e34 Heavy Metal Poisoning

Howard Hu

Metals pose a significant threat to health through occupational as well as environmental exposures. One indication of their importance relative to other potential hazards is their ranking by the U.S. Agency for Toxic Substances and Disease Registry, which lists all hazards present in toxic waste sites according to their prevalence and the severity of their toxicity. The first, second, third, and sixth hazards on the list are heavy metals: lead, mercury, arsenic, and cadmium, respectively. Specific information pertaining to each of these metals, including sources and metabolism, toxic effects produced, diagnosis, and the appropriate treatment for poisoning, is summarized in **Table e34-1.**

Metals are inhaled primarily as dusts and fumes (the latter defined as tiny particles generated by combustion). Metal poisoning can also result from exposure to vapors (e.g., mercury vapor in creating dental amalgams). When metals are ingested in contaminated food or drink or by hand-to-mouth activity (implicated especially in children), their gastrointestinal absorption varies greatly with the specific chemical form of the metal and the nutritional status of the host. Once a metal is absorbed, blood is the main medium for its transport, with the precise kinetics dependent on diffusibility, protein binding, rates of biotransformation, availability of intracellular ligands, and other factors. Some organs (e.g., bone, liver, and kidney) sequester metals in relatively high concentrations for years. Most metals are excreted through renal clearance and gastrointestinal excretion; some proportion is also excreted through salivation, perspiration, exhalation, lactation, skin exfoliation, and loss of hair and nails. The intrinsic stability of metals facilitates tracing and measurement in biologic material, although the clinical significance of the levels measured is not always clear.

Some metals, such as copper and selenium, are essential to normal metabolic function as trace elements (Chap. 71) but are toxic at high levels of exposure. Others, such as lead and mercury, are xenobiotic and theoretically are capable of exerting toxic effects at any level of exposure. Indeed, much research is currently focused on the contribution of low-level xenobiotic metal exposure to chronic diseases and to subtle changes in health that may have significant public health consequences. Genetic factors also may modify the impact of metals on health and thereby account, at least in part, for individual susceptibility to metal effects.

The most important component of treatment for metal toxicity is the termination of exposure. *Chelating agents* are used to bind metals into stable cyclic compounds with relatively low toxicity and to enhance their excretion. The principal chelating agents are dimercaprol (British Anti-Lewisite, BAL), edetate (EDTA), succimer (DMSA, dimercaptosuccinic acid), and penicillamine; their specific use depends on the metal involved and the clinical circumstances. Activated charcoal does not bind metals and thus is of limited usefulness in cases of acute metal ingestion.

In addition to the information provided in Table e34-1, several other aspects of exposure, toxicity, or management are worthy of discussion with respect to the four most hazardous toxicants (arsenic, cadmium, lead, and mercury).

Arsenic exposure from natural contamination of shallow tube wells inserted for drinking water is a huge environmental problem for millions of residents in parts of Bangladesh and Western India. Contamination was formerly considered only a problem with deep wells; however, the geology of this region allows most residents only a few alternatives for potable drinking water.

Serious *cadmium* poisoning from the contamination of food and water by mining effluents in Japan contributed to the 1946 outbreak of "itai-itai" ("ouch-ouch") disease, so named because of cadmium-induced bone toxicity that led to painful bone fractures. Modest exposures from environmental contamination near a smelter in Belgium were recently associated with a lower bone density, a higher incidence of fractures, and a faster decline in height in both men and women, ef-

