ORAL CHELATION THERAPY FOR PATIENTS WITH LEAD POISONING

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Literature Review

The studies for this review were identified by performing a search of the PubMed and Medline databases using the search terms: “lead poisoning” and “chelation”, “lead poisoning” and “penicillamine”, “lead poisoning” and “DMSA”, “lead poisoning” and “succimer”, “lead poisoning” and “DMPS”, and “lead poisoning” and “provocative urine excretion”. The dates included 1970-2007. The Cochrane Database for Systematic Reviews was also searched; however, no pertinent reviews were found. The bibliographies of selected articles were also reviewed to identify any studies not found by the original literature search. Inclusion of articles was dependent on the age of the subjects or patients included in the literature, with primary focus on children under the age of 21 years.

Background of Lead Poisoning

Clinical Significance of Lead Measurements. Lead poisoning, usually, is a chronic disease, due to cumulative intake of lead, the course of which may or may not be punctuated by acute symptomatic episodes. The clinical signs and symptoms of lead poisoning are nonspecific; therefore, a lead measurement, preferably a venous blood lead measurement, is essential for diagnosis. Ancillary tests such as those involving heme precursors (urinary delta-aminolevulinic acid, coproporphyrin, and erythrocyte protoporphyrin) may be helpful in making a diagnosis, but by themselves are inadequate for definitive diagnosis. In the majority of cases, children with lead poisoning are asymptomatic resulting in a delay in the appropriate diagnosis. However, during this time effects on a cellular level are occurring resulting in subtle changes in the child. These include impairment of IQ and other cognitive effects, decreased heme synthesis, and interference in vitamin D metabolism. In children, overt clinical symptoms of cumulative lead poisoning generally begin with loss of appetite and abdominal pain. They are, however, easily confused with other diseases that can cause the same symptoms. If the disease is not recognized at this stage, the clinical presentation in children may proceed to signs of increased intracranial pressure (projectile vomiting, altered state of consciousness, seizures).

The total body burden of lead may be divided into four compartments. The residence times of lead in these four compartments are estimated at about: 35 days in blood; 40 days in soft tissues; 3 to 4 years in trabecular bone; and 16 to 20 years in cortical bone. The disappearance time is largely dependent upon the degree of overall excess exposure. The greater the body lead burden the slower the rate of disappearance from the tissues, including blood. In blood lead measurements, however, may not be helpful in making a retrospective diagnosis. Injury from lead (for kidneys and CNS) may remain long after blood lead levels have decreased due to distribution and elimination. At present, there is no established way to make a retrospective diagnosis of lead toxicity in a child on the basis of current blood lead alone.

Absorption of Lead and Its Internal Distribution Within the Body. Inorganic lead is absorbed by both the respiratory route and the gastrointestinal tract. Inorganic lead is not absorbed through the skin, although organic lead compounds are. Studies in the past have indicated that 40 to 50% of small-particulate lead is absorbed and retained in the lung. Balance studies in young children show that 40 to 50% of dietary lead is absorbed, and that about one-half the amount absorbed is retained. Lead is distributed throughout the body with the major fraction being
absorbed in the bone (95% in the adult and about 70 to 75% in young growing children). The rate of turnover of lead in bone is higher in children than in adults. The two nonosseous organs with the highest lead contents are the liver and the kidney, the organs of excretion of lead. In general, the concentration of lead in other organs is comparable to that found in blood. Approximately 99% of the lead in blood is bound to red blood cells. The remaining 1%, i.e., plasma lead, serves as an intermediate in transporting lead from the erythrocytes to other body compartments.

Toxic Effects of Exposure to Lead in Children and Adults

Lead affects at least three major organ systems: (1) the central and peripheral nervous systems; (2) the heme biosynthetic pathway; and (3) the renal system. Clinical manifestations differ somewhat between children and adults. In the child, the most serious symptoms are found in the central nervous system with subtle effects (e.g., decreased IQ and cognitive effects) occurring at lower levels and severe effects (e.g., seizures, encephalopathy) occurring at higher levels. Chelation therapy has reduced the mortality rate and morbidity substantially at higher levels. However, chelation therapy at lower levels (< 45 µg/dL), it has not been shown to be as effective as removal of the lead source from the child’s environment. Children are much more sensitive than adults to the neurocognitive and behavioral effects of lead, probably primarily for two reasons: (1) children absorb 40 to 50% of dietary lead whereas adults absorb about 10%; and (2) the nervous system develops rapidly in the young child. The blood lead threshold (if there is one) for neurocognitive and behavioral effects is probably lower in children than in adults.

In the child, lead appears to have an effect on renal function even at levels below 10 µg/dL. This especially true if the lead exposure occurs over a sustained period of time. Subtle abnormalities in renal tubular function, associated with aminoaciduria, glycosuria, and increased excretion of low-molecular weight proteins can occur. Lead has been clearly demonstrated to produce tubular nephrotoxicity and chronic interstitial nephritis in humans and rodents after chronic exposure. In addition, lead in the kidney interferes with activation of vitamin D 1,2-dihydroxy cholecalciferol, a p450-dependent process.

Lead interferes in the formation of active vitamin D, which has an important role in its influence on calcium metabolism. Calcium is under tight homeostatic control in all cells. The active form of Vitamin D is produced, primarily, from activation of Vitamin D by sunlight on the skin. The circulating hormone binds to Vitamin D Receptors (VDRs) in the nucleus of cells in the gastrointestinal tract, kidney and bone. This binding activates a cascade of events to increase calcium absorption. Because of their similar biochemical nature, lead can be absorbed by this mechanism especially in children who have decreased calcium intake. In addition, calbindin-D, the binding protein that aids in calcium transport, binds to lead with high affinity and may increase transport of lead in low calcium states.

It is known that lead interferes with the utilization of iron for the formation of heme. This probably occurs in every cell, although it is best studied in the blood-forming organs. In chronic, moderately severe lead poisoning, anemia is commonly found. A decrease in hemoglobin is reported to occur in iron-sufficient children when blood lead concentration exceeds 60 µg/dL. The anemia is a normocytic, normochromic, well-compensated hemolytic anemia. However, in children with iron deficiency, the decrease in hemoglobin may occur at lower blood lead levels.
and present as a microcytic anemia. Anemia in lead poisoning results from impairment of hemoglobin production and changes in the red blood cell membrane. Lead’s interference in heme biosynthesis is characterized by several unique enzyme blockades causing increased urinary delta-aminolevulinic acid (ALA), urinary coproporphyrin, and erythrocyte zinc protoporphyrin. The enzymatic blocks responsible are partial. While anemia may not be seen until blood lead concentrations are markedly elevated, the effect on hemoglobin synthesis occurs at lower levels. ALA dehydratase is inhibited at levels of 15 µg/dL children. At levels of 30 µg/dL, elevation in erythrocyte protoporphyrin may be seen. Finally, at levels of 40, reduced hemoglobin synthesis may be found. The basophilic stippling of red cells is due to the presence of aggregated ribosomes, which may also include mitochondrial fragments. Conditions, such as lead poisoning, can result in altered ribosomes to have a higher propensity to aggregate. With staining, this appears as increased basophilic granulation.

The central nervous system can be affected by lead in children. Over the past several decades, epidemiologic studies have demonstrated that chronic, low-level lead poisoning may lead to CNS injury in young children. Earlier studies suggested that altered electrophysiologic responses and adverse effects on IQ occurred at blood lead concentrations of 30 µg/dL or higher. However, more recent data suggests environmental lead exposure in children at blood lead concentrations ≤ 7.5 µg/dL is associated with cognitive deficits. In fact, studies suggest that a permanent pattern of cognitive dysfunction may result from lead poisoning in the first several years of life. It should be noted that the variability in blood lead testing allows for statistical significance to be seen at levels, only, above 5 µg/dL. Consequently, it seems appropriate that blood lead test reports now inform providers that results in the range 5-9 µg/dL are associated with adverse health effects in young children aged 6 years and younger. Acute lead poisoning may produce encephalopathy in children. Ataxia, altered state of consciousness, and seizures have been reported in children with blood lead concentrations over 80 µg/dL.

**Reproductive and Developmental Effects** The reproductive toxicity which results from high-dose lead exposure was well known in the last century. In fact the data of the later half of the 1800s led a British royal commission to recommend in 1910 that women not be employed in the lead trades. This has only changed in the last 30 years, with the return of women to the work force. The obvious effects of lead in the 19th century were stillbirth and spontaneous abortion, which was usually recognized in women with occupational exposure to lead and other clinical manifestations of lead poisoning. In general, spontaneous abortion was an early event.

At the present time, we do not know the lowest blood lead at which this may occur, because lead apparently has an effect on the implantation of the fertilized ovum in the uterus. With the advent of human chorionic gonadotropin measurement procedures, it is now possible to detect the onset of pregnancy and early fetal loss as early as the first one to two weeks of pregnancy. Sexual dysfunction in the male has not been as closely studied. The studies that have been published, which suggest hypospermia and teratospermia, for example, have been criticized for faulty design. More recently, it has been found in workers employed for more than three years that serum testosterone and free-testosterone indices are decreased, at mean blood lead concentrations in excess of 60 µg/dL.
Prospective studies in infants and children, however, have detected some nonfatal effects of moderate increase in lead absorption during pregnancy. A lead-related decrease in the duration of pregnancy, decrease in birth weight, and small-for-gestational-age deliveries have been detected at cord blood lead levels of 10 to 19 µg/dL. These findings have not been consistent through all studies. It has been found during the postnatal stage of the prospective studies that the growth rate of infants is slowed. This effect was noted among infants born to women with blood lead concentrations greater than 8 µg/dL during pregnancy.

