Occupational and Community Exposures to Toxic Metals: Lead, Cadmium, Mercury and Arsenic

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Lead, cadmium, mercury and arsenic are widely dispersed in the environment. Adults are primarily exposed to these contaminants in the workplace. Children may be exposed to toxic metals from numerous sources, including contaminated air, water, soil and food.

The chronic toxic effects of lead include anemia, neuropathy, chronic renal disease and reproductive impairment. Lead is a carcinogen in three animal species. Cadmium causes emphysema, chronic renal disease, cancer of the prostate and possibly of the lung. Inorganic mercury causes gingivitis, stomatitis, neurologic impairment and nephrosis, while organic mercurials cause sensory neuropathy, ataxia, dysarthria and blindness. Arsenic causes dermatitis, skin cancer, sensory neuropathy, cirrhosis, angiosarcoma of the liver, lung cancer and possibly lymphatic cancer.

Toxic metals are ubiquitous in the modern industrialized environment.[1,2] Each year 1.3 million tons of lead,[3] 6,500 tons of cadmium,[4] 2,500 tons of mercury[5] and 24,000 tons of arsenic[6] are consumed in the United States. Also each year an estimated 100,000 tons of lead,[3] 5,500 tons of cadmium,[4] 2,000 tons of mercury[5] and 10,600 tons of arsenic[6] are released into air and water. Environmental concentrations of these metals have increased steadily since the industrial revolution, and in the past 40 years ambient levels of lead have risen especially rapidly due to the release into the air of several million tons of lead particulates from the combustion of leaded gasoline.[7] The concentrations of lead found today in urban residents of the United States are more than ten times greater than those of persons dwelling in the remote Himalayas[8] and orders of magnitude above those found in the skeletal remains of prehistoric man.[9]

Adults have their most serious exposures to toxic metals in the workplace. Not surprisingly, industrial workers are the subset of the adult population in the United States with the heaviest body burdens of toxic metals.[10] The major route of absorption of metals in the industrial workplace is by inhalation.[11]

Children are exposed to toxic metals from numerous sources. They inhale airborne metallic particulates and ingest metals dissolved in food and in drinking water.[3] In addition, because of their typically oral behavior, they are at risk of ingesting heavy metals from painted surfaces[12,13] and from contaminated dust and soil.[14] Further, children may be at risk of exposure to industrial metals—*in utero* if their mothers are employed in the metal trades,[15] through inhalation of contaminated air if they live near a smelting plant[16] or through exposure to parents who wear contaminated shoes and clothing home from a dusty workplace.[17]

Evaluation of a case of toxic metal poisoning requires that attention be directed not only to the presenting patient but also to the context in which the patient was exposed to the toxic metal. The sources of exposure must be determined and the pathways of absorption traced. The possibility of multiple additive sources must be considered. Such investigation is necessary not only for full understanding of the clinical case but, even more

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ABBREVIATIONS USED IN TEXT

ALA-D = aminolevulinic acid dehydratase
EDTA = ethylenediaminetetraacetic acid
EP = erythrocyte protoporphyrin
HANES II = Health and Nutrition Evaluation Survey

importantly, for the prevention of recurrent exposure in the affected patient and for prevention of poisoning of his workmates, siblings or neighbors.

Lead

Sources of Exposure

Occupational exposure to lead occurs in hundreds of industries. Among the more important are smelting, battery making, paint scraping, shipburning, soldering, stained glass manufacture, and brass and bronze foundry work.[18]

Children may be exposed to both high-dose and low-dose (that is, concentrated and diluted) sources of lead. Low-dose sources serve generally to increase baseline absorption and thus to reduce the margin of safety between background absorption and toxicity. Superimposed high-dose exposure accounts for most cases of symptomatic lead poisoning.

Lead-based paint continues to be the major source of high-dose lead exposure for children in the United States.[12] Although paint produced for household use must today (by a 1976 regulation of the US Consumer Product Safety Commission) contain no more than 0.06 percent lead by dry weight, interior paint manufactured before the 1940s in some instances contained more than 50 percent lead.

Lead paint poisoning classically occurs in children under the age of five years who live in deteriorated housing built before World War II.[12] Although most cases of lead paint poisoning occur in the "lead belts" of the older cities in the northeastern and north central United States, they have been reported in all regions of the country, including the far west, and in both urban and rural settings. Occasionally, lead paint poisoning has been reported in the children of relatively affluent parents who have moved into a city as "urban homesteaders" and inadvertently exposed their children to paint chips during household renovation. Increased lead absorption has also been reported in children exposed to chips of lead-based paint released into a community during the removal of paint by sandblasting from bridges and elevated expressways.[19]

Lead-glazed pottery, although not a widespread source of lead absorption, can on occasion release large amounts of lead into food and drink and has been responsible for outbreaks of serious poisoning.[20]

Airborne lead is generally a low-dose source of exposure. Automotive and industrial emissions are the major contributors to lead in air, and of the more than 100,000 tons of lead particles released into air each year in the United States, more than 95 percent derive from automotive emissions.[3] Studies of children living near freeways in New Jersey[21] and in California[22] have shown significantly higher blood lead levels in children living within 100 feet of major roadways than in those living at greater distances (Table 1). In those studies the children's blood lead levels were correlated with the average daily traffic volume on the roadways near their homes.[21]

TABLE 1.—*Blood Lead Levels in One- to Nine-Year-Old Children in Relation to Distance of Residence From a Major Roadway—Newark, New Jersey, 1971**

Distance of Residence From Roadway (feet)	Number of Children	Distribution (%) of Blood Lead Levels		
		40 μg/dl	40-59 μg/dl	60+ μg/dl
<100	758	42.6	49.3	8.1
100-200	507	72.4	24.2	3.4
>200	3,961	68.4	26.9	4.7

*From Caprio et al.[21]

Although industrial releases account for only a small fraction of airborne lead, these immobile sources can produce concentrated zones of high-dose exposure.[16] The worst such situation in the United States existed in the vicinity of a large lead ore smelter near Kellogg, Idaho.[23] In 1974, 99 percent of one- through nine-year-old children living within one mile of the Kellogg smelter had increased lead absorption (blood lead levels of 40 μg per dl or above) and 22 percent had blood levels diagnostic of lead poisoning (levels of 80 μg per dl or above).[23]