TABLE e34-1 HEAVY METALS

Main Sources	Metabolism	Toxicity	Diagnosis	Treatment
		Arsenic		
Smelting and microelectronics industries; wood preservatives, pesticides, herbicides, fungicides; contaminant of deep-water wells; folk remedies; and coal; incineration of these products	Organic arsenic (arsenobentaine, arsenocholine) is ingested in seafood and fish, but is nontoxic; inorganic arsenic is readily absorbed (lung and GI); sequesters in liver, spleen, kidneys, lungs, and GI tract; residues persist in skin, hair, and nails; biomethylation results in detoxification, but this process saturates.	Acute arsenic poisoning results in necrosis of intestinal mucosa with hemorrhagic gastroenteritis, fluid loss, hypotension, delayed cardiomyopathy, acute tubular necrosis, and hemolysis. Chronic arsenic exposure causes diabetes, vasospasm, peripheral vascular insufficiency and gangrene, peripheral neuropathy, and cancer of skin, lung, liver (angiosarcoma), bladder, kidney. Lethal dose: 120–200 mg (adults); 2 mg/kg (children).	Nausea, vomiting, diarrhea, abdominal pain, delirium, coma, seizures; garlicky odor on breath; hyperkeratosis, hyperpigmentation, exfoliative dermatitis, and Mees' lines (transverse white striae of the fingernails); sensory and motor polyneuritis, distal weakness. Radiopaque sign on abdominal x-ray; ECG–QRS broadening, QT prolongation, ST depression, T-wave flattening; 24-h urinary arsenic >67 μmol/d or 50 μg/d; (no seafood × 24 h); if recent exposure, serum arsenic >0.9 μmol/L (7 μg/dL). High arsenic in hair or nails.	If acute ingestion, ipecac to induce vomiting, gastric lavage, activated charcoal with a cathartic. Supportive care in ICU. Dimercaprol 3–5 mg/kg IM q4h × 2 days; q6h × 1 day, then q12h × 10 days; alternative: oral succimer.
		Cadmium		
Metal-plating, pigment, smelting, battery, and plastics industries; tobacco; incineration of these products; ingestion of food that concentrates cadmium (grains, cereals).	Absorbed through ingestion or inhalation; bound by metallothionein, filtered at the glomerulus, but reabsorbed by proximal tubules (thus, poorly excreted). Biologic $^1/_2$ life: 10–30 y. Binds cellular sulfhydryl groups, competes with zinc, calcium for binding sites. Concentrates in liver and kidneys.	Acute cadmium inhalation causes pneumonitis after 4–24 h; acute ingestion causes gastroenteritis. Chronic exposure causes anosmia, yellowing of teeth, emphysema, minor LFT elevations, microcytic hypochromic anemia unresponsive to iron therapy, proteinuria, increased urinary β_2- microglobulin, calciuria, leading to chronic renal failure, osteomalacia, and fractures.	With inhalation: pleuritic chest pain, dyspnea, cyanosis, fever, tachycardia, nausea, noncardiogenic pulmonary edema. With ingestion: nausea, vomiting, cramps, diarrhea. Bone pain, fractures with osteomalacia. If recent exposure, serum cadmium >500 nmol/L (5 μg/dL). Urinary cadmium >100 nmol/L (10 μg/g creatinine) and/or urinary β_2-microglobulin >750 μg/g creatinine (but urinary β_2-microglobulin also increased in other renal diseases such as pyelonephritis).	There is no effective treatment for cadmium poisoning (chelation not useful; dimercaprol can exacerbate nephrotoxicity). Avoidance of further exposure, supportive therapy, vitamin D for osteomalacia.

(continued)

TABLE e34-1 HEAVY METALS (CONTINUED)

