NLWJC - Kagan

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Health - Lead Poisoning

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Herbert L. Needleman, MD
Director

Ms Elena Kagan
The White House
Washington DC 20009

April 18, 1997

Dear Ms Kagan:

I mightily enjoyed having lunch with you yesterday. I want to sell you on the notion that you can't seriously address enhancing children's brains unless you include neurotoxins in the list of risk factors. Lead is among the most important neurotoxins; it is the best studied; and it is a model of other agents that we don't know as well.

Here is a brief summary of the case:

- At least a million children have blood lead levels greater than 10μg/dl, the current toxic definition.
- It is not a problem for poor blacks alone, but they get an unfair dose. About 20% of black children exceed 10μg/dl.
- Lead exposure during pregnancy affects IQ at 2 years. (NEJM 1987)
- The effects of lead exposure are permanent: High school failure rates are increased 7-fold; reading disabilities 6-fold (NEJM 1990)
- Lead exposure affects language competence, attention, and visual motor performance.(NEJM 1979)
- Lead exposure is associated with attentional deficits, increased aggression, and delinquent behavior. (JAMA 1996)
- The most important source of lead is household paint. Almost all houses built before 1960 have lead paint. There are about 2 million houses with deteriorated lead paint in which children reside. Almost all of these children have elevated blood lead levels.
- Lead is piled up in the same places where jobs and decent housing are scarce. Deleading could provide jobs where they are most needed, could return houses to decency, and wipe out the disease forever.

I don't want to swamp you, but enclose a few papers from my group. We are not the only ones reporting this, we are out in front of the others. I can let you have much more if you want.

Under separate cover, I am sending you a copy of a book by Phil Landrigan and me on avoiding toxins, aimed at parents. Phil was also at the meeting yesterday, and has recently taken on the Office of Children's affairs at EPA.

I hope that I have interested you in this important question, and would be pleased to speak with you further about neurotoxins and lead.

Sincerely,

Herbert L Needleman MD
Professor of Psychiatry and Pediatrics

Health - lead poisoning

DEFICITS IN PSYCHOLOGIC AND CLASSROOM PERFORMANCE OF CHILDREN WITH ELEVATED DENTINE LEAD LEVELS

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Abstract To measure the neuropsychologic effects of unidentified childhood exposure to lead, the performance of 58 children with high and 100 with low dentine lead levels was compared. Children with high lead levels scored significantly less well on the Wechsler Intelligence Scale for Children (Revised) than those with low lead levels. This difference was also apparent on verbal subtests, on three other measures of auditory or speech processing and on a measure of attention. Analysis of variance showed that none of these differences could be explained by any of the 39 other variables studied.

Also evaluated by a teachers' questionnaire was the classroom behavior of all children (2146 in number) whose teeth were analyzed. The frequency of nonadaptive classroom behavior increased in a dose-related fashion to dentine lead level. Lead exposure, at doses below those producing symptoms severe enough to be diagnosed clinically, appears to be associated with neuropsychologic deficits that may interfere with classroom performance. (N Engl J Med 300:689-695, 1979)

THE neurotoxic properties of lead at high dose are well known and not a subject of general controversy.[1,2] A source of considerable debate, however, is whether or not blood lead levels below those associated with obvious symptoms have adverse effects on the brain.[3,4] Because the symptoms of milder lead intoxication are not dramatic, and may therefore evade precise identification, many efforts have been made to determine whether these lesser levels of lead are associated with undetected neuropsychologic impairment.[5-11]

Among the reasons for discrepant conclusions in these earlier studies are the following methodologic difficulties shared to some extent by many of the reports:

Inadequate markers of exposure to lead. Most studies have relied on blood lead levels to classify subjects. Because blood lead is a marker of recent exposure, it may return to normal levels even though exposure was excessive. Errors are likely to occur, therefore, if blood lead is relied on to classify subjects after exposure has ceased.

Biased ascertainment of subjects. A study that attempts to provide conclusions applicable to the community at large must draw its sample from a representative population. Studies that select their subjects from health clinics, schools for the retarded or psychiatric clinics may not be representative of the population in general. Similarly, families who fear that their child has a deficit may respond to a study invitation in a systematically biased fashion, and either seek or avoid participation, depending on how the study is perceived.

Inadequate identification and handling of other confounding variables that affect development. A confounding variable is one that is differentially distributed in exposed and non-exposed groups and also affects the outcome under examination. Among the many potential confounders of effect of lead are genetic, perinatal, nutritional and socioeconomic variables. Because lead exposure is often associated with economic disadvantage, the multiple handicaps of poverty may frequently confound the effects of lead on development.

Insensitive measures of performance. Some studies have used group tests or mass screening examinations that cannot be expected to identify subtle degrees of neuropsychologic impairment. Sensitive measures are required to detect less than obvious deficit.

In this study we attempt to deal with these design issues while measuring neuropsychologic performance in relation to lead exposure in a group of children in the first and second grades, all of whom were considered asymptomatic for lead intoxication. Children were studied in two ways: those ranked in the highest and lowest 10th percentile for dentine lead concentrations were evaluated in the neuropsychologic laboratory. Their classroom behavior was also measured by teachers' ratings. In addition, all children whose teeth were analyzed had their classroom behavior evaluated by the same rating scale.

From the Mental Retardation Research Center of the Children's Hospital Medical Center and Harvard Medical School (address reprint requests to Dr. Needleman at the Children's Hospital Medical Center, 300 Longwood Ave., Boston, MA 02115).

The results of this study were reported in part at the Society for Pediatric Research, New York, NY, April 27, 1978.

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300:689-695 (March 29), 1979

Methods

Sample

The 3329 children attending first and second grades in the period between 1975 and 1978 in Chelsea and Somerville, Massachusetts, made up the population sampled. Children were asked to submit their shed teeth to the teacher, who then verified and recorded the presence of an appropriate fresh socket.

Tooth Analysis

Teeth were cleansed ultrasonically, and any with fillings were discarded from consideration. The specimens were then mounted in a lead-free wax on the cutting stage of a Buehler low-speed saw. A 1-mm slice was taken from the central sagittal plane of each tooth at a single pass. The central slice was then placed on an anvil and split with a small chisel along a line from the pulp canal to the dentine-enamel junction. The larger portions of the slices, along with the residual adjacent segments, were filed in numbered pill boxes for later confirmatory analysis. The smaller portion, composed primarily of dentine, was then analyzed for lead by anodic stripping voltammetry.[12]

Classification of Subjects' Lead Exposure

Subjects whose initial tooth slice was in the highest 10th percentile (> 24 ppm) or lowest 10th percentile (< 6 ppm) were provisionally classified as having high or low lead levels respectively (Fig. 1). Whenever possible, a second dentine lead level, either from the opposite half of the initial slice or from the remaining tooth substance, was obtained. In addition, we attempted to obtain and analyze other shed teeth from each subject provisionally classified in either group. On all but one subject, more than one analysis was obtained. Agreement between replicate samples was required before the subject was included in the study. If three values were obtained, complete concordance was required. If four values were obtained, one discordant value was allowed but discarded from analysis. If agreement was not found, the subject was designated "unclassified" and excluded from data analysis. To be classified as high lead required a mean of all concordant samples greater than 20 ppm. To be classified as low lead required a mean of less than 10 ppm.

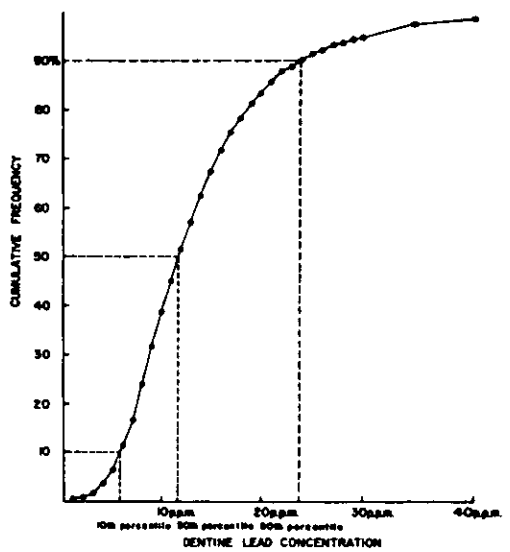

Figure 1. Cumulative Frequency Distribution of Dentine Lead Concentrations (3221 Specimens).
The points plotted are actual (unsmoothed) values.

Table 1. Reasons for Excluding Subjects and Distribution of Final Dentine Lead Levels in Included and Excluded Groups.

Group		No.	Dentine Lead Level		
			Low	High	Unclassified
Provisionally eligible subjects:		524	258	187	79
Excluded from neuropsychologic testing:		254*	123	101	30
Bilingual home	84				
Not interested	57				
Moved	19				
Other†	94				
Total	254				
Subjects tested:		270‡	135	86	49
Excluded from data analysis:		112	35	28	49
Later tooth discordant	36				
Not discharged from nursery with mother, possible head injury, reported to have plumbism or bilingual home	76				
Total	112				
Cases scored & data analyzed		158	100	58	—

*Teachers' behavioral assessment available on 235.
†Infant at home, two working parents, etc.
‡Teachers' behavioral assessment available on 253.

Criteria for Exclusion

Parents of children with confirmed high and low levels were invited to participate in the further neuropsychologic evaluation of their child. Excluded, usually by telephone interview, were children from homes in which English was not the first language, whose parents either did not wish to participate, or were not able to participate for other reasons — e.g., an infant child at home or two working parents. Also excluded, after a medical history was obtained, were children whose birth weight was below 2500 g, who were not discharged at the same time as their mother after birth or who had a history of noteworthy head injury. Any child who had been diagnosed as lead poisoned was excluded. Some subjects, initially confirmed as having high or low lead levels, were later excluded from analysis because teeth subsequently submitted had values discordant from initial determinations (Table 1).

The Neuropsychologic Evaluation

The parent (usually the mother) and child were brought by taxi to the testing location. While the parent filled out a comprehensive medical and social history, received a 58-item questionnaire evaluating parent attitude in six areas and received a Peabody Picture Vocabulary I.Q. Test,[13] the child received a comprehensive neuropsychologic battery, administered in fixed order, beginning with the Wechsler Intelligence Scale for Children — Revised. The examiners were blind to the child's lead burden during the conduct of the examination and remained so until all tests were coded. After examination was completed and all tests scored, the principal investigator informed the parents of the child's lead status and counseled them about the proper course of action.

The following tests were administered as the neuropsychologic battery to the subjects who qualified and whose parents elected to participate in the detailed evaluation:

Psychometric intelligence. Wechsler Intelligence Scale for Children — Revised[14]: six verbal and six performance subtests.

Concrete operational intelligence. Piagetian conservation of number, substance and continuous quantity.[15]

Academic achievement. Peabody tests[16] of mathematics, reading recognition and reading comprehension.

