REVIEW ARTICLE

CURRENT CONCEPTS

The Toxicology of Mercury — Current Exposures and Clinical Manifestations

Thomas W. Clarkson, Ph.D., Laszlo Magos, M.D., and Gary J. Myers, M.D.

From the Departments of Environmental Medicine (T.W.C.) and Neurology and Pediatrics (G.J.M.), University of Rochester School of Medicine, Rochester, N.Y.; and the Medical Research Council Laboratories, Carshalton, United Kingdom (L.M.). Address reprint requests to Dr. Clarkson at the Department of Environmental Medicine, Box EHSC, University of Rochester School of Medicine, Rochester, NY 14642, or at twc30@aol.com.

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Mercury has been used commercially and medically for centuries. In the past it was a common constituent of many medications. It is still used in hospitals in thermometers and blood-pressure cuffs and commercially in batteries, switches, and fluorescent light bulbs. Large quantities of metallic mercury are employed as electrodes in the electrolytic production of chlorine and sodium hydroxide from saline. These uses still give rise to accidental and occupational exposures.[1]

Today, however, exposure of the general population comes from three major sources: fish consumption, dental amalgams, and vaccines. Each has its own characteristic form of mercury and distinctive toxicologic profile and clinical symptoms. Dental amalgams emit mercury vapor that is inhaled and absorbed into the bloodstream. Dentists and anyone with an amalgam filling are exposed to this form of mercury. Liquid metallic mercury (quicksilver) still finds its way into homes, causing a risk of poisoning from the vapor and creating major cleanup costs. Humans are also exposed to two distinct but related organic forms, methyl mercury (CH_3Hg^+) and ethyl mercury ($CH_3CH_2Hg^+$). Fish are the main if not the only source of methyl mercury, since it is no longer used as a fungicide. In many countries, babies are exposed to ethyl mercury through vaccination, since this form is the active ingredient of the preservative thimerosal used in vaccines. Whereas removal of certain forms of mercury, such as that in blood-pressure cuffs, will not cause increased health risks, removal of each of the three major sources described in this article entails health risks and thus poses a dilemma to the health professional.

Exposure to mercury from dental amalgams and fish consumption has been a concern for decades, but the possible risk associated with thimerosal is a much newer concern. These fears have been heightened by a recent recommendation by the Environmental Protection Agency (EPA) that the allowable or safe daily intake of methyl mercury be reduced from 0.5 μg of mercury per kilogram of body weight per day, the threshold established by the World Health Organization in 1978,[2] to 0.1 μg of mercury per kilogram per day.[3]

Table 1 summarizes the clinical toxicologic features of mercury vapor and methyl and ethyl mercury. It also includes data on inorganic divalent mercury, since this is believed to be the toxic species produced in tissues after inhalation of the vapor.[5] It is also responsible for kidney damage after exposure to ethyl mercury, since ethyl mercury is rapidly converted to the inorganic form.[13] Inorganic mercury as both mercuric and mercurous salts was also the chief cause of acrodynia, a childhood disease that is now mainly of historical interest.[14] The clinical symptoms of acrodynia consist of painful, red, swollen fingers and toes in association with photophobia, irritability, asthenia, and hypertension. It is believed to be a hypersensitivity reaction.

Table 1. The Major Clinical Toxicologic Features of Mercury.*

Variable	Mercury Vapor	Inorganic Divalent Mercury	Methyl Mercury	Ethyl Mercury
Route of exposure	Inhalation	Oral	Oral (from fish consumption)	Parenteral (through vaccines)
Target organ	Central nervous system, peripheral nervous system, kidney	Kidney	Central nervous system	Central nervous system, kidney
Local clinical signs				
Lungs	Bronchial irritation, pneumonitis (>1000 μg/m³ of air)			
Gastrointestinal tract	Metallic taste, stomatitis, gingivitis, increased salivation (>1000 μg/m³ of air)	Metallic taste, stomatitis, gastroenteritis		
Skin		Urticaria, vesication		
Systemic clinical signs				
Kidney	Proteinuria (>500 μg/m³ of air)	Proteinuria, tubular necrosis		Tubular necrosis
Peripheral nervous system	Peripheral neuropathy (>500 μg/m³ of air)	Acrodynia		Acrodynia
Central nervous system	Erethism (>500 μg/m³ of air), tremor		Paresthesia, ataxia, visual and hearing loss (>200 μg/liter of blood)	Paresthesia, ataxia, visual and hearing loss
Approximate half-life (whole body) (days)	60	40	70	20†
Treatment‡	Meso-2,3-dimercaptosuccinic acid	Meso-2,3-dimercaptosuccinic acid	Chelators not effective§	Chelators not effective§

