Chapter 95: Mercury

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INTRODUCTION

Mercury (Hg)		
Atomic number	=	80
Atomic weight	=	200.59 Da
Normal concentrations		
Whole blood	<	10 mcg/L (50 nmol/L)
Urine	<	20 mcg/L (100 nmol/L)

HISTORY AND EPIDEMIOLOGY

Mercury is a metal that is widely toxic to multiple organ systems. Its toxicologic manifestations are well known as a result of thousands of years of medicinal applications, industrial use, and environmental disasters.[69,112] Mercury occurs naturally in small amounts as the elemental (Hg^0) silver-colored liquid (quicksilver); as inorganic compounds such as mercuric (Hg^{2+}) sulfide (cinnabar), mercurous (Hg^+) chloride (calomel), mercuric chloride (corrosive sublimate), and mercuric oxide; and as organic compounds (methylmercury and dimethylmercury). Mercury's gastroenteric irritant effects led to its use as a therapy for constipation. In recent (16th–19th), centuries, mercury-containing preparations, advocated for their potent diuretic and sialogogic properties, were widely used to treat syphilis to "flush" the "virus" out.[81] The musician Paganini was one of several famous persons whose gingivitis, dental decay, ptyalism (excessive salivation), and erethism (pathologic irritability and emotional instability) were attributed to mercury therapy.[80] In the 1800s, the United States witnessed an epidemic of "hatters' shakes" or "Danbury shakes" and "mercurial salivation" in hat industry workers.[123] Danbury, Connecticut, was a US center of felt hat manufacturing in which mercuric nitrate was used to mat animal furs into felt.[112,123]

In the early 1900s, acrodynia, a painful dusky pink discoloration of the hands and feet, or "pink disease," was described in children who received calomel for ascariasis or teething discomfort.[16] Vividly described in a series of 41 children, the development of acrodynia was more common in younger children, did not seem to correlate with mercury dose, and was not necessarily related to urine concentrations of mercury.[122]

One of the most devastating epidemics of mercury poisoning occurred as the result of a decade of contamination of Minamata Bay in Japan by a nearby vinyl chloride plant during the 1940s. Methylmercury accumulated in the bay's marine life and poisoned the inhabitants of the local fishing community. Although officially only 121 victims were reported, thousands more are believed to have been affected by what has subsequently been named Minamata disease.[88,113] The largest outbreak of methylmercury poisoning to date occurred in Iraq in late 1971. Approximately 95,000 tons of seed grain intended for planting and treated with methylmercury as a fungicide were baked into bread for direct consumption, resulting in widespread neurologic symptoms, 6,530 hospital admissions, and more than 400 deaths.[5,23,96]

In 1990, the US Environmental Protection Agency (EPA) banned mercury-containing compounds from interior paints.[3] However, mercury-containing paints manufactured before that ruling may still be on interior walls, and mercury-containing paint can still be sold for outdoor use. In 1997, a scientist succumbed to delayed, progressive neurologic deterioration after a minute dermal exposure to dimethylmercury.[77] Contemporary exposures occur in the form of mercury-tainted seafood, mercury-based preservatives (thimerosal), and artisanal gold mining.[36]

However, a once widely feared source of potential poisoning, mercury-containing dental amalgam does not result in clinical poisoning.[14] Occasionally, exposure to mercury from broken thermometers leads to poisoning in the home, but such thermometers are becoming less common because of recent efforts to replace mercury with digital thermometers and other electronic devices.[78]

More recently, the ongoing movement to replace incandescent light bulbs with compact fluorescent bulbs has once again raised the concern of exposure to mercury in the home and environment. Promoted to reduce greenhouse gas emissions, each bulb contains about 4 mg of elemental mercury.[2]

Table 95–1 lists some potential sources of mercury exposure.

TABLE 95–1

Exposures to Mercury

	Elemental	Inorganic	Organic
Manufacturing/Industrial	Barometers Bronzing Ceramics Chlorine manufacture Electroplating Jewelry Metal refineries Paints Paper pulp Photography	Batteries Chemistry sets Dyes Explosives Fireworks Laboratory reagents Tanneries Taxidermy Vinyl chloride manufacture	Agriculture Embalming Fungicides Laboratory reagents Pesticides Wood preservatives
Medical/Medicinal	Amalgam Sphygmomanometry Tissue fixatives Thermometers Weighted nasogastric tubes	Antiseptics Calomel Disinfectants Laxatives Nonprescription medications	Bactericidals Pharmaceuticals Preservatives
Food/Other	Ritualistic, complementary	Aesthetic, cosmetic Ayurvedic	Grains (contaminated) Seafood

FORMS OF MERCURY AND TOXICOKINETICS

The 3 clinically important forms of mercury—elemental, inorganic, and organic—differ with respect to their toxicodynamics and toxicokinetics (Table 95–2). Each produces distinct clinical patterns of poisoning stemming in part from their unique kinetic features (Table 95–3). For each form, the specific manifestations are determined by the route of exposure, rate of exposure, distribution, biotransformation of mercury within the body, and relative accumulation or elimination of mercury by the target organ systems. Whereas elemental mercury produces pulmonary toxicity, inorganic mercury initially causes gastrointestinal (GI) symptoms followed by nephrotoxicity. A nearly pure neurologic toxicity results from organic (methylmercury) exposure.

