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CHILDHOOD LEAD POISONING AND ITS TREATMENT

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INTRODUCTION

The 30-year federal war on childhood lead poisoning began in the activist days of the 1960s and was codified in the Lead Paint Poison Prevention Program of 1970 (1) introduced by Senator Edward Kennedy. Since that time the mean blood lead of US children has decreased from above 1 μmol/L (20.7 μg/dL) to below .25 μmol/L (5.2 μg/dL). With only two reported deaths in children from acute lead encephalopathy in the past 20 years (2), the politically attuned could call it a preordained triumph. The clinically oriented will credit early screening and diagnosis with the infrequency of life-threatening symptoms. The environmentalist can relate the elimination of leaded gasoline to the decline in mean blood lead. The skeptic might question the validity of current evidence for the neurobehavioral risk of low-level lead. The pharmacologist might express astonishment at the limited evidence for the therapeutic efficacy of chelation therapy acquired over all these years. To address the latter two concerns, this is a review of the current status of childhood lead poisoning and its treatment. To facilitate comparisons of data relating to blood lead, all subsequent values of blood lead are cited as the traditional μg/dL rather than as the molar concentration (1 μg/dL = .0483 μmol/L)

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LEAD POISONING

Growth

Runting, squint, foot drop, and albuminuria, typical of chronically elevated blood leads of 60–100 μg/dL, were the diagnostic criteria for chronic endemic lead poisoning in Australian children in the 1920s (3). Delayed growth, a general and relatively culture-free index of toxicity, is still with us. An inverse correlation of blood lead with height, weight, and chest circumference, independent of all recognized confounders, was evident in the analysis of the second National Health and Nutrition Survey (NHANES 11) data from 2695 children 6 mo through 7 years of age (Figure 1; 4).

The deleterious effect of low-level lead on growth, defined in the analysis of NHANES by Schwartz et al (4), led Huseman et al (5) to investigate the possible neuroendocrine effects of lead in children. All 12 children with blood leads above 40 μg/dL had growth retardation. On provocative growth hormone

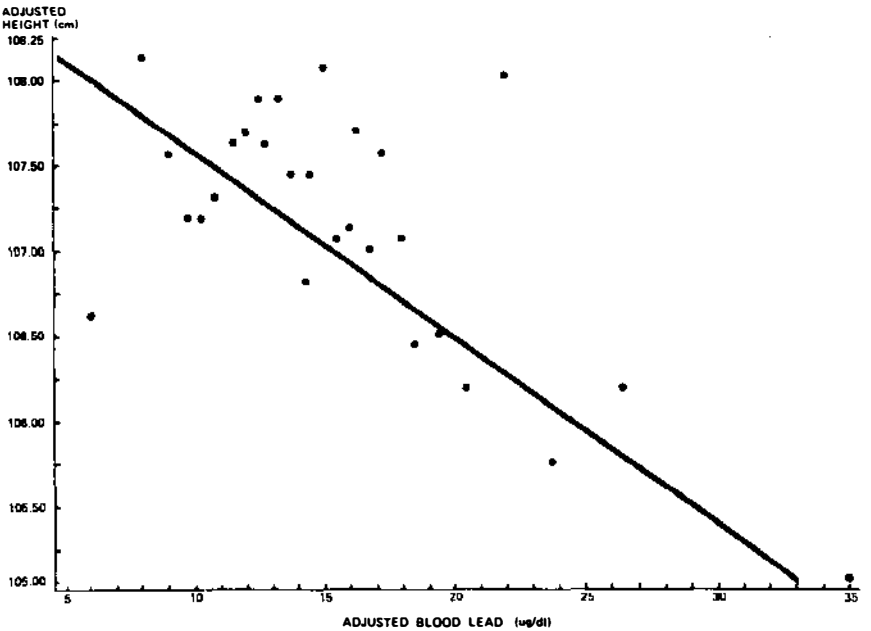


Figure 1 Adjusted height and adjusted blood lead levels for children aged 7 years and younger in Second National Health and Nutrition Examination Survey. Both height and blood lead level have been adjusted by regression for effects of age, race, sex, and all other variables significant at .05 level. Each point is the mean height and mean blood lead level of approximately 100 consecutive observations, ordered by blood lead levels. Regression line reflects slope of coefficient obtained from multiple regression analysis of all 2695 observations. (Reprinted with permission, Ref. 4)

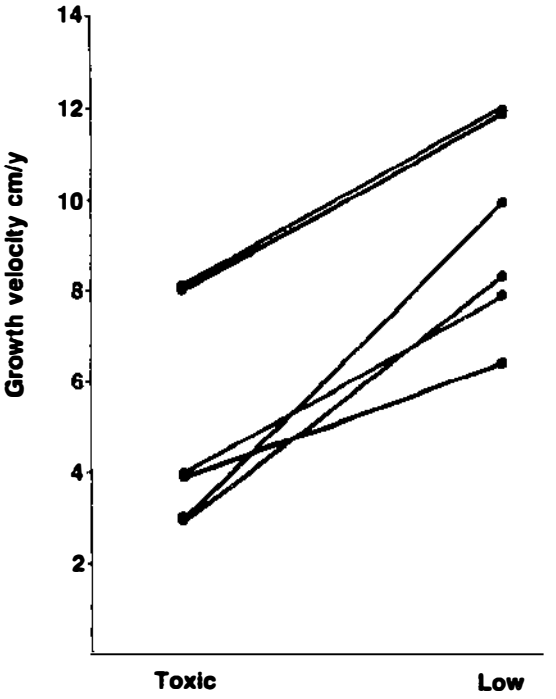


Figure 2 Growth velocity during toxic and low blood lead levels in six children who received chelation therapy ($p < .05$). (Reprinted with permission, Ref. 5)

stimulation they had low normal peak growth hormone responses but decreased insulin-like growth factor 1 (IGF-1) and evidence for a diminished 24-h secretion of growth hormone. Remarkably, growth velocity (Figure 2) and IGF-I (Figure 3) returned to normal after chelation and sustained blood leads below 25 μg/dL (5).

