

OVERVIEW OF CLINICAL MERCURIALISM

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- Goals:**(a) To provide a review of the xenobiotics, toxicology and treatment of elemental, inorganic and organic mercury compounds.
(b) To provide a discussion of amalgam hypersensitivity and recommend clinical guidelines to better understand this problem.
(c) To review the amalgam controversy without negative bias or political encumbrances and set initial guidelines based on clinical experience.

Mercury is ubiquitous in our environment. It is found naturally in our atmosphere from evaporation and in the earth's crust in its elemental form as well as inorganic and organic compounds. The crust contains 0.05 to 0.08 micrograms/gram. It is well known that mercury is a severe protoplasmic poison and may express itself in different ways depending on the physical state of the mercury, the chemical valency of mercury, length of exposure, method of absorption, age of the patient and other factors.[1] Industrial usage of mercury is increasing and this element or its compounds are commonly employed in the chlor-alkali industry and in the manufacturing of electrical apparatus elements. Until recently, mercurials were also used as additives to some outdoor paints. The Environmental Protection Agency banned the use of mercury in indoor paints after August 20, 1990 and banned it from outdoor paint after September 1991 as well. Mercury can still be found in medicinals - usually topically, and serves as a catalyst in plastic manufacturing. as a fungicide in agriculture, and as a slimicide in paper products. A 1980 survey by the National Institute of Occupational Safety and Health (NIOSH) estimates that 70,000 workers, of whom about one third were women, were potentially exposed to mercury (especially mercury vapor) in the workplace. Occupations at risk are found in Table 1.[2] Federal regulations and advisories for various mercury compounds are in Table 2 [3] and various common forms of mercury in usage are in Table 3.[4]

Mercury can be found in many non-occupational sources. The most common is predatory fish. As acid rain causes an alteration of the pH of our inland lakes, mercury from the earth's crust becomes increasingly soluble where potential methylation by water and soil microorganisms occurs. Mercury then enters the aquatic ecosystem where it eventually concentrates in our gamefish and bottom feeders. Swordfish and tuna are among the most common contaminated ingested sources. Other sources of contamination include the burning of fossil fuels, crematoriums, broken thermometers, dental waste, and runoff from hazardous landfills. Elevated mercury concentrations have been detected in about twenty five percent of the groundwater and surface-water samples from 2783 hazardous waste sites tested by the Environmental Protection Agency. [5] Disposal of solid waste (such as batteries, electrical switches and thermometers) and

recreational exposure are still other sources of mercury exposure. Dental silver amalgam fillings contain between forty eight and fifty two percent mercury which can vaporize in the dental work environment as well as intraorally. Though not agreed to by all organizations, especially the American Dental Association, the World Health Organization, after a thorough review of the literature, has officially stated that mercury from amalgam is the most common source of inorganic (elemental) mercury in humans in a non-industrialized setting and several European countries are limiting the use of amalgam in dentistry.[6]

ELEMENTAL MERCURY

Mercury exists in three basic forms: the elemental, (H₀ inorganic salts (H₂ and H₃) and the organic state. The elemental state is a silver-gray liquid, will volatilize slowly at room temperatures, and vaporizes more rapidly when heated. This form accounts for most occupational exposures. Inhalation of the elemental vapor is very hazardous and nearly one hundred percent is absorbed and seventy five percent retained. Following vapor inhalation, only seven percent is expelled through exhalation. Only about 0.01% is absorbed from the gastrointestinal tract when ingested. The fecal route is probably the primary route of excretion for elemental mercury with the urine also being an important route. The saliva and sweat are also potentially capable of excreting mercury.