TABLE 95–2

Classes of Mercury Compounds

	Nomenclature	Example
Elemental	Hg^0	Quicksilver
Inorganic	Hg^+ HgCl Hg^{2+} $HgCl_2$	Mercurous ion Calomel, mercurous chloride Mercuric ion Mercuric chloride
Organic	Short-chain alkyl–mercury compounds Long-chain mercury compounds Aryl mercury compounds	Methylmercury Ethylmercury Dimethylmercury Methoxyethylmercury Phenylmercury

TABLE 95–3

Differential Characteristics of Mercury Exposure

	Elemental	Inorganic	Organic
Primary route of exposure	Inhalation	Oral	Oral
Primary tissue distribution	CNS, kidney	Blood (transient, acute) Kidney CNS (delayed)	CNS, kidney, liver, blood, hair
Clearance	Kidney, GI	Kidney, GI	Methyl: GI Aryl: kidney, GI
Clinical effects			
CNS	Tremor	Tremor, erethism	Paresthesias, ataxia, tremor, tunnel vision, dysarthria
Pulmonary	+++	–	–
Gastrointestinal	+	+++ (caustic)	+
Renal	+	+++ (ATN)	+
Acrodynia	+	++	–
Therapy	BAL, succimer	BAL, succimer	Succimer (early)

ATN = acute tubular necrosis; BAL = British anti-Lewisite; CNS = central nervous system; GI = gastrointestinal; + to +++ = present with increasing importance; - = absent.

ABSORPTION

Elemental Mercury

Elemental mercury (Hg^0) is absorbed primarily via inhalation of vapor, although slow absorption after aspiration, subcutaneous deposition, and direct intravenous (IV) embolization occurs.[60,74,121] Volatility, moderate at room temperature, increases significantly with heating or aerosolization, both of which occur with vacuuming.[44,102] When inhaled by human volunteers, 75% to 80% of mercury vapor is absorbed.[44] However, elemental mercury is negligibly absorbed from an anatomically and functionally normal GI tract, and it is usually considered nontoxic when ingested. Abnormal GI motility prolongs mucosal exposure to elemental mercury, and massive ingestion increases subsequent ionization to more readily absorbed forms. Similarly, anatomic GI abnormalities such as fistulae or perforation are associated with extravasation of mercury into the peritoneal in which where elemental mercury is oxidized to more readily absorbed inorganic forms.

Inorganic Mercury

The principal route of absorption for inorganic mercury is the GI tract. Approximately 10% of soluble divalent (Hg^{2+}) mercuric salts such as mercuric chloride ($HgCl_2$) are absorbed following ingestion and dissociation.[66] Absorption of a relatively insoluble monovalent (Hg^+) mercurous compound, such as mercurous chloride (calomel; HgCl), is dependent on its oxidation to the divalent form.[79] Inorganic mercury is also absorbed across the skin

and mucous membranes, as evidenced by urinary excretion of mercury after dermal application of skin-lightening mercurial ointments and powders containing HgCl.[106,122]

The degree of dermal absorption varies by the concentration of mercury, skin integrity, and lipid solubility of the vehicle. With substantial dermal exposures to mercury salts, skin absorption may be difficult to distinguish from concomitant absorption via other routes, such as ingestion.

Organic Mercury

As in the case of inorganic mercury, organic mercury is primarily absorbed from the GI tract. Methylmercury, considered the prototype of the short-chain alkyl compounds, is approximately 90% absorbed from the gut. Aryl and long-chain alkyl compounds have more than 50% GI absorption.[79] Although both dermal and inhalational absorption of organic mercury is reported, precise quantitation and exclusion of concomitant absorption by ingestion are difficult to determine.

DISTRIBUTION AND BIOTRANSFORMATION

After absorption, mercury distributes widely to all tissues, predominantly the kidneys, liver, spleen, and central nervous system (CNS). The initial distributive pattern into nervous tissue of elemental and organic mercury differs from that of the inorganic compounds because of their greater lipid solubility.

Elemental Mercury

Although peak concentrations of elemental mercury are delayed in the CNS as compared with other organs (2–3 days versus 1 day),[44] significant accumulation in the CNS occurs after an acute, intense exposure to elemental mercury vapor. Conversion of elemental mercury to the charged mercuric (Hg^{2+}) cation within the CNS favors retention and local accumulation. Because elemental mercury does not covalently bind to other compounds, its toxicity depends on its oxidation initially to the mercurous ion (Hg^{+}) and then to the mercuric ion (Hg^{2+}) by the enzyme catalase.[66] Because this oxidation–reduction reaction favors the mercuric cation at steady state, the distribution and late manifestations of metallic mercury toxicity eventually resemble those of inorganic mercury poisoning. Conversely, and to a lesser extent, inorganic mercuric ions are reduced to the elemental state (Hg^{0}), although the site and mechanism of this reaction are not well understood.[79]

Inorganic Mercury

The greatest concentration of mercuric ions is found in the kidneys, particularly within the renal tubules. At least in animal studies, administration of mercury induces the renal synthesis of metallothionein, a compound that binds to and detoxifies mercuric ions.[12] Very little mercury is found as free mercuric ions. In blood, mercuric ions are found both within the red blood cells (RBCs) and bound to plasma proteins in approximately equal proportions. Blood concentrations are greatest immediately after inorganic mercury exposure, with rapid waning as distribution to other tissues occurs. Although penetration of the blood–brain barrier is poor because of low lipid solubility, slow elimination and prolonged exposure contribute to significant CNS accumulation of mercuric ions. Within the CNS, mercuric ions concentrate in the cerebellum and hippocampus, and to a lesser degree, the cerebral cortex.[35] Although inorganic mercurials undergo organification in marine life, as in the Minamata Bay disaster,[9,85] the importance of this conversion in humans is unknown. Animal studies demonstrate that the placenta functions as an effective barrier to mercuric ions.[79]

Organic Mercury

Once absorbed, aryl (phenyl mercury) and long-chain alkyl mercury compounds differ from the short-chain organic mercury compounds (methylmercury) in an important way—the former possess a labile carbon–mercury bond, which is subsequently cleaved, releasing the inorganic mercuric ion. Thus, the distribution pattern and toxicologic manifestations produced by the aryl and long-chain alkyl compounds that occur beyond the immediate postabsorptive phase are comparable to those of inorganic mercury, but organification has facilitated absorption and reduced the local caustic effects.[79] In contrast, short-chain alkyl mercury compounds possess relatively stable carbon–mercury bonds that survive the absorptive phase, although conversion to the inorganic mercuric cation at a rate of less than 1% per day occurs after absorption.[124] Because it is lipophilic, methylmercury readily distributes across all tissues, including the blood–brain barrier and placenta.[46] An important consequence of this property is

the devastating neurologic degeneration that develops in prenatally exposed infants with Minamata disease. The rapid decline of blood mercury concentrations in both suckling rats and breastfeeding human infants is attributed to rapid growth of body volume combined with limited transport of mercury by milk.[76,97,98]

