Lead toxicity update. A brief review

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Summary

Lead is a metal which has been associated with human activities for the last 6000 years. In ancient civilizations, uses of lead included the manufacture of kitchen utensils, trays, and other decorative articles. However, lead is also toxic to humans, with the most deleterious effects on the hemopoietic, nervous, reproductive systems and the urinary tract. The main sources of lead exposure are paints, water, food, dust, soil, kitchen utensils, and leaded gasoline. The majority of cases of lead poisoning are due to oral ingestion and absorption through the gut. Lead poisoning in adults occurs more frequently during exposure in the workplace and primarily involves the central nervous system. Symptoms of hemopoietic system involvement include microcytic, hypochromic anemia with basophilic stippling of the erythrocytes. Hyperactivity, anorexia, decreased play activity, low intelligence quotient, and poor school performance have been observed in children with high lead levels. Lead crosses the placenta during pregnancy and has been associated with intrauterine death, prematurity, and low birth weight. In 1991, the Centers for Disease Control and Prevention in the USA redefined elevated blood lead levels as those ≥10 µg/dl and recommended a new set of guidelines for the treatment of lead levels ≥15 µg/dl.

key words: lead toxicity • encephalopathy • hypochromic anemia • chelation therapy

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BACKGROUND

Lead is a widely used metal, but it is simultaneously a versatile, subtle, and persistent poison. Significant exposure to lead is an environmental threat to optimal health and to physical development in young children that affects all socioeconomic groups [1]. However, the deleterious effects of lead may be efficiently prevented by applying specific regulations to its use. Metallic lead has constituted a part of the human environment for over 5000 years [2]. The characteristic features of lead toxicity, including anemia, colic, neuropathy, nephropathy, sterility, and coma, were noted both by Hippocrates and Nikander in ancient times [3]. In 370 BC, Hippocrates first described abidental colic in a man who mined metals [2]. The effects of lead toxicity on young children were first described in 1892 in Brisbane, Australia [4]. Even though two thousand years have passed since Vitruvius chronicled the dangers of lead in water supplies, this threat to public health still remains with us [5]. Besides drinking water, paint and leaded gasoline have also been identified as major sources of lead exposure. Lead in household paint was recognized as a danger early in the 20th century [6]. In 1923 a General Motors chemist, Thomas Miggely, found that tetraethyl lead was an effective anti-knocking agent and boosted engine power. When this company began to manufacture tetraethyl lead, workers started to display signs and symptoms of psychosis, and much fatal mortality. In spite of this, leaded gasoline continued to be used for almost 70 years. The removal of lead from gasoline in 1990, regarded by many as one of the major public health triumphs of the 20th century, was a major victory for the environment and had an immediate impact [7,8].

ABSORPTION OF LEAD

Lead may enter the body by ingestion through the intestines, through the lungs by inhalation, through the skin, or by direct swallowing and ingestion [9]. Inorganic lead absorption takes place throughout the respiratory and gastrointestinal tracts. For adults with occupational exposure, the most significant route for absorption is through the respiratory tract [2,9]. Respiratory lead absorption is primarily dependent on particle size. The percentage of inhaled lead reaching the bloodstream is estimated to be 30–40% [2]. Rates of absorption through the gastrointestinal tract depend on the nutritional status and the age of the individual exposed. Therefore, while adults absorb an average of 10 to 15% of the ingested quantity, this amount can increase to 50% in infants, young children and pregnant women [2,9]. Absorption through the gut is the predominant route for children and increases when dietary intakes of iron, calcium, phosphorus, or zinc are low [2,9,10]. There is little transcutaneous absorption of lead when inorganic lead compounds, such as those found in paint, are applied to the skin. In contrast, organic (tetraethyl) lead, which is that found in gasoline, can be absorbed via the skin. This route may have contributed to the lead poisoning in chemical workers during the development of this gasoline additive in the 1920s [2,9,11].