Lead contained in dust and soil is also generally a source of low-dose exposure, although near smelters the dust lead concentration may be as high as 10 percent by weight.[23] Precipitated particles of airborne lead are the major contributor to the lead found in dust and soil; in urban areas, flaking paint adds an additional amount. Lead deposited in soil tends to remain in the topmost centimeter and not to migrate downward. In general, lead in dust and soil appears to be responsible for elevations in children's blood lead levels above background when the concentration of lead in the dust or soil exceeds 500 to 1,000 ppm.[24]

Lead workers' children may be exposed to lead dust transported home from the workplace on workers' shoes and clothing.[17] In an evaluation of lead exposure in workers' children in Tennessee a close correlation was found between children's blood lead levels, the severity and duration of parental lead exposure, and the lead concentration of household dust. In that episode, 38 (41.8 percent) of 91 workers' children had elevated blood lead levels, and 10 required treatment for lead poisoning.[17] Under regulations set forth in 1978 by the Occupational Safety and Health Administration, industries using lead are now required to provide changing and showering facilities for their workers.[15]

Lead in food and drinking water, although almost never responsible for lead poisoning, is a ubiquitous source of low-dose exposure. Canned foods may have a particularly high lead content, because lead may be leached from the seams of soldered cans.[25]

Lead fumes, produced by the burning of lead batteries in home stoves to generate heat during the winter,

is a recently rediscovered source of childhood lead poisoning.[26] Lead exposure from battery burning was a serious cause of lead intoxication during the Great Depression[12] and may increase again in frequency if fuel prices continue to rise.

Toxicity

Lead toxicity is evident principally in three organ systems: the red blood cells and their precursors, the central and peripheral nervous system, and the kidneys. Lead has also been shown to have adverse effects on reproduction in both males and females[27] and has been shown to be a potent carcinogen in three animal species.[28]

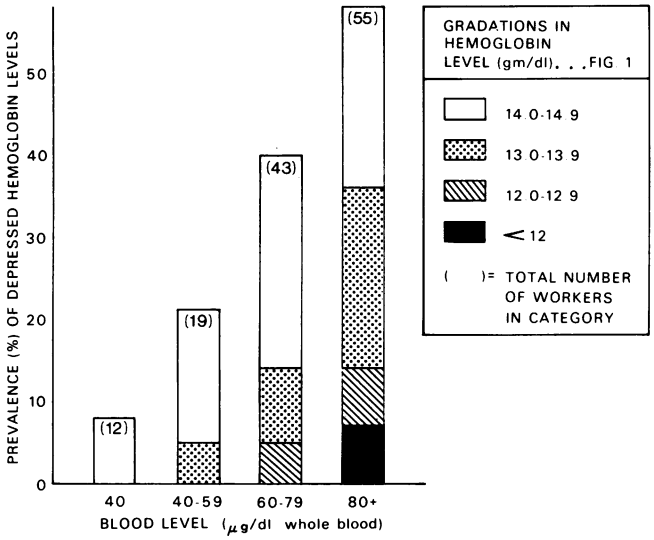

Figure 1.—Prevalence of depressed hemoglobin values by blood lead level in adult workers—United States, 1975-76 (adapted from Baker et al[29]).

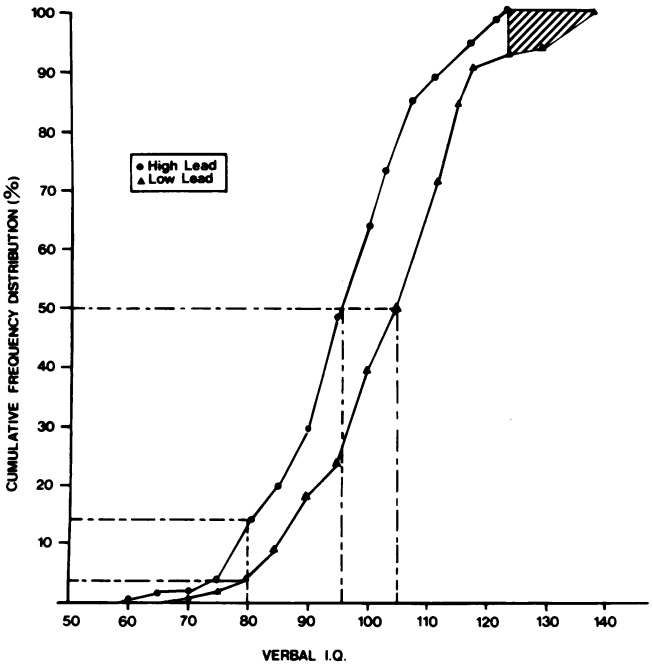

Figure 2.—Cumulative frequency distribution of verbal IQ scores in subjects with low or high levels of lead (adapted from Needleman et al[34]).

Anemia is the most serious manifestation of the hematologic toxicity of lead. Among the children who lived near the smelting plant in Kellogg, Idaho, 17 percent of those with blood lead levels of 80 μg per dl and above had hematocrits of 33 percent or below, whereas only 1.6 percent of children with blood lead concentrations below 80 μg per dl had depressions in hematocrit.[23] Among adult workers, anemia first becomes evident at blood lead levels between 40 and 60 μg per dl and increases in frequency and severity with increasing lead absorption (Figure 1).[29] The anemia of lead poisoning is occasionally accompanied by basophilic stippling of the red blood cells. Stippling is, however, an inconstant feature, and its absence does not exclude a diagnosis of lead poisoning.[13]

The anemia induced by lead may be either normochromic or hypochromic and is often associated with an increased reticulocyte count. It is caused principally by impairment of heme biosynthesis, but an increased rate of red blood cell destruction may also occur. At blood lead levels as low as 10 μg per dl, lead begins to inhibit the cytoplasmic enzyme delta aminolevulinic acid dehydratase (ALA-D) in the heme biosynthetic pathway; ALA-D inhibition is virtually complete at lead levels of 70 to 90 μg per dl.[30] Also at blood lead levels of 15 μg per dl in children and of 25 to 30 μg per dl in adults, lead begins to inhibit the mitochondrial enzyme ferrochelatase, which is responsible for catalyzing the transfer of iron from ferritin to protoporphyrin to form heme.[31,32] Ferrochelatase inhibition causes the metabolic intermediate erythrocyte protoporphyrin (EP) to accumulate to excess in red blood cells. EP elevation is thus a measure of both lead absorption and toxicity. Close correlations (as high as 0.91 in a steady state of exposure) have been noted in both adults[29] and children[23] between blood lead levels and EP concentrations.