After methylmercury is distributed to brain tissue, its fate is uncertain. Animal evidence indicates that methylmercury is converted to inorganic mercury in brain tissue.[63] Primates fed oral methylmercury daily for periods exceeding 1 year and then killed within days of the last exposure demonstrated an average brain inorganic mercury fraction of only 19%. By contrast, when the postexposure period was extended to between 150 and 650 days, the inorganic mercury fraction increased to 88%. Similarly, long-term survivors of methylmercury poisoning had a higher ratio of inorganic mercury to total mercury in their brains.[29] In one patient who survived 22 years after methylmercury ingestion, autopsy revealed that the brain mercury was nearly completely in the inorganic form.

Methylmercury concentrates in RBCs to a much greater degree than do mercuric ions, with an RBC-to-plasma ratio of about 10:1 (in contrast to 1:1 RBC-to-plasma ratio for inorganic mercury).[124] However, despite this apparent affinity for nervous tissue and RBCs, the greatest methylmercury concentrations are found in the kidneys and liver. In addition, because of the extensive sulfhydryl bonds in hair, methylmercury deposits in hair at concentrations approximately 250 times that found in whole blood.[55]

ELIMINATION

Elemental Mercury and Inorganic Mercury

Mercuric ions are excreted through the kidney by both glomerular filtration and tubular secretion and in the GI tract by transfer across gut mesenteric vessels into feces. Small amounts are reduced to elemental mercury vapor and volatilized from skin and lungs. The total-body half-life of elemental mercury and inorganic mercury was previously estimated at approximately 30 to 60 days.[22,66] However, a recent review of case studies indicates that the half-life of inorganic mercury in human brains is on the order of several years to several decades.[92]

Organic Mercury

In contrast to elemental mercury and inorganic mercury, the elimination of short-chain alkyl mercury compounds (such as methylmercury) is predominantly fecal. Enterohepatic recirculation contributes to its somewhat longer total body half-life of about 70 days. Less than 10% of methylmercury is excreted in urine and feces as the mercuric cation.[124]

PATHOPHYSIOLOGY

The pervasive disruption of normal cell physiology by mercury arises from its avid covalent binding to sulfur, replacing the hydrogen ion in the body's ubiquitous sulfhydryl groups. Mercury also reacts with phosphoryl, carboxyl, and amide groups, resulting in widespread dysfunction of enzymes, transport mechanisms, membranes, and structural proteins.

Because mercury deposits in all tissues, the clinical manifestations of mercury toxicity involve multiple organ systems with variable features and intensity. Necrosis of the GI mucosa and proximal renal tubules, which occurs shortly after mercury salt poisoning, is thought to result from the direct oxidative effect of mercuric ions. An immune mechanism is attributed to membranous glomerulonephritis and acrodynia associated with the use of mercurial ointments.[13]

Neurologic manifestations of methylmercury poisoning correlate with pathologic findings in the brains of both adults and children who were prenatally exposed.[68,113] Grossly, atrophy of the brain is more severe in children who had prenatally or postnatally acquired methylmercury compared with the brains of those exposed as adults. In the adult brain, neuronal necrosis and glial proliferation are most prominent in the calcarine cortex of the cerebrum and in the cerebellar cortex. In fetal Minamata disease, similar lesions are present but in a more diffuse and severe form. Atrophy of the cerebellar hemispheres, postcentral gyri, and calcarine area of the brain demonstrated on magnetic resonance images in organic mercury–poisoned patients correlates with clinical findings of ataxia, sensory neuropathy, and visual field constriction, respectively.[58] Neuropathologic examination of the brain of a scientist who died after unintentional dermal exposure to dimethylmercury revealed lesions in the cerebellum, temporal lobe, and visual

cortex.[105]

In rats, neuronal cytotoxicity of methylmercury may result partly from muscarinic receptor–mediated calcium release from smooth endoplasmic reticulum of cerebellar granule cells.[62] There is animal evidence that methylmercury may trigger reactive oxygen species production. In addition, methylmercury inhibits astrocyte uptake of cysteine, the rate-limiting step in the production of glutathione, a major antioxidant in mammalian cell systems.[104] Cultured astrocytes accumulated methylmercury and exhibited increased mitochondrial permeability and oxidative injury.[125] Complexing of methyl- mercury with L-cysteine may enhance brain uptake by mimicry of methionine, a substrate of the endogenous L amino acid transport system. Uptake of the L-isomer significantly exceeds that of methylmercury–D-cysteine. Careful selection of stereospecific thiol complexing agents may lead to strategies to limit brain uptake of methylmercury.[56,70]

CLINICAL MANIFESTATIONS

Elemental Mercury

Symptoms of acute elemental mercury inhalation occur within hours of exposure and consist of cough, chills, fever, and shortness of breath. Gastrointestinal complaints include nausea, vomiting, and diarrhea accompanied by a metallic taste, dysphagia, salivation, weakness, headaches, and visual disturbances. Chest radiography during the acute phase reveals interstitial pneumonitis and both patchy atelectasis and emphysema. Symptoms either resolve with lesser exposures or progress to acute respiratory distress syndrome (ARDS) with respiratory failure and death. Some survivors of severe pulmonary toxicity develop interstitial fibrosis and residual restrictive pulmonary disease. The acute respiratory symptoms occur concomitantly with or precede the development of subacute inorganic mercury poisoning manifested by tremor, kidney dysfunction, and gingivostomatitis.[17,54,94] Thrombocytopenia is also reported to occur during the acute phase.[38]

