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Poisoning, Drug Overdose, and Envenomation PART 14 Howard Hu

Heavy Metal Poisoning Toxic metals (hereafter referred to simply as “metals”) pose a significant threat to health through low-level as well as high level environmental and occupational exposures. One indication of their importance rela tive to other potential hazards is their ranking by the U.S. Agency for Toxic Substances and Disease Registry, which maintains an updated list of all hazards present in toxic waste sites according to their preva lence and the severity of their toxicity. The first, second, third, and seventh hazards on the list are heavy metals: arsenic, lead, mercury, and cadmium, respectively (http://www.atsdr.cdc.gov/spl/), positions they have held for many years. All four are also listed by the World Health Organization as among the 10 chemicals of highest concern in relation to health, globally. Specific information pertaining to each of these four metals, including sources and metabolism, toxic effects produced, diagnosis, and the appropriate treatment for poisoning, is summarized in Table 469-1. 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 biotrans formation, 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 clear ance 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. 344) 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 contribu tion of low-level xenobiotic metal exposure to subtle changes in health, chronic diseases, and/or increased risks of adverse events such as heart attacks, stroke, or cancer that may have significant public health consequences given the widespread nature of their exposures. Metals are well-known to be able to cause toxicity through the inhibition of enzymes,

damage to subcellular organelles and DNA, covalent modifi cation of proteins, formation of reactive oxygen species, and displace ment of essential metals in metal dependent proteins. Recent research has also elucidated how metals may affect DNA methylation and other changes to the epigenome, thereby resulting in altered gene expression as well as the dysregulated expression of microRNAs. Genetic factors, such as polymorphisms that encode for variant enzymes with altered properties in terms of metal binding, transport, and effects, may modify the impact of metals on health. Nutritional status, comorbidi ties, and other factors can also contribute to variations in individual susceptibility to metal effects. The most important component of treatment for metal toxicity is the recognition and 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]), ethylenediamine tet raacetic acid (EDTA), succimer (dimercaptosuccinic acid [DMSA]),

and penicillamine; their specific use depends on the metal involved and the clinical circumstances. For the most part, they are reserved for treating acute, symptomatic metal toxicity. 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 469-1, 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, even at moderate levels of exposure, has been clearly linked with increased risks for cancer of the skin, bladder, renal pelvis, ureter, kidney, liver, and lung. These risks appear to be modified by smoking, folate and selenium status, genetic traits (such as ability to methylate arsenic), and other factors. Based on the accumulation of evidence, the American Heart Association concluded that low-level exposures to arsenic, lead, and cadmium are risk factors for hypertension, sub clinical atherosclerosis, coronary artery stenosis, and calcification as well as ischemic heart disease and stroke, left ventricular hypertrophy and heart failure, and peripheral artery disease. Recent studies in community-based populations have also generated strong evidence that arsenic exposure is a risk factor for lung function impairment, acute respiratory tract infections, respiratory symptoms, and nonma lignant lung disease mortality. The association with cardiovascular disease may hold at levels of exposure in drinking water that are below the World Health Organization (WHO) provisional guideline value of 10 µg/L. Evidence has also continued to build indicating that low-level arsenic is a likely cause of neurodevelopmental delays in children and likely contributes to the development of type 2 diabetes and possibly nonalcoholic fatty liver disease and cirrhosis. 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 cadmiuminduced bone toxicity that led to painful bone fractures. Modest expo sures from environmental contamination have been associated in a growing number of studies with lower bone density, higher incidence of fractures, and faster decline in height in both men and women, effects that may be related to cadmium’s calciuric and other toxic effects on the kidney. Cadmium burdens have also been associated with an increased risk of long-term kidney graft failure, and there is evidence for synergy between the adverse impacts of cadmium and lead on kidney function. Environmental exposures have also been linked to lower lung function (even after adjusting for smoking cigarettes, which contain cadmium) and, as noted earlier, the American Heart Association considers cad mium as a risk factor for cardiovascular disease and mortality, stroke, and heart failure. Cadmium triggers pulmonary inflammation, and recent population-based studies of U.S. adults found that higher cad mium burdens are associated with higher mortality from influenza, pneumonia, and COVID-19. The International Agency for

