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Mercury Exposure: Evaluation and Intervention The Inappropriate Use of Chelating Agents in the Diagnosis and Treatment of Putative Mercury Poisoning

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Abstract

Public awareness of the potential for mercury to cause health problems has increased dramatically in the last 15 years. It is now widely recognized that significant exposure to all forms of mercury (elemental/metallic and both inorganic and organic compounds) can result in a variety of adverse health effects, including neurological, renal, respiratory, immune, dermatologic, reproductive, and developmental sequellae. And while the various media have made the general population cognizant of the need to avoid unnecessary exposure to this naturally occurring element, there has also evolved a growing tendency to attribute unexplainable neurologic, as well as other, signs and symptoms to mercury, whether or not significant exposure to mercury has actually occurred.

For the physician, making a diagnosis of mercury intoxication can be difficult, because many of the clinical signs and symptoms of mercury exposure can also be attributed to any number of causes, including undiagnosed neurological diseases, pharmacotherapy, vitamin or mineral deficiencies, and psychological stress. The physician must be able to recognize the clinical manifestations of mercury intoxication, and understand the importance of biological markers in making a definitive diagnosis of mercury poisoning. In a desire to treat the patient complaining of symptoms similar to some that can be caused by mercury, a growing number of physicians, particularly those in alternative medicine fields, result to chelation to "rid" the body of the mercury, believed to be the cause of the ailments. And although the use of chelation is increasing, controlled studies showing that this procedure actually improves outcome are lacking. If chelation therapy is considered to be indicated, the attending physician should communicate the risks of chelation to the patient before beginning treatment with metal-chelating drugs.

Keywords: Metallic mercury; Mercury poisoning; Chelation

INTRODUCTION

Mercury is a naturally occurring constituent of the Earth's crust. In its elemental (metallic) form, mercury is the only metal that exists in a liquid state at room temperature. Mercury readily volatilizes at standard temperature (O °C) and pressure (1 atm), and its presence in open containers can result in biologically significant air concentrations in unventilated or poorly ventilated spaces. Elemental mercury vapors are virtually odorless and very toxic. In recent years, elemental mercury has proven to be a potential source of toxicosis in children through either unintentional exposure or

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exposure resulting from inappropriate handling of liquid mercury obtained from school science laboratories, abandoned industrial facilities, or warehouses (Amler, 2002; Nickle, 1999; Orloff et al., 1997; Risher et al., 2003). The shiny, silvery appearance of mercury in its liquid form makes it particularly enticing to children, and its insolubility in water and tendency to form beads when disturbed add to its mystique.

Exposure to metallic mercury can occur through either the inhalation, oral, or dermal routes, with the particular route most dependent upon the specific type of mercury. In the case of metallic (liquid, elemental) mercury, only the inhalation route has proven to be biologically relevant in most instances. When taken orally, less than 0.01% is typically absorbed through the gastrointestinal (GI) tract (ATSDR, 1992). In understanding the relative lack of toxicity of metallic mercury by the oral route, it should be kept in mind that the GI tract is merely a long tube, open at both ends (mouth and anus); thus, the mere swallowing of mercury does not necessarily mean that it will be absorbed from the GI tract into the bloodstream and be distributed throughout the body. Skin contact normally results in even less absorption in most instances. In sharp contrast, however, up to 80% of inhaled mercury vapor can be expected to be absorbed through the lungs into the blood (Hursh et al., 1976; Teisinger and Fiserova-Bergerova, 1965).

Another common exposure to mercury is to organic, alkyl mercurials. The typical sources of such exposures are through ingestion of contaminated seafood (methylmercury) and through multidose vials of vaccine, in which ethylmercury is used as a preservative (in Thimerosal). Unlike inorganic forms of mercury, organic mercurials are readily absorbed through the digestive tract (∼95%). For organomercurials, blood is a good indicator of exposure, and urine is a poor indicator, due to differences in the pharmacokinetics of these compounds. Hair is also a suitable indicator of a history of organic mercury exposure, since incorporation into the hair follicle of both methylmercury and ethylmercury is a known route of elimination of these organomercurials from the body (Cernichiari et al., 1995; Zareba et al., 2003).