Although acute exposure to elemental mercury vapor occurs most commonly in the occupational setting, poisonings caused by mishandling of the metal in the home are well reported.[19,29,50,72,108] In fact, attempts at home metallurgy using metallic mercury have resulted in fatalities with ambient air concentrations of mercury as high as 0.9 mg/m^3. The current US Occupational Safety and Health Administration permissible exposure limit (PEL) for mercury vapor is 0.1 mg/m^3 of air as a ceiling limit.[82]

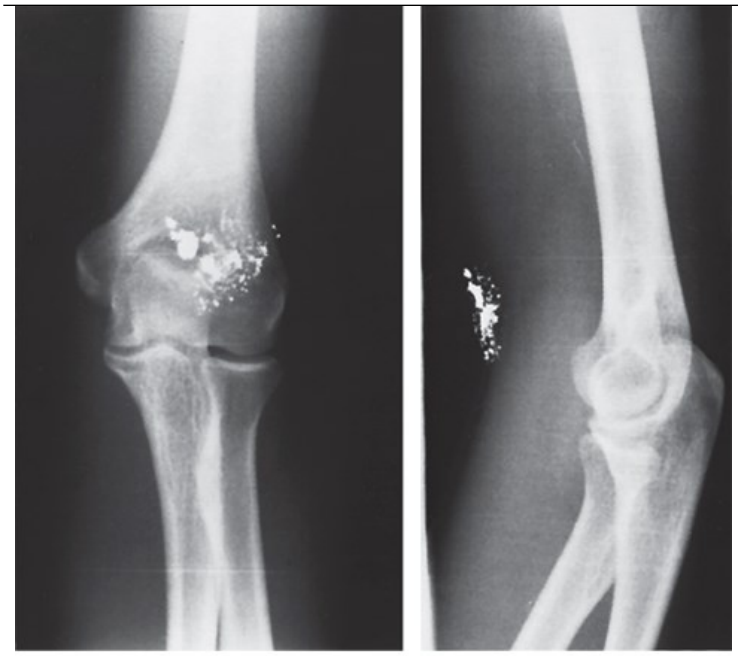
As with other inhaled toxins, children are likely to be more sensitive to the pulmonary toxicity of mercury vapor because of their ratio of minute ventilation volume to body size.[72] Although pulmonary toxicity from elemental mercury usually results from inhalation of vapor, massive endobronchial hemorrhage followed by death has occurred secondary to direct *aspiration of metallic mercury* into the tracheobronchial tree.[127] Gradual volatilization of elemental mercury results in chronic toxicity from improper handling, such as vacuuming spilled mercury.[102]

The clinical importance of volatilized metallic mercury from dental amalgams for both the dentist and patient is controversial. The preponderance of evidence refutes the idea that dental amalgam causes mercury poisoning. Several comprehensive reviews of the subject conclude that (1) occupational exposure to mercury from dental amalgam is acceptably low, provided that recommended preventive measures such as adequate ventilation are adhered to; (2) the quantity of mercury vaporized from dental amalgam by mechanical forces, such as chewing, is clinically insignificant; and (3) only in exceedingly rare cases will immunologic hypersensitivity to mercury amalgam (manifested as cutaneous signs and symptoms and confirmed by patch testing) necessitate removal of the amalgam.[33,34,37,61,107]

Unusual cases of chronic toxicity have resulted from intentional subcutaneous or IV injection of elemental mercury (Figs. 8–6 and 95–1).[49,74] Aside from management of systemic mercury toxicity, local wound care and excision of deposits of mercury are additional therapeutic challenges presented by these cases. Serial or repeat radiographs are useful in guiding the removal of the radiopaque deposits.

FIGURE 95–1.

Anteroposterior (A) and lateral (B) views of the elbow after an unsuccessful suicidal gesture involving an attempted intravenous injection of elemental mercury in the antecubital fossa. Note the extensive subcutaneous mercury deposition, which was partially removed by surgical intervention. (*Used with permission from Diane Sauter, MD.*)



A B

Source: L.S. Nelson, M.A. Howland, N.A. Lewin, S.W. Smith, L.R. Goldfrank, R.S. Hoffman: Goldfrank's Toxicologic Emergencies, Eleventh Edition

Inorganic Mercury

Acute ingestion of mercuric salts produces a characteristic spectrum from severe irritant to caustic gastroenteritis. Immediately after the ingestion, a grayish discoloration of mucous membranes and metallic taste typically accompany local oropharyngeal pain, nausea, vomiting, and diarrhea followed by abdominal pain, hematemesis, and hematochezia. The lethal dose of mercuric chloride is estimated to be 30 to 50 mg/kg.[116] The life-threatening manifestations of severe acute mercuric salt ingestion are hemorrhagic gastroenteritis, massive fluid loss resulting in shock, and acute kidney failure.[100]

Oropharyngeal injury, nausea, hematemesis, hematochezia, and abdominal pain were the most prominent symptoms in a series of 54 patients who presented after ingesting up to 4 g of mercuric chloride.[116] In this series, fatality was associated with the early development of oliguria (within 3 days) likely due in large part to lack of routinely available hemodialysis at that time. The development of anuria appeared to be related to the dose of mercuric chloride ingested. The histopathologic finding of proximal tubular necrosis after mercuric salt poisoning results both from direct toxicity to renal tubules and from renal hypoperfusion caused by shock. Consequently, aggressive fluid therapy to maintain perfusion is recommended.[101]

Acute ingestion of mercuric salts is usually intentional, but unintentional ingestion occurs sporadically in both children and adults.[51] Although ingestion of older button batteries containing mercuric oxide was associated with a greater incidence of fragmentation than with other batteries, clinically significant systemic mercury toxicity by this route was not reported.[64,67] Mercuric chloride–containing stool preservatives are another potential source of unintentional inorganic mercury poisoning. Ingestion of 10 to 20 mL of a polyvinyl alcohol preservative that contained 4.5% mercuric chloride resulted in bloody gastroenteritis and proteinuria.[103] Nonprescription[49] and Ayurvedic[99] medicines are also associated with unintentional inorganic mercury poisoning (Chap. 43).[53] These xenobiotics are not subject to US Food and Drug Administration (FDA) regulation, available without prescription, of variable composition, and are often inadequately labeled (Chap. 43).