In the peripheral nervous system, lead causes segmental demyelination. In extreme cases, this demyelination produces palsy of the wrist or ankle extensor muscles to cause "wrist drop" or "ankle drop." At lower levels of exposure, insufficient to produce overt symptoms, lead has been shown in both adults and children to produce a dose-related slowing of motor nerve conduction velocity.[23,33]

In the central nervous system, high doses of lead cause encephalopathy characterized in the most severe cases by coma, convulsions and death.[12] At lower levels of exposure, lead has been found to cause subtle but apparently irreversible deficits in intelligence, behavior and school performance.[34-39] In a carefully controlled epidemiologic study, Needleman and co-workers[34] found that clinically asymptomatic children with elevated body lead burdens had on average a four-point deficit in mean verbal IQ score as compared with children with lower lead burdens. Further, this four-point shift in mean IQ was found to be associated with a tripling in the number of children with IQ scores below 80 and also with a significant reduction in the number with

IQ's in the superior range (about 125)[35] (Figure 2). Similar results have been reported in studies in the United States by Landrigan and associates,[36] in Germany by Winneke and colleagues,[37] and in Britain by Yule and co-workers.[38]

The renal toxicity of lead is incompletely defined. Animal and human studies suggest that the proximal tubular lining cells are the tissue in the kidneys most sensitive to lead.[31] The first demonstrable renal effect of lead is the formation in these cells of densely staining intranuclear inclusion bodies.[31] Generalized aminoaciduria is another feature of early lead nephropathy in both children and adults. With continuing high exposure to lead, such as may occur in the industrial setting, various irreversible abnormalities in renal function become evident, including decreased glomerular filtration and decreased tubular concentrating ability.[29,40] Hyperuricemic gout, caused apparently by lead-induced impairment in the tubular secretion of uric acid, has been noted in a high proportion of cases of lead nephropathy.[41] The end-stage of lead nephropathy is chronic renal failure, characterized pathologically by interstitial fibrosis and by atrophy and cystic dilatation of the tubules with relative sparing of the glomeruli.[31] Excess mortality from chronic unspecified nephritis has been observed among lead smelter and battery workers in the United States.[42]

Evaluation and Diagnosis

The symptoms of lead toxicity are nonspecific.[12] Nausea, vomiting, diarrhea, and constipation are commonly reported.[29] Abdominal colic is a classic symptom, and can on occasion be so severe as to mimic symptoms of acute abdominal conditions that require operation. Tremor and muscle weakness have been noted. Frequently, symptoms consist only of fatigue, insomnia, irritability or headache.

A high index of suspicion is the essential prerequisite for making a diagnosis of either increased lead absorption or lead poisoning. Because none of the clinical features (except the inconstant finding of red blood cell stippling) are at all specific for lead intoxication, the diagnosis depends upon finding an elevated blood lead or EP level.

In children, the following diagnostic criteria have been developed:[13]

- *An elevated blood lead level,* which reflects increased absorption of lead, is defined as a confirmed concentration of lead in whole blood of 30 μg per dl or greater.
- *Lead toxicity* is defined as an EP level in whole blood of 50 μg per dl or above.
- *Lead poisoning* exists when a child has two successive blood lead levels of 70 μg per dl or greater and an EP level of 250 μg per dl or above, or both, in either the presence or absence of clinically evident symptoms.

In adults, whole blood lead levels of 40 μg per dl and above are considered to represent increased lead absorption.[15] Under regulations set forth by the Occupational Safety and Health Administration, adult workers with blood lead levels of 50 μg per dl or above must be removed from occupational lead exposure until their blood lead levels have fallen to below 40 μg per dl.[15]

Measurements of lead concentration in hair and in urine have not proved to be reliable indicators of lead absorption or toxicity, and a diagnosis of increased lead absorption or lead poisoning cannot be based on unsupported data from analysis of hair or urine for lead.

Chelating agents, such as calcium EDTA, which have proved extremely useful in the treatment of lead poisoning,[43] can also be administered diagnostically in a single intravenous dose to assess the mobile or potentially toxic fraction of the total body lead burden.[13] The EDTA mobilization test has no place, however, as a primary screening instrument because it involves administration of a drug with potential renal toxicity. Instead, use of this test should be restricted to confirmation in carefully selected cases of the results of blood lead and EP screening.[13]

Chelating agents have not been shown to restore subtle neuropsychological deficits in children chronically exposed to lead.

Measurement of nerve conduction velocity has also been used as a screening evaluation for heavy metal toxicity. However, numerous factors other than toxic metals, including trauma, diabetes, renal disease, chronic alcoholism and metabolic disorders, can influence motor nerve conduction velocity. Thus a finding of decreased nerve conduction velocity, unsupported by other measures of increased absorption of toxic metal, cannot by itself support a diagnosis of lead or other metal intoxication.

Recently, it has been shown that bony lead stores can be accurately measured by the technique of x-ray fluorescence analysis.[45] This noninvasive technique may gain wide acceptance in the future as a means of assessing lead burden.

Cadmium

Sources of Exposure

Cadmium is used in the manufacture of storage batteries, pigments, jewelry, electroplated materials and neutron absorbers in nuclear power plants.[4] Occupational exposure to cadmium can occur during its extraction and smelting or in the manufacture and use of materials containing the metal.[46] Because cadmium and lead frequently occur in the same ore bodies and have many similar uses in industry, exposure to cadmium is frequently accompanied by lead exposure.

