Canfield, et al, *Exposure to Lead in Children – How Low is Low Enough?* NEJM, 2003, 348; 16: 1517-1526, April 17 2003.
[73] *Blood Lead Levels and Mortality,* Archives of Internal Medicine, 2002 Nov 25 162 (21) 2443-9.
[74] Fowler, B. (Chief toxic metals consultant, ATSDR / CDC) Presentation on Lead and Metal Binding, International College of Integrative Medicine. Sept. 2003.
[75] Needleman, HL, et al. *Low-Level Lead Exposure and IQ of children: a meta-analysis of modern studies.* JAMA, Feb 2, 1990, Vol 263, No 5, pp 673-677.
[76] Needleman, HL, et al. *The long-term effects of exposure to low doses of lead in childhood.* NEJM, Vol 322, No 2, Jan 11, 1990. pp 83-88.
[77] Schubert J. *Combined effects in toxicology*. J Toxicol Environ Health 1978;4:2472-76.
[78] Godfrey, et al. *Apolipoprotein E genotyping as a potential biomarker for mercury neurotoxicity.* Journal of Alzehemer's Disease, 5(2003) 189-195.
[79] Great Lakes College of Clinical Medicine, A Useful Tool: Mercury: A Risk Realized, March 21-22, 2001, Baltimore, MD
[80] 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.
[81] 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.
[82] Testimony from the Immunization Safety Review Committee, (ISRC), for the National Institute of Medicine, (NOM), under the US National Academy of Sciences, (NAS):
http://www.universityofhealth.net/PR/3304PRUSNOMHearing.htm
http://www.iom.edu/subpage.asp?id=18065 www.uninformedconsent.com
http://www.autismcanada.org/News/Weldon.pdf.
[83] http://www.epa.gov
[84] HazDat: ATSDR's hazardous substance release / health effects database.
http://atsdr1.atsdr.cdc.gov:8080/hazdat.htm#A3.1http://www.atsdr.cdc.gov/alerts/970626.html
[85] http://www.osha-slc.gov/SLTC/healthguidelines/mercuryvapor/recognition.html
[86] http://www.iom.edu/
[87] NEJM, Jan 23, 2003, Vol. 348, No. 4, p 277-286
[88] http://www.ewg.org/reports/bodyburden/toc.php.
[89] Bjorksten, J. *Possibilities and limitations of chelation as a means for life extension.* J Adv Med, 1989, 2:77-88.
[90] Canfield, *Exposure to Lead in Children – How Low is Low Enough?* NEJM (April 17 2003 Vol. 348 Number 16)
[91] *Blood Lead Levels and Mortality,* Arch Int Med, 2002 Nov 25 162 (21) 2443-9.
[92] Blumer, Cranton, et al. *Ninety Percent Reduction in Cancer Mortality after Chelation Therapy with EDTA.* J Adv Med 2(1,2) 183-188.
[93] Glotzer, DE, Freedberg, KA, Bauchner, H. *Management of childhood lead poisoning: clinical impact and cost effectiveness.* Med Decis Making 15(1):13-24, Jan-Mar. 1995.
[94] Crichton, et al. *Aluminum and iron in the brain - prospects for chelation.* Coordination Chemistry Reviews, 2002, 228:2, 365-371.
[95] Aposhian, HV, et al. Urinary mercury after administration of 2,3-dimercaptopropane-1-sulfonic acid: correlation with dental amalgam score.

[96] Siblerud R. *The relationship between mercury from dental amalgam and mental health.* Am J Psychother 1989;18:575-587.
[97] Lindh U, Hudecek R, Danesrund A, Ericksson S, Lindvall A. Removal of dental amalgam and other metal alloys supported by antioxidant therapy allerviates symptoms and improves quality of life in patients with amalgam-associated ill health. Neuroendocrinol Lett. 2002; 23: 459-482.
[98] Bock S, *Diagnosis and treatment of heavy metal toxicity.* Int J Integr Med, Vol 1, No 6, Nov/Dec 1999.
[99] *Lead Mobilization During Calcium EDTA Chelation Therapy In Treatment Of Chronic Lead Poisoning*, Am J Kidney Dis 2002 Jul; 40 (1):51-8
[100] Rosen JF, et al. *Importance of sequential measurements of bone lead content by L x-ray fluorescence in CaNa2EDTA treated lead toxic children.* J Environ Health Perspect 93:271:277, Jun 1991.