Prospective studies on the adverse effects of low-level increase in lead absorption have revealed that there is no association between blood lead concentration at birth and neurobehavioral effects beyond 24 months of age. However, these and other studies suggest that the effects on learning behavior are associated with the degree of lead exposure occurring between 12 and 36 months of age. For example, in the Bellinger study, a significant portion of the variance in cognitive abilities and performance on school test at 10½ years of age is partially predicted by blood lead concentration at 24 months of age. The consensus is that lead has an adverse effect on neurodevelopment and cognition. For an increase of 10 µg/dL during the preschool years, an average IQ loss of 2.6 points is predicted. While this may seem like a small difference, it is associated with large changes in the percentage of children classified as intellectually gifted or intellectually challenged based on the shift in the IQ distribution.

Furthermore, in the few studies that have had the chance to study children with blood leads below 10 µg/dL (0.48 µmol/L), some adverse effects on neurodevelopment have been found. Indeed, there may be no blood lead threshold for subtle adverse effects on neurodevelopment.

Mechanisms of Lead Toxicity We do not yet understand the mechanisms by which lead interferes with calcium functions. These changes may be mediated through lead’s effects on intracellular calcium homeostasis, or in the brain, for example, by activation of protein kinase C. Lead may interfere with calcium-dependent signal-transduction processes, especially those associated with neurotransmitter function. The latter may be reversible if cellular change has not occurred prior to effective intervention. Although studies using animal models of low-dose lead exposure have shown alterations in cognition and behavior, the mechanisms by which lead affects CNS function have not been elucidated. Furthermore, in vitro studies have shown that lead alters very basic nervous system functions, such as calcium-modulated signaling, at very low concentrations; however, the importance of this mechanism is not known.

Concentration of Lead in Blood Deemed Safe for Children There probably is no such thing as a “safe” blood lead concentration in humans. Indeed, some subtle but statistically significant adverse effects have been found in children on neurodevelopment. Currently, the Centers for Disease Control and Prevention (CDC) in the United States consider the action level for children as 10 µg/dL. However, this level, which was intended to be a trigger for community wide prevention, has been misused as a level to define toxicity. Recent data suggests environmental lead exposure in children at blood lead concentrations ≤ 7.5 µg/dL (0.36 µmol/L) is associated with cognitive deficits. In fact, studies suggest that a permanent pattern of cognitive dysfunction may result from lead poisoning in the first several years of life. It should be noted that the variability in blood lead testing allows for statistical significance to be seen at levels, only, above 5 µg/dL. Primary prevention should be the goal of all childhood lead screening.
programs, even though in fact they result at the present largely in secondary prevention. The data from National Health and Nutrition Examinations Survey II (NHANES II) and NHANES III give cause for encouragement as the average blood lead concentration in the United States has dropped from 15.9 µg/dL in 1978 to 1.4 µg/dL in children in 2004. The most recent CDC Report on Lead Poisoning agrees that evidence exists regarding the association between adverse of health effects in children and blood lead levels less than 10 µg/dL. Currently, no effective clinical or public health intervention has been shown to lower blood lead levels less than 10 µg/dL (0.48 µmol/L). While more research is needed, this should not prevent primary prevention strategies from occurring. The removal of lead in gasoline and the removal of food cans with lead-soldered seams have substantially decreased the overall risk in the United States, leaving old paint as the major cause of lead toxicity in children.

Use of Blood Lead Measurements as a Marker of Lead Exposure  The serial venous blood lead measurement is the best available marker of current and recent lead exposure. It is appropriate for healthcare providers to consult the laboratory in which the measurement is to be made, in order to make certain that the collection and analytic procedures are compatible. Many providers are unaware of the fact that blood samples may be easily contaminated with environmental lead unless drawn with the proper needles (stainless steel), syringes (polypropylene), and selected sample containers. Laboratories will generally provide a guideline to the interpretation of individual blood lead measurements, which are usually modeled after the most recent CDC recommendations.

Because virtually 99% of the lead in blood is bound to red blood cells whole blood (not serum or plasma) is required for its measurement. Healthcare providers should be made aware of the uncertainty in each measurement. The laboratory should be willing to provide healthcare providers with the results of their performance in blind interlaboratory proficiency programs, as well as the precision and trueness of measurements made in their own laboratories.

Where sudden changes in blood lead concentration occur, further investigation is necessary to confirm the change and find the reason for the change. A sudden increase in blood lead concentration may be due to a lead exposure. A thorough environmental history may reveal the source of lead exposure. However, contamination may occur, especially if the sample is from a capillary draw. While the clinical history may give a clear indication, confirmation of elevated blood lead concentrations should be obtained. Alternatively, chelation therapy can temporarily and precipitously drop the blood lead level. Depending on the extent of body burden, the blood lead concentration will gradually increase as the lead equilibrates between the bone, organs and blood compartments. It is important to remember that risk of adverse effects of lead is related to average blood lead concentrations. Concurrent and recent exposures may confound the interpretation. A change in blood lead concentration of 5 µg/dL or more should be considered clinically significant, whereas smaller changes may not be significant owing in large part to limitations in sampling and analysis.
Management of Children with Elevated Blood Lead Concentrations

Decreasing Exposure  By far, the most successful management occurs due to the removal of the lead risk from the environment and, ultimately, the child. Upon finding an elevated blood lead level, the local health department should be notified, and a home risk assessment should be performed. Once the source of lead is found in the home, soil, or workplace every effort should be made to remove this source. This may be accomplished by home lead paint abatement (by license and trained professionals with the family, preferably, out of the home), home dust reduction techniques, decreasing bare soil available to children, and nutritional evaluation and counseling. As noted above, those children with iron deficiency should be treated as anemia may be worse with high lead and low iron. In addition, a diet sufficient in trace elements including calcium and vitamin C should be encouraged. (See Appendix).

Chelation Therapy  Once lead has entered the body, especially bone, it is very difficult to remove. Accordingly, prevention is the mainstay of treatment. However, chelation therapy may be used to decrease the blood lead concentrations acutely. The final component of treatment is chelation therapy. Chelating agents bind metals at two or more sites. Ideally, the chelated metal would be excreted; however, the lead:chelate complex may persist in tissues where the binding occurred or be redistributed to other tissues. An optimal chelating drug should increase lead excretion, be administered easily, and be affordable and safe. Lead removal should halt further toxicity and reverse previous effects. 23

Several chelating agents are effective in lead excretion, but the chelator of choice depends on the blood lead concentration, the patient’s symptoms and the environmental lead burden. Symptomatic patients should be hospitalized and chelation therapy with Edetate Calcium Disodium (CaNa2EDTA). CaNa2EDTA is an intravenous formulation that has been shown to be effective with British AntiLewisite (BAL, Dimercaprol) for removal of lead in patients with encephalopathy. Edetate calcium disodium, used alone, may aggravate symptoms in patients with very high blood lead levels. When clinical symptoms consistent with lead poisoning or when blood lead levels are greater than 70 micrograms/deciliter, it is recommended that edetate calcium disodium be used in conjunction with dimercaprol.24 British-Anti-Lewisite (BAL) or dimercaprol is a small molecule drug which will cross into cells and may prevent the worsening of clinical and biochemical status on the first day of EDTA therapy.25 Oral chelating agents are available for treatment of lead poisoned patients who have elevated blood lead concentrations and asymptomatic. In the United States, 2,3 Dimercaptosuccinic Acid (DMSA, Succimer) is the drug most commonly used. Other oral agents that may be used are DMPS (Unithiol) and penicillamine.

Oral Chelation Therapy

2,3 Dimercaptosuccinic Acid (DMSA, Succimer)
Succimer is an orally chelating agent that is commonly used for the treatment of blood lead concentrations above 45 mcg/dL in the United States. It is a water soluble analog of dimercaprol. However, it has a wider therapeutic index and has advantages over dimercaprol and CaNa2EDTA.
Pharmacology and pharmacokinetics: Succimer is a four carbon molecule with two carboxyl groups and two sulfur groups. Lead and cadmium bind to adjoining sulfur and oxygen atoms whereas arsenic and mercury bind to both sulfur atoms resulting in a pH dependent water-soluble compound. The pharmacokinetics of succimer have been assessed in primates and humans. In primates, the absorption has been shown to be rapid with the time to peak concentration occurring within 1-2 hours. In adult human volunteers, the peak concentration occurred in 3.0 ± 0.45 hours after 10 mg/kg dosing orally. DMSA has been found to be, primarily, albumin-bound in plasma through a disulfide bond with cysteine with very little remaining unbound. It is unknown if protein bound DMSA is able to bind lead. While DMSA is primarily distributed in the extravascular space, nonhuman primate models have shown that the volume of distribution is greater than plasma volume and estimated to be 0.4 L/kg. DMSA is metabolized in humans to mixed disulfides of cysteine. Only 20% of the administered dose was eliminated unchanged in the urine after oral dosing compared to 80% after intravenous dosing. However, fecal elimination (nonabsorbed drug and biliary elimination) was not assessed. While DMSA is primarily distributed in the extravascular space, nonhuman primate models have shown that the volume of distribution is greater than plasma volume and estimated to be 0.4 L/kg. DMSA is metabolized in humans to mixed disulfides of cysteine. Only 20% of the administered dose was eliminated unchanged in the urine after oral dosing compared to 80% after intravenous dosing. However, fecal elimination (nonabsorbed drug and biliary elimination) was not assessed. The majority of the elimination occurs within 24 hours and as DMSA-cysteine disulfide conjugates. Renal clearance is greater in healthy adults than in children or adults with lead poisoning. The elimination half-life in nonhuman primates is 35 and 70 minutes for the parent and parent plus metabolites, respectively.