Pica, pallor, and irritability, seen at blood leads of about 40–60 μg/dL, were the clinical indications for a blood lead and a full evaluation prior to the national blood screening programs. The children typically had both an iron-deficient and hemolytic anemia with basophilic stippling, "lead lines" in the bone and the abdominal radioopacities of ingested lead. Glycosuria, aminoaciduria, abnormal liver function tests, and peripheral neuropathy were common. Screening of risk children, usually at 10–18 mo, has reduced the prevalence of symptomatic lead poisoning and of children first diagnosed with blood leads ≥ 40 μg/dL. The current consensus (6) is that a childhood blood lead of 10 μg/dL is not only the threshold for inhibition of erythrocyte ALA dehydratase (porphobilinogen synthetase) but appears to be the threshold for

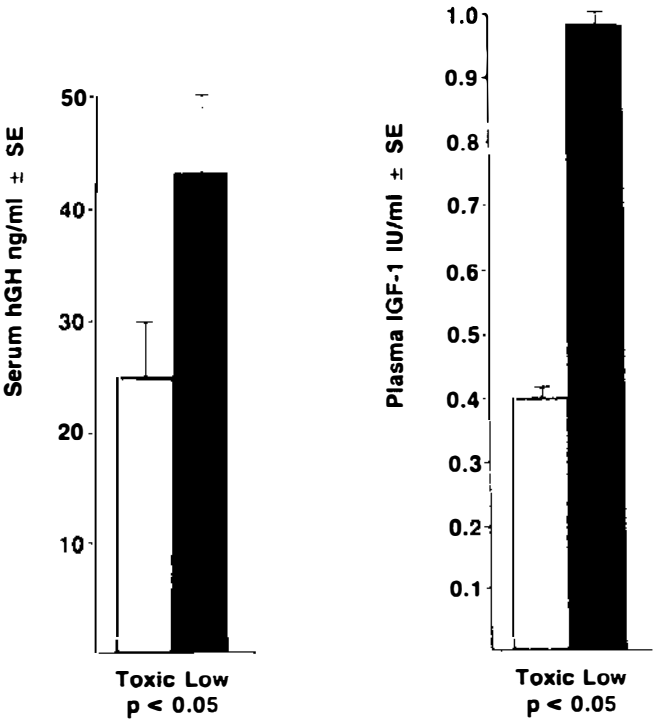


Figure 3 Comparison of peak human growth hormone (hGH) and insulin-like growth factor 1 (IGF-1) responses to L-dopa insulin test during toxicity and after chelation ($p < .05$). (Reprinted with permission, Ref. 5)

association with detectable effects on fetal maturation, mental development, and hearing in preschool children and on behavior and cognitive performance of school-age children.

Behavior and Cognition

On review of the major retrospective and cross sectional studies of the association of low-level blood lead and the cognitive performance of preschool and school-age children, it is evident that most (7–12), but not all (13), show a significant decrease in the cognitive and behavior scores of children with sustained average blood leads or dentine leads consistent with blood leads in the range of 10 to 30 μg/dL.

It is still not known if cultural differences obscure lead effects or are the source of spurious associations. In Taiwan, for example, Rabinowitz et al (14) did not find an association of increasing dentine lead with hyperactivity or limited attention to a task. The average tooth lead in Taiwan (4.6 μg/g)

was higher than concurrent sampling in Boston (3.5 μg/g) but much lower than the average tooth lead of 13 μg/g in the still newsworthy study of Needleman et al that was first published in 1979 (15).

Since maternal blood lead is a major predictor of childhood blood lead, studies beginning in pregnancy with serial evaluation of the children from birth through school age are of maximal interest. Six major prospective studies, usually referred to by locale: Boston, Cincinnati, Cleveland, Port Pirie (Australia), Sydney, and Yugoslavia, are similar in design and in application of the Bayley Mental Development Index (MDI) in the first two years and of general cognitive indices (GCI) beyond 2 years, with little testing of neurophysiologic or behavioral outcome. The Boston Study of Bellinger et al (16) followed 169 infants from a middle-class population with cord blood leads stratified as < 3, 3-, 10 and > 10 μg/dL and a mean blood lead of 7 ± 6.6 μg/dL at 24 mo. The upper strata showed detectable decrements in the MDI at 12, 18, and 24 mo of age when compared with the lowest but the effect was no longer detectable on cognitive testing (GCI) at 57 mo.

The prospective longitudinal studies in Cleveland by Ernhart (17) followed 156 disadvantaged children, 33% black. Half of the maternal sample were women with a history of alcoholism. The mean maternal IQ was 74 after adjustment for covariance. Maternal blood lead related to MDI at 6 mo but not to later MDI or to cognitive score at 58 mo. The Cincinnati (18, 19) study of 237 disadvantaged children, 85% black, maternal IQ 75, did relate the maternal and cord blood lead to the birth weight and to the MDI and psychomotor development index (PDI) scores at 6 mo but there was a paradoxical increase in the 24 mo MDI with increasing blood lead. In both the Cleveland and Cincinnati populations, the overwhelming effects of other factors may have obscured any effect of lead.

In a study of intact white families in the smelter town of Port Pirie, Australia (20, 21) cord blood lead was related to preterm delivery and neonatal head circumference, while postnatal blood leads adversely affected the 24 mo MDI. As the blood lead increased from 10 to 30 μg/dL the GCI at age 4 decreased approximately 7 points. Detectable (5 point decrements) in the GCI persisted at age 6 if the blood lead continued to average 30 μg/dL.

In the Sydney study (22) of 318 infants born to white middle-class families, all blood leads were below 15 μg/dL through 5 years of age. There was no significant association of pre- or postnatal blood lead with outcome.

All of these studies have been subject to intense scrutiny and detailed criticism (23, 24), with particular concern over the difficulty in control for confounding by genetic and environmental factors and for overlooked influences. As an example, iron deficiency increases lead absorption and is independently related to child development. Lozoff et al (25) documented a

sustained 5 point decrement in GCI in 5-year old children with a hemoglobin < 10 μg/dL at 24 mo, independent of blood lead.

The only lead study to independently analyze the effects of anemia on development is that of Wassermann, Graziano, Factor-Litvak et al (26), who prospectively evaluated mothers and offspring in the Yugoslavian smelter town of Kosovo and in a nonexposed town. At 24 mo, geometric mean blood lead concentrations of the exposed and nonexposed were 35.5 and 8.4 μg/dL, respectively. The regression model predicted a loss of 2.5 MDI points as blood lead at 24 mo rises from 10 to 30 μg/dL, with similar results observed using the cord blood lead, the blood lead at birth, 6, 12, and 18 mo of age. A loss of 1.7 MDI points was predicted as hemoglobin at 24 mo decreased from 12 to 10 μg/dL. This effect was present in both towns. Since the magnitude and persistence of the adverse effect of anemia on performance is quantitatively comparable to that of lead, failure to analyze for this effect is a serious flaw common to most population studies of childhood blood lead. The Yugoslavian study provides the strongest evidence of the adverse effects of asymptomatic lead toxicity, independent of anemia, on child development.

Indices of Lead Burden

Prior to October 1991 the CDC lead-screening program recommended a fingerstick sample for red cell zinc erythroporphyrin as a reasonably sensitive index of the inhibition of heme synthesis at blood leads of 25 μg/dL (6). The current recommendations are for an uncontaminated venous blood sample for blood lead.

Capillary (fingerstick) specimens are subject to both contamination and dilution by extracellular fluid and can be used only as a preliminary index. All blood leads are subject to diurnal and analytic variability (27). Even more relevantly, a single blood lead is an unsatisfactory index of the total body burden. Hair lead is not a valid index. In vitro measurement of the lead levels of deciduous teeth as a general index of body burden is obviously limited in use. Even when deciduous teeth are available there are significant differences among tooth types and sample sites that relate to the blood lead level during the time of tooth formation and calcification (28, 29).