Table 1
Some effects of high-level exposure to metallic mercury vapor

Body system	Effect	Reference
Nervous	Restlessness, memory loss, headaches, irritability, fatigue, confusion, insomnia, mood lability, erythism, irrational behavior; weakness; tremors; polyneuropathy (*above for metallic Hg*); distal paresthesias, delayed attainment of neurodevelopmental milestones; altered performance on neurobehavioral/ neuropsychological tests; frank neurodevelopmental effects; delay in auditory evoked potentials (*for MeHg*)	Adams et al. (1983), Bluhm et al. (1992), Fagala and Wigg (1992), Hallee (1969), Jaffee et al. (1983), Karpathios et al. (1991), McFarland and Reigel (1978), Risher et al. (2003), Bakir et al. (1973), Grandjean et al. (1997a,b, 1998), Murata et al. (1999, 2004), Myers et al. (2003), and Davidson et al. (2004)
Cardiovascular	Tachycardia, elevated blood pressure, arythmias, elevated plasma catecholamines, decreased autonomic modulation of heart rate, some symptoms similar to pheochromacytoma	Bluhm et al. (1992), Haddad and Stenberg (1963), Taueg et al. (1992), Torres et al. (2000), Velzeboer et al. (1997), and Grandjean et al. (2004)
Respiratory	Cough, dyspnea, tightness of chest, pulmonary edema	Bluhm et al. (1992), Haddad and Stenberg (1963), Hallee (1969), Kanluen and Gottlieb (1981), and Rowens et al. (1991)
Excretory (renal)	Tubular dysfunction, dysuria	Bluhm et al. (1992), Hallee (1969), Kanluen and Gottlieb (1991), Campbell (1948), and Rowens et al. (1991)
Integumentary	Erythema, rash, pruritus, desquamation	Aronow et al. (1990), Bluhm et al. (1992), Fagala and Wigg (1992), Karpathios et al. (1991), Risher et al. (2003), and Velzeboer et al. (1997)
Digestive	Stomatitis, metallic taste in mouth, abdominal pain, nausea, vomiting, diarrhea, colitis	Bluhm et al. (1992), Campbell (1948), Haddad and Stenberg (1963), Kanluen and Gottlieb (1991), and Taueg et al. (1992)
Hepatic	Biochemical changes, hepatomegaly, central lobular vacuolisation	Jaffe et al. (1983), Kanluen and Gottlieb (1991), and Rowens et al. (1991)
Muscular	Fasciculations, tremors, myalgia, myoclonus	Aronow et al. (1990), Bluhm et al. (1992), McFarland and Reigel (1978), and Taueg et al. (1992)

MERCURY TOXICITY

Metallic mercury can cause a variety of neurologic and somatic symptoms. The effects of mercury on the body vary with the magnitude and duration of exposure, and with the age and overall health status of the exposed individual. Exposure to significant levels of metallic mercury can result in neurologic, respiratory, renal, reproductive, immunologic, dermatologic, and a variety of other effects (Table 1). However, neurologic effects are the most prominent feature of excessive exposure to mercury vapors, as well as organic mercury compounds, in most cases. (For a detailed discussion of mercury species-specific effects, the reader is referred ATSDR, 1999, 1992.)

DIAGNOSIS

Mercury intoxication produces a spectrum of neurologic, as well as other, symptoms and clinical indicators of toxicity (ATSDR, 1999, 1992; Clarkson et al., 2003), many of which can also be associated with a large number of other causes. Analysis of urine and/or blood, depending upon the type of mercury to which exposure is suspected, are useful in separating mercury-induced symptoms from those caused by disease, pharmaceuticals, psychogenic, and other causes.

Once in the blood, the half-life of metallic mercury is relatively short (~3 days for a single exposure), as it quickly partitions to other body compartments. The overall half-life of metallic mercury in the body averages approximately 2 months (Rahola et al., 1973; Hursh et al., 1976), with a range of ~30–90 days, depending on the duration and magnitude of exposure (Barregard et al., 1992; Hursh et al., 1976; Takahata et al., 1970). Virtually, all of the absorbed metallic mercury is excreted in the urine, with exhaled breath being a significant avenue of excretion only in extremely high exposures. In cases of acute metallic mercury poisoning, blood analysis is considered useful *only* when samples are taken within a few days of exposures. A 24-h urine specimen is preferred in all cases to provide a more appropriate index of exposure. Urine creatinine measurements should be carried out simultaneously to control for the effects of hydration (Fischbach, 1992).

