Lead Toxicity, A Review of the Literature. Part I: Exposure, Evaluation, and Treatment

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Abstract

The phasing out of leaded gasoline for transportation vehicles between 1973 and 1995 and the removal of lead from paint by federal mandate by 1978 have resulted in substantial lowering of mean blood lead levels in all segments of the U.S. population. However, because lead is a persistent metal, it is still present in the environment – in water, brass plumbing fixtures, soil, dust, and imported products manufactured with lead. Diagnosis of lead toxicity has traditionally been based on significantly elevated blood lead levels. However, data now implicates low-level exposures and blood lead levels previously considered normal as causative factors in cognitive dysfunction, neurobehavioral disorders, neurological damage, hypertension, and renal impairment. Chelation is the conventional recommendation in the case of blood levels associated with acute toxicity and encephalopathic damage. Issues surrounding the assessment of body lead burden and the consequences of low-level environmental exposure are critical in the treatment of chronic disease related to lead toxicity. *(Altern Med Rev* 2006;11(1):2-22)

Introduction

The removal of lead from paint and leaded gasoline in the 1970s resulted in a substantial lowering of blood lead levels in the U.S population. Lead is a persistent metal, however, and is still present in the environment – in water, brass plumbing fixtures, soil, dust, and imported products manufactured with lead. Lead-based paint covers five billion square feet of nonresidential surface area in the United States and almost 90 percent of the nation's bridges.[1] Children are continuing to bear the burden of sensitivity to lead exposure. The Centers for Disease Control (CDC) currently considers lead poisoning the foremost environmental health threat to children in the United States. The diagnosis of lead toxicity has traditionally been based on significantly elevated blood lead levels. However, data now indicates that low-level exposures resulting in blood lead levels below 10 μg/dL result in cognitive dysfunction, neurobehavioral disorders, neurological damage, hypertension, and renal impairment. While chelation is the convention recommendation for acute lead toxicity with encephalopathic damage, treatment for low-level, chronic exposure is still under investigation. Issues surrounding the assessment of body lead burden and the consequences of low-level environmental exposure are critical in the treatment of chronic disease related to lead.

Sources of Lead Exposure

Lead paint is a primary source of lead exposure and the major source of lead toxicity in children. The U.S. Department of Housing and Urban Development currently estimates that 38 million homes in the United States contain lead paint. Of those, 24 million are considered to contain significant lead-based paint hazards, including deteriorating paint and/or contaminated dust or soil outside the home.[2] As lead paint deteriorates and airborne lead settles, it contaminates dust and soil.[3] Exposure to soil that contains particulate lead has been shown to be significantly hazardous for children, who are more commonly exposed by ingestion of house dust or soil than by paint chips. Blood lead levels are more closely related to indoor

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dust exposure than to outdoor soil exposure.[4] Lead exposure can also occur during remodeling of a home built prior to 1978, when lead-based paints were still in commerce. In a population-based study, children who lived in a home that had undergone some type of renovation, repair, or remodeling work in the prior year were at 1.3 times greater risk of having an elevated blood lead level than children not exposed to such activities.[5] The risk was even higher among children living in homes where practices, such as the removal of paint with heat guns, had been used.

Drinking water is also a major source of lead exposure, estimated to be responsible for approximately 20 percent of the total daily exposure experienced by the majority of the U.S. population.[6] The 1986 amendments to the federal Safe Drinking Water Act banned the use of lead solder and leaded pipes from public water supply systems and plumbing, and limited faucets and other brass plumbing components to no more than eight-percent lead. Leaded plumbing components continue to be used in schools and daycare centers, however, and pose a significant contribution to lead in drinking water in these buildings.[7] Even valves currently used in drinking water supply lines may contain 5-7 percent leaded brass ("lead-free" brass fixtures), have been shown to discharge lead into drinking water, and constitute a significant source of lead in the water supply.[8] Drinking water in public schools in Seattle, Washington, in August 2005 still contained elevated levels of lead, after 2004 testing revealed more than 20 ppb.[9] After replacing 387 fountains and fixtures, 46 percent of tests failed a self-imposed limit of 10 ppb. The water quality testing facility believed that leaded brass fixtures in the new systems may have contributed to lead contamination in the water.

A recent episode of lead contamination in the District of Columbia water supply illustrates other problems inherent in urban water supplies. The U.S. Environmental Protection Agency (EPA) reported in January 2004 that the majority of 23,000 homes known to have lead service pipes had lead levels that exceeded the EPA's action level of 15 ppb.[10] A water decontamination chemical added to the city water supply resulted in the corrosion of lead inside the lead service pipes. One hundred sixty-three homes had lead levels over 300 ppb, 20 times higher than the EPA action level. As a result, the EPA has taken legal action against the District of Columbia Water and Sewer Authority.[11]

Lead contamination of municipal water supplies may be an under-reported problem. Ellen Silbergeld, PhD, EPA Science Advisory Board Committee Member and lead toxicologist, stated in testimony before the Oversight Committee on Government Reform in the U. S. House of Representatives: "[lead contamination of the water supply] is unlikely to be limited to the District of Columbia. There are likely to be many public water supplies in this country where water is not being tested, or if it is tested where the information is not promptly or fully communicated to consumers, and where appropriate actions are not being taken."[12] Since 2000, the EPA has received elevated lead-level reporting information from 274 water utility services serving a total of 11.5 million people. The EPA Inspector General issued a finding in 2004 that the EPA's national drinking water database is incomplete and out of date, and that the EPA has not communicated accurately to the public about drinking water quality and compliance because violations are seriously under-reported.[13]

Lead is also found in lead-glazed ceramics; and food eaten or stored in containers painted with lead-based paint or lead-containing glaze may contain significant amounts of lead. One study associated the storing of food in lead-glazed containers with elevated blood lead levels.[14] Leaded crystal, cigarette smoke, lead solder used in canned foods produced outside the United States, children's toys, vinyl lunchboxes, contaminated candy imported from Mexico, and children's jewelry produced outside the United States have all been shown to contain significant amounts of lead.[15] Vinyl mini-blinds manufactured outside the United States before 1996 have been shown to be a significant contributor to childhood lead poisoning. In a 1996 North Carolina survey, 75 percent of childhood lead poisoning cases in a six-month period included lead dust from vinyl mini-blinds as a contributing factor.[16] In nine percent of the cases, vinyl mini-blinds were the only source of lead exposure identified. Other products manufactured with soft vinyl, specifically children's lunchboxes, have been found to contain more than 90 times the legal limit for lead in paint.[17]

Herbal remedies from India, China, and other parts of Asia may be potential sources of lead exposure. Certain Ayurvedic herbal products manufactured in South Asia were found to be contaminated with lead ranging from 5-37,000 μg/g.[18] Since 1978, 55 cases of acute lead toxicity have been directly related to the ingestion of Ayurvedic medicines in the United States and other countries.[19]

Workers in certain occupations are also exposed to high levels of lead. Lead exposure occurs during the manufacture of ammunition, batteries, sheet lead, solder, some brass and bronze plumbing, ceramic glazes, caulking, radiation shields, circuit boards, military equipment (jet turbine engines, military tracking systems), intravenous pumps, fetal monitors, and some surgical equipment. Construction workers are known to have a high risk for lead exposure.[1]

Toxicology of Lead

Absorption and Storage

Lead is unique in that man-made sources contribute almost solely to exposure in the post-industrial era. Pre-industrial blood lead levels of Native Americans living in the United States 700-1,000 years ago are estimated to have been 0.016 μg/dL.[20] These levels are 50-200 times lower than those currently reported in individuals living in remote regions of the Himalayas with no known lead exposure (0.78-3.2 μg/dL). On the other hand, children with lead dust or soil dust exposure can have blood lead levels as high as 90 μg/dL.[20] Bone levels in pre-industrial skeletal remains indicate that current body lead burdens are 500-1,000 times greater than in individuals with pre-industrial exposure to lead.[21]