This element has a short span in the body once inhaled and oxidizes to the mercuric ion at the cellular level, much of this prior to breaching the blood brain barrier. Elemental mercury vapor readily cross the placental and blood brain barrier where further conversion to the mercurinc ion occurs. Elemental mercury accumulates in the brain, kidneys, liver, testes, adrenal glands, thyroid, ovaries and the gastrointestinal tract. The highest concentration accumulates in the kidneys but the longest half life occurs in the brain. The average half life of elemental mercury is 58 days in man though fifteen percent of a dose has a secondary half life of over 2 years. The half life of mercury can be prolonged by ethanol even in non-intoxicating dosages. [7]

Toxicity of mercury is, in part, related to alteration of enzyme and other protein function and structure by binding to sulfhydryl, amine and phosphoryl groups. Alteration of neurotransmission also has been postulated.[8]

Mercury can be measured in blood, urine, hair and as a direct vapor in the oral cavity. The latter method is investigation but may correlate with the contribution of amalgam vapor release more closely than urine or blood mercury. The half life of mercury in blood is 3 days so blood testing in whole blood is valuable only if continued exposure or acute exposure is occurring. If utilized, blood samples should be collected in a heparinized vacutainer or special heavy metal galssware and refrigerated. Colorimetric urine studies, as a part of the common urinary "heavy metal screen", the Reinsch Test, are insensitive and may miss lower levels of mercury and

cold vapor atomic absorption spectrophotometry analysis on an aliquot of 24 hour urine, collected in an acid-washed special heavy metal container, is preferred for chronic poisonings. A urine mercury concentration over 20 micrograms/Liter or a blood level over 4 micrograms/dl is considered abnormal but often blood levels of 20 micrograms/dl are seen before symptoms appear with acute inorganic toxicity. [9] The first morning void, if adjusted for the concentration of the urine, can provide a close approximation. Both the urine and blood may sometimes have poor correlation with clinical manifestations though in most industrial poisonings there is a reasonable correlation with urinary testing and 24 hour urine mercury measurements should be done on all workers who have occupational exposure to this element every six months. If air monitoring indicates that the work area mercury level exceeds the Threshold Limit Value, an immediate 24 hour urine test and physical examination should be performed. It is advisable to perform blood or urine testing with properly sealed mercury free glassware and in as short a period of time as possible due to vaporization losses. [10]

Acute poisoning by mercury vapor is rare today with increasing federal standards and enforcement and industrial process modifications. Acute elemental mercurialism is characterized by chills, fever, shortness of breath, metallic taste in the mouth (these first four symptoms are characteristic of metal fume fever), confusion, chest pain, nausea, vomiting, and diarrhea, colitis, interstitial pneumonitis, necrotizing bronchiolitis, and pulmonary edema. Interstitial fibrosis, interstitial emphysema, pneumothorax, pneumatocele formation and mediastinal emphysema can result, especially in adults where an obstructive mechanism is more likely to result. Neuropsychological symptoms can also be present and permanent neurological damage can remain. The lung is the primary target for acute vapor exposure. Symptoms may resolve in 2 to 7 days or progress into more serious pulmonary involvement. Infants less than 30 months of age are especially likely to have a fatal outcome.[11]

The elemental form is poorly absorbed from the gut and is rarely a problem unless massive doses have occurred. Reports of nonfatal ingestion up to 204 grams have been reported in a 17 year old boy. [12] Clinical problems may occur however if ingestion occurs in the case of inflammatory bowel disease. Occasionally surgery is required if mercury is caught in the appendix and causing symptoms. Mercury embolism in the lung is the greatest cause of fatality in suicide attempts to inject metallic mercury.[13]

Chronic manifestations from elemental mercury (usually as vapor) occur gradually and may take months or years to develop. Since mercury vapor is oxidized to and eventually excreted as the mercuric ion by the catalase system at the cellular level, this form of chronic elemental mercury accumulation eventually develops a form of intracerebral mercuric poisoning. The brain and peripheral nervous system is the primary target for chronic elemental mercurialism. Accordingly neuropsychological including autonomic nervous system symptoms result. Tremors occur,

which may be of a fine type at rest. They characteristically become more coarse on intention. Early detection of tremor can be facilitated by the use of a 10 or 15 pound weight. [14] Overwhelming fatigue, short term memory dysfunction, cognitive impairment, confusion, anxiety, and decrements in performance of psychomotor skills are other neurologic manifestations. A critical analysis of the long term neurobehavioral effects of elemental mercury was recently conducted and indicates that workers with a higher mercury burden scored less well on the Recurrent Figures, the SCL-90R, but were the same on the WAIS, Rey's AVL, PASAT, BGT, Grooved pegboard, and Finger Tapping Tests. Chronic subtoxic levels of this substance appear to produce "mild changes in short-term nonverbal recall, and heightened distress generally, and particularly in categories of obsessive compulsion, anxiety, and psychoticism, without alterations in general intellectual functioning, attention, verbal recall, and motor skills." [15]