Dosing: While few studies have been performed to determine appropriate dosing in humans, only one pediatric study is available. Oral DMSA at 30 mg/kg/day (1050 mg/m²/day) was used and based on previous adult studies. This dose in children produced significantly (p<0.0001) greater lead excretion than 10 mg/kg/day (350 mg/m²/day) or 20 mg/kg/day (700 mg/m²/day). The current recommended dose for DMSA in the United States for children is 30 mg/kg/day for 5 days followed by a 14-day course of 20 mg/kg/day to prevent or blunt the rebound of the blood lead concentration. However, the duration of dosing has been controversial. In a study of 19 lead poisoned children, the DMSA dosing was randomized to include 30 mg/kg/day for 5 days followed either by no chelation, DMSA 10 mg/kg/day for 14 days or DMSA 20 mg/kg/day for 14 days. Rebound blood lead concentrations were noted in all groups, but was less for the 20 mg/kg/day group. However, there was no difference in the mean blood lead concentration between any groups at 2 weeks implying that there may not a benefit for an extended course of therapy. A second study (n=11) compared the effect of the traditional 19-day DMSA course and two 5-day courses (30 mg/kg/day) separated by a week. Blood lead concentrations were obtained at the time of chelation and 4 weeks after treatment. No difference between groups was noted showing that two 5-day courses of DMSA (30 mg/kg/day) may be comparable to the 19-day course. Limitations to both studies exist including the small sample sizes and failure to obtain urine lead excretion tests to assess for efficacy.

Efficacy: The precise nature of the lead-chelating moiety is not known. Thus, the assessment of the efficacy of a chelating agent is difficult to determine. The blood lead concentration is the most widely used “biomarker” to assess for efficacy of DMSA. It assesses the concentration of lead in the vascular compartment and may be considered a continuum to the soft tissues. As the blood lead concentration is what treatment is based, it aids the practitioner on the “success” of the chelation therapy. However, this laboratory value does not measure total body burden (e.g.
Researchers have argued that the urine lead excretion is a better indication for the body burden of lead, but this test is not as readily available to practitioners and is difficult to assess (See Section 4: Provocative Excretion Test for Lead Body Burden). In addition, the efficacy of the chelating agent should not only be measured by the decrease in the lead body burden, but also by the improvement or prevention of adverse events related to lead.

A number of studies have been performed to assess the efficacy of DMSA in the lead poisoned child using the blood lead concentration as the primary measure. All have results consistent with a decrease of blood lead concentrations over the short- and long-term. An open-label study in 59 children (age 12 – 65 months) with blood lead concentrations of 25 – 66 mcg/dL who received 26-28 day courses of DMSA. Children who completed the study showed a significant decrease in blood lead concentrations during therapy but had rebound levels to 58% of pretreatment. A commonly cited study is a large trial in the United States in which 780 children (age 12-33 months) with blood lead concentrations between 20-44 mcg/dL were randomized to receive placebo or up to three (26-day) courses of DMSA. While the children in the treatment group were noted to have a blood lead concentration 4.5 mcg/dL lower than the placebo group at 6 months, this difference had “largely disappeared” at the one year follow-up. Limitations to this study exist in that the commonly used dosing of a 19 day course was not used in the treatment arm which may result in less of a significant difference at the 6 month time point. In addition, as the CDC guidelines state, children with blood lead concentrations below 45 mcg/dL are commonly referred for chelation therapy. However, this study does confirm that removal of the source of lead from the child will result in a decrease in blood lead concentrations to the same degree over time as does chelation therapy.

Likewise, urine lead excretion has shown to increase as a result of chelation therapy. In the study by Graziano et al. to establish the DMSA dose, an 28-fold increase was seen in the urinary lead excretion after the first 5 doses. Over time, the amount of excretion decreased, but remained higher than baseline. This data was replicated in a similar study in which urinary lead excretion increased by as much as 16-fold during a 5 day (30 mg/kg/day) course of DMSA. However, significant interindividual variability was seen. Specific to children, Chisholm found a mean increase of 5.1 ± 2.9 (range 1.8 - 9.8) fold in urinary lead excretion between urine collected pretreatment and one week into therapy. However, the time of the urine collection in therapy as compared to the last dose of DMSA was not stated making the interpretation of the data difficult. A third study by Graziano, found urinary lead excretion increased by 20-fold in 19 children who received a 5-day course (30 mg/kg/day) of DMSA.

Non-human studies have been performed to measure blood and brain lead measurements as a measure of efficacy and have found that the use of DMSA results in a decrease of brain lead concentrations. In a non-human primate model, adult rhesus monkeys were chronically exposed to chronic high levels of lead to reach and maintain a blood lead concentration of 35-40 mcg/dL. They were randomized to placebo or DMSA for 19 days (30 mg/kg/day for 5 days and 20 mg/kg/day for 14 days). After treatment, brain tissue was analyzed for total lead. Upon analysis, there were no significant differences in brain lead concentrations between the two groups implying a lack of efficacy in removing lead from the brain. However, succimer-induced reductions in the brain may lag behind that of the blood and may be less significant. The
authors caution the use of the blood lead concentration as a surrogate for CNS lead concentrations as the correlation may be overestimated.

Probably, the best way to assess for chelation efficacy is by evaluation of neurodevelopmental outcomes in children with elevated blood lead concentrations. However, a large study of 780 lead poisoned patients with blood lead concentrations between 20 and 44 mcg/dL, chelation therapy did not improve cognitive outcomes. No significant improvements were found for neurodevelopmental, cognitive and behavioral benefits, growth or blood pressure. There is some belief that improvement with chelation does not occur as the neurologic damage occurred at the time of initial elevation and not at the time of discovery.

Safety: Use of DMSA for chelation treatment has resulted in few adverse effects. A number of studies have assessed the impact of DMSA on other metals. The only essential metal that has consistently been found to be adversely affected by DMSA is zinc. However, differences have been found between children and adults. Zinc urine concentrations were found to increase significantly after a 5-day course of DMSA in adults with occupational exposure after one and repeated doses. Evaluation in children have not had similar findings. Graziano and Chisholm in separate studies did not find a significant effect on copper and zinc elimination in 5 and 59 patients, respectively. However, the elimination of zinc in children did increase two-fold, the authors did not report significance.

Laboratory values have also been shown to be adversely affected with the therapeutic use of DMSA. Mild elevation of hepatic transaminases is not an uncommon event in the treatment of children with elevated blood lead concentrations. It is also a common adverse event with DMSA. A prospective study in children found children with elevated transaminases that improved with the use of DMSA. Liebelt et al. found mild increases in alanine transaminases in 57% of children during treatment with DMSA that resolved with discontinuation of treatment suggesting that a rise in hepatic transaminases are not a contraindication for treatment. A potentially serious complication of DMSA therapy is the rare instance of neutropenia requiring monitoring of the complete blood count during therapy.

Other adverse reactions related to the therapeutic use of DMSA. Cutaneous reactions are uncommon, but may occur in up to 6-10% of the population. According to the manufacturer, dermatologic reactions such as papular rash, pruritis and mucocutaneous reactions have occurred during clinical trials. The reaction resolved with discontinuation of therapy. Most commonly to affect the compliance with the medication are gastrointestinal side effects with acute and chronic use of DMSA. Especially in children, this may limit the ability to complete a course of chelation treatment.

**Racemic-2,3-dimercapto-1-propanesulfonic acid (DMPS, Unithiol, Dimaval)**

DMPS is a chelating agent that is related to dimercaprol and DMSA. It is water soluble and is reported to be less toxic than dimercaprol. It is available for oral, intravenous and intramuscular use for the treatment of mercury, arsenic, lead, chromium and copper (Wilson’s Disease) poisoning. Currently, it is not FDA approved in the United States, but is used more commonly in the Soviet Union and Europe.
Pharmacokinetics: The pharmacokinetic data is available due to the long-standing use of DMPS in the Soviet Union and Germany.56-58 DMPS is distributed extracellularly and, to a smaller extent, intracellularly. It is found to be greater than 80% bound by protein, mainly albumin, in the plasma and is presumed to be highly stable prolonging the heavy metal mobilizing activity59. This results in the half life extending from 1.8 hours of the parent compound to 20 hours of the altered (bound) drug. DMPS is metabolized to acyclic polymeric disulfides and cyclic polymeric disulfides. Chelation requires the two sulfhydryl group of DMPS to occur, whereas the disulfide group is not an effective moiety for chelation of lead or mercury. Oral DMPS appears to be less effective as the oral bioavailability is 60%.57 The elimination half-life is longer after intravenous dosing (20 hours compared to 9.5 hours after oral dosing) and is presumed to be due to first-pass metabolism in the gastrointestinal tract. DMPS undergoes renal excretion with 46 to 59% of the dose detected in the urine after 24 hours of dosing56.