DISTRIBUTION OF LEAD AFTER ABSORPTION

Following exposure to lead, the element is absorbed into and transported by the bloodstream to other tissues. Once absorbed, lead accumulates in three compartments: blood, soft tissues, and bone. In blood, approximately 99% of the lead is found in the erythrocytes, leaving about 1% in the plasma and serum [12]. The concentration of lead in plasma is more significant than that in whole blood as the means of distribution to target organs, i.e. brain, lungs, spleen, renal cortex, aorta, teeth, and bones [2,13]. The kinetics of lead transfer from blood to soft tissues is low and takes approximately 4 to 6 weeks [2]. Lead in blood has an estimated half-life of 35 days [14], in soft tissue 40 days [15], and in bones 20 to 30 years [16]. The biological half-life of lead may be considerably longer in children than in adults [15]. Blood lead concentrations reflect the intake of only the previous 3 to 5 weeks and thus cannot be used as indices of chronic exposure [2,9,12]. The initial distribution of lead throughout the body is dependent on blood flow to the tissues. More than 95% of lead is deposited in skeletal bone as insoluble phosphate [2]. Autopsy studies have shown that 90 to 95% of the body's burden is present in cortical bone and teeth. In adults, some 80–95% of the total body burden of lead is found in the skeleton, compared with about 75% in children. The residence period of lead in bone is up to 30 years, with lead concentrations in bone and teeth increasing as a function of age. Bone lead may be regarded as two physiologically distinct pools: an inert pool, with a half-life of decades, and a labile pool that readily exchanges with lead present in blood or soft tissues [2,12].

It has been determined that lead crosses the placental barrier, with fetal uptake, beginning at 12 weeks gestation and continuing throughout development up to birth. Concentrations of lead in umbilical cord blood were found to be 80–100% of the maternal blood lead level [2,17,18].

Several conditions known to increase bone turnover, such as pregnancy, lactation, chemotherapy, tumor infiltration of the bone, or postmenopausal osteoporosis, may be associated with the mobilization of lead in bone stores, leading to chronic lead toxicity [18–21]. Although hyperthyroidism also increases bone turnover, it has only rarely been implicated in the pathogenesis of lead poisoning, with only two reported cases [19].

EXCRETION OF LEAD

Inorganic lead is not metabolized; however, alkyl lead compounds are oxidized by the hepatic P 450 system. Generally, lead excretion is low, with the most significant route being via the urinary tract. The use of chelating agents can enhance lead excretion in urine and this constitutes the basis of the therapeutic approach to lead poisoning. Lead may also be excreted with bile through the gastrointestinal tract. Although minute amounts of lead are excreted through the sweat and the nails, these routes do not have any practical significance. In general, lead is excreted extremely slowly from the body, with its biological half-life estimated at 10 years, thus facilitating accumulation in the body [2].

EPIDEMIOLOGY OF LEAD TOXICITY. SOURCES OF LEAD TOXICITY

Lead is found in mineral deposits and is released into the environment from natural causes as well as through human industrial activity. It does not dissipate, nor is it biodegradable. Therefore, lead in dust becomes a long-term source of
lead exposure. Because of its malleability, low melting point, and ability to form compounds, it has been used in hundreds of products such as pipes, solder, brass fixtures, crystal paint, cable, ceramics, and batteries [2,9]. There are basically two routes for lead exposure: inhalation and swallowing. Worldwide, six categories of products account for most cases of lead exposure: gasoline additives, food-can soldering, lead-based paints, ceramic glazes, drinking water pipe systems, and folk remedies [9]. Inhalation of lead fumes or lead-containing dust is mainly a problem in occupational settings, such as smelting, recycling facilities, production of storage batteries, and lead-glazed ceramics. Swallowing of lead-containing particles, food or drinks is an important route for both occupational and environmental exposure to lead [22]. Airborne lead eventually settles on land, in water supplies, and on buildings, and thus can enter the food chain. Besides the settling of atmospheric lead, surface contamination also occurs from contact with industrial waste containing lead. Furthermore, lead may leach into drinking water from water pipes and solder [2,5]. Human beings are also exposed to lead from cigarette smoking [23].