Erethism (shyness, insomnia, and excessive irritability) occurs, as well as enhanced sensitivity to sounds and other stimuli, excessive salivation, and gingivostomatitis. In more severe cases, constriction of visual field, delayed peripheral neuritis (usually sensory), discoloration of the lens (a brown light reflex reflects from a brownish pigmentation of the anterior capsule of the lens), proteinuria, dermatitis, chronic pneumonia, kidney failure and psychosis can occur. Conjunctivitis and a pruritic erythematous rash may occur from mild exposures to this element. [16].

Some interesting observations of occupational exposure problems and unusual disease states associated with inorganic mercury should be mentioned. The average dentist uses more than 1 kilogram of mercury each year. CNS effects have been reported and are prevalent in those dentists who frequently place dental amalgams. [17,18,19]

Mad as a hatter, in Lewis Carrol's Alice in Wonderland, is a 19th Century account of hatters (hat makers) becoming psychotic from mercury fulminate used to stiffen the brims of felt hats). [20]

Acrodynia, a rare syndrome characterized by severe leg cramps, irritability, paresthesias, painful pink fingers and peeling hands, feet and nose may occur in children exposed to elemental mercury, mercury salts or phenylmercury. Adults are not affected with this disease. [21,22,23,24] A pattern of illness similar to Amyotrophic Lateral Sclerosis (ALS) has been found in relationship to abnormal exposure with elemental mercury. [25]

Traditionally treatment in acute elemental and inorganic mercury cases, consists of BAL (British anti-Lewisite) 4mg/kg, deep IM, every 4 hours, monitoring urinary mercury levels. After the initial 24 hour course of BAL, the dose is reduced to every 12 hours for the next 24 hours then once a day for 3 days. A 2 day rest is followed by another 5 day course until urinary goals are met (when levels are below 50 micrograms/liter). D-penicillamine may be used in cases allergic to BAL or in less seriously poisoned patients as it is less toxic (100mg/kg/24hrs divided every 6 hours). BAL can be quite toxic and side effects include nausea and vomiting, headache, tachycardia,

fever, conjunctivitis, rash, lacrimation and blepharospasm.[26]

A newer penicillamine is NAP (N-acetyl penicillamine). This agent is more effective than D-penicillamine and can be offered as an oral treatment but is also becoming less popular with the advent with third generation chelating agents.[27,28]

Recently released in oral form by the FDA is 2,3-dimercaptosuccinic acid (DMSA, Chemet, Succimer). Though approved for childhood lead poisoning, this agent has been successful in treating mercury poisoning. DMSA is essentially a water soluble form of BAL and is less toxic than its parent compound. It is used in doses of 10 mg/kg three times a day for 5 days then twice a day for another 14 days. [29,30] After appropriate monitoring, one or more rounds may be required with two weeks allowed between chelation therapies. With more evaluation DMSA may well become the therapy of choice if a parental route is not required. Another effective BAL analogue, not yet released in the United States, is 2,3-dimercaptopropane-1-sulfonate (DMPS). When DMPS was administered to workers with elemental mercury poisonings, it reduced the half life from 33.1 to 11.2 days. [31]

There is some evidence corroborating the efficacy for EDTA (ethylenediaminetetraacetate) therapy but, in general, this chelator lacks the efficiency of the other, newer chelating agents in dealing with mercury poisoning. A natural factor, odorless garlic, is popular in Japan. The disulfide bonds of garlic permit mild chelation capability for various heavy metals. Cysteine, and methionine also have sulfur bonds to act as weak chelation agents to assist in the removal of heavy metal. Selenium supplementation has certain theoretical considerations since selenium is an essential element, important in the integrity of the immune response. Elemental mercury after oxidation to mercuric ion binds to metallothionein and is known to competitively displace a portion of the essential cofactor selenium in the body. When selenium levels are raised, a complex is formed with mercury which prolongs the half life but is less toxic, according to animal studies. [32]

Cleaning up a mercury spill, such as a broken blood pressure device or dental spills should not be attempted with an ordinary vacuum cleaner as more vapor hazard will be generated. Special clean-up crews should be called. They can be located with help from the Environmental Protection Agency or the Occupational Safety and Health Administration. Porous carpeting should be properly discarded after a spill. Proper disposal of industrial, non-occupational and dental waste is essential and help is available from the respective federal agencies to assist in this area.

