THE EFFECT OF CHELATION THERAPY WITH SUCCIMER ON NEUROPSYCHOLOGICAL DEVELOPMENT IN CHILDREN EXPOSED TO LEAD

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ABSTRACT

Background Thousands of children, especially poor children living in deteriorated urban housing, are exposed to enough lead to produce cognitive impairment. It is not known whether treatment to reduce blood lead levels prevents or reduces such impairment.

Methods We enrolled 780 children with blood lead levels of 20 to 44 μg per deciliter (1.0 to 2.1 μmol per liter) in a randomized, placebo-controlled, double-blind trial of up to three 26-day courses of treatment with succimer, a lead chelator that is administered orally. The children lived in deteriorating inner-city housing and were 12 to 33 months of age at enrollment; 77 percent were black, and 5 percent were Hispanic. Follow-up included tests of cognitive, motor, behavioral, and neuropsychological function over a period of 36 months.

Results During the first six months of the trial, the mean blood lead level in the children given succimer was 4.5 μg per deciliter (0.2 μmol per liter) lower than the mean level in the children given placebo (95 percent confidence interval, 3.7 to 5.3 μg per deciliter [0.2 to 0.3 μmol per liter]). At 36 months of follow-up, the mean IQ score of children given succimer was 1 point lower than that of children given placebo, and the behavior of children given succimer was slightly worse as rated by a parent. However, the children given succimer scored slightly better on the Developmental Neuropsychological Assessment, a battery of tests designed to measure neuropsychological deficits thought to interfere with learning. All these differences were small, and none were statistically significant.

Conclusions Treatment with succimer lowered blood lead levels but did not improve scores on tests of cognition, behavior, or neuropsychological function in children with blood lead levels below 45 μg per deciliter. Since succimer is as effective as any lead chelator currently available, chelation therapy is not indicated for children with these blood lead levels. (N Engl J Med 2001;344:1421-6.)

I N children, peak blood lead levels as low as 10 to 20 μg per deciliter (0.5 to 1.0 μmol per liter) are associated with reduced scores on developmental tests at 4 to 10 years of age.[1-5] Such blood lead levels occur in tens of thousands of children in the United States each year,[6] usually at about two years of age. It is not known whether chelation therapy can protect these children from the developmental consequences of exposure to lead.

In 1991, the Food and Drug Administration licensed succimer (dimercaptosuccinic acid), the first approved oral lead chelator, for use in children with blood lead levels of at least 45 μg per deciliter (2.2 μmol per liter).[7] Succimer reduced blood lead levels at least as well as parenteral treatment with edetate calcium disodium in children with levels of 30 μg per deciliter (1.4 μmol per liter) or higher.[8] Also in 1991, universal screening of children for elevated blood lead levels was recommended by the Centers for Disease Control (CDC),[9] and the threshold of concern was lowered from 25 μg per deciliter (1.2 μmol per liter) to 15 μg per deciliter (0.7 μmol per liter) — a level associated with cognitive impairment but not symptoms of lead poisoning. However, the CDC made no specific recommendation about chelation therapy in children with blood lead levels of 20 to 44 μg per deciliter (1.0 to 2.1 μmol per liter).[9] Because of the increase in screening, the wide availability of an oral chelator, and the lack of data on lead chelation for the prevention of cognitive impairment, we conducted a multicenter, randomized, placebo-controlled clinical trial. Our study was designed to test the hypothesis that children with moderate blood lead levels who were given succimer would have better scores than children given placebo on a range of tests measuring cognition, neuropsychological function, and behavior at 36 months of follow-up.

METHODS

Referral and Prerandomization Activities

We accepted referrals of children 12 to 33 months of age (a range that includes the age at which lead levels peak) who had blood lead levels of 20 to 44 μg per deciliter, had no more than two main residences, and could be tested in English (or Spanish, at one site). Children with blood lead levels greater than 44 μg per deciliter were referred to local clinics for treatment. We measured lead levels in venous blood, serum ferritin levels, blood counts, renal func-

tion, and serum enzyme levels. We provided a vitamin and mineral supplement but later recalled one batch because of lead contamination; however, the amounts were too low to affect the children's blood lead levels.[10] We inspected the children's homes to determine whether cleaning and minor repairs could be expected to reduce exposure to lead dust.

