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Heavy metal poisoning: management of intoxication and antidotes

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Abstract. Of the known elements, nearly 80% are either metals or metalloids. The highly reactive nature of most metals result in their forming complexes with other compounds such oxygen, sulfide and chloride. Although this reactivity is the primary means by which they are toxic, many metals, in trace amounts, are vital to normal physiological processes; examples include iron in oxygen transport, manganese and selenium in antioxidant defense and zinc in metabolism. With these essential metals toxicity occurs when concentrations are either too low or too high. For some metals there are no physiological concentrations that are beneficial; as such these metals only have the potential to cause toxicity. This chapter focuses on four of these: arsenic, mercury, lead and thallium.

Arsenic poisoning

Arsenic's history is marked by great successes and tremendous tragedies. Used by Greek and Roman physicians as far back as 400 B.C. [1], arsenic is still used in traditional Chinese and Indian folk medicine [2, 3]. In western medicine it has recently been used as a treatment for late-stage African trypanosomiasis (melarsoprol) [4] and for acute promyelocytic leukemia (arsenic trioxide, Trisenox®) [5]. Arsenic also enjoys an illustrious place in history as a frequently employed homicidal agent. The historical use of arsenic as a poison has earned it the title of "Poison of Kings and the King of Poisons" [6].

Toxicology

As the 20th most abundant element in the earth's crust, arsenic can be found in all living organisms as one of several varieties: elemental, organic, inorganic, and gaseous [7, 8]. In nature arsenic is found in rocks, soil, minerals, and metals ores such as lead and copper; environmental arsenic contamination may occur through water runoff and leaching, wind, and volcanic eruptions. Mining and smelting of arsenic-containing ores, combustion of fossil fuels in coal-fired power plants and incinerators, as well as the use of organic arsenic in pesticides and animal feed contribute to environmental contamination [6, 9, 10].

Human exposure to arsenic primarily occurs through food, particularly seafood, rice, mushrooms, and poultry. Air and water represent alternative sources of exposure. In Bangladesh tube-wells were built to provide safe drinking water, but inadvertently exposed the population to elevated arsenic from contaminated ground water [11, 12]. Generally, residents of the United States consume only about 50 μg of arsenic per day with 3.5 μg being inorganic. Occupational contact represents an additional route of arsenic exposure with metal workers, electronic workers, and glass and ceramic manufacturing workers being at highest risk.

Elemental arsenic is nontoxic. Organic arsenicals can be found in fish and shellfish, in the form of arsenobetaine and, like elemental arsenic, these forms pose a low risk for human toxicity [9]. Arsenic toxicity primarily results from exposure to inorganic arsenicals, which are found in trivalent (As^{3+}, arsenite, more toxic) and pentavalent (As^{5+}, arsenate, less toxic) forms. Arsenate compounds have little protein binding and are free to be excreted. Arsenite compounds on the other hand have high protein binding, resulting in both toxicity and a potential storage depot for further exposure [13]. Once arsenic reaches hepatocytes, it undergoes conversion from an inorganic compound to an organic compound through alternating reduction and methylation reactions. This process detoxifies the parent compound but creates carcinogenic metabolites [6, 7, 13]. Arsenate is reduced to the more toxic arsenite form prior to being converted into monomethyl arsenic (MMA) and ultimately dimethyl arsenic (DMA). Both MMA and DMA can be reduced into the more toxic trivalent form [6, 13, 14]. The final effects of this bioactivation and detoxification pathway depends on the rate of each step in the tissue exposed [14].

Arsenic disrupts cellular functioning though two distinct mechanisms of action. Arsenic, particularly trivalent forms, binds sulfhydryl groups, disrupting essential enzyme activity, and leads to impaired gluconeogenesis and oxidative phosphorylation. Pentavalent arsenic can serve as a phosphorous substitute, forming less stable bonds in high energy compounds such as ATP. This ‘arsenolysis’ causes rapid hydrolysis of these bonds, uncoupling oxidative phosphorylation [15].

Clinical presentation

The clinical presentation of arsenic toxicity differs depending on the species of arsenic, the amount, and the route and duration of exposure. Acute occupational contact to arsenic may occur following inhalational exposure to inorganic arsenic or arsine gas [6, 9, 16]. Symptoms from arsine gas exposure differ from other types of arsenic exposure, and are discussed separately.

Acute arsenic toxicity from ingestion is characterized by gastrointestinal (GI) symptoms, including abdominal pain, nausea, emesis, and profuse watery or bloody diarrhea [6, 17, 18]. Subsequent hypotension, heart failure, pulmonary edema and shock can be seen as a result of capillary dilation with

third spacing of fluid, cardiomyopathy, and ventricular arrhythmias [6, 18]. Altered mental status with confusion can be seen [17] and "seizures" or hypoxic convulsions may signal a pre-terminal event [8, 19]. Cardiac abnormalities have been noted following arsenic exposure, particularly following treatment with arsenic trioxide. These abnormalities may include QTc prolongation, pericardial effusion, myocarditis and serositis, T-wave abnormalities, second-degree heart block, QRS widening, non-conducted P-waves, torsade de pointes, and asystole [18, 20–24]. There are multiple theories regarding the etiology of these cardiac abnormalities. Patients receiving arsenic trioxide may have been exposed to other cardiotoxic medication in their previous chemotherapeutic regimen. In addition, arsenic trioxide therapy itself is associated with hypokalemia and hypomagnesemia [14]. The combination of these two factors may account for cardiac effects seen with arsenic trioxide in chemotherapy patients. Arsenic has also been shown to have direct cardiac effects including blockade (I_{Kr} and I_{Ks}) and activation ($I_{K\text{-}ATP}$) of cardiac ion channels – effects that may account for arsenic's variability of QT prolongation [18].

Peripheral neuropathy typically occurs 2–8 weeks after arsenic exposure, although it may occur within hours of a severe exposure [6, 25]. Early symptoms consist of a symmetric sensorimotor neuropathy, which may be initially misdiagnosed as Guillain-Barré syndrome [6, 26]. Patients who develop arsenic-induced neuropathy note pain, numbness, and paresthesias in a stocking glove distribution [6, 17]. Electrophysiological studies are consistent with axonal degeneration, showing a decrease in amplitude, and with severe poisonings velocity [6]. Arsenic-induced cellular toxicity results in cytoskeleton protein changes, which may be the etiology of arsenic-induced neuropathy [6].

Chronic arsenic toxicity is characterized by macrocytosis, pancytopenia, hyperkeratotic lesions noted on the extremities, hyperpigmented melanosis described as "raindrops in the dust", bronze pigmentation, GI symptoms, anemia, and liver disease [6, 27, 28]. In addition, Mees' lines – transverse white striae on the fingernails (Fig. 1), a sensation of a metallic taste [6] and peripheral neuropathy have all been characterized in chronic arsenic exposure [27].

