Toxic Metals and their Detoxification

The information in this monograph is intended for informational purposes only and is meant to help users better understand health concerns. Information is based on review of scientific research data, historical practice patterns, and clinical experience. This information should not be interpreted as specific medical advice. Pregnant women, should seek the advice of a physician before using any protocol listed in this monograph. The protocols described are for adults only, unless otherwise specified. The metal detoxification protocols raise many issues that are subject to change as new data emerge. National, state, and local laws may vary regarding the use and application of many of the treatments discussed. The reader assumes the risk of any injuries. None of the suggested protocol regimens can guarantee health benefits. Users should consult with a qualified healthcare provider for specific questions regarding therapies, diagnosis and/or health conditions, prior to making therapeutic decisions.

Introduction to Metal Toxicity and its Detoxification

Metal intoxication is an important concern in the world today owing to high industrial and chemical exposure to humans. These metal toxicities have been extensively studied with underlying mechanisms revealed up to molecular levels. However, much emphasis and focus on managing these metal-induced toxic manifestations is still needed. The presence of toxic metals in the environment has received increasing attention in recent years. Metals comprise a complex group of elements with a broad range of toxic effects, including cancer,

neurotoxicity, immunotoxicity, cardiotoxicity, reproductive toxicity, teratogenesis, and genotoxicity. Some metals are toxic at very low levels. Their accumulation in the environment is of concern because they are not biodegradable; their chemical state may change, however, and this may affect their toxicity. Metals exist in several valence states and form a vast variety of inorganic and organic compounds. Although metals may be toxic, many are essential to living systems because they participate in a variety of cellular, physiological, and structural functions.

All metals can cause disease through excess. Toxic effects are dependent upon the amount of metal ingested, entry rate, tissue distribution, concentration achieved, and excretion rate. Mechanisms of toxicity include inhibition of enzyme activity and protein synthesis, alterations in nucleic acid function, and changes in cell membrane permeability.

The heightened concern for reduction of environmental pollution that has been occurring over the past 30 years has stimulated active continuing research and literature on the toxicology of certain metals. While the toxic effects of these substances are a widespread concern in the modern industrial context, humans have succeeded in poisoning themselves repeatedly throughout recorded history. Lead usage dates back 2000 BC and arsenic was used as a decoration in Egyptian tombs. Historians contend that the fall of the Roman Empire was hastened by the chronic lead poisoning experienced by the ruling classes who had water conducted through lead plumbing and drank wine from goblets which had lead/alloy composition. Virtually all metals can produce toxicity when ingested in sufficient quantities, but there are several which are especially important because either they are so pervasive or produce toxicity at such low concentrations. Bear in mind that there is a considerable crossover in many of the toxic manifestations of the different metals, and in the agents used to treat the toxicity.

Acute metal toxicity due to occupational/industrial exposure can be readily diagnosed by means of patient history, overt symptoms and certain toxicological tests. However, the subtler effects of chronic, low-level exposures are associated with rather nondescript symptoms, and overt expressions of physiological aberrations are often not realized until later in life. This is particularly apparent for the neurotoxic effects associated with the sulfhydryl-reactive metals like arsenic (As), cadmium (Cd), lead (Pb), mercury (Hg), and palladium (Pd).

Biological Interactions of Toxic Metals

Generally, metals produce their biological toxicity by forming complexes or "ligands" with organic compounds. These modified biological molecules lose their ability to function properly and result in malfunction or death of the affected cells. The most common groups involved in ligand formation are oxygen, sulfur, and nitrogen. When metals bind to these groups they make inactive important enzyme systems or affect protein structure. Persons with a metal-metabolism disorder can be especially at risk since they may tend to accumulate, rather than eliminate, these toxins.

Toxic metals tie up the cysteine in our food and, when the protective endogenous thiols (metallothionine and glutathione) are saturated, they also trap, proteins, peptides, enzymes, lipoic acid, other thiols critical to the proper functioning of our bodies. This causes nutritional deficiencies of critical amino acids, enzymes, and minerals necessary for numerous metabolic functions.

The sulfhydryl-reactive metals mentioned above have three major properties that mechanistically explain how they elicit a majority of their toxic effects. First, they are transition metals that promote the formation of hydrogen peroxide and enhance the subsequent iron- and copper-induced production of lipid peroxides and the highly reactive hydroxyl radical. Lipid peroxides alter membrane structure and are highly disruptive of mitochondrial function.

The pro-oxidant properties of the metals are exacerbated by their inhibitory effects on antioxidant processes. Hg and Cd have high affinities for glutathione (GSH), which is the primary intracellular antioxidant and conjugating agent. Importantly, a single atom of Cd or Hg can bind to, and cause the irreversible excretion of, up to two GSH tripeptides. The metal-GSH conjugation process is desirable in that it results in the excretion of the toxic metal into the bile. However, it can deplete the cell of GSH and thus decrease antioxidant capacity. Lead-induced depletion of intracellular GSH and increased levels of malondialdehyde in brain and liver have been demonstrated in animal models. It has also been demonstrated that Hg not only directly removes GSH from the cell, but also inhibits the activities of two key enzymes involved in GSH metabolism: GSH synthetase and GSH reductase. Hg also inhibits the activities of the free radical quenching enzymes catalase, superoxide dismutase, and perhaps GSH peroxidase. The inhibition of GSH peroxidase has been attributed to the formation of a mercury-selenide complex. Selenium is an integral component of GSH peroxidase.

In addition to promoting lipid peroxidation, depleting GSH and inhibiting antioxidative processes, the sulfhydryl-reactive metals disrupt the structure and function of numerous important proteins through direct binding to free sulfhydryl groups. Intact sulfhydryl groups are critical for the biological activities of virtually all proteins, including Na/K ATPase. Metal-induced inhibition of Na/K ATPase can result in astrocytic swelling and destruction; astrocytes are the primary cells responsible for the homeostatic regulation of synaptic pH, Na/K and glutamate, and metal sequestration in the CNS. Recent studies clearly illustrate how destructive the interaction between Hg and sulfhydryl groups can be. Hg inhibits the polymerization of tubulin, causes depolymerization of existing microtubules, and in animal studies results in brain lesions that closely resemble those found in patients with Alzheimer's disease.

Certain “transition metals” like nickel, cadmium, mercury and palladium are carcinogenic to humans. However, certain mechanisms of their carcinogenic activity remain obscure. One possible mechanism would involve metal-mediated promutagenic oxidative damage to DNA and nuclear proteins. Another one would include adverse effects on the fidelity of DNA replication and repair processes, as well as derangement of gene expression and cell signaling, through interactions with essential metals and/or induction of conformational changes in biomolecules.

As with all metals, these “transition metals” are both ductile and malleable and conduct electricity and heat. The interesting thing about transition metals is that their valence electrons, or the electrons they use to combine with other elements, are present in more than one shell. This is the reason why they often exhibit several common oxidation states. And it is this unique ability that allows them to inhibit antioxidative processes and thereby create reactive oxygen toxic species (ROTS). In general, the transition metals promote excessive production of lipid peroxides and hydroxyl radicals that inhibit antioxidative enzymes. These also inhibit a plethora of other enzyme families by virtue of their high affinity for free sulfhydryl groups (e.g. Creatinine kinase, Na/K ATPase). The metals deplete intracellular glutathione (GSH), and inhibit enzymes involved in the synthesis and metabolism of the important antioxidant and metal-conjugating peptide. Thought this manual introduces only 5 of the 38 transition metals (cadmium, copper, mercury, nickel, and palladium) there are other *potentially* toxic transition metals noteworthy of mention. They are: iron, cobalt, gold, manganese, chromium, and tungsten.

The elements classified as "other metals" are ductile and malleable; they are not the same as the transition elements. These elements, unlike the transition elements, do not exhibit variable oxidation states, and their valence electrons are only present in their outer shell. All of these elements are solid, have a relatively high density, and are opaque. They have oxidation numbers of +3, ±4, and -3. Of

these aluminum and lead are explained in this paper; other noteworthy *potentially* toxic metals in this category are: tin, bismuth and thallium.

Adaptive Responses to Metal Toxicity

The body makes important adaptive changes in response to exposure to sulfhydryl-reactive metals. Studies in rats illustrate the importance of Glutathione (GSH) metabolism in the presence of Hg exposure. Short and long-term exposure to methyl-mercury (MeHg) in drinking water resulted in a two- to three-fold up-regulation of mRNA encoding for g-glutamylcysteine synthetase, which is the rate-limiting enzyme in GSH synthesis. Concomitantly, there was a similar magnitude of increase in the steady state levels of GSH, and the activities of GSSH reductase and GSH peroxidase. These data illustrate a protective, adaptive response to Hg exposure in renal epithelial cells. Neurons do not appear to have such adaptive capacity, which may partially explain why Hg is relatively more neurotoxic then nephrotoxic.

A second adaptive and protective response to toxic metal exposure is induction of metallothionein synthesis. Metallothioneins are a fascinating group of low molecular weight, intracellular proteins that serve as a storage depot for copper and zinc, and "scavenge" sulfhydryl-reactive metals that enter the cell. Metallothioneins across species are rich in cysteine (~30%) and have higher affinities for the transition metals mercury and cadmium than for zinc. Therefore, as Hg and Cd bind to metallothionein, and are restricted from entering the mitochondria, zinc is released. The free, ionized zinc, which would be toxic if permitted to accumulate, binds to a metal regulatory element on the promoter region of the metallothionein gene and "turns on" the synthesis of metallothionein. Such induction of metallothionein provides increased binding capacity for both toxic metals (protective) and zinc (functional). The displacement of zinc in the presence of toxic metal burden may explain in part why increased levels of zinc are so commonly seen in the scalp hair of patients exhibiting significant levels of toxic metals Hg, Cd, Cu, Pb.

The importance of metallothionein in the protection against certain toxic metals is evident. Mammalian cell lines with the greatest number of copies of the metallothionein gene, and the highest levels of metallothionein survived exposure to Cd in culture media. MT-null mice, genetically engineered to have inactivated metallothionein genes, died within three days of exposure to Cd in drinking water, while control (normal) mice did not exhibit any signs of Cd toxicity. Rat pups exposed to Hg vapor in utero were born with higher levels of metallothionein mRNA and metallothionein levels in astrocytes. Metallothionein levels are also induced in primary astrocyte cultures by CdCl2 and MeHg. The induction of metallothionein in astrocytes is very important in protecting the CNS since neurons cannot up-regulate GSH or metallothionein synthesis in response to metal exposure.

Chelation and Detoxification for Toxic Metals

Toxic metals form one of the most hazardous environmental toxicants posing deleterious health risk in humans due to continued exposure. Researchers dedicated to investigating metal toxicity have achieved considerable success in analyzing risk assessments in humans, identifying the diagnostic markers and revealing the underlying pathways.

Chelation therapy has been the mainstay therapy in metal poisoning and related disorders. The term chelate was first applied by Sir Gilbert T. Morgan and H.D.K. Drew in 1920. They suggested the term for the caliper-like groups which function as two associating units and fasten to a central atom to produce heterocyclic rings. The Greek word chelate means claw and the process of ring formation is termed chelation. In molecular terminology, the larger the number of ring closures to a metal atom, the more stable the compound. This phenomenon is called the “chelate effect” and it is generally attributed to an increase in the thermodynamic quantity called entropy that accompanies chelation. The stability of a chelate is also related to the number of atoms in the chelate ring.

Chelating agents offer a wide range of sequestrants to control metal ions in aqueous systems. By forming stable water-soluble complexes with multivalent metal ions, chelating agents prevent undesired interaction by blocking normal reactivity of metal ions.

For these compounds to be of therapeutic relevance they must

i) be water soluble,
ii) be resistant to biotransformation,
iii) cross through physiological barriers into compartments where a toxic metal ion is accumulated (the mesenchyme, the cells),
iv) form a stable complex with the metal that is non-toxic,
v) be easily excreted from the site of deposition and body and not recycled into other tissue,
vi) exhibit low affinity for essential metals (Ca, Zn, Cu, Mn, Mg, Se, Fe).

Commonly known chelating agents used in chelation therapy include calcium disodium ethylenediaminetetraacetic acid (CaNa2EDTA), 2,3-dimercaptopropanol also known as British Anti-Lewisite (BAL), D-Penicillamine, meso-2, 3-dimercaptosuccinic acid (DMSA), 2, 3-dimercaptopropanesulfonic acid (DMPS), polyaminocarboxylic acids diethylenetriaminepentaacetic acid (DTPA), cyclohexanediaminetetraacetic acid (CDTA), hydroxycarboxylic acid sodium catechol 3, 5-disulfonate (Tiron), dithiocarbamates (DDC), desferrioxamine (DFO) and deferiprone (L1). CaNa2EDTA is probably one of the most commonly used chelating agents (mainly known for application against lead poisoning). CaNa2EDTA is administered intravenously as dextrose or saline infusion due to poor gastric absorption.

The most commonly prescribed oral chelator today is DMSA (its chemical acronym), also known as Chemet. This is a prescription drug available in an oral formulation only; it is approved for use in the treatment of lead poisoning in

pediatric patients with blood lead levels >45 µg/dL. While generally safe, DMSA has been associated with mild elevations in hepatic transaminases and allergic reactions. DMSA is also used in the treatment of mercury and arsenic poisoning although these are not FDA-approved indications.

Most chelating agents used today have side effects, some potentially serious - caused primarily by the release of toxic metals into the bloodstream and into the kidneys. Most of the â€œsaferâ€ chelating agents (CaNa2EDTA, DMSA) show partial efficacy in case of chronic metal exposure due to their inability to cross physiological barriers. CaNa2EDTA cannot pass through cellular membranes and therefore its use is restricted in removing metal ions from their complexes in the extracellular fluid. Similarly, conventionally used DMSA shares the limitation of extracellular distribution.

This is why chronic poisoning (the slow accumulation of metal inside the cells) becomes difficult to address, and why chelation therapy has been both challenging and long debated. Although conventionally known chelating agents do show therapeutic efficacy, more specific and safer compounds are needed. Moreover, supplementing conventional chelation therapy with essential minerals and metals (zinc, selenium, sulfur, manganese) has also been shown to improve metal detoxification outcomes.

Oxidative stress may be considered one of the prime contributing mechanisms in metal toxicity and thus provides a strong rationale for including antioxidants during chelation therapy. Combinational therapies with antioxidants like lipoic acid, vitamin C, N-acetyl cysteine, and glutathione have shown considerable promise in improving clinical recoveries in animal models. Several botanicals and naturally occurring substances (algae, cilantro, clay, shilajit, gossypin), also are effective compounds for chelation support or substitution.

This paper provides insight into ten common and highly toxic metals: aluminum (Al), antimony (Sb), arsenic (As), beryllium (Be), cadmium (Cd), copper (Cu), lead (Pb), mercury (Hg), nickel (Ni) and palladium (Pd). The specific sources of exposure, biochemical interactions, body tissues in which the metal tends to be deposited, and health effects of each metal are briefly identified. A reference of common chelating, complexing and conjugating agents of detoxification is included at the end of the toxic element descriptions.

Aluminum	Al	Atomic number 13	Atomic mass 26.9815

Sources of Exposure

Third only to oxygen and silicon in its prevalence, aluminum is estimated to be the most abundant metal in the Earth's crust. The following are all potential sources: tap water (especially if clarified by alum), and corrosion of the sacrificial anode rod (if it contains aluminum) in hot water tanks can be a further source. Fluoride-treated water increases aluminum bioavailability and uptake. It may generally be seen that the highest aluminum exposure is most frequently due to the chronic consumption of aluminum hydroxide antacids. An examination of labels on consumer products will reveal that many of them contain aluminum. Aluminum in consumer drugs is a big problem. Aspirin is commonly buffered with aluminum hydroxide, aluminum glycinate and other aluminum compounds. Aluminum is present in vaccines such as hepatitis A, hepatitis B, diphtheria-tetanus-pertussis, Haemophilus influenzae type b, human papillomavirus and pneumococcus. Aluminum is placed in the vaccines to selectively target the up-regulation of the humoral arm (TH2 cells) of children’s immune systems, to drive the production of antibodies. This topic of aluminum dangers in vaccines deserves its own 100-page paper.

Other sources of aluminum are vaginal douches that contain potassium aluminum sulfate, ammonium aluminum sulfate, and alum. Some antacids contain aluminum hydroxide, dihydroxyaluminum, and aluminum oxide. Anti-diarrheal drugs contain aluminum magnesium silicate and kaolin, an aluminum salt.

Regarding aluminum in foods, starting sometime in the late 19th century and progressively more so since the mid-20th century, large-scale industrial food production the world over has enabled the abrupt and dramatic switch from a largely unprocessed to processed diet, the so-called 'Western' diet. Doing so has

only increased aluminum bioavailability, especially human oral exposure. Such additives are found in dairy (milk, processed cheese, yogurt), staples (cereals, flours, grains), sweets (sugar, jams, jellies, baking sodas, powdered or crystalline dessert products). Use in food thus ranges from anticaking agents, to buffers, emulsifying agents, firming agents, leavening agents, neutralizing agents and texturizers. Aluminum contaminates drinking water, milk and other products. Other sources include: antiperspirants, food additives, lipstick, hemorrhoid medications, "softened" water, and tap water.

Target Tissues

Aluminum toxicity is usually found in patients with renal impairment. Acute intoxication is extremely rare; however, in persons in whom aluminum clearance is impaired, it can be a source of significant toxicity. Aluminum accumulates progressively in bone, lung, liver, kidney and brain. Of the total body burden of aluminum, about one-half is in the skeleton, and about one-fourth is in the lungs. Research shows that aluminum builds up in the body over time; thus, the health hazard to older people is greater.

Biochemistry

It appears that humans do not need aluminum for any biochemical purpose. Approximately 95% of an aluminum load becomes bound to transferrin and albumin intravascularly and is then eliminated renally. In healthy subjects, only 0.3% of orally administered aluminum is absorbed via the gastrointestinal (GI) tract, and the kidneys effectively eliminate aluminum from the human body. When the GI barrier is bypassed, such as by intravenous infusion, intramuscular injection (vaccines) or in the presence of advanced renal dysfunction, aluminum has a potential to significantly accumulate.

Absorption from the GI tract is normally minimal, being decreased by the presence of dietary phosphates, but increased by the presence of citric or malic acids (carboxylic acids). Individuals with kidney disorders such as azotemia or

uremia may absorb increased quantities of this element. Current evidence shows that aluminum exposure becomes most toxic when dietary magnesium is low. Excretion of aluminum from blood is primarily by urine, while RBC-bound aluminum is mostly excreted via the bile.

Once in the body aluminum follows increasing concentrations of phosphate. It may also bind to transferrin in the blood and to citric or malic acids (carboxyl acids). Binding and increasing transport also occurs with the amino acid glycine. Aluminum may bind to DNA, ATP, NADP, NADPH or phosphorylated proteins, once inside the cell. Aluminum impairs production of alpha-ketoglutaric acid in cell mitochondria by interfering with the enzyme, isocitrate dehydrogenase. Low alpha-ketoglutaric acid may then lead to disordered nitrogen balance that may impair protein synthesis, especially in neurological tissues. This depletion in alpha-ketoglutarate also causes an interference with bone mineralization, binds to brain calmodulin, and may enhance acetylcholine turnover that results in its depletion and results in neuronal plaques.

Signs and Symptoms Research

There are numerous studies that have examined aluminum's potential to induce toxic effects in humans exposed via inhalation, oral, dermal exposure or by injection with vaccines. Most of these findings are supported by many studies in laboratory animals. Occupational exposure studies and animal studies suggest that the lungs and nervous system may be the most sensitive targets of toxicity following inhalation exposure. Most of the animal studies have focused on neurotoxicity and neurodevelopmental toxicity.

Neurodegenerative changes in the brain, manifested as intraneuronal hyperphosphorylated neurofilamentous aggregates, is a characteristic response to aluminum in certain species and nonnatural exposure situations generally involving direct application to brain tissue, particularly intracerebral and

intracisternal administration and in vitro incubation in rabbits, cats, ferrets, and nonhuman primates.