Children with confirmed blood lead levels of 20 to 44 μg per deciliter who lived in housing that could be cleaned or who could move to lead-safe housing returned for a second visit. A child was enrolled if his or her blood lead level at the time of the second visit was also 20 to 44 μg per deciliter. About half the children referred to us were enrolled; most disqualifications were due to a blood lead level below 20 μg per deciliter.

We vacuumed the residences of the enrolled children (using a high-efficiency particle-arrestor vacuum cleaner), mopped floors and wiped walls and surfaces with a trisodium phosphate solution, made minor repairs, and performed paint stabilization (by scraping loose paint and doing minor carpentry) at about the time of randomization. The homes of 16 of the 396 children given succimer and 5 of the 384 children given placebo were never cleaned; among these, 3 of the children given succimer and 2 of the children given placebo were moved with their families to lead-safe housing.

Using supplies known to be lead-free, we collected venous blood for measurement of blood lead levels twice before randomization and then on days 7, 28, and 42 after the beginning of each course of treatment. The blood lead levels were measured at the Nutritional Biochemistry Branch of the CDC.[11] After treatment was stopped, blood lead levels were measured every three to four months. A total of 780 children were enrolled; we randomly assigned 396 to succimer and 384 to placebo. Treatment assignments were stratified according to clinical center, body-surface area, blood lead level, and language (because of the tests administered in Spanish). The study was approved by the institutional review boards at the clinical centers, the Harvard School of Public Health, the CDC, and the National Institute of Environmental Health Sciences. The parents of all the children provided written informed consent at enrollment for prerandomization activities and at the initiation of treatment for treatment and follow-up activities.

Succimer and Placebo

We administered succimer (Chemet) or placebo in 100-mg capsules of identical appearance (both provided by McNeil Consumer Products, Fort Washington, Pa.). We used 26-day courses of therapy and aimed to provide 1050 mg per square meter of body-surface area per day for the first seven days and 700 mg per square meter per day thereafter.[12] Children could receive up to three courses of treatment; those who had blood lead levels of 15 μg per deciliter or higher two weeks after the completion of a first or second course of succimer were given another course. Eighty-three percent of the children assigned to succimer required a second course, and 83 percent of those receiving a second course required a third. Children in the placebo group were assigned to retreatment to match the frequency of retreatment in the succimer group, within the strata used for initial randomization. If a child had a confirmed blood lead level above 44 μg per deciliter, the study treatment was stopped, and the child was referred for treatment according to the usual standards of the clinical center.[13]

Developmental, Neuropsychological, and Behavioral Tests

Before treatment began, we administered to the children the Bayley Scales of Infant Development II (BSID-II),[14] the current edition of the most widely used scales of infant development. At 18 months of follow-up, if the child was still younger than 42 months of age, we administered the BSID-II again; if the child was 42 months of age or older, we administered the Wechsler Preschool and Primary Scales of Intelligence–Revised (WPPSI-R).[15] At 36 months of follow-up, we administered the WPPSI-R and the Developmental Neuropsychological Assessment (NEPSY),[16] a battery of tests designed to identify neuropsychological deficits that interfere with learning. The NEPSY evaluates the domains of atten-

tional and executive, sensorimotor, visuospatial, language, and memory function. At 36 months of follow-up, we also administered to the parent the short form of the Conners' Parent Rating Scale–Revised (CPRS-R).[17] The CPRS-R is a 27-item scale that provides four behavioral indexes, of which we used the three that are applicable to younger children: Oppositional Index, Hyperactivity Index, and Attention-Deficit–Hyperactivity Disorder Index. We then averaged the CPRS-R index scores and called the average the Behavioral Index.