Subacute or chronic mercury poisoning occurs after inhalation, aspiration, or injection of elemental mercury; ingestion or application of mercury salts; or ingestion of aryl or long-chain alkyl mercury compounds. Slow in vivo oxidation of elemental mercury and dissociation of the carbon–mercury bond of aryl or long-chain alkyl mercury compounds result in the production of the inorganic mercurous and mercuric ions.

The predominant manifestations of subacute or chronic mercury toxicity include GI symptoms, neurologic abnormalities, and renal dysfunction. Gastrointestinal symptoms consist of a metallic taste and burning sensation in the mouth, loose teeth and gingivostomatitis, excessive salivation

(ptyalism), and nausea.[122] The neurologic manifestations of chronic inorganic mercurialism include tremor, as well as the syndromes of neurasthenia and erethism. Neurasthenia is a symptom complex that includes fatigue, depression, headaches, hypersensitivity to stimuli, psychosomatic complaints, weakness, and loss of concentrating ability. Erethism, derived from the Greek word *red*, describes the easy blushing and extreme shyness of affected individuals. Other symptoms of erethism include anxiety, emotional lability, irritability, insomnia, anorexia, weight loss, and delirium. Mercury produces a characteristic central intention tremor (Chap. 22) that is abolished during sleep. In the most severe forms of mercury-associated tremor, choreoathetosis and spasmodic ballismus are also reported. Other neurologic manifestations of inorganic mercurialism include a mixed sensorimotor neuropathy, ataxia, concentric constriction of visual fields ("tunnel vision"), and anosmia.

Chronic poisoning with mercuric ions is associated with renal dysfunction, which ranges from asymptomatic, reversible proteinuria to nephrotic syndrome with edema and hypoproteinemia. An idiosyncratic hypersensitivity to mercury ions is thought to be responsible for acrodynia, or "pink disease," which is an erythematous, edematous, and hyperkeratotic induration of the palms, soles, and face, and a pink papular rash that was first described in a subset of children exposed to mercurous chloride powders.[122] The rash is described as morbilliform, urticarial, vesicular, and hemorrhagic. This symptom complex also includes excessive sweating, tachycardia, irritability, anorexia, photophobia, insomnia, tremors, paresthesias, decreased deep tendon reflexes, and weakness. The acral rash frequently progresses to desquamation and ulceration. The prognosis is favorable after withdrawal from mercury exposure. Childhood acrodynia has become uncommon since the abandonment of mercurial teething powders and diaper rinses. Occasional case reports still implicate improperly disposed fluorescent light bulbs and phenylmercuric acetate–containing paint.[3,117]

Thimerosal is an example of an aryl mercury compound that results in chronic inorganic mercury toxicity. It is a compound that was widely used as a preservative in the pharmaceutical industry (Chap. 46). Although initial kinetics suggested a stable ethyl–mercury bond, the later elimination phase more closely resembles that of the inorganic mercury compounds. Thimerosal is approximately 50% mercury by weight. Although generally considered safe, toxicity and death can occur after both intentional overdose and excessive therapeutic application of merthiolate (0.1% thimerosal or 600 mcg/mL mercury).[87,95]

Concern that the cumulative dose of thimerosal in childhood immunizations exceeded federally recommended maximum mercury doses (EPA, 0.1 mcg/kg/day; Agency for Toxic Substances and Disease Registry, 0.3 mcg/kg/day; FDA, 0.4 mcg/kg/day) led to a call by the American Academy of Pediatrics to reduce or eliminate thimerosal from vaccines.[4] Thimerosal continues to be used in medically underserved nations as a preservative in multidose vials in areas with inadequate refrigeration.[31] Nevertheless, since 2001, routinely administered childhood vaccines in the United States no longer contain thimerosal.[4,47]

Although sensitization after use in vaccinations has been reported in atopic children,[86] clinical mercury toxicity has not been reported in appropriately immunized children. The claim that thimerosal-containing vaccines causes autism has been refuted by numerous studies and meta-analyses.[8,65,84,109] No causal association with early thimerosal exposure and adverse neuropsychological outcomes was shown in children tested at 7 to 10 years of age.[115] Clearly, the risk to child health from the diseases targeted for prevention by vaccines far exceeds the risk from thimerosal preservative in vaccines.[39,114,119] In 2010, US courts rejected a causal relationship between thimerosal and autism.[32]

Organic Mercury Compounds

In contrast to the inorganic mercurials, methylmercury produces an almost purely neurologic disease that is usually permanent except in the mildest of cases. Although the predominant syndrome associated with methylmercury is that of a delayed neurotoxicity, acute GI symptoms, tremor, respiratory distress, and dermatitis are also reported.[124] In addition, ST segment changes on electrocardiography and renal tubular dysfunction are associated with this poisoning.[45] However, no increase in cardiovascular disease risk was reported with mercury exposure in a large cohort of US adults.[73]

The lipophilic property and slower elimination of methylmercury likely contribute to its profound neurologic effects. Characteristically, clinical manifestations occur after the initial poisoning by a latent period of weeks to months. Consequently, the lethal dose of methylmercury is difficult to determine. As noted previously, infants exposed prenatally to methylmercury were the most severely affected individuals in Minamata. Often born to mothers with little or no manifestation of methylmercury toxicity themselves, exposed infants exhibited decreased birth weight and muscle tone, profound developmental delay, seizure disorders, deafness, blindness, and severe spasticity.