Adult lead poisoning is primarily a result of exposure by inhalation of lead fumes or ingestion of lead particles during activities in the workplace which involve the production, extraction, or reclamation of lead [2,9]. Lead poisoning in children is a characteristic disease usually occurring between the second and third year of life as a result of ingestion of lead particles from household or outdoor environmental sources. Children are exposed to lead from a variety of sources and through various pathways, as well as via normal, repetitive hand-to-mouth activity, which is now recognized as a major contributor to the total body burden of lead in children. Lead-based paint was the most widespread and dangerous source of high-dose lead exposure in pre-school children, as paint in most homes in the late 1940s was, in essence, a crust of lead [9,24]. Moreover, many consumer products, including toys, have been made of, or painted with, lead. Over the last 40 years, attempts have been made to remove lead from all these sources [2,9,24]. However, lead poisoning may also appear, although rarely, in the first year of life. In infancy it comes from unusual sources, such as in utero transmission of lead from women exposed to lead poisoning, or, in infants, through formula prepared with lead-contaminated water [24].

Lead exposure in developing countries may have different sources from those in the Western World. In certain Asian and Latin American countries, populations with a low socioeconomic background may use lead-contaminated folk medicines. Known sources of lead poisoning in Arabian communities are traditional remedies for abdominal colic and early passage of meconium after birth [25], called “bint adh Dhahab” (Daughter of Gold), or a locally used teething powder in Saudi Arabia known as “Saot” and “Cebagin” prescribed by traditional healers [26,27]. Furthermore, “Kalhal”, a commonly used eye cosmetic in the Arabian peninsula [27], involves a formula prepared with lead-contaminated water, or in a lead-soldered samovar [24].

**Effects of Lead**

Lead is a poison that affects virtually every system in the body. Children are more vulnerable to lead exposure than adults because of the frequency of pica, hand-to-mouth activity, and a higher rate of intestinal absorption and retention. The most deleterious effects of lead are on erythropoiesis, kidney function, and the central nervous system [28,29].

**Hemopoietic system**

The adverse effects of lead appear even with blood concentrations as low as 10 µg/dl. The best understood toxic effects of lead involve heme synthesis, as lead inhibits three important enzymes participating in the process, i.e., delta aminolevulinic acid dehydratase, delta aminolevulinic acid synthase, and ferrochelatase [30]. It is suggested that the inhibition of delta aminolevulinic acid dehydratase starts at values as low as 5 µg/dl. At higher lead concentrations this inhibition is very pronounced, reaching 50% inactivation at blood lead levels of 16 µg/dl and 90% inactivation at 55 µg/dl, resulting in the accumulation of delta aminolevulinic acid in plasma and its excretion in urine. Because this enzyme is normally present in great quantities, the inhibition of its activity may pass unnoticed [30,31]. Ferrochelatase is the enzyme that catalyzes the incorporation of iron into the porphyrin ring. If, as a result of lead toxicity, the enzyme is inhibited and its pathway is interrupted, or if adequate iron is not available, zinc is substituted for iron, and zinc protoporphyrin concentrations increase. The critical target, however, seems to be the enzyme’s heme synthesis, essential for the insertion of iron into the precursor, protoporphyrin IX [32,33]. The major consequences of this effect, which have been evaluated in both adults and children, are reduction of circulating levels of hemoglobin and the inhibition of cytochrome P 450-dependent phase I metabolism [32]. Lead clearly inhibits normal hemoprotein function in both respects, which results in basophilic stippling of erythrocytes related to clustering of ribosomes and microcytosis when blood lead levels are 20 µg/dl. Thus microcytic hypochromic anemia is often diagnosed in victims of lead exposure. Compared with adults, children, especially in their first year, develop certain toxic effects at lower blood lead levels, and lead induced-anemia has been related to age [11,15,18,24–28].