Long-term effects

Arsenic is considered a known human carcinogen by the U.S. Department of Health and Human Services, the International Agency for Research on Cancer (IARC), and the U.S. Environmental Protection Agency (EPA) [9]. Specifically, arsenic has been shown to alter gene expression through induction, down-regulation, and up-regulation of various genes involved in damage response, apoptosis, cell cycle regulation, cell signaling, and growth factor response [13]. Multiple cancers have been linked to arsenic in populations with increased occupational or environmental arsenic exposure, including

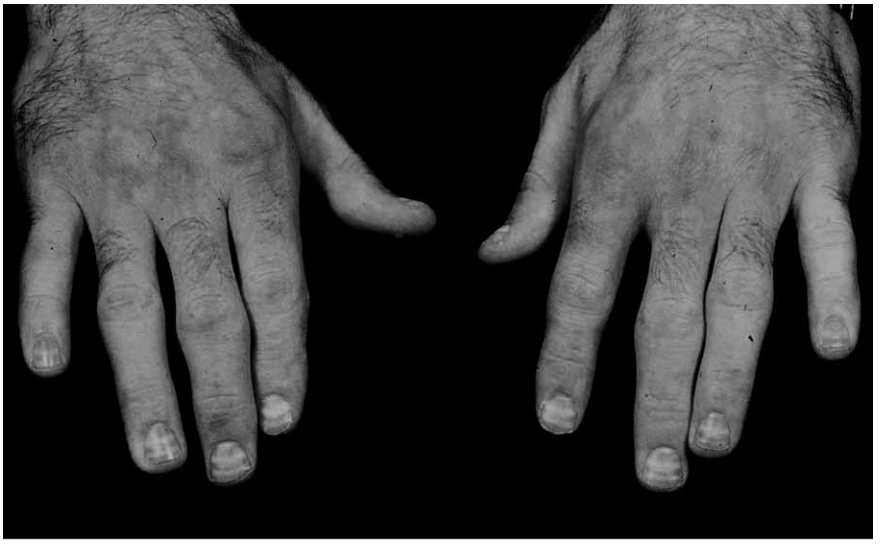

Figure 1. Mees' lines from two separate incidences of arsenic poisoning (courtesy of R. Pascuzzi, MD, Indianapolis, IN).

liver, bladder, lung, digestive tract, lymphatic, hematopoietic, and skin cancer [9, 11, 29–31].

Diagnosis

The diagnosis of arsenic toxicity depends on combining the clinical history with the possibility of exposure. If the exposure is recent, urine and blood testing can confirm or refute suspected arsenic toxicity [6, 9]. Arsenic has been shown to clear from blood in three phases [32]. Due to the rapid clearance seen during phases 1 and 2, blood testing may only be reliable during the early stages (typically <7–10 days after acute arsenic poisoning) [8]. The long half-life of arsenic in phase 3 of elimination (estimated 230 hours), however, may make urinary arsenic concentrations detectable for weeks after an acute exposure [32]. Arsenic speciation may be helpful to separate inorganic and organic arsenic species, since only inorganic arsenic is of toxicological concern. If the sample was collected in a metal-free container and there was no recent seafood ingestion, a urinary arsenic level greater than 50 μg/L in a random sample or greater than 100 μg in a 24-hour sample should be considered elevated [6]. In cases of suspected chronic arsenic toxicity, hair and nails can also be used to confirm the diagnosis [6]. Since hair grows at rate of 0.4 mm a day, hair studies may be used to help determine an approximate time of exposure based on the distance of an arsenic peak from the hair root [33].

Treatment

As with any toxin, it is important to remove the patient from the source of their exposure. While not well studied, gastric lavage and activated charcoal have been used to decrease absorption [6]. Initial treatment of arsenic toxicity is geared towards intensive supportive care. Additionally, hemodialysis has shown some benefit in treating arsenic-poisoned patients who present with significant renal dysfunction. Once renal function recovers, urinary arsenic excretion may exceed the amount removed by dialysis [34].

Since arsenic is a metalloid, chelation therapy may be used [6]. Dimercaprol (2,3-dimercaptopropanol, British Anti-Lewisite, BAL), at a dose of 3–4 mg/kg intramuscularly every 4–12 hours can be used as a chelator following acute arsenic toxicity [8, 19]. In a patient able to take an oral medication, dimercaprol may be discontinued, and *meso*-2,3-dimercaptosuccinic acid (DMSA) given at a dose of 10 mg/kg every 8 hours for 5 days then every 12 hours can be applied [8]. Treatment duration is based on clinical course and may be influenced by urinary arsenic levels [19]. However, increased urinary arsenic clearance has not been consistently demonstrated following DMSA therapy [33, 35]. Neuropathy progression despite chelation therapy has been reported [17, 33]. DMSA is only U.S. Food and Drug Administration (FDA) approved for the treatment of lead toxicity in children but has orphan status for the treatment of mercury poisoning [35]. While historically D-penicillamine was also recommended as an oral chelating agent, animal studies have suggested it to be inferior to dimercaprol and DMSA [36].

Arsine gas

Arsine gas is liberated when an acid contacts arsenic containing compounds or when water contacts metallic arsenide. Industrial processes at risk of generating arsine gas include galvanizing, soldering, etching, and lead plating. Arsine gas is colorless, nonirritating, and possesses a slight garlic odor, which may not be detected following an industrial exposure [37]. Arsine toxicity presents very differently from arsenic toxicity. Within hours of significant arsine exposure, patients develop headache, abdominal pain, nausea, and emesis, followed by hemolysis, gross hematuria, scleral icterus, bronze skin discoloration, and acute renal failure. A classic triad of abdominal/flank pain, hematuria, and jaundice has been described. While recovery is possible, patients may experience chronic renal dysfunction [38] and peripheral neuropathy following arsine exposure [39].

Laboratory evaluation following exposure to arsine gas reveals a Coombs negative hemolytic anemia with mildly elevated serum bilirubin and lactate dehydrogenase levels. Erythrocyte lysis and renal failure may lead to massive elevations of serum potassium requiring treatment. Urinalysis reveals hemoglobinuria, albuminuria, and occasional tubular casts consisting of erythrocytes and hemoglobin [37].

Treatment of exposed individuals begins with removing the patient from the source of their exposure. Exchange transfusion can restore functional red blood cells [39, 40] and remove hemoglobin pigment and the toxic products formed from the effect of arsine on hemoglobin [39]. The successful use of plasmapheresis in addition to red blood cell (RBC) exchange has also been described [37, 38]. Hemodialysis should be considered in any patient experiencing renal failure [40]. Chelation therapy is controversial in the acute management of arsine toxicity, and may not influence outcomes or the development of peripheral neuropathy [39].

Chromated copper arsenate

First used as a wood preservative during the 1930s, chromated copper arsenate (CCA) became the main preservative used in residential settings in the United States by the 1970s [41, 42]. Despite its popularity, concern arose regarding the potential for arsenic toxicity from its use in children's playground equipment. While this potential exposure is smaller than what children receive through food and water [9], a 2001 petition was presented to the Consumer Product Safety Commission requesting a ban on the use of CCA in playground equipment [42]. Although chronic arsenic toxicity has only occurred following the burning of CCA-treated wood in an enclosed environment [43], production of CCA for consumer products was halted in December of 2003 following a voluntary agreement between CCA manufacturers and the Environmental Protection Agency [42]. Today, CCA-treated wood can still be found in industrial settings [9].

Mercury poisoning

Mercury is a naturally occurring metal that exists in three forms: elemental, inorganic salt, and organic. Documented use of mercury dates back to 1500 B.C. and over the ensuing centuries it has been used as decoration, in cosmetics, and even as a medicine. The clinical syndromes associated with mercury exposure vary with the dose, length of exposure, and form of mercury [44–47].