* Data were adapted from Gossel and Bricker.[4] Clinical manifestations vary with the degree and length of exposure. The values in parentheses are the approximate range of mercury concentration in air (expressed as micrograms per cubic meter) and in blood (expressed as micrograms per liter) associated with the onset of clinical signs and symptoms. Epidemiologic studies that did not use specific end points such as IQ score indicate a risk of adverse effects (approximately 5 percent) at lower concentrations (e.g., 25 to 50 μg of mercury vapor per cubic meter and 40 μg of methyl mercury per liter of blood are associated with an increased risk of prenatal damage to the developing central nervous system).[3,5] In general, the atmospheric concentration of mercury vapor equals the urinary concentration. The mean urinary concentration in the U.S. general population is 0.72 μg per liter (95 percent confidence interval, 0.6 to 0.8), and the mean blood concentration is 0.34 μg per liter (95 percent confidence interval, 0.3 to 0.4).[6] In Europe[7] and other parts of the world,[8] blood concentrations appear to be somewhat higher. The mean urinary concentrations increase according to the number of dental amalgam surfaces, and blood concentrations increase according to the level of fish consumption.[6] No reliable data are available on the concentration of inorganic divalent mercury associated with adverse effects.

† The half-life in blood is about 20 days in adults but may be as short as 7 days in infants.

‡ Details of meso-2,3-dimercaptosuccinic acid treatment have been published.[9-11]

§ Chelators can remove methyl and ethyl mercury from the body; they cannot reverse the damage to the central nervous system. They may, however, prevent further deterioration.[12]

MERCURY VAPOR FROM DENTAL AMALGAMS

Dental amalgams have been in use for over 150 years. They are inexpensive and thought to be more durable and easier to use than other types of fillings. The amalgam consists of approximately 50 percent mercury combined with other metals such as silver and copper. Since their introduction, dental amalgams have been a source of controversy because of the assumed health risks of mercury. The arguments between the protagonists and antagonists have been referred to as the "amalgam wars" and became more heated around 1970 with the discovery that amalgams can release mercury vapor into the oral cavity in concentrations that are higher than those deemed safe by occupational health guidelines.

Subsequently, it was realized that the actual inhaled dose was small, owing to the small volume of the oral cavity. Nevertheless, amalgam fillings are the chief source of exposure to mercury vapor in the general population.[8] Brain, blood, and urinary concentrations correlate with the number of amalgam surfaces present. It has been estimated that 10 amalgam surfaces would raise urinary concentrations by 1 μg of mercury per liter, roughly doubling the back-

ground concentrations.[15] Higher urinary concentrations are found in persons who chew a great deal. For example, the long-term use of nicotine chewing gum will raise urinary concentrations close to occupational health limits.[16] The removal of amalgam fillings can also cause temporary elevations in blood concentrations,[17] since the process transiently increases the amount of mercury vapor inhaled.

What is the health risk from such exposures? Cases of poisoning from inhalation of mercury vapor have been recognized for centuries.[18] Severe cases are characterized by a triad of intentional tremor, gingivitis, and erethism (Table 1). Erethism consists of bizarre behavior such as excessive shyness and even aggression. The Mad Hatter in *Alice in Wonderland* was probably a victim of occupational mercury intoxication.