Auditory and language processing. Sentence Repetition Test,[17] Token Test,[18] Seashore Rhythm Test[19] and Wepman Auditory Discrimination.[20]

Visual motor competence. Visual Motor Integration Test[21] and Frostig Test.[22]

Attentional performance. Reaction time under intervals of varying delay[23] and cognitive control battery.[24]

Motor co-ordination. Elements of the Halstead-Reitan Battery.[25]

Table 2. Comparison of Tested and Excluded Subjects on Teachers' Behavioral Rating Scale — the Numbers Show the Per Cent of Students in Each Group Receiving a Negative Response.

Item	Tested Group (%)	Excluded Group (%)
Distractible	26	34
Not persistent	15	19
Dependent	17	20
Disorganized	18	18
Hyperactive	9	7
Impulsive	13	14
Easily frustrated	18	23
Daydreamer	25	23
Not able to follow:		
Simple directions	7	12
Sequence of directions	19	24
Low overall functioning	17	25

Teacher's Behavioral Rating

The teacher of every child who gave a tooth was asked to fill out an 11-item forced-choice behavioral rating scale scoring the child as "yes" or "no" on the following questions:

1. Is this child easily distracted during his/her work?
2. Can he/she persist with a task for a reasonable amount of time?
3. Can this child work independently and complete assigned tasks with minimal assistance?
4. Is his/her approach to tasks disorganized (constantly misplacing pencils, books, etc.)?
5. Do you consider this child hyperactive?
6. Is he/she over-excitable and impulsive?
7. Is he/she easily frustrated by difficulties?
8. Is he/she a daydreamer?
9. Can he/she follow simple directions?
10. Can he/she follow a sequence of directions?
11. In general, is this child functioning as well in the classroom as other children his/her own age?

This form was completed by the teachers (who were blind to the lead level) after at least two months of classroom experience with the child. Sum scores (11 = good, 0 = poor) and item analyses were computed. The scale was obtained for the 2146 subjects who submitted at least one tooth. These 2146 subjects were then divided into six groups according to dentine lead level: Group 1, < 5.1 ppm; Group 2, 5.1 to 8.1 ppm; Group 3, 8.2 to 11.8 ppm; Group 4, 11.9 to 17.1 ppm; Group 5, 17.2 to 27.0 ppm; and Group 6 > 27.0 ppm. The boundaries were chosen to achieve a symmetrical distribution in each cell around the median.

Data from this rating scale were evaluated in three ways. Scores of participating and excluded subjects were first compared to evaluate any bias in sampling that might have occurred (Table 2). The incidence of negative reports on each item in relation to dentine lead level was then compared for the entire sample of 2146 subjects (Fig. 2). Finally, item and sum scores were compared for the 58 children with high and the 100 with low lead levels who received the neuropsychologic evaluation (Table 3).

Control Variables

Thirty-nine non-lead variables that could affect the subject's development were scaled and coded. A partial list is shown in Tables 4 to 6. The variables not included did not differ between groups. Data were obtained by a paper-and-pencil questionnaire. Parental socioeconomic status was estimated by a two-factor Hollingshead index.[24]

Data Analysis

The scores of children with high and low lead levels on 39 control variables were compared with use of the Student t-test. We then compared outcome measures in the 58 children with high and the 100 with low levels, using analysis of covariance (Statistical Package for the Social Sciences) with dentine lead level as the main effect, and the following covariates: mother's age at subject's birth; mother's educational level; father's socioeconomic status; number of pregnancies; and parental I.Q. We normalized outcomes for which age-normed scores were not available by regressing for age before analysis of covariance.

Frequency of negative reports on teachers' behavioral ratings was evaluated by chi-square test, both for the 158 subjects with high and low lead levels and for the entire sample of 2146 subjects as well. Non-lead covariates were not controlled in these analyses. Sum scores of teachers' ratings for subjects with high and low lead levels were compared by analysis of covariance with the covariates listed above.

Results

Dentine Lead Levels in Somerville and Chelsea

Of the total population of 3329 eligible children, 2335 (70 per cent) submitted at least one tooth for analysis (Fig. 1). Although the distribution of dentine lead levels in the first slice was closely balanced between high and low concentrations, more subjects with initially high values required reassignment as "unclassified" on the basis of later analyses. As a result, the final sample was composed of a larger number of subjects with confirmed low lead levels (Table 1).

Twenty-three subjects with "high dentine lead" and 58 with "low dentine lead" were discovered to have had blood lead determinations in an earlier screening project (1973-1974, four to five years before

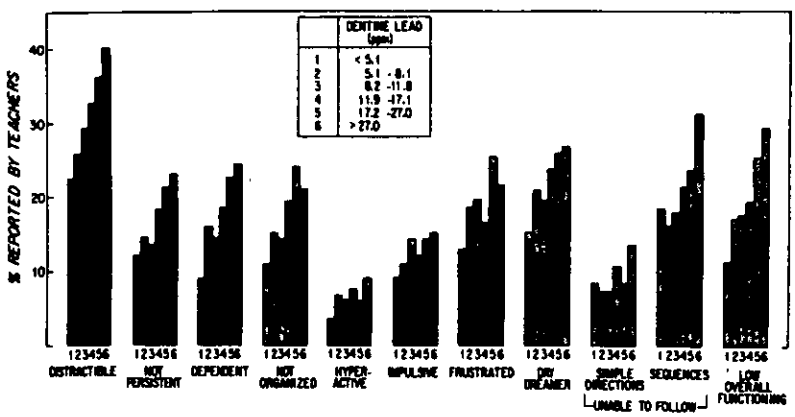

Figure 2. Distribution of Negative Ratings by Teachers on 11 Classroom Behaviors in Relation to Dentine Lead Concentration.

The group boundaries were chosen to obtain symmetrical cell sizes for the median (Groups 1 and 6 = 6.8 per cent, Groups 2 and 5 = 17.6 per cent, and Groups 3 and 4 = 25.6 per cent).

Table 3. Comparison of High and Low Lead Subjects on Teachers' Behavioral Rating Scale. The Numbers Show the Per Cent of Students in Each Group Receiving a Negative Response.

Item	Low Lead (%)	High Lead (%)	P Value
Distractible	14	36	0.003
Not persistent	9	21	0.05
Dependent	10	23	0.05
Disorganized	10	20	0.14
Hyperactive	6	16	0.08
Impulsive	9	25	0.01
Easily frustrated	11	25	0.04
Daydreamer	15	34	0.01
Does not follow:			
Simple directions	4	14	0.05
Sequence of directions	12	34	0.003
Low overall functioning	8	26	0.003
Sum score (mean)	9.5	8.2	0.02*

*Analysis of covariance.

shedding teeth). Their records were obtained and previous blood levels in the two groups compared. The mean blood lead level in 1973-1974 was 35.5±10.1 μg per deciliter for the group with high dentine lead and 23.8±6.0 μg per deciliter for the group with low dentine lead ($P<0.001$, by two-tailed t-test). The highest blood lead level in the children with high dentine lead levels was 54.0 μg per deciliter.

Evaluation of Sampling Bias

The teachers' behavioral assessment was available for 253 of the 270 children who did participate in the neuropsychologic evaluation and for 235 of the 254 who did not participate. Comparison of dentine lead levels (Table 1) and teachers' scores (Table 2) in tested and excluded subjects demonstrated that the two groups did not differ in either lead exposure or classroom behavior.

Table 4. Comparison of Non-Lead Variables in High and Low Lead Groups.

Variable	Low Dentine Lead	High Dentine Lead	P Value*
General			
%Male	49.5	55.9	NS‡
%White	97.0	98.3	NS
%Father head of household	77.2	67.8	NS
%Completed immunizations	98.0	98.3	NS
%Positive pica history	10.9	28.8	0.008
Physical variables at date of testing			
Age (mo)	87.2±7.7†	90.7±8.4	0.009
Height (cm)	126.6±6.3	126.4±6.3	NS
Weight (kg)	25.8±4.9	26.5±4.6	NS
Head circumference (cm)	51.8±1.6	51.7±1.5	NS
Skinfold:			
Right arm (mm)	9.5±3.5	9.8±4.2	NS
Left arm (mm)	9.5±3.4	9.7±4.2	NS
Past medical history			
Birth weight (g)	3,400.0±448.6	3,346.0±514.0	NS
Length of infant hospital stay (days)	4.9±1.8	4.4±1.5	NS
Birth order	2.4±1.7	2.7±2.0	NS
No. of hospital admissions	0.47±1.2	0.42±1.6	NS

*2 tail. †Mean ± S.D. ‡Not significant.

Control Variables

Children with high and low lead levels were quite similar in most non-lead variables measured (Tables 4-6). The following variables, which differed at $P<0.1$, were controlled as covariates in analysis of covariance: fathers' socioeconomic status (consisting of education and occupation score); mothers' age at subjects' birth; number of pregnancies; mothers' education and parental I.Q.

Outcome Measures

Children with high lead levels performed significantly less well on the Weschler Intelligence Scale (Table 7), particularly the verbal items, on three measures of auditory and verbal processing (Table 8), on attentional performance as measured by reaction time under conditions of varying delay (Table 8 and Fig. 3) and on most items of the teachers' behavioral rating (Table 3).

Table 5. Comparison of Parental Non-Lead Variables in High and Low Lead Groups.

Variable	Low Dentine Lead	High Dentine Lead	P Value*
No. of pregnancies	3.3±1.8†	3.8±2.3	0.10
Mother's age at subject's birth (yr)	26.2±5.5	24.5±5.8	0.07
Mother's social class (2-factor Hollingshead)	4.1±0.8	4.2±0.8	NS
Mother's education (grade)	11.9±2.0	11.4±1.7	0.08
Mother's occupation	5.5±1.1	5.5±1.3	NS
Father's age at subject's birth (yr)	28.8±7.1	27.5±7.9	NS
Father's social class (2-factor Hollingshead)	3.8±1.0	4.1±0.8	0.02
Father's education (grade)	12.7±2.8	11.1±2.3	0.001
Father's occupation	4.7±1.6	5.0±1.2	NS
Parent IQ	111.8±14.0	108.7±14.5	NS

*2 tail. †Mean ± S.D. ‡Not significant.

As compared to controls, children with high lead levels appeared particularly less competent in areas of verbal performance and auditory processing. They had lower scores on all tests of the Seashore Rhythm Test, which requires the subject to discriminate whether pairs of tone sequences of increasing complexity are alike or different. In the Token Test the task is to respond to verbal instructions of increasing complexity and to manipulate tokens of different shapes and colors. The four subtests are presented in order of increasing complexity and difficulty. The Sentence Repetition Test, which requires the immediate repetition of previously uttered sentences of increasing length and syntactic complexity, was also sensitive to the effect of lead exposure.

The ability of subjects with high lead levels to sustain attention was clearly impaired, as measured by reaction time at varying intervals of delay. Their reaction time was significantly slower on Blocks 2 and 3 (at 12 seconds' delay) as well as on Block 4 (at three seconds' delay). This final block was administered after about 15 minutes of repetitive testing, when subjects began to become distracted.