The children were tested with a parent or guardian present between the hours of 9 a.m. and 4 p.m. in a quiet room. The tests were rescheduled if the child was acutely ill, and the child was fed if he or she had not recently eaten. The testing psychologists did not know whether the children had been given succimer or placebo. The IQ of the caregiver (the mother for 88 percent of the children, the father for 4 percent, and another caregiver for 8 percent) was assessed during one of the follow-up visits with the short form of the Wechsler Adult Intelligence Scale–Revised.[18]

Statistical Analysis

Our study was designed to have 82 percent power to detect a 3-point difference between groups in the children's mean IQ at 36 months of follow-up at a two-sided significance level of 0.05. The actual power of the study was 96 percent, because the number of children with data at 36 months of follow-up was higher than expected and the correlation between base-line and follow-up psychometric tests was better than expected.

Nine children in the placebo group and five in the succimer group attended the 36-month follow-up appointment but were unable to complete the WPPSI-R test for developmental reasons. So that these children could be included in the analysis, their scores were imputed on the basis of the sum of scaled scores for the completed subtests or by assigning the score to the value below the lowest possible score for the corresponding domain. The data from three children who could not be tested were treated as missing.

In addition, 10 children in the placebo group and 8 in the succimer group completed the WPPSI-R at 18 months of follow-up but did not attend the appointment at 36 months. For these children, we substituted the WPPSI-R score at 18 months of follow-up for the score at 36 months, since the correlation between the two test scores was 0.83 for full-scale IQ.

We used the two-sample t-test to compare unadjusted mean scores in the two treatment groups. We also used multiple linear regression analysis to adjust the mean differences for a set of base-line covariates chosen in advance. These covariates included the variables specifically balanced by the strata used for randomization (clinical center, body-surface area, blood lead level, and language [Spanish or English]), the caregiver's IQ, the child's base-line score on the Mental Development Index from the BSID-II, and a term for the interaction between the Mental Development Index score and age. For the analyses of NEPSY subscale scores, we included an indicator variable for the version of the test administered (age of 3 to 4 years vs. age of 5 to 12 years) and a term for the interaction between the version and the age at testing. All analyses were performed according to the intention-to-treat principle. Since drug therapy was completed long before follow-up testing was performed, there was no need for stopping rules or interim analyses.

RESULTS

Randomization, Adherence, and Retention

The two treatment groups were balanced with respect to base-line characteristics (Table 1), so the estimates of the effect of treatment are similar for the adjusted and unadjusted scores. The level of precision, however, is much higher for the adjusted estimates. According to the parents' reports, over 90 percent of the assigned doses of study drug were given. When

TABLE 1. BASE-LINE CHARACTERISTICS OF ENROLLED CHILDREN ACCORDING TO TREATMENT GROUP FROM 1994 THROUGH 1997.*

CHARACTERISTIC	PLACEBO GROUP (N=384)	SUCCIMER GROUP (N=396)
Age — mo	24±6	24±6
Blood lead level — µg/dl	26±5	26±5
Weight — kg	12.3±1.9	12.3±2.0
Body-surface area — m²	0.53±0.1	0.52±0.1
Reported birth weight — g†	3169±620	3136±551
Bayley Scales of Infant Development		
Mental Development Index‡	82±14	84±14
Psychomotor Development Index§	93±13	93±15
IQ of the caregiver¶	80±11	81±11
Female sex — no. (%)	165 (43)	178 (45)
Ethnic group or race — no. (%)		
Hispanic	19 (5)	20 (5)
Black	292 (76)	309 (78)
Single parent — no. (%)	277 (72)	281 (71)
Parent with less than a high-school education — no. (%)	153 (40)	162 (41)
At least one employed parent — no. (%)	165 (43)	162 (41)
Annual family income — no. (%)		
<$10,000	137 (36)	152 (38)
≥$10,000	102 (27)	107 (27)
Unknown	145 (38)	137 (35)
Parent receiving public assistance — no. (%)	371 (97)	376 (95)

*Plus−minus values are means ±SD.

†These data were available for 361 children in the placebo group and 380 children in the succimer group.

‡These data were available for 375 children in the placebo group and 390 children in the succimer group.