Although cadmium is not so extensively dispersed in the environment as lead, community residents may be exposed to it by many of the same routes as they are to lead. Cadmium is released into the air by smelting plants, particularly by zinc and lead smelters. Near such plants, cadmium levels have been found to be high in air, dust and surface soil, and children living near zinc smelters have been shown to have significantly elevated body burdens of cadmium.[44] Cadmium may also be

released into the air at scrap recycling plants,[47] either from the burning of cadmium batteries or from the heating of plastics that contain cadmium as a pigment or stabilizer. Cigarette smoke contains measurable amounts of cadmium, and children living in the same households as smokers have significantly higher blood cadmium levels than the children of nonsmokers.[48] Children may be exposed to cadmium in foodstuffs, particularly in vegetables grown in soils enriched with sewage sludge; sewage sludge used as fertilizer has been shown to have a high cadmium content.[49]

Toxicity

Acute oral exposure to cadmium resulting from the use in food preparation of electroplated ice trays or pitchers coated with cadmium can cause gastrointestinal poisoning characterized by vomiting, diarrhea and crampy abdominal pain of sudden onset.[1] Acute exposure to airborne cadmium, as has occurred among persons fabricating jewelry with cadmium solder, produces a reversible syndrome of acute respiratory irritation characterized by conjunctivitis, rhinitis, anosmia, dyspnea and chest pain.[50]

The principal chronic toxic effect of cadium is on the kidney. Chronic exposure produces proximal tubular dysfunction, characterized initially by proteinuria, in particular by excretion of the low-molecular-weight protein, beta-2-microglobulin, and followed eventually by renal failure.[51] In populations of older adults in Japan chronically exposed to industrial cadmium effluents in contaminated rice, cadmium was found to be the cause of an acquired renal Fanconi's syndrome with severe osteomalacia termed itai-itai disease.[52] Chronic inhalation exposure to cadmium has been associated with development of emphysema. In occupationally exposed populations, cadmium has been associated with the development of cancer of the prostate and possibly of the lung.[53]

Evaluation and Diagnosis

Cadmium is extremely persistent in the human body, and its biologic half-life in humans has been estimated to be 17 to 33 years.[51] Most absorbed cadmium accumulates in the renal cortex.

Cadmium that has been absorbed in the recent past is most accurately assessed through measurement of the cadmium concentration in whole blood.[54,55] Although analytical results vary from study to study, it appears on the basis of best current techniques that the mean whole blood cadmium concentration of persons without occupational or unusual exposures is approximately 0.25 μg per dl, and that no more than 2.5 percent of persons in any population would be expected to have a blood cadmium concentration above 0.7 μg per dl. Thus the occurrence of a confirmed blood cadmium concentration above 0.7 μg per dl deserves careful investigation.

Measurement of urinary excretion of cadmium has also been used to assess cadmium exposure. However, the urine cadmium level appears more to reflect cadmium-induced renal tubular injury than cadmium absorption, and the concentration of cadmium in urine does not generally begin to increase above background until some degree of tubular injury has occurred.[51]

Determination of the urine concentration of beta-2-microglobulin by radioimmunoassay in persons exposed to cadmium is a useful confirmatory evaluation. The results of this test can be used to evaluate the presence of early cadmium-induced renal dysfunction.[51]

Determination of the cadmium content in hair has also been used to estimate cadmium exposure. However, this analysis does not distinguish externally deposited from systemically absorbed cadmium, and has not proved as reliable as the blood cadmium determination as an index of exposure.[50] A diagnosis of cadmium absorption or intoxication cannot be based on an unsupported hair cadmium determination. Diagnostic chelation has no role in the evaluation of cadmium absorption and has, in fact, been reported anecdotally to worsen the prognosis in cadmium nephropathy (H. Blejer, MD: personal communication, 1982).

Measurement of the cadmium content of the renal cortex by partial body neutron activation analysis[56] appears to be a promising noninvasive technique for evaluation of the body burden of cadmium and for relating body burden to external exposures as well as to pathologic outcomes.

Mercury

Sources of Exposure

Two forms of mercury with differing chemical and toxicologic properties are used commercially in the United States. Inorganic or elemental mercury is almost entirely an industrial poison, and is encountered by miners, smelter workers, mirror makers, mercury battery makers, instrument makers, jewelers, photographers, dentists and dental assistants.[57] Also children who play with droplets of metallic mercury may be at risk of exposure to mercury vapor.

Organic compounds of mercury, in particular the methyl and ethyl mercurials, are used as pesticides and as antifungal seed dressings. Thus organic mercury poisoning has occurred among pesticide formulators and seed handlers.[58] Much greater attention has, however, been directed to widespread outbreaks of organic mercury poisoning that have occurred in community populations as a result of their consumption of mercury-contaminated foodstuffs.[59] Major epidemics have occurred in Minamata Bay, Japan, where exposure resulted from ingestion of contaminated shellfish,[60] and in Iraq,[61] where exposure was caused by consumption of seed grain treated with mercurial fungicides.

Toxicity

The cellular mechanisms of mercury toxicity are poorly understood. Biochemical studies indicate, however, that the mercuric ion has a high affinity for sulfhydryl (-SH) groups in cellular proteins and that through reaction with sulfhydryl groups mercurial compounds can inhibit a wide variety of enzymes and also

disrupt membrane functions (active transport and permeability).[62]

Clinical Features

Acute absorption by inhalation of high doses of metallic mercury vapor causes symptoms of pulmonary irritation and encephalopathy. Deaths from this syndrome have occurred among children who threw globules of mercury on a hot stove to watch the droplets disappear. Acute oral exposure to inorganic mercury, which usually occurs as the result of attempted suicide, can cause a syndrome of gastroenteritis with abdominal pain, nausea, vomiting and bloody diarrhea; severe renal impairment leading to uremia frequently ensues.[57]