**Nervous system and neurodevelopmental sequelae**

Headaches, poor attention span, irritability, loss of memory, and dullness are the early symptoms of the effects of lead exposure on the central nervous system. The ability to think and reason is extremely sensitive to toxic metal assault. The developing nervous system of the child makes it more sensitive to lead-induced impairment. The most serious manifestation of lead poisoning is acute encephalopathy, the symptoms of which include persistent vomiting, ataxia, seizures, pappiledema, impaired consciousness, and coma. Lead encephalopathy rarely occurs at blood lead levels below 100 µg/dl. Poor attentiveness, impulsiveness, inability to follow sequences or directions, decreased play activity, low intelligence quotient, and poor school performance are neurobehavioral abnormalities observed in affected children whose blood lead levels are approximately 35 µg/dl. Similar abnormalities have appeared at even lower levels of lead exposure. A growing body of evidence suggests, however, that the functional integrity of the central nervous system can be compromised at substantially lower levels of lead exposure, particularly in the human fetus and young child. Early post-natal neurobehavioral development is compromised by maternal or cord blood lead levels of somewhat
less than approximately 10 µg/dl (a level of lead not uncommon in the general population). Results of more recent cross-sectional and prospective studies indicate that postnatal lead exposure resulting in blood levels as low as 25 µg/dl, and probably lower, are also associated with deficits in intellectual attainment, achievement, and affect behavior. Impaired hearing has been observed at blood concentrations of 10 to 20 µg/dl [29,33].

Peripheral neuropathy, on the other hand, is the most common manifestation among adults with occupational lead exposure, but it is rarely seen in children except for those with sickle cell disease. Typically, the peripheral neuropathy of lead toxicity is seen as involving the extensor muscles, with minimal sensory loss. Lead-induced neuropathy on the radial and peroneal nerve in adult lead toxicity results in the characteristic “wrist drop” and “foot drop”. Gastrointestinal colic is caused by high lead exposure and may be associated with lead neuropathy [29,33,34].

Needleman and his associates summarized the observations of teachers that lead-exposed students exhibited behavior characterized as distractable [35], not persistent, dependent, not organized, hyperactive, impulsive, frustrated, daydreaming, and unable to follow directions and sequences, with low overall functioning. The outcomes of four key studies of the neurobehavioral effects of low-level lead exposure in children were reviewed and analyzed by Davis, who concluded from these data that impaired performance can be caused by lead levels of 10 to 15 µg/dl or lower [36]. Electrophysiological changes on sensory functioning occur in children at exposure levels below 10 µg/dl [37]. Furthermore, changes in cortical visual-evoked potentials have been reported in children aged 3 to 12 years associated with blood lead levels from 6 to 59 µg/dl [38]. Recently, Rothenberg and colleagues recorded the brainstem auditory-evoked response in children 5–7 years of age who had been exposed to lead prenatally and observed that a mean maternal lead level of 7.7 µg/dl at 20 weeks of pregnancy was associated with changes in the auditory threshold have been reported with blood lead levels ranging from 6 to 18 µg/dl [40]. There are few symptoms of chronic lead poisoning and they are mostly non-specific, involving abdominal and muscle pain, arthralgia, irritability, depression, altered sleep, memory disturbances, and hyperactivity in children [41]. Needleman et al. [42] also warned that childhood lead exposure is associated with deficits in central nervous system functioning that persist into adulthood. Long-term neurobehavioral effects of childhood lead poisoning were assessed in individuals 50 years after known exposure. The results of this long-term follow-up study indicate that a history of childhood plumbism is associated with cognitive dysfunction still evident in adulthood [43]. The effects of chronic lead toxicity on psychological development were first described by Byers and Lord in 20 children who suffered lead poisoning during the first two years of life from eating paint chips. These children were re-assessed during the primary school period, and a high frequency of educational and behavioral problems was noted [44].

The magnitude of the effects of blood lead on the IQ of young children has been estimated as an average loss of two to three points for lead levels averaging 20 µg/dl compared with lead levels averaging 10 µg/dl. A number of studies recently reviewed by the National Research Council found an association between lead levels and intellectual functioning in children [45]. In one population, lead levels >30 µg/dl were correlated with an increase in the percentage of children with severe deficits (i.e. IQ<80), from an expected 4% to 16%, and a decrease in the percentage of children with an IQ ≥125 from the expected 5% [35,46]. From animal models there is evidence that lead can disrupt several steps involved in neuronal plasticity, which includes the brain’s capacity to be shaped by experience, the capacity to learn and remember, and the ability to reorganize and recover after injury [47]. Studies using an immature animal model suggest that lead impairs neuronal growth and activity-dependent refinement of synaptic connections in the developing brain [48]. Recently it has also been reported that in developing rodents, environmental enrichment can reverse the cognitive and molecular deficits induced by developmental lead exposure [49].