§These data were available for 335 children in the placebo group and 348 children in the succimer group.

¶These data were available for 370 children in the placebo group and 375 children in the succimer group.

TABLE 2. UNADJUSTED WPPSI-R, NEPSY, AND CPRS-R SCORES AT 36 MONTHS OF FOLLOW-UP, ACCORDING TO TREATMENT GROUP, FROM 1997 THROUGH 2000.*

TEST	PLACEBO GROUP	SUCCIMER GROUP	P VALUE
WPPSI-R			
Full-scale IQ†			0.98
No. tested	368	377	
Score	80.6±13.1	80.6±13.3	
Verbal IQ			0.86
No. tested	368	377	
Score	81.7±12.8	81.9±12.6	
Performance IQ			0.76
No. tested	369	377	
Score	83.3±14.1	83.0±14.5	
NEPSY			
Attentional and executive†			0.82
No. tested	320	339	
Score	87.4±18.0	87.7±18.5	
Sensorimotor†			0.59
No. tested	331	341	
Score	85.5±15.9	86.1±15.3	
Memory			0.42
No. tested	330	342	
Score	87.7±15.4	88.6±14.7	
Language			0.41
No. tested	321	319	
Score	83.6±14.9	84.5±13.6	
Visuospatial			0.48
No. tested	341	347	
Score	89.9±12.3	90.5±12.4	
CPRS-R			
Behavioral Index†‡			0.22
No. tested	355	366	
Score	59.8±11.6	60.9±12.4	
Oppositional Index			0.36
No. tested	355	366	
Score	57.2±13.5	58.1±14.4	
Hyperactivity Index			0.40
No. tested	355	366	
Score	63.1±13.6	64.0±13.8	
Attention-Deficit–Hyperactivity Disorder Index			0.12
No. tested	355	366	
Score	59.1±12.3	60.6±13.2	

*Plus−minus values are means ±SD. WPPSI-R denotes the Wechsler Preschool and Primary Scales of Intelligence–Revised, NEPSY the Developmental Neuropsychological Assessment, and CPRS-R the Conners' Parent Rating Scale–Revised.

†The a priori primary outcome within each domain is indicated.

‡The CPRS-R Behavioral Index is the mean of the scores on the Oppositional, Hyperactivity, and Attention-Deficit–Hyperactivity Disorder Indexes.

the pills were counted, about 76 percent of the capsules had been removed from the bottles. Forty percent of the families whose children were given succimer and 26 percent of the families of children given placebo reported difficulty administering the drug. Interruptions in the administration of the drug occurred at similar rates in the succimer group (30 percent) and the placebo group (27 percent). Of the children in whom administration of the drug was interrupted, 39 percent of those receiving succimer and 45 percent of those receiving placebo resumed taking the study medication.[13]

Scores were obtained or imputed on the WPPSI-R for 745 of the 780 enrolled children (96 percent), on one or more of the NEPSY subscales for 688 (88 percent), and on the CPRS-R for 721 (92 percent) (Table 2).

Blood Lead Level

We observed the largest estimated mean difference between groups in blood lead levels, 11 µg per dec-

