73 Lead

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At a Glance...

- Lead is a potent biologic toxin that possesses no physiologic benefit.
- Anthropogenic activity has placed enormous amounts of lead in the environment, resulting in almost universal exposure in humans.
- The major organ systems affected by lead are the brain, kidneys, bone marrow, skeleton, and reproductive tract.
- Lead is particularly harmful to young children, producing permanent effects to the brain and kidneys.
- Adults with lead poisoning can develop effects including emotional lability, memory difficulties, loss of libido, difficulty concentrating, and peripheral neuropathy.
- Treatment of lead poisoning in children consists of termination of exposure and nutritional supplementation; chelation therapy may also be necessary.
- Treatment of lead poisoning in adults consists of termination of exposure; chelation therapy is typically reserved for those with blood lead levels greater than 60 to 100 µg/dL.

Lead was once prized as one of the most valuable elements on earth. Because it has a number of highly desirable properties (low melting point, malleability, durability, low cost, octane-boosting), lead is ubiquitous in the environment. Both industrial and developing nations have found beneficial uses for lead. However, lead is also a potent toxin. In the past century, an explosion of scientific data has demonstrated the toxic effects of lead on the human body. This has been highlighted by the growing body of evidence that even small amounts of lead can produce permanent harm, particularly in young children. Lead poisoning (plumbism) is now considered one of the most common diseases of environmental origin.[1]

This chapter reviews the toxicology of lead poisoning. Because of unique differences in the epidemiology, clinical toxicity, and treatment strategies of lead poisoning in adults compared with children, the chapter is later subdivided into lead poisoning in adults and then children.

HISTORY

Lead has been mined for thousands of years; the earliest recorded lead mine reportedly existed in Turkey in 6500 BC.[2,3] Evidence of high lead use can be found in the skeletons of ancient Egyptians. By the Greek Bronze Age, lead was widely used in the manufacture of brass and cosmetics. Also, because lead geologically coexisted with silver, the mining of silver resulted in a marked increase in lead exposure. It is estimated that as long as 2200 years ago, 25,000 tons of lead were produced annually.[2] Reflecting the increased use of lead over time, contemporary skeletons have bone lead concentrations 500 times higher than skeletons from ancient societies.[2,4]

The fall of the Roman Empire is thought to have resulted from lead intoxication.[3-5] During this era, lead-induced gout was endemic. Romans used lead in their plumbing (the word *plumbing* is derived from the traditional use of lead in water conduits), in their cooking utensils, and in the vessels that concentrated grape juice for wine. Lead was popular in wine because it enhanced color, wetness, and bouquet. The lead content of wine in the Roman era may have been as high as 15 to 30 mg/L. In fact, well into the 20th century, wines contained added lead. Lead poisoning was described at the same time that the metal became popular. Hippocrates wrote descriptions of lead colic. Similar descriptions have been recorded throughout history by Benjamin Franklin and others.

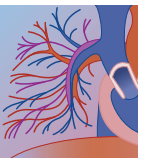
Initial interest in the illnesses caused by lead poisoning has been attributed to an 1839 publication by Tanquerel des Plances in which he described the clinical course of workers, primarily painters, who developed lead colic.[4] In 1860, corresponding with the industrialization of Europe, epidemiologists described widespread reproductive toxicity in those with lead-related occupations as well as their spouses. In the 20th century, these occurrences, which were also being identified in the United States, led to regulations that protected workers from occupational exposure to lead. At an extreme, laws were passed to exclude women from lead-related occupations; the U.S. Supreme Court later reversed such laws.[4]

The increasing desire to reduce exposure to lead also resulted in legislation to protect not only workers but also the public at large from the hazards of lead exposure. Establishment of the Environmental Protection Agency (EPA) and passage of important laws including the Clean Air Act, the Clean Water Act, the Lead Poisoning Prevention Act, and the Housing and Community Development Act (Title X) all have served to dramatically reduce nonoccupational exposure to lead.

EPIDEMIOLOGY

Population Rates

The blood lead level of Americans has been monitored through the periodic conductance of the National Health and Nutrition Examination Survey (NHANES). The results of the most recent surveillance indicate that mean blood lead level has declined more than 80% since the performance of NHANES II (1976–1980), from 12.8 µg/dL to a current level of about 2 µg/dL.[6-8] In



males, blood lead levels begin to rise in adolescence, continuing through most of adulthood, reflecting occupational exposure.[9] In both elderly men and women, blood lead levels rise again, representing remobilization of lead as bone resorption occurs.

No particular blood lead level clearly defines lead poisoning in adults. In the past, the reference range for blood lead in adults was up to 60 µg/dL. The normal range is now considered to be less than 40 µg/dL. However, many clinicians continue to believe that lead poisoning in adults is defined only by the presence of clinical symptoms, not by any particular blood lead level. The increasing evidence of subclinical effects at low blood levels in adults argues for defining lead intoxication as a blood lead level of greater than 25 µg/dL.

Sources

Lead can be found throughout the environment. Exposure to lead therefore usually occurs from a number of sources (Fig. 73-1). Many of these sources are highly age dependent. For example, most (but not all) lead-based occupations expose adults but not children to excess lead. Although lead exposure can occur after a single event—for example, after inhalation of lead fumes during welding—it is usually chronic.

OCCUPATIONAL

In adults, the most significant exposures to lead usually occur in the workplace. The list of occupations associated with lead exposure is large (Box 73-1). Occupation-specific tasks including demolition, radiator repair, home remodeling, burning, blasting, firearm instruction (indoor and outdoor), grinding, and sanding all can result in frank lead poisoning.[10-12]

Occupational lead standards were introduced by the Occupational Safety and Health Administration (OSHA) in 1978 and have not been significantly revised.[13] Under these guidelines, the permissible exposure limit for lead is 50 µg/m^3 for an 8-hour time-weighted average. Employers are responsible for maintaining proper working conditions, as well as for environmental and medical monitoring.[13] Workers with blood lead levels of 60 µg/dL or greater must be removed from the workplace; those with blood lead levels of 50 µg/dL or greater on three occasions at 1-month intervals in the prior 3 months must also be removed from work. Those with blood lead levels of 40 µg/dL or greater must undergo medical evaluation.[11] Employers are responsible for paying the salaries of employees who are removed from work for lead-related reasons.[13] Because of the reproductive effects of lead at lower lead levels, recommendations have been made that the permissible blood lead level in workers be reduced to 10 µg/dL.[1]

LEAD PAINT

Lead has been added to paint for centuries in order to make pigments more vivid, colors more stable, and the paint more durable. For the years that these beneficial properties were exploited, the addition of lead to paint was an industry standard. It is because of its durability under adverse weather conditions that lead-based paint became most popular in the northeastern United States. Interestingly, in Canada, which has even harsher climatic conditions, lead was banned from residential paint early in the 20th century. In the United States, however, lead was added to paint until 1978, when, in an effort to reduce lead exposure, particularly among young children, lead was effectively banned (restricted to a concentration of no more than 0.06%) from use in

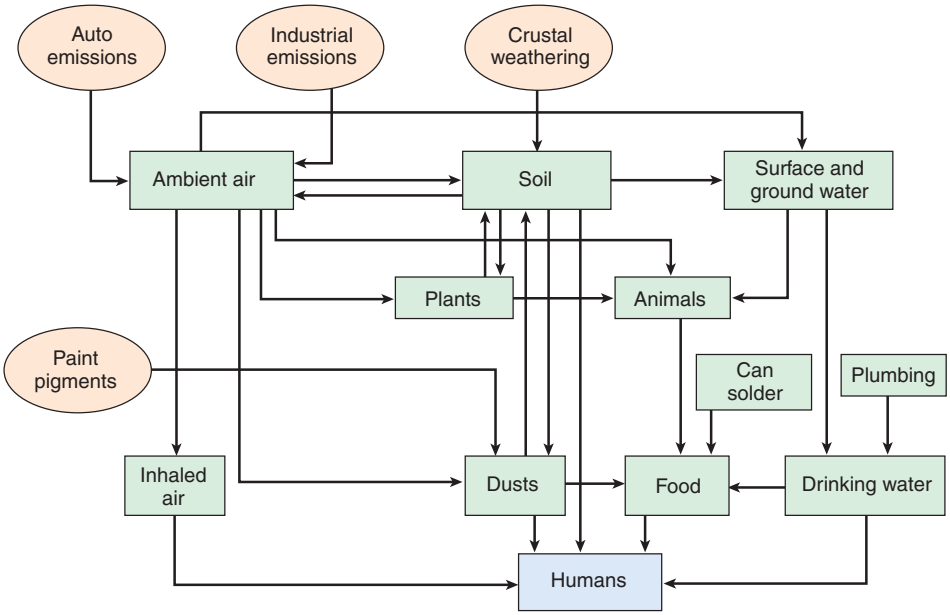


FIGURE 73-1 Sources and pathways of lead from environment to humans. (From U.S. Environmental Protection Agency: Air Quality Criteria for Lead. EPA-600/08_83/028aF-dF. Research Triangle Park, NC, Author, 1986.)