The lead mobilization test (LMT) utilizes the urine lead excreted in response to a single dose of $CaNa_2EDTA$ as an index of chelatable body burden. It predicts the response to a full course of chelation, and has a somewhat stronger correlation with urine ALA than with blood lead (30). The LMT correlation with urine coproporphyrin, red cell ALA dehydratase and bone lead is also equivalent to or slightly better than blood lead (31, 32). Unfortunately, the LMT is affected by the rates of chelate infusion as well as the iron status of the child and is not comparable for the response to other chelates (33). Although widely used (34), re-evaluation of its role has been recommended

pending more specific information on the source and significance of the mobilized lead (30, 35).

The development of in vivo x-ray fluorescence (XRF) of bone lead at probably acceptable levels of minimal radiation exposure (36) offers a presumptively better index of the total body burden of lead, most of which is stored in bone. The relative strength of the three currently available XRF systems is reviewed by Chettle et al (37, 38). The first uses ^{57}Co to fluoresce the K-shell x rays and a 90° geometry. The measurement site was the phalanx and the achieved detection limit was about 20 μg lead/μg bone wet wt. Most studies in children have measured tibial bone lead by fluorescing the L-shell x rays using a partly plane-polarized output of an x-ray generator (39). Rosen et al (40, 41) are currently employing the L-line x-ray fluorescence to evaluate the response to chelation therapy and the correlation of the change in bone lead with any possible cognitive benefits.

Relatively more studies have been done in adults employing the 88.035 kEv gamma rays from ^{109}Cd to fluoresce the K-shell x rays. Data acquired from the tibia, patella, and calcaneus are correlated but quantitatively distinct with unexpectedly higher values from the trabecular bone of the calcaneus than the cortical bone of the tibia (38). Bone lead increases at less than 0.5μg/g/year of age and the average bone lead in adults is ≤20 μg/g. The ratio of lead x ray to coherent (elastic) scatter counts yields a measure in units of μg lead/g bone mineral with a detection limit of about 10 μg/g. The effective dose values for an in vivo measurement of tibial lead concentration in 1 and 5 year olds are calculated to be 1100 and 420 nSv, respectively, with an in vivo median precision of 4.9 μg lead/g bone mineral over 30 min (36).

Further reductions in radiologic exposure to below the current equivalency of a dental x ray and a single screening of the tibia or calcaneus may eventually supersede blood lead screening in populations with low blood leads.

Despite the role of chelatable lead and bone lead in evaluation of the body burden, the current recommendations of the CDC concerning screening continue to center on a venous blood lead (6) and are summarized as follows:

Blood Lead μg/dL

≤ 9 Rescreen in 1 year (6 mo if child is high risk)

10–14 Rescreen every 3–4 mo. Community intervention if many children in this range.

15–19 Rescreen every 3–4 mo. History concerning exposure and diet with recommendations. Test for and treat iron deficiency.

20–44 Complete medical evaluation. Environmental assessment and remediation (EAR). Chelation optional.

45–69 Chelation with DMSA or $CaNa_2EDTA$, EAR.

≥ 70 Immediate chelation with BAL and $CaNa_2EDTA$, EAR.

TREATMENT

Remediation

The primary goal of lead screening is the identification and elimination of lead sources in the child's environment. Deteriorated paint and plaster, construction and heavily contaminated soil are the primary causes. Shannon & Graef (42) point out that remodeling is the leading cause of lead poisoning in children under 1 year. The environmental assessment programs of most communities are unfortunately limited and quantitative assessments are not always available. The current recommendations (6) are that surface paint contain $\leq$ .06% lead, household soil and dust lead $<$ 1000 ppm, tap water lead $<$ 15 ppm, with the following maximum loading of lead in household dust: floors 200 $\mu g/ft^2$; window sills 500 $\mu g/ft^2$; window wells 800 $\mu g/ft^2$.

Individual households may also be contaminated by other sources such as folk remedies (Alarcon, Alkohol, Azarcon, Bali Goli, Coral, Ghasard, Greta, Liga, Pay-loo-ah, Rueda); cosmetics; household casting of ammunition, fish weights and toys; making stained glass, pottery; refinishing furniture; burning lead-painted wood; soldered tea kettles and water heaters; ceramic containers and glasses; and leaded crystal (6).

The CDC Strategic Plan (43, 44) offers a necessarily fallible estimate of the cost to delead and improve the two million dangerous houses in which children live and the paint is peeling. The costs may be challenged, but not the benefits of household remediation. Chisolm (35) reports that for children hospitalized for chelation of blood leads $>$ 60 $\mu g/dL$, but returning to the unmodified home environment, the blood lead was 50 $\mu g/dL$ at 1 mo and remained above this level for a full year. Children able to move to lead-free housing or totally rehabilitated housing had all subsequent blood leads below 30 $\mu g/dL$. In the absence of remediation, single and even multiple courses of chelation will have no significant effect on the body burden of lead.

Nutrition

Experimentally, lead absorption is facilitated by iron deficiency (45, 46) and this is supported but not quantitated by clinical data (47). Since an iron deficiency of 2g hemoglobin has an effect on cognitive development equivalent to an increase in the blood lead to 20 or 30 $\mu g/dL$ (25), improvement of iron status and correction of anemia is of critical importance in all children independent of the blood lead.

Ascorbic acid, folic acid, pyridoxine, vitamin B complex, and thiamin (48) all reduce experimental lead retention with and without chelation but the clinical benefits are not established. In the Omaha Duplicate Diet Study of nutrition and blood lead in preschool children of normal stature and normal blood leads, almost all diets were relatively deficient in zinc, iron, and calcium, consistent with national observations. In children treated with

$CaNa_2EDTA$ there is a massive diuresis of zinc and careful attention to zinc balance is recommended. Flora & Tanden (49) noted that the addition of zinc to $CaNa_2EDTA$ chelating therapy in rats enhanced lead excretion and the reversal of red cell ALA-D.

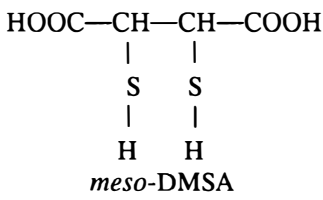
Chelation

Prior to the October 1991 recommendations of the CDC concerning treatment of lead poisoning, 29 of 30 major lead poison treatment clinics employed chelation therapy for children with blood leads ≥ 25 μg/dL and a positive lead mobilization test with one clinic recommending penicillamine for blood leads of 20 to 24 μg/dL (34). In January 1991 the FDA approved *meso*-2,3 dimercaptosuccinic acid (DMSA, Succimer) for the treatment of children with blood lead levels ≥ 45 μg/dL (50–52). Since that time there has been an increasing use of oral DMSA for the pharmacological treatment of children with blood leads ≥ 20 μg/dL.