Occupational exposure to inorganic mercury is usually more chronic in nature, and the onset of toxicity is insidious. Inorganic mercury typically produces a syndrome of dermatitis, gingivitis, stomatitis and tremor, together with central nervous system dysfunction.[63] The neurological symptoms include irritability, pathologic shyness and the loss of attention span, memory and intellect and are collectively referred to as erethism. Lewis Carroll's mad hatter in *Alice in Wonderland* exhibited the symptoms of erethism, presumably as the result of his exposure to inorganic mercury in the old process of carroting felt in hat manufacture. Nephrosis may occasionally occur as a late result of chronic exposure to inorganic mercury. Today the full syndrome of inorganic mercury poisoning is seldom seen, but any of its components may be encountered in occupationally exposed groups.[57]

Poisoning by the organic compounds of mercury produces an almost purely neurologic illness.[64] Early symptoms include paresthesias, perioral numbness and other signs of sensory neuropathy. With continued exposure, the syndrome progresses to an almost pathognomonic triad of ataxia, dysarthria and visual field constriction. A devastating neurologic syndrome of congenital organic mercury poisoning has been observed in the children of women exposed to organic mercurials during pregnancy.[60]

Evaluation and Diagnosis

Recent absorption of inorganic mercury can best be assessed through measurement of the mercury content of whole blood. In an international study, the average concentration of mercury in the blood of persons without occupational or unusual exposure to mercury was found by atomic absorption spectrophotometry to be 5 ng per gram (0.5 μg per dl); 95 percent of values were below 30 ng per gram (3μg per dl).[5]

A diagnosis of organic (ethyl or methyl) mercury absorption or intoxication is based primarily on a history of exposure plus finding the classic signs on physical examination. In acute exposure to organic mercurials, a high degree of correlation has been found between average daily exposure and the total blood mercury concentration, as determined by atomic absorption spectrophotometry.[65]

Determination of the mercury content in hair is an unreliable diagnostic index of mercury absorption or toxicity.[5] Diagnostic chelation is of unproved efficacy and safety as a technique for evaluating increased absorption of merury.

Arsenic

Sources of Exposure

Arsenic exists in two chemical forms—trivalent (+3) and pentavalent (+5). In general, the trivalent form is the more highly toxic.

Human exposure to arsenic occurs mainly through ingestion, particularly of seafood, or through inhalation of arsenic-containing airborne particulates.[6] Adults may be exposed to arsenic in the smelting of nonferrous ores, particularly copper.[6] More than 80 percent of the arsenic consumed industrially each year in the United States is used in the manufacture of pesticides, herbicides and other agricultural products.[66] Occupational exposures occur among chemical workers, pesticide formulators and pesticide applicators.[6] Arsenical salts, especially ammonia, copper and arsenic, and chromated copper arsenic, are widely used as antifungal wood preservatives. Increased absorption of arsenic has been found among carpenters working with treated woods, such as marine pier construction workers and also among workers engaged in arsenic application in wood processing plants.[67]

Community exposure to arsenic has been caused by airborne emissions from smelters—copper and gold smelters in particular.[44,68] Highest arsenic exposures have been found in children living very near to smelting plants, and exposures decrease geometrically with distance; near smelters, contaminated air, dust and soil appear to be the principal routes of exposure.[68]

Contaminated drinking water has also been found to be a source of chronic arsenic exposure.[69,70] Among a group of persons evaluated in Fairbanks, Alaska, the source of arsenic in their well water was found to be the native rock underlying the city; the gold-bearing strata in those rock formations were also rich in arsenic.[69] A similar explanation has been offered for the occurrence of high arsenic concentrations in well water in areas of Taiwan[70] and Chile.[71]

Toxicity

Acute arsenic poisoning almost always results from the ingestion of contaminated food or drink and is very frequently associated with homicidal or suicidal intent. The symptoms are those of profound gastrointestinal inflammation, sometimes with hemorrhage, and of cardiogenic shock.[6] Symptoms resemble those of cholera and may include difficulty in swallowing, abdominal pain, projectile vomiting, "rice-water" diarrhea, dehydration, a weak irregular pulse and a loss of blood pressure that is followed by the development of stupor, coma, convulsions and death. The fundamental lesion appears to be dilation and increased permeability of the small blood vessels in the gastrointestinal tract and elsewhere. Pathological examination shows extensive inflammation and necrosis of the mucosa and submucosa of the stomach and intestine. The necrosis sometimes progresses to perforation of the gut wall. Fatty

degeneration of the liver and kidneys has been observed.[66]

Chronic arsenic poisoning is associated with lesions of the skin, nervous system, liver, cardiovascular system, hematopoietic system and respiratory tract.[66]

The dermatologic toxicity of chronic exposure to arsenic is characterized by eczematous dermatitis and by the appearance of hyperpigmented areas, warts (arsenical keratoses) and hyperkeratosis of the palms and soles. In an outbreak of arsenical dermatitis in a gold mining community in the Dakotas, 32 of 40 children (80 percent) who attended elementary school close to an arsenic-emitting ore processing plant were found to have arsenical dermatitis.[72]

Chronic arsenic exposure is associated with the occurrence of three types of skin cancer: squamous cell carcinoma, basal cell carcinoma and Bowen's disease; those lesions are frequently multiple in origin and develop primarily from arsenical keratoses.[66] The incidence of skin cancer in persons exposed to arsenic is related directly to their cumulative arsenic dose.

The principal neurologic abnormality associated with arsenic exposure is sensory neuropathy.[73]

In the liver, chronic exposure to arsenic has been associated with cirrhosis.[66] Chronic arsenic exposure has also been associated with angiosarcoma of the liver.[74]

Peripheral vascular disease has been observed among persons in Chile[71] and Taiwan[70] who had had chronic exposure to arsenic in drinking water. Early symptoms included acrocyanosis and Raynaud's phenomenon. Those changes were associated with hyperpigmentation and hyperkeratosis. They progressed in severe cases to frank gangrene of the extremities ("blackfoot disease"), associated with endarteritis obliterans. The prevalence and severity of blackfoot disease appeared to be related to the cumulative dose of ingested arsenic.

In the red blood cells, chronic exposure to arsenic has been associated with disturbed erythropoiesis, and megaloblastic formation has been noted.[66] These changes appear to reflect the inhibitory effects of arsenic on cellular respiration.