BOX 73-1 SITES, INDUSTRIES, AND ACTIVITIES ASSOCIATED WITH LEAD EXPOSURE

Sites

Firing ranges
Lead smelters
Homes and communities near lead smelters

Industries

Battery manufacture
Cooper smelting
Gasoline additive production
Ore crushing and grinding
Paint and pigment manufacture
Plastics industry
Printing industry
Rubber industry
Solid waste combustion
Zinc smelting

Activities

Auto repair
Construction and demolition
Firearm instruction
Home renovation
Professional painting
Plumbing
Radiator repair
Soldering of lead products
Welding and cutting operations

From Keogh JP, Boyer LV: Lead. In Sullivan JB, Krieger GR (eds): Hazardous Materials Toxicology, 2nd ed. Baltimore, Williams & Wilkins, 2001.

residential paint. Lead-containing paint is still used in nonresidential settings.[11] As a result of its extensive application, lead paint can be found in more than 38 million housing units in the United States.[14]

The presence of lead-based paint in homes has led to several problems. First, the natural decay of paint results in both chipping and the creation of lead dust. Also, when lead-containing homes undergo renovation of any type (e.g., scraping, demolition, window or wall removal), lead is released into the environment.[15] Certain types of renovation, particularly paint removal with a heat gun, are extremely hazardous, resulting in the creation of highly toxic lead fumes.[16] Even when homes are undergoing deleading in an effort to reduce lead hazards, improper techniques can result in lead poisoning in all family members.[17] The EPA has established guidelines for safe levels of lead in household dust as follows: maximum lead concentration in uncarpeted floors, 40 μg/ft^2; interior window wells, 250 μg/ft^2; and window wells, 400 μg/ft^2 (www.epa.gov).

AIR

Industrial and automobile emissions are historically a major source of lead exposure. In the United States, leaded gasoline released more than 30 million tons of lead into the air before it was banned.[4] The extent of airborne lead's contribution to lead levels is seen in the effect of its removal from gasoline; when lead was phased out of gasoline in the 1970s, the mean blood lead of all Americans promptly declined by 35%. In the United States, the phase-out of leaded gasoline was completed in December 1995.

WATER

Water has become an increasingly important source of lead exposure, particularly as the contributions of paint, dust, food, and air diminish. Lead has contaminated many bodies of water as it has settled from the atmosphere. The increasing acidity of fresh water, due to acid rain, increases the solubility of waterborne lead. Soft water presents more of a lead hazard than hard water.[18]

Regulation of lead in public water supplies is the responsibility of the EPA. In a 1991 revision of the Clean Water Act, the maximum contaminant level of lead in water, which had been 50 parts per billion (ppb, μg/L), was replaced by an action level of 15 ppb. Under these new regulations, water suppliers must implement measures to reduce the level of lead in water if a significant number of homes are found to have elevated levels of lead.

Plumbing is an important cause of lead contamination in residential water. When public plumbing systems became widespread in the early 20th century, lead pipes served as the primary conduits directing water from public water sources into the home. In the 1950s, the use of lead pipes declined considerably. However, old public water systems continue to have extensive networks of lead pipe plumbing. Lead pipes have been largely replaced by copper or polyvinylchloride (PVC) pipes. The use of lead-based solder to join copper pipe joints was permitted until 1986. Therefore, homes with copper plumbing can be assumed to have lead in their water circuit. Because of the continued presence of lead pipes and copper pipes with lead solder joints, many cities in the United States have a high prevalence of lead-contaminated water.

Bottled water, which is under the regulation and oversight of the U.S. Food and Drug Administration, must have a lead content of no more than 5 ppb.

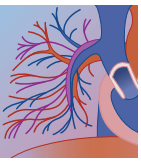
SOIL

Lead in soil can result either from its natural occurrence or contamination. The latter is responsible for most surface water lead in the United States. For example, studies of soil surrounding lead-emitting industries (e.g., smelters) have revealed soil lead concentrations higher than 60,000 parts per million (ppm, mg/L). In homes, lead contamination of soil occurs as painted exterior surfaces deteriorate.

Lead in soil is an important vector for human exposure. The EPA, in conjunction with the U.S. Department of Housing and Urban Development, has sought to reduce lead exposure through the development of guidelines on safe levels in soil. Under these standards, a safe concentration of lead in soil is considered to be less than 400 ppm.

HOBBIES

Certain household hobbies can result in lead exposure. These include any work that involves the use of solder



(which, when volatilized, produces highly absorbable lead fumes), the manufacture of fishing weights, and various aspects of artisanship. In the latter category, ceramic glazes occasionally contain lead. Although the use of lead glaze has been markedly reduced, it still occurs.

FOLK AND ALTERNATIVE MEDICINES

As discussed in Chapter 68, lead is sometimes found in alternative medicines, including Ayurvedic and folk remedies.[19-23] Dolomite, clamshell powder, and other calcium supplements may contain lead, particularly if their source is pulverized bone.[20-28]

FOOD

Food can be another source of chronic lead exposure. Lead enters the food chain through various routes. Vegetables, particularly homegrown vegetables that are grown in lead-contaminated soil, can introduce lead into the diet. Storage cans ("tin cans") were previously manufactured with a lead-solder seam. This seam, coming into direct contact with food, could readily release lead, particularly into acidic foods. In some studies, the solder seam raised the lead content of food as much as 4000-fold. The use of lead solder for the seam was banned in November 1991.[8] However, its widespread use has left many lead-containing cans still available.[8] Also, cans brought from other areas of the world are likely to contain lead.

Kitchenware can also be a source of lead. Previous reports have identified frank lead poisoning from the use of lead-containing vessels. These include samovars (heating urns), plates, bowls, cups, pots, and containers made of pewter.[29]

OTHER

Lead exposure can result from various types of substance abuse. First, the age-old practice of "moonshining"—that is, making illicit ethanol—has long been associated with lead poisoning from the use of lead-containing vessels such as discarded automobile radiators.[30,31] Lead poisoning can be caused by sniffing leaded gasoline; this is one of the few causes of organic lead exposure. Finally, the synthesis of methamphetamine may involve lead acetate. Sporadic reports have described lead intoxication from the injection of lead-contaminated methamphetamine.

Lead absorption from retained bullets can occur in those with gunshot wounds.[32,33] However, the kinetics of lead absorption from soft tissue have not been well characterized. For example, in animal models, lead appears to be poorly absorbed from muscle and fat; lead absorption from pleura and synovial fluid is most efficient.[34] Data from armed conflicts since the Civil War have documented lead poisoning in troops.[34]

TOXICOKINETICS

Lead is variably absorbed after ingestion. Its absorption is active, mediated by the same mucosal transport proteins that mediate calcium transport.[35] However, absorption is dependent on several factors, including the form of lead, particle size, gastrointestinal (GI) transit time, nutritional status, and chronologic age. Lead absorption is inversely proportional to size; the smaller the particle, the more complete the absorption. This is why exposure to lead dust results in higher lead concentrations than ingestion of an equal amount of lead from a paint chip.