INORGANIC MERCURY

Mercuric salts are usually colorless or white crystals or intensely yellow or red powders. Examples include mercuric chloride, an antiseptic and disinfectant; mercuric cyanide and oxide, disinfectants; and mercuric

nitrate, used in the felt hat business. Mercurous salts are colorless, white or light yellow powders. Examples include mercurous acetate, an antiseptic; calomel (mercurous chloride), a diuretic, cathartic, and anti-syphilitic; mercurous nitrate, used to blacken brass and mercurous oxide which is used in producing electric batteries.

In general, mercuric compounds (H3) are more soluble and produce more serious poisonings than the mercurous salts (H2). A high index of suspicion and a good history of exposure are as important as lab indices to establish the diagnosis in inorganic mercury poisoning as in all mercury intoxication states. Whole blood mercury and urine is preferable for the measurement of inorganic mercury exposures. A 1 to 1 plasma to red cell relationship is generally present with inorganic mercury as compared to a 1 to 10 relationship with organic mercury. Most adults have blood levels of less than 2 micrograms/dl and urinary mercury is less than 10 micrograms/l.[33]

With ingestion, seven to fifteen percent of the oral dose is absorbed while large amounts remain bound to the gastrointestinal mucosa. Very little crosses the blood brain or placenta barriers. Once absorbed, the inorganic mercurous and mercuric ions accumulate in the kidney, in the liver, spleen, bone marrow, RBCs, intestine, skin and respiratory mucosa. It is excreted mainly through the kidneys and feces and, to a lesser extent, in sweat and parotid fluids. The biological half life of inorganic mercury is about 40 days. Dermal absorption of ionic mercury salts also can cause toxicity.

With acute inorganic mercury poisoning (the mercuric and mercurous ion), ingestion is the primary route. The immediate problems are a local corrosive action on mucosal tissue in the mouth, esophagus and intestine. The patient may die from shock and hypovolemia. Abdominal pain, gastrointestinal bleeding, nausea and vomiting are common.

The second problem is organ damage at the sites of excretion. Renal involvement is that of a brief diuresis sometimes followed by acute tubular necrosis. Anuria develops in 24 hours in 50 % of cases. After ingestion of nonfatal amounts of inorganic salts, however, increasing amounts of mercury accumulate in the kidney and this is the primary organ involved in inorganic mercury poisonings. Alteration in the permeability of the tubular epithelium occur. A dose dependent proteinuria or nephrotic syndrome develops. [34]

Chronic poisoning with inorganic mercury salts is not well described in the literature. Two case reports of chronic ingestion of mercury salts in the form of a laxative resulted in the patients having irritability, colitis, and chronic renal failure. Nephrotic syndrome and renal tubular acidosis [35] has been reported with the chronic use of ointments containing mercurials. Gingivitis, stomatitis and salivation can also occur and one fatality has been reported. As previously mentioned, cases of acrodynia have occurred in children treated for eczema with yellow mercuric oxide, mercurous chloride in teething lotions and diaper powder and from mercury exposure

from broken fluorescent light bulbs.