Table 6. Parental Attitude Scores in High and Low Lead Subjects.*

Control Variable	Low Dentine Lead	High Dentine Lead
Parental aspirations for child	19.7±5.6†	19.5±4.6
Home learning environment	37.6±6.3	37.1±5.4
Parental attitude toward school:		
Resignation	17.4±3.4	17.1±2.9
Futility	17.8±2.7	17.7±2.5
Conservatism	20.3±2.2	20.4±1.9
Parental attitude toward child	34.4±4.3	34.5±4.8
Parental restrictiveness	19.1±2.1	19.4±2.2

*No significant differences found. †Mean ± SD.

Teachers' reports of classroom behavior showed that children with high lead levels were rated significantly poorer on nine of 11 items, and that the sum score of these subjects was lower.

Teachers' Behavioral Rating on Entire Study Sample

Teachers' behavioral ratings were available for 2146 (92 per cent) of the 2335 children who submitted teeth. The frequency of negative teachers' ratings for every item increased with increasing dentine lead level, and was not limited to the group with highest lead levels (Fig. 2).

Discussion

The confidence with which the performance deficits reported here can be attributed to past lead exposure depends on whether this investigation has successfully addressed the four methodologic issues raised earlier (lead markers, sampling bias, confounding variables and sensitive outcome measures).

The classification of earlier lead exposure according to dentine lead levels has been validated in a number of earlier studies. Lead exists in dentine in a closed storage system. Tooth lead levels in baboons do not change after a pulsed dose of ^{203}Pb.[27] They are elevated in children with unequivocal plumbism,[28] urban children living in the "lead belt"[29] and those who live in decaying homes, or intact homes near a major lead processor.[12] Tooth lead levels also vary in relation to the concentration of lead in the domestic water supply and the duration of exposure to that water.[30]

In our present study, the small number of blood lead levels in subjects drawn four to five years before tooth shedding documents the point that children with higher tooth lead levels tended to have had higher blood lead levels years previously.

Table 7. Full-Scale and Subtest Scores of the Wechsler Intelligence Scale for Children (Revised) (WISC-R) for High and Low Lead Subjects.

WISC-R	Low Lead (Mean)	High Lead (Mean)	P Value*
Full-scale IQ	106.6	102.1	0.03
Verbal IQ	103.9	99.3	0.03
Information	10.5	9.4	0.04
Vocabulary	11.0	10.0	0.05
Digit span	10.6	9.3	0.02
Arithmetic	10.4	10.1	0.49
Comprehension	11.0	10.2	0.08
Similarities	10.8	10.3	0.36
Performance IQ	108.7	104.9	0.08
Picture completion	12.2	11.3	0.03
Picture arrangement	11.3	10.8	0.38
Block design	11.0	10.3	0.15
Object assembly	10.9	10.6	0.54
Coding	11.0	10.9	0.90
Mazes	10.6	10.1	0.37

*These 2-tail P values are those for any single comparison between high & low lead groups. It should be remembered that when a large no. of simultaneous comparisons are made between 2 groups of subjects, the probability that a "significant" result may be found is larger than the P value for the single test. An approximate & conservative adjustment for this fact may be obtained if the reported P value is multiplied by the no. of simultaneous tests. In this sense the "full-scale IQ" above constitutes a single test, & the "verbal IQ" and "performance IQ" constitute a pair of simultaneous tests. Within the verbal WISC there are 6 simultaneous tests, and within the performance WISC there are another 6 simultaneous tests. Thus, with the conservative adjustment described above the following P values would be obtained: full-scale IQ, P = 0.03; verbal IQ, P = 0.06; & digit-span, P = 0.12.

Table 8. Verbal Processing Scores and Reaction Times in High and Low Lead Subjects.

Test	Low Lead Values (Mean)	High Lead Values (Mean)	P Value*
Seashore Rhythm Test			
Subtest A	8.2	7.1	0.002
Subtest B	7.5	6.8	0.03
Subtest C	6.0	5.4	0.07
Sum	21.6	19.4	0.002
Token Test			
Block 1	2.9	2.8	0.37
Block 2	3.7	3.7	0.90
Block 3	4.1	4.0	0.42
Block 4	14.1	13.1	0.05
Sum	24.8	23.6	0.09
Sentence-Repetition Test	12.6	11.3	0.04
Reaction time under varying intervals of delay			
Block 1 (3 sec)	0.35±0.08†	0.37±0.09	0.32
Block 2 (12 sec)	0.41±0.09	0.47±0.12	0.001
Block 3 (12 sec)	0.41±0.09	0.48±0.11	0.001
Block 4 (3 sec)	0.38±0.10	0.41±0.12	0.01

*2 tail. See footnote to Table 6. The conservative adjustment for multiple simultaneous comparisons would yield the following P values: Subtest A of the Seashore Rhythm Test, P = 0.006; Block 4 of the Token Test, P = 0.20; & Blocks 2 & 3 of the Reaction Time Test, P = 0.004.

†Seconds — mean ± SD.

Subjects with high and low lead levels accepted for neuropsychologic evaluation in this study are an unbiased sample of children with lead burdens of this order in their communities. Subjects tested in this study do not differ in gender, prevalence of elevated dentine lead levels or classroom behavior from those excluded.

The problem of potentially confounding variables was handled by comparison of subjects on a large number of variables and by control, in the biostatistical analysis, for those differing between samples. Groups with high and low lead levels who were evaluated in this study were remarkably alike in most of the 39 non-lead variables measured, and only differed at $P<0.05$ on three variables: fathers' education, fathers' socioeconomic status and subjects' age at time of testing.

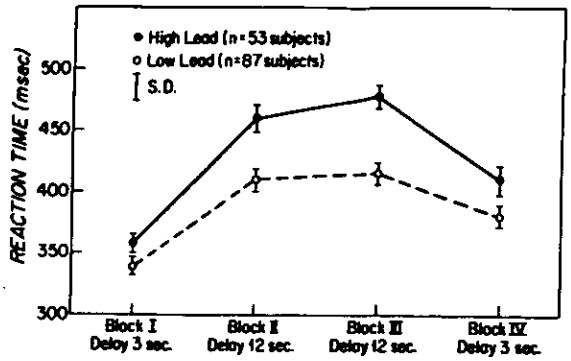

Figure 3. Reaction Time under Varying Intervals of Delay. "Delay 3 sec." indicates a three-second period between a warning signal (the spoken word, "ready") and the onset stimulus. Each subject received six trials in each block.

In this study, outcome measures that appear to be most sensitive to lead effects are those evaluating verbal and auditory processing, attention (as measured by reaction time) and classroom behavior. At the relatively low dose experienced by our exposed group, verbal and attentional processes appear most vulnerable.

Other investigators[5,7] have reported that lead effects are most evident in the performance areas of the Wechsler Intelligence Scale for Children — Revised, and in perceptual and motor function. The differences in the expression of the effect of lead may reflect many factors, including magnitude and duration of exposure and age at time of exposure.

Reaction time under varying intervals of delay is one measure of the attentional process.[23] Needleman[31] found that boys seven and eight years old with earlier blood lead levels higher than 50 μg per deciliter had longer reaction times at trial Blocks 2, 3 and 4 than controls whose earlier blood levels were less than 30 μg per deciliter. This replicated finding suggests that disturbances of attentional function are a consistent effect of lead exposure. The validity of this finding is further supported by the teachers' reports of increased distractibility, increased prevalence of daydreaming, lack of persistence, inability to follow directions and lack of organization in subjects with high lead levels. These behaviors are often found in children labeled as "hyperactive." Hyperactive behavior is a frequent sequel of frank lead poisoning,[7,32] and is suspected of being an effect of lead at lower dose.[33] The items of hyperactivity and impulsivity, however, were reported relatively infrequently at all levels of dentine lead (Fig. 2). Although the frequency of these two behaviors is related to dentine lead burden, it appears that teachers in our study were reluctant to apply these labels to their students. The deficit of attention in the children with high lead levels demonstrated here may be responsible in part for impaired verbal learning.

The teachers' behavioral rating scale was found to be sensitive to the degree of lead exposure on almost all items across the entire range of dentine lead levels in a dose-related fashion. This observation suggests that lead may increase the risk of undesirable behaviors in the classroom at doses considerably below those found in our group with high lead levels.

The defined "no-effect" levels for children exposed to lead has undergone a steady downward revision over the past three decades as new data have shown effects at lower doses. Currently, the Center for Disease Control has defined a blood lead level of 30 μg per deciliter as the threshold for undue lead absorption.[2] Among the reasons for this evolution in medical judgment has been the demonstration of the inhibitory effect of lead at extremely low concentrations on enzymes such as δ-aminolevulinic acid dehydratase[34] and brain adenylcyclase[35] and on mitochondrial function.[36] Piomelli[36] has recently reported that elevation of free erythrocyte protoporphyrin begins to occur in children at blood lead levels of 15 μg per deciliter. Although many investigators believe that alterations in free erythrocyte protoporphyrin, adenylcyclase, and δ-aminolevulinic acid dehydratase are among the first signs of impaired tissue function and therefore represent adverse health effects, it has been questioned whether at the lower levels of lead these alterations are health effects or merely biochemical events of little consequence.

The impaired function of children with high lead levels, demonstrated in the neuropsychologic laboratory, mirrored by disordered classroom behavior, appears to be an early adverse effect of exposure to lead. Permissible exposure levels of lead for children deserve re-examination in the light of these data.

We are indebted to Janice Adams, Margaret Nichols and Ruth Barrett, who performed the psychological tests, and to Lee Davidowski and Hamdi Maksoud, who analyzed the dentine specimens, to the teachers, principals and nurses of Somerville and Chelsea, Massachusetts, and to the late Dr. James Bryant, of the Somerville Board of Health, for help in the early days of the study.

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THE LONG-TERM EFFECTS OF EXPOSURE TO LOW DOSES OF LEAD IN CHILDHOOD

An 11-Year Follow-up Report

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Abstract To determine whether the effects of low-level lead exposure persist, we reexamined 132 of 270 young adults who had initially been studied as primary schoolchildren in 1975 through 1978. In the earlier study, neurobehavioral functioning was found to be inversely related to dentin lead levels. As compared with those we restudied, the other 138 subjects had had somewhat higher lead levels on earlier analysis, as well as significantly lower IQ scores and poorer teachers' ratings of classroom behavior.

When the 132 subjects were reexamined in 1988, impairment in neurobehavioral function was still found to be related to the lead content of teeth shed at the ages of six and seven. The young people with dentin lead levels >20 ppm had a markedly higher risk of dropping out of high school (adjusted odds ratio, 7.4; 95 percent confidence interval, 1.4 to 40.7) and of having a reading disability (odds ratio, 5.8; 95 percent confidence interval, 1.7 to 19.7) as compared with those with dentin lead levels <10 ppm. Higher lead levels in childhood were also significantly associated with lower class standing in high school, increased absenteeism, lower vocabulary and grammatical-reasoning scores, poorer hand–eye coordination, longer reaction times, and slower finger tapping. No significant associations were found with the results of 10 other tests of neurobehavioral functioning. Lead levels were inversely related to self-reports of minor delinquent activity.