Main Sources	Metabolism	Toxicity	Diagnosis	Treatment
Lead				
Manufacturing of auto batteries, lead crystal, ceramics, fishing weights, etc.; demolition or sanding of lead-painted houses, bridges; stained glass making, plumbing, soldering; environmental exposure to paint chips, house dust (in home built <1975), firing ranges (from bullet dust), food or water from improperly glazed ceramics, lead pipes; contaminated herbal remedies, candies; exposure to the combustion of leaded fuels.	Absorbed through ingestion or inhalation; organic lead (e.g., tetraethyl lead) absorbed dermally. In blood, 95–99% sequestered in RBCs—thus, must measure lead in whole blood (not serum). Distributed widely in soft tissue, with $^1/_2$ life ~30 days; 15% of dose sequestered in bone with $^1/_2$ life of >20 years. Excreted mostly in urine, but also appears in other fluids including breast milk. Interferes with mitochondrial oxidative phosphorylation, ATPases, calcium-dependent messengers; enhances oxidation and cell apoptosis.	Acute exposure with blood lead levels (BPb) of > 60–80 μg/dL can cause impaired neurotransmission and neuronal cell death (with central and peripheral nervous system effects); impaired hematopoiesis and renal tubular dysfunction. At higher levels of exposure (e.g., BPb > 80–120 μg/dL), acute encephalopathy with convulsions, coma, and death may occur. Subclinical exposures in children (BPb 25–60 μg/dL) are associated with anemia; mental retardation; and deficits in language, motor function, balance, hearing, behavior, and school performance. Impairment of IQ appears to occur at even lower levels of exposure with no measurable threshold above the limit of detection in most assays of 1 μg/dL. In adults, chronic subclinical exposures (BPb > 40 μg/dL) are associated with an increased risk of anemia, demyelinating peripheral neuropathy (mainly motor), impairments of reaction time, hypertension, ECG conduction delays, interstitial nephritis and chronic renal failure, diminished sperm counts, spontaneous abortions.	Abdominal pain, irritability, lethargy, anorexia, anemia, Fanconi's syndrome, pyuria, azotemia in children with blood lead level (BPb) >80 μg/dL; may also see epiphyseal plate "lead lines" on long bone x-rays. Convulsions, coma at BPb > 120 μg/dL. Noticeable neurodevelopmental delays at BPb of 40–80 μg/dL; may also see symptoms associated with higher BPb levels. In the U.S., screening of all children when they begin to crawl (~6 months) is recommended by the CDC; source identification and intervention is begun if the BPb > 10 μg/dL. In adults, acute exposure causes similar symptoms as in children as well as headaches, arthralgias, myalgias, depression, impaired short-term memory, loss of libido. Physical exam may reveal a "lead line" at the gingiva-tooth border, pallor, wrist drop, and cognitive dysfunction (e.g., declines on the mini-mental status exam); lab tests may reveal a normocytic, normochromic anemia, basophilic stippling, an elevated blood protoporphyrin level (free erythrocyte or zinc), and motor delays on nerve conduction. In the U.S., OSHA requires regular testing of lead-exposed workers with removal if BPb > 40 μg/dL.	Identification and correction of exposure sources is critical. In some U.S. states, screening and reporting to local health boards of children with BPb > 10 μg/dL and workers with BPb > 40 μg/dL is required. In the highly exposed individual with symptoms, chelation is recommended with oral DMSA (succimer); if acutely toxic, hospitalization and IV or IM chelation with edentate calcium disodium (CaEDTA) may be required, with the addition of dimercaprol to prevent worsening of encephalopathy. It is uncertain whether children with asymptomatic lead exposure (e.g., BPb 20–40 μg/dL) benefit from chelation. Correction of dietary deficiencies in iron, calcium, magnesium, and zinc will lower lead absorption and may also improve toxicity. Vitamin C is a weak but natural chelating agent.