iliter (0.53 µmol per liter), at one week after the beginning of treatment (Fig. 1). A rebound in blood lead levels in the succimer group, presumably due to lead stored in calcified tissue, began at one week and continued. At 49 days after the beginning of treatment, the mean blood lead level in children given succimer was 72 percent of the base-line mean, as compared with 88 percent in the children given placebo. Blood lead levels dropped again in the children given second and third courses of succimer, and in each case the levels then rebounded, whereas the mean blood levels in children given placebo declined steadi-
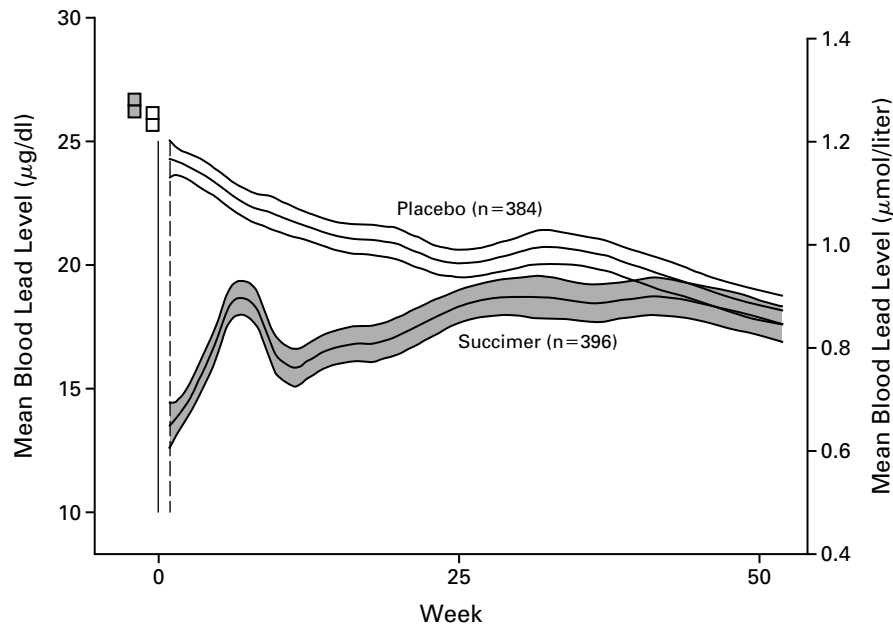
Figure 1. Mean Blood Lead Levels and 95 Percent Pointwise Confidence Intervals at Base Line and after the Initiation of Treatment in Children in the Succimer and Placebo Groups.

The squares in the upper left are the base-line values, which were measured about nine days before treatment was initiated (shaded squares indicate the succimer group, and open squares the placebo group). Means for the curves were calculated by locally weighted regression. The broken vertical line marks one week after randomization, which is the first time blood lead levels were measured after the initiation of treatment. (Adapted from the Treatment of Lead-Exposed Children Trial Group[13] with the permission of the publisher.)

ly but slowly. One year after treatment began, the difference in mean blood lead levels between the two groups had largely disappeared. The mean blood lead level of the children treated with succimer was lower by 4.5 μg per deciliter (95 percent confidence interval, 3.7 to 5.3 μg per deciliter [0.2 μmol per liter; 95 percent confidence interval, 0.2 to 0.3 μmol per liter]) than the mean level of the children given placebo over the 6 months after the initiation of treatment, and lower by 2.7 μg per deciliter (95 percent confidence interval, 1.9 to 3.5 μg per deciliter [0.1 μmol per liter; 95 percent confidence interval, 0.1 to 0.2 μmol per liter]) over the 12 months after the initiation of treatment (Fig. 1).[13]

Safety Monitoring

Of 10 children who were receiving succimer when their blood lead levels exceeded 44 μg per deciliter, 9 were hospitalized for treatment; of 7 children who were receiving placebo when their blood lead levels exceeded 44 μg per deciliter, 4 were hospitalized. Five of the children given succimer and none of those given placebo were hospitalized for trauma, with no common pattern or site of injury. A history of trauma or evidence of trauma on physical examination was noted for 15 percent of the children given suc-

cimer and 10 percent of those given placebo. There was no significant excess of any other category of symptoms, individual symptom, or laboratory abnormality in either group.[13] (Full data are available on the study Web site at http://dir.niehs.nih.gov/direb/tlc1/home.htm). We monitored the children's growth and found that those given succimer had grown 0.25 cm (95 percent confidence interval, 0.05 to 0.45) less than those given placebo over 12 months of follow-up and 0.35 cm (95 percent confidence interval, 0.05 to 0.72) less over 34 months of follow-up.