There is an interesting parallel between the incidence of Alzheimer's disease and similar memory disorders, and the amount of aluminum in drinking water. Aluminum emerged as a potential cause of Alzheimer's disease in the 1960s when a 1965 study observed neurofibrillary tangle-like degeneration after directly injecting aluminum into rabbit brains, i.e., lesions *similar but not identical* to those considered a hallmark of Alzheimer's disease. A 1973 study followed-up with the report of higher levels of aluminum in post-mortem Alzheimer's disease brain samples. A study published in Lancet, involved an evaluation of the geographical relationship between the aluminum content of drinking water and the prevalence of Alzheimer's over a ten-year period. The study reported a 50% increase in the risk of Alzheimer's disease in areas with high concentrations of aluminum. Even a small presence of aluminum in water has an effect. Researchers learned that the risk of Alzheimer's was 1.5 times higher when the aluminum concentration exceeded 0.11 mg/l than in areas where the concentration was 0.01 mg/l. There was no evidence of any relationship between any other form of dementia, including epilepsy, and the presence of aluminum in drinking water.

It is interesting that about 50% of British drinking water is also treated with iron, which is also suspected of being a co-factor in dementia. These studies have been corroborated by studies done in other countries (other than the United States, in which such a study would be a conflict of interest with the industry), especially in Norway and Australia.

It is also interesting that studies of motor-neuron diseases in Guam, where a tremendous increase in amyotrophic lateral sclerosis (ALS) has occurred, found parallels between ALS and high concentrations of aluminum in drinking water. Swedish studies of the Guam ALS problem conclude that mortality from motor-neuron disease, especially among women, varies with the local water

concentration of aluminum. Ten percent of the total populations of native Guamanians die of brain disease. Fifteen percent of the natives in the Mariana Islands die of neurodegenerative disease. Why? Part of the answer is that there are high levels of aluminum in the drinking water. There are also high levels of aluminum in the food.

Research conducted in 1988 conducted by the Medical Research Council revealed that long-term exposure to aluminum contributed to plaque deposits in the cerebral cortex and aluminum deposition in neurons. Patients with loss of memory frequently have high blood aluminum levels above 20 ppb. As magnesium, zinc and vitamin C. are given the high blood aluminum level decreases to normal (less than 10 ppb) and memory improves.

Many human studies have examined the occurrence of cancer among aluminum industry workers and found a higher-than-expected cancer mortality rate, but this may also be due other potent carcinogens to which they are exposed, such as polycyclic aromatic hydrocarbons (PAHs) and tobacco smoke. Available cancer studies in animals have not found biologically relevant increases in malignant tumors. The International Agency for Research on Cancer (IARC) concluded that aluminum production was carcinogenic to humans and that pitch volatiles have consistently been suggested in epidemiological studies as being possible causative agents. The Department of Health and Human Services and EPA have not evaluated the human carcinogenic potential of aluminum.

Certain vaccines contain aluminum salts as adjuvants. Despite almost 90 years of widespread use of aluminum adjuvants, medical science's understanding about their mechanisms of action is still remarkably poor. There is also a concerning scarcity of data on toxicology and pharmacokinetics of these compounds. Aluminum is present in the following U.S. childhood vaccines: hepatitis A, hepatitis B, diphtheria-tetanus-pertussis (DTaP, Tdap), Haemophilus influenzae type b (Hib), human papillomavirus (HPV) and pneumococcus

infection. Each of these vaccines contains aluminum, and multiple doses (booster shots) are required. Hence, babies are injected with 1,225 mcg of aluminum instantaneously at age 2 months, and 4,925 mcg of accumulated aluminum by age 18 months. As a result, vaccinated children following the CDC recommendations are exposed to up to 6 mg of aluminum in the first 2 years of life. Experimental research clearly shows that aluminum adjuvants have a potential to induce serious immunological disorders in humans. Aluminum in adjuvant form carries a risk for autoimmunity, long-term brain inflammation and associated neurological complications and may thus have profound and widespread adverse health consequences.

Some people develop macrophagic myofasciitis (MMF) after receiving an aluminum-containing vaccine. MMF is characterized by an aluminum-filled lesion (wound) at the site of an earlier vaccination. MMF lesions occur when the aluminum adjuvant from a vaccine remains embedded in the muscle tissue and causes a continuous immune reaction. The lesions are persistent, long-term granulomas (or inflammatory tumors) found in the quadriceps in children and deltoid muscles of adults, common vaccination sites. Several vaccines contain aluminum hydroxide, which has been identified as the causal factor of MMF lesions.

Nutrients Known to be Protective Against Aluminum

Silica, phosphorus, magnesium, zinc, iron, calcium, glycine, and vitamin C are antagonistic for aluminum uptake and retention. The chemical affinity of silica for aluminum has been shown to reduce the bioavailability of aluminum in studies of human gastrointestinal absorption. Mg, Na2EDTA has been clinically shown to be an effective IV chelating agent for aluminum.

Specific Protocols for Aluminum Detoxification

As with all detoxification protocols, the type, dose and duration of detoxification agents should always be individually assessed. The following may serve as a

basic guideline for detoxification of excess aluminum from chronic exposure. After 60 days laboratory and electrodermal screening should be used to reassess the protocol. Before initiating a detoxification program, a CBC with chemistry, including a thyroid panel with lipids should be performed. In addition, whole blood elements to assess the mineral status and a urine creatinine clearance should be performed every 60 days when using synthetic detoxifying agents (EDTA). Administration of synthetic agents may cause a depletion of essential elements such as zinc, iron, calcium, magnesium, copper and other trace minerals. Of greatest concern is potential kidney toxicity that can occur when the body releases its aluminum stores for excretion through the kidneys. Those with underlying kidney disease may not be able to undergo aggressive aluminum detoxification therapy.

1. To evaluate aluminum toxicity a 24-hour urine analysis is the most definitive test. An oral dose of glycine, 80-mg/Kg body weight, given in divided doses over a 24-hour urine collection period provides a non-invasive, diagnostic procedure for flushing out aluminum. Glycine is an excellent complexing agent for aluminum. However, glycine by itself is *not* recommended as a daily or periodic detoxification remedy for aluminum excess. Because it has been shown to move aluminum about, it may increase aluminum uptake and transport into other tissues.
2. First, remove any known sources of aluminum.
3. Assess whole blood cell element analysis to determine mineral nutrient deficiency and supplement appropriately.
4. Supplement with a silica source. Silica is found in all tissues and organs of the body including the skin, hair, nails, teeth, bones, tendons and ligaments. It restores the necessary balance between calcium and magnesium. Hence, not only does it help eliminate excess aluminum, but it is nutritional as well. Silica comes in powder and colloidal forms and may be taken daily. Silica supplements can product toxicity in people at doses over 100 mg per day, but horsetail supplements (which are a natural source of silica) have less toxicity

at higher doses than other sources of silica. A recommended daily intake of silica has only been established for adults aged 19-50 years with a range of 10-15 mg per day. The best way to eat a diet rich in silica is to include a lot of raw organic radish, alfalfa, cucumber, romaine lettuce, watercress, capsicum, wheatgrass and marjoram.

5. Vitamin C (non-corn source) may be utilized to help detoxify aluminum excess. Administer gram quantities to bowel tolerance.
6. Administer magnesium glycinate 100 to 300 mg daily (watch for diarrhea and if present reduce dose of magnesium).
7. Algal cells have a remarkable ability to take up and accumulate heavy metals from their external environment. The primary ones used for toxic metal excess are Chlorella vulgaris, a green microalga, and Laminaria japonica, a brown alga. Chlorella and Laminaria japonica are both chelators, moving toxic metals out of the body and transporters, moving metals from deeper stores to more readily removal areas. Both work in unison with each other and can remove toxic metals from the body through urinary excretion. Administer 1000 to 2000 mg of Laminaria japonica concentrate (Modifilan) daily and 1000 to 2000 mg of chlorella. Adjust dosage to bowel tolerance; may be taken for long periods of time.
8. Cilantro works well with alga to chelate, or bind, up toxic metals. The issue with cilantro taken alone is that although it chelates metals, it does not remove them in the urine. This means they can recirculate to deposit elsewhere in the body. Hence, taken with algas metals are more effectively eliminated in the urine.
9. Shilajit is an ancient traditional medicine (Tibetan and Ayurvedic) and has been ascribed a number of pharmacological activities and has been used for ages as a rejuvenator and for treating a number of disease conditions. It is an effective detoxifier of metals and contains over 60 minerals. Modern scientific research has systematically validated a number of properties of shilajit and has proven that shilajit is truly a panacea. It is important to purchase the highest grade of shilajit.

10. Instruct patient to drink adequate amount of pure water (Adult's urine volume should be about 2 liters per day).

More aggressive treatment for aluminum excess involves the use of magnesium disodium ethylene diamine tetraacetate (Mg, Na2EDTA) chelation. EDTA is an excellent chelator of trivalent ions that are in the bloodstream. The glycine may assist the Al excretion and can transfer it to the EDTA. Check for renal clearance first. The protocol for IV EDTA chelation is available from the American College for the Advancement in Medicine (ACAM), http://www.acam.org/ If you are unfamiliar with EDTA therapy, you may wish to refer the patient to a physician who is board certified by the American Board of Chelation Therapy (ABCT), http://chelation.me/

In conventional medicine the treatment of *Acute* aluminum toxicity is often with desferrioxamine, a synthetic chelator of aluminum and iron. Desferrioxamine (DFO) is used primarily as an iron-chelating agent but does have affinity for aluminum as well. DFO has a high and almost specific affinity for the ferric ion. It is poorly absorbed from the GI tract, but when administered by mouth it can chelate iron within the GI tract. DFO used to be thought of as an agent with antioxidant potential as it chelates ferric iron in various parts of the body. However, there is evidence suggesting that it may paradoxically and adversely affect red blood cells by *inducing intracellular oxidant stress.* Also, DFO increases the growth of human Kaposi's sarcoma (KS) xenografts in immunodeficient mice. According to investigators in Belgium, this drug should be avoided in patients with KS. With this chelator there is also the risk of inadvertently mobilizing large amounts of aluminum into the brain, which may enhance encephalopathy rather than improving it. Hence, due to these potential side effects, DFO *is not recommended* for aluminum excess due to chronic exposure.

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Antimony	Sb	Atomic number 51	Atomic mass 121.760

Sources of Exposure

Antimony (Sb) (pronounced an'ti-mo'nee) ores are a silvery-white metal that are mined and then mixed with other metals to form Sb alloys or combined with oxygen to form antimony oxide. Antimony oxide is a white powder that is insoluble in water. Little Sb is currently mined in the United States. It is brought into this country from other countries for processing. However, there are companies in the United States that produce antimony as a by-product of smelting lead and other metals. When mixed into alloys, it is used in lead storage batteries, solder, sheet and pipe metal, bearings, castings, and pewter. Antimony oxides (primarily antimony trioxide) are used as fire retardants for plastics, textiles, rubber, adhesives, pigments, and paper. It is also used in paints, ceramics, semiconductors, fireworks, and explosives and as enamels for plastics, metal, glass.

Everyone is exposed to low levels of Sb in the environment. Antimony and its compounds are naturally present in the Earth's crust and are released into the environment by natural discharges such as windblown dust, volcanic eruptions, sea spray, forest fires, and biogenic sources. Antimony is also released into the environment from industry and is found in air near industries that process or release it, such as smelters, coal-fired plants, and refuse incinerators. Workers in industries that process it or use antimony ore may be exposed to higher levels.

In the air, Sb is attached to very small particles that may stay in the air for many days. Most Sb ends up in soil, where it attaches strongly to particles that contain iron, manganese, or aluminum. Antimony is found at low levels in some rivers, lakes, and streams.

Antimony toxicity is dependent on the exposure dose, duration, route (breathing, eating, drinking, or skin contact), other chemical exposures, age, sex, nutritional status, family traits, lifestyle, and state of health. Toxic exposure can take place in the mining and extraction industries. Antimony released from smelters may remain in particulate quantities in the air, some of which reaches the soil during rainfall - where it attaches strongly to particles containing iron, manganese, or aluminum.

The Occupational Safety and Health Administration (OSHA) has set an occupational exposure limit of 0.5 milligrams of Sb per cubic meter of air (0.5 mg/m^3) for an 8-hour workday, 40-hour workweek. The American Conference of Governmental Industrial Hygienists (ACGIH) and the National Institute for Occupational Safety and Health (NIOSH) currently recommend the same guidelines for the workplace as OSHA.

Because Sb is found naturally in the environment, the general population is constantly exposed to low levels daily primarily from food and drinking water. The EPA allows 0.006 parts of Sb per million parts of drinking water (0.006 ppm). The EPA requires that discharges or spills into the environment of 5,000 pounds or more of Sb be reported.

Biochemistry

Antimony has no biological role in the human body, though in small doses it is said to stimulate metabolism. Antimony is in the same periodic group as nitrogen, phosphorus and arsenic, and exhibits toxic properties and biological activity similar to that of arsenic. Like arsenic, it is often described as a metalloid element. Acute (short-term) exposure to Sb by inhalation in humans results in effects on the skin and eyes. Respiratory effects, such as inflammation of the lungs, chronic bronchitis, and chronic emphysema, are the primary effects noted from chronic (long-term) exposure to antimony in humans via inhalation. Acute excess exposure also causes loss of hair, dry scaly skin and weight loss.

Damage to the heart, liver and kidney can occur and death from myocardial failure may follow. With chronic exposure, there are effects on the skin (antimony spots), mucous membrane (irritation) and pneumoconiosis.

Antiparasitic treatment of Leishmaniasis or Schistosomiasis with antimony compounds can also lead to toxicity. Inhalation of the highly toxic gas stibine (SbH_3) can result in headache, nausea and vomiting, jaundice and anemia. All antimony compounds are highly toxic and cause severe liver damage.

The British Pharmaceutical Codex from 1907 points out its highly poisonous nature, but indicates that certain forms of Sb were used in various forms as a medicine, for instance to induce vomiting and as a diaphoretic (to induce sweating). It seems that antimony chloride was used (rarely) as a medicine of last resort against "poisoned wounds and cancerous growths".

One study indicated that women workers exposed in an Sb plant experienced a greater incidence of spontaneous abortions than did a control group of non-exposed working women. A high rate of premature deliveries among women workers in Sb smelting and processing was also observed.

The Department of Health and Human Services, the International Agency for Research on Cancer, and the Environmental Protection Agency (EPA) have not classified Sb as to its human carcinogenicity. Lung tumors have been observed in rats exposed to Sb trioxide by inhalation. No human carcinogenicity studies have been published, but many toxicologists have suspected it to be a human carcinogen.

The EPA's Office of Air Quality Planning and Standards, for a hazard ranking under Section 112(g) of the Clean Air Act Amendments, considers Sb pentafluoride to be a "high concern" pollutant based on severe acute toxicity.

Target Tissues and Organs

Daily consumption of Sb is estimated at 0.1 mg and is usually poorly absorbed and eliminated in the feces and urine. However, some Sb is stored in the skin, eyes, liver, spleen, kidneys, heart, blood, and connective tissues.

Signs and Symptoms of Toxic Excess

Exposure to antimony at high levels can result in a variety of adverse health effects. The primary effects from chronic (long-term) exposure to antimony in humans are respiratory effects that include antimony pneumoconiosis (inflammation of the lungs due to irritation caused by the inhalation of dust), alterations in pulmonary function, chronic bronchitis, chronic emphysema, inactive tuberculosis, pleural adhesions, and irritation. Other effects noted in humans chronically exposed to antimony by inhalation are cardiovascular effects (increased blood pressure, altered EKG readings and heart muscle damage) and gastrointestinal disorders such as stomach pain, diarrhea, vomiting, and stomach ulcers. Skin effects consist of a condition known as antimony spots, which is a rash consisting of pustules around sweat and sebaceous glands, while effects on the eye include ocular conjunctivitis.

Exposure to high levels of Sb for short periods of time causes nausea, vomiting, and diarrhea. In short-term studies, animals that breathed very high levels of Sb died. In long-term studies, animals that breathed very low levels of antimony had eye irritation, hair loss, lung, heart, and kidney damage. Problems with fertility were also noted. In animal studies, problems with fertility have been seen when rats breathed very high levels of Sb for a few months.

In one human study, inhalation exposure to Sb did not affect the incidence of cancer in workers employed for 9 to 31 years. Lung tumors have been observed in rats exposed to Sb-trioxide by inhalation. The EPA, however, has not classified antimony for carcinogenicity.

Nutrients Known to be Protective Against Antimony

Sulfur containing amino acids; calcium, iodine, selenium, zinc and vitamin C are antagonistic for Sb uptake and retention. EDTA has been clinically shown to be an effective IV chelating agent for excess Sb.

Specific Protocols for Antimony Detoxification is like Arsenic detoxification (see Arsenic).

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Arsenic	As	Atomic number 33	Atomic mass 74.9216

The word arsenic (As) is derived from the Greek word *arsenikon*, which itself is derived from the Persian word *Zarnikh*, meaning yellow orpiment, a brightly colored compound of arsenic and sulfur. Although it is a metalloid with characteristics of both metals and nonmetals, arsenic is commonly characterized as a heavy metal. Arsenic compounds have been known for at least 5000 years. Although As compounds were mined and used by the early Chinese, Greek and Egyptian civilizations, it is believed that As itself was first identified by Albertus Magnus, a German alchemist, in 1250. The first precise directions for the preparation of metallic arsenic, however, are found in the writings of Paracelsus, a physician-alchemist in the late Middle Ages who is often called the father of modern toxicology. In Europe from the time of the Roman Empire through the Middle Ages and the Renaissance, arsenic was the king of poisons. The odorless and tasteless properties of inorganic arsenic compounds such as arsenic trioxide (white arsenic) made them an ideal poison. Hence, arsenic has been used as a means for settling old scores, an instrument for personal advancement, to execute criminals, and by those who found life to be an intolerable burden.

In 1940, it became known to Allied intelligence that the Germans had developed an organic blistering war gas containing As, which was known by the code name Lewisite. On contact with the skin, the gas reacted with sulfur on keratin, a skin protein, to produce huge blisters that were worsened by the release of caustic hydrochloric acid, also produced by the chemical reaction.

The British response to this threat was an intensive research program that culminated in the discovery of a simple sulfur-containing organic molecule which was highly effective in inactivating Lewisite on the skin, since it attracted arsenic away from biologically more important sites. This effective antidote became

known by the acronym of BAL, for British Anti-Lewisite. Later it was given the generic name, dimercaprol.

After the war, interest in dimercaprol continued, and in view of its low toxicity, it was tested against As that had been taken internally. It was found to bind arsenic tenaciously and to hasten its excretion in the urine. It thus became the first rationally developed chelating agent - a chemical trap that sequesters and disables toxins. It is also used in treating people with mercury and gold poisoning.

In both 2007 and 2011, arsenic topped the Agency for Toxic Substances and Disease Registry (ATSDR) Priority List of Hazardous Substances, which ranks hazardous substances based on their frequency, toxicity, and potential for human exposure from hazardous waste sites.

Sources of Exposure and History of Use

Arsenic is a naturally occurring element but is most often found in the minerals arsenopyrite (FeAsS), realgar (AsS) and orpiment (As_2S_3). Inorganic As compounds are more toxic than organic compounds, but organic As compounds are converted to inorganic compounds when absorbed in biological systems.

The following are all potential As sources: air pollution, antibiotics given to commercial livestock, certain marine plants, chemical processing industry (reagents, catalysts), electroplating, galvanizing and etching processes, coal-fired power plants, tap water, drying agents for cotton, contaminated shellfish (mussels, oysters), or other seafood, defoliants, some fungicides, insecticides - especially those used to treat lumber, meats (from commercially raised poultry and cattle), metal ore smelting, fireworks (intense white and blue colors), leather tanning and taxidermy, textile printing, lead and copper alloys (cable sheaths, solders, shot), specialty glass (opal glass, IR transmitting, decolorizing).

Arsenic is no longer produced in the United States; all the As used in the United States is imported. Arsenic is found in the preservative chromated copper arsenate (CCA) used to preserve wood. 90% of all As consumed in the U.S. is used in the production of CCA. The CCA treated wood is referred to as “pressure-treated". There is considerable concern over this type of arsenic introduced into the environment. In the past, As was primarily used as a pesticide on cotton fields and in orchards. Inorganic As compounds can no longer be used in agriculture in the US. However, organic arsenicals, namely cacodylic acid, disodium methylarsenate (DSMA), and monosodium methylarsenate (MSMA) are still used as pesticides, principally on cotton. Small quantities of As metal are added to other metals forming metal mixtures or alloys with improved properties. The greatest use of As in alloys is in lead-acid batteries used in automobiles. Another important use of As compounds is in semiconductors and light-emitting diodes.