We conclude that exposure to lead in childhood is associated with deficits in central nervous system functioning that persist into young adulthood. (N Engl J Med 1990; 322:83-8.)

WITHIN the past three years, the Environmental Protection Agency and the Agency for Toxic Substances and Disease Registry have concluded in policy statements that lead at low doses is a serious threat to the central nervous systems of infants and children.[1,2] These policy statements have been based on a growing convergence of results from both epidemiologic and experimental studies of lead toxicity in the United States, Europe, and Australia.[3-8] Whether the effects on the central nervous system of exposure to low doses of lead that have been observed in infants and children persist has received limited attention. Only three follow-up studies have been published to date, and the longest follow-up has been five years.[9-11] No data have yet been reported on whether early disturbances influence functional abilities in later life.

In 1979 we reported that first- and second-grade children without symptoms of plumbism, but with elevated dentin lead levels, had deficits in psychometric intelligence scores, speech and language processing, attention, and classroom performance.[3] When they were studied in the fifth grade, the children with high dentin lead levels had lower IQ scores, needed more special academic services, and had a significantly higher rate of failure in school than other children.[9] We have now evaluated the neuropsychological and academic performance in young adulthood of 132 of the original sample of 270 subjects, and we report the relation of their recent performance to their exposure to lead, as measured 11 years earlier.

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METHODS

Sample

The initial sample was chosen from the population of 3329 children enrolled in the first and second grades in the Chelsea and Somerville, Massachusetts, school systems between 1975 and 1978. Of this population, 70 percent provided at least one of their shed primary teeth for lead analysis. From this sample of 2335 children, 97 percent of whom were white, we identified 270 from English-speaking homes whose initial dentin lead levels were either >24 ppm or <6 ppm. These children (mean age, 7.3 years) underwent an extensive neurobehavioral examination. More teeth were subsequently collected and analyzed, and the subjects whose teeth were discordant with respect to lead level according to a priori criteria were excluded from the data analysis. Also excluded from the analysis were children who had not been discharged from the hospital after birth at the same time as their mothers, who had a noteworthy head injury, or who were reported to have had plumbism.[3]

In a later reanalysis, conducted in response to suggestions from the Environmental Protection Agency,[12] the tooth lead level was treated as a continuous variable. A mean dentin lead level was computed for each subject from all the teeth collected. The exclusionary factors previously used were found not to be related to outcome scores. The subjects initially excluded were therefore not excluded from this follow-up sample.

The 270 subjects tested from 1975 to 1978 constitute the base population for this report. From old research records, telephone directories, town records, and driver's-license rolls, we located 177 subjects. Of these, 132 agreed to participate, and the remaining 45 declined. The subjects were paid $35 each and received travel expenses. Ten subjects tested in 1988 had been excluded from the analysis reported in 1979 because their parents stated at the time of testing that the children had elevated blood lead levels or had undergone chelation for lead poisoning. This group is discussed separately in this report. The mean age of the 132 subjects at the 1988 reexamination was 18.4 years; the mean length of time between the two examinations was 11.1 years. All but four subjects in the current follow-up study were white. No clinical manifestations of lead exposure were recorded in the earlier interviews for the 122 subjects who were not treated with chelating agents.

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The research protocol and informed-consent procedures were approved by the institutional review boards of the Children's Hospital of Pittsburgh and the Children's Hospital, Boston. Informed consent was given by all the subjects or their parents.

Classification of Lead Exposure

All the dentin lead levels measured from 1975 through 1977 were used to compute an arithmetic mean lead concentration for each subject. The lead burden was treated in two ways: as an interval variable in linear regressions and as a categorical variable — i.e., high (>20 ppm), medium (10 to 19.9 ppm), and low (<10 ppm) — in the logistic regressions described below. Lead levels in venous blood were measured at the time of the reexamination to estimate current exposure. This practice was discontinued after the first 48 subjects were tested, because none had a lead level exceeding 0.34 μmol per liter (7 μg per deciliter), well below the Centers for Disease Control's definition of undue lead exposure of 1.25 μmol per liter (25 μg per deciliter).

Behavioral Evaluation

The subjects were evaluated individually by a single examiner, who remained blinded to their lead-exposure status until all the data had been coded and entered into a computer data base. All assessments were carried out in a fixed order; the duration of the testing was about two hours.

Neurobehavioral Evaluation System

The subjects completed an automated assessment battery in which they used a personal computer, joystick, and response key.[13] We selected the following items from the battery for evaluation:

Continuous-performance test.[14]

Symbol-digit substitution, an adaptation of the Wechsler item for computer administration.

Hand–eye coordination. Using a joystick to move the cursor, the subject traced over a large sine wave generated on the monitor screen; deviations from the line (root mean square error) were recorded.

Simple visual-reaction time. Subjects pressed the response key when an O appeared on the screen; the interval before the stimulus was varied randomly.

Finger tapping. The subject pressed a response button as many times as possible during a 10-second period; both hands were tested.

Pattern memory. The subject was presented with a computer-generated pattern formed by a 10-by-10 array of dark and bright elements. After a brief exposure, the subject was presented with three patterns, only one of which was identical to the original pattern. The number of correct responses and the length of time to the correct choice were recorded.

Pattern comparison. The subject was presented with three computer-generated patterns on the 10-by-10 array. Two were identical, and one differed slightly from the other two. The subject was required to select the nonmatching pattern.

Serial-digit learning. The subject was presented with a string of 10 digits, then asked to enter the string into the computer. After an error, the same stimulus was presented, and the second trial began.

Vocabulary. For each of 25 words, the subject chose the word most nearly synonymous from a list of four choices.

Grammatical reasoning. The subject was presented with a pair of letters, A and B, whose relative position varied. Then the screen cleared, and the letters were replaced by a sentence that described the order of the letters. The sentence might be active or passive, affirmative or negative, true or false (examples are "A follows B" and "B is not followed by A"). The subject had to choose the correct sentences, and the number of errors was recorded.

Switching attention. The subject was required to choose which key to press in response to three different instructions. In the "side" trials, the subject had to press the key on the same side as the stimulus. In the "direction" trials, the correct choice was the direction in which an arrow pointed. Before each trial in the third set, the subject was told whether to choose the side the arrow was on or the direction in which it pointed.

Mood scales. This test was derived from the Profile of Mood States.[15] Five scores were computed for tension, anger, depression, fatigue, and confusion.

The following tests were also used to evaluate neurobehavioral functioning:

California Verbal Learning Test

The California Verbal Learning Test[16] was used to assess multiple strategies and processes involved in verbal learning and memory. Scores for immediate and delayed recall were also obtained.

Boston Naming Test

In the Boston Naming Test,[17] the subject was presented with 60 pictures in order of increasing difficulty and asked to name the objects shown.

Rey–Osterreith Complex Figure Test

The Rey–Osterreith Complex Figure Test[18] was used to evaluate visual–motor and visual–spatial skills. The subject was asked to copy an abstract geometric figure and then to draw it from memory both immediately and after 30 minutes. Accuracy and organization scores were calculated.

Word-Identification Test

Form B from the Woodcock Reading Mastery Test was used to evaluate reading skill. Grade-equivalency scores were calculated from raw scores. Reading disability was defined as indicated by scores two grade levels below the score expected on the basis of the highest grade completed.

Self-Reports of Delinquency

The subjects completed a structured questionnaire from the National Youth Survey[19] that included scales for minor antisocial behavior and for violent crimes.

Review of School Records

High-school records were obtained for all but two of the subjects tested. Class size and rank, the highest grade completed, and the number of days absent and tardy in the last full semester were recorded. Students who were still in the 11th grade at the time of testing were not included in analyses of the highest grade completed. Class rank was computed as 1 − (class rank/class size).

Statistical Analysis

To evaluate whether the participants in this follow-up evaluation were representative of the original cohort, subjects who were tested and not tested in 1988 were compared in terms of variables reported in 1979, including dentin lead levels, covariates not related to lead exposure, teachers' ratings of classroom behavior, and IQ scores. In addition, we carried out separate regressions of dentin lead level against IQ score as measured between 1976 and 1978 for subjects tested and not tested in 1988. We then performed a regression on both groups taken together, entering both a dummy term for participation in the current follow-up (yes or no) and a lead-level-by-participation status term.

To evaluate the relation between early exposure to lead and each of the continuously distributed outcome variables, subjects were classified according to dentin lead-level quartiles, and mean scores, adjusted for covariates, were computed. Ordinary least-squares lin-

ear regression, with the mean or log-mean dentin lead level as the main effect, was used to estimate the significance of the relation. Outcomes that were significantly associated with lead exposure in these bivariate analyses were further evaluated by multiple regression analysis. Ten covariates were included in the model. They were the mother's age at the time of the subject's birth, the mother's educational level, the mother's IQ, family size, socioeconomic status (a two-factor Hollingshead index), sex, age at the time of testing, birth order, alcohol use, and whether the subject and the mother left the hospital together after the subject's birth. The lead measure (the mean or the log of the mean) that produced the best-fitted model (highest R^2) is reported. Five of these covariates were employed in the first study of these subjects and shown to be influential. Five others (sex, age at testing, prolonged hospitalization as a neonate, birth order, and current alcohol use) were added to the model on the basis of prior knowledge of their effects on psychometric function. Logistic-regression analysis was used to model the association of lead level and two outcomes treated categorically (failure to graduate from high school and reading disability). In this analysis, we controlled for the covariates listed above. Two indicator variables were used to represent the three exposure groups. Odds ratios and 95 percent confidence intervals, adjusted for covariates, were computed for the high-lead-level group, with the low-lead-level group used as the reference group.

Results

Selection Bias

The 132 subjects who were retested in 1988 (Table 1) were not representative of the group of 270 subjects tested in 1979. The subjects we retested tended to have slightly lower dentin lead levels, more highly educated families of higher socioeconomic status, and mothers with higher IQs and better obstetrical histories; a higher proportion of the retested subjects were girls. In addition, they had had fewer head injuries and had significantly higher IQ scores and better teachers' ratings as reported in 1979. The slope of the regression of childhood IQ on dentin lead level was steeper in the group not tested in the follow-up study, although the difference from the slope in the group we retested was not statistically significant ($F = 1.82$, 1,196 df; $P = 0.18$).