Today's occupational exposures, such as in the dental office, are lower and may lead to mild, reversible effects on the kidney or mild cognitive changes and memory loss.[5] However, urinary concentrations in people with amalgams (about 2 to 4 μg of mercury per liter) are well below concentrations found in people who are occupationally exposed to mercury (20 to 50 μg of mercury per liter) unless they are also excessive chewers. Current concern arises from claims that long-term exposure to low concentrations of mercury vapor from amalgams either causes or exacerbates degenerative diseases such as amyotrophic lateral sclerosis, Alzheimer's disease, multiple sclerosis, and Parkinson's disease. Speculation has been most intense with respect to Alzheimer's disease after a report that the brains of patients with Alzheimer's disease had elevated mercury concentrations. However, several epidemiologic investigations failed to provide evidence of a role of amalgam in these degenerative diseases, including a long-term study of 1462 women in Sweden,[19] an ongoing Swedish twin study involving 587 subjects,[20] and a study of 129 nuns 75 to 102 years of age, which included eight tests of cognitive function.[21] Nevertheless, in vitro studies have indicated that mercury can affect the biochemical processes believed to be involved in Alzheimer's disease.[22] The problem is that mercury can inhibit various biochemical processes in vitro without having the same effect in vivo.

Patients who have questions about the potential relation between mercury and degenerative diseases can be assured that the available evidence shows no connection. Some will ask whether their mercury fillings should be removed. They should be reminded that the process of removal generates mercury vapor and that blood concentrations will subsequently rise substantially before they eventually decline.[17] There is no clear evidence supporting the removal of amalgams.

MERCURY VAPOR FROM QUICKSILVER IN THE HOME

Recent attempts by power companies to replace pressure-control devices for the domestic gas supply have led to spills of liquid mercury, affecting some 200,000 homes in one incident.[23] Spills of liquid mercury in the home carry a risk of vapor inhalation. Quicksilver is an attractive play object for children and is found in many homes, especially in developing countries. High levels of exposure to mercury vapor can result from the cultural and religious use of elemental mercury, including sprinkling mercury on the floor of a home or car, burning it in a candle, and mixing it with perfume.[24]

Infants and young children, whose breathing zones are closest to the floor, are at highest risk, since mercury vapor is heavy and tends to form layers close to the floor. Ingested liquid mercury passes through the gastrointestinal tract essentially unabsorbed. Centuries ago a tablespoonful of quicksilver was used to treat constipation.[25] It arguably represents one of the first uses of gravity in medicine.

METHYL MERCURY

Among humans, the sole source of exposure to methyl mercury is the consumption of fish and sea mammals. Methyl mercury is produced environmentally by biomethylation of the inorganic mercury present in aquatic sediments (Fig. 1). It accumulates in the aquatic food chain and reaches its highest concentrations in long-lived, predatory fish such as swordfish and shark in the oceans and pike and bass in fresh water. Concentrations of mercury in ambient air and water are too low to pose a serious risk to the general population.

EXPOSURE IN ADULTS

Cases of severe, even fatal, methyl mercury poisoning date back to the 1860s in England, when such mercurials were first synthesized.[28] Subsequent cases arose through occupational and dietary exposures. Several large outbreaks were caused by the consumption of bread mistakenly made from methyl mercury–coated seed grain; for example, an out-