In the 19th century, women applied As powder to whiten their faces as well as to their hair and scalp to destroy vermin. It was also thought that As consumption by women gave "beauty and freshness" to the skin, an appearance of “*pour rajeunisante*”.

In 1786, Thomas Fowler, a British physician, published a study on the effectiveness of his solution of 1% potassium arsenite which he called "Liquor mineralis", for "agues, remittent fevers, and periodical headaches". In 1809, "Liquor mineralis", known by that time as "Fowler's solution", was accepted into the London Pharmacopeia and became widely used as an alternative to quinine for "agues" (malaria) and was used for "sleeping sickness" (trypanosomiasis). By the 1880s, Fowler's solution was used for a variety of other ailments including asthma, eczema, psoriasis, anemia, hypertension, gastric ulcers, heartburn, rheumatism, and tuberculosis, and arsenic paste was used to treat cancers of the skin and breast. Taking Fowler's solution as a treatment for various chronic

disorders was popular with Victorian prostitutes to give them rosy cheeks, an effect due to damage to the capillaries of the skin.

Other As preparations at that time included Donovan's solution (arsenic triiodide and mercuric iodide) and de Valagin's solution (arsenic trichloride), both used to treat similar disorders. In 1878, Fowler's solution was discovered to lower the white cell count in chronic myelogenous leukemia and was used as the main treatment for leukemia until the advent of radiation and chemotherapy in the 20th century. Fowler's solution remained a treatment for many conditions well into the 20th century, and is listed along with As-trioxide and sodium arsenate in the 1914 edition of the American Medical Association's Handbook of Useful Drugs as treatment for skin cancer, chronic inflammatory skin disorders, malaria, syphilis and protozoal diseases.

In 1918, the US Army Chemical Warfare Service developed As-based Lewisite and Adamsite to counter the Central Powers' effective use of gas agents against the Allies in the trenches of Western Europe. Lewisite is C2H2AsCl3, dichloro(2-chlorovinyl)arsine, also called "L" and "M-1" agent. Lewisite is primarily a vesicant (or blistering agent) but is also a potent respiratory and eye irritant and a systemic poison when absorbed. Upon contact with skin and mucous membranes, it immediately causes large, painful, fluid-filled blisters. When inhaled, it causes severe respiratory tract inflammation and necrosis resulting in acute pneumonitis.

During and after the Second World War, many countries stockpiled chemical weapons, particularly the United States and the former Soviet Union. Both the U.S. and the Russian Federation have since destroyed most of their chemical munitions, and as of January 2012, seven of nine U.S. chemical weapons destruction sites had been closed or were under closure. However, as time goes on, remaining munitions continue to deteriorate with an increasing risk of explosion or leakage - they also pose a potentially serious bioterrorism threat.

Remaining stockpiles of Lewisite and Adamsite are still of international concern and are still listed by the CDC as potential bioterrorism agents.

In 2000, the US FDA approved As-trioxide for the treatment of acute promyelocytic leukemia (APL). In 2001, researchers from the University of Arkansas for Medical Sciences demonstrated the “efficacy” of As-trioxide in the treatment of end-stage high-risk multiple myeloma. Currently, As-trioxide is still approved to treat relapsed or refractory APL and research is continuing to determine its efficacy in other hematological cancers.

Arsenic is the 20th most abundant element in the Earth's crust and is a component of more than 245 minerals. Arsenic and its compounds are mobile in the environment. Weathering of rocks converts As-sulfides to As-trioxide, which enters the As cycle as dust or by dissolution in rain, rivers, or groundwater. Wastes generated by the mining of gold and other base metals often contain elevated concentrations of As and there are many examples of environmental arsenic enrichment near mining operations. Arsenic toxicity has become an especially serious problem in Mexico, China, and Southeast Asia, where As is used in the rapidly growing semiconductor industry.

Environmental contamination of As - particularly in drinking water - is a major cause for concern in many parts of the world. Reports of large-scale As contamination in the Gangetic Delta region in Bangladesh and India have drawn significant attention. In this part of the world alone, more than 38 million people are at risk of developing arsenic-related health hazards. The World Health Organization recommends maximum permissible value for As in drinking water to be 10 ppb. However, many countries like Argentina (200 ppb), Mexico (400 ppb), and the Indo-Bangladesh region (800 ppb) have extremely high As concentrations in their drinking water.

Biochemistry

Arsenic belongs to the same group of the periodic table as antimony, nitrogen, phosphorus and bismuth, and is often described as a metalloid element. In most situations, however, its chemical behavior can be considered that of a non-metal. Arsenic exerts its toxicity by inactivating up to 200 enzymes, especially those involved in cellular energy pathways and DNA synthesis and repair. Trivalent As is the primary toxic moiety and binds avidly to enzymes and proteins with thiol (-SH) groups. Lipoic acid is an important enzyme cofactor that has two thiol groups. Arsenic binds and depletes lipoic acid in cells, interfering with the production of chemical energy (adenosine triphosphate - ATP). Multiple enzymes use lipoic acid as cofactors and are blocked as arsenic interferes with function particularly pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. In addition, arsenic can be methylated, although this process may increase arsenic toxicity rather than contributing toward detoxification.

Acute poisoning has a mortality rate of 50-75% and death usually occurs within 48 hours. A lethal dose will vary with compound, but 0.2-0.3 g of arsenic trioxide (As_2O_3) is usually fatal in an adult. Of even more concern, however, is epidemiological evidence that long-term exposure to lower doses of As causes cancers of the lung, skin, bladder, and liver. Due to its apparent carcinogenicity and high concentrations in certain pollution sites, the U.S. Environmental Protection Agency puts As at the top of its list of hazardous chemicals. The Department of Health and Human Services, the International Agency for Research on Cancer, the EPA and the National Toxicology Program have all classified inorganic arsenic as a known human carcinogen.

Scientists have found it very difficult, however, to study how As might cause cancer. For unknown reasons, arsenic does not cause cancer in laboratory animals. Cell-culture studies have shown that As can break chromosomes, stop cell division, and inhibit DNA repair, among other effects. However, cell mutation assays have generally come up negative. These results led to unconfirmed

hypotheses that arsenic causes cancer by inducing DNA hypomethylation and abnormal gene expression.

Target Tissues

Arsenic can produce all three types of toxicity at difference dosages: acute, sub-acute, and chronic. One sign of acute exposure is edema of the eyelids; moreover, gastrointestinal irritation and both central and peripheral neuropathies frequently occur. During chronic intoxication "garlic breath", skin sensitivity, and dermatitis frequently occur. All types of arsenic exposure can cause kidney and liver damage, and in the most severe exposure there is erythrocyte hemolysis.

The long-term retention of arsenic is most apparent in hair and skin, squamous epithelium of the upper gastrointestinal tract (oral cavity, esophagus, and the esophageal part of the stomach mucosa), the epididymis, thyroid (see Blackfoot disease below), lens and skeleton. The accumulation in hair, skin and the upper gastrointestinal tract may be ascribed to a binding to keratin, the content of which is high in squamous epithelia.

Blackfoot disease is an endemic peripheral vascular disorder that is confined to a limited land area on the southwest coast of Taiwan. It has long been related to the consumption of high levels of As found in the artesian well water. Arsenic-contaminated substances have been extracted from the well water and have been reported as a primary source of environmentally induced goiters.

Signs and Symptoms

Inorganic As has been recognized as a human poison since ancient times, and large oral doses (above 60,000 ppb in food or water) can cause death. If you swallow lower levels of inorganic As (ranging from about 300 to 30,000 ppb in food or water), you may experience irritation of your stomach and intestines, with symptoms such as stomachache, nausea, vomiting, and diarrhea. Other effects might include decreased production of red and white blood cells which may

cause fatigue, abnormal heart rhythm, blood-vessel damage resulting in bruising, and impaired nerve function causing a "pins and needles" sensation in the hands and feet.

Perhaps the single most characteristic effect of long-term oral exposure to inorganic As is a pattern of skin changes. These include a darkening of the skin and the appearance of small "corns" or "warts" on the palms, soles, and torso. A small number of the corns may ultimately develop into skin cancer. Swallowing As has also been reported to increase the risk of cancer in the liver, bladder, kidneys, prostate, and lungs. If inhaled at high levels of inorganic As, you are likely to experience a sore throat and irritated lungs. The exposure level that produces these effects is uncertain, but it is probably above 100 micrograms of As per cubic meter (g/m3) for a brief exposure. Longer exposure at lower concentrations can lead to skin effects, and also to circulatory and peripheral nervous disorders. There are some data suggesting that inhalation of inorganic As may also interfere with normal fetal development, although this is not certain. An important concern is the ability of inhaled inorganic As to increase the risk of lung cancer. This has been seen mostly in workers exposed to As at smelters, mines, and chemical factories, but also in residents living near smelters and arsenic chemical factories. People who live near waste sites with As may have an increased risk of lung cancer as well.

Nutrients Known to be Protective Against Arsenic

There are limited evidence-based treatment regimens to treat chronic arsenic poisoning, but the nutrients selenium, zinc, lipoic acid and vitamin C appear to be antagonistic for arsenic uptake and retention. The focus of management is to reduce As ingestion from drinking water and there is increasing emphasis on using alternative supplies of water. Certain sulfur-containing amino acids and sulfur compounds (Dimercaprol, DMSA, DMPS), as well as EDTA have been clinically shown to be an effective IV chelating agent for arsenic. Dimercaprol

(BAL), 2,3-dimercaptopropanesulphonate sodium (DMPS) and *me*so-2,3-dimercaptosuccinic acid (DMSA) are effective arsenic antidotes.

It is rather surprising that since the late 1940s, Dimercaprol (BAL) has remained the drug of choice in the United States for the treatment of As poisoning. It has many disadvantages, e.g. high toxicity, low therapeutic index, unpleasant side effects, limited water solubility, instability in solution, and the need to administer by im injection. Side effects, including nausea, vomiting, and headache, have been experienced by 50% of patients receiving BAL. By 1958, however, publications were beginning to appear in the Soviet literature indicating the superiority of DMPS as an antidote for As poisoning. By 1965, the effectiveness of DMSA for this purpose was reported in the Chinese and Soviet literature.

The newer antidotes DMPS and DMSA feature low toxicity and high therapeutic index. They can be given orally or intravenously due to their high-water solubility. While these advantages make it likely that DMPS and DMSA will replace Dimercaprol for the treatment of chronic arsenic poisoning, acute intoxication - especially with lipophilic organoarsenicals - may pose a problem for the hydrophilic antidotes, because their ionic nature can adversely affect intracellular availability. Be advised: although DMSA is efficacious against arsenic toxicity, the US FDA has only approved DMSA for lead chelation in children.

Testing for Arsenic Toxicity

Blood Testing: Commercial blood tests are available for many metals (universally toxic metals, such as lead and mercury, as well as essential metals that are toxic above certain thresholds, such as iron or copper). Blood levels of cadmium and lead are usually indicative of recent exposures and may not reflect whole body burdens. For example, in the case of lead, blood levels are only indicative of exposure over the previous 90 days. In the case of arsenic, which is cleared rapidly from the blood, blood tests may only be reliable during early stages of intoxication (< 7-10 days after exposure).

Urine: Arsenic toxicity may be determined by urine analysis. Comparison of urine As levels pre- and post-provocation (DMPS, DMSA, D-penicillamine) permit differentiation between recent uptake and body stores. Generally, post-challenge or post-provocation urine tests, which involve the measurement of urine metal concentrations following administration of a chelator, may reveal sources of stored toxic metals. However, since there are no broadly accepted reference ranges for urine metals determined by this technique, these tests are likely of limited diagnostic value and are not completely validated. Reference ranges for individual tests depend on the laboratory performing the analysis.

Hair, in general, provides a rough estimate of exposure to As absorbed from food and water. However, hair can be contaminated externally with As from air, water, dust, shampoos and soap. When in doubt, As burden can be confirmed by urine elements analysis.

Specific Protocols for Arsenic Detoxification

Acute arsenic poisoning is a medical emergency. For acute exposure seek immediate medical attention and call Poison Control Services. As with all detoxification protocols, the type, dose and duration of detoxification agents should always be individually assessed.

The following may serve as a basic guideline for detoxification of excess arsenic from chronic exposure. After 60 days, laboratory screening may be used to reassess the protocol. Before initiating a detoxification program, a CBC (anemia is common) with chemistry, including a thyroid panel with lipids should be performed. In addition, whole blood elements to assess the mineral status and a urine creatinine clearance should be performed every 60 days when using synthetic detoxifying agents (EDTA, DMSA, DMPS).

Administration of synthetic agents may cause a depletion of essential elements such as zinc, iron, calcium, magnesium, copper and other trace minerals. Of greatest concern is potential kidney toxicity that can occur when the body releases its arsenic stores for excretion through the kidneys. Those with underlying kidney disease may not be able to undergo aggressive arsenic detoxification therapy.

1. First, remove any known sources of arsenic. Assess whole blood cell element analysis to determine mineral nutrient deficiency and supplement appropriately.
2. Supplement with pure L-methionine (never D, L-methionine), 500 mg twice daily. Methionine is contraindicated in sulfite oxidase deficiency or sulfite intolerance, B6, B12, or folate deficiency, and in severe cystinuria. It is best to supplement folic acid and B12 when using L-methionine to prevent homocysteine elevation.
3. Supplement with vitamin C (corn free source) to reduce oxidative stress caused by excess arsenic. May administer gram quantities to bowel tolerance.
4. Supplement with magnesium glycinate 100 to 300 mg daily (watch for diarrhea and if present reduce dose of magnesium).
5. Supplement with selenium 200 mcg daily. As is a major biological antagonist to selenium.
6. Supplement with zinc 50 mg daily.
7. Supplement with alpha lipoic acid at 100 twice daily.
8. Algal cells have a remarkable ability to take up and accumulate heavy metals from their external environment. The primary ones used for toxic metal excess are Chlorella vulgaris, a green microalga, and Laminaria japonica, a brown alga. Chlorella and Laminaria japonica are both chelators, moving toxic metals out of the body and transporters, moving metals from deeper stores to more readily removable areas. Both work in unison with each other and can remove toxic metals from the body

through urinary excretion. Administer 1000 to 2000 mg of Laminaria japonica concentrate (Modifilan) daily and 1000 to 2000 mg of chlorella. Adjust dosage to bowel tolerance; may be taken for long periods of time.

9. Cilantro works well with alga to chelate, or bind up toxic metals. The issue with cilantro taken alone is that although it chelates metals, it does not remove them in the urine. This means they can recirculate to deposit elsewhere in the body. Hence, taken with algae, metals are more effectively eliminated in the urine.
10. Shilajit is an ancient traditional medicine (Tibetan and Ayurvedic) and has been ascribed a number of pharmacological activities and has been used for ages as a rejuvenator and for treating a number of disease conditions. It is an effective detoxifier of metals and contains over 60 minerals. Modern scientific research has systematically validated a number of properties of shilajit and has proven that shilajit is truly a panacea. It is important to purchase the highest grade of shilajit.
11. *Do not* give cysteine. Although it will readily combine with As, it will also move it around in the body tissues, into the cells, and will not necessarily clear it from the body.
12. Instruct patient to drink adequate amount of pure water (Adult's urine volume should be about 2 liters per day).

Intravenous chelators enhance the elimination of metals (both toxic and essential) from the body. Their use to ameliorate metal toxicity has been validated by several human case reports and animal models. They are most often used in cases of acute intoxications; the efficacy of chelation therapy in chronic metal intoxication is less clear, as chelation therapies are more effective when administered close to the time of exposure.

More aggressive treatment for arsenic excess involves the use of IV chelators such as magnesium disodium ethylene diamine tetraacetate (Mg, Na2EDTA), DMPS and DMSA. EDTA is an excellent chelator of trivalent ions that are in the

bloodstream. Check for renal clearance first. The protocol for IV EDTA chelation is available from the American College for the Advancement in Medicine (ACAM), http://www.acam.org/. If you are unfamiliar with EDTA, DMPS or DMSA therapy, you may wish to refer the patient to a physician who is board certified by the American Board of Chelation Therapy (ABCT), http://chelation.me/.

Be advised that ideally intravenous DMPS should not be used in patients who still have mercury/silver amalgam fillings. DMPS seems to appear in the saliva and dissolves the surfaces of the existing amalgam fillings. This process occurs over a series of several days. However, the blood concentration of DMPS lessens very quickly. Therefore, the patient with amalgam fillings can become acutely toxic from heavy metal injury to the mucosa of the gut following a DMPS injection.

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Beryllium	Be	Atomic number 4	Atomic mass 9.01218

Sources of Exposure

Beryllium (Be) was discovered in 1798 by the French chemist Louis Nicolas Vauquelin, who found it in the oxide form in beryl and a green-colored variety of beryl, emerald. The metal was isolated in 1828 by two chemists, Friedrich Wölhler from Germany and Antoine Bussy from France, who independently reduced beryllium chloride ($BeCl_2$) with potassium in a platinum crucible. These days, Be is typically obtained from the minerals beryl and bertrandite in a chemical process - or through the electrolysis of a mixture of molten Be chloride and sodium chloride.

Pure Be metal is used in the manufacture of aircraft disc brakes, nuclear weapons and reactors, missile parts, heat shields, X-ray machine parts, and mirrors. Soluble salts, such as beryllium fluoride, chloride, and sulfate, are used in nuclear reactors, in glass manufacture, and as catalysts for certain chemical reactions. Be oxide is used in ceramics for electronics and high-tech applications. Beryllium-copper (BeCu) alloys usually contain about 2% beryllium, but vary greatly in composition to meet different industrial and consumer needs. For example, BeCu springs "bounce back" to their original shape again and again.

Among other uses for beryllium alloys are electrical connectors, precision instruments, aircraft engine parts, wheels and pinions, televisions, calculators, computers, special non-sparking tools, dental alloys and dental bridges, switches, relays, connectors in automobiles, radar and telecommunications equipment, molds or casts to make metal-glass-plastic items, sports equipment such as golf clubs and bicycle frames.

Be used in industry begins as a silicate (BeSiO3) in beryl and bertrandite ores. Bertrandite is mined in Utah, but other ores and scrap are imported into the

United States, which is the world's leading producer, processor, and consumer of Be products. According to the U.S Geological Survey reports, total U.S. use of all forms of Be in 1996 was about 234 metric tons. According to data collected by the Environmental Protection Agency (EPA), the average concentration of airborne beryllium in the United States is very small (0.03 nanogram/cubic meter - a nanogram is one-billionth of a gram).

Probably, the greatest exposures to beryllium occur in the workplace where it is mined, processed, or converted into alloys and chemicals. People living near these industries may also be exposed to higher than normal levels of Be in the air. People living near uncontrolled hazardous waste sites may be exposed to higher than normal levels of Be. Individuals may also be exposed by inhalation of beryllium dust or fumes from the burning of coal or fuel oil and in tobacco smoke, by the ingestion of many fruits and vegetables and water, or through natural occurrence in the soil. The average concentration of Be measured in the air in the United States during the 1980s was 0.03 nanograms per cubic meter (ng/m^3). Ambient concentrations measured in 50 cities between 1977 and 1981 were 0.1-0.4 ng/m^3.

Physical Characteristics

Beryllium is one of the lightest of all metals and has one of the highest melting points of any light metal. Be metal is used principally in aerospace and defense applications because of its stiffness, light weight, and dimensional stability over a wide temperature range. Beryllium-copper alloys are used in a wide variety of applications because of their electrical and thermal conductivity, high strength and hardness, good corrosion and fatigue resistance, and nonmagnetic properties. Beryllium oxide is an excellent heat conductor, with high strength and hardness, and acts as an electrical insulator in some applications.

Beryllium's brittleness is the downside of its advantageous stiffness. Brittleness also increases the hazards associated with Be toxicity. Unless ventilation and

other controls are used, small particles and chips of insoluble beryllium-containing materials break off during the machining processes and spread through the air in the work area. Inhalation of these tiny particles is the type of exposure that can lead to chronic beryllium disease (CBD).