Treatment is similar to elemental mercury poisoning as described above. The goals are to remove mercury from the body and provide hydration to prevent renal failure, shock and dehydration. Ingested mercury of this type can be removed by emesis, catharsis or lavage. BAL or other appropriate agent should be given immediately. With a potentially lethal dose, dialysis may be considered. [36]

ORGANIC MERCURY

Starting in 1913, organic mercury was observed to act as a diuretic and this led to the development of mercurial diuretics. They were used for 30 years until replaced in the mid-1960s by less toxic products. Organic mercurials today are found mainly as preservatives and antiseptics. Their antifungal and antibacterial properties prompted their use as seed dressings. Methyl, ethyl and phenyl mercury compounds are used in this manner. Poisonings usually occur these days from misuse of treated seed though the latter two compounds were recently banned as seed preservatives in the United States. A recent case of phenylmercury poisoning was reported in a child from a preservative in indoor paint [37]. Though banned, indoor paint containing mercury still exists from supplies purchased before the ban. As much as 35% of all outdoor paint contained mercury before the ban. Much of this is still available for use. For a list of mercury-containing paints call the National Pesticide Telecommunications Network at (800) 858-7378. [38] Mercurochrome, phenylmercuric acetate, phenylmercuric nitrate, phenylmercuric borate, and thiomersol are all antiseptics found primarily in eyedrops and contact lens solutions. They are also found as preservatives in gamma globulin injectable formulations, vaccines, and nasal sprays. They are found in vaginal creams and may be readily absorbed.

In aryl compounds, mercury is joined to an aromatic (benzene) ring. With alkyl compounds it is not, but instead is attached to either long chain or short chain simple hydrocarbons. The long chained alkyl and aryl compounds behave like inorganic mercury toxicologically.

Most daily exposure with organic mercurials, and the primary source of mercury exposure in the general nonoccupational population, occurs due to ingestion of foods, especially seafood, according to the federal government. The Food and Drug Administration is responsible for evaluating the safety of seafood in regard to the concentration of mercury in the United States. Farmers, wood preservers, lumberjacks, seed handlers and workers manufacturing disinfectants and fungicides may be exposed to organic mercury.

The well publicized clusters of organic mercury poisoning in the population in proximity to Minimata Bay and Nagaiita, Japan are examples of industrial contamination of the food chain.. Water born microflora in the Minimata Bay incident converted factory generated effluent inorganic mercury (used as a catalyst in the manufacture of vinyl chloride) into methyl mercury and

this was concentrated up the aquatic food chain. Fish have an effective half life for methylmercury of several hundred days, permitting significant concentration to occur. The affected public then consumed an estimated 4 mg/day greatly exceeding daily standards resulting in organic mercury poisoning.

More reports of poisonings came from Iraq, Pakistan, Ghana, and Guatemala from mercury fungicide-treated grain made into bread. Other sources of toxic reactions were alkyl mercury compounds in industrial and agricultural settings, teething preparations, and diaper powders. Fetuses, infants and young children are at increased risk of methylmercury poisoning. Methylmercury readily crosses the placental barrier and concentrates in breast milk so nursing infants can be affected. There is evidence that this agent is fetotoxic. There is no convincing evidence that this compound or other mercury groups are carcinogenic though chromosome abnormalities can be seen in elemental mercury industrial workers.

The organic alkyl and aryl compounds, mostly methyl mercury and phenyl mercury are the most dangerous mercurials. Methyl mercury is estimated to be 100 times more toxic than elemental mercury. Ninety percent of methylmercury is absorbed from the GI tract and eighty percent is absorbed through inhalation. Methyl mercury is distributed uniformly to all tissues though accumulates in red blood cells, liver and central nervous system. It is excreted in bile after conjugation and reabsorbed through the GI tract. About ninety percent is excreted in the stool and ten percent in the urine. One percent of methyl mercury is excreted per day with a half life of 52 to 70 days. Phenylmercury is not as well absorbed from the gastrointestinal tract and its primary excretion route is the urinary system. Short chain alkyl mercury compounds cross the red cell membrane and bind to hemoglobin. Blood levels equilibrate with tissue levels making the RBC mercury blood test a good indicator of exposure to organic mercury. Blood levels over 3 micrograms/ deciliter of methyl mercury is considered the threshold for beginning symptoms of toxicity. The blood should be collected as described under elemental mercury. Hair levels can be of value with epidemiological studies of organic mercury compounds. Hair levels of 400 to 500 microgram/gm may be associated with neurotoxicity but is not used more often with organic mercury due to concerns about external contamination.[39] Urine testing is of no value except for phenylmercury. Symptoms resulting from organic mercury depend on the specific chemical. Many months may pass before symptoms develop from both acute and chronic organomercury exposure.