Dosing: Different dosing is required depending on the heavy metal toxicity. As DMPS is primarily used for the treatment of arsenic and/or mercury poisoning60,61, more information is available with different dosing parameters. Oral doses of 200 to 400 mg in 2-3 divided doses increase the mercury excretion and reduce the body burden in adults.61 DMPS has been shown to be effective when copper levels are elevated and has been dosed as single oral dose of 300 mg daily or 100 mg three times daily for up to 15 days in adults. Little data is available regarding its use in children. However, for the treatment of lead poisoning in children, the oral daily dose of 200 to 400 mg per meter squared BSA has been used safely.62

Efficacy: Few studies are available comparing the efficacy of DMPS to other chelating agents. One animal study63 found that administration of CaNa2EDTA or DMSA was more effective than that of DMPS. In addition, the combination of CaNa2EDTA and DMSA was more efficient than that of CaNa2EDTA and DMPS or the individual chelators in enhancing urinary/fecal excretion of lead. The brain lead was depleted by DMSA only. In addition, DMPS has been found to be an equally effective chelator for other heavy metals such as arsenic and bismuth60,64,65.

Safety: The safety of DMPS has largely been assessed with intravenous dosing. Common adverse reactions that have occurred in patients treated for heavy metal poisoning include nausea, vomiting, headache, fatigue, rash, and pruritis.61,66 More severe rash and anaphylactic reactions have occurred, but more commonly in patients with a history of allergic reactions. No nephrotoxicity has been observed, but caution is recommended in patients with renal impairment as the parent compound and heavy metal complexes are eliminated in the urine. Intravenous DMPS should be given over 5 minutes to prevent resulting hypotension. At higher doses, IV and subcutaneous administration has resulted in necrotization and ulceration at the site.67 DMPS does not significantly alter the concentrations of copper (at normal levels) or zinc.62 Comparatively, DMSA is thought to be the least toxic of the two agents and has the highest LD50 due to its inability to move into the intracellular space.

Penicillamine:
Penicillamine is a D-B, B-dimethylcysteine, a penicillin degradation product. It is a potent gold, lead, mercury, zinc and copper chelator and is the drug of choice for treating Wilson’s disease. It has been used since 1957 for the treatment of lead poisoning and was the only oral chelator for
lead until the availability of DMSA. However, it is not FDA approved in the United States. Its sulfhydryl group combines with lead to form ring compounds increasing elimination. In addition, it has been used to treat cystinuria and rheumatic disorders.

Pharmacokinetics: Penicillamine is absorbed rapidly, but has an oral bioavailability of 40 to 70%. It is not dose dependent. Food, antacids, and iron decrease absorption. The peak occurs within 1 to 3 hours regardless of the dose. Penicillamine forms disulphide bonds with many proteins in the blood and tissues, creating potential slow release reservoirs of the drug. Only a small portion of the parent compound is metabolized in the liver to S-methylpenicillamine. Fecal elimination does occur, but accounts for a small portion of the total. The primary route of elimination is through the kidneys. The elimination half-life of unchanged penicillamine after single dosing ranges from 1.6 to 3.2 hours. After a steady state concentration is obtained, the elimination is prolonged (4 to 6 days) suggesting a slow release from deep tissues and skin.

Dosing: The dose for penicillamine was, largely, established during the treatment of toxicity from other heavy metals such as arsenic and copper. An early case report documented the effectiveness of D-penicillamine in three children with arsenic poisoning treated with 4 daily doses of 25 mg/kg/dose. The standard dose for the treatment of lead poisoning used similar daily dosing at 25 to 30 mg/kg/dose for several months. However, a further study by Shannon and Townsend showed similar effectiveness at a lower daily dose of 15 mg/kg/dose with decreased adverse reactions. Currently, the most commonly used dose in the United States is 30 to 40 milligrams/kilogram/day or 600 to 750 milligrams/square meter/day for 1 to 6 months, given 2 hours before or 3 hours after meals.

Efficacy: In an early study of occupational exposed workers, the efficacy between IV CaNa2EDTA was compared to oral penicillamine and oral CaNaEDTA. While all three agents increased the urinary excretion of lead in the workers, the greatest elimination of lead occurred with the IV formulation. As penicillamine was the only oral chelation therapy available for a number of years, early studies assessed exposed patients and the efficacy of penicillamine compared to placebo. In a retrospective cohort study, penicillamine was found to decrease the blood lead concentration by 33% compared to no significant change in the placebo group. Studies have not been performed to compare the efficacy between penicillamine and DMSA or DMPS. However, it has been found to be at least as effective as dimercaprol and EDTA.

Safety: Since the introduction of penicillamine, its use has been limited due to the significant adverse effects that result. This has led to the development of the thiol chelators (DMSA and DMPS) which are considered safer alternatives. Early studies of penicillamine in the treatment of Wilson’s disease resulted in adverse reactions that were attributable to zinc deficiency such as skin lesions on pressure points, desquamations, delayed wound healing, alopecia and sometimes glossitis, and stomatitis. While efficacy has been proven to occur during the treatment of lead poisoned patients, therapy can be affected by the adverse reactions that occur. In a study of 84 patients treated with penicillamine, an adverse reaction occurred in 33% of patients and included transient leucopenia, transient thrombocytopenia, rash, enuresis, and abdominal pain. This lead to a follow up study in which a retrospective analysis in children with elevated blood lead concentrations less than 40 mcg/dL. were treated at a reduced dose (15 mg/kg/dose). Less severe adverse reactions occurred including transient leucopenia (10%) and rash (4.5%)
requiring termination of therapy. No cases of transient thrombocytopenia, enuresis or abdominal pain occurred. All adverse reactions resolved with discontinuation of therapy. The authors conclude that a reduced dose is efficacious and only results in “benign and transient” adverse reactions.

**Provocative Excretion Test for Lead Body Burden**

In 1963, Emmerson of Brisbane, Australia introduced the calcium disodium EDTA mobilization test as a means of discriminating between those young adults with chronic nephritis with or without a history of lead poisoning during childhood. Those without a history of childhood lead poisoning showed a complete and lower response to this test in 24 hours (< 650 µg/24 h). In those with chronic renal injury apparently due to lead, a four-day collection of urine was necessary, while the peak output often occurred on the second and third day after a single, intravenous infusion of calcium disodium EDTA. In the past, this test has been used in children and had been recommended for children with blood lead levels between 25 and 40 µg/dL.

Dimercaptosuccinic acid (DMSA) has long been recognized as a potent chelator of lead. While there is some extracellular space in the bone marrow, lead is tightly bound to calcium in the bone and tissues. The active form of DMSA binds onto free lead for excretion in the urine. In addition to removal of lead from the blood, the majority of removed lead in tissues is from the kidneys. Thus, little lead will be removed from bone using the recommended doses for this test. In the average person, the lead mobilization test is not effective in predicting the body burden of lead.

In addition, while normal reference intervals for non-challenge urine metal testing are available, scientifically acceptable normal reference values for post-challenge urine metal testing have not been established. While the blood lead concentration is a poor indication of body burden, it is the test for which treatment is based. Practitioners should not treat with chelation therapy based on the lead mobilization test, as there are no standards for therapy including when to start, doses to be used or duration of therapy.

**Summary**

Lead poisoning is a chronic disease, due to cumulative intake of lead. The clinical signs and symptoms of lead poisoning are nonspecific; therefore, a lead measurement, preferably a venous blood lead measurement, is essential for diagnosis. In the majority of cases, children with lead poisoning are asymptomatic but can lead to impairment of IQ and other cognitive effects, decreased heme synthesis, and interference in vitamin D metabolism. The most successful management occurs due to the removal of the lead risk from the environment and, ultimately, the child. Prevention is the mainstay of treatment. However, chelation therapy may be used to decrease the blood lead concentrations acutely. Oral chelating agents are available for treatment of lead poisoned patients who have elevated blood lead concentrations and asymptomatic. In the United States, 2,3 Dimercaptosuccinic Acid (DMSA) is the drug most commonly used. Other oral agents that may be used are DMPS and penicillamine. Efficacy and safety studies suggest that DMSA may be the most appropriate oral chelator to use in children with elevated blood lead concentrations.

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Draft Formulary for Meso-2,3-Dimercaptosuccinic Acid (DMSA) in the Pediatric Patient

**Uses:** Chelation (binding of heavy metal) of lead in the child with an elevated blood lead concentration.

Given by mouth, **DMSA** can bind heavy metals (ie. Lead) in the blood and extracellular space, thereby increasing elimination. It is relatively safe and particularly useful for decreasing the blood lead concentration and increasing urine lead excretion. Prolonged courses may the brain lead concentration.

**Contra-indications:** Use should be primarily reserved for children with an elevated blood lead concentration greater than 45 mcg/dL or in symptomatic children at lower concentrations. Hypersensitivity to DMSA is a contraindication to its use.

**Precautions:** DMSA should not be used as a substitute for abatement of the lead exposure. Use during active exposure may lead to an increase in absorption. Elevated hepatic transaminases are not a contraindication for therapy. Neutropenia or elevated transaminases during therapy may require discontinuation after weighing the risks and benefits to treatment. Caution should be used in patients with compromised renal function.