Target Tissues

Be accumulation occurs primarily in the lungs, heart, spleen, liver, mesenchyme, and skin.

Pathophysiology

Beryllium has no biological role in the human body. Although the molecular basis for its toxicity is not well understood, it is well established that micromolar concentrations of beryllium specifically inhibit certain enzymes. As such, Be causes disturbances of calcium and vitamin D metabolism that may eventually result in the manifestation of rickets and mineral depletion. Be disease primarily affects the lungs, which occurs when people inhale beryllium dust or fumes. Occupational exposure most often occurs in mining, extraction, and in the processing of alloy metals containing Be. The adverse health effects of beryllium exposure are caused by the body's immune system reacting with the metal, resulting in an allergic-type response. Dust control is the primary preventative measure.

Skin disease with poor wound healing and rash or wart-like bumps can also occur. A person can develop beryllium disease even after being away from the beryllium industry for many years. There are two forms of beryllium disease:

- Acute Beryllium Disease usually has a quick onset and resembles pneumonia or bronchitis. Excess exposure may result in death; however, the effects may be delayed. It is now rare due to improved industrial protective measures designed to reduce beryllium exposure levels.

- What eventually came to be known as Chronic Beryllium Disease (CBD) was first identified in the 1940s, when a cluster of cases was observed in workers from the fluorescent light industry. CBD has a very slow onset. It still occurs in 1 - 6% of exposed people. CBD is an inflammation in the lungs that can occur when a person is exposed to respirable Be fumes, dusts or powder, and subsequently demonstrates an allergic reaction to beryllium. CBD is an occupational disease that may occur in the manufacture of metallic beryllium, beryllium oxide ceramic, or alloys containing Be. It was first identified more than 50 years ago. Interestingly, some individuals who are diagnosed with CBD do not develop clinical symptoms at all. In others, the disease can lead to clinical symptoms that include scarring and damage of lung tissue, causing shortness of breath, wheezing and/or coughing. Extreme cases of CBD can cause disability or death. The course of the disease can range from a few years to decades.

Be has also been shown to cause cancer in several species of animals including humans. Workers in some Be producing facilities have had an increased rate of lung cancer, as have Be cases in the U.S. Beryllium Case Registry. Be has recently been classified as a human carcinogen by the International Agency for Research on Cancer (IARC).

The current Be exposure standard has been recently revised. OSHA's current general industry standard sets a permissible exposure limit for Be at two micrograms per cubic meter (2 ug/m3) of air for an 8-hour time-weighted average or five micrograms per cubic meter of air not to exceed 30 minutes at a time. OSHA says employees should never be exposed to more than 25 micrograms of the metal, regardless of how short the exposure.

Signs and Symptoms

Topical

- Beryllium compounds may cause contact dermatitis.
- Beryllium ulcers occur where a beryllium crystal penetrates the skin at a site of previous trauma.
- Beryllium chloride, fluoride, nitrate or sulphates are acute eye irritants.

Ingestion

- Gastrointestinal beryllium absorption is poor and systemic toxicity via this route does not occur.

Inhalation

Mild inhalation:

- Metallic taste, cough, breathlessness.

Substantial inhalation:

- Cough, chest pain, metallic taste, exertional breathlessness, nasopharyngitis, tracheobronchitis, conjunctivitis, pneumonitis, epistaxis and fever.
- Additional features seen in chronic beryllium disease include fever, anorexia, arthralgia, nausea, vomiting, hemoptysis, palpitation, convulsions, renal calculi, corneal calcification, hepatosplenomegaly (secondary to corpulmonale) and systemic granulomas causing lymphadenopathy and parotid gland enlargement.
- Chest X-ray may show upper zone nodules and fibrosis and there may be a restrictive ventilatory defect.

The average time from first beryllium exposure to the development of CBD symptoms (the latency period) can be a few months or as long as 40 years. Once

a person has been exposed to beryllium, there is a lifelong risk of developing the disease.

There are no studies on the health effects of children exposed to Be. It is likely that the health effects seen in children exposed to Be will be like the effects seen in adults. It is undetermined whether children differ from adults in their susceptibility to Be. It is also undetermined if exposure to Be will result in birth defects or other developmental effects in people. The studies on developmental effects in animals are not conclusive.

Testing for Beryllium Toxicity

As with other toxic metals, Be can be measured in the urine, blood and hair.

Blood Testing: Commercial blood tests are available for many metals; however, the amount of Be in blood may not indicate as to amount or how recent the exposure. Another blood test, the blood beryllium lymphocyte proliferation test (BeLPT), identifies beryllium sensitization and has predictive value for chronic beryllium disease.

Urine: Because of differences in the rates of excretion for toxic metals, urine tests are indicative of cumulative exposure/total body burden for some metals (e.g., cadmium) and recent exposure for others (e.g., mercury). Urine element analysis is an invaluable tool for the identification or confirmation of Be toxicity and most toxic element burdens, as well as for monitoring of detoxification therapy.

It is very important to note the total time and volume of urine collections. Otherwise, one cannot calculate the actual mass or rate of excretion of elements (i.e., ug/24 hours). This can be especially problematic during detoxification therapy that is associated with markedly increased urine volume.

For increased convenience, urine elements can also be analyzed in specimens that are collected for less than 24 hours. For shorter collection periods, elements will be reported per mg creatinine.

Post-challenge or post-provocation urine tests, which involve the measurement of urine metal concentrations following administration of a chelator, may reveal sources of stored toxic metals. However, since there are no broadly accepted reference ranges for urine metals determined by this technique, these tests are likely of limited diagnostic value and are not completely validated. Reference ranges for individual tests depend on the laboratory performing the analysis.

Hair analysis for beryllium reflects a more chronic long-term exposure pattern. Beryllium levels can also be measured in lung and skin samples, though this is rarely done.

Nutrients Known to be Protective Against Beryllium

Iron, magnesium, zinc, calcium, selenium, and vitamin C are antagonistic for Be uptake and retention. Mg, Na2EDTA has been clinically shown to be an effective IV chelating agent for Be.

Specific Protocols for Beryllium Detoxification

Acute beryllium poisoning is a medical emergency. For acute exposure, seek immediate medical attention and call Poison Control Services. As with all detoxification protocols, the type, dose and duration of detoxification agents should always be individually assessed.

The following may serve as a basic guideline for detoxification of excess Be from chronic exposure. After 60 days, laboratory screening should be used to reassess the protocol. Before initiating a detoxification program, a CBC with chemistry, including a thyroid panel with lipids should be performed. In addition, whole blood elements to assess the mineral status and a urine creatinine

clearance should be performed every 60 days when using synthetic detoxifying agents (EDTA or DMPS). Administration of synthetic agents may cause a depletion of essential elements such as zinc, iron, calcium, magnesium, copper and other trace minerals. Of greatest concern is potential kidney toxicity that can occur when the body releases its beryllium stores for excretion through the kidneys. Those with underlying kidney disease may not be able to undergo aggressive cadmium detoxification therapy.

1. First, identify the source(s) of Be in the individual's environment and remove them or remove the individual from the source(s).
2. Assess whole blood cell element analysis to determine mineral nutrient deficiency and supplement appropriately. Assess ferritin levels and administer iron if needed.
3. Supplement with vitamin C (corn free source) to reduce oxidative stress caused by excess Be. May administer gram quantities to bowel tolerance.
4. Supplement with magnesium glycinate 100 to 300 mg daily (watch for diarrhea and, if present, reduce dose of magnesium).
5. Supplement with selenium 200 mcg daily.
6. Supplement with zinc 50 mg daily.
7. Supplement with alpha lipoic acid at 100 twice daily.
8. Algal cells have a remarkable ability to take up and accumulate heavy metals from their external environment. The primary ones used for toxic metal excess are Chlorella vulgaris, a green microalga, and Laminaria japonica, a brown alga. Chlorella and Laminaria japonica are both chelators, moving toxic metals out of the body, and transporters, moving metals from deeper stores to more readily removable areas. Both work in unison with each other and can remove toxic metals from the body through urinary excretion. Administer 1000 to 2000 mg of Laminaria japonica concentrate (Modifilan) daily and 1000 to 2000 mg of chlorella. Adjust dosage to bowel tolerance; may be taken for long periods of time.

9. Cilantro works well with alga to chelate, or bind up toxic metals. The issue with cilantro taken alone is that although it chelates metals, it does not remove them in the urine. This means they can recirculate to deposit elsewhere in the body. Hence, taken with algae, metals are more effectively eliminated in the urine.
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11. Instruct patient to drink adequate amounts of pure water (Adult's urine volume should be about 2 liters per day).

It has been suggested through animal studies that N-(2- hydroxyethyl) ethylene diamine triacetic acid (HEDTA) is more effective than calcium disodium ethylenediamine tetraacetic acid (CaNa 2EDTA) in reducing the Be concentration of the blood. More aggressive treatment for Be excess also involves the use of sodium 2,3-dimercaptopropane-1-sulfonate (DMPS) and selenium. In one study it was shown that D-penicillamine (DPA] in combination with antioxidant (sodium selenite) was the most effective therapeutic agent followed by DMPS + sodium selenite and glutathione (GSH). Check for renal clearance first. The protocol for IV HEDTA chelation is available from the American College for the Advancement in Medicine (ACAM), http://www.acam.org/ If you are unfamiliar with HEDTA or DMPS chelation therapy, you may wish to refer the patient to a physician who is board certified by the American Board of Chelation Therapy (ABCT), http://chelation.me/

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Cadmium	Cd	Atomic number 48	Atomic mass 112.41

Cadmium (Cd) was discovered by Friedrich Strohmeyer, a German chemist, in 1817 while studying samples of calamine ($ZnCO_3$). When heated, Strohmeyer noticed that some samples of calamine glowed with a yellow color while other samples did not. After further examination, he determined that the calamine that changed color when heated contained trace amounts of a new element – cadmium.

Like zinc, Cd can be electroplated to other materials to protect them from corrosion. In the last 30 years, the use of Cd for electroplating has dropped by about 70% due to environmental concerns. Discarded electroplated steel puts Cd into the environment. Another important use of Cd is in the production of nicad (nickel-cadmium), or rechargeable batteries. Cd easily absorbs neutrons and is used to make control rods for nuclear reactors. Cd is alloyed with silver to form solder, a metal with a relatively low melting point used to join electrical components, pipes and other metallic items. Cd-based solders must be handled with care to prevent Cd poisoning. Cd compounds are used as coloring agents - cadmium sulfide and cadmium selenide. The sulfide is yellow, orange, or brown, while the selenide is red. These compounds are used to color paints and plastics. There is concern about possible environmental effects of using cadmium for this purpose. Despite Cd being ranked 8th in the Top 20 Hazardous Substances Priority List, human activity has markedly increased the distribution of Cd in the global environment.

Sources of Exposure

The major sources of Cd in humans are cigarette smoking, certain foods grown in cadmium-laden soil, seafood (crab, flounder, mussels, oysters, scallops), liver and kidney meats, coal burning, and contaminated water. Other sources of

cadmium are: paints colored with Cd, bone meal, fungicides, highway dusts, and nickel-cadmium batteries. Phosphate fertilizers also show a big Cd load. Although some cadmium-containing products can be recycled, a large share of the general Cd pollution is caused by dumping and incinerating cadmium-polluted waste. Cd can escape from landfills (where trash is buried) and get into the ground and groundwater. From there, it can become part of the food and water that humans and animals ingest. Smelting plants and welding fumes are also a source. Regular cigarette smoking doubles the daily intake of Cd, as compared to the normal intake that results mostly from exposure through ingestion of foods with trace levels of Cd.

Biochemistry

Basically, there are three possible ways of Cd resorption: gastrointestinal, pulmonary and dermal. Once taken up by the blood, most Cd is transported bound to proteins, such as albumin and metallothionein. The first organ reached after uptake into the GI-blood is the liver. Here cadmium induces the production of metallothionein. After consecutive hepatocyte necrosis and apoptosis, Cd-Metallothionein (Cd-MT) complexes are washed into sinusoidal blood. From here, parts of the absorbed cadmium enter the entero-hepatical cycle via secretion into the biliary tract in form of cadmium-glutathione conjugates. Enzymatically degraded to cadmium-cysteine complexes in the biliary tree, cadmium re-enters the small intestines.

The main organ for long-term Cd accumulation is the kidney. Here the half-life period for cadmium is approx. 10 years. A life-long intake can therefore lead to a Cd accumulation in the kidney, consequently resulting in tubulus cell necrosis. An increasing cadmium load in the kidney may also result in a higher calcium excretion, thus leading to a higher risk of kidney stones. Excretion of Cd takes place via feces and urine.

Numerous other target organs are likely for Cd accumulation, as experimental poisonings with cadmium have also been shown to have cardiovascular effects such as increased blood pressure, anemia, and cardiomyopathy, effects on the reproductive system in both sexes, and skeletal effects.

Cd and mercury, along with zinc, are Group II transition metals. Not surprisingly, both Cd and mercury antagonize processes that require zinc, although cadmium does this much more readily than mercury due to its smaller molecular weight. Zinc participates in about 18 metalloenzymes and about 15 Zn^{2+} ion-protonated enzymes.

Listed below are a few such zinc dependent enzymes:

Zinc Metalloenzymes

Enzyme or Protein	Reaction
carbonic anhydrase	$CO_2 + OH^- \text{---> } HCO_3$
superoxide dismutase	$2\ O_2 - + 2H^+ \text{---> } H_20_2 + O_2$
aldolase	aldol condensation in glycolysis cycle
DNA polymerase	polymerization of DNA
RNA polymerase	polymerization of RNA
transcarboxylase	rearrangement of carboxylates
carboxypeptidase A	hydrolysis of C-terminals of amino acids
pyruvate carboxylase	glycolysis reaction
alcohol dehydrogenase	dehydrogenation of alcohols
estrogen receptor	activation of estrogen-inducible genes

While Cd has been shown to inhibit these enzymes/proteins in a test tube, it is not as clear the extent to which cadmium readily inhibits these enzymes in vivo, and whether this occurs through direct displacement of zinc from the apo-enzyme. Nevertheless, this list should serve to illustrate the vast number of

potential molecular targets that cadmium can affect. Aside from zinc, Cd can inhibit the metabolism and transport of other divalent cations, such as calcium and copper.

Because Cd has an outer shell filled with electrons, it tends to form tight covalent bonds with positively charged molecules, such as proteins and DNA. It readily binds to proteins with sulfhydryl groups and may inactivate enzymes in this way. It may also directly damage DNA through direct binding, or indirectly through production of reactive oxygen species. It decreases the cytochrome P450 mixed oxidase system, and therefore, impends detoxification of other metals and xenobiotics. It may also modify catecholamine activity.

Target Tissues

The main site of accumulation of Cd is the proximal tubules of the kidneys, but Cd also accumulates in the brain (appetite and pain centers), heart and blood vessels (changes in arterial endothelium seen), liver and lungs.

Signs and Symptoms

The effects of extensive Cd exposure are not known, but are thought to include heart and kidney disease, high blood pressure, and cancer.

A Cd poisoning disease called *itai-itai*, Japanese for “ouch-ouch", causes aches and pains in the bones and joints. *Itai-Itai* disease manifests a wide range of symptoms such as: low grade of bone mineralization, high rate of fractures, increased rate of osteoporosis, and intense bone-associated pain. An epidemic of the *Itai-Itai* disease was observed in the Jinzu river basin (Japan) in the 1940s. In a study on this occasion, patients were found to show the characteristic symptoms after having eaten rice, grown on fields irrigated with highly cadmium-polluted water. Pseudo-fractures characteristic of osteomalacia and severe skeletal decalcification were also observed. This study, however, came under criticism because most of the patients observed were post-menopausal women.

(Underlying osteoporosis, possibly enhanced by cadmium intoxication, was suggested to be the actual reason for the observed symptoms.) The Belgian CadmiBel study – conducted between 1985 and 1989 – came to similar conclusions: Even minimal environmental exposure to cadmium may cause skeletal demineralization. Lead and cadmium interact with renal mitochondrial hydroxylases of the vitamin D3 endocrine complex. Hence, a likely explanation for demineralization is the disturbance in vitamin-D metabolism.

There is evidence that Cd can cause cancer. Studies have shown that a subcutaneous injection of Cd chloride can induce prostate cancer in Wistar rats. Some studies have suggested an association of Cd and renal cancer in humans. This assumption was confirmed in 2005 by a systematic review of seven epidemiological and eleven clinical studies. Consequently, the IARC (International Agency for Research on Cancer) decided to classify cadmium as a human carcinogen group I. More recent data, however, supports the assumption that only an uptake of cadmium via the respiratory system has carcinogenic potential.

Nutrients Known to be Protective Against Cadmium

Zinc, calcium, magnesium and copper are all antagonistic for reuptake and retention of Cd. Zinc is probably the most important nutrient that protects the body against cadmium - as it helps to increase thionein and metallothionein and protects the prostate in males. Zinc can induce protective levels of metallothionein even before the body is exposed to Cd; to a lesser extent, copper can do this as well. Iron, ascorbic acid, and protein can also reduce the absorption of low levels of dietary Cd. Calcium and thiols like cysteine reduce the toxicity of oral Cd.

Selenium also protects against Cd toxicity, probably by a unique mechanism: in male Wistar rats, selenium co-treatment with cadmium increased survival, increased distribution of cadmium to the liver and testes, and reduced kidney

distribution compared to Cd treatment alone. As no enhancement of liver metallothionein was observed when rats were pre-treated with selenium, the authors speculate that other mechanisms of protection must be involved, including the formation of direct complexes with selenium, or the antioxidant effects of selenium.

Testing for Cadmium Toxicity

Blood Testing: Commercial blood tests are available for many metals including cadmium. However, blood levels of cadmium are usually indicative of recent exposures and may not reflect whole body burdens.

Urine: Because of differences in the rates of excretion of toxic metals, urine tests are indicative of cumulative exposure/total body burden for some metals (e.g., cadmium) and recent exposure for others (e.g., mercury). Post-challenge or post-provocation urine tests, which involve the measurement of urine metal concentrations following administration of a chelator, may reveal sources of stored toxic metals. However, since there are no broadly accepted reference ranges for urine metals determined by this technique, these tests are likely of limited diagnostic value and are not completely validated. Reference ranges for individual tests depend on the laboratory performing the analysis.

Hair toxic element analysis is an excellent test for cadmium exposure. Toxic elements may be 200 to 300 times more highly concentrated in hair than in blood or urine. Therefore, hair is an excellent tissue for detection of recent exposure to elements such as arsenic, aluminum, cadmium, lead and antimony.

Specific Protocols for Cadmium Detoxification

Acute cadmium poisoning is a medical emergency. For acute exposure seek immediate medical attention and call Poison Control Services. As with all detoxification protocols, the type, dose and duration of detoxification agents should always be individually assessed.

The following may serve as a basic guideline for detoxification of excess Cd from chronic exposure. After 60 days, laboratory screening should be used to reassess the protocol. Before initiating a detoxification program, a CBC with chemistry, including a thyroid panel with lipids should be performed. In addition, whole blood elements to assess the mineral status and a urine creatinine clearance should be performed every 60 days when using synthetic detoxifying agents (EDTA). Administration of synthetic agents may cause a depletion of essential elements such as zinc, iron, calcium, magnesium, copper and other trace minerals. Of greatest concern is potential kidney toxicity that can occur when the body releases its Cd stores for excretion through the kidneys. Those with underlying kidney disease may not be able to undergo aggressive cadmium detoxification therapy.

1. First, identify the source(s) of cadmium in the individual's environment and remove them - or remove the individual from the source(s).
2. Assess whole blood cell element analysis to determine mineral nutrient deficiency and supplement appropriately.
3. Supplement with vitamin C (corn free source) to reduce oxidative stress caused by excess cadmium. May administer gram quantities to bowel tolerance.
4. Supplement with oral zinc 50 mg daily for 50 days.
5. Supplement 200 mcg of selenium daily.
6. Algal cells have a remarkable ability to take up and accumulate heavy metals from their external environment. The primary ones used for toxic metal excess are Chlorella vulgaris, a green microalga, and Laminaria japonica, a brown alga. Chlorella and Laminaria japonica are both chelators, moving toxic metals out of the body, and transporters, moving metals from deeper stores to more readily removable areas. Both work in unison with each other and can remove toxic metals from the body through urinary excretion. Administer 1000 to 2000 mg of Laminaria japonica concentrate (Modifilan) daily and 1000 to

2000 mg of chlorella. Adjust dosage to bowel tolerance; may be taken for long periods of time.