Lead exposure occurs mainly through the respiratory and gastrointestinal (GI) tracts. Approximately 30-40 percent of inhaled lead is absorbed into the bloodstream.[22] Gastrointestinal absorption varies depending on nutritional status and age. Iron is believed to impair lead uptake in the gut, while iron deficiency is associated with increased blood lead concentrations in children.[23] Calcium supplementation studies demonstrate that increased dietary calcium in animals, infants, and children result in consistent decreases in the absorption of lead.[24,25] Increased intakes of magnesium, phosphate, alcohol, and dietary fat have also been shown to decrease gastrointestinal absorption of lead.[26,27] GI absorption of lead is greatest in infancy; infants can absorb up to 50 percent of lead ingested from food, water, contaminated dust, or soil, while adults absorb only 10-15 percent.[28] Inorganic lead (food, water, paint, toys, vinyl products) is minimally absorbed through the skin, but tetraethyl- or alkyl-lead (leaded gasoline), which is still legally allowed in aircraft, watercraft, and farm machinery, is well absorbed through the skin.[29]

Once absorbed, 99 percent of circulating lead is bound to erythrocytes for approximately 30-35 days (only one percent of absorbed lead is found in plasma and serum) and is dispersed into the soft tissues – liver, renal cortex, aorta, brain, lungs, spleen, teeth, and bones – over the following 4-6 weeks. Due to the short half-life (35 days) in the bloodstream, blood lead levels cannot be used to diagnose or rule out evidence of exposure that occurred more than six weeks prior to testing.[30]

In adults approximately 80-95 percent of retained lead is stored in the bone, while in children approximately 70 percent is stored in bone, resulting in more soft tissue lead in children compared to adults.[22] Lead is stored in bone for extended periods of time, with half-life estimates of 20-30 years. Even with the bone turnover that occurs in childhood and adolescence, there is evidence to suggest that by the seventh decade of life, more than one-third of bone mass contains lead acquired in childhood and adolescence.[31] Due to the net slow turnover and release of lead from bone, lead in bone appears to increase significantly with age. Mean tibia lead concentrations for adolescents have been measured at 3 μg/g, concentrations for adults 30-50 years at 17 μg/g, and at 30 μg/g for adults over 75 years.[32]

Storage of lead in different compartments of bone is also an age-dependent process. During infancy and childhood, lead is deposited in trabecular bone because it is the most active site of remodeling; whereas, in adults lead is deposited in both trabecular and cortical bone.[33] Although by adulthood most of the lead burden is stored in cortical bone and teeth, what is stored in trabecular bone is partially labile and is released back into the bloodstream and soft tissues by diffusion as well as resorption.[34] Bone lead can contribute to elevated blood lead levels long

after the exposure no longer exists.[35] Situations that increase bone turnover, such as pregnancy, lactation, postmenopausal osteoporosis, hyperthyroidism, and cisplatin chemotherapy, have been shown to increase blood lead levels as a result of the mobilization of bone stores.[36-39] Bone lead is also readily transferred to the fetal skeleton during pregnancy.[40]

Hepatic Metabolism/Excretion

Inorganic lead is not metabolized but is excreted unchanged, primarily in the urine. The mechanisms for fecal excretion of absorbed lead are not clearly understood; however, pathways of excretion may include secretion into the bile, gastric fluid, and saliva, accounting for approximately one-third of total excretion of absorbed lead.[30] Organic or alkyl-lead, (leaded gasoline, also identified as tetraethyl- and tetramethyl-lead) undergoes oxidative dealkylation to the highly neurotoxic metabolites, triethyl- and trimethyl-lead.[41] In the liver, the reaction is catalyzed by a cytochrome p450-dependent monooxygenase system.[42] Lead can also be excreted through the nails and sweat; two studies have shown significant losses of lead in the sweat of study subjects undergoing sauna therapy compared to urine levels.[43,44]

Understanding Lead Toxicity – Diagnosis and Monitoring

Blood Lead Concentrations

Measuring blood lead is the most commonly accepted and verifiable biomarker for lead exposure. Lead is unique as a toxicant in that there is agreement among the CDC, the Agency for Toxic Substances and Disease Registry, and the Environmental Protection Agency that there is no toxic threshold for lead. This means there is no measurable level of lead in the body below which no harm occurs.[12] The EPA has listed a Maximum Contaminant Level Goal (MCLG) of zero ppb for lead in water, and states, "At relatively low levels of exposure, [adverse health effects] may include interference with red blood cell chemistry, delays in normal physical and mental development in babies and young children, slight deficits in attention span, hearing, and learning abilities in children, and slight increases in the blood pressure of some adults. It appears that some of these effects, particularly changes in the levels of certain blood enzymes and in aspects of children's neurobehavioral development, may occur at blood lead levels so low as to be essentially without a threshold."[45] Current excessive exposure guidelines developed by the CDC and the American Pediatric Association (APA) consider blood levels ≥10 μg/dL to be excessive for infants, children, and women of childbearing age. Occupational exposure is unsafe when worker's blood levels exceed 30 μg/dL. In occupational settings, air exposure levels are set to limit exposure so blood lead levels do not exceed 60 μg/dL.[46]

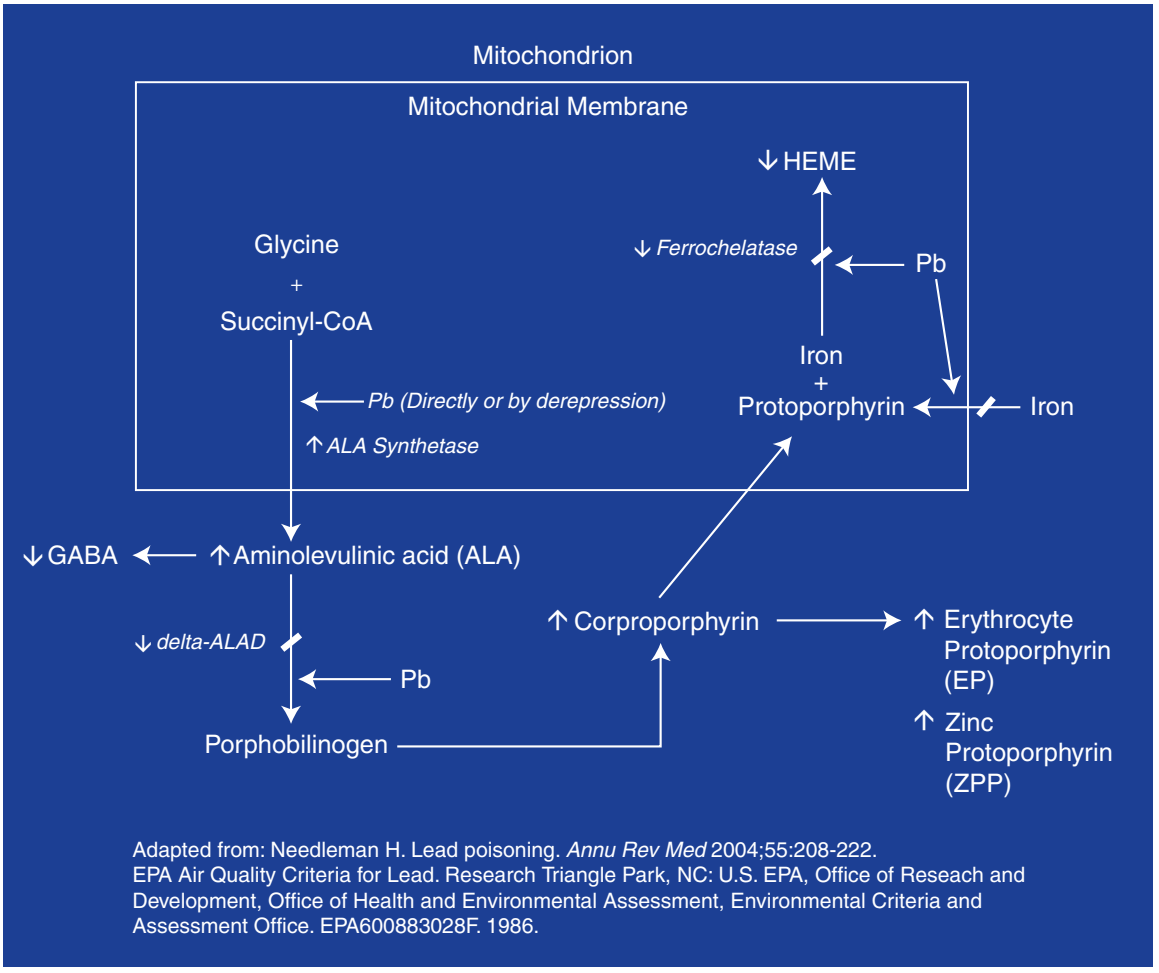
Mean blood lead levels in the United States have dropped significantly since federal regulations decreased production of leaded gasoline and lead-containing paints. Between 1976 and 1980, children ages 1-5 years had a median blood lead level of 15.0 μg/dL;[47] by 1999 the median blood lead level had dropped to 1.9 μg/dL. There are still 454,000 children in the United States with blood lead levels greater than 10 μg/dL.[48] Current median blood lead levels in U.S. adults, ages 20-59 years, estimated from the National Health and Nutrition Examination Surveys (NHANES) III 1999-2002, are 1.5 μg/dL (95% CI, 1.5-1.6). Blood lead concentrations are highest in the strata that includes adults 60 years and older (2.2 μg/dL; 95% CI, 2.1-2.3).[49]