[101] Eisenberg, NEJM, January 1993.
[102] Astin, JAMA, July 1997 and Nov. 1998.
[103] Source for appendices: "Diagnostic and Treatment Protocols for safer, effective mercury human biohazard management", Consensus Development Working Group of the International College of Integrative Medicine, Review date: 14 March 2003.
[104] Lee, BK, Schwartz, DS, Stewart,W, and Ahn, KD. *Provocative chelation with DMSA and EDTA: Evidence for differential access to lead storage sites.* Occup Environ Med 51(1):13-9, Jan.1995.
[105] Cecil Textbook of Medicine, 18th Edition, Chapter 542: Trace Metal Poisoning. Pages 2386-87.
[106]Aposhian, et al. *Mobilization of heavy metals by newer, therapeutically useful chelating agents.* Toxicol 97(1-3):23-38, Mar 31, 1995.
[107] Godfrey, M, Campbell, N. *Confirmation of mercury retention and toxicity using DMPS.* J Adv Med. Vol 7, No1, Spring 1994.
[108] Hibberd, AR, Howard, MA, Hunnisett, AG. *Mercury from dental amalgam fillings: Studies on oral chelating agents for assessing and reducing mercury burdens in humans*. J. Nutr Environ. Med (1998) 8:219-231.
[109] Introduction to Clinical Metal Toxicology and Basic Chelation Therapy Workshop.
[110] Rozema, T. *Protocol for the safe and effective administration of EDTA and other chelating agents for vascular disease, degenerative disease, and metal toxicity.* J Adv Med, Vol 10, No 1, Spring 1997.
[111] Jones, MM. *Chemistry of chelation: Chelating agent antagonists for toxic metals.* Toxicology of metals: biochemical aspects. Goyer, RA, Cherlan, MG, eds., Springer-Verlag (New York), 279-304, 1995.
[112] Goyer, RA, Cherian, MG, Jones, MM, Reigart, JR. *Role of chelating agents for prevention, intervention, and treatment of exposures to toxic metals.* Environ Health Perspect 103(11):1048-1052, Nov 1995.
[113] Klassen, CD, *Heavy metal antagonists: Edetate calcium disodium*, Goodman and Gilman's The Pharmacologic Basis of Therapeutics. 8th Ed. Pergamon Press (New York), 1607-1608, 1990.
[114] www.ATSDR,cdc.gov
[115] Physicians Desk Reference. Thomson PDR. 2004.
[116] Messirli, editor. Cardiovascular Drug Therapy. 2nd Ed,1996, pg. 1613-1617.
[117] Olmstead, SF. *Review of EDTA Chelation Therapy in Treatment of Occlusive Atherosclerotic Vascular Disease.* (monograph)
[118] Cranton, EM, Textbook on EDTA Chelation Therapy, 2nd Ed, 2001.
[119] Halstead, Rozema, The Scientific Basis of EDTA Chelation Therapy. 2nd Ed, 1997.
[120] Chappell, LF, Stahl, JP, Evans, R, *EDTA chelation therapy for vascular disease: a meta-analysis using unpublished data.* J Adv Med, 7:131-142, 1994.
[121] Chappell, LT, Margolis, S, *Point-Counterpoint on EDTA chelation therapy.* Alternative Therapies 1:53-57, 1994.
[122] McDonagh, EW, Rudolph, CJ, *Noninvasive treatment for sequellae of failed coronary circulation: 100% occlusion of left anterior descending coronary artery, 30% stenosis of right coronary artery, and left ventricular contractility defect.* J Neurol Orthop Med Surg 14:169-173, 1993.
[123] Riordan HD, Cheraskin E, Dirks M, Tadayon F, Schultz M, Brizendine P: EDTA chelation/hypertension study: clinical patterns as judged by the Cornell Medical Index questionnaire. J Ortho Med 1989; 4(2): 91-95.
[124] Olszewer E, Carter JP: EDTA chelation therapy in chronic degenerative disease. Med Hyp 1988; 27(1): 41-49.

[125]Valstar E, Trossel RTHK. Statistical evaluation of 3 double-blind studies of intravenous EDTA chelation for treatment of intermittent claudication. Clinical Prac Alt Med 2000;1:243-248.