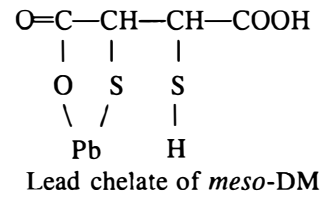
In our own clinic the policy has been to recheck any blood lead of 20 to 24 μg/dL within one month, initiate lead abatement, and treat any iron deficiency. We begin oral DMSA treatment if the repeat blood lead is significantly increased or exceeds 25 μg/dL. We usually treat all children with blood leads ≥ 25 μg/dL. Children with blood leads of 45–69 μg/dL are hospitalized for treatment with $CaNa_2EDTA$ if they are symptomatic or do not tolerate DMSA. At blood leads ≥ 70 μg/dL, we use the recommended combination of BAL and $CaNa_2EDTA$.

DMSA

The chemical, pharmacologic and toxicologic properties of DMSA are reviewed in *Annual Review Pharmacology and Toxicology,* 1990 by Aposhian & Aposhian (53) and by Mann & Travers (51). DMSA is the stable *meso* isomer of 2,3 dimercaptosuccinic acid:



meso-DMSA



Lead chelate of *meso*-DMSA

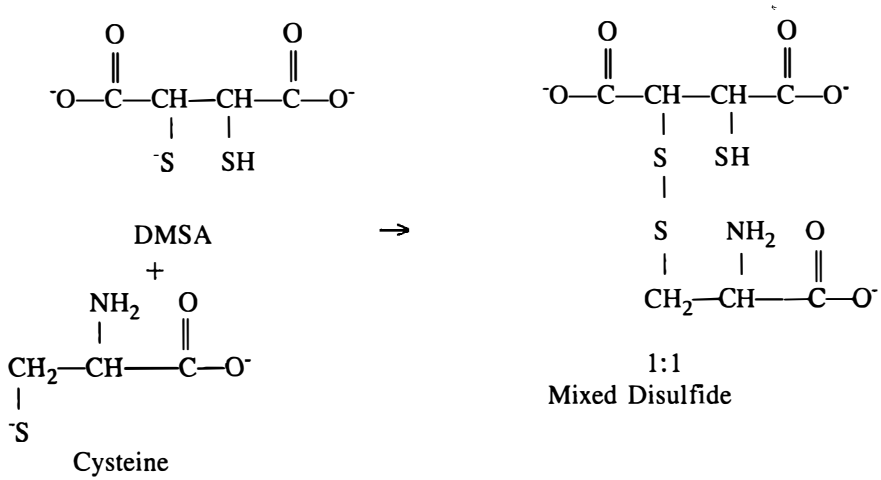
The empirical formula is $C_4H_6O_4S_2$, molecular weight 182.2. DMSA is a white crystalline powder with a characteristic mercaptan odor and taste. It is almost insoluble in water, very slightly soluble in acetone and ethanol and very soluble in aqueous alkaline solutions. DMSA has a pka of 3.0 and a pka_2 of 3.9. DMSA is an orally active, heavy metal chelating agent that forms

stable water-soluble complexes with lead in vitro. DMSA chelates mercury and nickel with each of the two sulfur atoms but cadmium, like lead, coordinates with one of the sulfur and one of the oxygen atoms. Clinical studies of DMSA (54–59) show DMSA to be specific for lead without clinically important elevations in the excretion of calcium, zinc, or iron, although zinc excretion has increased to 1.8 times baseline during treatment and copper excretion varies. Clinically DMSA 1050 mg/m^2/d lowers the blood lead concentrations with no increase on day 1. Over 5 days it decreases blood lead more effectively than $CaNa_2EDTA$ 1000 mg/m^2/d (58) but the increase in urine lead is only half that evoked by $CaNa_2EDTA$ (54, 60). Secondary indicators of efficacy include restoration of red blood cell ALA dehydratase activity and decreased urinary ALA, and coproporphyrin. In contrast to EDTA and dimercaprol, DMSA reduces the gastrointestinal absorption and retention of oral lead. Unlike $CaNa_2EDTA$, DMSA does not result in an increase in brain or liver lead.

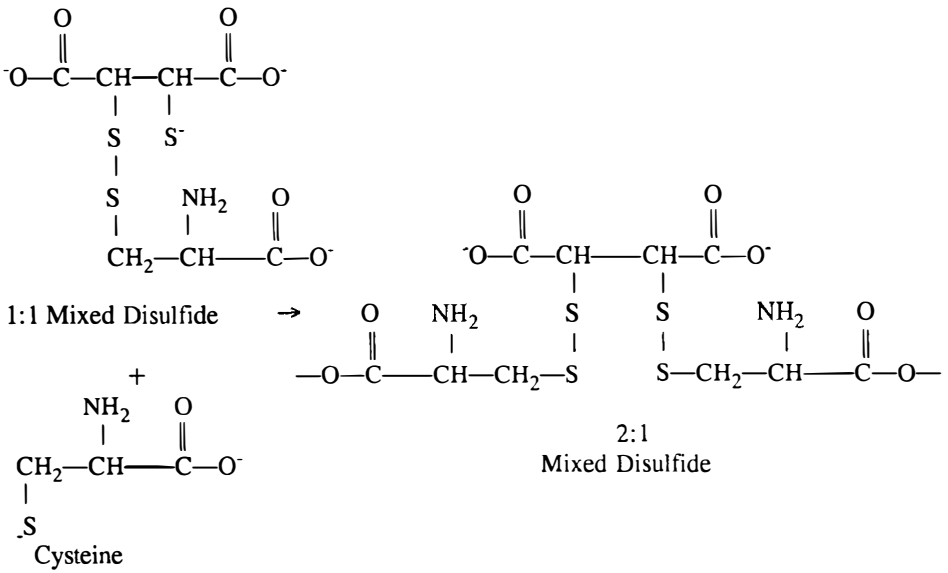
Pharmacokinetics

Oral DMSA 10 mg/kg is rapidly absorbed with a peak concentration at 3 h and an elimination half-life of 3.2 h (53). DMSA has a small volume of distribution, with 95% protein binding in the blood.

Aposhian et al (61) infer that plasma DMSA is bound to the one available thiol group in human albumin. The other SH group on the DMSA molecule may be part of the active chelating moiety or bind to any free cysteine in the plasma. Aposhian proposes that the albumin DMSA complex travels to the kidney where the albumin leaves a cysteine DMSA 1: 1 complex. The SH group of the 1: 1 complex, perhaps with an oxygen, is then available for chelation:



The kidney accounts for the majority of total clearance with 75 % renal elimination in the first 24 h. Approximately 95 % of the urine drug is mixed 2: 1 DMSA-cysteine disulfide:



Less than 2 % of the DMSA in the urine is the simple disulfide of DMSA. It is proposed that most of the metal chelation occurs in the kidney.