Arsenic is a potent irritant of the respiratory tract. In adults with chronic occupational exposure to arsenic, inflammatory and erosive lesions of the respiratory mucosa, including perforation of the nasal septum, have been noted.[66,72] Arsenic has also been shown to be responsible for the development of carcinoma of the lungs and bronchi.[66] Among 8,047 copper smelter workers exposed to arsenical dust in Anaconda, Montana, a threefold increase in the death rate from respiratory cancer was found over statewide rates.[75] Further, there was a systematic gradient in lung cancer mortality according to the duration and intensity of arsenic exposure; in the subgroup of workers with the heaviest and longest (more than 15 years) exposure, excess mortality from lung cancer was found to be increased eightfold over expected rates. Likewise, a study of 1,393 pesticide workers in Baltimore found mortality from lung cancer in all workers exposed to arsenic significantly higher than that in all Baltimore city workers.[76] Using a standardized mortality ratio of 100 to indicate that the number of deaths from a particular cause in a population equals the number expected from that cause (on the basis of age, sex and race) and ratios above 100 to indicate increased mortality, a positive dose-response relationship was noted in that study between lung cancer mortality and the duration of arsenic exposure. Mortality ratios ranged from less than 100 in workers exposed for less than one year to 2,750 (2 observed versus 0.1 expected) in workers heavily exposed for 25 or more years.

Evaluation and Diagnosis

Clinical evaluation of a person suspected of having been exposed to arsenic must take cognizance of the fact that arsenic has a biological half-life of only about ten hours; in primates, excretion of a single injected dose of arsenic is virtually complete within six days.[66] Arsenic is mainly excreted via the urine.

Human absorption of arsenic has been assessed through measurement of the total arsenic concentrations of blood, hair and urine.[69] Because of the short half-life of arsenic in blood,[66] the blood arsenic determination has been found to be of little practical value.[77] Also, given the short half-life of arsenic in the human body, provocative chelation is of little value as a diagnostic technique.

The determination of arsenic in hair is a semiquantitative indicator of past exposure to arsenic. In a nationwide survey of children living near primary smelters in the United States, the mean hair arsenic concentration in 972 children from 11 towns with copper smelters was found to be 2.60 μg per gram; the highest concentration (19.88 μg per gram) was found in Anaconda, Montana, the most heavily polluted town in the study.[44] By contrast, the mean hair arsenic content in 160 children from three towns without smelters was 0.09 μg per gram ($t=9.72$, $P<0.01$). The major drawback to the determination of arsenic in hair is that it does not distinguish systemically absorbed from externally deposited arsenic. Thus the intrinsic arsenic content of hair can be modified by bathing in arsenic-contaminated water, by contamination with arsenic excreted in sweat or by exposure to airborne arsenic. For those reasons, a diagnosis of arsenic absorption or toxicity cannot be based on an unsupported determination of hair arsenic content.

The urine arsenic concentration appears to be the best indicator of current or of recent (one to three days) past exposure to arsenic.[69] However, it is very important, given the short biological half-life of arsenic, to consider the timing of the collection of samples in assessing the biological significance of the arsenic concentration in urine.

Although the range of values considered "normal" in previous studies of urine arsenic concentration has varied, due primarily to differences in laboratory methods, most urine arsenic concentrations in unexposed populations have been found to be below 50 μg per liter.[66] Three studies[78-80] reported mean urinary arsenic concentrations in allegedly unexposed persons of 80, 85 and 130 μg per liter; however, in each of

TABLE 2.—*Percent of Children Ages Six Months to Five Years With Blood Lead Levels of 30 μg/dl or More* United States—1976-1980*

	Race		
	White	*Black*	*All Races*
Both sexes	2.0	12.2	3.9
Boys	2.1	13.5	4.3
Girls	1.8	10.9	3.5

*From Annest & Roberts.[81]

those studies, persons in the control groups either worked in proximity to arsenic-contaminated areas or had previous occupational exposure to arsenic.[66]

Discussion

Toxic metals—lead, cadmium, mercury and arsenic —are ubiquitous environmental contaminants in an industrialized society. Although all of these metals are natural constituents of the earth's crust, their distribution has been radically altered by human activity, and they are now dispersed widely in air, food, soil and water.[3-6]

Absorption of these metals has become the norm rather than the exception among residents of the United States, and the margin of safety between present-day background levels and the levels associated with toxicity has become vanishingly small.

The extent of the problem of toxic metal exposure among residents of the United States is well illustrated by recently developed data from the national Health and Nutrition Evaluation Survey (HANES-II); HANES-II is based on a probability sample of the entire noninstitutionalized population of the United States. These data indicate that 3.9 percent of all United States children between the ages of six months and five years examined from 1976 to 1980 had blood lead levels of 30 μg per dl or more. With projection of that finding to the entire population of the United States, it may be estimated that 675,000 young children have elevated blood lead levels. There was, in addition, a pronounced racial discrepancy in the HANES-II data. While only 2.0 percent of white children had elevated blood lead levels, the prevalence in black children was 12.2 percent (Table 2), and among black children residing in the central core areas of large cities and in families with an annual income of less than $6,000, the prevalence was 18.6 percent. Given recent evidence that blood lead levels above 30 μg per dl in young children are associated with the development of irreversible intellectual and behavioral deficits,[34-39] the HANES-II data have profoundly disturbing implications not only for the future health of the affected children, but also for the integrity of the whole fabric of urban society.