In the case of methylmercury and ethylmercury, the biologic half-life is also about two months, but the biologic indicators are different than inorganic mercury exposure. In these cases, whole blood in the primary indicator of exposure, and only that portion of mercury that is oxidized to the cationic form is eliminated in the urine. Hair is a reliable indicator of prior or ongoing exposures to methylmercury and ethylmercury, since a small portion of it is incorporated into the hair follicle. Recent data from the National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention (CDC) reported that 95% of sampled U.S. women between the ages of 16 and 49 have blood mercury levels of 7.1 μg/L or less and urine mercury concentrations of 5 μg/L or less (CDC, 2003). A mercury urine mercury concentration of 20 μg/L (again, prior to chelation) is widely considered to be without accompanying adverse health effects (ATSDR, 1999; Goldwater, 1972; Nordberg et al., 1992). Physicians not familiar with mercury are advised to consult ATSDR's *Case Studies in Environmental Medicine: Mercury Toxicity* (ATSDR, 1992) for further guidance in diagnosing mercury poisoning.

TREATMENT

The first consideration in treatment should be removing the patient from the source of exposure. Since mercury of all types is gradually eliminated from the body over time by normal physiological processes, this alone may be sufficient to ameliorate or reverse the symptoms. In those cases in which mercury exposure can be verified, and/or in which biological indicators (urine and/or blood), clinical signs, and symptomatology are corroborative, more aggressive treatment may be indicated. In some cases, symptom-based supportive treatment may be appropriate, whereas high urine or blood levels and more profound symptoms such as respiratory distress or acrodynia might warrant consideration of chelation.

Chelation

The term chelate is derived from the Greek word *chelos*, meaning claw; and the term describes the physical process well. Chelation consists of the introduction of a charged molecule (typically containing one or more sulfhydryl groups) into the body for the purpose of binding specific metal ions of opposite electrical charge, and facilitating the elimination of the formed complex from the body in the urine.

Chelation therapy has historically been used in attempts to reduce the body burden of mercury and other toxic metals in highly symptomatic patients with elevated biological markers (Baum, 1999; Bluhm et al.,

Table 2
Chelating agents used for mercury toxicity: 2,3-dimercaptopropanol

Chelator (trade name)	Possible adverse responses[a]	Essential minerals chelated[b]	Route of excretion
British anti-lewisite (BAL); Dimercaprol	Urticaria; elevated B.P. (transient) and H.R.; nausea, vomiting; abdominal pain; headache; convulsions; burning sensation in lip, mouth, and throat; salivation; lacrimation; conjunctivitis; blepharospasm; rhinorrhea; paresthesias; diaphoresis; anxiety; hemolytic anemia in patients with G-6-P deficiency	Not reported	urine (~50%); bile and feces (~50%); some enterohepatic circulation

[a] Baum (1999), Hardman et al. (2001), and Janakiraman et al. (1978).
[b] All chelating agents that bind the divalent cations zinc and copper also have the ability to bind other divalent cations of comparable atomic weight, such as chromium, iron, manganese, and to a lesser extent, calcium; however, none of the modern chelating agents bind calcium in biologically significant amounts in most cases.

1992; Guldager et al., 1996; Florentine and Sanfilippo, 1991; Fournier et al., 1988; Madhok et al., 1997; McFee and Caraccio, 2001). Another more recent use of chelation is as a provocative mercury ''challenge'' (Frumpkin et al., 2001). In this procedure, the patient is administered a single dose (oral or parenteral, depending on the particular agent used) of the chelating chemical and sent home to collect urine for a 24-h period. Often, no pre-chelation urine sample is collected and analyzed for mercury, making a comparison of the person's actual (pre-chelation) urine mercury level with population background levels impossible.

Each year, ATSDR receives dozens of calls from individuals who have been chelated (challenged) with DMPS or DMSA prior to collection of any urine samples, and subsequently been diagnosed as having mercury poisoning. The sole basis of these diagnoses was laboratory reports that indicated that the individual had been determined to have toxic levels of mercury, based solely upon comparison of post-chelation mercury values with historical (typically pre-chelation) values. Without exception these individuals have been advised to undergo additional chelation.