Table 1. Comparison of Subjects Tested and Not Tested in 1988.*

Characteristic	Tested (N = 132)	Not Tested (N = 138)	P Value
Lead-level group (%)			
Low	50	47.8	—
Middle	22.7	16.7	—
High	27.3	35.5	0.7†
Birth order	2.3±1.6	2.8±1.9	0.016
No. of live births	2.8±1.5	3.2±1.6	0.05
Father's education (yr)	12.2±2.6	11.4±2.6	0.009
Mother's education (yr)	12.0±2.2	11.1±2.1	0.0005
Mother's IQ	112±15	108±15	0.017
Mother's age at subject's birth (yr)	25.5±5.9	25.3±5.8	0.7
Father's age at subject's birth (yr)	28.3±7.8	28.8±7.9	0.6
Gestation (wk)	39.9±2.0	40.0±1.7	0.7
Birth weight (g)	3776±608	3712±600	0.40
Sex (%)			
Female	55.3	42.8	
Male	44.7	57.3	0.04
Head injuries (%)	3.8	8.7	0.09
Teachers' ratings (1979 sum score)	9.3±2.8	8.2±3.6	0.004
Full-scale IQ (1979)	107.5±14	99.5±15	0.001

*Plus–minus values are means ±SD. †By chi-square test for all lead-level groups.

Academic and Neurobehavioral Outcome

Table 2 shows the covariate-adjusted scores of the 122 subjects who did not have clinical plumbism, according to their dentin lead concentrations. Table 3 summarizes the results of modeling the relation between early exposure to lead and outcome by multiple regression. Earlier exposure to lead was significantly associated with diminished academic success. Among children with dentin lead levels >20 ppm, as compared with those whose dentin lead levels were <10 ppm, the unadjusted odds ratio for failure to graduate from high school was 4.6 (95 percent confidence interval, 1.2 to 17.4). Adjustment for covariates increased the odds ratio to 7.4 (95 percent confidence interval, 1.4 to 40.8). Higher dentin lead levels were also associated with lower class rank, increased absenteeism, lower scores on vocabulary and grammatical-reasoning tests, significantly slower finger-tapping speed, longer reaction times, poorer hand–eye coordination, and lower reading scores. In subjects with dentin lead levels >20 ppm, the unadjusted odds ratio for having a reading disability, defined by a score two grades below that expected for the highest grade completed, was 3.9 (95 percent confi-

Table 2. Outcomes in Young Adulthood According to Dentin Lead Concentration in Childhood.*

Outcome Variable	Lead Concentration			
	Lowest (<5.9 ppm)	Low (6.0–8.2 ppm)	High (8.3–22.2 ppm)	Highest (>22.2 ppm)
No. of subjects	30	31	30	31
Reading score (words read correctly)	143.8	142.7	140.2	135.2
Reading grade equivalent (grade level)	12.2	11.9	11.2	10.1
Highest grade achieved (grade level)	11.7	11.9	11.5	11.3
Class standing (percentile)	0.60	0.59	0.48	0.45
Absence from school (no. of days/semester)	12.0	12.0	17.9	20.8
Vocabulary (words correct)	18.0	16.4	17.6	14.6
Grammatical reasoning (no. incorrect)	13.1	13.0	12.8	15.8
Hand–eye coordination†	5.1	5.4	5.5	6.2
Reaction time (msec)				
Preferred hand	246.6	255.5	267.3	275.1
Nonpreferred hand	241.2	238.2	258.4	261.2
Finger tapping (no./10 sec)	46.6	47.2	45.9	43.5

*The subjects were divided into groups according to lead-level quartiles. The values shown are least-square mean scores, after adjustment for covariates. Subjects with clinical plumbism have been excluded.

†For hand–eye coordination, larger numbers indicate more errors.

Table 3. Regression of Outcomes in Young Adulthood on Dentin Lead Levels in Childhood.*

Outcome Variable	Bivariate Regression				Multiple Regression			
	R^2	Parameter Estimate	SE	P value	R^2	Parameter Estimate	SE	P value
Highest grade achieved	0.061	−0.027	0.009	0.008	0.319	−0.027	0.01	0.013
Reading grade equivalent	0.121	−0.07	0.018	0.0001	0.229	−0.072	0.021	0.001
Class standing	0.039	−0.006	0.003	0.048	0.248	−0.006	0.003	0.048
Absence from school†	0.071	4.8	1.7	0.006	0.209	4.73	1.8	0.01
Grammatical reasoning	0.051	0.159	0.062	0.012	0.197	0.178	0.068	0.011
Vocabulary	0.108	−0.124	0.032	0.000	0.324	−0.122	0.033	0.001
Finger tapping	0.031	−0.104	0.05	0.05	0.336	−0.133	0.05	0.01
Hand–eye coordination	0.043	0.041	0.018	0.02	0.195	0.048	0.019	0.01
Reaction time†								
Preferred hand	0.025	11.8	6.66	0.08	0.242	12.9	6.3	0.042
Nonpreferred hand	0.03	11.5	0.05	0.056	0.229	10.3	5.5	0.06
Minor antisocial behavior†	0.025	−0.639	0.36	0.082	0.306	−0.739	0.35	0.038

*The following covariates were controlled for in the multiple regression analysis: age, sex, birth order, family size, mother's age at the subject's birth, length of the neonatal stay in the hospital, mother's education level, mother's IQ, socioeconomic status, and current alcohol use.

†The natural log of the mean dentin lead level was used as the main effect.

dence interval, 1.5 to 10.5). Adjustment for covariates increased the odds ratio to 5.8 (95 percent confidence interval, 1.7 to 19.7). For most outcomes, neither the size of the lead regression coefficients nor their standard errors were substantially changed by adjustment for covariates.

Of the 10 children with clinical plumbism (who either underwent chelation or were reported to have had elevated blood lead levels), 3 of 7 (43 percent) dropped out before graduating from high school (3 others are still in school), and 5 of 10 (50 percent) have reading disabilities. When the children with plumbism were grouped with the other subjects according to quartiles for dentin lead levels, a dose–response relation was evident for both outcomes (Fig. 1 and 2).

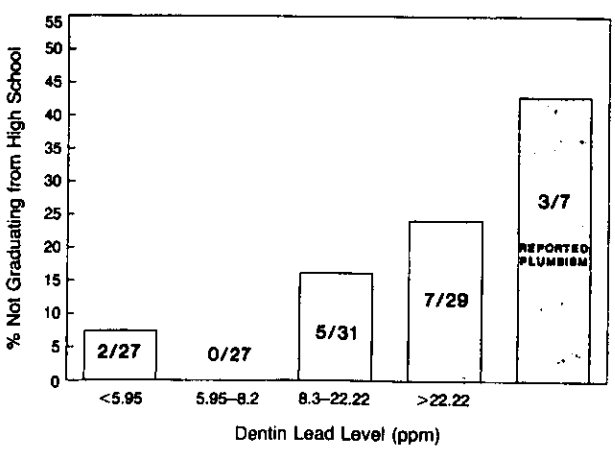

Figure 1. The Proportion of Subjects Who Did Not Graduate from High School, Classified According to Their Past Exposure to Lead.

Asymptomatic subjects are classified according to lead-level quartiles. Seven of the 10 subjects who were earlier reported to have clinical plumbism are shown in a separate column. No school records were found for two subjects. One subject was not tested but reported that she had graduated from high school. (There are therefore 121 subjects represented in this figure.) Ten subjects (three with reported plumbism and seven asymptomatic subjects) are still attending high school and are therefore not shown here. The numbers in each column indicate the number who did not graduate and the total number in the category.

Early exposure to lead was not significantly associated with performance on the symbol-digit or serial-digit tests, the continuous-performance test, pattern memory or pattern comparison, switching attention, the California Verbal Learning Test, the Rey–Osterreith figures, the Boston Naming Test, or mood scores. The lead level was inversely related to the summed score on the self-report of delinquency questionnaire, which consisted primarily of reports of minor antisocial behavior.

When subjects were divided into two groups according to their dentin lead levels (<10 ppm vs. ≥ 10 ppm), high dentin lead levels predicted future failure to graduate from high school with a sensitivity ($\pm$SE) of 0.71 ± 0.12 and a specificity of 0.61 ± 0.05 (Table 4).

Discussion

In this extended follow-up study, in which the mean length of follow-up was 11.1 years, we found that the associations reported earlier between lead and children's academic progress and cognitive functioning persisted into young adulthood. The persistent toxicity of lead was seen to result in significant and serious impairment of academic success, specifically a sevenfold increase in failure to graduate from high school, lower class standing, greater absenteeism, impairment of reading skills sufficiently extensive to be labeled reading disability (indicated by scores two grades below the expected scores), and deficits in vocabulary, fine motor skills, reaction time, and hand–eye coordination.

A number of issues require consideration when one is interpreting the data reported here. The first is the influence of selection bias on the associations we observed. The subjects retested in 1988 had more favorable characteristics than those who could not be located or who declined to participate. The subjects who were not retested tended to have had higher lead lev-

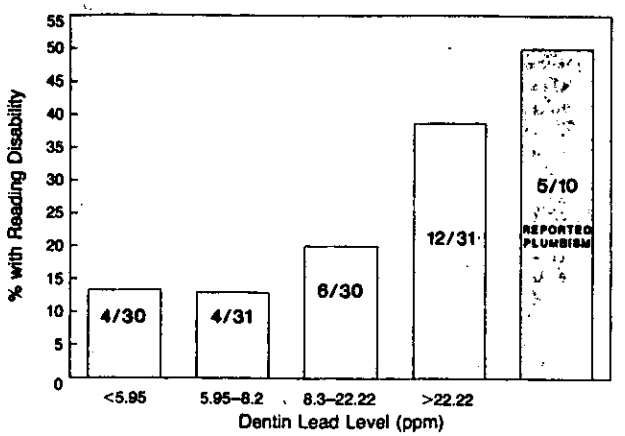

Figure 2. The Proportion of Subjects with Reading Disabilities, Classified According to Their Past Exposure to Lead.

Asymptomatic subjects are classified according to lead-level quartile, and 10 children with a history of clinical plumbism are shown separately. Reading disability is defined as indicated by a reading level two or more grades below the expected level. The numbers in each column indicate the number with a reading disability and the total number in the category.

els, lower socioeconomic status, and lower IQ scores and teachers' ratings of classroom behavior. The inverse relation between dentin lead levels and IQ reported in 1979 was stronger for the subjects who were not retested in 1988 than for those we retested, although the difference did not reach statistical significance. This finding is in agreement with the observation, made by us and others, that children from families in lower socioeconomic groups are more vulnerable to the effects of lead than children from more favored economic backgrounds.[20] We infer that the estimates made on the basis of the data on the 132 subjects we restudied are likely to be conservative. Indeed, had all the original subjects been located and retested, the magnitude of the effect of lead exposure might have been even greater.