Elemental mercury

Elemental mercury (quicksilver or liquid mercury) is a silver colored liquid at room temperature. The primary means by which elementary mercury is absorbed is through inhalation of its vapor. The vapor pressure of mercury approximately doubles for every 10 °C temperature increase, so that its heating greatly increases exposure and toxicity. Approximately 80% of inhaled vapor is absorbed by the alveoli and passes rapidly into the blood where it is

taken up by red blood cells and converted to a less lipid soluble divalent (mercuric) form. A small amount of non-oxidized mercury vapor can penetrate the blood-brain barrier leading to central nervous system (CNS) toxicity in high-dose exposures [48]. Inhaled vapor is largely eliminated in the urine with an elimination half-life of about 60 days [49]. Compared to the respiratory tract, GI absorption is negligible [50] and represents little risk for patients with intact GI mucosa [51]. Toxicity can occur if the GI mucosa is not intact [52]. Two less common sources of exposure are intravenous (i.v.) and subcutaneous injection. Intravenous injection can lead to potentially fatal pulmonary emboli and mercury poisoning [53, 54]. Although small amounts can enter through intact skin [55], subcutaneous injection of elemental mercury tends to be limited to local symptoms; it may, however, cause increases in blood and urine mercury concentrations.

Toxicology

Target organs for elemental mercury vapor include the lungs, brain, and to a lesser degree the kidneys [47, 56, 57]. It appears to cross the blood-brain barrier in its vapor form concentrating in neuronal lysosomal dense bodies. Elemental mercury combines with sulfhydryl groups on cell membranes and interferes with protein and nucleic acid synthesis, calcium homeostasis and protein phosphorylation. Elemental mercury causes cellular damage and oxidant stress [58].

Clinical presentation

The dose and length of exposure are responsible for the wide variability in symptoms from elemental mercury toxicity. Within hours of an acute exposure, chills, GI upset, weakness, cough and dyspnea may develop. Adult respiratory distress syndrome and renal failure may occur in severe cases. Depending on the level of exposure, chronic mercury toxicity may develop over weeks to months. Early symptoms such as GI upset, poor appetite, abdominal pain, headache, dry mouth, and myalgia may mimic a viral illness. Two distinct syndromes, acrodynia and erethism have been associated with chronic exposure (Fig. 2). ‘Acrodynia’, alternately known as pink disease, Feer syndrome, or Feer-Swift disease, is a complex of symptoms that may be seen in chronic exposure to either elemental or inorganic mercury. It usually occurs in infants and children, but has been reported in adults. The symptom complex includes the following: (1) Autonomic changes – sweating, hypertension, tachycardia; (2) dermatological/dental changes – pruritus, erythematous rash on palms/soles, erythematous gingiva, ulceration of oral mucosa, loose teeth; (3) musculoskeletal – weakness, poor muscle tone.

Many of the adrenergic symptoms are thought to be due to mercury’s inactivation of coenzyme *S*-adenosylmethionine, which causes inhibition of catechol *O*-methyltransferase (COMT). A reduction in the breakdown of catecholamines produces the sympathetic symptoms such as hypertension and may result in a clinical picture mimicking pheochromocytoma [59–61].

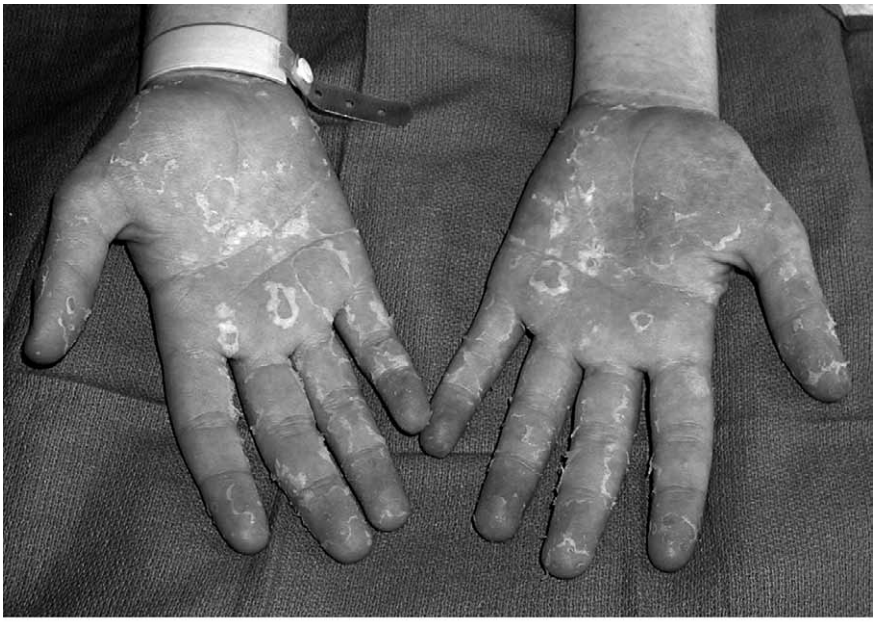

Figure 2. Acrodynia from elemental mercury vapor toxicity (courtesy of D. Rusyniak, MD, Indianapolis, IN).

'Erethism' refers to personality changes in affected individuals. They may exhibit memory loss, drowsiness, lethargy, depression, withdrawal, and irritability. Other neuropsychiatric findings are also reported: insomnia, shyness, confusion, hallucinations, manic-depressive episodes, emotional lability [56]. Some authors have suggested a link between mercury exposure, erethism, and parkinsonism [56, 62, 63]. Two studies from the 1980s [64, 65] and two case reports [62, 63] suggest this link; however, causation has not been established.

Diagnosis

The diagnosis of elemental mercury poisoning is based upon history, physical findings, and the demonstration of a significantly increased body burden of mercury.

After an acute exposure, whole blood mercury is reliably elevated for 2–3 days (the usual reference range is 0–10 μg/L). Urine 24-hour collection is the most useful indication of exposure to elemental and inorganic mercury. Samples need to be refrigerated to decrease bacterial reduction of mercury to volatile elemental mercury [66]. Excretion in excess of 50 μg/L is considered elevated but reference ranges vary and an exact threshold for toxicity does not exist [47, 56]. Care must be taken in interpretation of urine testing for metals as specimens collected after administration of chelators can increase excretion

of various metals even in patients without excessive exposure [67, 68]. The results of such tests should *not* be applied to reference ranges for non-chelated specimens.

Treatment

Removal of the patient from the source is a key intervention [47, 56, 57, 69]. Decontamination is of little use in either respiratory or GI exposure. While chelation is considered a mainstay of therapy, it is still somewhat controversial. DMSA, dimercaprol, and D-penicillamine have all been used; DMSA is considered the current treatment of choice in the United States. Chelation may take several months and studies showing a clear long-term benefit are lacking [57, 70]. Dialysis with or without the inclusion of a chelating agent, may be required in patients with renal failure.

Dental amalgam

Also known as mercury or silver amalgam, dental amalgam consists of up to 50% elemental mercury, copper or silver and also contains lesser concentrations of other metals such as zinc. For over a century, this durable compound has been widely used in dental restorations because it can be tightly inserted and expands in place to fill defects. In the latter part of the 19th century concerns were raised as to the potential mercury toxicity in dental fillings [71]. A German chemist, Alfred Stock, who suffered from erethism as a result of years of exposure to mercury, is credited with first recognizing that dental amalgam could elevate urine mercury concentrations [71]. In more recent years, animal studies have confirmed that mercury is released from amalgam fillings with the amount increasing with the size and number of fillings [72]. Some authors have suggested a causal relationship between a variety of diseases and dental amalgam including autoimmune disorders, renal disease, Alzheimer's disease, and autism [73]. Multiple human studies, however, have failed to establish causation [74–81]. Some studies have reported improvement in a variety of symptoms after the removal of mercury amalgam; however, these studies have not clearly established a link between amalgam removal and improvement of symptoms [82, 83]. It should be noted that removal of mercury amalgam appears to increase plasma mercury by three- to fourfold for a short time after removal [84, 85].