Several weeks after methylmercury contaminated grain was ingested in Iraq, patients began to appear with paresthesias involving the lips, nose, and distal extremities. Symptomatic patients also noted headaches, fatigue, and tremor. More serious cases progressed to ataxia, dysarthria, visual field constriction, and blindness. Other neurologic deficits included hyperreflexia, hearing disturbances, movement disorders, salivation, and dementia. The most severely affected patients lay in a mute, rigid posture punctuated only by spontaneous crying, primitive reflexive movements, or feeding efforts.[96]

Although the outlook for methylmercury neurotoxicity is generally considered dismal, observations over the subsequent 2 years in 49 Iraqi children poisoned during the 1971 outbreak revealed complete resolution or partial improvement in all but the most severely affected.[5] Of the 40 symptomatic children, 33 mildly to severely affected children showed partial to complete resolution of symptoms, but the 7 children classified as “very severely poisoned” remained dysarthric, ataxic, blind, and bedridden.

An important route of organic mercury exposure is through seafood consumption. The safe amount of methylmercury in seafood remains controversial. The FDA action concentration of 1 ppm for methylmercury in fish was set to limit consumption of methylmercury to less than 1/10th of amounts found in cases of symptomatic poisoning. The EPA established a reference dose for methylmercury of 0.1 mcg/kg/day.[90,118] Although elevated blood concentrations (19–53 mcg/L) of mercury were found in one group of self-reported high consumers of seafood, increased incidence of cognitive and GI complaints were not.[52] Even so, concentrations at which fetuses experience adverse effects are unknown. Longitudinal studies of fish-eating populations are conflicting. No effect of a high prenatal fish diet was found on developmental markers in children followed to 19 years of age in the Seychelles Islands.[27,28,120]

However, in the studies done in the Faroe Islands and New Zealand, a subtle but significant effect on neuropsychological development was reported.[25,42,110] In the Faroe Islands, this effect persisted when children were retested at 22 years of age.[30,31]

One reason for the discrepancy that occurs between the 2 populations may be the different patterns of seafood consumption and concentrations of methylmercury in the seafood consumed by each. The Faroese consume low level mercury–containing fish 1 to 3 times a week with episodic feasts of highly contaminated pilot whale, whereas the Seychellois consume a more steady diet of low level–contaminated fish on average 12 times per week. The pilot whales consumed in the Faroe Islands are also contaminated with neurotoxic polychlorinated biphenyls (PCBs), although these compounds were measured and considered a potential confounding variable. The mean concentration of methylmercury in the whale meat consumed in the Faroe Islands was 1.6 mcg/g, and the mean concentration of mercury found in New Zealand shark was 2.2 mcg/g. By contrast, the mean methylmercury content of Seychellois fish was 0.3 mcg/g.[75] The threshold concentration for neuropsychological effects may lie between these concentrations.

The development of neurologic symptoms in infants exclusively breastfed by women exposed to methylmercury after delivery and the detection of mercury in the milk of lactating women implies a risk for mercury poisoning via breast milk.[57] In one series of lactating women, mercury concentrations in milk were approximately 30% of the concentrations found in blood.[83] Perhaps because of high levels of PCBs in pilot whale meat, 7-year-old children from the Faroe Islands, who have a diet traditionally high in the mercury-containing sea mammals and were breast-fed as infants, exhibited a diminished benefit (but not deficit) on neuropsychological testing when compared with their counterparts fed formula.[48]

Further complicating findings in a cohort of Faroese children, the neurobehavioral deficits from methylmercury may be underestimated unless the protective effects of long-chain n-3 polyunsaturated fatty acids (n-3 PUFA, also found in fish) are included in the analysis.[21] Likewise, the Seychelles Child Development Study Nutrition Cohort 2 found no overall adverse association between prenatal methylmercury exposure and neurodevelopmental outcomes in children with high maternal n-3 PUFA concentrations.[111] The net neuropsychological effects of prenatal and dietary methylmercury result from dose and timing of fish in the diet as well as the concentrations of methylmercury, neurotoxic PCBs, and neuroprotective PUFA in the consumed fish.[111]

The FDA recommends that at-risk populations (pregnant women and women who may become pregnant, nursing mothers, and young children) avoid large predator fish (shark, swordfish, tilefish, and king mackerel) that contain concentrations of methylmercury approaching 1 ppm (1 mcg/g). The 2004 FDA/EPA consumer advisory emphasizes the health benefits of eating fish and allow for up to 12 ounces per week of fish and shellfish lower in mercury such as shrimp, canned light tuna, salmon, pollock and catfish and up to 6 ounces of albacore tuna per week. Given the beneficial effects of seafood, efforts should be aimed at decreasing anthropogenic release of mercury rather than elimination of dietary exposure.[91]

Although methylmercury has greater importance worldwide, the extreme toxicity of another organic mercurial, dimethylmercury, was tragically demonstrated by the delayed fatal neurotoxicity that developed in a chemist who inadvertently spilled dimethylmercury on a break in the gloves on her hands.[77] Over a period of several days, she developed progressive difficulty with speech, vision, and gait. Despite chelation and exchange transfusion, she died of mercury neurotoxicity within several months of the exposure.

DIAGNOSTIC TESTING

The dual findings of unexplained neuropsychiatric and kidney abnormalities in an individual should alert the clinician to the possibility of mercurialism, as should an at-risk occupation or access by the patient to a mercurial product (Table 95–1). Occupational or environmental exposure and a consistent clinical scenario are suggestive of mercury poisoning, but demonstration of mercury in blood, urine, or tissues is necessary for confirmation of exposure. Of the many methods available to measure mercury, cold atomic absorption spectrometry is rapid, sensitive, and accurate but cannot distinguish the various forms of mercury. Thin-layer and gas chromatographic techniques are recommended to distinguish organic from inorganic mercury. Whole blood should be collected into a trace element collection tube obtained from the laboratory performing the assay. Urine should be collected for 24 hours into an acid-washed container obtained from a laboratory. Spot collections must be adjusted for creatinine concentration. Attempts to measure or otherwise handle the specimen should be avoided to prevent external contamination (Table 95–4).