Is the nature of the relation between lead and later outcome causal, or does it result from confounding by other variables? The association between lead and outcome reported here meets six criteria for valid causal inference: proper temporal sequence, strength of association, presence of a biologic gradient, nonspuriousness, consistency, and biologic plausibility.[21]

In this study, the exposure to lead preceded the school failure and the reading disabilities measured. The strength of the association, as measured by adjusted odds ratios of 7.4 and 5.8, was substantial. A dose–response relation has been demonstrated between exposure and numerous outcome variables (Table 2, Fig. 1 and 2). "Nonspuriousness" indicates that the association observed is not due to confounding. In this analysis, we controlled for both the covariates that were identified in 1979 as potential confounders and others we suspected were important. The magnitude of the effect of lead was reduced only slightly, if at all, by this procedure. The zero-order correlation between socioeconomic status and dentin lead levels in this sample was not great ($r = 0.04$). Many covariates that were important contributors to performance in the early grades (e.g., the mother's IQ and the mother's educational level) had less effect on the subject's performance in young adulthood. The results, moreover, are consistent with those of several other studies by workers who have reported lead-associated deficits in reading[4,22,23] and early classroom behavior.[24,25] The lead-related deficits in IQ, speech and language processing, and attention reported in 1979 provide plausible mechanisms by which lead could impair performance in class and produce eventual failure. Similar effects on learning have been demonstrated in the experimental studies by Gilbert and Rice of subhuman primates.[7] In these investigations, rhesus monkeys, administered lead only in the first 100 days of life, had impairments in learning as adolescents. In adolescence, the mean blood lead level of these monkeys was 0.73 μmol per liter (15 μg per deciliter).

The value accepted as the threshold for lead-engendered neurotoxicity in children has declined steadily over the past decade as more sophisticated population studies, with larger samples, better designs, and better analyses, have been conducted.[4,5,11,22,24,26-29] When this study was begun in 1975, the toxic level of lead in the blood was defined by the Centers for Disease Control as 2.0 μmol per liter (40 μg per deciliter). In 1973, the mean blood lead level in a subsample of 23 children chosen from among those with the highest dentin lead levels in an earlier study was 1.7 μmol per liter (34 μg per deciliter).[3] None of our subjects were symptomatic. That these subjects were exposed to high doses of lead after the original study was completed is unlikely. Lead exposure, the incidence of pica, and hand-to-mouth behavior diminish after the fifth year of life. The low blood lead levels found in these subjects in young adulthood (all <0.034 μmol per liter) provide convincing evidence that their later exposure to lead was not excessive.

The consensus on what level of lead is toxic has changed in recent years. After reviewing the studies published up to 1987, the Agency for Toxic Substances and Disease Registry defined the threshold for neurobehavioral toxicity as 0.5 to 0.7 μmol per liter

Table 4. Sensitivity and Specificity of the Dentin Lead Level in Childhood as a Predictor of Failure to Graduate from High School.*

High-School Graduation	Lead Level	
	≥10 ppm	<10 ppm
No	10	4
Yes	39	61

Sensitivity = 10/(10+4) = 0.71

Specificity = 61/(61+39) = 0.61

*Of the 122 asymptomatic subjects studied, 7 subjects who were still attending school at the time of this analysis were excluded. One subject's school records were not found. Of the 132 subjects retested in 1988, the 10 with clinical plumbism have been excluded.

(10 to 15 μg per deciliter).[1] The agency estimated that 3 to 4 million American children have blood lead levels in excess of 0.7 μmol per liter. The mean blood level among our subjects with high tooth lead levels, estimated in 1979 from a limited lead-screening program, was 1.6 μmol per liter (34 μg per deciliter) (range, 0.87 to 2.6 μmol per liter [18 to 54 μg per deciliter]). For subjects with low tooth lead levels, it was 1.2 μmol per liter (24 μg per deciliter) (range, 0.58 to 1.7 μmol per liter [12 to 36 μg per deciliter]). Thus, the lead levels in the reference sample used in the calculation of the odds ratios for one high-lead-level group were relatively high by contemporary standards.

The data presented here indicate that exposure to lead, even in children who remain asymptomatic, may have an important and enduring effect on the success in life of such children and that early indicators of lead burden and behavioral deficit are strong predictors of poor school outcome. For the small group of 10 subjects who were diagnosed earlier as having plumbism, the outcome was especially dire; half of these young people have reading disabilities, and almost half left high school before graduation. Given the federal estimates that 16 percent of children in the United States have elevated blood lead levels (>0.7 μmol per liter [15 μg per deciliter]), the implications of these findings for attempts to prevent school failure are intriguing. The practical importance of early detection and abatement of lead in the environment, before it enters the bodies of children, is borne out by these long-term findings in young adults.

We are indebted to Drs. Richard Frank, Constantine Gatsonis, Alan Mirsky, and Rolf Loeber for their careful review and critiques of the manuscript and to Ms. Pat Hadidian for her careful work in finding subjects and reviewing records.

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Measuring Children's Antisocial Behaviors

In this issue of THE JOURNAL, Needleman and colleagues[1] report that elevated bone lead is associated with young boys' attention problems, aggression, and delinquency. Certainly the tibia does not deceive about its lead burden. But can we really expect boys to confess their transgressions truthfully? Skepticism is partially allayed because the research links lead and antisocial behavior using not only boys' reports, but also their teachers' and parents' reports. Nonetheless, one might challenge the study's measures of behavior problems. What are these measures? How accurate are they? Are they applicable to children beyond the study participants? Perhaps most important, do they predict behavior later in life?

See also p 363.

What are these measures? Needleman et al selected widely respected measures of children's antisocial behavior: the Child Behavior Checklist (CBCL)[2] for parents and teachers and the self-reported delinquency interview for the boys.[3] Parents and teachers selected items from a list of 113 symptoms of behavior disorders of childhood, eg, "cruelty, bullying," "shoplifts," "sets fires," "doesn't seem guilty after misbehaving." The boys were interviewed (to circumvent reading difficulties) with 35 questions including, "How many times in the past 6 months have you . . . attacked someone with a weapon?" and ". . . been drunk in a public place?"

How accurate are these measures? Although common sense counsels skepticism about boys' reports of delinquency, 40 years of research counters with evidence that such self-reports are trustworthy, when collected under certain conditions.[3,4] Those conditions, met in the study by Needleman et al, demand a reporting period of less than 12 months, a private face-to-face interview, and a convincing guarantee of confidentiality. Face-to-face interviews have been shown superior even to anonymous questionnaires and telephone interviews. The boys Needleman et al studied have been interviewed about delinquency twice yearly since the age of 7 years with no betrayal of confidentiality; by the time the boys reached the age of 11 years the researchers had earned their trust. Of course, self-reported delinquency does have foibles. Innocents sometimes overreport because their rare transgressions are so salient or because they wish not to appear babyish. High-rate offenders sometimes underreport, because their offending is so commonplace that specific acts are forgotten.

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Sexual crimes are usually concealed. However, across many studies, the reliability of self-reported delinquency measures administered 7 to 30 days apart is 0.75 to 0.80, where 0 indicates no correspondence and +1 indicates perfect duplication.[3,4] Similarly, the reliability of the CBCL is 0.87 to 0.89.[2]

Researchers measure delinquency from youngsters' own reports because official records from police, courts, and clinics have two fundamental flaws as indicators of antisocial behavior. Such records reveal only the tip of the iceberg; many more youngsters engage in serious antisocial behavior than those arrested or treated, and most illegal behaviors go undetected. Not only do official records overlook much, but also the offenders they identify are unrepresentative in momentous ways. Research reveals that "official" delinquents often differ from the full population of offending youngsters on race, class, sex, and family composition. Parents' and teachers' reports provide more sensitive and less biased measures of youngsters' antisocial behavior, but they too have flaws. Parents' reports are influenced by cultural norms, parents' own mental health, and how assiduously the son is supervised. Teachers' knowledge of pupils is limited to classroom behaviors. For all these reasons, when researchers calculate correlations between different reports of antisocial behaviors (police, parents, teachers, boys), the "validity" estimates are near 0.40.[5] On a scale from 0 (no agreement) to +1 (perfect agreement), 0.40 does not seem to inspire confidence. However, we have the aforementioned justifications for imperfect agreement. Because each source's flaws are complementary, researchers should gather two or three and then report whether a finding replicates across the sources despite the flaws of each. Because lead was associated with behavior problems reported by boys, parents, and teachers, we may be appropriately skeptical of each measure, without being skeptical of the overall finding.

How generally applicable are these measures? Self-reports of delinquency have been measured across the United States and in 20 countries, including cultures as varied as Finland, Greece, China, and New Zealand. The CBCL has been administered in 43 languages and 30 cultures. Notably, although rates of delinquency vary somewhat from place to place, its risk correlates are markedly uniform across cultures: maleness, school failure, lax parental supervision, and weak parent-child attachment are linked with antisocial behavior wherever it is measured.[6] My own research shows that relations between intelligence, impulsivity, and antisocial behavior are consistent among boys and girls, blacks and whites, and New Zealanders and Americans, whether measured by self-reports, parent CBCL, teacher CBCL, or court records.[7]

How predictive are these measures? It is generally accepted that antisocial behavior is among the most stable of human attributes, showing continuities from childhood to adulthood that match those of measures of intelligence.[8,9] Moreover, prediction is improved if delinquency coincides with attention deficit disorder,[10] another problem that can be lead related. I estimated the predictive significance of Needleman's measures of antisocial behavior using data from my own 21-year longitudinal study of 536 boys, 33 of whom have been court convicted as adults of one or more violent crimes (assault, robbery, homicide). In a classification analysis, parent reports, teacher reports, and self-reports of antisocial behavior from ages paralleling those studied by Needleman et al predicted conviction of violent crimes with 61% sensitivity and 85% specificity.

Measures of childhood antisocial behavior are reasonably accurate, broadly applicable, and moderately predictive of adult violent crime and related outcomes such as alcoholism and domestic abuse.[10] Links between such measures and lead exposure warrant careful attention.

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1. Needleman HL, Reiss JA, Tobin MJ, Biesecker GE, Greenhouse JB. Bone lead levels and delinquent behavior. *JAMA*. 1995;275:363-369.
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intent with owners of inexpensive vs expensive guns. We are suggesting that the inexpensive product we identified in our study should be examined just as vigorously as the 2 other parts of the public health triad.

Finally, we agree with Ferguson's final comment that the effect of data on intentional gun-related deaths is still open to debate. However, we feel strongly that there should not be any debate for compiling complete and accurate information.

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1. Kellermann A. Prevention of penetrating trauma in adults. In: Ivatury R, Cayten C, eds. *The Textbook of Penetrating Trauma*. Baltimore, Md: Williams & Wilkins; 1996:80-88.
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These letters were shown to Mr Teret, who declined to reply.—ED.

Clinical Forensic Medicine

To the Editor.—We read with interest Dr Uva's[1] Resident Forum article concerning clinical forensic medicine. While reinforcing her comments concerning the need for proper assessment of survivors of violence, we feel it is necessary to emphasize that clinical forensic medicine should not be solely defined, as in her article, as "the application of forensic medical techniques to the survivors of violence."