Intelligence, Neuropsychological Development, and Behavior

Unadjusted mean scores on the WPPSI-R, NEPSY, and CPRS-R were similar in the two treatment groups (Table 2). After adjustment for the variables listed in the Statistical Analysis section above, the mean full-scale IQ score on the WPPSI-R for children given succimer was 1.1 points (95 percent confidence interval for the difference, −2.6 to 0.5) lower than that for children given placebo (Fig. 2). The children given succimer scored slightly higher on four of the five domains of the NEPSY; the differences did not vary according to age at testing. For the CPRS-R, the behavioral index was 1.2 points (95 percent con-
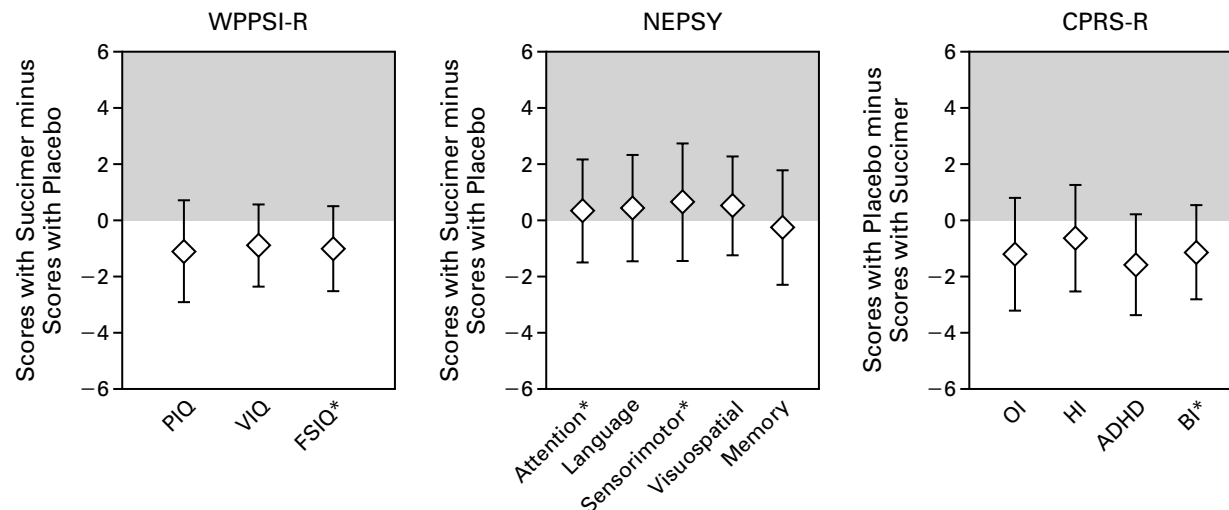
Figure 2. Difference in Adjusted Mean Scores on the WPPSI-R, NEPSY, and CPRS-R Scales between the Children Given Succimer and Those Given Placebo 36 Months after the Initiation of Treatment.

Diamonds in the upper, shaded half of the graph represent differences in scores that favor the children given succimer. I bars are 95 percent confidence intervals for the difference in means. For the Wechsler Preschool and Primary Scales of Intelligence–Revised (WPPSI-R), PIQ denotes performance IQ, VIQ verbal IQ, and FSIQ full-scale IQ. For the Developmental Neuropsychological Assessment (NEPSY) subscales, Attention denotes attentional and executive function, Language language function, Sensorimotor sensorimotor function, Visuospatial visuospatial function, and Memory memory function. For the Conners' Parent Rating Scale–Revised (CPRS-R), OI denotes the Oppositional Index, HI the Hyperactivity Index, ADHD the Attention-Deficit–Hyperactivity Disorder Index, and BI the Behavioral Index, an average of the preceding indexes. Asterisks denote variables for which there were a priori hypotheses.

fidence interval for the difference, -0.5 to 2.8) higher (i.e., worse) in children given succimer. None of these differences approached statistical significance. Adjustment had little effect on the estimates of the differences in means, as would be expected given the similarity of the groups at base line (Table 2 and Fig. 2). When we excluded the 32 children for whom we imputed the WPPSI-R scores or substituted the scores obtained at 18 months, the estimates were very similar; for adjusted full-scale IQ scores, the difference (succimer scores minus placebo scores) with imputation was -1.1 (95 percent confidence interval for the difference, -2.6 to 0.5), and without imputation it was -1.3 (95 percent confidence interval for the difference, -2.8 to 0.1).