Nutritional status is being increasingly shown to influence the extent of lead absorption. For example, iron deficiency results in increased lead absorption, probably because these atoms are linked to the same transport system.[35,36] Iron deficiency also alters lead distribution within the body.[37] The prevalence of lead intoxication in childhood results, in part, from the relatively high incidence of iron deficiency in this population. Similarly, calcium deficiency is associated with increased lead absorption. High fat intake and inadequate calories have also been associated with enhanced lead absorption. Lead absorption is increased when the stomach is empty; small frequent meals reduce absorption, probably through lead binding by dietary phytates and other complexing agents.[35] Finally, lead absorption is inversely proportional to chronologic age. As a general rule, 30% to 50% of ingested lead is absorbed from the gut of a child, compared with less than 10% in an adult.[11,35] This may be related to a higher density of intestinal transport proteins during periods of rapid growth.[35] Lead is also readily absorbed after inhalation of dust or fumes. Generally speaking, lead particles must be less than 0.5 μm to be absorbed from the respiratory tract.[38] Although inorganic lead is not absorbed through intact skin, organic lead compounds are.[11]

After absorption, lead circulates in blood, having a half-life of about 30 days in adults.[39] However, half-life is related to the duration of exposure. Those with short-term exposure experience more rapid disappearance of lead from blood than those with long-term exposure.[40] In the blood, 95% of lead is attached to (or within) the erythrocyte; thus, it is *blood lead* and not serum lead levels that are measured. The volume of distribution of lead is unclear but is presumed to be large; only 1% to 5% of the body's lead burden is in the circulation.[1] Lead readily crosses the placenta; fetal blood lead levels are typically 30% to 35% higher than maternal blood levels.[11,41-43]

The distribution kinetics of lead follows a three-compartment model. From blood, lead diffuses into soft tissues, including the liver, kidneys, bone marrow, and brain. This compartment is the primary site of lead's cellular toxicity. After a period that corresponds to a half-life of 1 to 2 months, lead diffuses from these tissues into bone. In bone, lead is incorporated into the hydroxyapatite lattice.[11] Lead is similarly incorporated into teeth. Once it is a part of bone, lead is presumed to be inert and nontoxic; however, this issue has been revisited as it becomes clear that conditions associated with bone mobilization (e.g., zero gravity, complete bed rest, medications, advancing years, and thyrotoxicosis) can also result in mobilization of lead.[44] Several researchers have described recurrent lead intoxication in children

with a prior history of lead intoxication when they suffer conditions producing bone mobilization.[45,46] Concerns have been expressed that pregnancy, another state of bone resorption, can result in increased lead mobilization with the potential for fetal exposure to excess lead.[47-49]

Because of lead's incorporation into bone, most lead is retained in the body with very little elimination (in the absence of chelation); only about 30 µg/day is excreted by the kidneys.[11] Therefore, declining blood lead levels in those with lead poisoning not undergoing chelation represent only lead's distribution into soft tissues, not its excretion. In occupational monitoring, urinary lead excretion of less than 50 µg/g of creatinine is within normal limits. Lead's overall half-life is about 10,000 days (20–30 years).[1,3,50]

MECHANISMS OF TOXICITY

The cellular mechanisms of lead's toxicity are multiple and involve many different physiologic actions. Lead is particularly toxic to enzymes, particularly zinc-dependent enzymes. The blood lead levels at which adverse health effects occur are variable (Table 73-1).

Organs most sensitive to lead's toxicity are the kidneys, hematopoietic system, and nervous system. In the kidneys, lead interferes with the heme-containing hydroxylase enzyme, which converts 25-vitamin D to 1,25-vitamin D, an effect that is reversible.[11,51] In addition, a toxic action affects the renal tubules, producing a tubulopathy characterized by selective proteinuria. At blood levels as low as 40 µg/dL, lead produces dense intranuclear inclusion bodies in renal tubules.[1] More advanced stages of lead nephropathy are associated with interstitial fibrosis, as well as tubular atrophy, with relative sparing of the glomeruli.[1]

Lead has a high affinity for sulfydryl groups, particularly those of metalloenzymes. Such enzymes include those in the heme synthetic pathway, particularly δ-aminolevulinic acid dehydratase, coproporphyrinogen oxidase, and ferrochelatase.[40] δ-Aminolevulinic acid dehydratase activity is inhibited at blood lead levels as low as 5 µg/dL.[40,52] This results in accumulation of δ-aminolevulinic acid, a putative neurotoxin.[43,53] Inhibition of ferrochelatase, which is responsible for incorporating iron into the porphyrin core, leads to elevated levels of erythrocyte protoporphyrin (EP).

Lead also affects neurotransmitter production.[48] This may be related to its ability to inhibit calmodulin, pyruvate kinase, and other enzymes essential to neuronal function. Many of lead's neurotoxic effects appear to result from its inhibition of cellular functions requiring zinc and calcium (which are also divalent cations).[53,54] Lead interferes with normal calcium metabolism, causing intracellular calcium buildup; it binds to most calcium-activated proteins with 100,000 times greater affinity.[4]

LEAD POISONING IN ADULTS

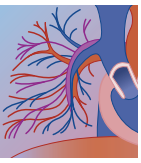
Clinical Manifestations

Acute lead intoxication in adults is rare but can occur after high-dose respiratory exposure, such as use of a heating gun, acetylene torching of lead-coated metal, or organic lead exposure.[11] Acute intoxication can produce

TABLE 73-1 Significant Health Effects of Lead at Lowest Observed Blood Lead (PbB) Levels in Adults

LOWEST OBSERVED EFFECT PbB (µg/dL)	HEME SYNTHESIS AND HEMATOLOGIC EFFECTS	NEUROLOGIC EFFECTS	EFFECTS ON THE KIDNEYS	REPRODUCTIVE FUNCTION EFFECTS	CARDIOVASCULAR EFFECTS
100–120		Encephalopathic signs and symptoms	Chronic nephropathy		
80	Frank anemia				
60				Female reproductive effects	
50	Reduced hemoglobin production	↑ Subencephalopathic neurologic symptoms		Altered testicular function	
40	Increased urinary ALA and elevated coproporphyrins	↓ Peripheral nerve dysfunction (slowed nerve conduction)			
30					Elevated blood pressure (white males, ages 40–49)
25–30	Erythrocyte protoporphyrin elevation in males				
15–20	Erythrocyte protoporphyrin elevation in females				
<10	ALA-D inhibition				

ALA-D, δ-aminolevulinic acid dehydratase.



encephalopathy, severe GI upset, and renal failure. More commonly, lead intoxication results from long-term exposure.

Central nervous system (CNS) manifestations predominate in lead-poisoned adults. Signs and symptoms include fatigue, irritability, lethargy, insomnia, headache, difficulty concentrating, memory loss, and tremor.[11,55] Other symptoms include myalgias, vomiting, constipation, and loss of libido.[11] Severe lead intoxication can result in an encephalopathy characterized by depressed consciousness, seizures, and coma, in association with cerebral edema. Life-threatening neurotoxicity usually develops with blood lead levels exceeding 150 μg/dL. Another CNS effect of lead poisoning is an abnormal auditory brainstem evoked potential.[11,56]

Lead is also toxic to the peripheral nervous system, producing an axonopathy that results in motor disturbances.[13,56] The distinctive pattern of lead-induced peripheral neuropathy affects the upper extremities more than the lower extremities, the extensors more than the flexors, and the dominant more than the nondominant arm. Painter's wristdrop is a once-endemic syndrome of upper extremity paresis found in painters who regularly used or removed lead-based paint. The initial segmental demyelination eventually leads to injury of both the axon and cell body.[3] Nerve conduction studies have shown that ulnar nerve conduction is disturbed at lead levels as low as 30 μg/dL.[1,11,50,56]

The kidneys are a third major site of lead's clinical toxicity. After lead exposure, lead concentrations are highest in the kidneys, particularly in the proximal tubules. As a result, lead, like cadmium, produces a renal injury characterized by excretion of β_2-microglobulin and *N*-acetylglucosidase.[57,58] These proteins have been suggested as early markers of subacute lead-induced renal injury. Finally, chronic exposure to lead can result in hypertension; animal models suggest that hypertension results from disturbances in vasomotor tone.[3,58-60]

Lead's effect on the hematopoietic system is one of its most described toxicities and has been used as a measure of its lead-induced physiologic dysfunction. *Basophilic stippling of erythrocytes, the precipitation of nuclear material, is a hallmark of severe lead exposure.* In fact, before laboratory techniques were available for measuring blood lead levels, the degree of basophilic stippling served as a diagnostic tool. Lead is also a potent suppressor of heme synthesis, producing anemia once lead levels exceed 50 μg/dL; the anemia can be either normochromic or hypochromic.[1]