**Dose:**

For the treatment of lead poisoning in children with blood lead concentrations above 45 mcg/dL

The initial oral dose of succimer is 10 mg/kg or 350 mg/square meter every 8 hours for 5 days; after 5 days, the dose should be decreased to 10 milligrams/kilogram or 350 milligrams/square meter every 12 hours for an additional 14 days. A course of therapy lasts a total of 19 days.

In children unable to swallow capsules, the capsules may be separated and the contents sprinkled onto a small amount of soft food or put into a spoon to be followed by a fruit.

No data are available regarding the use of DMSA in children under one year of age.

For the treatment of lead poisoning in adults with blood lead concentrations

Although DMSA is not indicated for the treatment of lead poisoning in adults, adults have been successfully treated with oral doses of 10 to 30 mg/kg/day; 30 mg/kg/day for 5 days appears to be the optimal dose in adults.

**Adverse-effects:** nausea, vomiting, elevated hepatic enzymes, neutropenia, rash
Appendix

Lead Exposure in Children: Prevention, Detection, and Management

Lead Exposure in Children: Prevention, Detection, and Management

ABSTRACT. Fatal lead encephalopathy has disappeared and blood lead concentrations have decreased in US children, but approximately 25% still live in housing with deteriorated lead-based paint and are at risk of lead exposure with resulting cognitive impairment and other sequelae. Evidence continues to accrue that commonly encountered blood lead concentrations, even those less than 10 µg/dL, may impair cognition, and there is no threshold yet identified for this effect. Most US children are at sufficient risk that they should have their blood lead concentration measured at least once. There is now evidence-based guidance available for managing children with increased lead exposure. Housing stabilization and repair can interrupt exposure in most cases. The focus in childhood lead-poisoning policy, however, should shift from case identification and management to primary prevention, with a goal of safe housing for all children. Pediatrics 2005;116:1036–1046; child, lead, environmental exposure, chelation therapy, succimer, cognition, clinical trials, housing, prevention, behavior.

BACKGROUND

In 1991, when 1 in 11 US children had a blood lead concentration greater than 10 µg/dL, both the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) recommended that all US children have their blood lead concentration measured at around 1 and 2 years of age, when concentrations increase and then peak. By 1997, the median blood lead concentration in the United States had decreased, and screening in some areas with newer housing turned up few cases of elevated blood lead concentration. The CDC and AAP then began to recommend screening only those children with a greater chance of having an elevated blood lead concentration—those in older housing, those who had a sibling or playmate with an elevated blood lead concentration, or those who had lived in or visited a structure that might contain deteriorated, damaged, or recently remodeled lead-painted surfaces. Screening of all children eligible for Medicaid, among whom were found 80% of those with increased blood lead concentration, continued to be recommended and had been required by Health Care Financing Administration (now the Centers for Medicare and Medicaid Services) regulation since 1989.

This new policy statement replaces the 1998 statement and includes discussion of new data, including:

- Reliable estimates of the percentage of the US homes containing lead hazards;
- Results from a large clinical trial showing that chelation in children with moderately elevated blood lead concentrations does not improve cognitive or neuropsychologic test scores;
- Documentation of unacceptably low screening rates among Medicaid-eligible children;
- Further confirmation of the link between lead exposure in early childhood and delinquent behavior during adolescence; and
- New data showing inverse associations between blood lead concentrations less than 10 µg/dL and IQ.

The best approach to lead poisoning is to prevent exposure in the first place, but it will be years before that goal is realized. In the meantime, case finding, case management, and prevention of additional exposure will still be required. This document considers relevant aspects of the epidemiology, clinical toxicology, prevention, and treatment of lead exposure in young children and provides recommendations for pediatricians as well as public health authorities.

DECLINE OF LEAD POISONING IN THE UNITED STATES

Lead is an element and occurs naturally, but blood lead concentrations are quite low in the absence of industrial activities. In the United States, there were historically 2 major sources of industrially derived lead for children: airborne lead, mostly from the combustion of gasoline containing tetraethyl lead; and leaded chips and dust, mostly from deteriorating lead paint. Both contribute to soil lead. A steep decrease in exposure to airborne lead in the United States has occurred since 1980. Federal legislation in the 1970s removed lead from gasoline and decreased smokestack emissions from smelters and other sources, causing blood lead concentrations in children to decrease. From 1976 to 1980, before the regulations had their full effect, US children 1 to 5 years
of age had a median blood lead concentration of 15 μg/dL. In 1988–1991, the median was 3.6 μg/dL; in 1999, the median was 1.9 μg/dL. Although concentrations have decreased in all children, black children and poor children continue to have higher blood lead concentrations. Airborne lead should no longer be a source of community exposure in the United States, but individual counties sometimes still exceed airborne lead regulations, and continued vigilance is warranted. Individual children may still be exposed to airborne lead in fumes or respirable dust resulting from sanding or heating old paint, burning or melting automobile batteries, or melting lead for use in a hobby or craft.

**SOURCES OF LEAD EXPOSURE**

**Lead Paint, Dust, and Soil**

The source of most lead poisoning in children now is dust and chips from deteriorating lead paint on interior surfaces. Children who developed lead encephalopathy with blood lead concentrations more than 100 μg/dL often had chips of lead paint visible on abdominal plain films. Children who live in homes with deteriorating lead paint, however, can achieve blood lead concentrations of 20 μg/dL or greater without frank pica. The use of leaded paint on interior surfaces ceased in the United States by the mid-1970s. However, in 1998, of the 16.4 million US homes with ≥1 child younger than 6 years, 25% still had significant amounts of lead-contaminated deteriorated paint, dust, or adjacent bare soil (“lead hazard”). Dust and soil are also a final resting place for airborne lead from gasoline and dust from paint. Lead in dust and soil can recontaminate cleaned houses and contribute to elevating blood lead concentrations in children who play on bare, contaminated soil.

**Transplacental Exposure and Lead in Human Milk**

Lead crosses the placenta, and the blood lead concentration of the infant is similar to that of the mother. The source of lead in the infant’s blood seems to be a mixture of approximately two thirds dietary and one third skeletal lead, as shown by studies that exploited the differences in lead isotopes stored in the bones of women migrating from Europe to Australia. Although lead appears in human milk, the concentration is closer to plasma lead and much lower than blood lead, so little is transferred. Because infant formula and other foods for infants also contain lead, women with commonly encountered blood lead concentrations who breastfeed their infants expose them to slightly less lead than if they do not breastfeed. In Mexico, giving women supplemental calcium during lactation resulted in a small (less than 2 μg/dL) decrease in the mother’s blood lead concentration, presumably by decreasing skeletal resorption. Theoretically, this could diminish transfer of lead through breast milk even further. In the United States, however, where calcium intake may be higher, calcium supplementation does not prevent bone loss during lactation and, thus, might not affect lead transfer at all.

**Other Sources**

Lead plumbing (in Latin, “plumbus” = lead) has contaminated drinking water for centuries, and lead in water can contribute to elevated blood lead concentrations in children. In 2003–2004, some tap water in Washington, DC, was found to exceed Environmental Protection Agency (EPA) regulations. This was thought to be caused by a change in water disinfection procedures, which increased the water’s ability to leach lead from connector pipes between the water mains and interior plumbing in old houses. The extent of this problem in Washington and other cities is not yet known. Affected families are drinking filtered or bottled water until the pipes can be replaced. (Most bottled water is not fluoridated; its consumption may lead to marginal fluoride intakes in children.) Much more about lead in drinking water is available on the EPA Web site (www.epa.gov/safewater/lead/index.html).

Table 1 includes questions about less common sources of lead exposure, which include hobbies, contaminated work clothes, ceramics, cosmetics, imported canned foods, etc. Such questions may be useful if a child has an elevated blood lead concentration but no exposure to leaded dust or soil. They have not been validated for the purpose of deciding whether to screen.

The lead concentration of blood for transfusion is not routinely measured. After exchange transfusion in the extremely low birth weight infant, 90% of the infant’s blood is donor blood. Bearer et al recommended that only units with lead concentrations of less than 0.09 μmol/L be used in these patients, on the basis of their adaptation of the World Health Organization tolerable weekly intake from ingestion to intravenous injection. Approximately one third of the units of blood that they measured were above this concentration. The effect of lead in transfused blood used in older children has not been considered.

**TOXICITY OF LEAD**

**Subclinical Effects**

At the levels of lead exposure now seen in the United States, subclinical effects on the central nervous system (CNS) are the most common effects. The best-studied effect is cognitive impairment, measured by IQ tests. The strength of this association and its time course have been observed to be similar in multiple studies in several countries. In most countries, including the United States, blood lead concentrations peak at approximately 2 years of age and then decrease without intervention. Blood lead concentration is associated with lower IQ scores as IQ becomes testable reliably, which is at approximately 5 years of age. The strength of the association is similar from study to study; as blood lead concentrations increase by 10 μg/dL, the IQ at 5 years of age and later decreases by 2 to 3 points. Canfield et al recently extended the relationship between blood lead concentration and IQ to blood lead concentrations less than 10 μg/dL. They observed a decrease in IQ of more than 7 points over the first 10 μg/dL of...
lifetime average blood lead concentration. Bellinger and Needleman subsequently reported a similarly steep slope in a reanalysis of data from their study of children with blood lead concentrations similar to those in the Canfield et al study. To confirm the adverse effects of lead on IQ at these concentrations, however, more children whose blood lead concentration has never been more than 10 μg/dL should be studied. A reanalysis of the primary data from several of the prospective studies is underway to help resolve this issue. At the moment, however, these data have not yet been incorporated into policy, and the CDC and AAP both currently use 10 μg/dL (Table 2) as the blood lead concentration of concern.