DISCUSSION

Our study was a randomized trial of chelation therapy in children exposed to lead that was designed to examine developmental end points. Treatment with succimer did not lead to better scores on cognitive, neuropsychological, or behavioral tests than placebo.

Observational data suggest that the effect on IQ of an increase in the blood lead level from 10 to 20 μg per deciliter is a decrease of about 2 to 3 points.[19] The difference in blood lead levels between the children given succimer and those given placebo exceed-

ed 10 μg per deciliter only briefly, and the mean difference was 4.5 μg per deciliter (0.2 μmol per liter) during the six months after the initiation of treatment. Thus, it could be that the failure of our study to demonstrate a difference in test scores is due to the small difference in blood lead levels that we observed. However, succimer is as effective as any chelating agent currently available, and we used it for 26 days per course rather than the usual 19 days. We also used the (higher) loading dose for the first seven days, rather than the first five days, of each course, with the dose calculated according to body-surface area rather than weight.[20] When the pills were counted, 76 percent were gone, so adherence to therapy was as high as has been reported among children in trials lasting longer than a week.[21,22] We believe it is unlikely that another chelation regimen would have been more effective.

Ruff et al.[23] treated children with blood lead levels of 25 to 55 μg per deciliter (1.2 to 2.6 μmol per liter) using parenteral edetate calcium disodium as a chelation agent. Chelation was not randomly assigned but was used when clinically indicated and had no relation to blood lead level or IQ at follow-up. However, the children whose blood lead levels fell the most had the greatest improvement in IQ. The non-randomized design of the study by Ruff et al. made

it difficult to control for environmental and parenting differences that might lead to both larger drops in blood lead levels and increased IQ, and the six-month follow-up period was relatively short. However, Australian children whose blood lead levels fell more quickly as toddlers had higher IQ scores at seven years of age.[24] The children in our study completed their 36 months of follow-up at about five years of age and are now being evaluated at seven years of age.

Unless a more positive outcome becomes apparent at seven years of age, these results suggest that drug therapy should be used with caution in young children with blood lead levels below 45 μg per deciliter. The treatment in our study did not reduce the number of children whose blood lead levels exceeded 45 μg per deciliter and did not improve the cognitive, behavioral, or neuropsychological outcome 36 months later. The regimen is expensive and a significant burden on the families. In addition, the slight slowing of linear growth and the evidence of more frequent trauma in children receiving succimer are not reassuring. Since lead poisoning and its sequelae are entirely preventable, our inability to demonstrate effective treatment lends further impetus to efforts to protect children from exposure to lead in the first place.

APPENDIX

The following persons also participated in the study: J.R. Serwint, Johns Hopkins Hospital, Baltimore; M. Brophy, C.T. Davoli, M.R. Farfel, and G.W. Goldstein, Kennedy Krieger Institute, Baltimore; J. Rubin, University of Maryland, Baltimore; O. Berger, R.L. Bornschein, C. Wesolowski, and S. Wilkins, University of Cincinnati Medical Center, Cincinnati; G. Maynard-Wentzel and M.E. Mortensen (to 1994), Children's Hospital of Columbus, Columbus, Ohio; S. Adubato, M. Elsafty, M. Heenehan, A. Sheffet, A. Ty (to 1997), and R.P. Wedeen, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark; C. Campbell, F.M. Gill (to 1996), J. Guinn, F. Henretig, D. Knight, and D.F. Schwartz, Children's Hospital of Philadelphia, Philadelphia; B.B. Bowman (to 1996), E. Gunter, D. Huff, D.T. Miller (to 1995), and D.C. Paschal, Nutritional Biochemistry Branch, Centers for Disease Control and Prevention, Atlanta; and A.J. Bernstein, A.I. Damokosh, M.E. Fay, and T.V. Kotlov, Harvard School of Public Health, Boston; Data and Safety Monitoring Committee — C.R. Angle, J. Faison, S.H. Gehlbach (chair), B. Gray-Little, S.A. James, L.A. Moyé, and H.L. Needleman.

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