Clinical forensic medicine may relate to any area in which medicine, law enforcement, and the judiciary come into contact. The Association of Police Surgeons in the United Kingdom, originally established in 1951, is the largest body undertaking such work, representing approximately 1000 clinicians, and clinical forensic medicine has its own section within the Royal Society of Medicine. Within the United Kingdom there are an increasing number of specialist forensic physicians devoting all or a substantial part of their clinical workload to forensic medicine. They are self-employed, independent, and individually appointed to specific police authorities. Such work relates to the living individual, as opposed to the work of the forensic pathologist. For example, forensic physicians may provide medical care and forensic assessment of prisoners and suspects in police custody, of complainants (alleged victims) of crime, of police officers injured while on duty, and of victims in allegations of police assault, and forensic physicians attend scenes of death (Table). In each case, the physician may be required (subject to consent and obligations of confidentiality) to provide interpretation of findings for the police, for courts, and for social services. Statements for the court and for presentation of evidence may be required. Forensic physicians may also provide independent expert opinions for both the defense and prosecution.

Potential Types of Evaluations Conducted by Forensic Physicians

Prisoner Examinations
Determine fitness to be detained in police custody (eg, general medical assessment, need for referral to hospital, treatment)
Assess fitness to be charged with offense (competent to comprehend charge)
Determine fitness to be interviewed by police (particularly for cases in which mental health is an issue or alcohol or other drugs are involved)
Conduct examinations related to the Road Traffic Act of 1988
Assist in body searches for drugs
Suspect and Alleged Victim Examinations
Accurately assess, record, define, and interpret injuries
Obtain forensic samples
Undertake mental health examinations
Assess and give advice at scenes of death
Assist police investigators with appropriate advice
Examine adult complainants of sexual assault
Examine (jointly with pediatricians) alleged child victims of neglect and physical or sexual abuse

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1. Uva J. Clinical forensic medicine as a means to stem violence. *JAMA*. 1996;275:106.

In Reply.—The letter from Drs Payne-James and Stark illustrates the international history of clinical forensic medicine. The United Kingdom has more than 40 years of experience in this arena compared with the mere 5-year initiation in the United States. The expansion of the definition of clinical forensic medicine, especially the application of the theory to concrete examples, is beneficial.

To increase the role of clinical forensic medicine in the United States, several obstacles must be overcome. Education of physicians on clinical forensic medicine and application of the techniques on living patients need to be encouraged. Acceptance of these techniques may require research for the benefits and possible complications of using clinical forensic medicine. With all of the changes in health care financing today, clinical forensic medicine will need to prove its economic benefits as a medical discipline vs only a theoretical perspective.

Although clinical forensic medicine is recognized worldwide, the United States still lags behind in knowledge, application, and acceptance. Interaction between the United States and countries with more established forensic medicine systems may prove to be fruitful to increase the communication on information pertaining to clinical forensic medicine. Clinical forensic medicine is applicable to all disciplines of medicine as well as law and public policy. Moreover, examining the well-established practice of clinical forensic medicine internationally may facilitate efforts to stem violence.

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Bone Lead Levels and Delinquent Behavior

To the Editor.—Contrary to the results of the study by Dr Needleman and colleagues,[1] after a 3-decade follow-up study of more than 69 of 110 (63%) of my former patients whose blood lead levels were between 4.83 and 22.68 μmol/L (100 and 470 μg/dL), I have yet to encounter the predicted outcome. Eighty percent of this cohort of inner-city black subjects graduated from high school, a third entered college, and 6 have already obtained 1 or 2 degrees. Three of the college graduates had symptoms of incipient encephalopathy before they received chelation therapy.[2]

Needleman et al leave several questions unanswered. Has the x-ray fluorescence (XRF) technique been validated on children with known lead poisoning (ie, lead concentrations in blood of 3.86 μmol/L [80 μg/dL] or more)? Their study lacks a proper control population.

We have lead in our red blood cells at the time of birth, and we continue to accumulate lead throughout our lives, yet the authors found 57 of their subjects had negative bone lead

values. How reliable is the XRF technique? Can it distinguish lead accumulated gradually over 12 years from lead acquired rapidly by a 12-year-old who had pica when he was 2 years old? Is a child whose blood lead remains in the range of 0.96 to 1.45 μmol/L (20 to 30 μg/dL) for several years at a risk equal to the child who briefly reaches 6.03 μmol/L (125 μg/dL)? Hardly!

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1. Needleman HL, Riess JA, Tobin MJ, Biesecker GE, Greenhouse JB. Bone lead levels and delinquent behavior. *JAMA*. 1996;275:363-369.
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To the Editor.—The recent publication by Dr Needleman and colleagues[1] linking delinquent behavior to bone lead content causes me great concern. I have had an interest in the lead exposure of children for many years, including demonstrating that lead in dust is a potent contributor to the low levels of lead found in children.[2] As a pediatric primary practitioner in an inner city, I've followed many children with lead exposure. Many have done well and are now in college or working productively, raising families of their own. In these same settings, we see many disrupted families whose children are aggressive and delinquent although the children's lead levels were never high.

Violence and youthful aggression in our time has exploded in the last decade, reaching frightening proportions. Coincident with this worsening of behavior there has been a remarkable drop in blood lead levels. Delinquent behavior has many important driving forces that are now worsening, including drug and alcohol addiction, family disruption, child neglect, and watching violence. Thus, children exposed to these forces derive an early imprint of unpleasant family interactions and uncontrolled behavior that can be indelible for life.[3] However, Needleman et al write, under "Covariates": "Family function was estimated by scoring the presence of both parents in the home, mothers' age at subjects' birth, and number of children in the family. In addition, subjects' race and history of noteworthy medical problems were obtained by structured questionnaire." While these variants are easily quantified, they grossly underestimate relevant forces of family life, do not come out in a questionnaire, and cannot be measured in numbers.

In discussing their findings, the authors state the following: "While we did not control for all nonlead covariates, the factors we entered into the model did capture parental education and occupation (an index of socioeconomic status), race, mother's age at subject's birth, and presence of the father in the home (indexes of family intactness and support)."

In recent years, great effort has been made toward prevention of delinquency and violence, including teaching new mothers about bonding with their babies, parenting programs discussing family functioning, and day care to allow early infant stimulation. Drug and alcohol rehabilitation may allow the strengthening of families.

This study has the potential of turning us to yet more preoccupation with lead exposures that we adults somehow weathered at a time when lead levels were far higher. Unchallenged and eagerly received by some, this study will unleash yet more litigation, already at staggering levels. We should be careful how seriously we take the assertions of Needleman et al. Concurrent exposure does not establish a causal relationship.

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1. Needleman HL, Riess JA, Tobin MJ, Biesecker GE, Greenhouse JB. Bone lead levels and delinquent behavior. *JAMA*. 1996;275:363-369.
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To the Editor.—Dr Needleman and colleagues[1] report that lead exposure is associated with increased risk for delinquency in boys. However, their findings are far from definitive. Although the sample was adequate in size (212 after exclusions), and high-risk cases were oversampled, the measures of delinquency, including self-reports at ages 7 and 11 years, parent and teacher Child Behavior Checklist (CBCL) T scores greater than 70, and CBCL delinquency cluster scores, all failed to reach statistical significance. There were, however, some significant associations between lead level and parent and teacher ratings of aggression and other behavioral disturbances. The results of a replication 2 years later were not reported, and there was no indication as to whether they were confirmatory.

A major concern in research on lead effects is the control of confounding factors. These variables typically contribute appreciably more to analytic models than does lead. Thus, it was startling to note that covariate adjustments in the report by Needleman et al had little effect on the CBCL scores at age 7 years and no effect whatsoever at age 11 years. Because some of the covariates (maternal intelligence, single parent home, socioeconomic status, number of siblings, race, and history of medical problems) are known to be related to lead exposure and to behavior, adjustment should have modified the findings. Several factors known to contribute to delinquency (parental supervision and discipline and parent criminality[2]) were not entered as covariates. Parental supervision and discipline are known to be related to lead levels[3]; hence, failure to control for this important influence in the article by Needleman et al leaves the strength of the results uncertain.

Another issue that merits attention is the possibility of reverse causality, ie, children whose behavior is problematic may engage in activities that increase their risk of lead exposure.

The most striking finding was not mentioned in the abstract; the lead measure was positively and significantly related to IQ. This is also discrepant with previous reports by this investigator and with what some call a consensus of opinion regarding low-level lead exposure.[4,5] Poor school performance and results from a number of other psychometric measures were unrelated to the lead level. Thus, the study contributes to the uncertainty observed in research on this topic. An explanation that the positive association of lead and IQ was limited to the African-American children does not counter its importance. Nonwhite children comprised almost 70% of this sample. Because of poverty, African-American children are more at risk of lead exposure; hence, findings regarding these children are particularly important. A synergistic relationship (interaction) of ethnicity and lead with respect to IQ is not reported consistently in other research.[6]

It is hoped that the strongly stated conclusions in the media regarding the study are not used to misdirect the limited resources available for coping with adolescent delinquency.

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1. Needleman HL, Riess JA, Tobin MJ, Biesecker GE, Greenhouse JB. Bone lead levels and delinquent behavior. *JAMA*. 1996;275:363-369.
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To the Editor.—We applaud Dr Needleman and colleagues[1] in their effort to expand the use of bone lead measurement to younger, non–occupationally exposed subjects and to study delinquent behavior as a new aspect of lead exposure's potentially far-reaching consequences. However, we feel that there are aspects of this work that require more discussion.

As pointed out in their article, the individual K x-ray fluorescence (KXRF) measurements have large uncertainties. Owing to these uncertainties, the authors elected to present their data only in categorical form. Descriptive statistics, including the mean, and population variance would allow comparisons with other XRF studies of children and young adults.

The description of the KXRF technique itself raises some questions. No mention was made that calibration standards below 10 μg of lead per gram of bone mineral (expressed as μg/g) were used. In our experience, a standard of 5 μg/g is important since this low concentration standard significantly affects the slope of the calibration line used. Further, KXRF involves a mathematical fitting process that extracts lead information from 4 fluorescence peaks: the $K\alpha_1$ and $K\alpha_2$ and the $K\beta_1$ and $K\beta_2$ peaks in the emission spectra. The $K\alpha_1$ and $K\alpha_2$ peaks were not used to determine bone lead concentration in the article by Needleman et al since the authors state that the Kα signal was virtually undetectable. However, a major proportion of the information about the lead concentration comes from the Kα peaks,[2] in particular the $K\alpha_1$ peak. The expected loss of precision of the authors' technique deserves discussion.