TABLE 95–4

Diagnostic Testing for Mercury

	Whole Blood	24-hour Urine	Hair	Clinical
Elemental/Inorganic	**(+)** Acute, transient	**(++)** Confirm exposure Monitor chelation Poor correlation to TBB	**(+)** Reflects past exposure and external adsorption	**(+)** Poor correlation to TBB Early detection
Organic	**(++)** Best reflects TBB	**(–)** Fecal elimination	**(+)** Reflects past exposure and external adsorption	**(+)** Poor correlation to TBB Reflects irreversible CNS toxicity Early detection

CNS = central nervous system; TBB = total body burden; + to ++ = useful testing specimen; - = lack of utility.

There is considerable overlap among concentrations of mercury found in the normal population, asymptomatic exposed individuals, and patients with clinical evidence of poisoning. There is no definitive correlation between either whole blood or urine mercury concentration and mercury toxicity. However, mercury serves no useful role in human physiology, and concentrations of 1.0 mcg/L or less for whole blood and 0.5 mcg/L for urine are generally considered to reflect background exposure in nonpoisoned individuals. The inconsistencies of the values found in the literature for mercury exposure are a recurrent issue in metal testing. A credible and qualified laboratory should be employed and their reference ranges accepted when testing is desired.[20]

For inorganic mercury poisoning, urine mercury concentrations correlate roughly with exposure severity and neuropsychiatric symptoms,[93] but the relationship to total body burden is probably poor. Urine mercury determinations have their greatest usefulness in confirming exposure and monitoring the efficacy of chelation therapy. Whole blood mercury concentrations reflect intense, acute inorganic mercury exposure but become less reliable as redistribution to tissues takes place.

Because organic mercury is eliminated via the fecal route, urine mercury concentrations are not useful in methylmercury poisoning. Because methylmercury concentrates in RBCs, the total-body methylmercury burden is best reflected acutely by whole-blood concentrations. As methylmercury

distributes to and accumulates in brain, the severity of clinical manifestations probably more closely reflects the degree of the irreversible neuronal destruction that has taken place rather than the current body burden of mercury. Correlation of increasing whole-blood mercury concentrations with prevalence of paresthesias was suggested in a population of Iraqis studied early in the course of methylmercury poisoning.[24] However, in another group of patients, whole-blood concentrations did not correlate with severity of methylmercury poisoning.[96] This apparent discrepancy may have resulted from the finding that paresthesias are among the earliest reported symptoms of methylmercury poisoning.

Because mercury accumulates in the hair, hair analysis has been used as a tool for measuring mercury burden. However, because metal incorporation reflects past exposure and hair avidly binds to noningested environmental mercury, the reliability of this method is questionable and is not recommended.[89] In addition to mercury assays, neuropsychiatric testing, nerve conduction studies, and urine assays for *N*-acetyl-β-D-glucosaminidase and β_2-microglobulin are advocated for early detection of subclinical inorganic and organic mercury toxicity.[34,45,93]

GENERAL MANAGEMENT

After the initial assessment and stabilization, the early toxicologic management of a patient with mercury poisoning includes termination of exposure by removal from vapors, washing exposed skin, GI decontamination, supportive measures (eg, hydration, humidified oxygen), baseline diagnostic studies (eg, complete blood count, serum chemistries, venous blood gas, radiography, ECG), specific analysis of whole blood and urine for mercury, evaluation of possible cointoxicants, and meticulous monitoring.

Elemental Mercury

Inhalation of mercury vapors or aspiration of metallic mercury may result in life-threatening respiratory failure; in this situation, stabilization of cardiorespiratory function is the initial priority. Postural drainage and endotracheal suction are a reasonable technique to attempt to remove aspirated metallic mercury. Parenteral deposition of subcutaneous or intramuscular (IM) mercury is amenable to surgical excision, if well localized (Fig. 95–1).

An adjunct to the initial management of patients with mercury poisoning is environmental decontamination. Elemental mercury that spills onto solid surfaces should be adsorbed to sand and the resulting mixture then swept into tightly sealed containers. Ideally, a mercury decontamination kit should be used. The kit consists of calcium polysulfide, which contains excess sulfur to convert mercury to water-insoluble mercuric sulfide. Absorbent surfaces, such as carpets, should be removed. Spilled mercury compounds should not be vacuumed because vacuuming could volatilize the mercury.[18] Broken compact fluorescent light bulbs should be handled and disposed of according to EPA guidelines and local requirements.[2]

Recommendations for decontamination after breakage include opening windows to release vapor, using adhesive tape to pick up visible fragments, and discarding contaminated material in double-wrapped bags. Guidance for decontamination of major spills and disposal of materials can be provided by local and federal hazardous materials agencies.

Inorganic Mercury

Because ingestion of inorganic mercuric may lead to cardiovascular collapse caused by severe gastroenteritis and third-space fluid loss, fluid resuscitation is a priority. Gastrointestinal decontamination of ingested inorganic mercury is particularly problematic because of its causticity and risk for perforating injury. Nevertheless, one series of patients with mercuric chloride ingestion of up to 4 g reported recovery without long-term GI sequelae in patients who did not succumb to kidney failure.[116] Therefore, unless there is high suspicion for penetrating GI mucosal injury, removal of mercury from absorptive surfaces should take priority over endoscopic evaluation. The prominence of vomiting makes gastric lavage unnecessary for most patients with inorganic mercury poisoning.

Metals are among the substances that are often considered to be poorly adsorbed to activated charcoal. Nevertheless, the serious nature of late sequelae after mercury absorption, the typically small quantities of mercury ingested, and evidence that inorganic mercuric salts actually have substantial adsorption to activated charcoal (800 mg mercuric chloride can be adsorbed to 1 g activated charcoal) justify the routine administration of activated charcoal.[6] Whole-bowel irrigation with polyethylene glycol solution is a reasonable adjunct to remove residual mercury, and its progress can be followed with serial radiographs.