Other aspects of brain or nerve function, especially behavior, also may be affected. Teachers reported that students with elevated tooth lead concentrations were more inattentive, hyperactive, disorganized, and less able to follow directions. Additional follow-up of some of those children showed higher rates of failure to graduate from high school, reading disabilities, and greater absenteeism in the final year of high school. Elevated bone lead concentrations are associated with increased attentional dysfunction, aggression, and delinquency. In children followed from infancy with blood lead measurements, self-reported delinquent behavior at 15 to 17 years of age increased with both prenatal and postnatal lead exposure, and bone lead, thought to represent cumulative dose, is higher in adjudicated delinquents. These data imply that the effects of lead exposure are long lasting and perhaps permanent. Subclinical effects on both hearing and balance may occur at commonly encountered blood lead concentrations.

Although there are reasonable animal models of low-dose lead exposure and cognition and behavior, the mechanisms by which lead affects CNS function are not known. Lead alters very basic nervous system functions, such as calcium-modulated signaling, at very low concentrations in vitro, but it is not yet clear whether this process or some other one yet to be examined is the crucial one. Lead interferes detectably with heme synthesis beginning at blood lead concentrations of approximately 25 μg/dL. Both aminolevulinate dehydratase, an early step enzyme, and ferrochelatase, which completes the heme ring, are inhibited. Ferrochelatase inhibition is the basis of an erstwhile screening test for lead poisoning that measures erythrocyte protoporphyrin (EP), the immediate heme precursor. Because it is insensitive to the lower concentrations of lead.
blood lead that are of concern now, the test is obsolete for that use; however, EP measurement is still used clinically in managing children with higher blood lead concentrations.

**Clinical Effects**

Children with blood lead concentrations greater than 60 μg/dL may complain of headaches, abdominal pain, loss of appetite, and constipation and display clumsiness, agitation, and/or decreased activity and somnolence. These are premonitory symptoms of CNS involvement and may rapidly proceed to vomiting, stupor, and convulsions. Symptomatic lead toxicity should be treated as an emergency. Although lead can cause clinically important colic, peripheral neuropathy, and chronic renal disease in adults with occupational exposures, these symptoms are rare in children.

**Reversibility**

In an influential 1994 study, 154 children who were 13 to 87 months old and had blood lead concentrations between 25 and 55 μg/dL were given chelation with ethylenediaminetetraacetic acid (EDTA) and therapeutic iron when clinically indicated and then followed for 6 months. Those whose blood lead concentrations decreased the most had improved cognitive test scores independent of whether they had been given iron or chelation therapy. An Australian study of 375 children with longer follow-up, however, found only small and inconsistent improvement in the IQs of children.

**TABLE 2. Summary of Recommendations for Children With Confirmed (Venous) Elevated Blood Lead Concentrations**

<table>
<thead>
<tr>
<th>Blood Lead Concentration</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>10–14 μg/dL</td>
<td>Lead education</td>
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<td></td>
<td>Dietary</td>
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<td></td>
<td>Environmental</td>
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<tr>
<td></td>
<td>Follow-up blood lead monitoring</td>
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<tr>
<td>15–19 μg/dL</td>
<td>Lead education</td>
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<tr>
<td></td>
<td>Dietary</td>
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<td>Environmental</td>
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<td></td>
<td>Follow-up blood lead monitoring</td>
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<td></td>
<td>Proceed according to actions for 20–44 μg/dL if</td>
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<td></td>
<td>A follow-up blood lead concentration is in this range at least 3 months after initial venous test; or</td>
</tr>
<tr>
<td></td>
<td>Blood lead concentration increases</td>
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<tr>
<td>20–44 μg/dL</td>
<td>Lead education</td>
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<td></td>
<td>Dietary</td>
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<td></td>
<td>Environmental</td>
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<tr>
<td></td>
<td>Follow-up blood lead monitoring</td>
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<td></td>
<td>Complete history and physical examination</td>
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<td></td>
<td>Lab work</td>
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<td></td>
<td>Hemoglobin or hematocrit</td>
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<td>Iron status</td>
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<tr>
<td></td>
<td>Environmental investigation</td>
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<tr>
<td></td>
<td>Lead hazard reduction</td>
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<tr>
<td></td>
<td>Neurodevelopmental monitoring</td>
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<tr>
<td></td>
<td>Abdominal radiography (if particulate lead ingestion is suspected) with bowel decontamination if indicated</td>
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<tr>
<td>45–69 μg/dL</td>
<td>Lead education</td>
</tr>
<tr>
<td></td>
<td>Dietary</td>
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<tr>
<td></td>
<td>Environmental</td>
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<td></td>
<td>Follow-up blood lead monitoring</td>
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<td>Complete history and physical examination</td>
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<td>Hemoglobin or hematocrit</td>
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<td>Iron status</td>
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<td>Free EP or ZPP</td>
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<td></td>
<td>Environmental investigation</td>
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<td></td>
<td>Lead hazard reduction</td>
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<td></td>
<td>Neurodevelopmental monitoring</td>
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<td></td>
<td>Abdominal radiography with bowel decontamination if indicated</td>
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<tr>
<td></td>
<td>Chelation therapy</td>
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<tr>
<td>≥70 μg/dL</td>
<td>Hospitalize and commence chelation therapy</td>
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<tr>
<td></td>
<td>Proceed according to actions for 45–69 μg/dL</td>
</tr>
</tbody>
</table>

Not Recommended at Any Blood Lead Concentration

- Searching for gingival lead lines
- Evaluation of renal function (except during chelation with EDTA)
- Testing of hair, teeth, or fingernails for lead
- Radiographic imaging of long bones
- X-ray fluorescence of long bones

ZPP indicates zinc protoporphyrin.
whose blood lead concentrations decreased the most. A large (780-children) randomized trial of the use of succimer in children with blood lead concentrations of 20 to 44 μg/dL, the Treatment of Lead-Exposed Children (TLC) Trial, showed no benefit on cognitive or neuropsychologic testing despite an abrupt but transient decrease in the treated children’s blood lead concentrations. The children were randomly assigned at approximately 2 years of age and followed with cognitive, neuropsychologic, and behavioral tests until they were approximately 5 years of age. The large size of the trial permits confident exclusion of a drug-related improvement of 2 IQ points or more. Additional follow-up at 7 years of age with more sophisticated testing still showed no advantage for the succimer-treated children.

Because blood lead concentrations decreased as the children in the TLC Trial got older regardless of whether they had chelation, Liu et al used the TLC data to attempt to replicate the reported relationship between decreasing blood lead concentrations and improved cognitive test scores. Test scores were unrelated to decreasing blood lead concentrations at 6 months’ follow-up, but results from following the children for 36 months, when they were approximately 5 years of age, showed improved test scores with greater decreases in blood lead concentration but only in the placebo group. Additional research on whether some effective intervention can be isolated to account for this phenomenon is needed. There remains no evidence that chelation will reverse cognitive impairment, and the predominance of data is consistent with a noncausal association between decreasing blood lead concentrations and improved cognitive test scores.

COSTS OF CHILDHOOD LEAD POISONING AND BENEFITS OF PREVENTION

Cost-Benefit Analyses

The removal of lead from gasoline cost money, and it will cost more money to remove lead from housing. If childhood lead exposure, however, affects cognitive function and its consequences, such as graduating from high school, then it is plausible that it will affect social function, employment, and earnings. Several groups have estimated the long-term dollar costs of childhood lead exposure, assuming that the effect of lead on IQ is linear and permanent; they also assume a specific economic value of increased IQs. Grosse et al estimated the economic benefit of the 25-year secular downward trend in childhood lead exposure in the cohort of children 2 years of age in 2000. The estimated increase in earnings for the 3.8 million children would be between $110 billion and $319 billion over their lifetimes, compared with what they would have earned if they had been exposed to 1975 lead levels. Landrigan et al estimated the lifetime costs for each year’s cohort of children currently exposed to lead to be $43 billion. On the cost side, Needleman estimated a $10 billion cost for deleading the estimated 2 million lead-contaminated houses that existed in 1990. In 2002, a more reliable estimate is that there are 4 million such lead-contaminated houses, and when adjusting for inflation (with the Consumer Price Index inflation calculator [www.bls.gov/cpi]), Needleman’s estimate becomes approximately $28 billion in 2002. Combining these estimates leads to the conclusion that removing lead paint is cost-effective if it prevents even two thirds of lead exposure for any single year’s cohort of 2-year-olds. Similarly, a presidential task force estimated that the net nationwide benefit of interim control of lead hazards in the nation’s pre-1960 housing would be $1 billion to $9 billion over 10 years. The benefit of abating the hazards permanently would be $21 billion to $38 billion. Such quantitation allows planning and setting priorities to be done more transparently and allows comparisons to estimates of the cost for lead-abatement programs and other preventive activities. Although these are exemplary numbers in simplified analyses, all parts of which could be challenged, they illustrate the rationale for viewing lead exposure as a problem that should be solved, even on economic grounds.