[126] Rubin, M, Rozema, T, Casdorph, HR, Scarchilli, A, *Cardiac decalcification by Na2MgEDT.* American Chemical Society presentation 208th Meeting, Washington, DC, Aug 25, 1994.
[127] Cranton FM, Frackelton JP. Free oxygen radical pathology and EDTA chelation therapy: mechanisms of action. J Adv Med 1998;11:277-310.
[128] Voest, et al, *Iron-chelating agent in non-iron overload conditions.* Ann Intern Med 121(5):384-385, Mar 15, 1994
[129] Galis, et al, *Increased expression of matrix metalloproteinases and matrix degrading activity in vulverable regions of human atherosclerotic plaques.* J Clin Invest. 94:2493-2503, 1994.
[130] Galis, et al, *Cytokine-stimulated human vascular smooth muscle cells synthesize a complement of enzymes required for extra cellular matrix digestion.* Circ Res 75:181-189, 1994.
[131] Harada, T, Mayberg, MR, *Inhibition of delayed arterial narrowing by the iron chelating agent deferoximine.* J Neurosurg 77:763-767, 1992.
[132] Patterson, E. *Coronary vascular injury following transient coronary artery occlusion: prevention by pre-treatment with deferoximine, dimethylthiourea, and N-2-mercaptoproprionyl glycine.* J Pharm Esp Ther 266(1):528-535, 1993.
[133] Cranton EM, Frackelton JP: Free radical pathology in age-associated diseases: treatment with EDTA chelation, nutrition and antioxidants. J Hol Med 1984; 6(1): 6-37.
[134] Cranton EM. EDTA chelation therapy: a more comprehensive, scientific rationale. Clin Pract Alt Med 2001;2:26-30.
[135] http://nccam.hih.gov/nccam/fi/concepts/may2000/chelation.html
[136] http://nccam.hih.gov/nccam/fi/concepts/may2000/chelation.html
[137] Rozema, T. *Protocol for the safe and effective administration of EDTA and other chelating agents for vascular disease, degenerative disease, and metal toxicity.* J Adv Med, Vol 10, No 1, Spring 1997.
[138] Aposhian, et al. *Sodium 2,3 dimercapto-1-propan-sulfonate (DMPS) treatment does not redistribute lead or mercury to the brain of rats.* Toxicol 109(1):49-55. May 3, 1996.
[139] Miller A. Dimercaptosuccinic Acid (DMSA), a non-toxic, water-soluble treatment for heavy metal toxicity. Alt Med Rev, Vol. 3, No. 3, 1998.
[140] Dart, RC, Hurlbut, KM, et al. *Pharmacokinetics of meso-2,3-dimercaptosuccinic acid in patients with lead poisoning and in healthy adults.* J Pediatr 125(2):233-234, Aug 1994.
[141] Planas-Bohne F. The influence of chelating agents on the distribution and biotransformation of methylmercuric chloride in rats. *J.Pharmacol Exp Ther 1981;217:500-5004.*
[142] Walsh JM. Penicillamine, a new oral therapy for Wilson's disease. *Am J Med* 1956;21:487-495.
[143] 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.
[144] Hammond PB. The effects of d-penicillamine on the tissue distribution and excretion of lead. *Toxicol Appl Pharmacol* 1973;26:241-246.
[145] Sachs HK, Blanksma LA, Murray EF, O'Connell MJ. Ambulatory treatment of lead poisoning: report of 1155 cases. *Pediatrics* 1970;46:389-396.
[146] 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.
[147] Marcus SM. Experience with d-penicillamine in treating lead poisoning. *Vet Hum Toxicol* 1982;24:18-20.
[148] Chisolm JJ Jr. Poisoning due to heavy metals. Pediatr Clin North Am. 1970; 17(3):591-615.
[149] Greenhouse AH. Heavy metals and the nervous system. Clin Neuropharmacol. 1982;5(1):45-92.
[150] Satar S, Toprak N, Gokel Y, Sebe A. Intoxication with 100 grams of mercury: a case report and importance of supportive therapy. Eur J Emerg Med. 2001;8(3):245-248.
[151] Ozuah PO. Mercury poisoning. Curr Probl Pediatr. 2000;30(3):91-99.
[152] Rosenspire AJ, Bodepudi S, Mathews M, McCabe MJ Jr. Low levels of ionic mercury modulate protein tyrosine phosphorylation in lymphocytes. Int J Immunopharmacol. 1998;20(12):697-707.