Some physicians have also looked to mercury as a possible cause of undiagnosed health problems and subsequent chelation therapy as a treatment for those problems. As a result, the use of chelation has expanded in recent years to include the treatment of mildly symptomatic or asymptomatic patients with no documented history of mercury exposure (McKay et al., 2003), and it is becoming increasingly, and unfortunately, common for practitioners to make a diagnosis of mercury intoxication and begin treatment without carrying out an adequate clinical workup (McKay et al., 2003).

A number of chelating agents are currently either in practical use or under investigation for treating mercury poisoning (Tables 2–5). The available chelators differ in their efficacy for various forms of mercury, route of administration, side effects, and route of excretion. Depending on the specific type of mercury and the health status of the patient, different chelators

Table 3
Chelating agents used for mercury toxicity: calcium disodium ethylenediaminetetraacetic acid

Chelator (trade name)	Possible adverse responses[a]	Essential minerals chelated[b]	Route of excretion
EDTA; (Versene) calcium disodium versenate; edetate calcium disodium	i.m. injection site pain; fever; chills; malaise; fatigue; myalgia; arthralgia; tremors; tingling; headache; numbness; hypotension; cardiac rhythm irregularities; acute proximal tubular necrosis; glycosuria; proteinuria; hematuria; cheilosis; nausea; vomiting; anorexia; anemia; excessive thirst; mild increases in SGOT and SGPT (common); sneezing; nasal congestion; lacrimation; rash; zinc deficiency; hypercalcemia; lesions similar to Vitamin B_6 deficiency	Cu, Fe, Zn, Mg, Ca (to a lesser extent)	Primarily urine

[a] Boscolo et al. (1983), Hardman et al. (2001), Guldager et al. (1996), Kosnett (1992), Moel and Kumar (1982), PDR (2001), and Santiago et al. (1983).
[b] All chelating agents that bind the divalent cations zinc and copper also have the ability to bind other divalent cations of comparable atomic weight, such as chromium, iron, manganese, and to a lesser extent, calcium; however, none of the modern chelating agents bind calcium in biologically significant amounts in most cases.

Table 4
Chelating agents used for mercury toxicity: D-penicillamine; *N*-acetyl-D,L-penicillamine (NAP)

Chelator (trade name)	Possible adverse responses[a]	Essential minerals chelated[b]	Route of excretion
D-Penicill-amine; NAP (Cupramine; Depen)	High incidence of untoward reactions; pruritus; rashes; pemphigus; fever; arthralgia; lymphadenopathy; lupus erythematosus-like syndrome; urticaria; exfoliative dermatitis; anorexia; epigastric pain; nausea; vomiting; diarrhea; bone marrow depression; leukopenia; thrombocytopenia; agranulocytosis; aplastic anemia; sideroblastic anemia; proteinuria; hematuria; nephrotic syndrome; tinnitus; optic neuritis; peripheral sensory and motor neuropathies; wrinkling of skin	Cu, Zn, Fe (especially in children and menstruating women); (also associated with pyridoxine (Vitamin B_6) deficiency)	Primarily urine

[a] Florentine and Sanfilippo (1991), and PDR (2001).
[b] All chelating agents that bind the divalent cations zinc and copper also have the ability to bind other divalent cations of comparable atomic weight, such as chromium, iron, manganese, and to a lesser extent, calcium; however, none of the modern chelating agents bind calcium in biologically significant amounts in most cases.

may be considered. However, at present, no guidelines are available for physicians that specify the conditions under which chelation is medically indicated or contra-indicated, thereby contributing to a growing confusion over the appropriate use of chelating agents.

Considerations and Questionable Uses

Despite the growing use of chelating agents in the United States for putative mercury intoxication, many of these agents are being used ''off-label.'' While all but one of the agents listed in Tables 2–5 are approved by the U.S. Food and Drug Administration (FDA) for chelating metals, only DMSA is FDA-approved for pediatric use in treating mercury poisoning. DMPS is currently included on an FDA list of bulk chemicals that may be used in pharmacy compounding (http://www.fda.gov/cder/fdama), but it is not approved by FDA for any clinical use. Thus, the use of DMPS for the chelation of any metal is strictly off-label.