Biomarkers of Hematological Toxicity

Lead is a divalent cation; its strong binding capacity for sulfhydryl proteins creates interference with enzymes and structural proteins. The most well-known of these distortions involves interference with the heme synthetic pathway, specifically the enzyme delta-aminolevulinic acid dehydratase (delta-ALAD; ALAD). Interference with heme production and subsequent reduction of the heme body pool is one of the main causes of lead-related pathology. When whole blood lead levels (PbBs) exceed 20 μg/dL the activity of ALAD is inhibited by 50 percent. However, ALAD activity may also be impaired in porphyria, liver cirrhosis, and alcoholism. In addition, ALAD levels cannot be used to diagnose degrees of lead toxicity, since the correlation between PbBs and ALAD is not linear.[50]

A marked increase in urinary excretion of aminolevulinic acid (ALA), the substrate that accumu-

Figure 1. Effects of Lead on Heme Biosynthesis



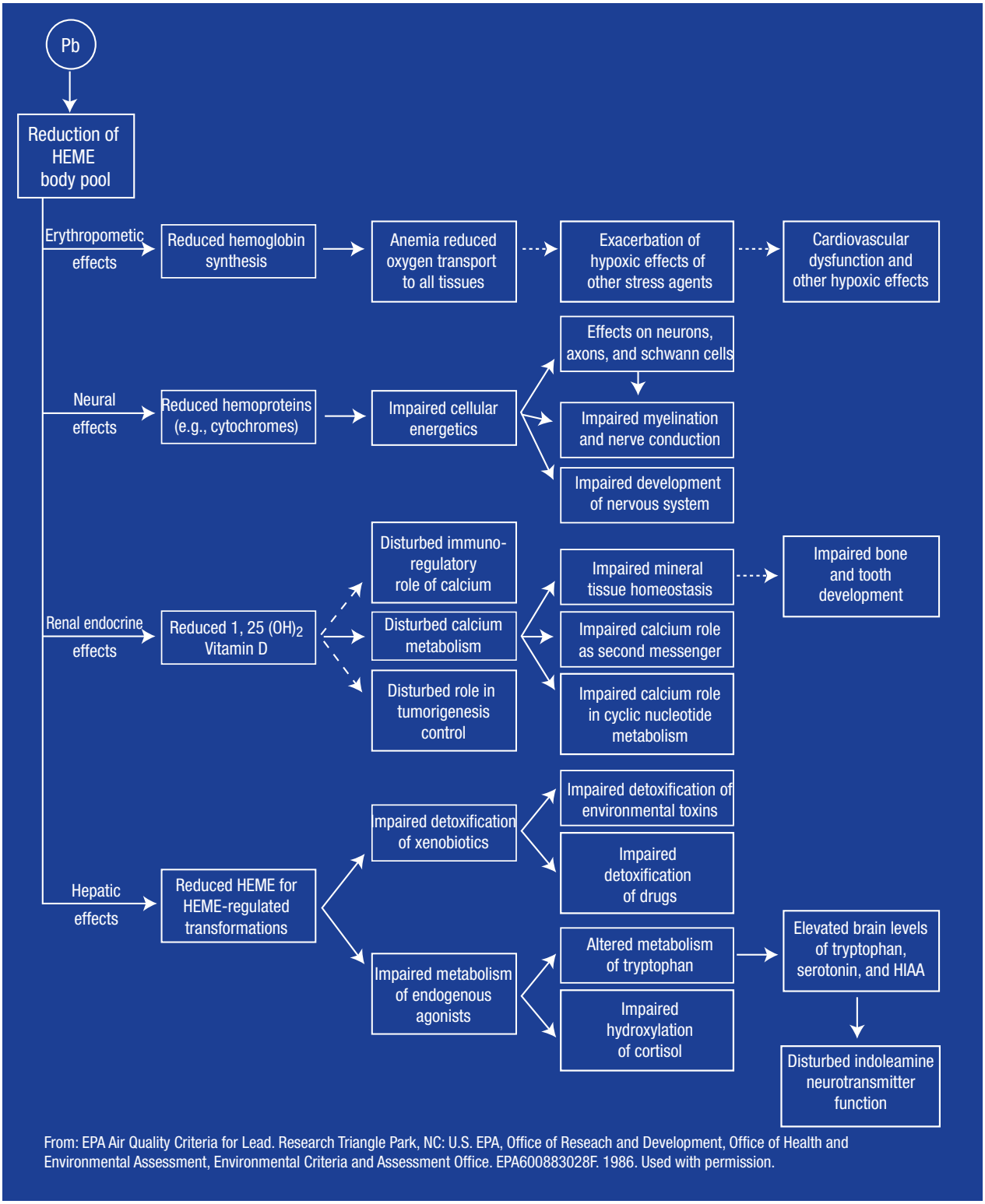
Adapted from: Needleman H. Lead poisoning. *Annu Rev Med* 2004;55:208-222.
EPA Air Quality Criteria for Lead. Research Triangle Park, NC: U.S. EPA, Office of Reseach and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. EPA600883028F. 1986.

lates as a result of decreased ALAD, has been used in the past as a marker for lead toxicity, but can be detected only when PbBs exceed 35 μg/dL in adults and 25-75 μg/dL in children. It is, therefore, not a useful biomarker in low-level toxicity.[51] Inhibition of delta-ALAD prevents ALA from being converted to porphobilinogen, inhibiting incorporation of iron into the protoporphyrin ring. The result is reduced heme synthesis, both for hemoglobin and for cellular respiration, contributing to the fatigue and anemia seen in chronic lead toxicity (Figure 1). In addition, inhibiting this enzyme results in increased circulating levels of ALA, leading to decreased GABA release in the central nervous system (CNS). This may explain some of the behavioral disorders seen in both porphyria and lead toxicity.[52]

Human ALAD has been shown to be a polymorphic enzyme with two common alleles, ALAD1 and ALAD2.[53] The genetic polymorphism resulting in the expression of the ALAD2 allele appears to increase susceptibility to lead toxicity. Studies in various populations with lead exposure have found consistent relationships between the ALAD2 allele and elevated levels of blood and bone lead.[53] Anemia due to glucose-6-phosphate dehydrogenase (G6PD) deficiency is also known to increase the susceptibility to lead toxicity.[54]

Ferrochelatase, the enzyme that catalyzes the insertion of iron into protoporphyrin IX, is also impaired by lead. Interruption of this enzyme results in an increase of the substrates erythrocyte protoporphyrin (EP), when bound to iron, and zinc

Figure 2. Multi-organ Impact of Reduced Heme Body Pool



From: EPA Air Quality Criteria for Lead. Research Triangle Park, NC: U.S. EPA, Office of Reseach and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. EPA600883028F. 1986. Used with permission.