Mercury				
Metallic, mercurous, and mercuric mercury (Hg^0, Hg^+, Hg^{2+}) exposures occur in some chemical, metal-processing, electrical-equipment, automotive industries; they are also in thermometers, dental amalgams, batteries. Mercury is dispersed by waste incineration. Environmental bacteria convert inorganic to organic mercury, which then bioconcentrates up the aquatic food chain to contaminate tuna, swordfish, and other pelagic fish.	Elemental mercury (Hg^0) is not well absorbed; however, it will volatilize into highly absorbable vapor. Inorganic mercury is absorbed through the gut and skin. Organic mercury is well absorbed through inhalation and ingestion. Elemental and organic mercury cross the blood-brain barrier and placenta. Mercury is excreted in urine and feces and has a $^1/_2$ life in blood of ~60 days; however, deposits will remain in the kidney and brain for years. Exposure to mercury stimulates the kidney to produce metallothionein, which provides some detoxification benefit. Mercury binds sulfhydryl groups and interferes with a wide variety of critical enzymatic processes.	Acute inhalation of Hg^0 vapor causes pneumonitis and noncardiogenic pulmonary edema leading to death, CNS symptoms, and polyneuropathy. Chronic high exposure causes CNS toxicity (mercurial *erethism*; see diagnosis); lower exposures impair renal function, motor speed, memory, coordination. Acute ingestion of inorganic mercury causes gastroenteritis, the nephritic syndrome, or acute renal failure, hypertension, tachycardia, and cardiovascular collapse, with death at a dose of 10–42 mg/kg. Ingestion of organic mercury causes gastroenteritis, arrhythmias, and lesions in the basal ganglia, gray matter, and cerebellum at doses >1.7 mg/kg. High exposure during pregnancy causes derangement of fetal neuronal migration resulting in severe mental retardation. Mild exposures during pregnancy (from fish consumption) are associated with declines in neurobehavioral performance in offspring. Dimethylmercury, a compound only found in research labs, is "supertoxic"—a few drops of exposure via skin absorption or inhaled vapor can cause severe cerebellar degeneration and death.	Chronic exposure to metallic mercury vapor produces a characteristic intention tremor and mercurial *erethism*: excitability, memory loss, insomnia, timidity, and delirium ("mad as a hatter"). On neurobehavioral tests: decreased motor speed, visual scanning, verbal and visual memory, visuomotor coordination. Children exposed to mercury in any form may develop *acrodynia* ("pink disease"): flushing, itching, swelling, tachycardia, hypertension, excessive salivation or perspiration, irritability, weakness, morbilliform rashes, desquamation of palms and soles. Toxicity from elemental or inorganic mercury exposure begins when blood levels >180 nmol/L (3.6 μg/dL) and urine levels >0.7 μmol/L (15 μg/dL). Exposures that ended years ago may result in a >20-μg increase in 24-h urine after a 2-g dose of succimer. Organic mercury exposure is best measured by levels in blood (if recent) or hair (if chronic); CNS toxicity in children may derive from fetal exposures associated with maternal hair Hg > 30 nmol/g (6 μg/g).	Treat acute ingestion of mercuric salts with induced emesis or gastric lavage and polythiol resins (to bind mercury in the GI tract). Chelate with dimercaprol (up to 24 mg/kg per day IM in divided doses), DMSA (succimer), or penicillamine, with 5-day courses separated by several days of rest. If renal failure occurs, treat with peritoneal dialysis, hemodialysis, or extracorporeal regional complexing hemodialysis and succimer. Chronic inorganic mercury poisoning is best treated with *N*-acetyl penicillamine.