Kidney

Renal toxicity in sub-clinical lead poisoning involves inhibition in the proximal tubular lining cells and renal insufficiency. Abnormalities include aminoaciduria, glycosuria, and phosphaturia (Fanconi’s syndrome). Characteristics of early or acute nephropathy include dysfunction of the proximal tubules (Fanconi’s syndrome), manifesting as aminoaciduria, glycosuria, and phosphaturia with hypophosphatemia, and increased sodium and decreased uric acid excretion. These effects are reversible. Characteristics of chronic lead nephropathy include progressive interstitial fibrosis, a reduction in the glomerular filtration rate, and azotemia. These effects are irreversible. The acute form of nephropathy is most frequently reported in children, while the chronic form is mainly reported in adults [29,33]. Loghman-Adham evaluated the parameters of renal tubular function in 134 children and young adults 8–13 years after chelation therapy for severe lead poisoning and concluded that a partial Fanconi’s syndrome can persist up to 13 years after lead poisoning [50].

Other systems

Lead in low doses is associated with increased blood pressure in adults. The effects are noted mainly in systolic pressure and are associated with blood concentrations starting at approximately 30 µg/dl [29,33]. From a pilot study which described 192 subjects from 1930–1942 with well-documented lead poisoning it was suggested that subjects with plumism had significantly lower hemoglobin concentrations and hematocrit than controls and an increased risk of clinically significant hypertension [51]. Lead toxicity typically causes constipation and colic [26]. Kafouros and her associates investigated the adverse effects of blood lead concentrations on the somatic growth of primary school-aged children. This study’s findings led the authors to conclude that a reduction in growth in children may be associated with blood lead concentrations [52]. Reduced sperm counts and motility have also been associated with chronic lead exposure [33,53].

Effects on the fetus

Abortions, miscarriages, and stillbirths have all been reported among women working in lead-associated trades. Pre-
nental exposure to lead has been associated with toxic effects on the fetus. These include reduced gestational age, birth weight, and adversely delayed cognitive development. Significantly, sources of maternal exposure to lead may be current or the result of mobilization from bone stores remaining from previous exposure. Recent studies have suggested that a significant amount of bone lead is mobilized, enters the circulation during pregnancy and lactation, and crosses the placenta [17,18,29,53–55].

Acute and long-term exposure

Overt signs of acute toxicity include dullness, restlessness, irritability, poor attention span, headaches, muscle tremor, abdominal cramps, kidney damage, hallucinations, and loss of memory with encephalopathy, all occurring at blood lead levels of 100–120 µg/dl in adults and 80–100 µg/dl in children. Signs of chronic lead toxicity, including tiredness, sleeplessness, irritability, headaches, joint pain, and gastrointestinal symptoms, may appear in adults at blood lead levels of 50–80 µg/dl. After 1–2 years of exposure, muscle weakness, gastrointestinal symptoms, lower scores on psychometric tests, mood disturbances, and symptoms of peripheral neuropathy were observed in occupationally exposed populations at blood lead levels of 40–60 µg/dl. There is no safe level of blood lead below which children are not affected [15].

LABORATORY TEST FOR LEAD

The most commonly used biological marker is the concentration of lead in blood. The concentrations of lead in plasma are so low that they have hitherto been extremely difficult to measure. The free erythrocyte protoporphyrin or zinc protoporphyrin levels reflect impaired heme synthesis. These may therefore be increased in children with increased lead levels, but they can also be increased in iron deficiency or hemolytic anemia. As this test is not sensitive enough to identify blood levels between 10 and 25 µg/dl, it is no longer recommended as a screening test [9,33,56,57]. If either blood lead or free erythrocyte protoporphyrin is elevated, then other tests for lead effects on the kidneys (urea nitrogen, creatinine, and urinalysis) and blood (complete blood count with smear) should be performed. It is important to note that urea nitrogen and creatinine are not sensitive indicators of renal damage, since it is known that they do not rise until a large part of renal function is lost [33].