In rats treated with i.p. DMSA 25 or 50 mg/kg for 1 to 5 days after 4 mo of lead loading, Cory-Slechta (62) found that the lead concentration of kidney declined immediately, brain lead decreased on day 3 and liver lead on day 4. An initial decline in bone lead was followed by an increase on days 3–5. At 4 mo post chelation there was no difference in the blood, bone, brain, liver or kidney lead of treated and untreated animals.

The decrease in blood lead observed during and the rebound increase after 23 21-day courses of DMSA given on an outpatient basis to 19 Omaha children, 2 to 6 years old are shown in Figure 4.

ADVERSE EFFECTS The most common adverse effects reported in clinical trials with children and adults were gastrointestinal, including nausea, vomiting, diarrhea, appetite loss, and loose stools. The odor reduces patient acceptance. Rashes have been reported in about 4% of patients, primarily adults. Transient elevations of the serum aminotransferase have been reported in 6–10%. In our own experience in Omaha with 19 preschool children treated for blood leads of 19–44 μg/dL, over 90% of children had elevation of the

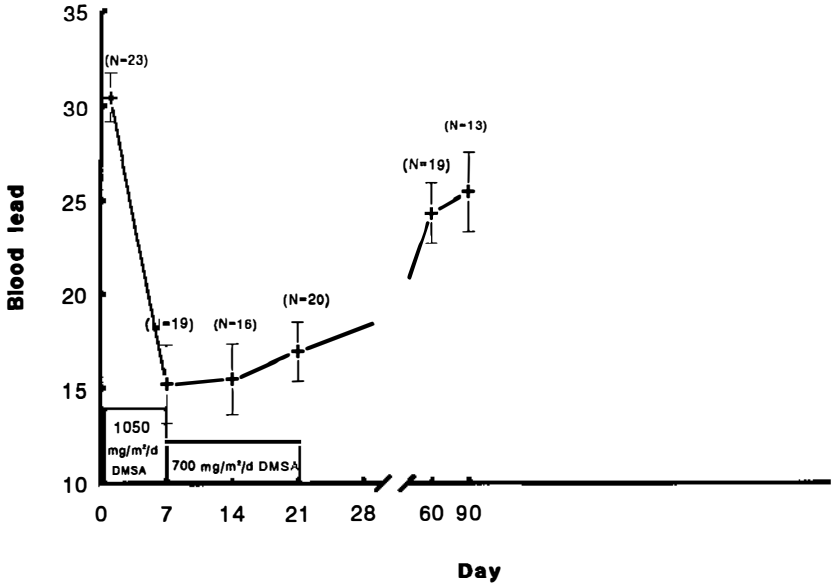


Figure 4 Blood lead, x ± S. E., of 19 children given 23 courses of oral DMSA 1050 mg/m^2/d x 5 d plus 700 mg/m^{2}d x 15 d.

serum aminotransferase above the reference range prior to beginning therapy but no patient had a higher serum enzyme level on day 5 than day 1. As shown in Figure 5, the AST declined during DMSA therapy and increased with the subsequent rebound in blood lead. We propose that abnormalities of liver enzymes are additional evidence of lead toxicity in asymptomatic children with increased blood leads.

DISEASE AND DRUG INTERACTIONS A small number of children with glucose-6-phosphate dehydrogenase deficiency and sickle cell anemia have been treated with DMSA without incident. Iron therapy concomitant with DMSA seems effective. Although dimercaprol (BAL) reportedly forms an antigenic complex with iron there has been no evidence of a similar toxic chelate in the small number of children treated with DMSA and iron supplements. Haust et al (63) successfully treated an adult with lead poisoning and iron deficiency with simultaneous administration of intramuscular iron and oral DMSA.

PREPARATION, DOSAGE, AND ADMINISTRATION The recommended initial dosage in children is 30 mg/kg/d or 1050 mg/m^2 for five days in three divided doses. After the initial five days the dose is reduced by 1/3 to 20 mg/kg/d or 700 mg/m^2 in two divided doses for an additional two weeks. The course of treatment lasts 19 days. In young children the 100-mg capsule is opened and

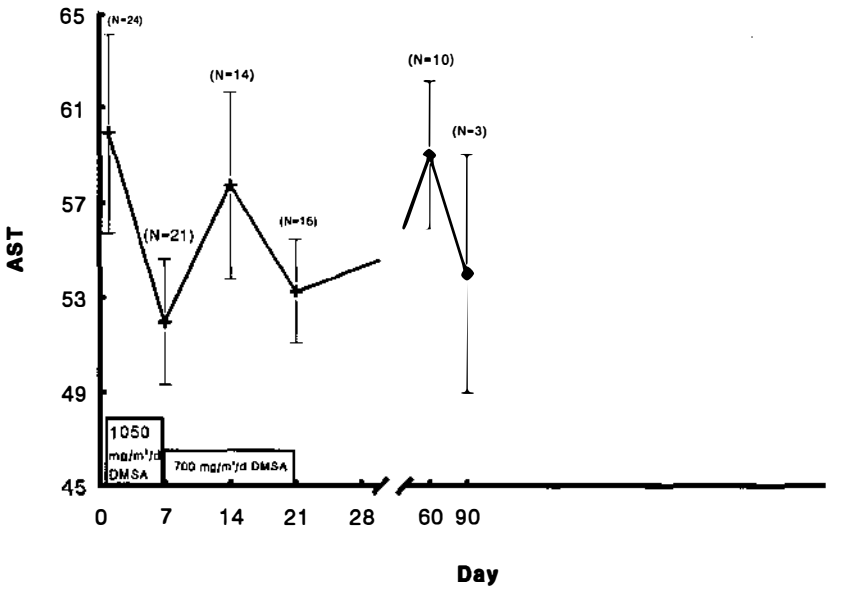


Figure 5 Serum aspartate aminotransferance (AST) of 19 children before, during and after 23 courses of DMSA. Comparison with blood lead (Figure 4) suggests that AST is sensitive to both blood lead and DMSA.

the contents are sprinkled on unchilled juice, jam, or some other acceptable vehicle. The rotten egg odor decreases on standing. The usual retail price of a bottle of 100 capsules is about $300, equivalent, in our area, to 65% of the maximum welfare payment and to the monthly rent for an adequate lead-free housing unit.

SURVEILLANCE CBC, liver function tests with transaminase and blood lead are recommended at the baseline, day 7, day 21, and at two to four weeks follow up. A spot urine lead: creatinine ratio, obtained on the same time schedule, is an index of compliance and urinary excretion of lead at two dose levels.