Table 1. Lead-Related Symptoms

Earliest Symptoms	Symptoms of chronic exposure
• diffuse muscle weakness • general fatigue/lethargy • myalgia • joint pain/arthritis • loss of appetite • unusual taste in mouth/ change in taste of food • headache • insomnia • irritability • diminished libido • weight loss of 10 lbs or more without known cause • tremulousness • personality changes	• abdominal pain/cramping • nausea/vomiting • short-term memory loss • depression • incoordination • numbness and tingling in extremities • constipation • inability to concentrate • impotence **Severe toxicity** (The chances of the following symptoms resulting from lead exposure rise significantly when the blood lead is elevated over 30 µg/dL.) • frank paralysis • somnolence/severe lethargy • abdominal colic

protoporphyrin (ZPP), when bound to zinc. Although used to diagnose acute lead toxicity, these elevations do not appear in the blood until lead levels reach 35 µg/dL. The threshold for EP or ZPP is 30 µg/dL in adults and the threshold for ZPP in children is 15 µg/dL.[55] Another limitation for using EP levels to assess lead exposure is that other diseases or conditions such as porphyria, liver cirrhosis, iron deficiency, age, and alcoholism may also produce similar effects on heme synthesis.[51] Figure 2 summarizes the far-reaching effects that reduction of the body heme pool can have on major organ systems.

Lead can also impair the activity of pyrimidine 5'-nucleotidase, increasing the pyrimidine nucleotides in red blood cells and preventing the maturation of erythroid elements, which leads to decreased red blood cell counts and eventually anemia. A potential biomarker for the hematological effects of lead is the observation of basophilic stippling and premature erythrocyte hemolysis. This effect, however, can occur in other toxicant exposures, including benzene and arsenic, and in a genetically-induced, enzyme-deficiency syndrome.[56] Basophilic stippling and microcytic or normocytic, hypochromic anemia only occur after significant levels of exposure – at PbBs over 50 µg/dL in adults and 25-40 µg/dL in children. Neither basophilic stippling nor hypochromic anemia are indicators of low level exposure.[57] Hemoglobin levels do not start to decrease as a result of lead exposure until blood lead levels are 50 µg/dL for adults and 40 µg/dL for children.[55]

Bone Lead

Lead is considered to be stored in one of two compartments in the bone – the exchangeable pool at the bone surface and the non-exchangeable pool deeper in cortical bone.[58] Lead can readily enter the plasma from the exchangeable pool, but can only leave the non-exchangeable pool and move to the surface of the bone when bone is actively being resorbed. A study of lead-stable isotope signatures revealed that approximately 40-70 percent of blood lead in adults

comes from bone lead.[58] During pregnancy, this figure is more variable; 10-88 percent of blood lead may come from bone due to increased mobilization of bone during pregnancy. In the same study, the author concluded that approximately 80 percent of cord blood may result from liberated bone lead in the mother.[40]

Mobilization of bone during pregnancy may contribute not only to increased blood lead levels in pregnancy, but also during lactation.[59] The same phenomenon of fetal exposure from maternal bone has been documented in primates where 7-39 percent of the maternal lead burden transferred to the fetus appeared to have been derived from lead in the maternal skeleton.[60] Lead appears to have an osteoporotic effect in bone. In a study examining NHANES data from 1988-1994, bone mineral density alone was inversely correlated with blood lead levels in women ages 40-59. Menopause appeared to compound the problem; lead levels were 25-35 percent higher in both natural and surgical menopause.[61]

Cortical bone lead, currently measured by x-ray fluoroscopy (XRF), is considered a sensitive biomarker for cumulative lead exposure and correlates well with historical rather than current blood lead measurements. Current blood lead levels do not reflect total body burden as measured by bone stores.[62] Both EDTA mobilization testing (detailed in the later section, Toxic Effect of Lead on the Renal System) and bone XRF are considered the most consistent and sensitive tools for assessing body lead burden.[63,64]

Lead in Soft Tissue

Lead is stored in soft tissue; autopsy studies show the liver to be the largest repository of soft tissue lead (33%), followed by kidney cortex and medulla, pancreas, ovary, spleen, prostate, adrenal gland, brain, fat, testis, heart, and skeletal muscle. Levels of lead in soft tissue appear to be relatively constant during life, despite a fairly high turnover rate.[65]

Toxic Effects of Lead

Lead toxicity affects the central and peripheral nervous systems, renal function, and the vascular system. The toxic effects of lead vary greatly, manifesting as subtle changes in neurocognitive function in low-level exposure or as the potentially fatal encephalopathy of acute lead poisoning.[52] As exposure progresses, symptoms of toxicity may manifest differently. Tables 1 and 2 summarize clinical symptoms and signs in the different stages of lead toxicity. Laboratory abnormalities will also differ based on the chronicity and level of exposure. Table 3 outlines laboratory tests in lead exposure and their relationship to blood lead levels.

Table 2. Signs of Lead Toxicity

In General

- blood lead over 10 µg/dL
- hypertension
- decreased nerve conduction velocity
- hyper-reflexia
- tremors
- upper extremity weakness
- forearm extensor weakness (wrist drop)
- gingival lead lines (purple-blue lines within gingival tissue)
- buccal lead staining
- papilledema
- increased intracranial pressure
- macular gray stains

In Children

- aminoaciduria (reversible)
- growth failure
- language delay
- behavioral change/hyperactivity
- increased intracranial pressure
- abdominal pain

Effects of Lead on the Nervous System

Early symptoms of lead neurotoxicity in both adults and children include irritability, headache, decreased attention span, memory loss, and low-level cognitive impairment (Table 1). As childhood exposure increases, behavioral symptoms of

Table 3. Lab Abnormalities in Lead Toxicity

↓ Erythrocyte ALAD – correlates inversely with blood lead at levels as low as 3 µg/dL

↑ Urinary ALA – increased with blood lead levels > 25 µg/dL in children, > 35 µg/dL in women, > 45 µg/dL in men

↑ Erythrocyte protoporphyrin (EP) or zinc protoporphyrin (ZPP) – low sensitivity if blood lead is < 30 µg/dL in adults or < 15 µg/dL in children

CBC – normochromic or hypochromic anemia with basophilic stipling, elevated reticulocyte count (all red cell abnormalities are seen only when blood lead levels are significantly elevated – 50 µg/dL or above)

Bone radiographs – dense calcifications at the distal metaphyseal plate (lead lines most commonly seen in children 2-5 years of age)

The following lab abnormalities are seen only in acute lead toxicity:

↑ BUN
↑ Serum creatinine
↑ Serum uric acid
↑ Urinary amino acids, glucose, and phosphate

impulsiveness, inability to follow sequences or directions, decreased play activity, lowered IQ, and poor attentiveness are seen at PbBs of 10-35 μg/dL.[29,52]

The most commonly documented neurological symptom of lead exposure in adults is peripheral neuropathy, typically involving extensor muscle groups. There is minimal sensory involvement and if radial or peroneal nerves are involved, the neuropathy will be exhibited as wrist or foot drop.[50]