Lead's effects on reproduction are profound and multiple. For example, because of lead's diffusibility across the placenta, pregnant women with lead intoxication invariably have lead-poisoned offspring.[49] Also, because pregnancy is a condition associated with bone mobilization, women with a past history of lead poisoning may have elevated lead levels during pregnancy. Other reproductive effects of lead poisoning in women include a higher rate of spontaneous abortion and stillbirth.[3,4,49] Lead is one of the few toxins in which paternal exposure is also associated with adverse reproductive outcomes.[1,61] Lead-poisoned men have decreased sperm counts and a higher number of abnormal sperm; these effects can appear at blood lead levels as low as 40 μg/dL.[11,13,62]

Other complications of lead intoxication include hypertension, GI disturbances, mild liver function abnormalities, gingival lead lines (blue discolorations of the gingiva), muscle and joint aches, and gouty arthritis.[3,11,63]

Assessment

The diagnostic evaluation of lead intoxication focuses on identification and quantification of those disturbances that can be readily diagnosed. The most important test is measurement of blood lead level. Because of lead's 30-day half-life and large volume of distribution, blood lead level is a relatively poor measure of total body burden; however, because blood is easy to obtain and provides useful information after recent exposure, blood lead determination remains valuable. Blood lead levels can currently be measured by a number of techniques, including atomic absorption spectrometry, anodic strip voltammetry, thermal-ionization mass spectrometry, and inductively coupled plasma–mass spectrometry (ICP-MS).[4] All of these, when performed with appropriate quality control measures, are extremely accurate.

Because blood lead levels can be a poor representation of body lead burden, better methods of assessing lead exposure are being sought. With lead ultimately deposited in bone, and the skeleton serving as the primary in situ reservoir, diagnostic tools that measure lead in the skeleton are being developed. One of the most promising of these is x-ray fluorescence (XRF).[64-66] XRF works by emitting x-rays at bone in order to activate electrons in valence shells, a process that produces energy that can be measured. L-line XRF stimulates electrons in the L electron shell, whereas K-line XRF acts only at electrons in the K shell. The latter technique appears to have greater accuracy in assessing total bone lead concentration. Studies are demonstrating that XRF analysis of bone assesses body lead burden far more accurately than does blood lead determination. For example, Hu and colleagues showed that among carpenters with long-term lead exposure, lead burden as assessed by XRF correlated more closely with lead suppression of heme synthesis than did blood lead level.[66] Although promising, XRF has been difficult to develop in children because they have relatively little bone calcification and because lead incorporation into bone appears to occur at less predictable rates; however, the procedure has been used in several pediatric studies. XRF has the potential to replace blood lead measurement as a method of assessing lead exposure.

EP measurement remains important in the evaluation of lead exposure. Because it is not only the quantity of lead in blood that is important but also the effect of that lead burden on body function, EP measurement serves to provide information on lead's organ toxicity. EP is easily measured through hematofluorometry.[27] As a general rule, adults with lead poisoning have less EP disturbance than children. It is also notable that rises in

EP lag behind lead exposure by several days; therefore, if measured shortly after exposure, EP levels may not yet be abnormal.

Other laboratory tests useful in the evaluation of lead exposure include abdominal radiographs, renal function tests, complete blood count, and δ-aminolevulinic acid dehydratase activity. Abdominal radiographs are useful only if acute lead ingestion is suspected. Blood urea nitrogen and serum creatinine levels should be measured, and a urinalysis should be performed. Although investigators have suggested that *N*-acetylglucosidase can be used as a marker of lead-induced renal injury, the clinical utility of this test has not yet been proved. A complete blood count (CBC) serves to identify either preexisting iron deficiency anemia or lead suppression of hematopoiesis; also, basophilic stippling can be identified on blood smear.

Methods of assessing nervous system function after lead intoxication include measurement of auditory brainstem evoked potentials and nerve conduction velocity.[67] Lumbar puncture should not be performed in patients with altered mental status from suspected lead poisoning because the underlying cerebral edema can lead to herniation.

Treatment

Treatment of adult lead poisoning begins with cessation of further exposure. For those exposed in the workplace, OSHA standards must be implemented, if the business falls under OSHA regulations. Even for nonoccupationally exposed adults (e.g., artisans or family members with lead poisoning due to home renovation), the primary intervention is prevention of further exposure.

CHELATION THERAPY

Parenteral Agents

Chelators are agents that form stable ligands with metal, effecting enhanced renal or biliary excretion of the drug–chelate complex. Many chelators have been discovered during the past century. However, it was only after the mid-20th century that chelation therapy flourished. More than five lead chelators have been identified.

The most important lead chelator developed is *dimercaprol*. This agent was created in England during World War II after the search for an antidote to the deadly arsenic-containing gas lewisite. The resulting antidote was an arsenic chelator termed *British antilewisite* (BAL). Since its creation, BAL has proved to be one of the most potent heavy-metal chelators.[68] In addition to lead, BAL chelates mercury, arsenic, and gold. BAL forms a stable dithiol bond with lead; the resulting complex is eliminated in both bile and urine.

BAL has a significant adverse effect profile; as many as half of those who receive this drug develop an adverse reaction. Part of this results from BAL's required preparation in a peanut oil vehicle; having such an excipient, the drug can only be administered intramuscularly. BAL has oxidant properties that can produce hemolysis in those with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Other adverse effects include hypotension, rash, vomiting, and a metallic taste in the mouth.[69] Toxic reactions occur when BAL is administered to those taking oral iron supplements.

BAL should be administered to any patient with encephalopathy or a whole blood lead level greater than 100 μg/dL.[9] The dose is 4 to 6 mg/kg per dose (maximum 300 mg per dose). Because of its vehicle, BAL should not be administered to patients with a history of peanut allergy.[69]

Another effective lead chelator is calcium disodium ethylene diamine tetraacetic acid (CaNa2EDTA, *calcium edetate*). Developed in the 1950s, this chelator became an important intervention in the treatment of childhood lead intoxication. Like BAL, EDTA forms a stable bond with the lead atom. The resulting complex is excreted in urine. EDTA can be administered intravenously or intramuscularly; it is not administered orally, both because this route is less effective and because evidence suggests that oral EDTA can enhance GI absorption of ingested lead. EDTA has a very short half-life (about 65 minutes). As a result, it is ideally administered by continuous intravenous infusion. Alternative administration strategies include intramuscular or intravenous administration two to three times daily. The dose of EDTA given to adults is 1 to 2 g daily.

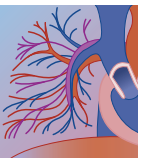
As with BAL, adverse effects of EDTA limit its use. EDTA chelates nutrients, particularly zinc, in addition to lead. Therefore, in order to avoid zinc deficiency, courses of EDTA are limited to 5 days, followed by at least a 48-hour hiatus for nutritional recovery. EDTA courses are also limited to minimize its nephrotoxicity (manifested by proteinuria, hematuria, or glycosuria).[69] A limitation of EDTA is its relative ineffectiveness with blood lead levels less than 30 to 35 μg/dL, which narrows its range of utility.

Oral Chelators

Oral chelators have been developed to permit outpatient therapy for those with significant lead intoxication. These include succimer and D-penicillamine. They are discussed in the section on childhood lead poisoning.

INDICATIONS

Because adults, compared with children, are considered relatively resistant to the toxic effects of lead, indications for chelation therapy are controversial. In occupational medicine practice, treatment of lead poisoning is typically reserved for symptomatic adults, independent of blood lead level. Therefore, chelation therapy is often withheld until blood lead levels exceed 70 μg/dL, the range at which adults typically develop overt signs of lead intoxication. In such patients, hospitalization for EDTA chelation is recommended. Experience with childhood lead poisoning has demonstrated that EDTA chelation can exacerbate CNS toxicity when it is used as sole therapy in those with blood lead levels greater than 70 to 100 μg/dL; this CNS toxicity probably represents EDTA



promotion of lead penetration into the brain. To prevent this, dual therapy with EDTA and BAL should be considered for adults with blood lead levels greater than 100 µg/dL. BAL can be discontinued once the blood lead level has fallen below the range of 70 to 80 µg/dL.