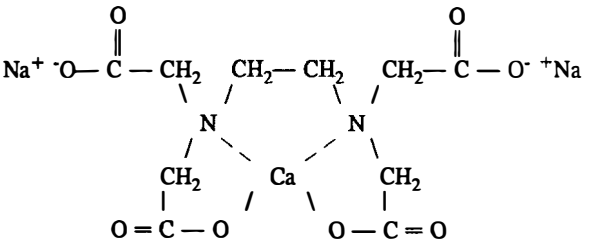
USE IN PREGNANCY There are no controlled studies in humans. DMSA is classified as category C agent indicating teratogenicity and fetotoxicity in mice (64, 65).

TOXICITY Single doses of 2300 mg/kg in rats and 2400 mg/kg in mice produced ataxia, convulsions, labored respirations, and frequently death. The median lethal dose of DMSA in mice and rats is above 3000 mg/kg. Six-day and 28-day oral toxicity studies in dogs indicate doses of 300 mg/kg/d to be lethal to some dogs. The kidneys and gastrointestinal tract were the major

organs for toxicity and deaths were due to renal failure. In a six-month chronic toxicity study in dogs thrombocytopenia was observed in animals receiving DMSA at 80 or 140 mg/kg/d for 3 mo (51).

EDTA

Ethylene diamine tetraacetic acid edetate calcium disodium, $CaNa_2EDTA$, used for over 50 years for the treatment of lead and other metal poisonings, has the following structure:



It chelates with the divalent and trivalent metals with a higher affinity for $CaNa_2EDTA$ than calcium with the mobilization of lead, zinc, manganese, and iron. As defined by Hammond (66, 67), bone is the primary source of lead that is chelated by $CaNa_2EDTA$ although the concentrations of bone lead change less than those of blood and kidney as shown in Figure 6, reproducing the data of Cory-Slechta et al (30).

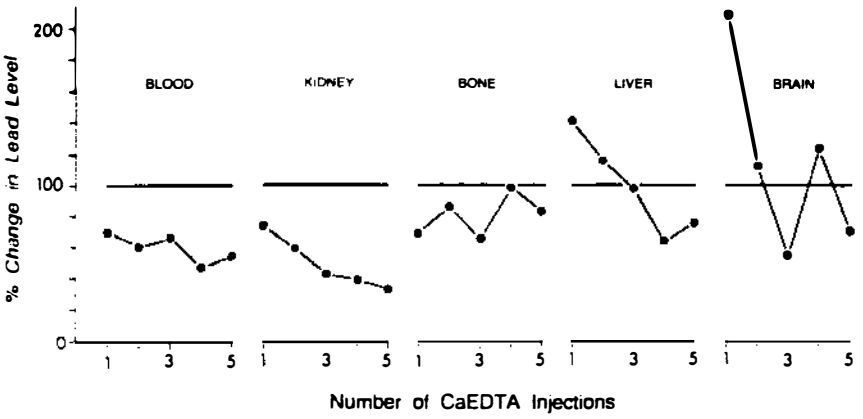


Figure 6 Mean change in tissue lead levels over the course of the five injections of 150mg/kg $CaNa_2EDTA$ to rats previously treated with lead for 4 mo. Data for each $CaNa_2EDTA$ were plotted as a percentage of the corresponding saline-control value for that particular injection (Reprinted with permission, Ref. 30)

The acute increase in brain lead evoked by $CaNa_2EDTA$ is paralleled, in humans, by an acute increase in plasma lead at 1.5 h after injection (31, 68). Smith (69) reported and many clinicians noted an adverse effect of $CaNa_2EDTA$ on lead encephalopathy. Chisolm (70) found no decrease in mortality from acute lead encephalopathy treated with $CaNa_2EDTA$ alone compared with BAL. This was attributed to diffusion of BAL, but not EDTA, into the spinal fluid with the presumptive chelation of brain lead. It resulted in the recommendations for the treatment of lead encephalopathy and of children with blood lead $\geq$ 70 μg/dL: BAL 450 mg/m^2 /d for 5 days with $CaNa_2EDTA$ 1500 mg/m^2/d for 5 days beginning after establishment of adequate renal function and output.

ABSORPTION, DISTRIBUTION AND EXCRETION Less than 5% of $CaNa_2EDTA$ is absorbed from the gastrointestinal tract into the plasma. After intravenous infusion it disappears with a half-life of 20 to 60 min.

About 50% is excreted in the urine in 1 h and over 95% in 24 h. Adequate renal function or concomitant dialysis is necessary for successful therapy (71). In dogs renal clearance equals that of inulin and glomerular filtration. Altering the pH or rate of flow of the urine has no effect on the rate of excretion. There is very little metabolic degradation. The drug is distributed mainly in extracellular fluid. The spinal fluid concentrations are approximately 5% of the plasma. It crosses the placenta and fetal distribution is probably similar to the maternal.

TOXICITY The principal toxic effect of $CaNa_2EDTA$ is on the kidney, with reversible nephrotoxicity in up to 16% of children treated for symptomatic lead poisoning (72). Repeated large doses cause hydropic vacuolization of the proximal tubule, loss of the brush border, and degeneration of the proximal tubular cells. Other side effects reported include malaise, fatigue, excessive thirst, sudden chills and fever, myalgia, frontal headache, anorexia, nausea, and vomiting. Urticaria and rashes may occur. Other effects include sneezing, nasal congestion, lacrimation, glycosuria, anemia, dermatitis with lesions similar to Vitamin B6 deficiency, hypotension, prolonged prothrombin time, and inversion of the T wave on ECG. The most consistent effect is massive diuresis of zinc. In children receiving 5-day courses of 1000 mg $CaNa_2EDTA/m^2/d$, there was an approximate 24-fold increase in the daily urinary loss of lead and about a 17-fold increase in the daily loss of zinc (73). There is no increase in urinary loss of copper above the endogenous level. Plasma zinc did not correlate with the urinary loss of zinc but monitoring of zinc status is needed during treatment.

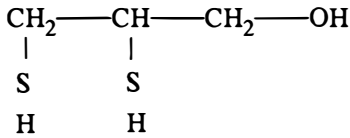
PREPARATION, ROUTES OF ADMINISTRATION AND DOSAGE For intravenous use it is diluted to $< 0.5\%$ in either 5% dextrose or .9% saline and is administered slowly by intravenous drip over at least 1 h. For children the usual dose is

1000 mg/m^2/d, preferably given by constant infusion or divided into two to six doses. Intramuscular $CaNa_2EDTA$ is painful but can be administered after mixing with procaine at a final procaine concentration of .5%. Individual courses are limited to 5 days and repeat courses given no closer than 2–5 days.

During chelation therapy, the urine output, urine sediment, BUN, serum creatinine, and liver enzyme levels are monitored closely, usually with blood chemistries on day 1 and day 5.

Dimercaprol

Dimercaprol (British Anti Lewisite, BAL) has the following structure (74):



It is an oily fluid with a pungent mercaptan odor, unstable in aqueous solutions and readily oxidized. Peanut oil is the solvent employed in pharmaceutical preparations.