One of the major reasons for lead's neurotoxic effects is that it competes with or mimics the action of calcium.[52] At extremely small picomolar concentrations, lead competes for binding sites in the cerebellum for phosphokinase C. This process affects calcium entry into cells and neuronal function, and alters mitochondrial structure, leading to inhibited cellular respiration and altered calcium-based reactions and neuronal signaling.[65,66] This results in an increase in spontaneous neurotransmitter release and an inhibition of what would otherwise be controlled stimulated release.[52] This toxicity is particularly damaging to the developing nervous system of the fetus that lacks the lead-binding proteins found in mature astroglia, which normally sequester and eliminate lead. Lead is toxic to immature astrocytes and interferes with myelin formation, both of which are involved in the formation of the blood-brain barrier. It is this disruption in maturation of the blood-brain barrier (not fully developed until age six months) during fetal development and early infancy that results in much of lead's neurotoxicity. When the barrier is disrupted, molecular proteins like albumin enter the tissues of the CNS, resulting in edema, increased intracranial pressure, and encephalopathy.[67]

Children are far more susceptible to lead neurotoxicity than adults because they absorb a higher fraction of bioavailable lead and have a developing system of cell differentiation and growth that is more

vulnerable to inhibition and damage.[52] The neurotoxicity of lead is one of the most well studied and verified examples of the sensitivity of a developing human to a toxicant. Because lead affects processes of neural development (synaptogenesis, cell migration, glial cell growth), the interruption of these processes can lead to permanently altered brain function.[67,68] Multiple studies have shown exposure to lead in infancy and early childhood is directly associated with reading disabilities, disturbances in fine motor function, poorer reading scores, failure to graduate from high school, and lower exam scores up to a mean age of 18.7 years.[69,70] A meta-analysis of four key studies on lead and behavior concluded that lead can cause impaired neurobehavioral activity at 10-15 μg/dL.[71]

Recent studies evaluating the relationship between blood lead levels and neurobehavioral performance have shown evidence of effect at levels below 10 μg/dL – the current level considered excessive for pediatric exposure. The first was an evaluation of 4,853 children in the NHANES III database.[72] The mean PbB was 1.9 μg/dL, with only 2.1 percent of the study population having a PbB over 10 μg/dL. A significant inverse relationship was observed between blood lead levels and reading and math test scores and comprehension testing. The correlation was noted at levels as low as 2.5 μg/dL. The effect of blood lead was stronger in those with levels below 5.0 μg/dL than those with levels above 5.0 μg/dL.

The second study evaluated the relationship between IQ and lead exposure in 172 children with blood lead levels measured serially between age six months and five years.[73] A significant inverse relationship between IQ and average lifetime blood lead was noted, even at the lowest measurable PbB – 1 μg/dL. A net increase of 1 μg/dL in the lifetime average blood lead level was associated with a loss of 0.46 IQ points. The total decrease in IQ for those who had lifetime average blood lead levels of 1-10 μg/dL was 7.4 points, significantly more than the loss of IQ points in those with average PbBs of 10-20 μg/dL.

Third was a cross-sectional study of blood lead levels and test scores in 501 children ages 6-9 years.[74] A small inverse relationship was noted between PbBs and tests of cognitive ability, number skills, and word reading, when 33 possible confounding variables were taken into account. The effect of PbBs in performance scores was greater for the range of 5-10 μg/dL than for those with lead levels of 10-20 μg/dL.

No clear explanation has been offered for the apparent greater neurotoxic effect of lead concentrations below 10 μg/dL compared to higher levels. Canfield cites evidence that higher concentrations of heavy metals might elicit defense mechanisms, like metallothionein and glutathione induction, not elicited by lower levels.[73,75]

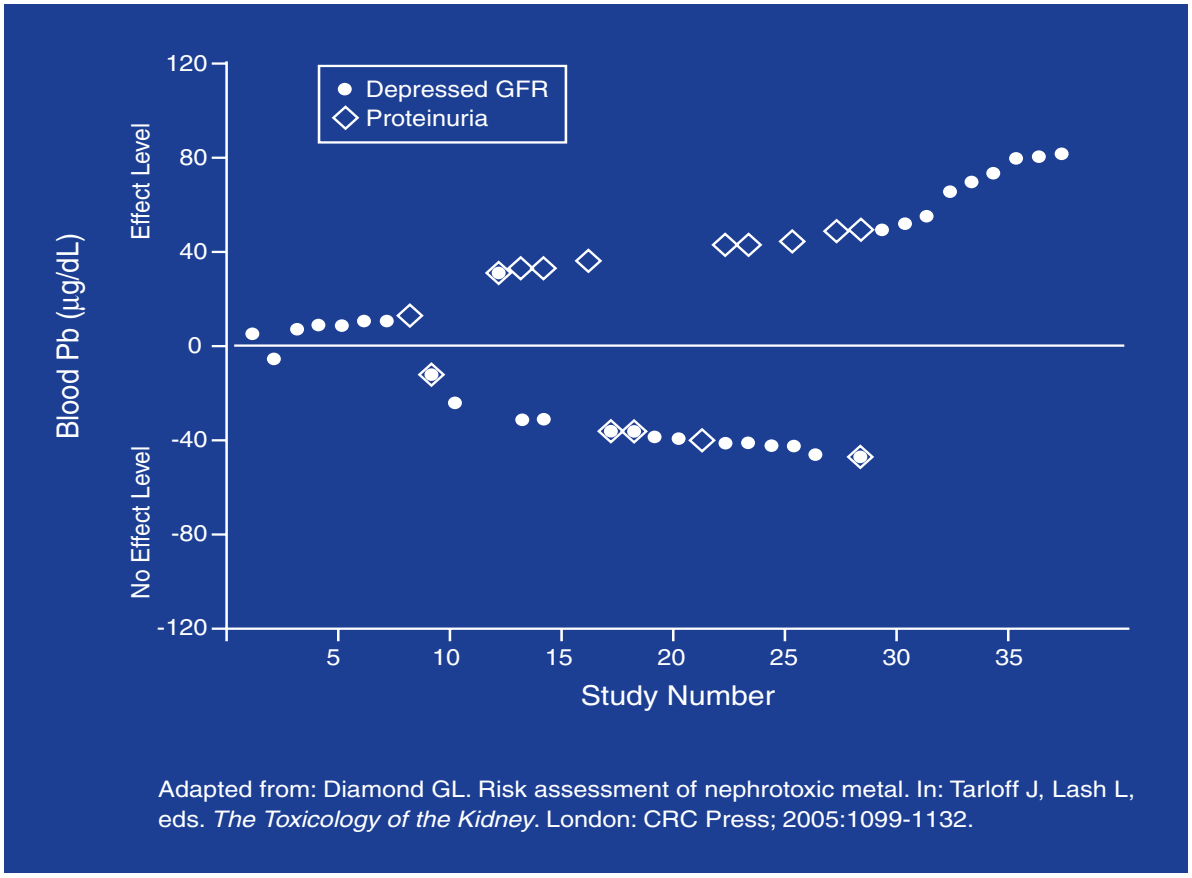
Lead exposure has been shown to affect all neurotransmitters in the brain – the dopaminergic, cholinergic and glutaminergic systems.[71] In rat studies, learning deficits induced by lead were mediated by defects in these systems.[76]

Multiple pathways may be responsible for the neurological deficits in lead toxicity contributing to irritability, fatigue, and depression. It is interesting to note that when healthy rats were given the option of drinking a 15-percent solution of alcohol they avoided it. But when blood lead levels were raised to 61 μg/dL, alcohol intake increased significantly in rats given a choice of water sources or in those offered only an alcohol solution.[77] The authors hypothesized the alcohol was acting as a sedative for lead-induced irritability.