As the subclinical toxicity of lead becomes more appreciated, a growing opinion is that in adults, chelation therapy should be provided before overt clinical symptoms appear in order to prevent long-term sequelae, such as renal injury, as well as to reduce overall lead burden. Therefore, clinically asymptomatic adults can be considered candidates for chelation therapy even at lead levels of 25 to 40 µg/dL. Pregnant lead-poisoned women, unless their plumbism is severe, should not undergo chelation because of the possibility that the chelating agent will enhance lead movement across the placenta and be teratogenic.[13]

CHILDHOOD LEAD POISONING

History

The history of childhood lead intoxication is comparatively brief. Childhood lead poisoning was first reported in Brisbane, Australia, in 1899, when, after extensive epidemiologic investigation, A. J. Turner and J. L. Gibson associated the poisoning of young children with the ingestion of paint in their homes. Through the 20th century, increasing reports described catastrophic illness in children related to their ingestion of lead paint. Clinical features included basophilic stippling, abdominal pain, irritability, and often coma, seizures, and death. In 1943, Byers and Lord published a seminal article indicating that although childhood lead poisoning had been thought of as an illness that, among survivors, produced no obvious sequelae, many children suffered cognitive disturbances or frank mental retardation. Since that paper, many additional studies have reported that lead poisoning in children can lead to subnormal intelligence, hyperactivity, aggression, and school failure.[4,70]

In the 1950s and 1960s, many areas of the United States were found to have endemic rates of lead poisoning. These so-called lead belts were synonymous with large inner-city slums.[40] This observation led to public outcries until, in 1959, the U.S. Public Health Service recommended that blood lead levels of 60 to 80 µg/dL be considered evidence of increased lead absorption in children; levels below this were not thought to have any clinical effect.[40] In 1970, the Surgeon General reduced the level of concern to 40 µg/dL and for the first time shifted the focus from case finding to prevention through mass screening for childhood lead poisoning. Mass screening was facilitated through passage of the 1971 Lead-Based Paint Poisoning Prevention Act.[40] In 1975, the Centers for Disease Control (CDC) began to establish classifications and risk categories for childhood lead poisoning. The blood lead level of concern was reduced to 30 µg/dL in 1975, to 25 µg/dL in 1985, and to 10 µg/dL in 1991. According to the 1991 CDC guidelines, the redefinition of childhood lead intoxication as a blood lead of 10 µg/dL or greater was based on increasing scientific data indicating that toxic effects of lead were demonstrable at this level.[40,71] Subsequent studies have suggested that neurodevelopmental harm can be demonstrated in children with blood lead levels below 10 µg/dL.[72,73] The 1991 CDC guidelines also moved from a single definition of lead poisoning to a tiered approach that recommended interventions based on a range of lead levels.[71]

The most important preventive legislative action to occur was the banning of lead from residential paint in 1978. However, with decades of use, the problem of lead poisoning from exposure to paint and dust continues.

Epidemiology

Childhood lead poisoning is currently defined as a blood lead level of 10 µg/dL or greater. The new classification of lead poisoning establishes degrees of lead exposure as a means of prioritizing interventions (Table 73-2).

Data from NHANES on the epidemiology of childhood lead poisoning indicate that the average lead level of American children is 2 µg/dL, which is 80% less than mean blood lead levels in 1976. This blood lead level represents "background" exposure, the sum of different environmental sources. An estimated 450,000 U.S. children have lead poisoning.[74] Childhood lead intoxication is more prevalent in minority groups and among those living in the Northeast. The peak onset of lead poisoning in children is the second year of life, although de novo lead poisoning can appear in later childhood years.[75] Refugee children and those adopted from foreign countries can have prevalence rates of lead poisoning as high as 10% to 15%.[76,77]

As with exposure to lead in adults, childhood lead exposure can result from many sources, including lead paint or dust, air, soil, water, and food.[4,40,71] However, there are significant differences in the etiology of frank lead poisoning according to age. For example, in children, lead paint and dust are the primary source of lead poisoning (in contrast to vocational or avocational exposure in adults). Also, children can develop congenital lead intoxication.[41,78]

Lead paint remains the most common cause of lead poisoning in children.[71] The singular importance of paint results from several factors: (1) lead-containing paint chips are relatively sweet; (2) the small size and color of paint chips make them attractive to curious young children; (3) containing up to 50% lead by weight, paint chips are a high-dose source of lead, capable of producing fatal degrees of exposure[79,80]; (4) pica, or repeated ingestion of nonfood objects, is most prevalent in early childhood, and in infants, hand-to-mouth activity is a completely normal developmental process; (5) children are more likely to have their hands dirtied by dust from the window well, the floor, or outdoor soil[81]; (6) household renovation of homes with lead generally results in greater contamination of the environment, a particular risk factor for lead poisoning in infancy[82]; and (7) even household deleading can

TABLE 73-2 Interpretation of Blood Lead Test Results and Recommended Follow-up for Children

CLASS	BLOOD LEAD CONCENTRATION (μg/dL)	COMMENT
I	≤9	A child in class I is not considered to be lead poisoned.
IIA	10–14	Many children (or a large proportion of children) with blood lead levels in this range should trigger community-wide childhood lead poisoning prevention activities. Children in this range may need to be rescreened more frequently.
IIB	15–19	A child in class IIB should receive nutritional and educational interventions and more frequent screening. If the blood lead level persists in this range, environmental investigation and intervention should be done.
III	20–44	A child in class III should receive environmental evaluation and remediation and a medical evaluation. Such a child may need pharmacologic treatment of lead poisoning.
IV	45–69	A child in class IV needs both medical and environmental interventions, including chelation therapy.
V	≥70	A child with class V lead poisoning poses a medical emergency. Medical and environmental management must begin immediately.

From the Centers for Disease Control and Prevention: Preventing Lead Poisoning in Children. Atlanta, Author, 1991.

result in greater exposure to lead if not performed properly. Children who live with an adult who has a lead-related occupation are at greater risk for lead intoxication as a result of dust importation by the adult.[83]

Exposure to lead in water has greater impact on young children because of their relatively small size, their greater daily water consumption, and the greater proportion of dietary lead absorbed by a child's gut. Lead poisoning from lead-contaminated water has been reported by several researchers.[82,84] In all these cases, water was being used to prepare infant formula. Water can become highly contaminated if warmed or boiled in a vessel that contains lead.[85,86]

Although soil has not been clearly associated with the development of lead poisoning, it clearly contributes to background lead levels in children. Also, in areas with highly contaminated soil (e.g., homes near smelter), children tend to have higher blood lead levels.[87] In a study of the impact of soil lead abatement on blood lead levels in children, Weitzman and colleagues[88] showed that elimination of lead in soil could effect a reduction in blood lead of about 1 μg/dL, an amount insufficient to justify large-scale soil abatement measures.

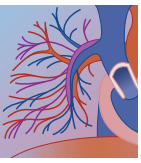
Other potential causes of lead poisoning in children include administration of folk remedies (e.g., greta, azarcon, or Paylooah), congenital exposure, and ingestion of foreign bodies.[4,42,71,89] A reported case of fatal childhood lead intoxication (blood lead level, 283 μg/dL) occurred after a child ingested a lead curtain weight, which was retained in the GI tract for several weeks.[90] Finally, lead intoxication has been reported in newborns who receive a blood transfusion from lead-poisoned donors.[91,92]

All children are not at equal risk for lead intoxication; rather, it is the unique relationship between the individual child and his or her environment that results in lead exposure. This explains the common phenomenon of one child's developing lead poisoning while living in a house that contains lead, although other children in the same environment do not have increased lead exposure. The most important risk factor is generally the oral habits of the child, particularly the presence of pica. Another risk factor for childhood lead poisoning is developmental delay. Children with significant delays—for example, those with autism—are more likely to develop lead poisoning.[71,93-95] Moreover, the pattern of lead poisoning in these children has atypical features, including its appearance at an older age and the tendency for recurrent exposure, despite environmental hazard reduction.[96] Finally, for reasons that are not clearly explained, childhood lead poisoning is more prevalent in summer than winter.

Toxicokinetics

The kinetics of lead in children have not been extensively analyzed but are thought, with some exception, to parallel the kinetics in adults.[4] However, certain differences have been well characterized. For example, the extent of lead absorption is greater in children than in adults (30% to 50% versus 10%). Also, nutritional factors have a greater role in the development of childhood plumbism. Inadequate intake of iron, calcium, and total calories, all of which are more prevalent in children, are associated with higher blood lead levels.[35,96]After its absorption, lead is distributed through soft tissues before its deposition into bone. The half-life of lead in the soft tissues of children may be longer, probably because children have less bone available for lead incorporation. As with adults, the estimated body elimination half-life of lead is 20 years.