Signs and symptoms of acute or high brief duration methylmercury poisoning usually develop gradually. The central nervous system is the main target organ. The damage in the brain is predominantly in the cerebellar granular layer, the calcarine fissures of the occipital areas and the precentral gyrus. Patients characteristically experience difficulty concentrating, short and long term memory loss, depression, emotional

volatility, ataxia and other cerebellar signs, sensory numbness with a glove and stocking distribution, scanning speech, motor spasticity, tremor, and ST-T changes on their electrocardiogram occur. This form of poisoning can lead to paralysis, coma and death. The prognosis, even with treatment, is poor. Short chain alkyl products such as methyl mercury are highly toxic, readily cross the placental barrier. Intrauterine exposure to organic mercury can lead to cerebral palsy, deafness, blindness, microcephaly, and impairment of mental and motor development.[40,41,42]

Chronic methylmercury exposure causes a tingling sensation in the extremities, tunnel vision, impaired hearing, memory loss, depression and insomnia. Such exposures can lead to permanent central nervous system damage.

The pattern of ethyl mercury poisoning, such as seen with contaminated seed ingestion, differs from the picture of methyl mercury. The kidney, GI tract, and skin are affected in a manner similar to that seen with inorganic mercury poisoning. Exfoliative dermatitis may be present. Frequent EKG changes and ectopic activity are often present. Although slurred speech and ataxia were present, mentation is not impaired.

A cluster of neurasthenia in an industrial setting has been linked to phenylmercurial fungicide. The same product is found in paint to prolong shelf life. This aryl compound is converted in vivo to inorganic mercury and its toxicity resembles that of inorganic mercury salts.[43]

Treatment of organic mercurialism is related to preventive measures such as reduction of the mercury burden in industry and reduction of mercury containing foods (especially certain fish species). BAL is contraindicated in organic mercury poisoning and will increase the amount of methylmercury in the brain and exacerbate symptoms. Short chain alkyl organic mercury compounds are harder to treat even with newer agents such as DMSA or N-acetyl penicillamine (NAP). Ordinary hemodialysis and hemoperfusion do not significantly reduce the amount of either inorganic or organic mercury but regional hemodialysis with L-Cysteine may be of some benefit. Oral polythiol resins for ingested organomercurials may be advantageous. Phenylmercuric compounds are more responsive to chelating agents.[44]

Continued on part II

Part II

ALLERGY:

It is well established that cutaneous allergy to mercury exists.

[45,46,47,48,49] Non-dermatological "Allergy" to mercury is controversial, but in clear examples of "clinical sensitivities" to mercury vapor removal from the workplace is warranted according to federal authorities.

More controversial is whether amalgam should also be removed if there is a temporal relationship between onset of neurological or rheumatologic or mental clinical problems and the introduction of new amalgam restorations.

It is known that either a hypersensitivity state or a toxicity to a heavy metal acts as a stressor on the homeostatic state of the body. Stress often contributes to the activations of an underlying genetic condition. Hypothetically, autoimmunity, as an example, may become activated from the introduction of such a heavy metal to the system due to immunologic compromise or maladaptation. It must be regarded as one of many stressors acting on a particular host. There is no firm evidence of IgE reagent mediation of such a phenomenon and the patch test results would indicate a probable type 4 Gell-Coombs or delayed hypersensitivity response.

If hypersensitivity to metals is suspected, patch allergy testing should be performed with suitable materials and procedures as recommended by the American Academy of Dermatology and standard texts of allergy and immunology and dermatology. Commercial ammoniated mercury 2% in petroleum [45] can be utilized, if available. However this product was deleted by federal reorganization of patch testing, which left only 23 approved substances on the marketplace. Such products are available abroad such as Finland. Some dentists and allergists use a variable amount of mercuric chloride liquid mixed in propylene glycol or straight on the skin and look for systemic manifestations immediately as well as cutaneous reactions. Studies performed by the author found this to be inappropriate and more of our patients "reacted" subjectively to the placebo patch and a control patch with propylene glycol than with the commercial patch previously available to the dental profession. The American Dental Association recommends that allergy studies for mercury and other potentially hazardous dental materials be performed by board qualified allergists.