Organic Mercury

Organic mercury exposures do not typically present as single acute ingestions but rather as chronic or subacute ingestion of contaminated food. Therefore, GI decontamination is generally moot with respect to organic mercury poisoning. Nevertheless, its irreversible toxicity coupled with unsatisfactory treatments calls for aggressive decontamination when acute ingestions or dermal exposures occur.

CHELATION

After initial stabilization and decontamination, early institution of chelators minimizes or prevents the widespread effects of poisoning. Dimercaprol was developed during World War II as an antidote against lewisite, an arsenical warfare agent. The water-soluble analogs DMPS and succimer were developed in the 1950s, and the 3 chelators have remained the mainstay of therapy for mercury poisoning.[59] A high degree of protein binding and distribution to the brain are responsible for the lack of efficacy of other measures to increase mercury clearance, such as peritoneal dialysis and hemodialysis.[100] In one report of the use of continuous venovenous hemodiafiltration in combination with a chelator in a patient with severe inorganic mercury poisoning, 12.7% of the ingested dose was recovered in the ultrafiltrate.[26] Hemodialysis may nevertheless ultimately be necessary because of the acute kidney failure that often occurs after mercuric chloride poisoning.

Chelators have thiol groups that compete with endogenous sulfhydryl groups for the binding of mercury, thereby preventing inactivation of sulfhydryl-containing enzymes and other essential proteins (Antidotes in Depth: A28 and A29). A history of significant mercury exposure combined with the presence of typical symptoms of mercury poisoning is an appropriate indication for the institution of chelation therapy. Elevated whole-blood and urine mercury concentrations help support the decision to begin chelation therapy in unclear cases and can also be used to guide the duration of therapy. Provocative chelation, in which urinary mercury excretion before and after a chelating dose is compared to determine the degree of mercury poisoning, is of no value.[52] Chelation tends to increase urinary elimination of mercury, regardless of exposure history and baseline excretion.

Elemental Mercury and Inorganic Mercury Salts

For patients with symptomatic acute inorganic mercury poisoning, dimercaprol should be administered for 10 days in dosages of 5 mg/kg/dose every 4 hours IM for 48 hours, then 2.5 mg/kg every 6 hours for 48 hours, followed by 2.5 mg/kg every 12 hours for 7 days. It is reasonable to adjust this dosing regimen, which was derived from lead poisoning, according to clinical response and the occurrence of adverse reactions.

When a patient can take oral medications, we recommend that dimercaprol be replaced with succimer at 10 mg/kg orally 3 times a day for 5 days, then twice a day for 14 days if the GI tract is clear. Because headache, nausea, vomiting, abdominal pain, and diaphoresis are common reactions during dimercaprol chelation therapy, oral succimer is recommended in patients who are not acutely ill or who have been chronically poisoned.

Either dimercaprol or succimer is considered the treatment of choice for inorganic mercury poisoning in the United States, but a few other chelators deserve mention. 2,3-Dimercapto-1-propanesulfonic acid (DMPS) is a water-soluble dimercaprol derivative that is used in Europe. It is administered both IV and orally. D-Penicillamine is an orally administered monothiol. Its adverse events—GI distress, rashes, leukopenia, thrombocytopenia, and proteinuria—although uncommon in therapeutic doses, seriously limit the usefulness of the drug. *N*-acetyl-D,L-penicillamine (NAP), an investigational analog of D-penicillamine, is thought to be a more effective chelator of mercury than is D-penicillamine, perhaps because of its greater stability.[11,40,43]

Organic Mercury Compounds

The neurotoxicity of methylmercury and other organic mercury compounds is resistant to treatment, and therapeutic options are less than satisfactory. In rats, both dimercaprol and D-penicillamine effectively reduced tissue mercury and prevented neurologic toxicity if administered within the first day of a methylmercury injection.[126] Neither treatment reversed neurologic toxicity when administered 12 days after methylmercury injection. 2,3-Dimercapto-1-propanesulphonate, D-penicillamine, NAP, and a thiolated resin all led to a marked reduction of blood half-life of mercury (ie, 10, 24, 23, and 19 days, respectively, versus 60 days) during the outbreak of methylmercury poisoning in Iraq in 1971.[24] Clinical improvement was not observed in any treatment group, but it is reasonable to postulate that reducing the total-body burden of methylmercury may prevent or limit the progression of disease. When studied in mice poisoned with methylmercury,[1] succimer was superior to NAP, DMPS, and a thiolated resin in decreasing brain mercury and increasing urinary excretion. Brain mercury was decreased to 35% of control, and the total-body burden fell to 19%. Some animal

evidence suggests that dimercaprol increases mercury mobilization into the brain.[7,10,15] For this reason, and the lack of serious GI symptoms necessitating parenteral chelation, We recommend against the use of dimercaprol the treatment of patients with organic mercury poisoning.

Because the neurologic impairment associated with methylmercury is both profound and essentially irreversible, early recognition of poisoning and prevention of neurotoxicity are essential to a successful outcome. At this time, succimer is the most reasonable treatment for methylmercury poisoning because of its apparently low toxicity and reported efficacy in animal trials.

SUMMARY

- Mercury poisoning by any of the 3 major forms—elemental, inorganic, and organic—presents a complex toxicologic problem associated with a large variety of clinical presentations.
- An ever present awareness of the signs and symptoms coupled with the knowledge of the differing clinical forms is essential for both early recognition and effective treatment.
- Although some chelators show promise in the treatment of mercury poisoning, neurologic sequelae, particularly those resulting from organic mercury exposures, remain largely irreversible.
- Dietary fish remains an important source of mercury exposure and mercurial neuropsychologic illness.
- There is no evidence for the role of mercury in the pathogenesis of autism.
- Promotion of public education regarding the dangers of mercury, its avoidance, and proper disposal may aid in the prevention of mercury poisoning.

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