Lead toxicokinetics in the pregnant and lactating woman have significant effects on children.[97] During both pregnancy and lactation, women mobilize skeletal



calcium.[47,98-100] In the process, lead is mobilized as well. Because lead freely crosses the placenta, the fetus invariably receives some amount of maternal lead, presumably in association with the degree of skeletal lead in the mother, reflecting her lifelong exposure. Maternal bone lead has been correlated with fetal neurotoxicity.[101] Lead is also mobilized with calcium during lactation.[102-105] However, several studies indicate that the amount of lead excreted into breast milk is negligible unless maternal blood lead level is greater than 40 to 50 µg/dL.[106,107]

Clinical Toxicity

Although the mechanisms of toxicity for lead poisoning in childhood are similar to those in adults, clinical manifestations are different. Also, the lead level at which these toxic manifestations appear is lower in children (Table 73-3). Children, for example, are more susceptible to all of lead's neurotoxic effects.

Lead encephalopathy in children has presenting features that are comparable to the disease in adults. However, encephalopathy appears in children at blood lead levels as low as 50 to 60 µg/dL.[40,108] Prominent features are irritability, anorexia, apathy, listlessness, abdominal pain, obtundation, and, if untreated, cerebral edema, seizures, and death.[108,109]

The CNS effects of lead have caused the greatest concern about childhood plumbism.[40,71,110] Exposure to lead during critical periods of neurodevelopment can produce permanent changes in cerebral architecture. The mechanisms of these changes have been described by Goldstein, Silbergeld, and others[53,111]: During the first 2 years of life, synaptic density and complexity are markedly increased such that by the third year of life, neuronal arborization exceeds the normal adult pattern almost twofold.[111,112] The enzymes that have an important role in mediating this process, including protein kinase C and calmodulin, are inhibited at very low concentrations of lead. Another critical factor in normal dendritic arborization is the activity of neural cell adhesions molecules; these proteins are also impaired by lead. The consequences of childhood lead exposure are thus reduced synaptogenesis and imprecise synaptic "pruning." Functional changes, including decreased neurotransmitter synthesis, also occur.[53,111,112] The hippocampus is thought to be the primary anatomic site for these effects, this being an area with a high zinc content.[48] Severe lead exposure can disturb the integrity of the already immature, permeable blood-brain barrier of a child.[40,113]

The clinical consequences of lead neurotoxicity are vast. At an extreme, children with severe lead intoxication can be left with profound cognitive disturbances (mental retardation). Estimates from several population-based studies are that children can lose about 5 points (95% confidence intervals ranging from 2 to 14) in intelligence quotient (IQ) for every 10 µg/dL elevation in their blood lead level.[13,69,114-116] Although a loss of 5 IQ points is arguably insignificant in any child, the potential left shift of the normal distribution of IQ among children would result in greater numbers of children with low IQ and a reduction in the number of children with superior IQ.[38] It is this principle that has, in part, maintained public health momentum to reduce blood lead levels in children to the lowest range possible. Other adverse developmental outcomes in lead-poisoned children include aggression, hyperactivity, school failure, and antisocial behaviors.[117-123] Childhood lead poisoning has been associated with juvenile delinquency and even homicidal tendencies.[124,125] Another

TABLE 73-3 Health Effects of Lead at Lowest Observed Blood Lead (PbB) Levels in Children

LOWEST OBSERVED EFFECT PbB (µg/dL)	NEUROLOGIC EFFECTS	HEME SYNTHESIS EFFECTS	OTHER EFFECTS
<10 (postnatal)	Deficits in neurobehavioral development		
10–15 (prenatal and postnatal)	Deficits in neurobehavioral development; electrophysiologic changes	ALA-D inhibition	Reduced gestational age and weight at birth; reduced size up to age 7–8 yr
15–20		Erythrocyte protoporphyrin elevation	Impaired vitamin D metabolism; pyrimidine-5′-nucleotidase inhibition
<25	Lower IQ, slower reaction time (studied cross-sectionally)		
30	Slowed nerve conduction velocity		
40		Reduced hemoglobin; elevated EP and ALA-U	
70	Peripheral neuropathies	Frank anemia	
80–100	Encephalopathy		Colic, other gastrointestinal effects; kidney effects

ALA, aminolevulinic acid; EP, erythrocyte protoporphyrin.
Adapted from Agency for Toxic Substances and Disease Registry: The Nature and Extent of Lead Poisoning in Children in the United States: A Report to Congress. Atlanta, U.S. Public Health Service, 1988.

relatively common consequence of lead poisoning is the development of a learning disability in which overall IQ is normal by standardized testing but the child demonstrates discrete learning weaknesses such as impairment in memory, auditory processing, and visual-motor integration.[70,115,126-128] Attentional weaknesses can give the appearance of attention-deficit hyperactivity disorder (ADHD).[129] These effects, which have been demonstrated in children with blood lead levels as low as 6 µg/dL, can persist through the preadolescent and adolescent years.[72,73,119,121,122,130,131] Recent data suggest that there is the potential for some reversibility in lead neurotoxicity, challenging assumptions that all neurodevelopmental effects of lead poisoning are reversible.[132,133] Some researchers believe that there is no clear evidence that lead poisoning causes learning problems in children[134,135]

Peripheral neuropathy can occur in children with lead intoxication[136]; children with sickle cell disease may be at higher risk for this complication.[136,137] Children can develop subclinical peripheral neuropathy at lead levels as low as 30 µg/dL.[137] Hearing is also significantly depressed by low levels of lead exposure[138,139] (Fig. 73-2). Motor disturbances, including reduced scores on bilateral coordination, upper limb speed, and dexterity tests, may also occur.[140,141]

Renal toxicity due to childhood lead poisoning includes impairment of vitamin D activation[51,140,141]; this appears to be a reversible effect. A 50-year follow-up of lead-poisoned children suggests that they have a sevenfold greater risk for adult hypertension.

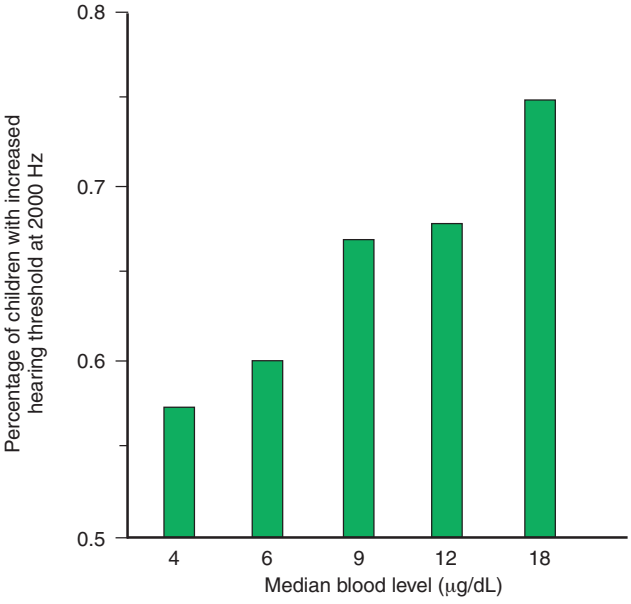


FIGURE 73-2 Fraction of children with hearing worse than a reference group stratified by quintiles of blood lead concentration, after adjustment for covariates. (From Schwartz J, Otto D: Lead and minor hearing impairment. Arch Environ Health 1991;46:300–305.)