Research on Cancer has classified cadmium as a known carcinogen, with evi dence indicating it contributes to elevated risks of prostate, lung, breast, and endometrial cancer. Overall, this growing body of research indi cates that cadmium exposure is contributing significantly to morbidity and mortality rates in the general population. Advances in our understanding of lead toxicity have recently ben efited by the development of 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. Higher levels of cumulative lead exposure in the general population are now wellestablished as a risk factor for chronic disease, even though blood lead levels have continued to decline in the general population over the past few decades following the removal of lead from gasoline, plumb ing, solder in food cans, and other consumer products, with mean levels in the U.S. population now hovering in the 1–2 µg/dL range. For example, higher bone lead levels measured by KXRF have been linked to increased risk of hypertension and accelerated declines in

TABLE 469-1 Heavy Metals MAIN SOURCES METABOLISM TOXICITY DIAGNOSIS TREATMENT Arsenic Smelting and microelectronics industries; wood preservatives, pesticides, herbicides, fungicides; contaminant of deepwater wells; folk remedies; and coal; incineration of these products. Organic arsenic (arsenobetaine, 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, ischemic heart disease, peripheral vascular insufficiency and gangrene, peripheral neuropathy, and cancer of skin, lung, liver (angiosarcoma), bladder, and kidney. Lethal dose: 120–200 mg (adults);

2 mg/kg (children). Cadmium Metal plating, pigment, smelting, battery, and plastics industries; tobacco; incineration of these products; ingestion of food that concentrates cadmium (grains, cereals, organ meats). Absorbed through ingestion or inhalation; bound by metallothionein, filtered at the glomerulus, but reabsorbed by proximal tubules (thus, poorly excreted). Biologic half-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 β2-microglobulin, calciuria, leading to chronic renal failure, osteomalacia, and fractures, ischemic heart disease and stroke. Cadmium exposure now known to cause lung, prostate, and kidney cancers. PART 14 Poisoning, Drug Overdose, and Envenomation 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 homes built <1975), firing ranges (from bullet dust), food or water from improperly glazed ceramics or lead-contaminated cookware; lead pipes and plumbing; contaminated spices, herbal remedies, candies; exposure to environmental pollution from the combustion of leaded fuels, recycling of automobile batteries and electronic waste. 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 half-life ~30 days; 15% of dose sequestered in bone with half-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 and hearing, accelerated declines in cognition, hypertension, ECG conduction delays, hypertension, higher risk of cardiovascular disease and death, interstitial nephritis and chronic renal failure, diminished sperm counts, and spontaneous abortions.

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. 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 β2-microglobulin 750 µg/g creatinine (but urinary β2-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. 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. Clinically-apparent neurodevelopmental delays can be seen at BPb of 40–80 µg/dL with subclinical

> declines in IQ expected at lower levels of BPb down to 1 µg/dL. Screening of all U.S. children when they begin to crawl (~6 months) is recommended by the CDC; source identification and intervention is begun if the BPb >3.5 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 examination may reveal a “lead line” at the gingiva-tooth border, pallor, wrist drop, and cognitive dysfunction (e.g., declines on the mini-mental state 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. U.S. OSHA requires regular testing of lead-exposed workers with removal if BPb >40 µg/dL.

Newer guidelines have been proposed recommending that BPb be maintained at <10 µg/dL, removal of workers if BPb >20 µg/dL, and monitoring of cumulative exposure parameters. Identification and correction of exposure sources are critical. In the United States, most states ask or require primary care physicians and/ or laboratories to report all BPbs to the appropriate health agency. In the highly exposed individual with symptoms, chelation is recommended with oral DMSA (succimer); if acutely toxic, hospitalization and IV or IM chelation with ethylenediaminetetraacetic acid calcium disodium (CaEDTA) may be required, with the addition of dimercaprol to prevent worsening of encephalopathy. A large multicenter randomized trial of chelation showed no improvement in measures of intelligence among children with asymptomatic lead exposure (e.g., BPb 20–40 µg/dL). It is possible but remains unclear whether chelation among adults with chronic lead exposure may improve cardiovascular outcomes. 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. Calcium supplements (1200 mg at bedtime) have been shown to lower blood lead levels in pregnant women. (Continued)