MECHANISM OF ACTION The pharmacologic actions of dimercaprol are the result of formation of chelation complexes between sulfhydryl groups and metals. Disassociation of the complex and oxidation of dimercaprol can occur in vivo. The sulfur-metal bond may be labile in the acidic tubular urine and increase renal toxicity. The dosage is designed to maintain a sufficient concentration of plasma:dimercaprol to favor the continuous formation of the more stable 2:1 BAL:metal complex and its rapid excretion. Unfortunately, dose-related side effects increase at excessive plasma concentrations, requiring repeated fractional dosage.

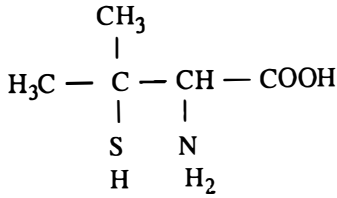
ABSORPTION, DISTRIBUTION, AND EXCRETION Dimercaprol cannot be administered orally. It is given by deep intramuscular injection as 10% solution in oil. Peak concentrations are obtained in 30–60 min. Metabolic degradation and excretion are essentially complete within 4 h.

TOXICITY Reactions to dimercaprol occur in approximately half of subjects receiving 5 mg/kg intramuscularly although the effects are not cumulative if an interval of at least 4 h elapses between injections. The most consistent response is an immediate rise in systolic and diastolic blood pressure up to 50 mm Hg accompanied by tachycardia, returning to normal within 2 h. Signs and symptoms that may parallel the hypertensive response include nausea and vomiting, headache, burning sensation in the lips, mouth and throat, feeling

of throat constriction, conjunctivitis, blepharospasm, lacrimation, rhinorrhea, salivation, abdominal pain, anxiety, and agitation. About 30% of children may also experience a fever that disappears upon withdrawal of the drug. BAL may cause hemolytic anemia in glucose-6-phosphate dehydrogenase-deficient subjects. The peanut oil vehicle may cause severe allergic reactions.

D-Penicillamine

D-Penicillamine is D-β-β-dimethyl cysteine or 3-mercapto-D-valine, with the following formula:



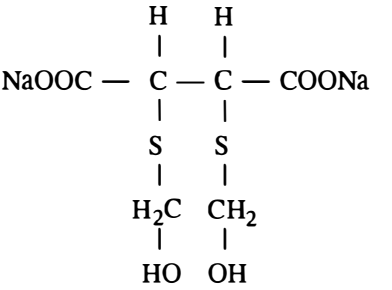
Penicillamine is approved by the FDA for the treatment of Wilson's Disease, cystinuria, and severe active rheumatoid arthritis. Before the approval of DMSA penicillamine was the only available oral chelator and has been used for the long-term treatment of children with blood lead levels of 20–40 μg/dL (75, 76).

ABSORPTION, DISTRIBUTION AND EXCRETION Penicillamine is well absorbed (40–70%) from the gastrointestinal tract but foods, antacids, and iron reduce its absorption (74). Peak concentrations in the blood are obtained between 1 and 3 h after administration. Hepatic bile transformation is responsible for most of the degradation of penicillamine and very little is excreted unchanged. Metabolites are found in both the urine and feces.

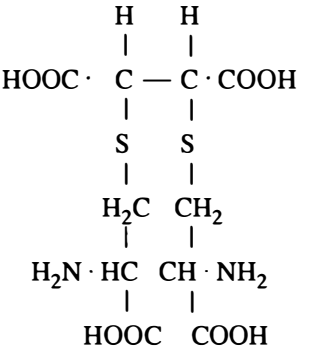
PRECAUTIONS AND TOXICITY Toxic side effects occur in as many as 33% of the patients given the drug (75, 76). The main side effects of D-penicillamine are reactions resembling penicillin sensitivity that include rashes, leukopenia, thrombocytopenia, hematuria, proteinuria, liver enzyme elevations, and eosinophilia. Anorexia, nausea, and vomiting are infrequent. Nephrotoxicity including nephrotic syndrome is the most serious side effect and the children are monitored with blood counts, urinalyses, and serum creatinine every 2–4 wk.

PREPARATION AND DOSAGE Penicillamine is available in capsules containing 125 or 250 mg that can be opened and sprinkled on an acceptable vehicle. The usual dose is 25 to 35 mg/kg/d in two or three doses. Side effects are minimized by starting at 25% of the dose and increasing slowly to the full dose by week 3.

OTHER CHELATING AGENTS A major drawback of all current chelating agents is the negligible or adverse effect on brain lead. Depending on the experimental conditions, DMSA results in stable or decreased brain lead. Chelating agents containing vicinal thioether groups, similar to DMSA, include DMES (disodium-3,6 dithia-1,8-octanediol-4,5 dicarboxylate):



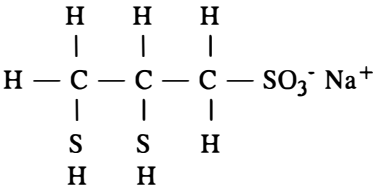
and DCSA (2,9 diamine-5,6 dicarboxy-4,7 dithiadecanedioc acid):



Tanden et al (77) conducted preliminary screening in lead-treated rats. DMES and DCSA were comparable to DMSA in efficacy and toxicity although none decreased brain lead. Xu & Jones (78) also included these agents in the screening, in mice, of 20 agents at ratios of 0.5 to 2 chelator:mmol lead. Under the conditions of the experiments DMSA, DMPS, and $CaNa_2EDTA$ were the most effective in reducing brain lead.

DMPS

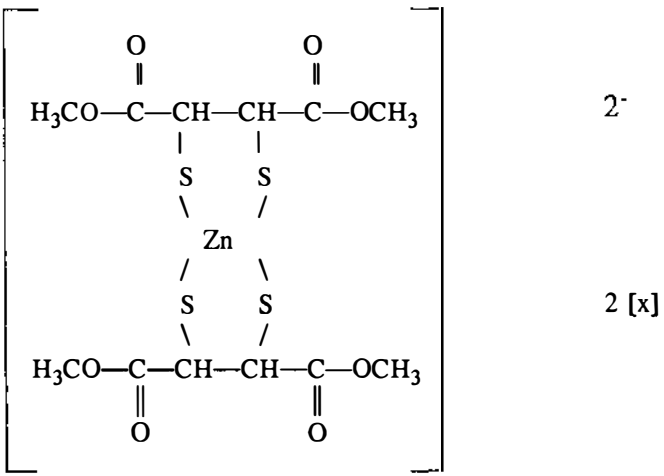
DMPS (Unithiol, Dimaval) is 2,3dimercapto-1-propane-sulfonic acid, sodium salt:



DMPS mobilizes mercury effectively and is used extensively in Europe in the diagnosis and treatment of mercury poisoning (79). DMPS has some intracellular distribution, has some biliary excretion, and is more toxic than DMSA. A pilot study of DMPS in lead-poisoned children by Thomas & Chisolm (73) indicated less efficacy than $CaNa_2EDTA$ and DMSA. Excessive urinary copper was noted. The occurrence of a severe case of Stevens-Johnson syndrome (35) terminated the trial.