Hematopoietic effects of lead poisoning in children include suppression of erythropoiesis with resulting anemia. Children are more sensitive to lead suppression of heme synthesis, as evidenced by their higher EP concentrations. However, the anemia that accompanies lead poisoning is sometimes cause rather than effect because iron deficiency results in greater lead absorption.[71]

Lead can disturb bone development, leading to the formation of growth arrest, or "lead lines." Lead lines are best identified at the metaphyses of long bones, particularly the distal radius and proximal fibula. These lines generally appear 3 to 6 weeks after a period of significant lead exposure and generally correlate with a peak blood lead level of greater than 45 to 50 µg/dL.[142] Childhood lead poisoning has also been associated with the development of dental caries.[143,144]

Diagnosis

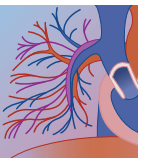
Assessment of children with known or suspected lead intoxication requires a careful physical evaluation that includes investigation of clinically overt signs and symptoms such as irritability and abdominal pain. The laboratory evaluation is an important adjunct. All children with lead intoxication should receive a venous blood lead and EP level, a CBC, measurement of blood urea nitrogen and creatinine, urinalysis, and measures of iron status (serum iron with total iron-binding capacity, serum ferritin, or reticulocyte hemoglobin). The need for radiographs should be individualized. If recent ingestion of lead-containing material is suspected, an abdominal radiograph should be obtained. Radiographs of the long bones can be useful as an assessment of timing and magnitude of exposure.[71] In children with blood lead level less than 45 to 50 µg/dL, long bone radiographs are usually valueless. As a general rule, long bone films never alter clinical management.

Newer means of assessing lead burden are being explored. For example, the research use of deciduous teeth has the potential to be clinically valuable. Also, XRF in children may ultimately prove to have the same value that is being found in the assessment of adult lead intoxication.[122,145]

Treatment

Treatment of lead intoxication in children focuses on three components, in descending order of importance: environmental inspection/hazard reduction, nutritional supplementation, and, if necessary, chelation therapy.[71,146]

Whenever a child is found to have lead poisoning, its etiology must be identified. Unless the source is clearly known, a complete environmental inspection is necessary. This inspection is guided by data obtained from an environmental history, including previous lead tests of the child, the age and condition of the child's housing, recent renovations, water intake, use of kitchenware that may contain lead, time spent elsewhere (including daycare, school, and relatives' homes), occupations of adult family members, oral habits of the child, and



siblings or playmates with lead intoxication. The results of the history should guide inspection of areas that may include the home interior and exterior, water, and alternate housing.[71,146] Inspections for lead are generally performed using either a sodium sulfide test (the reaction between this solution and lead produces gray-black lead sulfide) or XRF. The latter test is best able to detect lead paint that is covered by a nonlead surface. Interior home inspection should include dust wipings, especially when there are children younger than 1 year, who are more likely to have dust-laden hands because of their crawling. Household lead hazards, if found, should be reduced or fully abated (i.e., deleaded). In one study, deleading alone was shown to reduce blood lead levels by as much as 30%.[147] On the other hand, deleading has the potential to result in greater lead exposure if not conducted properly.[148] Therefore, it is important that work be done with minimal environmental contamination, with the family living elsewhere and with final inspection before reoccupancy. Methods of reducing without removing household lead hazards include use of trisodium phosphate detergent and the application of encapsulants, which are chemical polymers that effectively (albeit temporarily) cover lead surfaces.

Nutritional supplementation focuses on eliminating iron and calcium deficiency, both of which result in greater absorption of ingested lead.[35,71,149,150] Because there are no consistently accurate measures of iron status in children,[35,71] iron supplementation should be empirically initiated; iron sulfate elixir or drops can be prescribed in a dose of 3 to 6 mg/kg per day for a period of 4 to 6 weeks. Although evidence in animal models suggests that iron supplementation promotes the elimination of lead from the body, in human subjects, its only proven effect is reduction of further lead absorption.[35,71] Calcium deficiency is uncommon in children who have a varied diet with regular milk intake. If there is any question about calcium intake, however, the diet should be enhanced with calcium-rich foods (e.g., yogurt, cheese, milk) or calcium supplementation should be prescribed.[35,71] The combination of environmental abatement and nutritional supplementation is often sufficient to produce prompt reductions in blood lead level. However, the diminution in blood lead level may not be sufficient or may not occur rapidly enough to reduce the risk for multisystem injury. In these cases, chelation therapy is warranted.

Chelation Therapy

Chelation therapy for lead intoxication was initially developed to reduce the mortality associated with childhood lead poisoning. Increasing emphasis is being placed on its use to prevent morbidity as well. Therefore, although the same agents are available for both adults and children with lead intoxication, the greater focus, particularly the development of oral chelators, has been directed to pediatric treatment.

Increasing options in both parenteral and oral chelation therapy have brought into question the indications for hospitalization of lead-poisoned children. Decisions for hospitalization should be individualized. However, the goals of hospitalization are at least threefold: (1) to provide environmental protection so that the child has no further lead exposure, (2) to provide close monitoring for evidence of clinical toxicity, and (3) to provide aggressive chelation therapy.[60] With these principles, hospitalization should be considered for all children who are younger than 6 years and who have a blood lead level exceeding 45 to 55 μg/dL. Children who are hospitalized for lead intoxication should never be returned to the environment in which their lead poisoning occurred unless hazard reduction measures have been completed.

PARENTERAL CHELATING AGENTS

Parenteral agents for lead intoxication in childhood are BAL and EDTA. However, both of these agents are used in different fashions in the pediatric population. For example, because of the risk for CNS deterioration or death when EDTA alone is given to children with severe lead intoxication,[151] dual therapy with both BAL and EDTA should be instituted for children with blood lead levels of 70 μg/dL or greater.[69] EDTA is begun about 4 hours after the first dose of BAL. BAL is given every 6 to 8 hours until the blood lead level is less than 70 μg/dL. Adverse reactions and cautions are the same in children as in adults, although children appear to have a higher prevalence of febrile reactions.[69] BAL should be used cautiously in those with G6PD deficiency, and oral iron therapy must be discontinued. Peanut allergy is a contraindication to the use of BAL.[69]

EDTA is given in a daily dose of 35 to 50 mg/kg per day (1000 to 1500 mg/m^2). Although the agent can be given intramuscularly, intravenous administration is preferred because intramuscular EDTA is extremely painful and because brisk urine output, necessary to prevent EDTA nephrotoxicity, is better achieved with intravenous hydration. Because of EDTA's short half-life, continuous intravenous infusion is preferred; however, administration every 8 to 12 hours is an acceptable alternative. The duration of therapy is 3 to 5 days, depending on the blood lead level.[69] Thereafter, therapy is discontinued. A "rebound" blood lead level measurement should be obtained 2 to 3 days after the EDTA is discontinued for those in whom an immediate second course of EDTA chelation is anticipated. For others, a 2- to 3-week rebound level is obtained. Some degree of rebound, which represents redistribution of lead from soft tissues into blood, always occurs after chelation. Additional courses of EDTA may be necessary, depending on the degree of rebound. It is not uncommon for children with blood lead levels of 60 μg/dL or greater to require two or more courses of EDTA.[69]

Because not every child with lead intoxication has a gratifying response to EDTA chelation, particularly children with blood levels less than 45 μg/dL, the EDTA mobilization test was once a widely used method of identifying children who will benefit from chelation therapy.[152,153] To perform the test, a child is given a single dose of EDTA followed by an 8-hour collection of urine, which is analyzed for total lead excretion. A positive mobilization test is considered a ratio of greater than 0.6

between the dose of EDTA administered (in milligrams) and the quantity of urine excreted (in micrograms). The lead mobilization test, although valuable, has shortcomings.[69,154] First, it is difficult to collect 8 hours of urine in small children in the absence of catheterization, which is traumatic. Spilled or lost urine makes test interpretation difficult if not impossible.[155] The performance of the test is labor intensive and requires an 8- to 10-hour health care visit (or brief hospitalization).[156] Finally, there is little likelihood of a positive mobilization test result in children with blood lead levels less than 25 to 35 µg/dL.[153] Collectively, these factors have made the mobilization test relatively useless.[69]

ORAL CHELATING AGENTS

Numerous oral chelating agents have been used or are in current use for the treatment of lead poisoning. The two most commonly used agents are D-penicillamine and succimer.

D-Penicillamine was fortuitously discovered in 1953 by Walshe[157] and, because of its copper-chelating ability, was quickly used in the treatment of Wilson's disease. Its efficacy at chelating lead initially resulted in suggestions that penicillamine be used to treat lead-exposed workers without their removal from work.

D-Penicillamine has unique, incompletely understood chelating properties.[151] For example, it does not appear to be capable of forming stable bonds with the lead atom. Nonetheless, it does enhance urinary lead excretion, possibly by forming a heterocyclic ring (sulfur and nitrogen atoms binding the lead).[158] Like BAL, penicillamine is capable of chelating other metals, including arsenic and mercury.