To define a dose response curve in evaluating nonspecific sensitization, the author utilized 0.5% elemental mercury prepared from a thermometer which is absorbed in nonmedicated petroleum jelly. This was prepared by the pharmacist using a hood and appropriate safety standards and the petroleum was heated to ensure uniform dispersion. An appropriate control and patch test applicator (a Finn chamber) was utilized. This was read at 24 and 48 hours and 72 hours using the standard patch grading system. Some individuals reacted at 96 hours or longer and were advised that this may occur. The author has compared the metallic mercury patch with a 0.1% and 0.2% and 0.5% mercuric chloride/ petroleum mixture to obtain the cutaneous dose response curve. Of 310 patients tested, 34 patients were positive to metallic mercury having a positive patch test result at least 2 plus compared to a petroleum control, Of these patients, 32 were also positive at least 2 plus to the 0.2% mercuric chloride and 17 patients were positive to the 0.1% solution whereas 134 patients reacted to the 0.5% concentration. Fisher (50) states that mercuric chloride is prone to produce false positives and advises against using this substance. We feel that since mercury vapor may convert into the mercuric ion within cellular and neuronal tissue, the 0.1% mercuric chloride is a valid test material if

metallic mercury or ammoniated mercury is not available. Since amalgam is a complex mixture, skin testing with this substance is not specific for mercury. A correlation with a more acceptable testing vehicle such as metallic mercury is thus important. At levels over 0.2%, mercuric chloride was shown to give an unacceptable amount of false positives. We no longer use the 0.5% concentration which is a non specific sensitizer. In defining false positives, it behooves us to realize that all of the information regarding chronic internal or systemic effects of mercurialism are not yet known. Is it possible to have systemic modulation or focal internal delayed hypersensitivity to this compound with no intraoral or cutaneous clues? [51,52,53,54,55,56] Stock, an early investigator in the 1930's, noted that he got severe headaches when exposed to mercury vapor after having been "sensitized" to the product for many years as a chemist . [57] At times hypersensitive patients have reported profound fatigue, and confusion within minutes to hours after the application of a patch test. This is a subject that requires a great deal of further research.

THE AMALGAM CONTROVERSY:

Clinical symptoms occurring with amalgam placement and apparent clinical improvement with amalgam removal have been reported for many years. In the latter part of 1991, the FDA received more than 500 accounts of alleged illness from amalgam. In recent years there have been 8 published reports documenting the release of mercury from amalgam, sometimes in relatively large amounts.[58,59,60] Autopsy studies have confirmed that the intracerebral content of mercury can be correlated directly with the amount of amalgam surfaces. [61,62] Blood levels of mercury can be influenced by amalgam with significant decrease in levels several months after amalgam removal. [63,64] Analysis of all the vapor studies thus far suggest the average daily burden from mercury released from amalgam is approximately 9 micrograms/day. More recent reports have indicated that the amount of mercury excreted in nonoccupationally exposed subjects is much higher than previously calculated. Utilizing both fecal and urinary excretion, Skare and Engqvist found that the fecal excretions of mercury were twenty times the corresponding urinary excretion. Individuals with an average number of amalgams are predicted to show a fecal total mercury excretion of 60 micrograms per 24 hours.[65] To judge the significance of this, the current maximum allowable WHO standard for mercury intake from food per day is 45 micrograms/24 hours. Thus the total body burden of mercury has been shown to be significantly influenced by amalgam mercury release. [66]