The recent increase in the use of chelation, without first establishing the need for such therapy, raises concern. The authors of this paper have personally encountered numerous instances in both clinical and consultational settings in which chelation has been recommended by the attending physician or even requested directly by the patient. In one instance, the mother of a 6-year-old boy presented in a pediatric medical clinic and requested that her autistic child be chelated to remove the mercury, which she believed to

Table 5
Chelating agents used for mercury toxicity: *meso* 2,3-dimercaptosuccinic acid (DMSA) and sodium 2,3-dimercapto-1-propanesulfonate (DMPS)

Chelator (trade name)	Possible adverse responses[a]	Essential minerals chelated[b]	Route of excretion
DMSA (succimer; Chemet; Captomer)	Nausea; vomiting; diarrhea; appetite loss; metallic taste in mouth; back and other body pain; abdominal cramps; headache; chills; fever; moniliasis; elevated SGPT, SGOT, and serum cholesterol; drowsiness; dizziness; sensorimotor neuropathy; sleepiness; paresthesia; rash; pruritus; lacrimation; otitis; sore throat; rhinorrhea; nasal congestion; cough; dysuria; voiding difficulty; proteinuria; cardiac arrhythmia	Cu, Zn	Primarily urine
DMPS (Dimaval)	Skin rashes; nausea; weakness; vertigo (complete symptomatology not reported)	Cu, Cr, Zn	Primarily urine

[a] Fournier et al. (1988), Grandjean et al. (1997), Mann and Travers (1991), Marcus et al. (1991), PDR (2001), Sallsten et al. (1994), and Sandborgh Englund et al. (1994).
[b] All chelating agents that bind the divalent cations zinc and copper also have the ability to bind other divalent cations of comparable atomic weight, such as chromium, iron, manganese, and to a lesser extent, calcium; however, none of the modern chelating agents bind calcium in biologically significant amounts in most cases.

be the exclusive cause of her son's disorder. The purported source of the mercury was thimerosal in childhood vaccines. (Parker et al. (2004) reviewed all published epidemiologic and laboratory/clinical studies of thimerosal and autistic spectrum disorders (ASDs) and found no relationship between thimerosal or ethylmercury and ASDs.) In another instance in which we were involved as consultants, an emergency department physician (without our knowledge) preemptorily chelated an adolescent male solely on the basis of a headache and his association with friends who had played with metallic mercury.

The Agency for Toxic Substances and Disease Registry (ATSDR) frequently receive inquiries from persons who have been recommended, most typically by alternative medicine practitioners, to undergo a prolonged course of chelation therapy for supposed mercury intoxication. The causes of the purported intoxication include ingestion of methylmercury-contaminated fish, immunizations from thimerosal-containing vaccines, and dental amalgam fillings (containing ~50% metallic mercury). In some cases, previous medical opinions by specialists in more conventional fields were disregarded or ignored, while in other instances, a diagnosis of mercury toxicity was based exclusively upon post-challenge (chelation) mercury concentrations with no history of mercury exposure, other than possibly from dental amalgam fillings (McKay et al., 2003). (The U.S. Department of Health and Human Services reviewed the data regarding dental amalgams and confirmed the safety and efficacy of amalgam restorations (DHHS, 1997).)

The interpretation of mercury levels reported in laboratory analyses can create an additional problem. Many laboratories contrast the results of their mercury analyses with historical ranges for that particular lab, and some even suggest that the upper end of their historical range can be considered to be a surrogate for a toxicity threshold. Such practices can lead to an inappropriate diagnosis of suspected mercury intoxication. When evaluating laboratory reports, the physician must keep in mind that the range of mercury concentrations reported by individual laboratories varies from lab to lab, based on the samples that they have analyzed over the course of time. Since an actual toxicity threshold level for either urine or blood mercury has not been determined, population norms and background ranges should be used for comparison with reported patient mercury levels. The NHANES background level of 5.0 μg Hg/L for 95% of the general U.S. population would serve as a credible comparison measure of background urine mercury concentration for an asymptomatic, healthy population. The corresponding 95% blood level is 7.1 μg/L, and the 90% hair value is 1.2 μg/g (or ppm). Thus, pre-chelation values at or below these levels should be considered normal, or without health risk.