Inorganic mercury

Mercury occurs naturally as mercuric and mercurous salts. Cinnabar [mercury (II) sulfide, HgS] is the most common natural source. This mineral is used as the pigment vermilion. A wide variety of mercurial salts have been used in a variety of industries including medicine as antiseptics (i.e., mercuric chloride); cosmetics, explosives, dyes and pigments, and as antifungals in paints [47, 56, 86, 87].

Clinical presentation

Inorganic mercury may be absorbed *via* the GI or respiratory tracts as well as dermally. Ingestion is the most common route. Unlike the elemental form, mercury salts are very corrosive to the gut [56, 88]. Presenting complaints following ingestion may include nausea, vomiting, abdominal pain, or hematemesis. Colitis with necrosis or mucosal sloughing may occur in severe cases, leading to excessive volume loss [56, 88, 89].

Prolonged cutaneous application can cause hyperpigmentation, swelling, and vesicular or scaly rash. Hyperpigmentation is seen as a gray-brown discoloration of skin folds of the face and neck. Used as a topical analgesic for teething in the 19th century, calomel (mercuric chloride) caused loosening of teeth, bluish discoloration of the gingiva, and systemic toxicity [56, 90].

The half-life of inorganic mercury is 24–40 hours in the blood. It is excreted by the kidneys, which results in concentration and injury of the distal portions of the proximal convoluted tubules [91, 92]. These effects can be seen within 2 weeks of exposure and may reverse over time [93]. Chronic exposure can also cause membranous glomerulonephritis and nephrotic syndrome. Animal studies suggest that this is an autoimmune process. Spontaneous resolution of the nephrotic syndrome has been reported following termination of mercury exposure [47, 94]. Acrodynia and erethism have also been reported with inorganic mercury exposure [47, 56].

Diagnosis

As with elemental mercury exposures, 24-hour urine testing is the preferred method of measuring body burden. However, there is no clear threshold for toxicity (see diagnosis under elemental mercury).

Treatment

The GI tract and kidneys are the target organs of inorganic mercury. Injury to the gut in severe poisoning may require aggressive fluid resuscitation. Renal injury may necessitate hemodialysis. Dimercaprol has been reported to be most effective if started within 4 hours of oral exposure [95]. DMSA may be substituted when patients can tolerate oral medication.

Organic mercury

Recognition of organic mercury toxicity has been relatively recent. Organic mercurial compounds are used as preservatives, antiseptics and seed dressings. Two historical episodes of methylmercury exposure brought to the light the toxicity related to organic mercury. The first event occurred in the community of Minamata Bay, Japan. During the 1950s and 60s a local chemical company disposed waste into the neighboring bay where resident bacteria converted the inorganic mercury into methylmercury, which eventually found its way up the food chain and concentrated in larger fish. Over 2265 people who consumed

contaminated fish developed toxicity known as Minamata disease. Symptoms included ataxia, sensory disturbances, dysarthria, visual field constriction, auditory disturbances and tremor. Children born to mothers who were exposed to methylmercury *in utero* developed congenital Minamata disease characterized by spasticity, seizures, deafness and severe mental deficiency [96, 97].

The second event occurred in Iraq in 1971 when bread that was made from seed grain treated with a methylmercury fungicide was consumed by over 6500 people [98]. Studies from the Iraqi victims were used as the first standards for defining safe organic mercury exposure in adults. The FDA used these data to propose an acceptable daily intake of 0.4 μg/kg body weight per day [96].

Toxicology

Studies from the disasters in Japan and Iraq show that methylmercury primarily targets the CNS with fetal brain tissue being more susceptible than the adult CNS. Up to 90% of organic mercury is absorbed from the GI tract [99] after which it readily crosses the blood-brain barrier and placenta reaching levels in the brain three to six times those in the blood [100].

Clinical presentation

The most common presentation of organic mercury poisoning is concentric constriction of the bilateral visual fields, paresthesias of extremities and mouth, incoordination, ataxia, tremor, dysarthria and auditory impairment [97, 98]. Postmortem findings demonstrate neuronal damage in gray matter of the cerebral and cerebellar cortex, with the calcarine region of the occipital lobe and the pre- and postcentral and temporal cortex are the most affected. Granule cells in the cerebellum are lost, while neighboring Purkinje cells are preserved. Sensory fibers of the peripheral nerves may also be damaged [101, 102].

Among children with Minamata disease, all had mental retardation, cerebellar ataxia, primitive reflexes, limb deformities, and dysarthria. Chorea and hypersalivation were seen in 95%, while 60% had microcephaly [97, 103, 104]. Pathological changes were similar in adults and children: cortical atrophy and hypoplasia of the corpus callosum, demyelination of the pyramidal tracts, and hypoplasia of the granular cell layer of the cerebellum [103].

Diagnosis

Ninety percent of methylmercury is bound to hemoglobin in red blood cells [99]. Most elimination occurs through the GI tract rather than the kidneys. For that reason, whole blood mercury rather than urine mercury is a better indication of organic mercury burden. Whole blood mercury concentrations are usually less than 6 ng/mL, but diets rich in fish can increase levels to 200 ng/mL or higher [7].

Treatment

Chelating agents including D-penicillamine, *N*-acetyl-D,L-penicillamine, 2,3-dimercaptopropane sulfonate, and DMSA have all be utilized in cases of

organic mercury toxicity [98, 105, 106]. While all appear to increase excretion, none have been shown to lead to clinical improvement. Most cases are discovered after symptoms are pronounced, and treatment is likely more effective when begun early [107, 108].

Thimerosal and vaccines

Thimerosal is an organic mercury compound that contains ethylmercury bound to thiosalicylate. Since the 1930s it has been widely used as a preservative in certain vaccines. *In vitro* studies showed thimerosal to be 40–50 times as effective as phenol as an antimicrobial against *Staphylococcus aureus*. Before the introduction of thimerosal, there were several episodes of bacterial contamination of vaccines that resulted in illness and death in recipients [96]. Thimerosal is 50% mercury by weight and found in concentrations of 0.003–0.01% in vaccines. A vaccine containing 0.01% thimerosal contains 25 μg mercury per 0.5 mL dose. Before the marketing of thimerosal, high-dose toxicity studies were performed on animals, but no clinical studies formally evaluated its safety in humans. In 1929, a trial of high-dose thimerosal was given intravenously to 22 patients with meningococcal meningitis. Although not effective as treatment, these patients seemed to tolerate such high doses without observed toxic effects [96].

Toxicity has been observed with large amounts of thimerosal in reports of both accidental and intentional exposure [109–113]. There are limited data on toxicity from low dose exposures similar to that seen with vaccines. A formal review of thimerosal by the FDA in 1976 stated "no dangerous quantity of mercury is likely to be received from biological products in a lifetime" [114]. The low concentration of mercury within the vaccines was considered both safe and effective in practice.

The calculations used by the EPA, Agency for Toxic Substances and Disease Registry (ATSDR), World Health Organization (WHO) and the FDA were based on the assumption that ethylmercury was similar in toxicity to methylmercury; this was based on their related chemical structure and similar clinical effects at high doses [115, 116]. These two compounds, however, are not equivalent and have significant differences in pharmacokinetics. Ethylmercury has a half-life somewhere between 7 and 18 days whereas that of methylmercury can be as long as 1.5 months. In addition, ethylmercury has less movement across the blood-brain barrier in the CNS [116].