Radiological examination of the abdomen in children may reveal radiopaque densities or radiographic evidence of paint chip ingestion. At the ends of long bones the radiological finding is the appearance of dense transverse bands, “lead lines”, across the metaphyses of long bones and along the margins of flat bones, such as the iliac crest. The width of the lead line varies, depending upon the amount of lead involved and the length of time of exposure. Therefore radiological examination is not a sensitive method for diagnosing acute lead poisoning [29,33].

Nerve conduction velocity testing should be considered when there are persistent symptoms or clinical findings suggestive of the presence of peripheral neuropathy. Neurobehavioral testing is indicated in cases where there is persistent impairment of cognitive function and blood lead levels are usually above 80 µg/dl. This testing can demonstrate changes in manual dexterity, perceptual motor speed, and memory deficits, all characteristic of lead toxicity, and can sometimes be helpful in distinguishing it from other causes of cognitive dysfunction [58].

Sperm analysis is indicated in lead-exposed men with complaints of infertility.

DEFINITION OF LEAD POISONING

Prior to 1970, blood levels greater than 60 µg/dl defined significant lead poisoning. In 1971 the threshold for blood lead levels was reduced to 40 µg/dl. This was subsequently reduced to 30 µg/dl in 1975 and to 25 µg/dl in 1985 [1,9]. In 1991, the Centers for Disease Control and Prevention statement concerning lead poisoning in young children was refined. Lead levels have been redefined as follows: lead levels less than 10 µg/dl is 20 to 44 µg/dl, and within 1 month if the result is 10 to 19 µg/dl. If the confirmatory lead levels are still between 10 and 14 µg/dl, lead level testing should be repeated within 3 months [59]. For children with lead levels of 15 to 19 µg/dl, the pediatrician should take a careful history of the environment. Parents should receive guidance about intervention as well as optimal nutrition. Nutritional interventions include iron and calcium supplementation, a reduced-fat diet, and frequent meals, as well as these measures are associated with reduced gastrointestinal absorption of ingested lead [59]. If the confirmatory blood lead levels are still between 15 and 19 µg/dl, blood lead level testing should be repeated within 2 months. Individualized case management, which includes a detailed medical history, nutritional assessment, physical examination, environmental investigation, and hazard reduction, begins at a blood lead level of 220 µg/dl. Chelation therapy may be considered, but is not routinely recommended at blood lead levels of <15 µg/dl [60].

CHELATING AGENTS

Dimercaprol (BAL)

Dimercaprol, also known as British Anti-Lewisite (BAL), was developed in 1946 by the British to counteract German arsenic-based war gases. It increases the urinary excretion of heavy metals through the formation of stable, nontoxic, soluble chelates. BAL lacks stability in water and is administered in an oil solution as a deep intramuscular injection. It was the first chelating agent found to be useful in the treatment of childhood lead poisoning. Despite the high incidence of side effects (fever, allergy), BAL has remained in use for more serious lead poisoning because of concerns that CaNa2EDTA therapy may translocate lead into the central nervous system and increase the potential for encephalopathy. Traditionally, pre-treatment with BAL has been recommended to avoid precipitation of encephalopathy [60].
Calcium Disodium EDTA (CaNa2EDTA)

In 1950, a second chelating agent, calcium disodium ethylenediaminetetraacetate, was found to be useful in the treatment of lead poisoning. It increases the urinary excretion of lead through the formation of a non-ionizing, soluble chelate. Because the use of CaNa2EDTA may cause increased lead concentration in the central nervous system, it should be administered after BAL is given. Very low bio-availability from oral intake necessitates parenteral administration. Treatment with CaNa2EDTA should usually be performed in a hospital setting by physicians experienced with chelation therapy on patients with normal renal function and with careful monitoring of renal parameters.40

Succimer (2,3-meso-dimercaptosuccinic acid or DMSA)

This is an oral chelation agent that is approved by the United States Food and Drug Administration (FDA) for the treatment of lead poisoning in children and is also effective in adults. It is chemically similar to BAL, but has greater solubility in water, has a high therapeutic index, and is absorbed through the gastrointestinal tract. The recommended dose by the manufacturer is 10 mg/kg three times a day for five days, followed by 10 mg/kg twice a day for two weeks. This dose, which has been found to be acceptable in treating some adults, can be quite high for others, especially for heavier adults. Due to the lack of data on adult treatment with DMSA, an adult dose level of 500 mg twice a day for two weeks has also been given as a sensible maximum limit until additional clinical data become available for adults [60].