Federal Strategy to Prevent Lead Poisoning

The President’s Task Force on Environmental Health Risks and Safety Risks to Children was formed in 1997 by executive order. It consists of government officials from the EPA, the Department of Health and Human Services, the Consumer Product Safety Commission, the Department of Housing and Urban Development (HUD), and others. One of its first projects was to formulate a plan to eliminate childhood lead poisoning, a goal that was incorporated into the Healthy People 2010 goals for the nation (www.healthypeople.gov/Document/HTML/Volume1/08Environmental.htm#_Toc490564710). For the first time, the strategy concentrated on primary prevention and was directed at housing. It did not require that a lead-poisoned child first be identified before a house was considered eligible for participation (the principle of primary prevention). The core of the strategy is a grant-based program administered by the HUD that would accelerate the pace at which in-place management of lead hazards would occur in US homes. The strategy projected that more than 20 million houses could be remediated in the decade from 2000–2010, making lead-safe housing available to a large majority of US children. The strategy also included continued screening, especially among Medicaid-eligible children, enforcement of existing statutes and regulations, and research, especially on the effectiveness of in-place management of lead hazards. The HUD plans periodic evaluations and progress reports, which can be tracked on its Web site (www hud.gov/offices/lead).

DIAGNOSTIC MEASURES

The diagnosis of lead poisoning or increased lead absorption depends on the measurement of blood lead concentration. This is best performed by using a venous sample, but a carefully collected finger-stick sample can be used. Most blood lead measurements are now performed because the child meets some general eligibility criteria (screening) and not be-
because they are at especially high risk of exposure or have symptoms suggestive of lead poisoning (diagnosis).

Screening

Between 1991 and 1997, both the AAP and CDC recommended universal screening, that is, that all children have their blood lead concentration measured, preferably when they are 1 and 2 years of age. Because the prevalence of elevated blood lead concentrations has decreased so much, a shift toward targeted screening has begun, and the criteria for and implementation of targeted screening continues to develop. As of early 2005, the situation is as follows. All Medicaid-eligible children must be screened. Medicaid will reimburse 2 screenings, one at 1 year of age and one at 2 years of age. Most children with elevated blood lead concentrations are Medicaid eligible, and most Medicaid-eligible children have not been screened. The Advisory Committee on Childhood Lead Poisoning Prevention has proposed criteria by which a state could acquire an exemption from this requirement, and the proposal is under consideration in the Secretary of Health and Human Services’ office. Until such exemptions are granted, both the CDC and AAP support universal screening of Medicaid-eligible children. The thinking behind the availability of exemptions is not primarily to decrease the number of screenings performed but rather to increase it among groups in which increased lead absorption will be found. Children whose families participate in any assistance program but who, for whatever reason, are not eligible for Medicaid should also be screened.

For children not eligible for Medicaid, several states and some municipalities have developed targeted screening recommendations or policies using suggestions made by the CDC, their own data, or some combination of the 2. All practitioners should determine if such recommendations are in place where they practice. Appropriate contacts at state and city health departments with CDC-funded programs are listed on the CDC Web site (www.cdc.gov/nceh/lead/grants/contacts/CLPPP%20Map.htm).

The approach to screening children who are not eligible for Medicaid and who live in areas in which health authorities have not made locale-specific recommendations is less clear. Although targeted screening may be desirable, well-validated tools with which to achieve it are not yet in place. In the absence of policy, current recommendations support screening all children who are not enrolled in Medicaid and who live in areas in which local authorities have not issued specific guidance.

There are now many case reports of children who are recent immigrants, refugees, or international adoptees who have elevated (sometimes very elevated) blood lead concentrations. Such children should be screened on arrival in the United States.

Diagnostic Testing

Some experienced clinicians measure the blood lead concentration in children with growth retardation, speech or language dysfunction, anemia, and attentional or behavioral disorders, especially if the parents have a specific interest in lead or in health effects from environmental chemicals. However, a persistent elevation of blood lead concentration into school age is unusual, even if peak blood lead concentration at 2 years of age was high and the child’s housing has not been abated. This is probably because hard-to-mouth activity decreases and the child’s body mass increases. Thus, a low blood lead concentration in a school-aged child does not rule out earlier lead poisoning. If the question of current lead poisoning arises, however, the only reliable way to make a diagnosis is with a blood lead measurement. Hair lead concentration gives no useful information and should not be performed. Radiograph fluorescence measurement of lead in bone is available in a few research centers and has been used in children as young as 11 years with acceptable validity for research purposes, but it has no clinical utility as yet.

MANAGEMENT OF CHILDREN WITH ELEVATED BLOOD LEAD CONCENTRATIONS

In 2002, the national Advisory Committee on Childhood Lead Poisoning Prevention published a monograph, “Managing Elevated Blood Lead Levels Among Young Children.” The goal of the monograph was to provide an evidence-based, standard approach to management usable throughout the United States. Anyone involved with the management of children with elevated blood lead concentrations needs access to it. This section is consistent with the monograph.

The management of children with elevated blood lead concentrations is determined primarily by how high the concentration is (Table 2). Children with concentrations less than 10 μg/dL are not currently considered to have excess lead exposure. Children with concentrations 10 μg/dL or greater should have their concentrations rechecked; if many children in a community have concentrations greater than 10 μg/dL, the situation requires investigation for some controllable source of lead exposure. Children who ever have a concentration greater than 20 μg/dL or persistently (for more than 3 months) have a concentration greater than 15 μg/dL require environmental and medical evaluation.

Residential Lead Exposure

Most children with elevated blood lead concentrations live in or regularly visit a home with deteriorating lead paint on interior surfaces. Some children eat paint chips, but pica is not necessary to achieve blood lead concentrations of 20 μg/dL or greater. Children can ingest lead-laden dust through normal mouth behavior by simply placing their hand or an object in their mouth. This also happens when children handle food during eating. There is increasing evidence that professional cleaning, paint stabilization, and removal and replacement of building components can interrupt exposure. Cooperation with the health department in investigating and decreasing the source is necessary. Although some authorities insist that moving children to unleaded
housing or removal of all lead paint from their current housing is the only acceptable solution,\textsuperscript{51} alternative housing is rarely available and extensive on-site removal of leaded paint can raise the concentration in house dust and resident children.\textsuperscript{52}

Lead in soil is higher around houses with exterior lead paint and in places where there has been a smokestack or other point source or heavy traffic. Soil concentrations are related to blood lead concentrations but not as closely as are interior dust lead concentrations.\textsuperscript{13} Soil can be tested for lead content, and the EPA has guidelines for testing on its Web site (www.epa.gov/lead/leadtest.pdf). Lead should no longer be a problem in municipal water supplies, but wells, old pipes from the municipal supply to the house (as has been the case in Washington, DC), or soldered joints may add lead to water (see www.epa.gov/safewater/lead/index.html). Lead dust in carpet Cover or discard

**Other Sources**

Some children will have persistently elevated blood lead concentrations without access to lead paint, bare soil, or lead in their drinking water. Their exposure may come from any of the sources listed in Table 3. Blood lead concentrations should decrease as the child passes approximately 2 years of age, and a stable or increasing blood lead concentration beyond that age is likely to be caused by ongoing exposure.

The recommended approach to environmental investigation of a child with an elevated blood lead concentration consists of (1) an environmental history, such as the one shown in Table 1, (2) an inspection of the child’s primary residence and any building in which they spend time regularly, (3) measurement of lead in deteriorated paint, dust, bare soil, or water as appropriate, (4) control of any immediate hazard, and (5) remediation of the house, which may require temporary relocation of the child. If new or lead-safe housing is an option for the family, it offers a simple and permanent solution. These situations can be frightening for the families. Involving the family and providing them with information as it is obtained is the right thing to do and may help lessen anxiety.

Although intense regimens of professional cleaning decrease children’s blood lead concentrations, providing families with instructions and cleaning materials does not. Washing children’s hands has intuitive appeal, but no data support its role in decreasing exposure. Suggested prevention strategies are listed in Table 3.