A review of the FDA risk assessment found that the only established harm from thimerosal at doses found in vaccines is a delayed-type hypersensitivity reaction. However, because thimerosal vaccines could expose infants to cumulative mercury at levels that exceed the EPA recommendations (but not the ATSDR, WHO, or FDA) it was recommended that thimerosal be withdrawn from US vaccines. In July 1999, the American Academy of Pediatrics along with the Public Health Service called for the removal of thimerosal from further use in vaccines targeted for children [115]. Even though thimerosal was removed from childhood vaccines in the US in 1999, with the rise in neurode-

velopmental disorders including autism, thimerosal has been questioned as a potential risk factor for these disorders. Several studies looking at the association between autism and thimerosal have found no causal relationship [117–119]. Several organizations including the WHO and the Institute of Medicine (IOM) have developed statements addressing the safety of thimerosal-containing vaccines. The IOM concludes that the evidence to date indicates no causal relationship between these vaccines and autism [120]. The WHO also supports that "the most recent pharmacokinetic and developmental studies do not support concerns over the safety of thimerosal (ethylmercury) in vaccines" [121].

Fish consumption

Human exposure to methylmercury is almost exclusively from the consumption of fish and other seafood. Pregnant women who eat fish expose the fetus to methylmercury which crosses the placenta as well as the blood-brain barrier [122, 123]. Although Minamata bay clearly showed the dangers of eating fish with exceptionally high levels of methylmercury, the fetal risks of current day maternal fish consumption are unknown. In 1989, the Seychelles Child Development Study (SCDS) was designed to study maternal methylmercury exposure due to fish consumption and its impact on fetal neurodevelopment; inhabitants of the Seychelles rely primarily on fish as a source of protein. Assessments were made at 6, 19, 29, and 66 months that showed no association between prenatal maternal hair mercury levels and neurodevelopmental outcome [124]. The findings reported in the 9-year follow-up of the SCDS found 2 of 21 endpoints were associated with prenatal methylmercury exposure and developmental outcomes at 9 years of age. In one test for speed and coordination, there was diminished performance in children of mothers with higher mercury concentrations; however, these children also did better on ratings of hyperactivity as compared to children of mothers with lower concentrations. The authors contributed both findings to chance, and in their conclusion state that their data do not support a relationship of impaired neurodevelopment from prenatal exposure to methylmercury in fish consumption in the Seychelles islands [122, 123].

The second large longitudinal study conducted in the Faroe Islands produced results that differed from those of the Seychelles study. The Faroe children showed deficits in language, attention and memory at age seven [125]. Some have suggested that the positive findings in the Faroe Island study may be related to differences in diet. The Faroe Island inhabitants eat more shark and whale meat, which contains higher concentrations of methylmercury than the fish consumed in Seychelles. Others have suggested the difference in neurodevelopmental testing may account for these differences [96, 122, 125].

The EPA, ATSDR, FDA and WHO have each developed recommendations for limits of exposure to methylmercury in the diet ranging from 0.1 to 0.47 μg/kg body weight per day [115].

Lead poisoning

Lead is a gray-silver heavy metal with a variety of industrial uses. As it has no known physiological role, any lead present in the human body can be viewed as contamination. Lead has been utilized by humans because of its properties of malleability and resistance to corrosion. From the mining of lead by the ancient Egyptians, Phoenicians, Greeks, and Romans to the use of lead machinery and lead-containing products during the Industrial Revolution and the widespread use of leaded gasoline and lead-based paint in the United States in the 20th century, the human use of lead has led to unfortunate consequences. It is speculated that some of the leaders of ancient Rome suffered neurotoxicity and sterility as a result of lead poisoning [126]. In the 1700s in England an outbreak of lead toxicity occurred due to lead contaminated cider; the victims of this outbreak suffered from severe abdominal pain and were said to have "Devonshire Colic" [127]. In the United States, Benjamin Franklin was aware of the effects of lead poisoning and described both lead-inflicted abdominal colic and peripheral neuropathy in 1763 [128]. Despite recognition of lead toxicity in the United States, lead-based paints were not banned until 1978 and leaded gasoline not until the 1990s [129]. The elimination of lead along with initiatives focused on limiting lead exposure, screening appropriate populations for lead exposure, and intervening when elevated blood lead levels (BLLs) are detected, has resulted in a decrease in the number of U.S. lead toxicity cases [130]. There continues to be at-risk populations in the U.S. including patients age 1–5 years and older than 60 years, minorities, lower socioeconomic populations, and recent immigrants [130]. This, along with continued environmental lead contamination, mandates clinicians to continue to be aware of the presentation, care, and prevention of lead toxicity.

Toxicology

Pediatric exposure to lead is often a result of oral ingestion of lead-containing material, including lead-based paints and contaminated soil [129, 131]. Children, particularly from the ages of 18–36 months, are more susceptible than adults to exposure to lead because of their increased hand-to-mouth activity. Children are also more susceptible to toxicity from lead secondary to their increased GI absorption of lead, active growth of their organ systems, immature blood-brain barrier, and propensity for iron deficiency – which increases GI lead absorption [132]. Children tend to have higher BLLs in the summer months due to increased exposure to lead-contaminated soil and dust [131]. Pediatric lead exposure has been reported with ingestion of larger lead-containing objects such as necklace charms [133], window curtain weights, bullets [134], and fishing weights (Fig. 3). Lead exposure can also occur by tap water contamination in residences that still have lead plumbing.

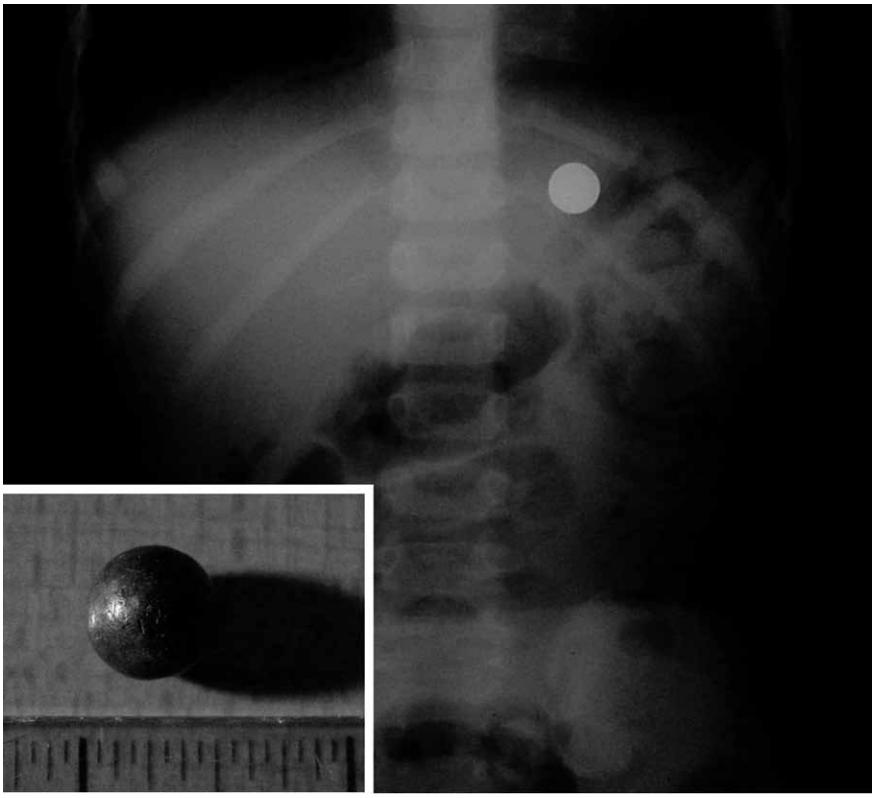

Figure 3. A 3-year-old swallowed a lead musket ball (insert). Two days later an x-ray revealed the ball in the stomach. The lead ball was removed by endoscopy without complication. A venous blood lead level, approximately 48-hour post ingestion, was at 89 μg/dL. The child underwent chelation therapy with succimer and a repeat lead level 1 week after chelation was 5 μg/dL. The child never developed symptoms and no other sources of lead were found in his environment (courtesy of C. Holstege, MD, Charlottesville, VA).