REFERENCES

1. Aitchison L: A History of Metals. London, MacDonald and Evans, 1960

2. Hunter D: The Diseases of Occupations, 4th Ed. Boston, Little Brown and Co, 1969

3. National Academy of Sciences: Lead: Airborne Lead in Perspective. Division of Medical Sciences, National Research Council, Committee on Biologic Effects of Atmospheric Pollutants, Washington, DC, 1972

4. National Academy of Sciences: Cadmium. Division of Medical Sciences, National Research Council, Committee on Biologic Effects of Atmospheric Pollutants, Washington, DC, 1977

5. Friberg L, Vostal J: Mercury in the Environment: An Epidemiologic and Toxicological Appraisal. Cleveland, Ohio, CRC Press, 1972

6. National Academy of Sciences: Arsenic. Division of Medical Sciences, National Research Council, Committee on Biologic Effects of Atmospheric Pollutants, Washington, DC, 1979

7. Murozomi M, Chow TJ, Patterson C: Chemical concentrations of pollutant lead aerosols, terrestrial dusts and sea salts in Greenland and Antarctic snow strata. Geochimica et Cosmochimica Acta 1969; 33:1247-1294

8. Piomelli S, Corash L, Corash MB, et al: Blood lead concentrations in a remote Himalayan population. Science 1980; 210:1135-1137

9. Settle DM, Patterson CC: Lead in albacore: Guide to lead pollution in Americans. Science 1980; 207:1167-1176

10. Frazier T: Blood lead levels among workers potentially exposed to metallic lead. Morbidity Mortality Weekly Rep, in press

11. Legge T: Industrial Maladies. London, Oxford University Press, 1934

12. Chisolm JJ Jr: Lead poisoning. Sci Am 1971; 224:15-23

13. Preventing Lead Poisoning in Young Children—A Statement by the Centers for Disease Control. Atlanta, Centers for Disease Control, Apr 1978

14. Charney E, Sayre J, Coulter M: Increased lead in inner city children: Where does the lead come from? Pediatrics 1980; 65:226-231

15. Occupational exposure to lead, final standard. Federal Register 43:52952-53014 (see 18.36, page 132)

16. Landrigan PJ, Gehlbach SH, Rosenblum BF et al: Epidemic lead absorption near an ore smelter: The role of particulate lead. N Engl J Med 1975; 292:123-129

17. Baker EL Jr, Folland DS, Taylor TA, et al: Lead poisoning in children of lead workers—Home contamination with industrial dust. N Engl J Med 1977; 296:260-261

18. National Institute for Occupational Safety and Health: Criteria for a Recommended Standard—Occupational Exposure to Inorganic Lead. 1972

19. Landrigan PJ, Baker EL Jr, Himmelstein JS, et al: Exposure to lead from the Mystic River Bridge: The dilemma of deleading. N Engl J Med 1982; 306:673-676

20. Klein M, Namer R, Harpur E: Earthenware containers as a source of fatal lead poisoning: Case study and public health considerations. N Engl J Med 1970; 283:669-672

21. Caprio RJ, Margulis HL, Joselow MM: Lead absorption in children and its relation to urban traffic densities. Arch Environ Health 1974; 28:195-197

22. Johnson DE, Tillery JB, Prevost RJ: Levels of platinum, palladium, and lead in populations of Southern California. Environ Health Perspec 1975; 12:27-33

23. Landrigan PJ Baker EL, Feldman RG, et al: Increased lead absorption with anemia and slowed nerve conduction in children near a lead smelter. J Pediatr 1976; 89:904-910

24. Air Quality Criteria for Lead. US Environmental Protection Agency, Office of Research and Development, publication No. EPA-600/8-77-017, December 1977

25. Lamm SH, Cole BL, Glynn KL, et al: Lead content in milks fed to infants—1971-1972. N Engl J Med 1973; 289:574-576

26. Dolcourt JL, Finch C, Coleman GD, et al: Hazard of lead exposure in the home from recycled automobile storage batteries. Pediatrics 1981; 68:225-230

27. Stowe HD, Goyer RA: The reproductive ability and progency of F1 lead-toxic rats. Fertil Steril 1971 Aug; 22:755-760

28. Kazantsis G: Role of cobalt, iron, lead, manganese, mercury, platinum, selenium, and titanium in carcinogenesis. Environ Health Perspect 1981; 40:143-161

29. Baker EL, Landrigan PJ, Barbour AG, et al: Occupational lead poisoning in the United States: Clinical and biochemical findings related to blood lead levels. Br J Industr Med 1979; 36:314-322

30. Hernberg S, Nikkanen J, Mellin G, et al: d-Aminolevulinic acid dehydrase as a measure of lead exposure. Arch Environ Health 1970; 21:140-145

31. Goyer RA, Rhyne B: Pathological effects of lead. Int Rev Exp Pathol 1973; 12:1-77

32. Roels H, Buchet J-P Lauwerys R, et al: Impact of air pollution by lead on the heme biosynthetic pathways in school-age children. Arch Environ Health 1976; 19:310-316

33. Seppalainen AM, Tola S, Hernberg S, et al: Subclinical neuropathy at "safe" levels of lead exposure. Arch Environ Health 1975; 30:180-183

34. Needleman HL, Gunnoe C, Leviton A, et al: Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N Engl J Med 1979; 300:689-695

35. Needleman HL, Leviton A, Bellinger D: Lead-associated intellectual deficits. N Engl J Med 1982; 306:367

36. Landrigan PJ, Whitworth RH, Baloh RW et al: Neuropsychological dysfunction in children with chronic low-level absorption. Lancet 1975; 1:708-712

37. Winneke G, Brockhaus A, Kramer U, et al: Neuropsychological comparison of children with different tooth lead levels: A preliminary report, *In* Proceedings of the International Conference on Heavy Metals in the Environment. Geneva, World Health Organization, 1981, pp 553-556

38. Yule W, Lansdown R, Millar IG et al: The relationship between blood lead concentrations, intelligence, and attainment in a school population: A pilot study. Dev Med Child Neurol 1981; 23:567-576

39. Needleman HL, Landrigan PJ: The health effects of low level exposure to lead. Annu Rev Publ Health 1981; 2:277-298

40. Wedeen RP, Maesaica JK, Weiner B, et al: Occupational lead nephropathy. Am J Med 1975; 59:603-651

41. Ball GV, Sorensen LB: Pathogenesis of hyperuricemia in saturnine gout. N Engl J Med 1969; 280:1199-1202

42. Cooper WC, Gaffey WR: Mortality of lead workers. JOM 1975; 17:100-107

43. Chisolm JJ Jr: The use of chelating agents in the treatment of acute and chronic lead intoxication in childhood. J Pediatr 1968; 73:1-38

44. Baker EL Jr, Hayes CG Landrigan PJ, et al: A nationwide survey of heavy metal absorption in children living near primary copper, lead, and zinc smelters. Am J Epidemiol 1977; 106:261-273