The efficacy of D-penicillamine in childhood lead intoxication has been demonstrated in studies by Sachs, Vitale, Marcus, Shannon, and others.[151,159-164] Data from these studies have shown that penicillamine can reduce blood levels, even in children with blood lead levels of 20 to 35 µg/dL. Blood lead levels as low as 3 µg/dL can be achieved using this drug.[163] D-Penicillamine can be considered for children with blood lead levels in the range of 2 to 35 µg/dL.[69]

D-Penicillamine is given in a dose of about 15 mg/kg daily.[159] Its use is initiated after baseline CBC. Available only in capsules or tablets of 125 and 250 mg, the tablets must usually be crushed or the capsules opened and placed in food or drink. Having an unpleasant odor and taste, penicillamine must often be concealed in juice or food. Because iron may decrease D-penicillamine absorption by as much as 65%, iron supplementation should be discontinued during penicillamine therapy.[158] The agent is given twice a day at home by the parents. During treatment, children must be monitored every 2 to 4 weeks for evidence of adverse effects. Monitoring laboratory tests include CBC, urinalysis, blood lead, and EP determinations. Typical courses of D-penicillamine therapy are 2 to 3 months in length.

Penicillamine has an overall adverse effect rate of 5% to 10%, a rate that has led to considerable reluctance to use it. The most common adverse effect is GI upset. More serious effects occur in about 7% of children and include rash white blood cell count depression. The occurrence of adverse effects should prompt discontinuation of therapy.[159] In all reported experience with D-penicillamine use for childhood lead poisoning in otherwise healthy children, these effects have been mild and reversible.

Succimer is an oral chelating agent that was discovered in the 1950s; in 1991, it became the first oral chelating agent ever approved for the treatment of lead intoxication.[158,165-167] An oral congener of BAL, succimer has, interestingly, not been approved for adult lead intoxication, in part because of the ever-present risk for its abuse by workers, employers, or physicians.[168]

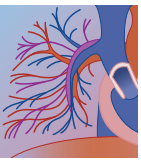
Succimer is has been approved for use in children with blood lead levels exceeding 45 µg/dL. However, studies have demonstrated that its safety and efficacy extend to children with blood lead levels between 25 and 45 µg/dL[167,169,170]; it is therefore a therapeutic option for these patients. Although there is no clearly defined upper limit of lead level for which succimer can be used, it is prudent to use conventional, dual parenteral therapy (EDTA and BAL) in children with blood lead levels of 70 µg/dL or greater.

Succimer is available in 100-mg capsules. The current treatment protocol is administration of 10 mg/kg per dose. For the first 5 days of succimer therapy, it is given three times daily. For the next 14 days, treatment is twice a day. A complete course of DMSA chelation is therefore 19 days. An alternative regimen is 10 mg/kg/dose, given twice a day for 28 days. Adverse effects associated with succimer, which occur in about 5% of patients, include rash and minor elevations in hepatic transaminases; monitoring should include periodic liver function testing.[158,162] Succimer, unlike BAL, does not produce hemolysis in those with G6PD deficiency. Also, succimer can be administered concomitantly with iron therapy. Mean reductions in blood lead with succimer are as great as 70% to 80%.[158,165,166] However, in contrast to penicillamine, succimer discontinuation is followed by a robust rebound in blood lead level, appearing 2 to 4 weeks after completion of therapy. It is not unusual to experience rebound lead values that approximate the pretreatment value. As a result, multiple courses of succimer are usually necessary to produce enduring reductions in blood lead levels. Because lead rebounds can be confused with reexposure to lead, it is important to monitor EP levels. Lead reexposure is associated with increases in EP values; lead rebound is not.

Additional agents that have been used for the treatment of lead intoxication are dimercaptopropanesulfonate (DMPS) and trientine.[171,172] Neither of these agents has moved beyond the investigational stage.

INDICATIONS AND GOALS FOR CHELATION THERAPY

The indications for initiating chelation therapy in children are controversial. For children with blood lead levels of 10 to 20 µg/dL (the majority of lead-poisoned children in the United States), chelation therapy is not



recommended, primarily because it is difficult to identify a single source of lead to abate and because for lead levels in this range, the risk for adverse effects from chelation therapy may outweigh the potential benefits.[71] Instead, education, hazard reduction (if a lead source is found), and nutritional supplementation are provided. For those children with blood lead levels of 20 μg/dL or greater, consultation with a lead specialist is recommended.[71] Among these children, chelation therapy should be considered. The decision to begin therapy should be based on (1) evidence that the blood lead level is not declining despite environmental abatement and nutritional supplementation, (2) the age of the child (evidence strongly suggests that the most neurodevelopmentally vulnerable age is the first 24 months of life[131], (3) evidence of biochemical disturbances (i.e., an elevated EP level), (4) the assumption that reducing lead burden does reverse some toxicity (e.g., renal and hematopoietic) and may reverse neurodevelopmental disturbances,[53,132,173] and (5) the desire to reduce lead burden to prevent its deposition in bone, where recrudescence later in life could occur. In initiating chelation therapy, the goals of treatment must also be established. Although this is also an area of some controversy, it is rational to have a goal of reducing blood lead level to the range of 10 to 15 mg/dL, if not lower. This requires long-term treatment strategies and frequent monitoring.

In children with more serious lead poisoning (blood lead > 30 to 35 μg/dL), formal cognitive or neuropsychological testing should be performed to identify neurodevelopmental weaknesses and initiate remedial programs as soon as possible. Because these weaknesses are generally not identifiable with gross developmental assessment (e.g., the Denver Developmental Screening Test) and may not be evident in the first few years of life, formal testing is recommended after the ages of 4 to 6 years of age, with close neurodevelopmental monitoring through adolescence.[174]

Prevention

Prevention of childhood lead poisoning has led to both primary and secondary prevention strategies.[71,110,175] Primary prevention consists of environmental inspection and abatement before a child develops lead intoxication. Because the cost of identifying and abating all homes (or other sources) with lead is prohibitive, primary prevention efforts have been difficult to implement. However, federal and state legislation that includes lead notification before home renting or purchase is being passed to ensure safe housing. Other primary preventive measures, including lead removal from soil, were attempted in a pilot study by Weitzman and colleagues, with little success.[88]

Prevention has focused primarily on secondary efforts. Under this philosophy, because lead poisoning is asymptomatic in its early phases, the goal is to identify children who have developed lead poisoning, in order to prevent their lead levels from rising further and to protect their siblings and playmates from lead exposure. Secondary prevention forms the basis of routine lead screening in children.

Secondary prevention through screening initially consisted of capillary (fingerstick) measurement of EP levels. This test was used both because EP level rises with lead intoxication and because capillary lead tests are easily contaminated by lead on the fingertip, leading to a high rate of false-positive results. When the definition of lead poisoning was reduced to 10 μg/dL in 1991, EP screening had to be abandoned because EP does not consistently rise until blood lead level exceeds 30 to 35 μg/dL.[176] Therefore, with a desire to identify all children who have blood lead levels of 10 μg/dL or greater, the current recommendation is to measure blood lead only. Although capillary lead testing can produce false-positive results, making it less useful, it is an acceptable means of screening children if performed properly.[177,178]

Another strategy for secondary prevention is universal lead screening. Because lead intoxication is present throughout the United States and there are no completely reliable means of case finding, recommendations have been that all children receive periodic lead screening, regardless of where they live or their socioeconomic status. This recommendation has been strongly criticized because it is costly and because, in many areas, its yield is extremely low.[177] Opponents believe that lead screening in areas that have a low incidence of lead poisoning are a financial waste.[179] Targeted screening—that is, screening of children thought to be at risk for lead exposure—may be a more cost-effective strategy.[180,181] Selective screening, if used, should target siblings and close playmates of lead-poisoned children. Lead poisoning in domestic pets may signal lead intoxication in the child.[182] Other children at risk for exposure include those with developmental delays, those with a history of foreign body ingestion or insertion, and those with a history of physical abuse.[71,183-185] Risk assessment questions have been created by the CDC and other researchers to use in identifying children at risk for lead exposure.[186,187]

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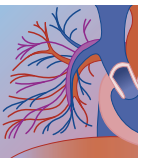

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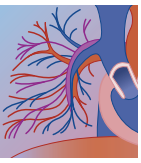

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