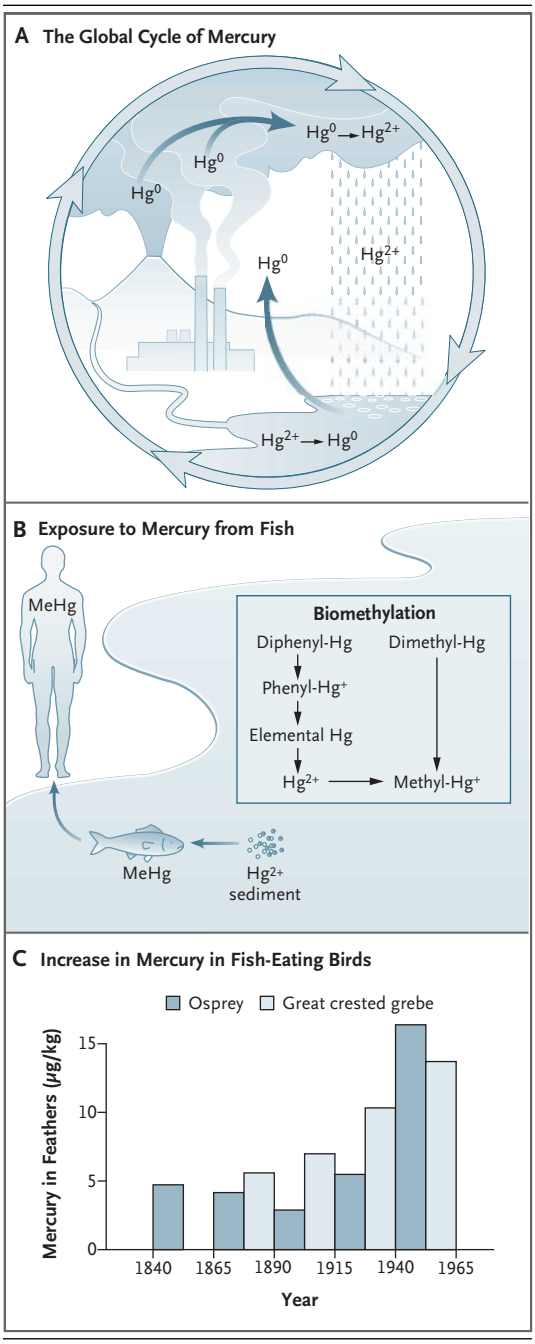

Figure 1. The Global Cycle of Mercury.

In nature, mercury vapor (Hg^0), a stable monatomic gas, evaporates from the earth's surface (both soil and water) and is emitted by volcanoes (Panel A). Anthropogenic sources include emissions from coal-burning power stations and municipal incinerators. After approximately one year, mercury vapor is converted to a soluble form (Hg^{2+}) and returned to the earth in rainwater. It may be converted back to the vapor form both in soil and in water by microorganisms and reemitted into the atmosphere. Thus, mercury may recirculate for long periods.

Mercury attached to aquatic sediments is subject to microbial conversion to methyl mercury (MeHg), whereupon it enters the aquatic food chain. It reaches its highest concentrations in long-lived predatory fish, such as sharks. Panel B indicates the routes of transformation to methyl mercury as originally suggested by Jernelöv.[26]

Panel C depicts the increase in mercury concentrations in feathers of fish-eating birds in Sweden.[27] The period covered by these data corresponds approximately to the growth of industrialization in Sweden.

break in 1971 and 1972 in Iraq caused hundreds of deaths and thousands of cases of severe intoxication.[29] The industrial release of methyl mercury into Minamata Bay and the Agano River in Japan resulted in the accumulation of the toxicant in fish and, subsequently, in two large epidemics related to fish consumption.[30] Overt cases of poisoning are now rare. In the United States, the only reported cases in the past 35 years involved a family that consumed the meat of a pig fed treated grain[31] and a university professor who was accidentally exposed in the laboratory.[11]

The brain is the primary target tissue. Adults present with paresthesias of the circumoral area and hands and feet, followed by visual-field constriction and ataxia. Neuropathological examination reveals regional destruction of neurons in the visual cortex and cerebellar granule cells. There is usually a latent period of weeks or months between exposure and the onset of symptoms.

Several studies have reported statistical associations between cardiovascular disease and mercury, mostly in the form of methyl mercury. One study found a direct relation between mercury concentrations and the risk of myocardial infarction,[32] whereas a nested case–control study of more than 300,000 health professionals found no such association.[33] A third study, from eastern Finland, where the consumption of saturated animal fat is high, found an association, but the authors suggested that their finding might be specific to the region.[34,35] A fourth study among seven-year-old children on the Faeroe Islands found that blood pressure was increased when the blood mercury concentration was below 10 μg per liter but not when it was higher.[36] "Contrary to expectation," as the authors stated, "this association occurred within an exposure range characteristic of communities not depending on marine food" such as the United States.[37] They also pointed

out that "the average birth weight in this fishing community is the highest in the world and therefore the community may represent a unique setting."

Thus, firm conclusions about cause and effect cannot be yet made, since cardiovascular disease has multiple risk factors (e.g., family history, stress, dietary habits, smoking, alcohol use, diabetes, and socioeconomic status). The researchers themselves recognize this complication and use extensive statistical measures to correct for these factors. Prospective studies are needed to settle this issue.[38]

PRENATAL EXPOSURE

The fetal brain is more susceptible than the adult brain to mercury-induced damage. Methyl mercury inhibits the division and migration of neuronal cells and disrupts the cytoarchitecture of the developing brain. In the past 15 years or so, epidemiologic studies have focused on the effects of prenatal exposure.[39-41] As a consequence of these epidemiologic data, the EPA reduced the allowable intake of methyl mercury from 0.5 to 0.1 μg of mercury per kilogram per day.[42] This threshold is lower than those used by other regulatory agencies. Moreover, it translates into a weekly consumption of one 198-g (7-oz) can of tuna for an adult. Given that canned tuna is the cheapest and most widely consumed fish in the United States and is approved by the American Heart Association as part of a diet low in saturated fat and cholesterol, the debate over the safety of tuna and fish in general will continue with some intensity.