Except for numerous anecdotal accounts, so far there is no firm direct relationship between amalgam placement and the initiation of medical problems, with the exception of lichen planus, pyorrhea and both local and systemic skin eruptions of various types. The significance of the release of this compound from amalgam is still being evaluated. Recent experimental studies conducted at the University of Calgary show that ewe (female sheep) provided with amalgam restorations have a significant and

persistent decrease in glomerular filtration rate compared to controls. [67] The advisory council of the Food and Drug Administration (FDA), the American Dental Association (ADA), and the appropriate branch of the National Institute of Health have all declared that there is not enough scientific evidence yet present to discontinue the use of amalgam.[68] The FDA, however, did not approve amalgam as safe and effective, and the ADA does not have strong scientific evidence validating its safety claims. Experimentally elemental, inorganic and organic mercury is immunosuppressive [69,70,71,72] and can induce an autoimmune reaction as well as a positive antinuclear antibody reaction in more than one animal species in a relatively short period of time. How this mercury release from amalgam may act as an environmental triggering agent in human autoimmune diseases is unknown and appropriate long term epidemiological and prospective clinical studies are needed. It is theoretically possible that a myriad of chronic medical problems can be aggravated by the constant inhalation of elemental mercury vapors. This might be especially true for demyelinating neurological diseases, and autoimmune diseases due to the experimental autoimmune activating findings. Recurrent candidiasis with partial anergy, often selective only to *Candida Albicans*, may be aggravated by a host of external environmental factors, one of which may be mercury. Perhaps some cases of chronic fatigue syndrome and biological depression may be modulated by external or environmental factors such as solvents, insecticides or heavy metals such as mercury.

Currently it is the author's recommendation to consider the possibility of amalgam replacement with composite, porcelain, gold or other restorative materials, if a patient presents with a combination of the following: (a) a positive patch test to a nonsensitizing concentration of metallic mercury or ammoniated mercury, plus (b) a mercury vapor release at rest (without mastication) which would indicate potential constant exposure and/or (c) a significant release of mercury vapor (as measured by a vapor analyzer) after mastication (i.e.greater than 20 micrograms/m³ is a number we have used arbitrarily). Any amount released with a clinically significant sensitivity state must be suspect however. plus (d) one of the clinical problems mentioned earlier.

This method is actually more clinically relevant than the official recommendation to consider removal if a mercury "allergy" exists as ascertained by a properly conducted patch test. How relevant is an isolated positive patch test?

It is common practice for some dentists to utilize an intraoral potentiometer to measure individual electrical activity of each restoration. Though some research value may exist for such studies regarding galvanism, there is no published study to document that such readings directly correlate with mercury release information. Dental amalgam removal should not be performed merely because they are there, or on the basis of potentiometer studies. Also blood, urine or lymphocyte subsets have not been

determined to be of value in predicting the need for removal. There are too many other medical problems that may affect an alteration in lymphocyte subpopulations.

Vapor as measured from amalgam or in an industrialized setting, is usually performed by a vapor analyzer specific for this compound. This equipment is not manufactured for amalgam vapor readings and such studies should be considered investigational at this time. Extrapolating information of an average daily body burden of mercury from the amount of vapor released and recorded by a vapor analyzer has certain pitfalls and requires understanding of numerous factors. These include respiratory rate, intraoral/ extraoral inhalation ratio, tidal volume, intraoral average vapor release before as compared to after mastication, length of time it takes the post mastication readings to return to baseline, exacting test procedures to ensure minimal mercury loss, smoking and mastication habits and other variables. [73] Even then only a crude determination can be made. All patients with amalgam are not affected with the same toxicological burden. (author's experience) Some emit no mercury vapor and other emit hundreds of micrograms after mastication. Future clinical studies must take this variation into account. Amalgam removal or replacement should also be avoided during pregnancy since the removal elevates the blood mercury levels. Amalgam removal, when appropriate, should be accompanied by a rubber dam technique.

SUMMARY

Mercury is a ubiquitous environmental substance with widespread industrial use with both occupational and non-occupational exposure. Manifestations from this element may be insidious and protean and require clinical awareness and a comprehensive occupational or environmental history. Mercury and its compounds may cause both acute and chronic health effects. Its organic compounds are fetogenic or teratogenic. Treatment methods have improved as have state and federal regulations. Cases of Acrodynia (pink disease), Kawasaki's disease, renal tubular acidosis, nephrotic syndrome and ALS and nonspecific T cell immunoregulatory dysfunction and chronic organic brain syndrome should be considered for evaluation for a mercury sensitivity or intoxication. Controversies in regard to amalgam and allergy has been reviewed. More clinical research is required in these areas.

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