**Medical Management**

If the blood lead concentration is greater than 45 μg/dL and the exposure has been controlled, treatment with succimer should begin. A pediatrician experienced in managing children with lead poisoning should be consulted; these pediatricians can be found through state health department lead programs, through pediatric environmental health specialty units (www.aoec.org/pehsu.htm), at hospitals that participated in the largest clinical trial of succimer,\textsuperscript{2} or by calling the local poison control center or the AAP Committee on Environmental Health. The most common adverse effects of succimer listed on the label are abdominal distress, transient rash, elevated hepatocellular enzyme concentrations, and neutropenia. The drug is unpleasant to administer because of a strong “rotten-egg” odor, and 40% of the families on active drug compared with 26% on placebo found the drug difficult to administer.\textsuperscript{53} The succimer label provides dosages calculated both by body surface area and by weight, but the equivalent dose by both methods would occur in a child approximately 5 years of age. For the younger children

### Table 3. Sources of Lead Exposure and Prevention Strategies\textsuperscript{59}

<table>
<thead>
<tr>
<th>Source</th>
<th>Prevention Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental</td>
<td></td>
</tr>
<tr>
<td>Paint</td>
<td>Identify and abate</td>
</tr>
<tr>
<td>Dust</td>
<td>Wet mop (assuming abatement)</td>
</tr>
<tr>
<td>Soil</td>
<td>Restrict play in area, plant ground cover, wash hands frequently</td>
</tr>
<tr>
<td>Drinking water</td>
<td>Flush cold-water pipes by running the water until it becomes as cold as it will get (a few seconds to 2 minutes or more; use cold water for cooking and drinking)</td>
</tr>
<tr>
<td>Folk remedies</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Cosmetics containing additives such as kohl or surma</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Old ceramic or pewter cookware, old urns/kettles</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Some imported cosmetics, toys, crayons</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Contaminated mineral supplements</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Parental occupations</td>
<td>Remove work clothing at work; wash work clothes separately</td>
</tr>
<tr>
<td>Hobbies</td>
<td>Proper use, storage, and ventilation</td>
</tr>
<tr>
<td>Home renovation</td>
<td>Proper containment, ventilation</td>
</tr>
<tr>
<td>Buying or renting a new home</td>
<td>Inquire about lead hazards</td>
</tr>
<tr>
<td>Lead dust in carpet</td>
<td>Cover or discard</td>
</tr>
<tr>
<td>Host</td>
<td>Frequent hand washing; minimize food on floor</td>
</tr>
<tr>
<td>Hand-to-mouth activity (or pica)</td>
<td>Adequate intake of calcium, iron, vitamin C</td>
</tr>
<tr>
<td>Inadequate nutrition</td>
<td>Enrichment programs</td>
</tr>
<tr>
<td>Developmental disabilities</td>
<td></td>
</tr>
</tbody>
</table>
typically given the drug, body surface area calculations give higher doses, which are those that are recommended.54

Although chelation therapy for children with blood lead concentrations of 20 to 44 μg/dL can be expected to lower blood lead concentrations, it does not reverse or diminish cognitive impairment or other behavioral or neuropsychologic effects of lead.3 There are no data supporting the use of succimer in children whose blood lead concentrations are less than 45 μg/dL if the goal is to improve cognitive test scores.

Children with symptoms of lead poisoning, with blood lead concentrations higher than 70 μg/dL, or who are allergic or react to succimer will need parenteral therapy with EDTA and hospitalization. Guidelines for these circumstances are beyond the scope of this statement, but the same consultation as described above is recommended. There are academic centers that use D-penicillamine, another oral chelator used in Wilson disease, for lead poisoning. Its safety and efficacy, however, have not been established,55 and the AAP Committee on Drugs considers it to be a third-line drug for lead poisoning.56

Dietary Intervention

The Advisory Committee on Childhood Lead Poisoning Prevention reviewed the evidence for dietary intervention in lead-exposed children.16 They concluded that there are no trial data supporting dietary interventions aimed specifically at preventing lead absorption or modulating the effects of lead. However, there are laboratory and clinical data suggesting that adequate intake of iron, calcium, and vitamin C are especially important for these children. Adequate iron and calcium stores may decrease lead absorption, and vitamin C may increase renal excretion. Although there is epidemiologic evidence that diets higher in fat and total calories are associated with higher blood lead concentrations at 1 year of age,57 the absence of trial data showing benefits and the caloric requirements of children at this age preclude recommending low-fat diets for them.

Psychological Assessment

The Advisory Committee on Childhood Lead Poisoning Prevention reviewed the evidence for psychological assessment and intervention in lead-exposed children.16 Despite data from several large epidemiologic studies suggesting that moderate exposure to lead produces specific deficits in attention or executive functions, visual-spatial skills, fine-motor coordination, balance, and social-behavioral modulation,58 there is no specific “signature” syndrome yet identified. In addition, although 2-year-olds tend to have the highest blood lead concentrations, they will usually not have detectable cognitive damage, which can be expected to become more apparent at 4 years of age and later. It seems reasonable to manage children whose blood lead concentration is 20 μg/dL or greater at its peak as having a higher risk of developmental delay and behavior abnormalities.16 Because the effects emerge later, after the child’s blood lead concentration will have decreased, the child’s record must be kept open even after the blood lead concentration has decreased.

Although there is not specific literature supporting the use of enrichment programs in lead-poisoned children, programs aimed at children with delay from another cause should be effective in lead-poisoned children.

RECOMMENDATIONS FOR PEDIATRICIANS

1. Provide anticipatory guidance to parents of all infants and toddlers about preventing lead poisoning in their children. In particular, parents of children 6 months to 3 years of age should be made aware of normal mouthing behavior and should ascertain whether their homes, work, or hobbies present a lead hazard to their toddler. Inform parents that lead can be invisibly present in dust and can be ingested by children when they put hands and toys in their mouths.

2. Inquire about lead hazards in housing and child care settings, as is done for fire and safety hazards or allergens. If suspicion arises about the existence of a lead hazard, the child’s home should be inspected. Generally, health departments are capable of inspecting housing for lead hazards. Expert training is needed for safe repair of lead hazards, and pediatricians should discourage families from undertaking repairs on their own. Children should be kept away from remediation activities, and the house should be tested for lead content before the child returns.

3. Know state Medicaid regulations and measure blood lead concentration in Medicaid-eligible children. If Medicaid-eligible children are a significant part of a pediatrician’s practice or if a pediatrician has an interest in lead poisoning, he or she should consider participating in any deliberations at the state and local levels concerning an exemption from the universal screening requirement.

4. Find out if there is relevant guidance from the city or state health department about screening children not eligible for Medicaid. If there is none, consider screening all children. Children should be tested at least once when they are 2 years of age or, ideally, twice, at 1 and 2 years of age, unless lead exposure can be confidently excluded. Pediatricians should recognize that measuring blood lead concentration only at 2 years of age, when blood lead concentration usually peaks, may be too late to prevent peak exposure. Earlier screening, usually at 1 year of age, should be considered where exposure is likely. A low blood concentration in a 1-year-old, however, does not preclude elevation later, so the test should be repeated at 2 years of age. Managed health care organizations and third-party payers should fully cover the costs of screening and follow-up. Local practitioners should work with state, county, or local health authorities to develop sensitive, customized questions appropriate to the housing and hazards encountered locally.

5. Be aware of any special risk groups that are prevalent locally, such as immigrants, foreign-born
adoptees, refugees, or children whose parents work with lead or lead dust in their occupation or hobby and, of course, those who live in, visit, or work on old houses.

6. In areas with old housing and lead hazards, encourage application for HUD or other moneys available for remediation.

7. Keep current with the work of the national Advisory Committee on Childhood Lead Poisoning Prevention and any relevant local committees. Although there is now evidence that even lower blood lead concentrations may pose adverse effects to children, there is little experience in the management of excess lead exposure in these children. Although most of the recommendations concerning case management of children with blood lead concentrations of 15 µg/dL should be appropriate for children with lower concentrations, tactics that decrease blood lead concentrations might be expected to be less and less effective as they are applied to children with lower and lower blood lead concentrations.

RECOMMENDATIONS FOR GOVERNMENT

1. Identify all children with excess lead exposure, and prevent further exposure to them. The AAP supports the efforts of individual states to design targeted screening programs, even for Medicaid children. However, the goal must be to find all children with excess exposure and interrupt that exposure, not simply to screen less. To do this, state and local government activities must focus on the children who are most at risk, which requires more and better data about the prevalence of elevated blood lead concentrations in specific communities. Prevalence estimates based on convenience samples or clinic attendees are not reliable and should not be used as the basis of policy.

2. Realize that case-finding per se will not decrease the risk of lead poisoning. It must be coupled with public health programs including environmental investigation, transitional lead-safe housing assistance, and follow-up for individual cases. Lead-screening programs in high-risk areas should be integrated with other housing and public health activities and with facilities for medical management and treatment.

3. Continue commitment to the Healthy People 2010 goal of eliminating lead poisoning by 2010. The AAP supports the current plan with emphasis on lead-safe housing. Continued monitoring and commitment will be necessary. Research findings on low-cost methods of remediating housing have become controversial. The federal government should support impartial scientific and ethical inquiry into the best way to carry out the needed research.

4. Minimize the further entry of lead into the environment. Regulations concerning airborne lead should be enforced, use of lead in consumer products should be minimized, and consideration should always be given to whether a child might come into contact with such a product.

5. Encourage scientific testing of the many simple, low-cost strategies that might decrease lead exposure. Examples include hand-washing and use of high chairs. Exploration of innovative, low-technology tactics should be encouraged, perhaps through the use of special study sections or review groups. Educational resources for parents and landlords need to be developed and tested.

6. Require coverage of lead testing for at-risk children by all third-party payers by statute or regulation.

7. Fund studies to confirm or refute the finding that blood lead concentrations of less than 10 µg/dL are associated with lower IQ. The next important step in lead research is conducting of studies in which confounding by socioeconomic factors is not so strong. Funding of studies in this area needs to be given high priority, as was done in the early 1980s when the question of effects of blood lead concentrations less than 20 µg/dL was raised.

8. Gather the nationally representative data necessary for a rational public health response to the problem of childhood lead poisoning. The federal government should continue measuring children’s blood lead concentrations in the National Health and Nutrition Surveys to allow national estimates of exposure and should periodically resurvey housing to measure progress in the reduction of lead-paint hazards. In addition, state governments can improve monitoring of trends among screened children by supporting electronic reporting of blood lead test results to the CDC.

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