Note: GI, gastrointestinal; ECG, electrocardiogram; ICU, intensive care unit; LFT, liver function tests; RBC, red blood cell; IQ, intelligence quotient; CDC, Centers for Disease Control and Prevention; OSHA, Occupational Safety and Health Administration; CNS, central nervous system.

fects that may be related to cadmium's calciuric effect on the kidney. Such research is creating concern that cadmium exposure may be contributing significantly to morbidity and mortality from osteoporosis in the general population.

Advances in our understanding of *lead* toxicity have recently benefited by the development of K-x-ray fluorescence (KXRF) instruments for making safe in vivo measurements of lead levels in bone (which, in turn, reflect cumulative exposure over many years, as opposed to blood lead levels, which mostly reflect recent exposure). High bone lead levels measured by KXRF have been linked to increased risk of hypertension in both men and women from an urban population. In addition, high maternal bone lead levels were found to predict lower birth weight, head circumference, birth length, and neurodevelopmental performance in offspring by age 2.

The toxicity of low-level organic *mercury* exposure (as manifested by neurobehavioral performance) is of increasing concern based on studies of the offspring of mothers who ingested mercury-contaminated fish. However, current evidence has not supported the recent contention that ethyl mercury, used as a preservative in multiuse vaccines administered in early childhood, has played a significant role in causing neurodevelopmental problems such as autism.

A few additional metals deserve brief mention but are not covered in Table e34-1 because of the relative rarity of their being clinically encountered, or the uncertainty regarding their potential toxicities. *Aluminum* contributes to the encephalopathy in patients with severe renal disease who are undergoing dialysis (Chap. 347). High levels of aluminum are found in the neurofibrillary tangles in the cerebral cortex and hippocampus of patients with Alzheimer's disease, as well as in the drinking water and soil of areas with an unusually high incidence of Alzheimer's. The experimental and epidemiologic evidence for the aluminum–Alzheimer's disease link is so far relatively weak, however, and it cannot be concluded that aluminum is a causal agent or a contributing factor in neurodegenerative disease. Hexavalent chromium is corrosive and sensitizing. Workers in the chromate and chrome pigment production industries have consistently had a greater risk of lung cancer. The introduction of *cobalt* chloride as a fortifier in beer led to outbreaks of fatal cardiomyopathy among heavy consumers. Occupational exposure (e.g., of miners, dry-battery manufacturers, and arc welders) to manganese can cause a Parkinsonian syndrome within 1–2 years, including gait disorders; postural instability; a masked, expressionless face; tremor; and psychiatric symptoms. With the introduction of methylcyclopentadienyl manganese tricarbonyl (MMT) as a gasoline additive, there is concern for the toxic potential of environmental manganese exposure. *Nickel* exposure induces an allergic response, and inhalation of nickel compounds with low aqueous solubility (e.g., nickel subsulfide and nickel oxide) in occupational settings is associated with an increased risk of lung cancer. Overexposure to selenium may cause local irritation of the respiratory system and eyes, gastrointestinal irritation, liver inflammation, loss of hair, depigmentation, and peripheral nerve damage. Workers exposed to certain organic forms of *tin* (particularly trimethyl and triethyl derivatives) have developed psychomotor disturbances, including tremor, convulsions, hallucinations, and psychotic behavior.

Thallium, which is a component of some insecticides, metal alloys, and fireworks, is absorbed through the skin as well as by ingestion and inhalation. Severe poisoning follows a single ingested dose of >1 g or >8 mg/kg. Nausea and vomiting, abdominal pain, and hematemesis precede confusion, psychosis, organic brain syndrome, and coma. Thallium is radiopaque. Induced emesis or gastric lavage is indicated within 4–6 h of acute ingestion; Prussian blue prevents absorption and is given orally at 250 mg/kg in divided doses. Unlike other types of metal poisoning, thallium poisoning may be less severe when activated charcoal is used to interrupt its enterohepatic circulation. Other measures include forced diuresis, treatment with potassium chloride (which promotes renal excretion of thallium), and peritoneal dialysis.

FURTHER READINGS

BRODKIN E et al: Lead and mercury exposures: Interpretation and action. CMAJ 176(1):59, 2007

CENTENO JA et al: Pathology related to chronic arsenic exposure. Environ Health Perspect 110(Suppl 5):883, 2002

JÄRUP L: Hazards of heavy metal contamination. Br Med Bull 68:167, 2003

MISRA UK: Thallium poisoning: Emphasis on early diagnosis and response to haemodialysis. Postgrad Med J 79:103, 2003

PARK S, JOHNSON MA: Awareness of fish advisories and mercury exposure in women of childbearing age. Nutr Rev 64:250, 2006

SAPER RB et al: Heavy metal content of ayurvedic herbal medicine products. JAMA 292: 2868, 2004