TABLE 469-1 Heavy Metals (Continued) MAIN SOURCES METABOLISM TOXICITY DIAGNOSIS TREATMENT Mercury Metallic, mercurous, and mercuric mercury (Hg, Hg+, Hg2+) exposures occur in some chemical, metalprocessing, 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) 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 half-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 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. Abbreviations: ATPase, adenosine triphosphatase; BPb, blood lead; CDC, Centers for Disease Control and Prevention; CNS, central nervous system; DMSA, dimercaptosuccinic acid; ECG, electrocardiogram; GI, gastrointestinal; ICU, intensive care unit; IQ, intelligence quotient; LFT, liver function tests; OSHA, Occupational Safety and Health Administration; RBC, red blood cell. cognition in both men and women living in urban communities. These relationships, in conjunction with other epidemiologic and toxicologic studies, persuaded multiple federal expert panels to conclude they were causal. Prospective studies have also demonstrated that higher bone lead levels, as well as blood lead levels as low as 1–7 µg/dL, are a major risk factor for resistant hypertension, coronary artery calcifications, and increased cardiovascular morbidity and mortality rates in both community-based and occupational-exposed populations. Lead expo sure at community levels has also been associated with increased risks of hearing loss, Parkinson’s disease, and amyotrophic lateral sclerosis. Occupational levels of lead exposures have been consistently linked with adverse indices of sperm health, such as reduction in semen volume, sperm concentration, total sperm count, sperm vitality, and total sperm motility. With respect to pregnancy-associated risks, high maternal bone lead levels were found to predict lower birth weight, head circumference, birth length, and neurodevelopmental perfor mance in offspring by age 2 years. Offspring have also been shown to have higher blood pressures at age 7–14 years, an age range at which higher blood pressures are known to predict an elevated risk of devel oping hypertension. In a randomized trial, calcium supplementation (1200 mg daily) was found to significantly reduce the mobilization of lead from maternal bone into blood during pregnancy. The toxicity of low-level organic mercury exposure (as manifested by neurobehavioral performance) is of increasing concern based on stud ies of the offspring of mothers who ingested mercury-contaminated fish. With respect to whether the consumption of fish by women during pregnancy is good or bad for offspring neurodevelopment, balancing the trade-offs of the beneficial effects of the omega-3-fatty acids (FAs) in fish versus the adverse effects of mercury contamination in fish has led to some confusion and inconsistency in public health

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. CHAPTER 469 Heavy Metal Poisoning recommendations. Overall, it would appear that it would be best for pregnant women to either limit fish consumption to those species known to be low in mercury contamination but high in omega-3-FAs (such as sardines or mackerel) or to avoid fish and obtain omega-3-FAs through supplements or other dietary sources. Well-conducted studies have convincingly debunked the contention that ethyl mercury, used as a preservative in multiuse vaccines administered in early child hood, has played a significant role in causing neurodevelopmental problems such as autism. With regard to adults, there is evidence that mercury exposure is associated with elevated markers of dyslipidemia and high-sensitivity C-reactive protein (a marker of chronic low-grade inflammation), but the direct evidence as to whether mercury exposure is associated with increased risk of hypertension and cardiovascular disease remains somewhat conflicting. There is also some evidence that mercury exposure in the general population is associated with the development of diabetes, perturbations in markers of autoimmunity, and depression. At this point, conclusions cannot be drawn and the clinical significance of these findings remains somewhat unclear. Heavy metals pose risks to health that are especially burdensome in selected parts of the world. For example, arsenic exposure from natural contamination of shallow tube wells inserted for drinking water is a major 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. Arsenic contamination of drinking water is also a major problem in China, Argentina, Chile, Mexico, and some regions of the United States (Maine, New Hampshire, Massachusetts). The global campaign to phase out leaded gasoline has successfully con cluded. However, significant population exposures to lead remain,

particularly in the United States with respect to older housing that contains lead paint or that receives drinking water through lead pipes, and evidence indicates that exposures are beginning to increase again in many low- and middle-income countries due to industrial pollution, the recycling of automobile batteries, electronic waste, mining, and a variety of contaminated consumer products. Populations living in the Arctic have been shown to have particularly high exposures to mercury due to long-range transport patterns that concentrate mercury in the polar regions, as well as the traditional dependence of Arctic peoples on the consumption of fish and other wildlife

that bioconcentrate methylmercury.