Singh et al (80) compared the efficacy of 2,3 dimercaprol (BAL) with three DMSA diesters [Ch(SH)COOR]$_2$:DMDMS (R = CH_3); DEDMS (R = C_2H5); and Di-PMDS [R = $CH(CH_3)_2$]. Each of the diesters reduced soft tissue and whole body lead below that induced by BAL and was comparable to BAL in reduction of brain lead.

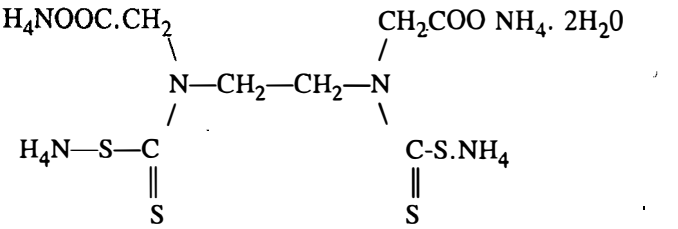
Aposhian et al (61) are investigating the DMSA monomethyl ester, in which one of the carboxyl groups is esterified, the dimethyl ester and the zinc chelate of the dimethyl ester, all synthesized by Rivera et al (81, 82):



x = Na^+
or
x = $(Me)_4 N^+$

The decreased polarity of the zinc chelate of DMSA favors an intracellular distribution and, unlike the parent compound, it does enhance the biliary excretion of cadmium and platinum (61) but the effect on brain lead has not been evaluated.

A series of dithiocarbamates was screened in rats by Tandon et al (83). All 5 dithiocarbamates reduced soft tissue and bone lead almost as effectively as DMSA but brain lead was increased by all except EDDTC (tetraammonium ethylenediaminediacetic acid dithiocarbamate:



MFA [α-mercapto-β-(2-furyl)acrylic acid] and its phenyl analogue MPA [α mercapto-β-(phenyl) acrylic acid] and MDS [α mercapto-β-(3,4-dimethoxyphenyl) acrylic acid], effective in experimental mercury poisoning, were screened in lead and nickel treated rats by Sharma et al (84). All decreased blood and liver lead but increased renal lead and, in most cases, brain lead.

Considerable evaluation is still needed for mixed ligand chelation, intended to prevent lead mobilized from one tissue into the blood from increasing in another target organ such as the brain. Combinations of agents with similar actions and distribution, such as MFA and NaB (N-benzyl-N-dithiocarboxy-D-glucamine) which both enter the cell, do not enhance efficacy (85) but the combination of DMSA and $CaNa_2EDTA$ may be a less toxic treatment of lead encephalopathy than BAL and $CaNa_2EDTA$.

Chelation Efficacy

Despite 50 years of chelation therapy, there is remarkably little objective evidence of efficacy. Combined therapy with BAL and $CaNa_2EDTA$ reduced the mortality of lead encephalopathy from 60% to 30% in the 1950s and to 5% in the 1960s (86), concurrent with both earlier diagnosis and advances in supportive therapy.

It is generally agreed (87) that lead chelation provides rapid relief of acute symptoms of colic, extreme malaise, and basophilic stippling and results in rapid restoration of red cell ALA dehydratase. As shown in Figures 2 and 3, in children with blood leads over 40 μg/dL, chelation therapy with a sustained reduction in the blood lead below 25 μg/dL resulted in an increase in growth

velocity and a normal IGF-1 response (5). Although the growth retardation in these children had neuroendocrine manifestations, the resumption of normal growth velocity is thought to be multifactorial.

There are no benefits of chelation for residual manifestations of chronic lead poisoning such as peripheral neuropathy, renal dysfunction, hypertension and hypertensive cardiovascular disease. Weeden et al (88) noted deterioration of renal function on chelation of some patients with chronic lead nephropathy. In our own clinic we have noted exacerbation of saturnine gout in adults receiving diagnostic or therapeutic $CaNa_2EDTA$.

The effects of short-term chelation are quantitatively modest compared with the total body burden. As Kosnett (87) points out, a 5-day course of chelation may mobilize 5 mg lead; in a 20-kg child the total skeletal lead may be 200–300 mg. This is reflected in the negligible influence of chelation on the blood lead of children 6 weeks after chelation vs untreated children (41).

A major concern is whether pharmacologic therapy of low-level lead modifies the neurobehavioral sequelae of childhood exposure. Cory-Slechta & Weiss (89) reviewed the lack of clinical evidence for benefit and investigated the effect of $CaNa_2EDTA$ on the abnormal response time of rats induced by low-level lead exposure. $CaNa_2EDTA$ by itself did not influence performance and failed to reverse the behavioral effects of lead-treated animals.

Rosen et al (41) report preliminary data on 162 children with blood leads 25–55 μg/dL. The bone lead of untreated children did not increase after environmental intervention. In those requiring only one course of therapy bone lead was decreased significantly 6 mo later; there was a similar trend in those receiving two or three courses.

A reduction in bone lead might be potentially beneficial since lead is mobilized from the bone under all conditions of demineralization ranging from acute childhood illness to aging (90, 91). The benefits may, however, be countered by the conversion of nonchelatable to chelatable lead (31, 32).

The relative efficacy of DMSA and $CaNa_2EDTA$ as lead chelates seems to relate to the source of the mobilized lead. For DMSA this is primarily the kidney while $CaNa_2EDTA$ initially mobilizes lead from bone or periosteal fluid as well as the kidney. At the usual doses employed (1050 mg or 5.76 mmol/m_2/d DMSA and 1000 mg or lg or 2.67 mmol/m^2/d $CaNa_2EDTA$), assuming 46% absorption of DMSA, the two compounds are administered as molar equivalents. Graziano et al (55) found the 5-day decrease in blood lead to be greater for DMSA than EDTA. The 5-day urine lead excretion, however, is approximately half that elicited by DMSA (55). Ching et al (60) state that in children $CaNa_2EDTA$ 75 mg/kg/d was four times as effective as DMSA 30 mg/kg/d in promoting lead excretion.

Beyond Chelation

More than a medical problem, childhood lead poisoning is an economic problem linked to the desquamation of lead paint from deteriorated housing and the associated dust and soil contamination (43). The prevalence of excessive body burdens of lead as well as the manifestations of neurobehavioral deficits are increased by poverty, deprivation and indifference of the part of the family and the community. Along with iron deficiency, lead toxicity is the most readily recognized and directly preventable cause of developmental delay. Needleman (44) asks if we will still be treating lead poisoning in the 21st century. Without 21st century housing, childhood lead toxicity indefensibly will still be with us.

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