7. Cilantro works well with alga to chelate, or bind up toxic metals. The issue with cilantro taken alone is that although it chelates metals, it does not remove them in the urine. This means they can recirculate to deposit elsewhere in the body. Hence, taken with algas, metals are more effectively eliminated in the urine.
8. Shilajit is an ancient traditional medicine (Tibetan and Ayurvedic) and has been ascribed a number of pharmacological activities. It has been used for ages as a rejuvenator and for treating a number of disease conditions. It is an effective detoxifier of metals and contains over 60 minerals. Modern scientific research has systematically validated a number of properties of shilajit and proven that shilajit is truly a panacea. It is important to purchase the highest grade of shilajit.
9. Administer vitamin D3 at 2000 - 5000 IU daily.
10. Calcium and phosphorus supplementation may also be necessary.
11. Instruct patient to drink adequate amounts of pure water (Adult's urine volume should be about 2 liters per day).
12. DMPS *has not* been found to be an effective chelator for cadmium.
13. Diethylenetriaminepentaacetic acid (DPTA) / pentetic acid is an effective chelator for cadmium, as well as lead. In 2004 the FDA determined zinc-DTPA and calcium-DTPA to be safe and effective for treatment of those who have breathed in or otherwise been contaminated internally by plutonium, americium, or curium. However, DPTA should be considered experimental for cadmium detoxification.
14. IV EDTA chelation (edetate calcium disodium ($CaNa_2EDTA$) (Calcium Disodium Edetate®) may be used for aggressive cadmium detoxification. The calcium form of EDTA may be more effective with cadmium chelation than the magnesium form. Reduced glutathione given orally before EDTA chelation can increase the urinary yield of excreted cadmium. Oral dosing of 10 mg per Kg of body weight divided in doses during the 24-hour period before IV EDTA

chelation treatment usually increases urinary Cd excretion. Check for renal clearance first. The protocol for IV EDTA chelation is available from the American College for the Advancement in Medicine (ACAM), http://www.acam.org/ If you are unfamiliar with EDTA chelation therapy, you may wish to refer the patient to a physician who is board certified by the American Board of Chelation Therapy (ABCT), http://chelation.me/

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Copper	Cu	Atomic number 29	Atomic mass 63.546

Copper (Cu) occurs in nature in its metallic form and in ores and minerals, and was one of the first metals used by humans. The use of Cu has been traced back to approximately 5000 BC in the Aegean regions, where it was employed for creating valuable art objects. Cyprus, which draws its name from the Latin word *cuprum*, was a major source of Cu, as were regions in Anatolia and Spain. Copper mixed with tin in a 9:1 ratio comprises bronze, and the ability to form this alloy marked the end of the Stone Age and the beginning of the Bronze Age. Copper and its alloys are now used extensively in domestic and other plumbing systems and to make cooking utensils. Copper is also used in the production of electrical wire and microelectronic applications, in electroplating and photography, as a roofing material, and as a catalyst in the chemical industry.

Copper is an essential transition element that plays a fundamental role in the biochemistry of all aerobic organisms. Proteins exploit the unique redox nature of Cu to undertake a series of facile electron transfer reactions required for cellular respiration, iron homeostasis, pigment formation, neurotransmitter production, peptide biogenesis, connective tissue biosynthesis and antioxidant defense. Conversely, exposure to high levels of copper can result in a number of adverse health effects. The reactivity of copper in biological systems also accounts for the potential toxicity of this metal when cellular Cu homeostasis is disturbed. For this reason, specific pathways have evolved for the trafficking and compartmentalization of Cu within cells.

As the body cannot synthesize copper, the human diet must supply regular amounts for absorption. The National Academy of Sciences (USA) recommends 2 to 3 mg of copper per day as a safe and adequate intake for adults. It is

possible to become copper-toxic or copper-deficient, and there is a condition called bio-unavailable Cu (Cu is present, but cannot be utilized).

Sources of Excess Exposure

Exposure of humans to copper occurs primarily from the consumption of food and drinking water. The relative copper intake from food versus water depends on geographical location; generally, about 20–25% of copper intake comes from drinking water. Drinking water sources become contaminated with copper primarily because of its use in many different types of plumbing supplies. Hence, the principal route of excess exposure is through ingestion, but inhalation of Cu dust and fumes also occurs in industrial settings.

Cu occurs naturally in elemental form and as a component of many different compounds. The most toxic form of Cu is thought to be that in the divalent state, cupric (Cu^{2+}). Because of its high electrical conductivity, copper is used extensively in the manufacturing of electrical equipment and different metallic alloys. Cu is released into the environment primarily through mining, sewage treatment plants, solid waste disposal, welding and electroplating processes, electrical wiring materials, plumbing supplies (pipes, faucets, braces, and various forms of tubing), and agricultural processes.

Copper is present in the air and water due to natural discharges like volcanic eruptions and windblown dust. It is a common component of fungicides and algaecides, and agricultural use of Cu for these purposes can result in its presence in soil, groundwater, farm animals (grazing animals like cows, horses, etc.). Cu is also present in ceramics, jewelry, monies (coins) and pyrotechnics.

Other sources of potential Cu excess include foods, particularly vegetarian proteins such as certain nuts, soybeans, seeds and grains. Meats contain Cu but are usually balanced by zinc that competes for its absorption and chocolate is high in copper. Cu cookware, hemodialysis units using copper-containing equipment,

dental materials, topical Cu compounds used in burn treatment, Cu containing food supplements, and copper intra-uterine devices are minor sources. In prolonged contact with Cu cooking utensils, an acidic food or beverage can dissolve milligram quantities of Cu, sufficient to cause acute toxicity symptoms such as self-limited nausea, vomiting and diarrhea. Elevated levels of estrogens predispose individuals to copper toxicity.

Insufficient intake of competitively absorbed elements such as zinc and molybdenum can lead to or worsen Cu excess. Since Cu and zinc compete for absorption in the gut and enzymatically, zinc deficiency may result in copper excess.

Biochemistry (Absorption, Metabolism, and Elimination)

Copper is an essential trace element for all biological organisms, from bacterial cells to humans. Depending on the source of the biological material, copper content ranges from parts per billion to parts per million. Copper's essentiality was first discovered in 1928 when Hart et al. demonstrated that rats fed a copper-deficient milk diet were unable to produce sufficient red blood cells.

Cu is critical for energy production in the cells. It is also involved in nerve conduction, connective tissue, the cardiovascular system and the immune system. Cu is closely related to estrogen metabolism and is required for women's fertility and to maintain a pregnancy. Cu stimulates production of the neurotransmitters epinephrine, norepinephrine and dopamine. It is also required for monoamine oxidase, an enzyme related to serotonin production.

The daily Cu requirement has been estimated at 30 micrograms/kg of body weight for an adult. After ingestion, maximum absorption of copper occurs in the stomach and jejunum.

The adult body contains between 1.4 and 2.1mg of copper per kilogram of body weight. In other words, a healthy human weighing 60 kilograms contains approximately 0.1 gram of Cu. However, this small amount is essential to the human's overall wellbeing.

Absorbed Cu is initially bound to albumin and is transported from the gastrointestinal tract to the liver - where it is transferred to ceruloplasmin, which binds more than 75% of circulating Cu. Ceruloplasmin is the major plasma antioxidant and Cu transport protein. It is synthesized in several tissues, including the brain. Absorption is increased in Cu deficiency and is impaired in small-bowel disease. Other factors that influence dietary copper absorption include competition by zinc, iron, molybdenum, lead, and/or cadmium. Zinc and cadmium appear to be the most potent inhibitors of copper absorption, possibly by competing with copper for transport and/or by increasing intestinal metallothionein concentrations. Metallothioneins are a group of small, heavy-metal binding proteins that serve in detoxification and metal buffering. Cu is distributed throughout the body, but is stored primarily in the liver, muscle, and bone. The normal concentration of Cu in blood plasma is 1 mg/liter.

Copper is an integral part of many important enzymes involved in a number of vital biological processes. Although normally bound to proteins, Cu may be released and become free to catalyze the formation of highly reactive hydroxyl radicals. Data obtained from *in vitro* and cell culture studies are largely supportive of Cu's capacity to initiate oxidative damage and interfere with important cellular events. Oxidative damage has been linked to chronic Cu-overload and/or exposure to excess Cu caused by accidents, occupational hazards, and environmental contamination. Additionally, Cu-induced oxidative damage has been implicated in disorders associated with abnormal Cu metabolism and neurodegenerative changes. Interestingly, a deficiency in dietary Cu also increases cellular susceptibility to oxidative damage.

In all mammals, Cu is an essential trace element involved in:

- fundamental cellular respiration
- free radical defense
- connective tissue synthesis
- iron metabolism
- neurotransmission

Copper Proteins

Copper is present in three different forms in proteins:

(a) *blue proteins* without oxidase activity (e.g., plastocyanin), which function in one-electron transfer

(b) *non-blue proteins*, which produce peroxidases and oxidize monophenols to diphenols

(c) *multicopper proteins* containing at least four copper atoms per molecule, which act as oxidases (e.g., ascorbate oxidase and laccase) and catalyze the reaction:

$$2AH_2 + O_2 \rightarrow 2A + 2H_2O$$

Cytochrome oxidase is a mixed copper-iron protein catalyzing the terminal oxidation in mitochondria.

Dioxygenases are enzymes that catalyze the incorporation of both atoms of molecular oxygen into organic substrates. They take part in the metabolism of biomolecules as different as amino acids, lipids, nucleic acids, and even carbohydrates. Their biological importance relates to their ability to catalyze the degradation of aromatic compounds. Quercetin 2,3-dioxygenase (2,3QD)1 is the only dioxygenase unambiguously known to contain copper. It cleaves the O-heterocycle of polyphenolic flavonols that represent a major class of flavonoids. These compounds are important dietary components and have attracted considerable attention in the past decade owing to their antioxidizing properties.

Deficiencies of manganese, iron, molybdenum, B-vitamins and vitamin C can cause Cu to accumulate. Adrenal hormones cause the liver to produce ceruloplasmin, the main copper-binding protein in the body. A functional impairment in the liver or adrenal glands may cause copper to build up in the tissues.

Physiological stress from any cause may lead to copper imbalance. Stress depletes the adrenal glands and lowers the zinc level in the body. Whenever zinc becomes deficient, Cu tends to accumulate. In addition, most US soil is deficient in zinc. Refined sugar, white rice and white flour have been stripped of their zinc. The trend toward vegetarianism reduces zinc in the diet, since red meat is a high dietary source of zinc. High Cu levels, especially when associated with low zinc levels, have been linked to a variety of symptoms and conditions.

Elimination of Cu is principally through the feces after excretion into the bile. Urinary excretion of copper is low in humans. Healthy adults have urinary concentrations of less than 100μg per 24 hours.

Target Tissues

Absorption of Cu occurs through the lungs, gastrointestinal tract and skin. The degree to which Cu is absorbed in the gastrointestinal tract largely depends upon its chemical state and the presence of other compounds, like zinc. Once absorbed, Cu is distributed primarily to the liver, kidneys, spleen, heart, lungs, stomach, intestines, nails, and hair. Individuals with Cu toxicity show an abnormally high level of Cu in the liver, kidneys, brain, eyes and bones.

Medical Conditions and Symptoms Associated with Copper Toxicity

Copper toxicity in the general population was not a public health concern until recently, mainly because of a lack of reported toxicity, despite centuries of Cu use in a wide variety of applications. The identification of genetic disorders of Cu metabolism leading to severe copper toxicity (Wilson’s disease) or Cu deficiency

(Menkes disease) has not only spurred research into the molecular genetics and biology of Cu homeostasis, but also focused attention on the potential consequences of Cu toxicity in normal and potentially susceptible populations.

Acute Toxicity

Mild forms of acute Cu toxicity produce nausea, vomiting, diarrhea, and malaise. Severe Cu poisoning, as through Cu sulfate ingestion, produces a severe inflammation of the gastrointestinal tract. Any amount in excess of 10 g of Cu sulfate is sufficient to cause abdominal pain, nausea, vomiting, diarrhea, malaise, and hematemesis. However, in severe acute ingestion, the following is also encountered: convulsions, dehydration, shock, cellular hemolysis, and liver and kidney necrosis.

Patients who developed intense jaundice from liver centrolobular necrosis after massive acute Cu sulfate poisoning had a more fulminant course than did patients with milder jaundice from intravascular hemolysis. Kidney abnormalities have been observed after acute Cu sulfate ingestion. Hematuria, rising blood urea nitrogen, and oliguria were frequently observed in a large series of poisonings. A picture of acute tubular necrosis was observed on urinalysis and renal biopsy in these cases.

Chronic Toxicity

The long-term toxicity of copper has not been well studied in humans. Medical conditions that may be associated with chronic Cu excess include: liver disease (hepatitis or cirrhosis), biliary obstruction (reduced ability to excrete copper and other toxic elements) and renal impairment.

Wilson’s disease, an inherited, autosomal recessive error in copper metabolism, epitomizes chronic disease from excessive Cu storage. Unless treated in time, Wilson’s disease is fatal. This disease is characterized by excess copper deposition in most organs, especially the liver, kidneys, brain, and eyes.

Manifestations of Wilson's disease include brain damage and progressive demylination, psychiatric disturbances, such as depression, suicidal tendencies and aggressive behavior, hemolytic anemia, cirrhosis of the liver, motor dysfunction and corneal opacities. Some patients may also experience poor coordination, tremors, disturbed gait, muscle rigidity, and myocardial infarction.

Menkes syndrome is an X-linked disorder of Cu transport characterized by progressive neurological degeneration and arterial changes. The disorder results in death in infancy.

Eczematous dermatitis and urticaria have been associated with the use of copper intrauterine devices. Except for adenocarcinoma of the lung and angiosarcoma of the liver seen in patients with vineyard sprayer's lung, no evidence corroborates carcinogenesis from copper exposure.

Symptoms associated with excess Cu accumulation are joint and muscle pain, irritability, tremor, hemolytic anemia, learning disabilities and behavioral disorders.

Today, many children are born with excessive tissue Cu. It is passed from high-copper mothers to their children through the placenta. The major syndrome with which copper excess is associated in younger children is with Attention Deficit Disorder (ADD). Increasing evidence indicates that Cu excess may be related to ADD with and without hyperactivity.

Management of Copper Toxicity

Careful history taking is essential to diagnose acute and chronic Cu toxicity. Attention should be given to ingestion of food and drink, especially acidic beverages or alcohol prepared in copper-containing vessels. Investigation for abnormal liver and renal function and hemolytic anemia should be conducted. Dermatitis is often a suspicious sign of copper toxicity. Inquiry as to exposure to copper salts at work, use of copper-containing jewelry, or use of a copper

intrauterine device should be conducted. Patch testing may be necessary to confirm the diagnosis.

The best means of testing for Cu toxicity are 24-hour urine copper or serum ceruloplasmin level tests. Also, serial hair mineral analysis every 120 days is valuable in following treatment. The normal concentration of copper in blood plasma is 1 mg/liter. 95% of the copper in plasma is in ceruloplasmin, but it is one of the acute-phase reactant proteins and it increases in acute and chronic inflammatory conditions. It is also elevated in patients taking estrogen and birth control pills and in those who are pregnant or have cirrhosis, cancer, or thyrotoxicosis. Erythrocytes also contain a significant portion of the Cu found in the blood in the form of an enzyme, superoxide dismutase. Hence, RBC mineral analysis will often reflect toxic levels.

Nutrients Known to be Protective Against Copper

The mineral antagonists such as zinc, manganese and iron compete with Cu for absorption and utilization. Vitamin B6 phosphate, gram quantities of vitamin C, folic acid, molybdenum and selenium are all helpful in displacing copper. Cu may be conjugated with glutathione and other sulfur-containing amino acids such as methionine and N-acetyl-cysteine. More powerful chelators such as D-penicillamine and DMPS also give excellent therapeutic results, but may involve side effects.

Testing for Copper Levels

As with other toxic metals, Cu can be measured in the urine, blood and hair.

Although several indicators are useful in diagnosing copper deficiency, there are no reliable biomarkers of copper excess resulting from dietary intake. Copper levels can be measured in a 24-hour urine collection as well as hair analysis. Probably the most reliable indicator of excess copper status is liver copper concentration.

Blood Testing: Increased serum copper or ceruloplasmin levels are not reliably associated with copper toxicity. Ceruloplasmin is an acute-phase reactant, and elevations in serum copper and ceruloplasmin concentrations are induced by inflammation, infection, disease, malignancies, pregnancy, and other biological stressors. Levels of copper-containing enzymes, such as cytochrome-c-oxidase, superoxide dismutase, and diaminase oxidase vary not only in response to copper state, but also in response to a variety of other physiological and biochemical factors and thus are inconsistent markers of excess copper status.

Urine element analysis is an invaluable tool for the identification or confirmation of copper deficiency and toxicity, as well as for the monitoring of detoxification therapy.

It is very important to note the total time and volume of urine collections. Otherwise, one cannot calculate the actual mass or rate of excretion of elements (i.e., ug/24 hours). This can be especially problematic during detoxification therapy that is associated with markedly increased urine volume. For increased convenience, urine elements can also be analyzed in specimens that are collected for less than 24 hours. For shorter collection periods, elements will be reported per mg creatinine.

Hair copper levels are usually indicative of body status, except that exogenous contamination may occur giving a false normal (or false high). If hair Cu is in the normal range, this usually means tissue levels are in the normal range. However, under circumstances of contamination, a real Cu deficit could appear as a (false) normal. If symptoms of Cu deficiency are present, a whole blood or red blood cell elements analysis can be performed for confirmation of Cu status.

Specific Protocols for Copper Detoxification

As with all detoxification protocols, the type, dose and duration of detoxification agents should always be individually assessed.

The following may serve as a basic guideline for detoxification of excess Cu caused by chronic exposure. Before initiating a detoxification program, a CBC with chemistry, including a thyroid panel with lipids, should be performed. In addition, whole blood elements to assess the mineral status and a urine creatinine clearance should be performed every 60 days when using synthetic detoxifying agents. Administration of glycine and synthetic agents may cause a depletion of essential elements such as copper, zinc, iron, calcium, magnesium, and other trace minerals. Of greatest concern is potential kidney toxicity - which can occur when the body releases its Cu stores for excretion through the kidneys. Those with underlying kidney disease may not be able to undergo aggressive copper detoxification therapy.

1. First, identify the source(s) of copper in the individual's environment and remove them or remove the individual from the source(s). Check food supplementation for copper excess.
2. Assess whole blood cell element analysis to determine mineral nutrient deficiency and supplement appropriately (often low zinc-high copper values exist).
3. Supplement with vitamin C (corn free source) to reduce oxidative stress caused by excess copper. May administer gram quantities to bowel tolerance.
4. Supplement with magnesium glycinate 100 to 300 mg daily (watch for diarrhea and, if present, reduce dose of magnesium).
5. Supplement natural vitamin E (D-alpha tocopherol) at 400 IU daily.
6. Supplement 200 mcg of selenium daily.
7. Administer alpha lipoic acid 200 to 500 mg daily.
8. Administer Vit B6 Phosphate 100 mg daily.
9. Administer molybdenum at 200-mcg daily.
10. Supplement zinc at 100 mg for 30 days, followed by 50 mg for 50 days.
11. Algal cells have a remarkable ability to take up and accumulate heavy metals from their external environment. The primary ones used for toxic metal excess are Chlorella vulgaris, a green microalga, and Laminaria japonica, a brown alga.

Chlorella and Laminaria japonica are both chelators, moving toxic metals out of the body, and transporters, moving metals from deeper stores to more readily removable areas. Both work in unison with each other and can remove toxic metals from the body through urinary excretion. Administer 1000 to 2000 mg of Laminaria japonica concentrate (Modifilan) daily and 1000 to 2000 mg of chlorella. Adjust dosage to bowel tolerance; may be taken for long periods of time.

12. Instruct patient to drink adequate amounts of pure water (Adult's urine volume should be about 2 liters per day).

13. IV Chelators: For most cases of copper toxicity, the above oral supplements will be adequate if taken over time. However, some individuals have a combination of mercury and copper toxicity that may require IV chelators. Sodium 2,3-dimercaptopropane-1-sulfonate (DMPS) is an effective means for reduction of both mercury and copper.