Toxic Effect of Lead on the Renal System

Lead nephropathy has been well documented in occupationally exposed workers. It manifests as proximal tubular damage, glomerular sclerosis, and interstitial fibrosis. Signs include proteinuria, impaired transport of glucose and organic anions, and lowered glomerular filtration rate (GFR) (Figure 3).[78] Classically, renal insufficiency is found in acute lead toxicity and is accompanied by abdominal pain (lead colic), cognitive defects, peripheral neuropathy, arthralgias, anemia with basophilic stippling, a "lead line" at the junction of the teeth and gums, and high PbBs >80 μg/dL.[79] However, there is significant evidence that renal damage occurs at much lower exposure levels in the general population. Multiple studies define a strong relationship between blood lead levels and a decline in renal function associated with age in study populations not occupationally exposed.[80-83] In

Figure 3. Indicators of Renal Functional Impairment at Various Blood Lead Concentrations



Adapted from: Diamond GL. Risk assessment of nephrotoxic metal. In: Tarloff J, Lash L, eds. *The Toxicology of the Kidney*. London: CRC Press; 2005:1099-1132.

these studies, significant correlations exist between PbBs <10 µg/dL and elevations in serum creatinine; serum creatinine increased 0.14 mg/dL for every 10-fold increase in blood lead. These studies have admitted limitations because they did not exclude confounding factors, including hypertension, use of angiotensin-converting enzyme inhibitors, or urinary protein excretion.[64,84]

A prospective trial of 448 adults, a subsample of the Normative Aging Study, found low-level lead accumulation (measured by XRF tibia bone lead) was associated with an increased risk for declining renal function (measured by increased serum creatinine).[85] This was true particularly for diabetics and hypertensives, who are already at risk for renal disease. It is important to note that the mean baseline and six-year follow-up PbBs in this population would otherwise be considered normal – 6.5 µg/dL and 4.5 µg/dL, respectively. However, in the diabetic subpopulation, both blood and bone lead levels were associated with significant increases in serum creatinine. When compared to non-diabetics, those in the highest quartile of bone lead had 17.6-fold higher serum creatinine and those in the highest quartile of blood lead had 12.8-fold higher serum creatinine.

In a prospective trial, EDTA-mobilization tests demonstrated that chronic low-level lead exposure is related to the progression of chronic renal insufficiency.[64] The trial revealed a significant relationship between blood lead levels, body burden as diagnosed by EDTA mobilization, and GFR. An elevated body lead burden was defined as 600 µg urine lead in a 72-hour collection after infusion of 1 g calcium disodium EDTA. Of 121 patients with chronic renal insufficiency, body lead burden and blood lead levels were significant predictors of progression of renal disease, the body lead burden being the most powerful predictor, followed by male gender and the

presence of chronic interstitial nephritis. Seventeen patients progressed (defined by a doubling of serum creatinine), and 15 of those had what were considered high normal body lead burdens – 80-600 μg and normal PbBs (4.9 ± 2.6 μg/dL).

Toxic Effects of Lead on the Cardiovascular System

Elevated PbBs (20-29 μg/dL) correlate with significant increases in all-cause circulatory and cardiovascular mortality.[86] Several clinical trials and population studies of occupationally exposed groups have shown that lead exposure correlates with increased incidence of hypertension, cerebrovascular disease, and cardiovascular disease.[87,88] There is substantial evidence that long-term, low-level exposure to lead can contribute to hypertension in both animals and humans.[89] This risk of hypertension and mortality is considerably higher for African-Americans than Caucasians and is thought to be related to increased levels of arterial blood pressure in African-American study populations when compared to Caucasian populations. In addition, African-Americans are also more susceptible to lead-related hypertension and have higher mortality rates at lower blood lead levels.[90]

An exhaustive report of research relating to lead and hypertension, as well as all other data relating to lead toxicology, has been drafted in a toxicological profile by the Agency for Toxic Substances and Disease Registry.[46] Major studies will be briefly mentioned here as the data on hypertension and its relationship to lead exposure is well established in the medical literature. Three meta-analyses of 61 collective studies show a positive relationship between increasing blood lead levels and elevated systolic and diastolic blood pressure.[91-93] Although these meta-analyses reveal only small rises in arterial pressures (1.0-1.25 mmHg and 0.6 mmHg for every doubling of PbBs), it is a significant finding because a population-wide reduction in diastolic blood pressure of as little as 2 mmHg results in a six-percent reduction in the risk of coronary heart disease, a 15-percent reduction in the risk of stroke and transient ischemic attacks, and a 17-percent reduction in the prevalence of hypertension.[94]

The increased risk of elevated blood lead in postmenopausal women secondary to bone resorption yields a concomitant risk for hypertension.[95] In an analysis of 2,165 peri- and postmenopausal women, blood lead levels and incidence of hypertension were analyzed.[95] Among women ages 40-59 years (both pre- and postmenopausal), those in the highest quartile of PbBs (mean value 6.3 μg/dL) had a 3.4-fold increased risk for diastolic hypertension, compared with the lowest quartile of PbBs (mean value 1.0 μg/dL). Looking at only postmenopausal women, those in the highest quartile of PbBs had an 8.1-fold increased risk for diastolic hypertension. Large scale trials have shown that postmenopausal women are at increased risk for hypertension, and that loss of estrogen is directly associated with this risk.[96] There are as yet no statistical analyses of the effects of lowered estrogen on bone resorption of lead into the systemic circulation.

In an analysis of 2,125 participants in the NHANES 1999-2000, blood lead and cadmium levels were correlated with the incidence of peripheral arterial disease (PAD) based on ankle-brachial blood pressure indices.[97] For the large majority (98.3%) of subjects in the study, PbBs measured under 10 μg/dL. Subjects with PAD had 13.8-percent higher PbBs and 16-percent higher blood cadmium levels than subjects without PAD, both statistically significant correlations even though levels of these toxic metals in those with PAD are still considered within normal limits. These effects were consistent, even after adjusting for GFR and C-reactive protein, ruling out inflammation and impaired renal function.

Tibia lead levels were found to be significantly associated with electrocardiographic changes in men ages 48-93.[98] Those under 65 had a significant increase in QT and QRS intervals for every 10-μg/g increase in tibia lead. After adjusting for high density lipoprotein (HDL; since low HDL levels are a risk factor for ECG abnormalities) and age, men under 65 with the same incremental increase in tibia lead had a 2.23-fold greater risk for intraventricular block. In men over 65 years, each 10-μg/g increase in tibial lead resulted in 1.2-fold higher risk for atrioventricular block. Blood lead levels in these men (5.8 μg/dL ± 3.4) were not associated with tibia lead levels.