A few additional metals deserve brief mention but are not covered in Table 469-1 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. 422). 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 inci dence of Alzheimer's. The experimental and epidemiologic evidence for the aluminum–Alzheimer's disease link remains 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 consum ers, a condition that has also recently been reported in conjunction with the cobalt exposure associated with metal implants used in hip arthroplasty. Occupational exposure (e.g., of miners, dry-battery manufacturers, and arc welders) to manganese (Mn) can cause a parkinsonian syndrome within 1–2 years, including gait disorders; postural instability; a masked, expressionless face; tremor; and psy chiatric symptoms. In contrast to typical cases of Parkinson's disease, manganese-induced parkinsonism is nonresponsive to treatment with L-dopa. With the introduction of methylcyclopentadienyl manganese tricarbonyl (MMT) as a gasoline additive, there is concern for the toxic potential of environmental manganese exposure. Some epidemiologic studies have found an association between the prevalence of parkin sonian disorders and estimated manganese exposures emitted by local ferroalloy industries; others have found evidence suggesting that man ganese may interfere with early childhood neurodevelopment in ways similar to that of lead. Manganese toxicity is clearly associated with dopaminergic dysfunction, and its toxicity is likely influenced by age, gender, ethnicity, genetics, and preexisting medical conditions. Nickel exposure induces an allergic response, and inhalation of nickel com pounds 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 inflam mation, 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. PART 14 Poisoning, Drug Overdose, and Envenomation 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 acti vated 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. Chelation therapy remains the treatment of choice for most toxic metals in the setting of severe acute clinical poisoning. However, the use of chelation for treating chronic diseases remains controversial, in

part because of the lack of evidence from rigorous randomized clinical trials. One area for which there is moderate evidence is the use of che lation in patients with higher than average levels of accumulated lead burdens as a means of improving kidney function. The results from a series of randomized trials conducted in Taiwan suggest that among individuals with mildly elevated lead burdens (defined as between 150 and 600 µg of lead per 72-h urine upon an EDTA mobilization test [1 g EDTA]), weekly calcium disodium EDTA chelation treatments for between 2 and 27 months can improve renal function outcomes, both in individuals with and without type 2 diabetes. The Trial to Assess Chelation Therapy (TACT-1), a multicenter, double-blind, placebo-controlled, prospective randomized trial funded by the National Institutes of Health of 1708 patients aged ≥50 years who had experienced a myocardial infarction (MI), found that a protocol of repeated intravenous chelation with disodium EDTA, compared with placebo, modestly but significantly reduced the risk of adverse cardio vascular outcomes, many of which were revascularization procedures. The effect was particularly pronounced among those with concurrent diabetes. However, the trial did not include rigorous measures of expo sure to lead or other metals or any selection criteria based on metals exposure. By contrast, the recently released results of the TACT-2 trial, which reproduced the TACT-1 protocol with the addition of measures of metals, did not show benefit. However, the metals exposure levels among subjects was very low, likely reflecting the known decline in metals exposure over time in a study conducted more than 10 years after TACT-1, and it remains unclear whether chelation has a role in treating individuals with significant chronic metals exposure. ■ ■FURTHER READING Aalami AH et al: Carcinogenic effects of heavy metals by inducing dysregulation of microRNAs: A review. Mol Biol Rep 49:12227, 2022. Basu N et al: Our evolved understanding of the human health risks of mercury. Ambio 52:877, 2023. Chen H et al: Associations of blood lead, cadmium, and mercury with resistant hypertension among adults in NHANES, 1999-2018. Envi ron Health Prev Med 28:66, 2023. Elkin ER et al: Metals exposures and DNA methylation: Current evi dence and future directions. Curr Environ Health Rep 4:673, 2022. Giulioni C et al: The influence of lead exposure on male semen parameters: A systematic review and meta-analysis. Reprod Toxicol 118:108387, 2023. Lamas GA et al: Contaminant metals as cardiovascular risk factors: A scientific statement from the American Heart Association. J Am Heart Assoc 12:e029852, 2023. Lanphear BP et al: Low-level lead exposure and mortality in US adults: A population-based cohort study. Lancet Public Health 3:e177, 2018. Lucchini R, Tieu K: Manganese-induced parkinsonism: Evidence from epidemiological and experimental studies. Biomolecules 13:1190, 2023. Martínez-Castillo M et al: Arsenic exposure and non-carcinogenic health effects. Hum Exp Toxicol 40:S826, 2021. Parida L, Patel TN: Systemic impact of heavy metals and their role in cancer development: A review. Environ Monit Assess 195:766, 2023. Park SK et al: Environmental cadmium and mortality from influenza and pneumonia in U.S. adults. Environ Health Perspect 128:127004, 2020. Ravalli F et al: Chelation therapy in patients with cardiovascular dis ease: A systematic review. J Am Heart Assoc 11:e024648, 2022. Shvachiy L et al: Uncovering the molecular link between lead toxicity and Parkinson’s disease. Antioxid Redox Signal 39:321, 2023. Smereczański NM et al: Current levels of environmental exposure to cadmium in industrialized countries as a risk factor for kidney dam age in the general population: A comprehensive review of

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