Be advised that ideally intravenous DMPS should not be used in patients who still have mercury/silver amalgam fillings. DMPS seems to appear in the saliva and dissolves the surfaces of the existing amalgam fillings. This process occurs over a series of several days. However, the blood concentration of DMPS lessens very quickly. Therefore, the patient with amalgam fillings can become acutely toxic from heavy metal injury to the mucosa of the gut following a DMPS injection.

In China there is substantial experience with the use of DMSA in the treatment of Wilson's disease. Comparing the long-term therapeutic effects between DMSA and d-penicillamine, it has been asserted that DMSA is superior to penicillamine because the former caused clinical symptoms to exacerbate less frequently than the latter did. It might be relevant that the DMSA molecule, which has a dithiol structure, can embrace and shield the deleterious and "soft" Cu(I)-species, whereas penicillamine presumably prefers Cu(II). Furthermore, side effect incidence of DMSA is lower than that of penicillamine.

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Lead	Pb	Atomic number 82	Atomic mass 207.2

Lead (Pb) is a metal which has been associated with human activities for the last 6000 years. Lead has no known beneficial function in human metabolism. It is one of the oldest known and most widely studied occupational and environmental toxins. In ancient civilizations, uses of lead included the manufacture of kitchen utensils, trays, and other decorative articles. However, Pb is quite toxic to humans, with the most deleterious effects on the hemopoietic, nervous, reproductive systems and the urinary tract. In the last century, Pb toxicity has been extensively studied. The greatest risk for harm, even with only minute or short-term exposure, is to infants, young children, and pregnant women. In recent years, the focus in Pb toxicity has shifted away from adults exposed to high doses in industrial settings to the larger population of asymptomatic children with lesser exposures.

The early victims of lead toxicity were mainly lead workers and wine drinkers. Lead's sweet flavor made it useful in winemaking, to counteract the astringent flavor of tannic acid in grapes. Lead-sweetened wine, containing as much as 20 mg of lead per liter, was an important part of the diet of upper-class Romans. The synchronous decrease in fertility and increase in psychosis among the Roman aristocracy has raised speculation implicating lead poisoning in the fall of Rome.

Sources of Exposure

The main sources of Pb exposure are paints, water, food stored in lead can liners, food stored in ceramic jars, dust, soil, kitchen utensils, and leaded gasoline (although banned in the United States in 1995 for automobiles, previous usage has widely dispersed it in the environment). Other potential sources are contaminated water (pipes cast in lead or soldered using lead solder), ammunition (shot and bullets), bathtubs (cast iron, porcelain, steel), batteries, ceramics, chemical fertilizers, leaded glass, newsprint and colored

advertisements, and tobacco smoke. Children absorb lead up to 8x more efficiently than adults. Ingestion of deteriorating lead-based paint chips or dust is the primary source of lead exposure in children. Also, toys and other children's products may contain lead or be painted with lead-based paint; imported children's products pose a greater risk. Animal models also suggest that lead can be absorbed through the skin. Lead acetate can be found in some cosmetic products, hair dyes and rinses. Safe cosmetics are listed on the Environmental Working Group website.

In 1989, the U.S. Environmental Protection Agency reported that more than one million elementary schools, high schools, and colleges are still using lead-lined water storage tanks or lead-containing components in their drinking fountains. The EPA estimates that drinking water accounts for approximately 20% of young children's lead exposure. Other common sources are lead paint residue in older buildings (as in inner cities) and living in proximity to industrial areas or other sources of toxic chemical exposure, such as commercial agricultural land.

Biochemistry

Lead is a divalent cation, and it binds strongly to sulfhydryl groups on proteins. Much of lead's toxicity can be attributed to distortion of enzymes and structural proteins, but this versatile toxicant has many other targets. Lead binds to hemoglobin and prevents heme synthesis and this depresses mitochondrial respiration and the electron transport chain. Lead also blocks the impulse transmission and release of acetylcholine that leads to neurological defects.

Chronic, low-level lead exposure (blood levels <10 μg/dL) is associated with increases in hypertension risk and reduction in kidney function. Higher levels of lead exposure affect the endocrine glands (changing the levels of thyroid hormones [at serum lead levels over 40-60 μg/dL] and reproductive hormones [at serum lead levels over 30-40 μg/dL] and lowering vitamin D levels).

Many of lead's toxic properties are due to its ability to mimic or compete with calcium. At picomolar concentrations, lead competes successfully with calcium for binding sites on cerebellar phosphokinase C and thereby affects neuronal signaling. It inhibits calcium entry into cells.

Delta aminolevulinic acid dehydratase is extremely sensitive to lead. Inhibition of this enzyme results in increased circulating aminolevulinic acid (ALA). ALA is a weak gamma-aminobutyric acid (GABA) agonist that decreases GABA release by presynaptic inhibition. Increased circulating ALA may account for some of the behavioral disorders seen in patients with porphyria and perhaps in lead toxicity.

Of the many organs affected by lead, the most important is the central nervous system (CNS). Lead has diverse impacts on the CNS. Immature astrocytes are sensitive to lead, and lead interferes with myelin formation and the integrity of the blood-brain barrier. Lead interferes with the synthesis of collagen and affects vascular permeability. At high enough doses, this results in brain edema and hemorrhage as well as brain lesions, cognitive deficits, and behavioral changes. Lead can leave the body through feces or urine.

Target Tissues

Lead deposits in the bone, teeth, kidney tubules, brain, thyroid, adrenals, liver, pancreas, heart and aorta. Lead in bone is of interest for two reasons. Bone is the largest repository of the body burden of lead, and, secondly, it is now recognized that lead may, in fact, influence bone metabolism. Lead may affect the ability of bone cells to respond to hormone regulation. A calcium-binding protein, osteocalcin, synthesized by osteoblasts, is inhibited at low levels of lead exposure, which may impair new bone formation as well as the functional coupling of osteoblasts and osteoclasts. Lead may also impair synthesis of components of bone matrix such as collagen or bone sialoproteins. A common molecular basis for the cellular effects may be altered or impaired calcium and cAMP messenger systems in cells.

In most individuals there is a "lead balance", that is one excretes as much as they take in, and the tissue levels are below the concentrations which result in pathological changes. However, an increase in the rate of intake will result in accumulation or a "positive lead balance". Since lead is chemically very similar to calcium, the body transports it as if it were calcium. Thus, the first place to which it is transported is to the plasma and the membrane sites in soft tissues. It is then distributed to the other sites mentioned above, where calcium plays an important role.

Signs and Symptoms

One of the earliest diagnostic signs present is the appearance of "lead lines" at the gingival border in the mouth. This occurs because the lead following calcium pathways is secreted with the saliva. It then is involved in a reaction with oral bacteria that produce sulfides. The lead reacts with these compounds to form a purplish, or black lead sulfide deposit which precipitates in the region of highest concentration, the "protected area" at the gingival border. Other metals also produce this phenomenon, but with differing colors for the deposit.

Following acute ingestion of a large amount of lead, there will be direct tissue interaction. This includes tissue mucosal tissue damage in the GI tract, and convulsion possibly resulting in death. The most sensitive system is the hematopoietic (blood forming) system, with hypochromic microcytic anemia common. The biosynthesis of hemes in general is deranged by the presence of lead. All actively dividing cells are especially susceptible; hence acute intoxication has major potential for GI and renal mucosal damage. In addition, there is a high risk of neurological damage. Over long-term exposure with a gradual build-up of a positive lead balance, there is no sudden onset of symptoms as seen with acute poisoning. The initial symptoms include clumsiness, ataxia, vertigo, irritability and insomnia. In affected children, they are often considered “slow" - the real basis for the difficulty is not recognized. As the

lead levels rise, hyper-excitability is seen. Confusion, delirium and convulsions may occur in some cases, while in others there is progressive lethargy leading to a comatose state. Studies have shown a slowing of sensory motor reaction time in male lead workers and some disturbance of cognitive function in workers with blood lead levels >40 µg/100 ml.

Lead is a known neurotoxin and excessive blood lead levels in children have been linked to learning disabilities, attention deficit disorder (ADD), hyperactivity syndromes, and reduced intelligence and school achievement scores.

Exposure to high Pb levels can produce renal tubular damage with glycosuria and aminoaciduria (saturnine gout). There are several experimental studies in rats and mice in which long-term administration of a lead compound in food or drinking water produced renal tumors. Further studies show that renal carcinogenicity occurs on a background of proximal tubular cell hyperplasia, cytomegaly and cellular dysplasia. Renal adenocarcinoma occurs in a high percentage of exposed animals, and incidence is dependent on length and severity of Pb exposure.

At very high blood Pb levels, lead is a powerful abortifacient. At lower levels, it has been associated with miscarriages and low birth weights of infants. Predominantly to protect the developing fetus, legislation for Pb workers often includes lower exposure criteria for women of “reproductive capacity".

Additional symptoms of chronic lead toxicity include: anemia, anorexia, anxiety, bone pain, brain damage, confusion, constipation, convulsions, dizziness, drowsiness, fatigue, headaches, hypertension, inability to concentrate, indigestion, irritability, loss of appetite, loss of muscle coordination, memory difficulties, muscle pain, pallor, tremors, vomiting, and weakness.

Lead Toxicity Evaluation

In adults, lead toxicity should be considered in the differential diagnosis of abdominal pain, arthralgia, hypertension, severe headache, increased intracranial pressure, CNS dysfunction, anemia, and renal dysfunction. An occupational history and an inventory of possible sources of exposure are useful. Measuring of blood lead concentration is the most effective and accepted diagnosis for lead exposure. The accepted toxic threshold for lead in infants, children and women of child bearing age is ≤ 10 μg/dL, approved by the American Pediatric Association. However, for adults there is no such threshold, as concentration of lead from 10 μg/dL and above in blood exhibits toxicity. Additionally, Pb blood levels are only indicative of exposure over the previous 90 days. Any child with growth failure, abdominal pain, behavior change, hyperactivity, language delay, or anemia should have a blood lead test to rule out lead toxicity.

Nutrients Known to be Protective Against Lead

Sulfur-containing amino acids, calcium, iron, zinc, vitamin C, vitamin E, certain algae (laminaria, fucus, chlorella) all are antagonistic for reuptake and retention of lead. EDTA has been clinically shown to be an effective IV chelating agent for lead and DMSA is an effective oral chelator of lead.

Toxicity from inorganic lead can be treated with EDTA chelation, but organic lead compounds such as tetra-ethyl lead produces a similar symptomology but cannot be treated with this agent because they have already formed strong ligands with their organic constituents. The alkyl lead is eventually converted to inorganic lead, which can be treated with EDTA.

In the United States, DMPS is not considered an appropriate drug against lead toxicity. DMPS, although known for its antidotal efficacy against mercury, has also been reported to have limited efficacy for treating lead and arsenic poisoning. The drug is registered in Germany for treatment of mercury

intoxication, but it is not approved in the United States, so unless special permission is given by the U.S. Food and Drug Administration, it is unlawful for physicians to use it in the United States (though some do) - nor is it lawful for pharmacies to compound it.

Specific Protocols for Lead Detoxification

Acute lead poisoning is a medical emergency. For acute exposure, seek immediate medical attention and call Poison Control Services.

As with all detoxification protocols, the type, dose and duration of detoxification agents should always be individually assessed. The following may serve as a basic guideline for detoxification of excess lead from chronic exposure. After 60 days, laboratory screening should be used to reassess protocol. Before initiating a detoxification program, a CBC with chemistry, including a thyroid panel with lipids, should be performed. In addition, whole blood elements to assess the mineral status and a urine creatinine clearance should be performed every 60 days when using synthetic detoxifying agents (EDTA). Administration of synthetic agents may cause a depletion of essential elements such as zinc, iron, calcium, magnesium, copper and other trace minerals. Of greatest concern is potential kidney toxicity that can occur when the body releases its lead stores for excretion through the kidneys. Those with underlying kidney disease may not be able to undergo aggressive lead detoxification therapy.

1. The cornerstone of lead toxicity management is the termination of exposure. For children, this means inspection of the home, and if this does not reveal lead, a survey of other possible sources.
2. Assess whole blood cell element analysis to determine mineral nutrient deficiency and supplement appropriately.
3. Supplement with calcium as MCHC 1000 mg daily.
4. Supplement with oral zinc 25 to 50 mg daily.
5. Supplement 200 mcg of selenium daily.

6. Assess vitamin D status (25-hydroxy vitamin D) and supplement vitamin D-3 accordingly.
7. Supplement buffered vitamin C (corn free source) at 500 mg up to 3000 mg daily adjusting to bowel tolerance. Vitamin C is a free-radical scavenger that can protect against oxidative damage caused by lead, mercury, and cadmium. It may prevent the absorption of lead as well as inhibit its cellular uptake and decrease its cellular toxicity. Observational data suggest an inverse relationship between serum levels of ascorbic acid and blood levels of lead; in other words, the higher the blood levels of vitamin C, the lower those of lead.
8. Supplement natural vitamin E (D-alpha tocopherol) at 400 IU daily.
9. Garlic has been shown to detoxify lead. Garlic contains many active sulfur compounds derived from cysteine with potential metal-chelating properties; these garlic constituents may also protect from metal-catalyzed oxidative damage. Add garlic to the diet and supplement with standardized garlic-allicin powder extract.
10. Algal cells have a remarkable ability to take up and accumulate heavy metals from their external environment. The primary ones used for toxic metal excess are Chlorella vulgaris, a green microalga, and Laminaria japonica, a brown alga. Chlorella and Laminaria japonica are both chelators, moving toxic metals out of the body, and transporters, moving metals from deeper stores to more readily removable areas. Both work in unison with each other and can remove toxic metals from the body through urinary excretion. Administer 1000 to 2000 mg of Laminaria japonica concentrate (Modifilan) daily and 1000 to 2000 mg of chlorella. Adjust dosage to bowel tolerance; may be taken for long periods of time.
11. Cilantro works well with alga to chelate, or bind up toxic metals. The issue with cilantro taken alone is that although it chelates metals, it does not remove them in the urine. This means they can recirculate to deposit elsewhere in the body. Hence, taken with algas, metals are more effectively eliminated in the urine.

12. Shilajit is an ancient traditional medicine (Tibetan and Ayurvedic) and has been ascribed a number of pharmacological activities. It has been used for ages as a rejuvenator and for treating a number of disease conditions. It is an effective detoxifier of metals and contains over 60 minerals. Modern scientific research has systematically validated a number of properties of shilajit and has proven that shilajit is truly a panacea. It is important to purchase the highest grade of shilajit.
13. Instruct patient to drink adequate amounts of pure water (Adult's urine volume should be about 2 liters per day).
14. More aggressive treatment involves the use of EDTA chelation (edetate calcium disodium) ($CaNa_2EDTA$) (Calcium Disodium Edetate®) or oral dimercaptosuccinic acid (succimer DMSA). $CaNa_2EDTA$ was the preferred method until recently, when dimercaptosuccinic acid, an oral agent, was found to have equal efficacy. Both agents will reduce an elevated blood lead level to 40%–50% of its baseline. After treatment is concluded (5 days for EDTA; 19 days for DMSA), body pools tend to equilibrate, and blood lead levels begin to rise, often requiring repeated courses.

Check for renal clearance first. The protocol for IV EDTA chelation is available from the American College for the Advancement in Medicine (ACAM), http://www.acam.org/ If you are unfamiliar with EDTA or DMSA chelation therapy, you may wish to refer the patient to a physician who is board certified by the American Board of Chelation Therapy (ABCT), http://chelation.me/

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Mercury	Hg	Atomic number 80	Atomic mass 200.59

As with other metals, mercury exists in multiple oxidative states, as inorganic salts, and as organic complexes. The oxidative states include elemental mercury (Hg0), mercurous (Hg+1), or mercuric (Hg+2). Inorganic mercury compounds which are generally in solid states as mercurous or mercuric salts and mercury compounds with chlorine, sulfur, or oxygen. Methylmercury and ethylmercury are common organic forms of mercury combined with carbon. Organic mercury compounds are formed when mercury combines with carbon. Microscopic organisms in water and soil can convert elemental and inorganic mercury into an organic mercury compound, methylmercury, which accumulates in the food chain. Mercury in any form is toxic.

Mercury is one of the most toxic elements on our planet and exhibits varying levels of toxicity in each form, caused in part by varying routes of exposure, doses, and sites of deposition. Toxicity aside, Hg has many chemical properties that have made it useful to humans. There is evidence that Hg has been utilized throughout antiquity. Prehistoric cave drawings were made using cinnabar, the red ore containing mercuric sulfide. The Romans mined cinnabar to extract mercury and operated a Hg mine in Spain with prisoner and slave labor. They used Hg as a pigment in their paint; mercury-containing paint has been found in Roman homes buried by the volcanic ash of Mount Vesuvius in 79CE. The use of Hg in paint has continued into the modern area, although in recent history, mercury was added as a fungicide rather than for its chromatic properties. It was not until 1991 that the use of Hg in paint was phased out in the United States.

Thomas Edison's incandescent lamp contained Hg (to this day compact fluorescent lightbulbs have Hg added to them). In 1894, H.Y. Castner discovered that Hg could be used in the chlor-alkali process to produce chlorine and caustic soda. And during WWII, the Ruben-Mallory battery (mercury dry-cell

battery) was invented and widely used. By the 1960s, the production of electrical apparati, caustic soda, and chlorine accounted for over 50% of mercury uses. Caustic soda is largely associated with the paper industry; it is used to achieve whiter paper. Except for manufactures in China, chlor-alkali production has now shifted to a non-mercury method. However, the chlor-alkali industry still accounts for 1% of total Hg emissions into the atmosphere and potentially a much larger contribution to water and land releases.

The historical use of Hg has set the stage for many of the modern products and processes that utilize mercury. It is estimated that, over the last 4000 years, historical and continued use of mercury have released 350,000 tons of Hg from the depths of the earth into air, surface land, and water, where its toxicity becomes problematic for human health and Earth's sensitive biosphere.

Early human interest in Hg was raised by its unique physical appearance: a liquid metal must have magical, and therefore, curative properties, and in this capacity, it was used as a germicide before the discovery of germs. Besides its germicidal effects, liquid mercury is a good electrical conductor, has high density and surface tension, and responds uniformly to changes in temperature and pressure.

Over the last three decades, numerous articles have appeared on the toxic effect of mercury on humans. This growing interest in mercury toxicity is due to increased exposure of mercury from the environmental sources as well as from dental mercury amalgams. Mercury contamination of the oceans eventually finds its way into food resources, and fish are becoming another primary source of this corruption. Over 20,000 tons of mercury are released into the environment each year by human activities, including byproducts from the combustion of fossil fuels and regular dumping of industrial waste.

Sources of Exposure

The following are all potential Hg sources: mercury amalgam dental fillings, air pollution – especially in dental offices and near crematoriums that incinerate mercury amalgam fillings, mercury batteries, cosmetics, diuretics (mercurial), vaccines (see thimerosal below) electrical devices and relays, explosives, foods (grains), fungicides, fluorescent lights, freshwater fish (especially large bass, pike, and trout), saltwater fish (especially large halibut, shrimp, snapper, and swordfish), shellfish, and tap water, mining, paints manufactured outside the United States. Mercuric chloride is used for many applications including wood preservative, photographic intensifier, dry battery depolarizer, tanning agent for leather, catalyst in the manufacture of chemicals such as vinyl chloride and disinfectants, separating lead from gold, and others. Mercuric nitrate, commonly used in the felting industry, is the source of the neurological changes observed in felters in the 1800s that led to the term “mad as a hatter.” Inorganic mercury, found mostly in the mercuric salt form (eg, batteries), is both toxic and corrosive.

Biochemistry

Elemental mercury is found as a liquid and is extremely volatile. Since mercury easily vaporizes at room temperature, the route of absorption is often through the lungs. In humans, approximately 70-85% of a dose is absorbed in this manner - whereas less than 3% of a dose will be absorbed dermally. If elemental mercury is ingested orally, less than 0.1% is absorbed from the gastrointestinal (GI) tract and, therefore, when orally ingested is only mildly toxic.