Other Lead-Exposure Related Effects

Lead interferes with the conversion of vitamin D to 1,25-dihydroxyvitamin D, the active hormonal form of the nutrient.[99] The final hydroxylation of vitamin D that leads to the active form takes place in the renal tubule, where lead is believed to interfere with the activation of vitamin D. Studies of lead-exposed children show significant reductions of serum 1,25-dihydroxyvitamin D levels at PbBs between 33-120 μg/dL, with the effect becoming measurable at levels as low as 12 μg/dL in those 2-3 years old.[99] In children with higher PbBs (>62 μg/dL), serum calcium depression (both total calcium and ionized calcium) and increases of serum parathormone have been documented. Because these events would normally lead to an increased level of serum 1,25-dihydroxyvitamin D, the authors theorized that lead may have an even more powerful effect on depressing active vitamin D production than observed in this study.[100] Studies of lead and vitamin D have concluded that the effect of lead on vitamin D is not evident in children when they have adequate nutritional intake of calcium, vitamin D, and phosphorus, and have PbBs under 20 μg/dL.[101]

Workers exposed to lead in manufacturing facilities demonstrate an increased frequency of stillbirths, miscarriages, and spontaneous abortion, reduced sperm counts and motility, decreased fertility, hypospermia, increased rates of teratospermia, and decreased libido.[1] Women who have lead-exposed male partners have higher rates of miscarriage.[102] Children of lead-exposed workers have increased rates of congenital epilepsy and cardiovascular disease.[103]

Lead was recently upgraded from the status of a possible to a probable human carcinogen by the International Agency for Research on Cancer (IARC), based on sufficient evidence for carcinogenic effects in humans.[104] Lead exposure has been related to increased incidence of overall cancers, as well as stomach, lung, and bladder cancer.[105]

A study of lead exposure and age-related cataract incidence in men found those with the highest tibial bone lead levels had more than 2.5-times greater risk for cataract compared to those with the lowest level of tibial lead.[106] Individuals with cataracts have significant levels of lead in the ocular lens along with decreased levels of zinc in lens tissue. An increased ratio of lead to zinc in the lens was related to decreased lens transparency.[107]

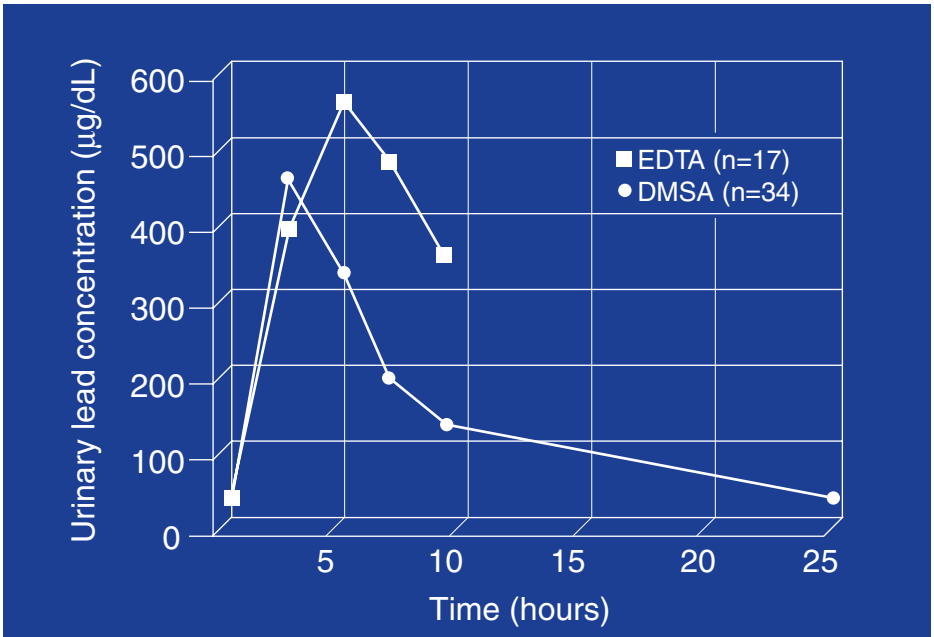
Blood Lead Levels in Children: Screening, Toxicity, and Treatment

Approximately 25 percent of U.S. children live in housing that places them at risk for lead exposure, consequent cognitive impairment, and other conditions related to lead toxicity.[15] The CDC estimates 454,000 school-aged children have PbBs over 10 μg/dL.[108] NHANES III data (1988-1994) indicated that 25.6 percent of 1-5 year-olds had PbBs over 5 μg/dL – including approximately 50 percent of non-Hispanic African-American children, 27.9 percent of Mexican-American children, and 18.7 percent of non-Hispanic Caucasian children tested.[109] Low-level toxicity symptoms that occur below 10 μg/dL include lowered IQ, hyperactivity, delinquency,[52] subclinical hearing[110] and balance[111] disturbances, increased dental caries,[112,113] and numerous neurobehavioral problems and cognitive defects.[52]

Due to evidence that significant decline in IQ occurs in children with blood lead levels below the current CDC intervention level of 10 μg/dL,[73] the CDC Advisory Committee on Childhood Lead Poisoning Prevention has taken the matter under consideration.[114] The Department of Health and Human Services, in their "Healthy People 2010" objectives, addresses the elimination of elevated blood lead levels in children by the end of the decade through a program that would fund management of lead hazards (specifically housing).[115] The American Academy of Pediatrics (AAP) and the CDC recommend all Medicaid-eligible children in the United States be screened for blood lead at 1-2 years of age, when PbBs are highest as a result of hand-to-mouth exposure and increased gastrointestinal absorption rates.[15] For non-Medicaid eligible children, the CDC has created criteria that are appropriate for specific localities.[116] The AAP also recommends screening all children who are recent immigrants, refugees, or international adoptees, due to the increased risk of lead exposure in their countries of origin.[117]

The AAP and the CDC recommend treatment criteria for children with elevated blood lead levels. Children with PbBs of 25 μg/dL should have the source of lead exposure identified and removed (remediation) or the family should be removed from the home if remediation is not possible. Actual intervention with a chelating agent is recommended with PbBs of 25-45 μg/dL if environmental remediation has not been sufficient to normalize levels. The AAP states that chelation therapy has been shown to decrease blood lead levels in children with concentrations of 20-44 μg/dL; however, no current data shows cognitive impairment can be reversed with the protocol of succimer (dimercaptosuccinic acid; DMSA) used in this research.

Figure 4. Estimated Urinary Lead Concentrations after EDTA or DMSA



Adapted from: Lee BK, Schwartz BS, Stewart W, Ahn KD. Provocative chelation with DMSA and EDTA: evidence for differential access to lead storage sites. *Occup Environ Med* 1995; 52:13-19.

Chelation as a Diagnostic Tool

Two recognized agents used for lead chelation are also effective for diagnostic purposes. Calcium disodium EDTA and DMSA have been used as provocative agents to evaluate elevated body burdens in both adults and children.[64,118-120]

Protocols using 1 or 2 g intravenous EDTA and a 6- to 72-hour urine collection beginning at the initiation of intravenous administration have been shown to reliably reflect the potentially toxic fraction of lead body burden.[64,121] EDTA-chelatable lead levels have been correlated with renal function decline, peripheral nerve damage, and neurobehavioral symptoms.[122-124] Although continuous EDTA therapy has been used extensively in acute lead toxicity in children, it is recommended that children who have a PbB of 45 μg/dL or higher not receive a provocative chelation test but be referred for appropriate evaluation and chelation therapy.[125] This concern arises from an animal study indicating single-dose EDTA therapy may redistribute lead into the CNS.[126] As therapy was continued in this study, however, the brain lead levels consistently declined. Further animal studies with radio-labeled lead do not support evidence that EDTA redistributes lead to the brain.[127] The additional evidence showed the opposite, that EDTA reduced brain lead levels after five days of chelation. Although EDTA provocation has been largely replaced by XRF as a diagnostic tool for long-term lead exposure, XRF is not readily available for standard diagnostic use and does not reflect bioavailable lead from the soft tissues.[128]

Provocative DMSA urine testing has also been evaluated as a diagnostic tool.[120,129] In a study of 95 male lead workers, DMSA provocation was evaluated using a protocol of oral administration of 10 mg/kg DMSA followed by a four-hour urine collection.[120]

The levels of urinary lead derived from DMSA provocation were the best predictor of symptom scores for lead exposure when compared to blood lead, blood ZPP, urine lead without provocation, and urinary aminolevulinic acid levels. The three symptoms best correlated with provoked urine lead were "muscle pain, tingling in the arms or legs, and feeling irritation at the slightest disturbance."