45. Ahlgren L, Haeger-Aronson B, Mattsson S, et al: In vivo determination of lead in the skeleton after occupational exposure to lead. Br J Industr Med 1980; 37:109-113

46. National Institute for Occupational Safety and Health: Criteria for a Recommended Standard—Occupational Exposure to Cadmium, 1976

47. Muskett CJ, Roberts LH, Page BJ: Cadmium and lead pollution from secondary metal refinery operations. Sci Total Environ 1979; 11:73-87

48. Wysowski DK, Landrigan PJ, Ferguson SW et al: Cadmium exposure in a community near a smelter. Am J Epidemiol 1978; 107:27-35

49. Linnman L, Andersson A, Nelsson KO, et al: Cadmium intake by wheat from sewage sludge used as a plant nutrient source. Arch Environ Health 1973; 27:45-47

50. Baker EL Jr, Peterson WA, Holtz JL, et al: Subacute cadmium intoxication in jewelry workers: An evaluation of diagnostic procedures. Arch Environ Health 1979; 31:173-177

51. Webb M: Cadmium. Br Med Bull 1975; 31:246-250

52. Nogawa J, Ishizaki A: Studies on women with acquired Fanconi syndrome observed in the Ichi River basin polluted by cadmium. Environ Res 1975; 10:280-307

53. Piscator M: Role of cadmium in carcinogenesis with special reference to cancer of the prostate. Environ Health Perspec 1981; 40:107-120

54. Lauwerys R, Roels H, Regniers M, et al: Significance of cadmium concentration in blood and in urine in workers exposed to cadmium. Environ Research 1979; 20:375-391

55. Kjellstrom T: Exposure and accumulation of cadmium in populations from Japan, the United States, and Sweden. Environ Health Perspec 1979; 28:169-197

56. Ellis KJ, Vartsky D, Zanzi I, et al: Cadmium: In vivo measurement in smokers and non-smokers. Science 1979; 205:323-325

57. Bidstrup PL: Toxicity of Mercury and its Compounds. Amsterdam, Elsevier Scientific Publishing Co, 1964

58. Ahlmark A: Poisoning by methyl mercury compounds. Br J Industr Med 1948; 5:117-119

59. Eyl TB: Organic mercury food poisoning. N Engl J Med 1971; 284:706-709

60. Kurland LT, Faro SN, Siedler H: Minamata disease. World Neurol 1960; 1:370-390

61. Bakir F, Damlogi SF, Amin-Zaki L: Methylmercury poisoning in Iraq. Science 1973; 181:230-241

62. Nordberg GF: Effects and dose-response relationships of toxic metals, *In* Proceedings from an International Meeting Organized by the Subcommittee on the Toxicology of Metals of the Permanent Commission and International Association on Occupational Health, Tokyo, Nov. 18-23, 1974. Amsterdam, Elsevier Scientific Publishing Co, 1976

63. Kazantsis G: Chronic mercury poisoning—Clinical aspects. Ann Occup Hyg 1965; 8:65-71

64. Hunter D, Bomford RR, Russell DS: Poisoning by methyl mercury compounds. Quart J Med 1940; 33:193-213

65. Englender SJ Landrigan PJ, Atwood RG, et al: Organic mercury exposure from fungicide-contaminated eggs. Arch Environ Health 1980; 35:224-228

66. Landrigan PJ: Arsenic—State of the art. Am J Industr Med 1981; 2:5-14

67. Rosenberg MJ, Landrigan PJ, Crowley S: Low-level arsenic exposure in wood processing plants. Am J Industr Med 1980; 1:99-107

68. Milham S Jr, Strong T: Human arsenic exposure to a copper smelter. Environ Research 1974; 7:176-182

69. Harrington JM, Middaugh JP, Morse DL, et al: A survey of a population exposed to high concentrations of arsenic in well water in Fairbanks, Alaska. Am J Epidemiol 1978; 108:377-385

70. Tseng WP: Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. Environ Health Perspect 1977; 19: 109-119

71. Borgono JM, Greiber T: Epidemiological study of arsenicism in the city of Antofagasta, *In* Hemphill DD (Ed): Trace Substances in Environmental Health-V—Proceedings of the University of Missouri's 5th Annual Conference on Trace Substances in Environmental Health, June 29-July 1, 1971, Columbia, Missouri. Columbia, University of Missouri, 1971

72. Birmingham DJ, Key MM, Holaday DA, et al: An outbreak of arsenical dermatoses in a mining community. Arch Dermatol 1965; 91: 457-464

73. Hindmarsh JT, McLetchie OR, Heffernan LPM, et al: Electromyographic abnormalities in chronic environmental arsenicalism. J Anal Toxicol 1977; 1:270-276

74. Falk H, Herbert JT, Edmonds L, et al: Review of four cases of childhood hepatic angiosarcoma—Elevated environmental arsenic exposure in one case. Cancer 1981; 47:382-391

75. Lee AM, Fraumeni JF Jr: Arsenic and respiratory cancer in man: An occupational study. JNCI 1969; 43:1045-1052

76. Mabuchi K, Lilienfeld AM, Snell LM: Lung cancer among pesticide workers exposed to inorganic arsenicals. Arch Environ Health 1979; 34: 312-320

77. Nordberg GF, Pershagen G, Lauwerys R: Inorganic Arsenic—Toxicological and Environmental Aspects. Odense, Denmark, Department of Community Health and Environmental Medicine, Odense University, 1979

78. Schrenk HH, Schreibeis L Jr: Urinary arsenic levels as an index of industrial exposure. Am Industr Hyg Assoc J 1958; 19:225-228

79. Perry K, Bowler RG, Buckel HM, et al: Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic—II. Clinical and environmental investigations. Br J Industr Med 1948; 5:7-15

80. Pinto SS, McGill CM: Arsenic trioxide exposure in industry. Ind Med Surg 1953; 22:281-287

81. Annest JL, Roberts J: Blood lead levels for persons 6 months to 74 years of age. Hyattsville, MD, National Center for Health Statistics, 1981