It is reassuring that the only clinical reports of mercury poisoning from fish consumption are those from Japan in the 1950s and 1960s.[8] The EPA guideline is derived from reports of subtle and small neuropsychological changes in children in the Faeroe Islands study, whose exposure was mainly from whale consumption.[36] A similar study in the Seychelles found no adverse effects from fish consumption alone.[41] The majority of the general population in the United States has levels of exposure well below the EPA guideline, but 8 percent or so have levels that are slightly higher. Although a National Academy of Sciences committee reported that 60,000 children in the United States were at risk as a result of prenatal exposure,[43] they failed to provide any justification or explanation for that conclusion.

Fish consumption has clear health benefits, and the risk posed by exposure to mercury is currently speculative. The Food and Drug Administration has recommended that pregnant women, nursing mothers, and young children avoid eating fish with a high mercury content (>1 ppm), such as shark, swordfish, tilefish, and king mackerel. Because whale meat contains up to 3 ppm of mercury, about half of which is in the form of methyl mercury,[44] consumption of whale meat should also be discouraged.

THIMEROSAL IN VACCINES

Thimerosal has been used as a preservative in many vaccines since the 1930s.[45,46] At concentrations found in vaccines, thimerosal meets the requirements for a preservative set forth by the U.S. Pharmacopeia[47] — that is, it kills the specified challenge organisms and can prevent the growth of the challenge fungi. It contains the ethyl mercury radical ($CH_3CH_2Hg^+$) attached to the sulfur group of thiosalicylate and is believed to behave toxicologically like other ethyl mercury compounds. Early toxicity studies found no adverse health effects; recently, however, Ball et al. reevaluated thimerosal by applying the revised EPA guideline for methyl mercury to ethyl mercury.[48] They calculated that infants undergoing the usual U.S. program of vaccines from birth to six months of age would receive more than 0.1 μg of mercury per kilogram per day.[8] Steps were rapidly taken to remove thimerosal from vaccines by switching to single-dose vials that did not require any preservative. This process is now virtually complete in the United States. The decision itself is remarkable, and the speed of execution even more so[49]; however, the EPA guideline is based on epidemiologic data on prenatal exposure to methyl mercury rather than postnatal exposure to ethyl mercury. Ethyl mercury has some similarities to methyl mercury. They are closely related chemically, have a similar initial distribution in the body, and cause similar types of damage to the brain in toxic doses.

They also have differences. Methyl mercury is more potent. Ethyl mercury is metabolized more rapidly to inorganic mercury; perhaps this is why ethyl mercury, unlike methyl mercury, causes kidney damage in humans. Of greater importance is the recent finding that the half-life of ethyl mercury in the body is much shorter.[50] The half-life of methyl mercury in blood, which is assumed to indicate the total body burden, is usually assumed to be about 50 days.[51] In contrast, in children receiving thimerosal in vaccines, the half-life of ethyl mercury in blood was 7 to 10 days, or 1/7 to 1/5 as long as that of methyl mercury.[50] Therefore, in the two-month periods between vaccinations (at birth and at two,

four, and six months), all of the mercury should have been excreted, so that there is no accumulation.

Given the short half-life of ethyl mercury, any risks of its damaging either the brain or kidneys would seem remote. A World Health Organization advisory committee recently concluded that it is safe to continue using thimerosal in vaccines.[52] This is especially important in developing countries, where the use of a preservative is essential in multidose vials. The known risk of infectious diseases far exceeds that of the hypothetical risk of thimerosal. Claims have been made that thimerosal in vaccines may be a cause of autism and related disorders, but studies testing that theory have yet to be performed.

All forms of mercury have adverse effects on health at high doses. However, the evidence that exposure to very low doses of mercury from fish consumption, the receipt of dental amalgams, or thimerosal in vaccines has adverse effects is open to wide interpretation. Moreover, attempts to reduce such exposure may pose greater health risks than those hypothesized to occur from mercury.

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