Elemental mercury (Hg0) is highly lipid soluble; a characteristic that facilitates its diffusion across the alveoli into the circulation, as well as its distribution throughout the lipophilic compartments of the body including passage across the blood-brain barrier into the central nervous system (CNS) and across the placenta. In the circulation, elemental mercury binds to numerous tissues, proteins, and erythrocytes. In erythrocytes, catalase can oxidize elemental mercury to an inorganic metabolite. If elemental mercury penetrates the blood-

brain barrier, it is ionized and becomes trapped in the compartment where it is available to exert its neurotoxicity. Elemental mercury has the longest retention in the brain with detectable levels present for years following exposure. The half-life of elemental mercury in adults is approximately 60 days (range: 35 to 90 days).

Inorganic mercury salts are found in 2 oxidation states: mercurous (Hg+1), or mercuric (Hg+2). Common routes of inorganic mercury exposure include the GI tract (following oral ingestion) and the skin. Studies using volunteers have shown that about 7% to 15% of an ingested dose of mercuric chloride is absorbed from the GI tract. Absorption is, in part, related to the water solubility of this compound. It has a non-uniform mode of distribution secondary to poor lipid solubility.

The highest accumulation of inorganic mercury is in the kidneys. Animal studies suggest that mercuric forms have a high affinity for metallothionein in renal cells. In contrast, methylmercury has low affinity for metallothionein. Excretion of inorganic mercury, as with organic mercury, is mostly through feces.

The organic mercury compounds are of great interest today because they are often found in the food chain and have been used to inhibit bacterial growth in medications. Organic mercury is also found in fungicides and industrial run-off. As a result, exposure to these materials is common. Organic mercurials are absorbed more completely from the GI tract than inorganic salts in part because they are more lipid-soluble and because they bind to sulfhydryl groups. More often, organic mercurials are absorbed from the GI tract by forming a complex with L-cysteine and crossing cell membranes on the large neutral amino acid carrier. They are also corrosive, although less corrosive than inorganic forms.

Organic mercurials also cross the blood-brain barrier and placenta and penetrate erythrocytes, attributing to neurological symptoms, and teratogenic effects. Methylmercury has a high affinity for sulfhydryl groups, which explains its effect on enzyme dysfunction. One enzyme that is inhibited is choline acetyl

transferase, which is involved in the final step of acetylcholine production. This inhibition may lead to acetylcholine deficiency, contributing to the signs and symptoms of motor dysfunction, like Parkinson's disease. Excretion of alkyl mercury occurs mostly in the form of feces (90%), secondary to significant enterohepatic circulation. The biological half-life of methylmercury is approximately 65 days.

Dental Mercury Amalgam

In the 1830′s, a revolutionary new dental restorative material called "amalgam" was introduced to the United States. This amalgam was developed in England and France and contained silver, tin, copper, zinc and mercury (as much as 50% mercury). The amalgam fillings were *not* openly embraced by organized dentistry in America: in 1840, members of the American Society of Dental Surgeons were required to sign pledges not to use mercury fillings. In fact, several New York City dentists were suspended from this organization in 1848 for "malpractice for using mercury fillings". In 1859, a new organization was formed as a result of the internal strife over the use of mercury in dentistry: the American Dental Association.

In 1988, the Environmental Protection Agency declared dental mercury amalgam a toxic material to be deposed of in toxic waste sites. In 1990, the World Health Organization stated that there is zero tolerance to mercury in humans. They further stated that the greatest source of mercury contamination in all populations was dental amalgam. Mercury comprises approximately 50% of an amalgam filling. When chewing or eating hot or acidic foods, mercury vapors are given off and small particles of mercury are released into the body. In addition, mercury vapors are inhaled, while particles are absorbed by tooth-roots, the mucous membranes of the mouth and gums. The esophagus and stomach lining directly absorb mercury into the lymphatic system and/or bloodstream. The output of mercury can be intensified by the number of fillings and other activities, such as chewing, teeth-grinding, and the consumption of hot liquids. Mercury is also

known to be released during the placement, replacement, and removal of dental mercury amalgam fillings.

In people with mercury amalgam fillings, measurements of the mercury level in the mouth ranges between 20 and 400 mcg/m3. Keep in mind that this is continuous exposure. The National Institute of Occupation Safety and Health places the safe limit of environmental exposure to mercury at 20 mcg/m3, but this assumes a weekly exposure of 40 hours (the work week) and that the mercury involved is outside the body. The Environmental Protection Agency's allowable limit for continuous mercury exposure is 1 mcg/m3 but, again, this is based on mercury sources outside the body. Neither figure addresses 24-hour-a-day exposure from mercury in one's mouth.

In 1984, the American Dental Association (ADA), without providing scientific evidence, claimed that only 5% of the U.S. population is reactive to mercury exposure, and that this figure is “insignificant”. Meanwhile, the ADA mandates that dentists alert all dental personnel to the potential hazards of inhaling mercury vapors. The Environmental Protection Agency (EPA) goes further, instructing dentists to treat mercury amalgam as a toxic material while handling before insertion, and as toxic waste after removal.

Ever since dentists first started installing amalgams in their patients' teeth, there has been an issue as to whether mercury would be released and cause health (pathophysiologic) problems. In 1984, a group of conscientious dentists formed the International Academy of Oral Medicine and Toxicology (IAOMT**)**. One of their objectives was to scientifically explore the safety of amalgam restorations. Members of the IAOMT have inspired many renowned medical scientists at universities around the world to research possible pathophysiologic effects associated with mercury leaking from amalgam restorations. To their credit is a growing number of scientific studies that document pathophysiologic effects associated with amalgam mercury.

The IAOMT has developed extensive safety recommendations for removal of existing dental mercury amalgam fillings. The IAOMT protocol recommendations were officially renamed the Safe Mercury Amalgam Removal Technique (SMART), and training courses for IAOMT dentists to become certified in SMART is now available. The IAOMT has published a position statement against dental mercury amalgam fillings for medical and dental practitioners, dental students, dental patients, and policymakers. It may be accessed from their website.

Thimerosal

Another source of mercury exists in the form of thimerosal (ethylmercury-thiosalicylate) which is 49.6% ethylmercury by weight. Developed by the pharmaceutical company Eli Lilly in 1928, over the years thimerosal has been used in a variety of medical products, including topical antiseptics, nasal sprays, eye drops, immune globulin products, and vaccines. The Eli Lilly Material Safety Data Sheet (MSDS) for thimerosal acknowledges that exposure to thimerosal in utero and in children can cause “mild to severe mental retardation and mild to severe gross motor impairment.” The Sigma Aldrich MSDS lists abortion and fetal death as possible outcomes of in utero exposure.

After increased concern and protest by numerous toxicologists that the amount of mercury in the childhood vaccination schedule recommended by the CDC exceeded all national and global maximum safety limits, the American Academy of Pediatrics and the United States Public Health Service called for the immediate removal of thimerosal from all vaccines on July 7, 1999. Today, however, several vaccines still contain thimerosal - the most notable being the seasonal influenza (flu) vaccine. Most, but not all, influenza vaccines still contain thimerosal. Also, many vaccines used in third world countries still contain mercury exceeding US safety guidelines. Because of its application as a vaccine preservative, almost every human and animal (domestic and farmed) that has

been immunized with thimerosal-containing vaccines has been exposed to ethylmercury.

Depending on the vaccines administered, at six months of age, infants born today to mothers who received flu vaccines during pregnancy could receive up to 71 mcg of ethylmercury compared to 187.5 mcg prior to efforts to decrease the amount of thimerosal in infant vaccines. Moreover, the new CDC guidelines recommend that all children from 2 to 5 years of age receive an annual influenza vaccine. As a result, the total amount of thimerosal given to children under 5 years of age is almost what it was prior to 2000.

The following data includes levels of mercury in parts per billion:

- 0.5 parts per billion (ppb) mercury = Kills human neuroblastoma cells (Parran et al., Toxicol Sci 2005; 86: 132-140).
- 2 ppb mercury = U.S. EPA limit for drinking water.
- 20 ppb mercury = Neurite membrane structure destroyed (Leong et al., Neuroreport 2001; 12: 733-37).
- 200 ppb mercury = level in liquid the EPA classifies as hazardous waste.
- 25,000 ppb mercury = Concentration of mercury in the Hepatitis B vaccine, administered at birth in the U.S., from 1990-2001.
- 50,000 ppb Mercury = Concentration of mercury in multi-dose DTaP and Haemophilus B vaccine vials, administered 4 times each in the 1990's to children at 2, 4, 6, 12 and 18 months of age.
- 50,000 ppb Mercury = Current "preservative" level mercury in multi-dose flu (94% of supply), meningococcal and tetanus (7 and older) vaccines. This can be confirmed by simply analyzing the multi-dose vials.

Further information on vaccines that contain significant amounts of thimerosal can also be found on the Food and Drug Administration's website and Johns

Hopkins Bloomberg School of Public Health's Institute for Vaccine Safety website.

For children, thimerosal is 50 times more toxic than methylmercury (MeHg). The reasons for this include:

- Injected mercury is more toxic than ingested mercury.
- The blood-brain barrier in infants is far more permeable than adults. Without a complete blood-brain barrier, an infant's brain and spinal cord are vulnerable to exposure.
- Mercury accumulates in brain cell and nervous tissue. Once in the nerve cells, mercury is changed back to the inorganic form and becomes tightly bound. Mercury can then remain for years, like a time-release capsule, causing permanent degeneration and death of brain cells.
- Infants do not produce bile, which is necessary to excrete mercury.

Thimerosal is a poison, neurotoxin, carcinogen, and can interrupt the immune system and the normal development of an unborn baby or a child. Studies show that thimerosal at relatively low doses causes apoptosis (cell death) in neuronal cells via the mitochondrial pathway. Continued efforts are needed to find an anti-microbial and preservative compound to replace thimerosal in vaccines, cosmetics, and ophthalmic solutions.

Target Tissues

Basically, mercury can travel anywhere in the body and especially gravitates into the nervous system (central and peripheral), appetite and pain centers in the brain, cell membranes, kidneys, liver, and glandular tissue such as thyroid, breast, prostate and ovaries. Other areas include, but are not limited to, the jawbone, eyes, ears, cranial nerves, connective tissue (extracellular matrix) bone and skin.

Cysteine and Mercury Translocate Across the Blood-Brain Barrier

Cysteine, an essential amino acid, can be depleted with the chronic stress of metal burden. Cysteine becomes a pivotal factor to support detoxification and the body's attempt to produce more GSH and metallothionein. Interestingly, evidence from animal studies clearly indicates supplementation of cysteine at high doses can increase the transport of Hg into the brain. Pregnant rats received intravenous infusions of saline, L-cysteine, L-leucine, or GSH prior to infusion of MeHg. Although total body Hg was similar for all groups of pups and dams, brain Hg concentrations were significantly increased in dams and pups given cysteine. In contrast, brain Hg levels were lower for the animals receiving intravenous GSH. In subsequent studies it was clearly demonstrated that the mechanism for transport of MeHg across the blood-brain barrier is the large neutral amino acid (LNAA) transport system, also known as the L (leucine-preferring) system. Based on these studies, it is suggested high doses (e.g. 500 mg three times daily) of cysteine (as L-cysteine or N-acetylcysteine) in a metal-burdened patient can facilitate redistribution of Hg from tissues and organs throughout the body into the brain, where it elicits its insidious neurotoxic effects. It should be noted intravenous administration of GSH had protective effects on brain Hg accumulation, but it cannot be assumed high doses of GSH administered orally would have the same beneficial effect, due to the potential for hydrolysis of GSH in the gastrointestinal tract.

L-leucine inhibits transport of the MeHg-cysteine complex across the blood-brain barrier. Therefore, it seems prudent to provide small amounts of cysteine in conjunction with sufficient quantities of leucine and the other amino acids which compete for the L-amino acid transport system, including valine, isoleucine, phenylalanine, tyrosine and tryptophan. Whey protein, derived from milk, contains about 2.53.0 percent cysteine/cystine and about 22 to 25 percent branched-chain amino acids. Therefore, a high quality, partially hydrolyzed whey protein product provides a good source of cysteine/cystine to support intracellular GSH production and metallothionein synthesis, yet adequate leucine to minimize

the transport of metals into the CNS. Partial hydrolysis of whey protein yields about 10 percent di-, tri-, and oligopeptides. Low temperature, enzymatic hydrolysis appears to be the preferred method of production. It is noteworthy that undenatured whey protein has been reported to enhance immune function. An alternative to whey protein might be to provide reasonable amounts of N-acetylcysteine (200-300 mg daily) with a relatively high (quantity and quality) protein diet. The important point here is that pharmacological doses of cysteine/ NAC, in the range of 1500 mg daily, have the potential to exacerbate the adverse neurological effects of toxic metals.

Provision of cysteine/cystine in a complete, balanced source of protein will also provide important amino acids that are precursors to neurotransmitters. Cell studies indicate Hg exposure directly affects uptake and release of dopamine, norepinephrine, and serotonin. Indirectly, Hg burden can be associated with depletion or poor assimilation of specific amino acids that are precursors of neurotransmitters. For example, taurine is a neurotransmitter derived from methionine/cysteine. Available pools of these sulfhydryl amino acids can be depleted by the metal-induced high turnover of GSH. Persistent candidiasis/ dysbiosis associated with Hg burden can compromise the absorption of aromatic amino acids such as phenylalanine/tyrosine and tryptophan, which are precursors to dopamine/norepinephrine and serotonin, respectively.

Signs and Symptoms

Mercury is called the “great masquerader” because of its many and varied symptomatic effects, such as: abnormal nervous and physical development (fetal and childhood), anemia, anorexia, anxiety, blood changes, blindness, blue line on gums, cancer, colitis, depression, dermatitis, difficulty chewing and swallowing, dizziness, drowsiness, emotional instability, fatigue, fever, hallucinations, headache, hearing loss, hypertension, inflamed gums, insomnia, kidney damage or failure, loss of appetite and sense of smell, loss of muscle coordination, memory loss, metallic taste in mouth, nerve damage, numbness, psychosis,

salivation, stomatitis, tremors, vision impairment, vomiting, weakness, and weight loss.

Mercury most commonly affects the neurologic, gastrointestinal, and renal organ systems. Because it can readily cross the blood-brain barrier, Hg exerts its toxic effects primarily on the central nervous system, but further studies have shown toxic effects on the immune system. Most toxicologists studying the effects of mercury agree upon the following six basic mercury-induced disorder categories:

1. **Neurological**

Emotional manifestations (depression, suicidal impulses, irritability, inability to cope) and motor symptoms (muscle spasms, facial tics, seizures, multiple sclerosis)

2. **Cardiovascular**

Nonspecific chest pain, arrhythmias, and cardiac myopathy

3. **Collagen Disorders**

Arthritis, bursitis, autoimmune diseases - scleroderma, and systemic lupus erythematosus

4. **Immunological Disorders**

Cancer and compromised immunity

5. **Allergenic Disorders**

Airborne allergies, food allergies, and "universal" reactors. One of the keys to mercury's effects on health may be its ability to block the functioning of minerals such as selenium, zinc, manganese and iodine.

6. **Endocrine Involvement**

The endocrine system is also affected by Hg burden. Like cadmium, Hg inhibits the conversion of thyroxine (T4) to active T3. It has been suggested the metal-induced inhibition of the 5'deiodinase enzyme is related to general peroxidative effects; however, the inhibition by Hg may be more specific. Hg is known to irreversibly bind to and "waste" selenium, and 5'deiodinase is a selenium-

dependent enzyme. Therefore, Hg may inhibit the conversion of T4 to T3 by interfering with selenium availability.

Hg may also interfere with progesterone metabolism without affecting serum levels of progesterone. In vitro studies indicate Hg binds to a free sulfhydryl group on the progesterone receptor and may thereby diminish progesterone binding and cellular response. The aforementioned Hg-induced disruptions in hormone metabolism could certainly contribute to chronic fatigue, which is one of the hallmark features of Hg burden. Another possible link of metal toxicity to chronic fatigue is via metal binding to the sulfhydryl-containing antioxidant, lipoic acid, making lipoic acid unavailable for its vital role in the energy-producing tricarboxylic acid (citric acid, Krebs) cycle.

Testing for Mercury Toxicity

For a long time, the finger-to-nose test was part of the periodic medical examination of mercury-exposed workers, but with decreasing level of exposure there was a need for instrumental tests which give numerical values for tremor, skill, coordination and nerve conduction velocity.

Nutrients Known to be Protective Against Mercury

Sulfur containing amino acids (L-cysteine or N-acetylcysteine, IV Glutathione), methylsufonyl methane, L-leucine, glycine, cilantro, certain algae (laminaria, fucus, chlorella), selenium, Vitamin E, and vitamin C all are antagonistic for reuptake and retention of mercury.

Specific Protocols for Mercury Detoxification

Acute mercury poisoning is a medical emergency. For acute exposure seek immediate medical attention and call Poison Control Services. As with all detoxification protocols, the type, dose and duration of detoxification agents should always be individually assessed.

There exist numerous opinions as to how to detoxify from and what to detoxify with regarding mercury. Some protocols are well thought out, whereas others are not. It appears that the jury is still out deliberating about the optimal mercury detoxification. The golden rule is to always *be cautious!*

The following may serve as a basic guideline for detoxification of excess mercury caused by chronic exposure. Before initiating a detoxification program, a CBC with chemistry, including a thyroid panel with lipids should be performed. In addition, whole blood elements to assess the mineral status and a urine creatinine clearance should be performed every 60 days when using synthetic detoxifying agents. Administration of glycine and synthetic agents may cause a depletion of essential elements such as zinc, iron, calcium, magnesium, copper and other trace minerals. Of greatest concern is potential kidney toxicity that can occur when the body releases its mercury stores for excretion through the kidneys. Those with underlying kidney disease may not be able to undergo aggressive mercury detoxification therapy.

1. First, identify the source(s) of mercury in the individual's environment (mouth) and remove them. Check for dental mercury amalgams and refer patient to a biological dentist that is SMART protocol certified as described by the International Academy of Oral Medicine and Toxicology (IAOMT)
2. Assess whole blood cell element analysis to determine mineral nutrient deficiency and supplement appropriately; repeat every 60 days.
3. Supplement 200 mcg of selenium daily. Do not use selenium concurrently with DMSA. (See DMSA precautions.)
4. Supplement buffered vitamin C (corn free source) at 2000 mg up to 5000 mg daily adjusting to bowel tolerance.
5. Supplement vitamin E at 400 to 800 IU daily.
6. Supplement Alpha Lipoic Acid at 250 mg twice daily.
7. Algal cells have a remarkable ability to take up and accumulate heavy metals from their external environment. The primary ones used for toxic

metal excess are Chlorella vulgaris, a green microalga, and Laminaria japonica, a brown alga. Chlorella and Laminaria japonica are both chelators, moving toxic metals out of the body, and transporters, moving metals from deeper stores to more readily removal areas. Both work in unison with each other and can remove toxic metals from the body through urinary excretion. Administer 1000 to 2000 mg of Laminaria japonica concentrate (Modifilan) daily and 1000 to 2000 mg of chlorella. Adjust dosage to bowel tolerance; may be taken for long periods of time.

8. Cilantro works well with alga to chelate, or bind, up toxic metals. The issue with cilantro taken alone is that although it chelates metals, it does not remove them in the urine. This means they can recirculate to deposit elsewhere in the body. Hence, taken with alga, metals are more effectively eliminated in the urine.
9. Shilajit is an ancient traditional medicine (Tibetan and Ayurvedic) and has been ascribed a number of pharmacological activities and has been used for ages as a rejuvenator and for treating a number of disease conditions. It is an effective detoxifier of metals and contains over 60 minerals. Modern scientific research has systematically validated a number of properties of shilajit and has proven that shilajit is truly a panacea. It is important to purchase the highest grade of shilajit.
10. Thiol-containing chelating agents such as 2,3-dimercaptosuccinic acid (DMSA, succimer) or 2,3- dimercapto-1-propane sulfonic acid (DMPS), which compete with endogenous sulfhydryl groups have all been used for treating mercury toxicity. One of the most effective of these detoxifying agents for mercury is DMPS which is usually administered by slow IV push or sometimes intramuscularly – but with some discomfort. Those versed in neuraltherapy have injected DMPS into mercury-intoxicated ganglia with excellent results. DMPS reaches the saliva, hence is not appropriate for those that still have amalgam fillings, unless used only as a challenge substance for testing. DMPS may be dosed orally as well (see DMPS information). Administer oral reduced L-glutathione at 5 to 10 mg

per KG of body weight in divided doses on the day before detoxification with DMPS. Reduced GSH further enhances urinary mercury excretion. Do not administer cysteine, N-acetylcysteine, or glutathione concurrently with DMPS, DMSA or D-Penicillamine. The result will yield disulfide formation with a reduced excretion of mercury. Glutathione is contraindicated in insulin deficiency.