Lead exposure in adults usually occurs *via* the respiratory route through many occupations: battery plant worker, metal welder, painter, construction worker, lead miner, firing range worker, glass blower, and ship builder. Another source of lead poisoning in adults is ingestion of "moonshine" alcohols that have been distilled in lead-containing pipes [135, 136]. Exposure to leaded gasoline can increase organic lead exposure.

After absorption, lead can have detrimental effects to many organ systems including the nervous, hematological, renal, cardiovascular, GI, and endocrine systems. Lead can cause a decrease in the integrity of the blood-brain barrier by disrupting the intracellular junction of capillary endothelium. This results in increased capillary leak into the CNS and a resultant increase in intracranial fluid. Lead can also disrupt several neurotransmitter systems in the CNS by increasing spontaneous release of dopamine, acetylcholine, and γ-aminobu-

tyric acid (GABA), by blocking *N*-methyl D-aspartate (NMDA) glutamate receptors and increasing levels of protein kinase C. A process termed "pruning" in which necessary neural pathways are protected and unnecessary neural pathways are destroyed, peaks when children are around 2 years of age. By interfering with the neurotransmitters of the CNS, lead causes ineffective "pruning" in which necessary neural pathways are destroyed and unnecessary neural pathways are enhanced [132, 137].

Microcytic anemia is a classic finding in lead toxicity. Lead inhibits several heme synthesis enzymes: aminolevulinic acid (ALA) synthetase, δ-ALA dehydratase, coproporphyrinogen decarboxylase, and ferrochelatase, leading to elevated erythrocyte protoporphyrin levels [138, 139]. In addition to decrease heme synthesis, lead weakens erythrocyte membranes shortening the erythrocyte life span. A clinical finding in, but not unique to, plumbism is basophilic stippling [140]. Basophilic stippling is a result of the inhibition of pyrimidine-5-nucleotidase. In children, the anemia caused by lead is often complicated by iron deficiency and other nutritional deficiencies that decrease effective hemoglobin synthesis [141].

Lead-protein complexes deposit in the proximal tubular cells of the kidney and are accompanied by mitochondrial swelling in this same region. Lead interferes with mitochondrial respiration and phosphorylation in the kidney, leading to glycosuria, aminoaciduria, and phosphaturia. Chronic high-dose lead exposure has been shown in animal models to cause renal failure through tubular atrophy, interstitial fibrosis, and glomerular sclerosis. These findings can also be seen in other forms of kidney failure [142].

The skeletal system serves as the main reservoir for lead. With chronic lead exposure lead stores in bone can have a half-life of 5–19 years [143]. Soft tissues may be subjected to increased lead exposure during times of accelerated bone turnover, such as during childhood growth, after a long bone fracture, or during pregnancy [144]. In children lead causes increased calcification of cartilage in the bone metaphysis resulting in increased metaphysis density [145].

Hypertension has been associated with chronic lead exposure. Lead likely affects vascular smooth muscle cells by causing a decrease in Na^+/K^+-ATPase activity with a subsequent increase in Na^+/Ca^{2+} pump activity, and increased calcium-mediated contractility. Lead may also alter vascular smooth muscle activity by increasing protein kinase C [146].

Clinical presentation

The clinical aspects of lead toxicity are widely described; however, there is no clear "toxidrome" and it is difficult to define expected symptoms at certain BLLs. The reason for this difficulty likely involves the many variables affecting the clinical effects of lead exposure: age at time of exposure, length of exposure time, genetic predisposition to effects, environmental factors, nutritional status, and underlying medical problems of the patient. Lead toxicity can present with

symptoms in a variety of different organs. There are both similarities and differences in the way that children and adults are affected by lead toxicity.

In children, the neurological consequences of plumbism are the greatest concern. Serious neurological problems from lead toxicity are most commonly described in children between the ages of 18–36 months. Symptoms at BLLs of 50–100 μg/dL may be obvious or subtle and can include intermittent irritability, hyperactivity, and developmental delay in one particular skill [132, 137]. Higher levels or more chronic exposure can result in ataxia, lethargy, seizures, and coma. There is controversy over the cognitive effects of lower BLLs (BLLs less than 10 μg/dL). Some epidemiological studies have reported an inverse correlation between elevated BLLs in children and IQ [147], but not all published data are in agreement with this association [148]. Epidemiological studies that examine this topic have the difficult task of trying to control for all possible confounding variables [149].

Adults can also experience neurological symptoms with plumbism. Signs of encephalopathy including seizure, coma, and papilledema usually occur at BLLs over 150 μg/dL. At BLLs above 80 μg/dL memory problems, insomnia, and personality changes have been reported [150]. More subtle signs are seen in adults with BLLs of 40–70 μg/dL and can be similar to those symptoms seen with depression [151, 152].

Other clinical manifestations of lead poisoning in children and adults include a normocytic or microcytic anemia, abdominal pain, constipation, hepatotoxicity, and pancreatitis. Peripheral neuropathy, with resultant foot and wrist drop, is well described in adults and is occasionally seen in children – particularly those with underlying sickle cell disease [153]. Nephrotoxicity has been reported in all age groups with lead toxicity; a Fanconi's syndrome with aminoaciduria, glycosuria, and phosphaturia has been more commonly described in the adult population [142]. Saturnine gout is a phenomenon seen in adult patients and is due to impaired uric acid clearance by the kidneys. There is concern that chronic lead exposure can raise blood pressure; however, two recent meta-analyses found a less than robust association [154, 155]. Sperm abnormalities have also been associated with BLL of ≥40 μg/dL in work-exposed men [156]. Lead can cross the placenta and has been associated with spontaneous abortion, prematurity, and developmental delay. Lead is also excreted in breast milk [157].

Lead exposure does not have any clear association with carcinogenicity in humans. Inorganic lead is classified as a probable carcinogen (group 2A) and organic lead is not classifiable in regards to carcinogenicity (group 3) by the IARC [158]. These data coupled with clinical studies suggest that lead is, at worst, a weak carcinogen [159].

Organic lead, such as tetraethyl lead, at high doses can cause predominately neurological symptoms similar to a generalized encephalopathy including delirium, ataxia, and seizures. Neurological symptoms from organic lead are reported at lower levels than what would be typically expected with inorganic lead [160].

Diagnosis

The best initial test for evaluating a patient with suspected lead poisoning is a whole BLL obtained by venipuncture. A BLL should be sent in a lead-free tube and is usually measured by atomic absorption spectrophotometry. It is important to recognize that whole BLLs can be used to guide management but may not reflect lead in other organ systems, such as the CNS or bone. Capillary lead levels can be used for screening purposes, but may be falsely elevated if there is lead on the skin where the sample is drawn from [161]. A disadvantage of BLLs is that most laboratories are not equipped to report same-day results. BLLs that are done during chelation therapy can be elevated from lead that is pulled out of soft tissues and into the bloodstream. Zinc or erythrocyte protoporphyrin may also be elevated with lead toxicity but are not a sensitive test and can be elevated in other conditions that interfere with heme synthesis such as iron deficiency, sickle cell anemia, and vanadium toxicity. The protoporphyrin tests are more likely to be elevated with chronic lead toxicity than with acute lead toxicity [162].