EFFECT OF CHELATION ON OUTCOME

The efficacy of the chelating agents shown in Tables 2–5 to complex mercury and temporarily facilitate the elimination of that metal in the urine is well established (Baum, 1999; Dargan et al., 2003; Florentine and Sanfilippo, 1991; Fournier et al., 1988; Frumpkin et al., 2001; Jaffe et al., 1983; McFee and Caraccio, 2001; Sallsten et al., 1994; Sandborgh Englund et al., 1994). However, while the use of chelation is increasing for known or suspected heavy metal exposure, there is a paucity of controlled studies showing that this procedure actually improves the long-term outcome of the patient (Chisolm, 2001; Kosnett, 1992; Liu et al., 2002; McFee and Caraccio, 2001). In fact, a number of studies found no clear clinical benefit from DMSA treatment of humans documented to have been poisoned, or suspected to have been poisoned, by elemental mercury vapor (Bluhm et al., 1992; Grandjean et al., 1997a,b; Sandborgh Englund et al., 1994). The use of chelating agents is even more questionable in cases where symptoms and/or clinical signs of severe mercury intoxication are absent and where urine and/or blood levels are within the normal background range. In addition to being unnecessary and financially burdensome, inappropriate use of chelators may present untoward danger to the patient and may also bind other divalent mineral cations essential for normal physiologic function (Tables 2–5) (Kosnett, 1992; Baum, 1999; Hardman et al., 2001; Guldager et al., 1996; Florentine and Sanfilippo, 1991; Fournier et al., 1988; Sallsten et al., 1994.)

Another consideration for the attending physician is that chelating agents are not without risk to the developing fetus. The chelating agent penicillamine has been shown to be teratogenic in rats when given in doses just six times higher than the highest dose recommended for human use (PDR, 2001). Skeletal defects, cleft palates, and fetal toxicity (evidenced by resorptions) have been reported in these animals. In humans, characteristic congenital *cutis laxa*, a disorder manifested by a lack of elasticity in connective tissue and the resultant sagging of the integument, has been reported, along with associated birth defects, in infants

born of mothers who received therapy with penicillamine during pregnancy. ''Penicillamine should be used in women of childbearing potential only when the expected benefits outweigh the possible hazards'' (PDR, 2001). Likewise, succimer (DMSA) has been shown to be teratogenic and fetotoxic in pregnant mice when given subcutaneously in a dose of 410–1640 mg/kg/day during the period of organogenesis, and ''should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus'' (PDR, 2001). In the case of female patients of childbearing age, attending physicians must recognize these risks and communicate them to the patient when chelation is deemed necessary for the patient's well being. The patient should also be made aware of off-label (other than FDA-approved) use of chelating agents.

It seems to us that until additional clinical data which more definitively elucidate the efficacy and potential adverse effects of chelating agents, particularly in young children, become available, the cautionary approach recommended for lead exposure by the American Academy of Pediatrics Committee on Drugs would apply equally well in the case of mercury exposures. Namely, ''Given the lack of data regarding an improvement in outcome associated with any chelation therapy and the lack of sufficient data on safety to exclude rare yet potentially severe side effects, therapy for lower-level exposures should include only environmental and nutritional intervention.'' (Anonymous, 1995).

CONCLUSIONS

A complete diagnosis of mercury intoxication should include analysis of blood and urine mercury concentrations. The primary action should always be the termination of exposure. When, in the absence of the biological indicators of mercury exposure, an exposure history and clinical signs and/or symptoms strongly suggest a mercury-origin for the manifestations, the physician should proceed with caution in determining whether to administer a chelating agent to the patient. Any potential benefits of chelation should be carefully weighed before use in asymptomatic, mildly symptomatic, or pregnant patients. The importance of obtaining baseline urine mercury and creatinine measurements before administrating a chelating agent, whenever possible, cannot be overstressed. This is important not only to have a comparison value to determine the effectiveness of chelation, but also to identify whether chelation is even appropriate for the patient. Thus, the use of chelation (a) for diagnostic purposes, (b) for asymptomatic patients with urine or blood mercury levels approximating normal/background population values, or (c) following the removal of dental amalgam fillings is considered to be unnecessary and to place the patient at some additional risk.

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