11. Instruct patient to drink adequate amount of pure water (adult's urine volume should be about 2 liters per day).

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Nickel	Ni	Atomic number 28	Atomic mass 58.71

Nickel (Ni) is a metallic element that is naturally present in the Earth's crust. Due to unique physical and chemical properties, metallic nickel and its various compounds are widely used in modern industry. It is only within recent decades that the hazards of exposure to Ni and nickel compounds have come to be recognized. Since Ni has not been recognized as an essential element in humans, it is not clear how nickel compounds are metabolized. It is known, however, that exposure to nickel compounds can have adverse effects on human health. Human exposure to Ni occurs primarily via inhalation and ingestion. Significant amounts of Ni in different forms may be deposited in the human body through occupational exposure and diet over a lifetime.

Sources of Exposure

Inhalation exposure in occupational settings is a primary route for nickel-induced toxicity and may cause toxic effects in the respiratory tract and immune system. The sources of environmental nickel contamination include the production and processing of Ni and its by-products, the recycling of nickel-containing products and nickel-containing waste disposal. The most toxic of all compounds of Ni that are encountered in industrial operations is nickel carbonyl ($Ni(CO)_4$). Hazards from exposure may arise from a variety of operations. These include:

(i) the separation of nickel from its ores;
(ii) the preparation of intermediates in organic syntheses, sometimes under extremely high pressures;
(iii) electroplating operations as a medium for depositing thin layers of metallic nickel in electronic circuits and magnetic tapes; and
(iv) inadvertent formation whenever carbon monoxide comes into contact with an active form of nickel.

Environmental sources of lower levels of Ni include tobacco, dental or orthopaedic implants, stainless steel kitchen utensils and inexpensive jewelry. Municipal drinking water in the United States generally contains Ni at concentrations less than 10 µg/l.

Occupational exposure to Ni compounds is dependent upon industrial processing and is usually substantially higher than work-unrelated nickel exposure. The form of Ni to which workers are exposed differs in the various industries in which Ni is used and occurs through inhalation or dermal contact (inhalation is the primary route of exposure), with ingestion taking place where there are poor industrial hygiene practices.

Tobacco and tobacco smoke - cigarettes - are also a source of bioavailable Ni (nickel carbonyl); one cigarette may contain 2 to 6 micrograms of nickel - of which up to 20% is inhaled in the smoke. Generally, daily oral intakes of nickel are extremely variable and may range from negligible amounts tp up to 900 micrograms.

Target Tissues

Nickel is normally present in human tissues and, under conditions of high exposure, these levels may increase significantly. In the general population, contributions to the body burden from inhalation of Ni in the air and from drinking water are generally less important than dietary intake and ingestion is considered to be the most important route of exposure.

Inhaled Ni is selectively concentrated in the lung, followed by heart, diaphragm, brain, and spinal cord tissues. In general, the lung has the tendency to retain significant amounts of Ni independently of the route of exposure. The kidney, in addition to the lung, brain, pancreas, and other tissues is considered a target organ for Ni retention following high levels of Ni exposure.

Biochemistry

The exposure to high doses of Ni disturbs established cellular homeostasis via changes of intracellular calcium levels and produces oxidative stress. Although nickel does not react significantly with DNA, it does interact strongly with proteins. The strength of the interaction is dependent on the identity of the amino acids present, and the greatest affinity is shown towards histidine residue. Several proteins with high affinity to nickel have been identified in recent years. They are mainly involved in Ni transport, detoxification and excretion. It is of interest to note that the metal-binding protein metallothionein does not appear to constitute a major nickel-binding component in different tissues. Serum albumin, L-histidine and α_2-macroglobulin have been identified as the main binding partners of nickel in blood serum. The ability of nickel ions to interact with a number of proteins raises the possibility that nickel may significantly change intracellular homeostasis by altering protein functions and producing stress similar to unfolded protein response.

Nickel is a known contact carcinogen and allergen. Ironically, at the same time that Ni presumably uncouples our protective mechanism against cancer, it over-stimulates at least one immune response (cytolytic antibody production) linked to cancer-negating activities. Thus, a misdirecting or uncoupling of our normal immune surveillance for cancer, while compensating with an over-escalation of an immune response that can produce hypersensitivity and perhaps even auto-immunity, essentially describes the immunopathology of nickel poisoning.

Inhaled Ni, especially nickel carbonyl, is a respiratory carcinogen, producing squamous cell carcinomas. The exact mechanism(s) of nickel carcinogenesis is still unknown. It has been suggested that solubility and removal rates of the various Ni compounds may be directly related to their relative carcinogenic potential in the respiratory tract. Crystal structure, particle size, and surface area may also be related to carcinogenicity. Nickel can displace copper and zinc at

enzyme-activator sites and thereby abnormally up- or down-regulate enzymatic processes. This then causes deregulation of metabolic and immunologic functions and potentiate carcinogenesis.

At low concentrations, nickel induces heme-oxygenase activity; at high concentrations it inhibits it, thus disordering heme metabolism. In addition, nickel toxicity causes a transient reduction of cellular glutathione. Nickel induces metallothionein synthesis in liver cells causing a dysfunction in arginase and carboxylase activities. This may result in an impairment of the urea cycle. Both nickel sulfide and sulfate can disrupt immune function by depressing natural killer cell and CD4 lymphocyte populations in blood. Nickel salts at low concentrations can also suppress the natural oxidant cascade following the respiratory burst in phagocytes; hydrogen peroxide formation is reduced, and the anti-microbial oxidant defense system of leukocytes is thus weakened.

It has been difficult to estimate the specific risks associated with individual species of Ni due to mixed exposures within the workplace. The overall evidence from studies of Ni workers suggests that respiratory cancer risks are primarily related to exposure to less soluble forms of nickel (notably sulfidic and oxidic nickel). In addition to the lung and nasal sinus cancers, cancers of the larynx, kidney, prostate, stomach, colon, bladder, buccal cavity, and pharynx have also been reported in excess of expected numbers in nickel-exposed workers.

Signs and Symptoms

Human exposure to highly nickel-polluted environments has the potential to produce a variety of pathological effects. Among them are skin allergies, lung fibrosis, cancer of the respiratory tract and iatrogenic Ni poisoning. Nickel is a ubiquitous metal frequently responsible for allergic skin reactions and has been reported to be one of the most common causes of allergic contact dermatitis, as reflected by positive dermal patch tests.

Nickel hypersensitivity also causes asthma, conjunctivitis, inflammatory reactions to nickel-containing prostheses and implants, and systemic reactions after parenteral administration of nickel-contaminated fluids and medications.

Epidemiological investigations and experimental studies have demonstrated that Ni metal dusts and some nickel compounds are extremely potent carcinogens after inhalation, but also that the carcinogenic risk is limited to conditions of occupational exposure Hence, probably the greatest danger from chronic Ni exposure is lung, nasal, or larynx cancers, and gradual poisoning from accidental or chronic low-level exposure, the risk of which is greatest for those living near metal smelting plants, solid waste incinerators, or old nickel refineries.

Nutrients Known to be Protective Against Nickel Accumulation

Sulfur-bearing amino acids, certain algae (laminaria, fucus, chlorella), selenium, vitamin C, manganese, zinc and copper are antagonistic for reuptake and retention of Ni.

Testing for Nickel Toxicity

Urine and serum nickel concentrations may be used as biological indicators of occupational, environmental and iatrogenic exposures to Ni compounds. However, they do not give a good picture of past exposure and they cannot be used for risk assessment as current knowledge is not sufficient to relate nickel concentrations in these indicator media to specific adverse health effects. Nickel concentrations in serum mainly reflect recent exposure because of the short biological half-time in this compartment. The Ni excretion in urine may reflect more extended exposure and is more practical than serum.

Specific Protocols for Nickel Detoxification

As with all detoxification protocols, the type, dose and duration of detoxification agents should always be individually assessed.

Nickel detoxification is like detoxification for mercury. The following may serve as a basic guideline for detoxification of excess Ni from chronic exposure. After 60 days, laboratory screening should be used to reassess protocol. Before initiating a detoxification program, a CBC with chemistry, including a thyroid panel with lipids should be performed. In addition, whole blood elements to assess the mineral status and a urine creatinine clearance should be performed every 60 days when using synthetic detoxifying agents. Administration of arginine and synthetic agents may cause a depletion of essential elements such as zinc, iron, calcium, magnesium, copper and other trace minerals. Of greatest concern is potential kidney toxicity that can occur when the body releases its nickel stores for excretion through the kidneys. Those with underlying kidney disease may not be able to undergo aggressive nickel detoxification therapy.

1. Identify the source (s) of nickel in the individual's environment and remove them or remove the individual from the sources. Check dental restorations and industrial exposure.
2. Assess whole blood cell element analysis to determine mineral nutrient deficiency and supplement appropriately.
3. Supplement 200 mcg of selenium daily.
4. Supplement buffered vitamin C (corn free source) at 2000 mg up to 5000 mg daily adjusting to bowel tolerance.
5. Supplement vitamin E at 400 to 800 IU daily.
6. Supplement Alpha Lipoic Acid at 250 mg twice daily.
7. Algal cells have a remarkable ability to take up and accumulate heavy metals from their external environment. The primary ones used for toxic metal excess are Chlorella vulgaris, a green microalga, and Laminaria japonica, a brown alga. Chlorella and Laminaria japonica are both chelators, moving toxic metals out of the body, and transporters, moving metals from deeper stores to more readily removable areas. Both work in unison with each other and can remove toxic metals from the body through urinary excretion. Administer 1000 to 2000 mg of Laminaria

japonica concentrate (Modifilan) daily and 1000 to 2000 mg of chlorella. Adjust dosage to bowel tolerance; may be taken for long periods of time.

8. Cilantro works well with alga to chelate, or bind up toxic metals. The issue with cilantro taken alone is that although it chelates metals, it does not remove them in the urine. This means they can recirculate to deposit elsewhere in the body. Hence, taken with algas, metals are more effectively eliminated in the urine.
9. Shilajit is an ancient traditional medicine (Tibetan and Ayurvedic) and has been ascribed a number of pharmacological activities and has been used for ages as a rejuvenator and for treating a number of disease conditions. It is an effective detoxifier of metals and contains over 60 minerals. Modern scientific research has systematically validated a number of properties of shilajit and has proven that shilajit is truly a panacea. It is important to purchase the highest grade of shilajit.
10. Administer oral reduced L-glutathione at 5 to 10 mg per KG of body weight daily. Do not overdose and check for renal clearance while using GSH. Glutathione is contraindicated in insulin deficiency.
11. Instruct patient to drink adequate amounts of pure water (Adult's urine volume should be about 2 liters per day).
12. Documented IV chelation therapy for nickel poisoning (for the treatment of persons exposed to nickel carbonyl) is sodium diethylcarbodithioate (DDTC). The use of DDTC was considered beneficial in a large number of anecdotal reports of human poisoning, although there are few adequately controlled human trials to support its effectiveness and lack of toxicity. Disulfiram is another nickel-chelating agent that has been used in nickel dermatitis and also in the case of nickel carbonyl poisoning. However, due to its hepatotoxicity and possible redistribution of nickel to the brain, its use in both indications is still controversial.

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Palladium	Pd	Atomic number 46	Atomic mass 106.42

Palladium is a silver-white ductile and malleable metal that belongs to the platinum group. William Hyde Wollaston discovered palladium in 1803 in crude platinum ore from South America. Palladium is also found in the platinum mines of Russia, Canada and Columbia. Palladium has a very similar chemistry to that of platinum. Since its discovery, palladium has been found to have no biological role.

At one time, palladium chloride was formerly prescribed as a treatment for tuberculosis at the rate of 0.065 g per day (approximately 1 mg kg^{-1}), but fell out of use due to its side effects.

In dentistry, palladium is a very common component of dental casting alloys of all types, and its use has increased over the past several decades in response to the increased cost of gold. However, current research has demonstrated that palladium as used in dentistry is biologically toxic and poses a health risk. Since 1993, the German Health Ministry has warned dentists not to use palladium-copper alloys. In Switzerland, palladium dental alloys have been banned. The carcinogenic potential of the palladium ion is still unclear, although there is some evidence that it is capable of acting as a mutagen.

The use of gold in dentistry dates to ancient times and, today, the gold used by most dentists contains dangerous amounts of palladium. German biological medical doctors refer to palladium/gold alloy as the “fool's gold” of dentistry, because it may be more dangerous than mercury. The amount of palladium used today in making dental crowns and bridges varies considerably, whereas gold restorations may contain up to 78.5% of other dangerous heavy metals.

Sources of Exposure

Palladium is primarily used in industry in electrical contacts as a catalyst, used to purify hydrogen gas, used in dentistry (as an alloy in gold crowns and bridges), used in fine instruments such as watches and some surgical instruments, and used in making jewelry and coinage. Pd has also been used as a radioactive isotope in the treatment of rapidly growing, high-grade prostate cancer. To date, the most identified sources of palladium exposure for the general population are dental restorations. In dentistry, palladium, gold, titanium, mercury, silver, tin, nickel, platinum, and rhodium, are still used in the production of various dental fillings.

Biochemistry

Like mercury, Pd is cytotoxic and kills or damages cells. Palladium also causes considerable damage and degradation of DNA and exacerbates hydroxyl radical damage. Palladium also damages cell mitochondria and inhibits enzyme activity and function. Tests in Germany showed the following toxic effects of palladium:

- Obstruction of important enzyme systems like creatin-linase, aldolase, alcalite phospatase, carbon-anhydrease, trypsin, chymotropsin, cellulase
- Disturbance of collagen synthesis like bone and cartilage
- Obstruction of thymidin in the DNA
- Accumulation in body organs
- Allergic reactions, especially for people with nickel allergies

Information on the elimination and excretion of Pd is scarce and refers mostly to palladium chloride and sodium tetrachloropalladate, which are eliminated in feces and urine. Urinary excretion rates of intravenously dosed rats and rabbits ranged from 6.4 to 76% of the administered dose over a time range of 3 h to 7 days. The elimination of palladium in feces ranged in these studies from traces up to 13% of the administered dose. Following oral administration of palladium chloride, >95% of palladium was eliminated in feces of rats due to non-absorption.

Subcutaneous or topical treatment with palladium sulfate ($PdSO_4$) or other palladium compounds resulted in detectable concentrations of Pd in the urine of guinea pigs and rabbits.

Half-lives calculated for the elimination of Pd from rats (whole body, liver, and kidney) ranged from 5 to 12 days.

Target Tissues

The Pd cations in dental alloys are continuously released and accumulate in the kidneys, liver, thyroid, brain, and CNS. The gold/palladium alloys in proximity to mercury/silver alloys create high levels of galvanic current densities. This causes extensive migration of mercury and palladium to saliva, tooth roots, jaw, gums, and other parts of the body.

Signs and Symptoms

Early symptoms of toxicity due to Pd dental crowns or bridges include: increased salivation, pain in teeth and jaw, burning tongue, metallic taste, peeling of mucous membrane around teeth, fungus-like coating in throat (thrush) and frequent sore throats, and painful, swollen lymph nodes in the neck.

Late symptoms of Pd toxicity include: teeth pulp death, granulomas, puss pockets with dead tissue, swollen tongue; nerve pain in the face; paralysis of face; muscle cramps of tongue, lips, around eyes; sinus infection, bronchitis and lung ailments without clear reason; difficulty breathing at night; problems with stomach, intestines, liver, bladder, kidneys; weight loss; joint and muscle pain; muscle cramps and weakness; tinnitus; visual disturbance; depression, insomnia; outbreaks of sweat, palpitations, difficulty concentrating.

Tumors associated with Pd exposure have been reported in two studies. Mice given palladium chloride (5 mg Pd^{2+}/litre) in drinking-water from weaning until natural death developed malignant tumors, mainly lymphoma-leukemia types and

adenocarcinoma of the lung, at a statistically significant rate, but concomitant with an increased longevity in males, which may explain at least in part the increased tumor rate. Tumors were found at the implantation site in 7 of 14 rats (it was not clear whether the tumors were due to the chronic physical stimulus or to the chemical components) 504 days after subcutaneous implantation of a silver-palladium-gold alloy. No carcinogenicity study with inhalation exposure was available.

Transfer of small amounts of Pd to offspring via placenta and milk was seen with single intravenous doses of palladium (II) chloride in rats.

Significant immune responses have been obtained with palladium chloride and/or chloropalladates using the popliteal and auricular lymph node assay in BALB/c mice. Preliminary data in an animal model suggest that Pd compounds may be involved in induction of autoimmune diseases.

Nutrients Known to be Protective Against Palladium

Owing to the ability of palladium ions to form binding complexes to proteins and amino acids, the following sulfur-bearing amino acids N-acetyl cystine, L-methionine are useful chelating agents. In addition, certain algae (laminaria, fucus, chlorella), vitamin C, selenium, and alpha lipoic acid are all antagonistic for reuptake and retention of palladium.

Specific Protocols for Palladium Detoxification

As with all detoxification protocols, the type, dose and duration of detoxification agents should always be individually assessed.

Palladium detoxification is like detoxification for mercury. The following may serve as a basic guideline for detoxification of excess palladium from chronic exposure. After 60 days, laboratory screening should be used to reassess protocol. Before initiating a detoxification program, a CBC with chemistry, including a thyroid panel

with lipids should be performed. In addition, whole blood elements to assess the mineral status and a urine creatinine clearance should be performed every 60 days when using synthetic detoxifying agents. Administration of glycine and synthetic agents may cause a depletion of essential elements such as zinc, iron, calcium, magnesium, copper and other trace minerals. Of greatest concern is potential kidney toxicity that can occur when the body releases its palladium stores for excretion through the kidneys. Those with underlying kidney disease may not be able to undergo aggressive palladium detoxification therapy.

1. First, identify the source of palladium (usually gold alloy dental restorations) and remove it. Though the International Academy of Oral Medicine and Toxicology (IAOMT) does not have a specific protocol for palladium removal, their “SMART” mercury removal protocol may be used as a substitute.
2. Assess whole blood cell element analysis to determine mineral nutrient deficiency and supplement appropriately.
3. Supplement 200 mcg of selenium daily.
4. Supplement buffered vitamin C (corn free source) at 2000 mg up to 5000 mg daily adjusting to bowel tolerance.
5. Supplement vitamin E at 400 to 800 IU daily.
6. Supplement Alpha Lipoic Acid at 250 mg twice daily.
7. Algal cells have a remarkable ability to take up and accumulate heavy metals from their external environment. The primary ones used for toxic metal excess are Chlorella vulgaris, a green microalga, and Laminaria japonica, a brown alga. Chlorella and Laminaria japonica are both chelators, moving toxic metals out of the body, and transporters, moving metals from deeper stores to more readily removable areas. Both work in unison with each other and can remove toxic metals from the body through urinary excretion. Administer 1000 to 2000 mg of Laminaria japonica concentrate (Modifilan) daily and 1000 to 2000 mg of chlorella. Adjust dosage to bowel tolerance; may be taken for long periods of time.

8. Shilajit is an ancient traditional medicine (Tibetan and Ayurvedic) and has been ascribed a number of pharmacological activities and has been used for ages as a rejuvenator and for treating a number of disease conditions. It is an effective detoxifier of metals and contains over 60 minerals. Modern scientific research has systematically validated a number of properties of shilajit and has proven that shilajit is truly a panacea. It is important to purchase the highest grade of shilajit.
9. There is clinical evidence that DMPS is a useful chelator for palladium. DMPS is usually administered by slow IV push or sometimes intramuscularly – but with some discomfort. DMPS reaches the saliva, hence is not appropriate for those that still have palladium or mercury dental restorations, unless used only as a challenge substance for testing. DMPS may be dosed orally as well.
10. Instruct patient to drink adequate amount of pure water (an adult's urine volume should be about 2 liters per day).

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