Consultation with clinicians who are experienced in lead chelation is useful in making the decision to apply chelation therapy in the case of every individual child. Support services from other professionals, including visiting nurses and environmental health specialists, are essential in providing assistance with environmental assessment, lead abatement, or alternative housing. Chelation therapy with any agent should not be undertaken unless exposure has definitively been curtailed, since its use in the presence of continuing exposure may result in enhanced absorption of lead and a worsening, rather than an amelioration, of toxicity [61]. One study revealed that the serum ascorbic acid level was inversely related to the blood lead level in the adults and children involved. Given the benign nature of vitamin C, supplements in modest doses (100 to 1000 mg per day) may be an attractive adjunct to the management of patients with mild lead toxicity [62].

For children with lead levels 25 to 44 µg/dl, the pediatrician should take a complete medical history and must provide education to decrease lead exposure and absorption. If these lead levels persist, oral chelation therapy can be considered (not currently recommended for blood lead levels <45 µg/dl). For children with lead levels of 45 to 69 µg/dl, chelation therapy, in consultation with clinicians, must be considered. In the absence of clinical symptoms suggesting encephalopathy, treatment may consist of DMSA, which can be given orally. An alternative treatment consists of CaNa2EDTA, 1000 mg/m²/24 hr intravenously in a 24-hr infusion, or in a short 20–30-min infusion for 5 consecutive days. Repeated courses of treatment may be necessary in these children until blood lead levels return to a safe margin (<20 µg/dl). In symptomatic children, regardless of blood lead levels, treatment is always administered in the hospital. Children with blood lead levels 270 µg/dl, even if asymptomatic, should be considered as medical emergencies and immediately hospitalized for treatment, which should consist of BAL at 75 mg/m² every 4 hours, with at total daily dose of 450 mg/m², followed by CaNa2EDTA at 1500 mg/m²/24 hr by continuous infusion. Treatment should be continued for 5 days. The BAL should be suspended as soon as blood lead levels fall below 60 µg/dl. Repeated courses of treatment may be necessary for these children until blood lead levels return to a safe margin (<20 µg/dl) [63].

In adults, reducing lead exposure is the first key step in treatment for all cases of excessive lead absorption. Given the growing information about the sub-clinical lead effects in blood lead levels of less than 40 µg/dl, efforts should be made to lower blood lead levels where they are found to be above 25 µg/dl. Removal from lead exposure is necessary when blood lead levels rise to 50 µg/dl, while workers can return to their work environment when blood lead levels are less than or equal to 40 µg/dl. In most cases, removal from exposure is the only treatment needed. However, the decision to administer chelating agents or not is based upon a number of factors, including the presence of clinical symptoms and their duration, current blood lead levels, and the duration of excessive lead exposure. Generally, there is a tendency to recommend chelation therapy for individuals with blood lead levels greater than 80 µg/dl, and for those with blood lead levels between 60 and 80 µg/dl if they show lead-related symptoms. In addition, chelation therapy is sometimes considered for individuals with blood lead levels between 40 and 60 µg/dl if they show continuing symptoms and elevated lead levels two weeks after removal from exposure [11].

In summary, lead toxicity is a significant but preventable health problem. In many cases, suspicion of lead toxicity does not come readily to mind. Once suspicion exists, however, the diagnosis is relatively easy to make. Blood lead levels confirm poisoning, and their determination helps with differential diagnosis. Identification of the various lead sources that surround us can help towards prevention of lead toxicity. We suggest that every case of encephalitis of unknown origin in children should undergo an X-ray of the knee, which can be rapidly performed and is easily available, because the presence of a dense metaphyseal band strongly supports a diagnosis of lead poisoning [64]. Medical practitioners and parents need to be made more aware of the problem. They must fully understand that “the less lead in the developing brain, the better” [65-67]. Continued public health initiatives to remove lead from the environment, in concert with routine lead screening of young children, will be the key for meeting the goal of the Centers for Disease Control and Prevention to eliminate childhood lead poisoning by the year 2011.

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