Additional laboratory tests that may be useful in the evaluation of a patient with suspected plumbism should be guided by the history and physical exam, and may include a complete blood count, a comprehensive metabolic panel, and a urinalysis. These tests can also provide a baseline for management of possible side effects if chelation therapy is initiated.

Radiographic imaging may help to support the diagnosis of lead poisoning and can also help to illicit the etiology of exposure in some cases. In a patient with the possible ingestion of a lead-containing object, an abdominal x-ray should be obtained. Any patient with suspected plumbism and a history of bullet wound, should have an x-ray of the area of bullet impact to visualize any retained bullet fragments [134] (Fig. 3). Radiographs of long bones of children with BLLs of 70 μg/dL or greater may show increased densities at the metaphyses, also referred to as “lead lines”. Findings indistinguishable from “lead lines” are also seen with bismuth, phosphate, and fluoride toxicity [145]. Chronic lead exposure may be quantified using bone x-ray fluorescence technology. This is a test that has been used in research studies and is not typically utilized in the clinical setting [163]. A head computed tomography scan should be obtained on any patient with suspected plumbism and acute CNS symptoms to evaluate for evidence of cerebral edema.

Treatment

The management of children with elevated BLLs should follow the guidelines set forth by the Centers of Disease Control and Prevention [164]. Some state health departments have slight variations in these guidelines. It is important to recognize that the first step in management of a patient with elevated lead levels is prompt removal from the source. The local health department should be

contacted and should assist with identification of the source and containment of the lead source in a pediatric patient with a BLL greater than 20 μg/dL or with two separate BLLs within the 15–19 μg/dL range. A recent Cochrane review of 12 studies concluded that there was no clear benefit of educational initiatives and/or dust control measures, and there was insufficient evidence to comment on soil abatement in regards to lowering pediatric BLLs in a population [165]. Chelation therapy in asymptomatic children is usually not initiated unless a patient has a BLL of 45 μg/dL or greater; chelating patients with levels less than this does not show any benefit on cognitive outcomes [166]. Oral chelation is recommended for those patients who are asymptomatic and have BLLs of 45–69 μg/dL. Patients who have BLLs greater than 69 μg/dL or who are symptomatic should have parenteral chelation [150].

Screening of adults that have workplace lead exposure should be guided by Occupational Safety and Health Administration's recommendations: Asymptomatic adults with BLLs less than 70 μg/dL do not require chelation, oral chelation is recommended for mild symptoms or BLLs of 70–100 μg/dL, and parenteral chelation therapy is advised for symptoms of lead-induced encephalopathy and/or BLLs greater than 100 μg/dL [150].

The oral chelator that is approved by the FDA for lead poisoning in children over 1 year of age is DMSA. The pediatric dose of DMSA is 10 mg/kg per dose every 8 hours for 5 days followed by 10 mg/kg per dose every 12 hours for 14 days. Although DMSA is not officially recommended in adults, the dose that has been most widely used is 10–30 mg/kg per day for 5 days. Adverse reactions are not limited to, but include, neutropenia, hemolytic anemia, and elevation of aspartate and alanine aminotransferase [167]. Edetate calcium disodium (Calcium EDTA) is a parenteral chelator approved by the FDA for adult and pediatric plumbism. Edetate calcium disodium can be administered intravenously or intramuscularly. The recommended intravenous dose in adults for severe lead poisoning is 1–1.5 g/m^2 per day infused over 8–12 hours for a total of 5 days; after 2 days a repeat 5-day course can be administered if indicated. The recommended pediatric intravenous dose for severe lead poisoning is 1–1.5 g/m^2 per day divided into equal doses infused every 8 or 12 hours, an additional 5-day course can be given after 2 days if indicated. The following serious side effects have been reported with edetate calcium disodium: fever, hypersensitivity immune reaction, hypotension, nephrotoxicity, and thrombophlebitis. Care should be taken when using edetate calcium disodium in a patient with renal insufficiency, and the dose may need to be modified or an alternative chelator may need to be used. Edetate calcium disodium may increase intracranial pressure and, in patients with cerebral edema, the manufacturer recommends using the intramuscular route or alternatively using the intravenous route with a slow infusion rate. It has been reported that edetate calcium disodium may exacerbate symptoms when given as the sole chelator to a patient with a high BLL, and that dimercaprol should be given in conjunction with edetate calcium disodium in the patient who has symptomatic lead poisoning or a BLL over 70 μg/dL. If the patient can take oral medications, DMSA

can be used instead of dimercaprol [168]. Edetate disodium without calcium should not be used because of the risk of hypocalcemia [169, 170]. Another FDA approved chelator for lead toxicity is dimercaprol. It is administered by deep intramuscular (i.m.) injection. In severe plumbism dimercaprol is administered at a dose of 4 mg/kg i.m. every 4 hours for 2–7 days in both pediatric and adult patients. In mild lead poisoning the recommended dose is 4 mg/kg i.m. for the first dose followed by 3 mg/kg i.m. every 4 hours for 2–7 days. Adverse reactions with dimercaprol include fever, hypertension, tachycardia, and injection site abscesses. Dimercaprol is administered in peanut oil and should usually be avoided in patients with peanut allergies [171]. Secondary to the number of side effects associated with dimercaprol, its use should be limited to symptomatic patients who cannot take oral DMSA. D-Penicillamine is not approved by the FDA for lead poisoning and should only be used in cases of serious lead poisoning in which other chelators have had unacceptable side effects. D-Penicillamine can cause the life-threatening side effect of agranulocytosis and can also cause severe dermatological and renal conditions [172].

Bowel irrigation with a polyethylene glycol-electrolyte solution should be considered if a patient has lead-containing objects in the GI tract that could easily transit through the GI tract. A gastroenterologist or surgeon may need to be contacted for removal of a larger lead-containing object out of the GI tract if it is likely that the object will not move adequately with GI peristalsis [173]. Likewise patients with evidence of lead poisoning may require surgical removal of lead containing bullet fragments lodged in soft tissues and/or joint spaces [134].

Thallium poisoning

In the late 19th century the spectro-chemical analysis of deposits from a sulfuric acid chamber resulted in the discovery of thallium [174]. Although useful in the manufacture of optic lenses, semiconductors and in very low concentrations as a radiocontrast agent, thallium is best known for its toxicity.

Toxicology

Thallium salts are tasteless, odorless, water soluble and rapidly absorbed and distributed throughout the body. By interfering with potassium and sulfhydryl-containing enzymes, thallium impairs energy production resulting, in severe cases, in cell death [175–178]. Although high concentrations of thallium are toxic to all organs, the peripheral nervous system and hair are particularly sensitive. Thallium does not undergo significant renal excretion, rather it undergoes entero-hepatic circulation with the primary means of elimination being fecal [179]. This makes treatment with the standard heavy metal chelators (DMSA, dimercaprol, edetate calcium disodium) less effective.

Clinical presentation

One of the earliest findings in thallium poisoning – typically within 2–3 days of exposure – is the development of a rapidly progressive painful peripheral neuropathy [180–182]. Symptoms begin in the feet and legs and may progress over time to involve the hands. The pain associated with thallium is described as "pins and needles" and may be severe enough to make the weight of a bed sheet intolerable [181–184]. With large exposures, motor nerves can also be affected including those innervating respiratory muscles [172, 185–187]. In these cases, the clinical picture of a rapidly progressive neuropathy can be misdiagnosed as Guillain-Barré [184]. Along with peripheral neuropathies, cranial neuropathies have also been reported [184, 186–191].