[153] inkelstein Y, Vardi J, Kesten MM, Hod I. The enigma of parkinsonism in chronic borderline mercury intoxication, resolved by challenge with penicillamine. Neurotoxicology. 1996;17(1):291-295.

[154] Goyer RA, Cherian MG, Jones MM, Reigart JR. Role of chelating agents for prevention, intervention, and treatment of exposures to toxic metals. Environ Health Perspect. 1995;103(11):1048-1052.
[155] Schwartz JG, Snider TE, Montiel MM. Toxicity of a family from vacuumed mercury. Am J Emerg Med. 1992;10(3):258-261.
[156] Snodgrass W, Sullivan JB Jr, Rumack BH, Hashimoto C. Mercury poisoning from home gold ore processing. Use of penicillamine and dimercaprol. JAMA. 1981; 246(17): 1929-1931.
[157] Cullen NM, Wolf LR, St Clair D. Pediatric arsenic ingestion. Am J Emerg Med. 1995;13(4):432-435.
[158] Mahajan SK, Aggarwal HK, Wig N, Maitra S, Chugh SN. Arsenic induced neuropathy. J Assoc Physicians India. 1992;40(4):268-269.
[159] Aaseth J. Recent advance in the therapy of metal poisonings with chelating agents. Hum Toxicol. 1983;2(2):257-272.
[160] Fesmire FM, Schauben JL, Roberge RJ. Survival following massive arsenic ingestion. Am J Emerg Med. 1988;6(6):602-606.
[161] Watson WA, Veltri JC, Metcalf TJ. Acute arsenic exposure treated with oral D-penicillamine. Vet Hum Toxicol. 1981;23(3):164-166.
[162] Lyle WH. Penicillamine in metal poisoning. J Rheumatol Suppl. 1981;7:96-99.
[163] Basinger MA, Jones MM, Holscher MA, Vaughn WK. Antagonists for acute oral cadmium chloride intoxication. J Toxicol Environ Health. 1988;23(1):77-89.
[164] Williams DR, Halstead BW. Chelating agents in medicine. J Toxicol Clin Toxicol. 1982;19(10):1081-1115.
[165] Freeman HC. Crystal structures of metal-peptide complexes. Adv Protein Chem. 1967;22:257-424.
[166] Shi X, Dalal NS, Kasprzak KS. Generation of free radicals in reactions of Ni(II)-thiol complexes with molecular oxygen and model lipid hydroperoxides. J Inorg Biochem. 1993;50(3):211-225.
[167] Sachs HK, Blanksma LA, Murray EF, O'Connell MJ. Ambulatory treatment of lead poisoning: report of 1155 cases. *Pediatrics* 1970;46:389-396.
[168] Shannon M, Graef J, Lovejoy FH Jr. Efficacy and toxicity of d-penicillamine in low-level lead poisoning. *J Pediatr* 1988;112:799-804.
[169] 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*.
[170] Rothschild B. Pyridoxine deficiency. *Arch Intern Med* 1982;142:840.
[171] Vitale, *op. cit.* and Marcus, *op. cit.*
[172] Holt GA. Food & Drug Interactions. Chicago: Precept Press, 1998, 203.
[173] Shannon, *op. cit.* and Chisholm, *op. cit.*
[174] "Diagnostic and Treatment Protocols for safer, effective mercury human biohazard management", Consensus Development Working Group of the International College of Integrative Medicine, Review date: 14 March 2003
[175] 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.
[176] Pfeiffer C. Mental and Elemental Nutrients, Keats Pub., New Canaan, Ct., 1983 .
[177] Quig, D. *Cysteine metabolism and metal toxicity.* Al Med Rev. Vol 3, No 4, 1998.
[178] Jaffe R. Determination of ascorbate physiologic need by calibration. *Health Studies Collegium Document 111*. Contact Client Services at 800-525-7372 for reprints.
[179] Quig, unpublished 1999.
[180] Jaffe R, Brown S. *Acid-Alkaline balance and its effect on bone health*. Intl J Integrative Med, 2001; 4 (6): 7-18.
[181] Adapted from the following Clinical Protocols 1) Dr. Anders Lindvall, Dept. Clinical Metal Biology (DCMB), University Hospital, Uppsala, Sweden, 2) The Health Studies Collegium's Protocol for Toxic Mineral Body Burden, and 3) 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.