DMSA provocation was also compared to EDTA provocation in a group of 34 lead-exposed workers.[128] All workers received a single oral dose of 10 mg/kg DMSA; 17 of the 34 also received 1 g IV EDTA either two weeks before or two weeks after the DMSA. Urine lead levels were tested at two, four, six, eight, and 24 hours. PbBs in these subjects were significantly elevated (29-77 μg/dL); only EDTA urine lead levels, however, correlated with whole blood lead. Cumulative lead elimination peaked at four hours for DMSA and 10 hours for EDTA. The elimination peaks were consistent in the group for all 34 workers. Mean cumulative urine lead levels eight hours after EDTA were 2.8 times higher than those resulting from DMSA (Figure 4). When 24-hour levels of lead excretion with DMSA were calculated, it was shown that an eight-hour urine sample was sufficient to replicate the data received with a 24-hour urine sample. Of note, the workers who had DMSA provocation two weeks after EDTA provocation had significantly higher urinary lead – on average 1,062 μg more – than those who did not have EDTA prior to DMSA provocation. The authors suggest EDTA chelates lead from bone and redistributes it to soft tissue, and DMSA then chelates the increased stores of more readily available soft tissue lead. The authors recommend that EDTA chelation should be followed by DMSA chelation to improve lead mobilization and removal.

Chelation as Treatment

DMSA is currently approved as a chelating agent for asymptomatic children with blood lead levels <45 μg/dL. An experimental protocol is available for mild encephalopathy and use in adults with elevated PbBs. Long-term DMSA chelation has been shown to be as effective as EDTA in increasing the urinary excretion of lead in children. Minimal adverse effects reported include anorexia, nausea, vomiting, and rashes. DMSA increases the excretion of zinc, but to a much lesser extent than other chelators, and has minimal effects on calcium, magnesium, iron, and copper.[129] Long-term DMSA chelation has been shown to be as effective as EDTA in increasing the urinary excretion of lead in children.[130]

The following are the AAP's treatment guidelines for lead exposure in children:[130]

"1. Chelation treatment is not indicated in patients with blood lead levels of less than 25 μg/dL, although environmental intervention should occur.

"2. Patients with blood levels of 25-45 μg/dL need aggressive environmental intervention, but should not routinely receive chelation therapy, because no evidence exists that chelation avoids or reverses neurotoxicity. If blood lead levels persist in this range despite repeated environmental study and abatement, some patients may benefit from (oral) chelation therapy by enhanced lead excretion.

"3. Chelation therapy is indicated in patients with blood lead levels between 45 and 70 μg/dL. In the absence of clinical symptoms suggesting encephalopathy (e.g., obtundation, headache, and persisting vomiting), patients may be treated with succimer [DMSA] at 30 mg/kg per day in three doses for five days, followed by 20 mg/kg per day in two doses for 14 days.

"Children may need to be hospitalized for the initiation of therapy to monitor for adverse effects and to institute environmental abatement. Discharge should be considered only if the safety of the environment after hospitalization can be guaranteed. An alternate regimen would be to use CaNa2EDTA as inpatient therapy at 25 mg/kg for five days. Before chelation with either agent is begun, if an abdominal radiograph shows that enteral lead is present, bowel decontamination may be considered as an adjunct to treatment.

"Patients with blood lead levels greater than 70 μg/dL or with clinical symptoms suggesting encephalopathy require inpatient chelation therapy using the most efficacious parenteral agents available."

Although chelation is not routinely recommended for PbBs below 45 μg/dL, it is important to note that the Committee on Environmental Health of the American Academy of Pediatrics states, "Children who have ever had a concentration greater than 20 μg/dL or a persistent (for more than three months) elevation greater than 15 μg/dL should have an environmental and medical evaluation."[15]

The AAP recommendation against routine chelation with blood levels between 25 and 45 μg/dL is based on a study looking at long-term neuropsychological changes in children who had been given treatment with DMSA. This study, the TLC trial, included a group of 780 children, ages 12-33 months, with PbBs between 25 and 44 μg/dL.[131] The group was randomized to placebo or treatment consisting of three, 26-day courses of DMSA using doses of approximately 30 mg/kg/day for the first seven days, followed by approximately 20 mg/kg/day for the next 19 days. (The treatment dosages were computed based on square meters of body mass, not weight.) Although blood levels were reduced in the treatment group to less than 15 μg/dL within the first week, they returned to a mean of only 2.7 μg/dL lower than the placebo group during the 12 months of ongoing chelation. Tests of cognition, behavior, and neuropsychological function over a period of 36 months were not significantly different between treatment and placebo groups. A further evaluation of this group at age seven years showed that chelation therapy with DMSA produced no long lasting benefit in cognitive, behavioral, and neuromotor function.[132]

Multiple studies examining the effectiveness of chelation for pediatric lead poisoning show DMSA to be effective in reducing blood lead levels. However, recent studies, including the TLC trial, have shown it may be no more effective than lead abatement in terms of long-term cognitive outcomes.[133] Unfortunately, studies focusing on lead abatement and education have resulted in only moderate reductions in PbBs that take significant amounts of time (24 months in one study) to decline below 10 μg/dL.[134]

One researcher suggests the reason the TLC trial did not demonstrate cognitive improvement is that the duration of DMSA treatment was not sufficient to decrease brain tissue levels of lead.[133] The researcher cites evidence from animal studies showing DMSA's effect on brain lead follows the normalization of blood lead levels, and that extended treatment can lower brain lead levels, although blood lead levels will not continue to decline.[135] This data calls into question the utility of using only blood lead levels to monitor the duration and cessation of treatment, particularly in the area of cognitive dysfunction.

Animal studies indicate that short repeated courses of DMSA are more effective for reducing brain lead than EDTA.[136] EDTA, however, is highly effective at chelating lead from the kidney and has been shown to prevent the progression of chronic renal disease.[137] A study of 200 patients with chronic renal insufficiency, normal PbBs (5.3 ± 2.9 μg/dL), and high-normal body lead burden (150.9 μg) defined by EDTA mobilization testing, evaluated the effect of EDTA chelation on renal function.[137] Subjects received EDTA chelation weekly for three months in a randomized, placebo-controlled fashion. Nineteen patients in the chelation group required one additional chelation treatment after the initial three months due to an elevation of serum creatinine above pre-chelation levels. After monitoring for 24 months, EDTA was shown to be effective at decreasing body lead burden to 43.2 ± 22.3 μg/g and preventing the progression of renal disease as defined by improvement of glomerular filtration rate. The improvement in GFR allowed subjects who received chelation to forestall dialysis for approximately three years, at a net saving of $57,250 per patient.[136] When looking at the predictors of progressive renal disease in these patients, the most sensitive predictors of declining kidney function, measured by change in GFR, were body lead burden and increased urinary protein excretion.

Conclusion

Given the current number of children at risk for lead exposure and its sequelae, and the accumulating data showing relationships between low-level environmental exposure to lead and a variety of chronic degenerative conditions, the diagnosis and management of low-level lead exposure deserves to be reevaluated. Cognitive disorders, hyperactivity, hypertension, renal insufficiency, cataract, cancer, and conditions that may result from increased bone

resorption of lead, as evidenced by data on hypertension and blood lead levels in menopausal women, may need to be approached from a completely new treatment perspective. Inarguably, lead abatement is crucial. However, the appropriate use of body burden assessment using XRF or DMSA and EDTA provocation in clinical settings needs to be critically evaluated and instituted when possible. Current treatment guidelines based solely on blood lead levels are not sensitive enough to detect effective chelation endpoints. Chelating protocols based on the same guidelines set for blood lead levels have not been shown to be effective in addressing the U.S. epidemic of cognitive and neurobehavioral damage caused by lead exposure in children.

In addition to appropriate treatment for toxic metal exposure and accumulation, it is also important to minimize the effects of these metals. As previously addressed in this series of articles, cadmium and arsenic initiate the production of free radicals and cause tissue inflammation and genetic damage as a result. In Part II of this article, the role of antioxidants in the treatment of lead-related pathologies will be addressed.

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