Perhaps the best-known complication of thallium poisoning is alopecia (Fig. 4). Beginning 5–14 days after exposure, victims begin painlessly losing

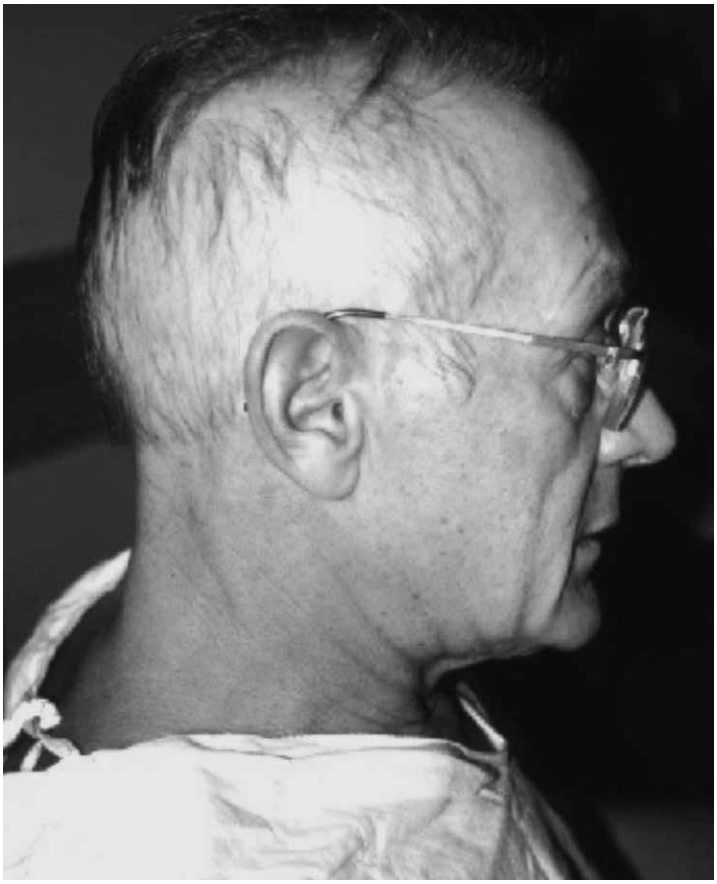

Figure 4. Alopecia in a case of thallium poisoning (courtesy of D. Rusyniak, MD, Indianapolis, IN).

their hair in clumps [182, 185, 187]. By 2–3 weeks patients may have developed total body alopecia – including axillary hair, pubic hair, and the lateral eyebrows [192–194]. The medial part of the eyebrow is typically spared as these hairs are commonly in a resting non-growth phase [194, 195]. While the exact cause of alopecia is not known, thallium's interruption of keratin synthesis and its interruption of hair matrix metabolism are likely responsible [196, 197]. While the most recognizable feature of thallium poisoning is alopecia, in mild cases peripheral neuropathies can occur without the development of hair loss [182].

Along with the peripheral nerves and hair, thallium can affect most major organ systems. Included amongst these are the CNS with hallucinations, altered mental status, insomnia, psychosis, ataxia and coma [181, 185–187, 189, 190, 198]; the GI tract with abdominal pain, vomiting, loose stools, and constipation or obstipation [182, 183, 186, 187, 194]; muscular systems with myalgias and pleuritic chest pain [182, 183, 199]; and the cardiovascular systems with ECG changes, arrhythmias, hypo- and hypertension [183, 200].

Diagnosis

Making the diagnosis of thallium poisoning early enough to institute effective therapy requires the early recognition of symptoms combined with neurological and clinical testing and analytical confirmation. This can be difficult as thallium poisoning is uncommon and its symptoms may be attributed to other etiologies [182]. Further hampering the early diagnosis, alopecia – the most recognizable feature of thallium poisoning [201] (Fig. 4) – may not be evident for up to 5–14 days after the exposure [197]. Despite these difficulties, two readily available tests may aid in making the early diagnosis of thallium poisoning: nerve conduction studies (NCS) and microscopic hair analysis.

NCS are useful in diagnosing and monitoring the recovery of patients with thallium poisonings [182]. They typical reveal a sensorimotor axonopathy with the severity of neuropathy correlating with the severity of other symptoms and findings. In cases of severe poisoning, a nerve biopsy may reveal Wallerian degeneration with axonal destruction and secondary myelin loss, although these findings are not specific to thallium [189, 202, 203].

Once it has been established that patients have a neuropathy suspicious for thallium, simply visually inspecting pulled hair under a low-powered light microscope may help make the diagnosis. When viewed under low power with a light microscope, the hair roots of thallium-poisoned patients appear darkened [182, 194]. This finding has been reported as early as 4 days after poisoning [194]. The darkened roots are seen in the highest percentage in pulled hair from the scalp (95%), followed by hairs of the chest and legs (50 to 60%), and less commonly from eyebrows and eyelids (30%) [194]. In cases of repeated poisonings, several bands may likewise be seen [194]. The blackened roots are not the accumulation of a pigment or the metal itself but rather represent

an optical phenomenon. As the interruption of cellular processes disorganizes the hair root matrix, the hair root accumulates gaseous inclusions which diffract light and cause the appearance of a black stain [192, 197]. Treatment with acid or mechanical pressure will cause the accumulated gas to escape the hair and subsequently the hair root darkening disappears [204].

The definitive diagnosis of thallium poisoning requires the identification of elevated concentrations of thallium in urine or hair. Like many other metals, a 24-hour urine is considered the gold standard in thallium poisoning. In most persons, there should be no detectable levels of thallium, but levels up to a level 20 μg/specimen may be considered normal depending on occupational or environmental exposures. Hair analysis is not thought to be as reliable as urine and a negative hair test should not exclude the possibility of thallium poisoning. Hair levels less than 15 ng thallium/gram hair are considered normal [178]. Along with hair and urine, postmortem tissues including paraffin tissue blocks and even cremated ashes can be used to confirm elevations of thallium in suspected criminal poisonings [203, 205].

Treatment

The primary objective in treating thallium-poisoned patients is to increase thallium's elimination preventing further toxicity. The best-studied and most effective antidote is a complex of potassium hexacyanoferrate known as Prussian blue. Recently, the FDA approved Prussian blue for the treatment of cesium or thallium poisoning under the brand name Radiogardase®, the recommended dose is 3 g orally three times a day. Poorly absorbed, Prussian blue exchanges potassium for thallium in the gut increasing the fecal excretion of a thallium-Prussian blue complex. Numerous animal studies have shown that Prussian blue increases fecal elimination, decreases mortality, and decreases brain thallium concentrations [206–213]. Although clinical trials are not possible for thallium poisoning, human case reports support the safety and efficacy of Prussian blue [180, 210, 214]. Based on its affinity for sulfhydryl groups, several sulfur chelators have been studied in animal models of thallium poisoning. None have shown significant improvement [213, 215–217], and some may actually increase toxicity [208]. As Prussian blue may not be stocked in some hospitals, activated charcoal can be used until Prussian blue is available. *In vitro* studies demonstrate that activated charcoal effectively adsorbs thallium [170, 218], although its benefit in animal studies is contradictory [207, 215] and benefits in human cases are anecdotal [182, 185].

Summary

Acute and chronic toxicity from exposure to arsenic, mercury, lead and thallium still occur and pose significant morbidity and mortality if they are not rec-

ognized and treated. With each of these, the diagnosis is based on combining clinical suspicion with analytical testing. If a patient is suspected of poisoning, they should be removed from the source and if symptoms are severe, treatment, including chelation, should begin prior to analytical confirmation.

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