Finally, it would be helpful to know if the "high" bone lead group had mean bone lead levels that were significantly greater than the "low" bone lead group in the measure used to categorize them. In our study of 23 subjects aged 18 to 21 years,[3] we determined that a 30-minute measurement was not of sufficient duration to obtain a stable measurement of tibia lead concentration. By increasing the measurement time to 1 hour, we were able to decrease the measurement uncertainty by a factor of the square root of 2. With this increase in measurement time, the mean measurement uncertainty was 3.3 μg/g (SD, 0.55 μg/g). For the population of 11-year-olds in the article by Needleman et al, based on extrapolations of our data for 30-minute measurements[3] and using the relative contribution-to-measurement uncertainty presented by Chettle et al,[2] we estimate a mean measurement error of 6.3 μg/g if all the lead peaks ($K\alpha_1$ and $K\alpha_2$ and $K\beta_1$ and $K\beta_2$) were used, and we estimate a mean measurement error of 10.8 μg/g if only the $K\beta_1$ and $K\beta_2$ peaks were used. By comparison, the mean bone lead concentration in our study population was 3 μg/g (SD, 2.3 μg/g). If we make the conservative assumption that no population variability exists within a subpopulation and, thus, measurement error is the only source of variability, the subpopulation variance for 11-year-olds would be approximately 116 μg/g.[2] Given the information provided by Needleman et al, we calculate that the high bone lead group contains 93 boys and the low bone lead group contains 119. Thus, we calculate that the study should have had 80% power to detect a difference of 4.2 μg/g with 95% confidence in 2 such groups. Such a difference would appear inconsistent with the range of mean bone lead concentrations reported in autopsy and KXRF studies of community-exposed individuals in the age group of 11 to 21 years (1.2 to 4.86 μg/g).[4-6]

We encourage the authors to provide more discussion for this important work with far-reaching implications.

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To the Editor.—Dr Needleman and colleagues[1] reported an association between bone lead levels and antisocial and delinquent behavior in a sample of boys aged 7 to 11 years. If true, this is an important finding with profound social, political, and medical implications. The article has already attracted public attention.[2] Thus, it is important to evaluate the validity of the study in terms of the generalizability of the findings to the whole population of US children. Epidemiologists call this "external validity." Needleman et al present evidence in support of the "internal validity" (ie, generalizability of the findings to the studied sample), but they fail to consider its external validity. In fact, examination of their data indicates that the examined sample may not have been unbiased.

In the authors' Table 1, data for a number of covariables used in the multivariate analyses of the examined sample data are shown for subjects included and excluded from the analyses. In all, the investigators were able to examine only 212 (42%) of the 503 subjects in the sample pool. Of the 291 subjects excluded, refusals accounted for 98, out-migration for 17, noncontact for 83, and broken schedules and missing data for 54 (a subtotal of 202 initial exclusions). The remaining 89 exclusions occurred at varying stages of follow-up for varying reasons. To assess the representativeness of the examined sample, the 202 initial exclusions have been compared with the 212 subjects examined with respect to socioeconomic status (Hollingshead Code) and percentage of white race (Table). To do this, SEs of the mean values for the Hollingshead Code and for the percentage of white race had to be calculated from the data in Table 1 from Needleman et al.[1]

Because the 95% confidence intervals for characteristics in the examined and unexamined subjects did not overlap, it can be confidently stated that socioeconomic status was higher and percentage white was lower in the examined subjects. Therefore, regardless of the validity of the findings of Needleman et al for the examined sample, it is clear that this group

Assessment of Representativeness of the Study Sample in the Article by Needleman et al[1]

	Hollingshead Code*		Race, % White	
	Examined	Unexamined	Examined	Unexamined
Mean	3.8	5.0	30.7	45.5
SE	0.14	0.20	3.2	3.5
95% Confidence interval	3.5-4.1	4.6-5.4	24.3-37.1	38.5-52.5

*Hollingshead Code value increases as socioeconomic status decreases.

of subjects was not representative of the total sample pool with respect to characteristics known to be related to environmental lead exposure and antisocial behavior. Furthermore, the investigators did not provide data that would permit an assessment of the representativeness of the sample pool to the target population.

Generalizations from multiple levels of potentially biased samples are always subject to serious distrust. In view of the obvious importance of the issue, replication of this study in a clearly defined representative sample is required.

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To the Editor.—The article by Dr Needleman and collegues[1] is based on analyzing bone lead by XRF, a method of unproven clinical reliability. An XRF registry has recently been developed by the lead-testing industry in response to increasing reports of poor and highly variable data quality of XRF analyses for industrial use. Analyses for medical studies should have more exacting requirements.

Needleman et al stated in their "Methods" that bone lead and psychological studies were done twice, 2 years apart. They indicated that the bone lead results of the first study were not usable (the lead x-ray levels from even the high-lead phantoms were obscured), although in the second study they were more readily "detectable." What does this mean in terms of specificity, sensitivity, and reproducibility? Further, why did the authors only compare the neuropsychological results of the first study with the XRF results of the second study?

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The Medical Editing Department, Kaiser Foundation Research Institute, provided editorial assistance.

1. Needleman HL, Riess JA, Tobin MJ, Biesecker GE, Greenhouse JB. Bone lead levels and delinquent behavior. *JAMA*. 1996;275:363-369.

In Reply.—Dr Sachs and Dr Sayres are skeptical; they have treated lead-poisoned children but have not observed antisocial behavior. Both relied on personal behavioral observation in a clinic setting; we used structured behavioral inventories from 3 separate informants, all of whom had the benefit of prolonged, close-up observation. Sachs notes that 69 subjects she treated with extreme elevations in blood lead levels (>4.83 μmol/L [>100 μg/dL]) seemed to be doing well on follow-up. She actually treated 105 children with lead levels in this dangerous range, but she ignores 36 subjects who were not located. Subjects not located after treatment generally have worse outcomes than those who are located. It is reasonable to ask how many of her missing lead-poisoned subjects are in special schools, are homeless, are in prison, or are dead.

Dr Ernhart criticizes our report because the CBCL delinquency clusters did not reach statistical significance when classified categorically. She is startled that adjustment for confounders did not alter the influence of lead, and she wonders whether bad behavior increased exposure to lead. There are 2 ways to deal with behavioral data: as dimensional traits or as categorical traits. Attentional disturbance, aggression, and delinquent behavior exist as continual from none to very severe: they are dimensional traits. Treated dimensionally, the data from parents and teachers showed statistically strong associations at the 11-year epoch.

When the unadjusted effect size is not altered by adjustment for covariates, this means that confounding has not occurred. We are satisfied to allow the data to speak for themselves.

The hypothesis that lead is an effect rather than a cause of disordered behavior has been effectively dismissed by animal studies in which lead is administered and behavior measured[1] and by forward studies in which infants' blood lead levels are measured at birth.[2] Both types of reports clearly establish that lead is the independent variable and behavior is dependent.

The positive relationship between bone lead and IQ is puzzling. The African-American children with high bone lead levels and high verbal IQ scores also had the most favorable social factors (more intact families, more educated parents, fewer siblings, and higher socioeconomic status scores), while the children with low bone lead levels and lower IQ scores were extremely disfavored on these factors. We are continuing to examine this association.

Dr Hoppin and colleagues believe that we lost accuracy by not using the Kα estimators and that we should have used a longer collection period. The fundamental limitation in KXRF measurements is destructive interference with the lead x-rays from background fluctuations. At low levels of bone lead concentration, background at the lead Kα spectral region is at least 1 order of magnitude higher than in the lead Kβ region, obscuring the information there. We concluded that the use of the Kα signal would introduce a null bias. Requiring an 11-year-old to sit still in a restrained position for more than 30 minutes was, in our opinion, an excessive and unachievable demand.

We recognized the possibility of selection bias discussed by Dr Winkelstein and Ms Balfour. That is why we stated, "If the findings reported herein are found to extend to the population of US children, the contribution of lead to delinquent behavior would be substantial." No single epidemiologic study by itself ever proves a point, and we hope that other investigators will examine this important question in different samples, with careful design and appropriate test instruments.

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Original Contributions

Bone Lead Levels and Delinquent Behavior

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Objective.—To evaluate the association between body lead burden and social adjustment.

Design.—Retrospective cohort study.

Setting.—Public school community.

Participants.—From a population of 850 boys in the first grade at public schools, 503 were selected on the basis of a risk scale for antisocial behavior. All of the 850 boys who scored in the upper 30th percentile of the distribution on a self-reported antisocial behavior scale were matched with an equal number drawn by lot from the lower 70% of the distribution. From this sample, 301 students accepted the invitation to participate.

Exposure Measure.—K x-ray fluorescence spectroscopy of tibia at subjects' age of 12 years.

Main Outcome Measures.—Child Behavior Checklist (CBCL), teachers' and parents' reports, and subjects' self-report of antisocial behavior and delinquency at 7 and 11 years of age.

Results.—Subjects, teachers, and parents were blind to the bone lead measurements. At 7 years of age, borderline associations between teachers' aggression, delinquency, and externalizing scores and lead levels were observed after adjustment for covariates. At 11 years of age, parents reported a significant lead-related association with the following CBCL cluster scores: somatic complaints and delinquent, aggressive, internalizing, and externalizing behavior. Teachers reported significant associations of lead with somatic complaints, anxious/depressed behavior, social problems, attention problems, and delinquent, aggressive, internalizing, and externalizing behavior. High-lead subjects reported higher scores in subjects' self-reports of delinquency at 11 years. High-lead subjects were more likely to obtain worse scores on all items of the CBCL during the 4-year period of observation. High bone lead levels were associated with an increased risk of exceeding the clinical score (T>70) for attention, aggression, and delinquency.

Conclusion.—Lead exposure is associated with increased risk for antisocial and delinquent behavior, and the effect follows a developmental course.

(*JAMA*. 1996;275:363-369)

PARENTS of lead-poisoned children and pediatricians who have cared for those children have often observed that after the acute toxic episode subsides children are aggressive and difficult to manage. Fifty years ago, Byers noticed that some children who had been treated for acute plumbism were referred back to him "for violent, aggressive behavioral difficulties, such as attacking teachers with knives or scissors" (R. K. Byers, MD, unpublished data, 1986). It was this observation that resulted in the first follow-up study of the behavioral consequences of acute lead toxicity.[1] Considerable speculation has recently been offered on the nature of the relationship between childhood lead exposure, aggression, and delinquency, but empirical data on the question are sparse.

Since 1943, most studies of the behavioral effects of lead exposure in children have focused on psychometric intelligence to the exclusion of other behavioral outcomes. Those studies that have looked at other measures have found lead-related impaired reaction time, distractibility, disorganization, impulsivity, and restlessness.[2-5] These findings suggest that regulation of attention may be a sensitive target. Lead is also associated with higher scores on the Rutter B2 behavioral scale and on the conduct problem, inattentive-passive, and hyperactive scales of the Connor questionnaire.[3] In Scottish children, lead was related to hyperactivity and aggressive antisocial scores on the Rutter teacher scale.[6] New Zealand children had higher inattention and restlessness scores in relation to dentine lead levels.[7] In males, when attention-deficit hyperactivity disorder is accompanied by aggression, an individual is at strong risk for later delinquent behavior.[8]

For editorial comment see p 403.

Only one investigation of lead in relation to disciplinary problems, juvenile delinquency, and adult criminality has been published.[9] Denno studied 987 African-American youths (487 males, 500 females) from birth through 22 years of age. After examining many factors, she found lead poisoning, in male subjects only, to be the most significant predictor of disciplinary problems and among the most significant predictors of delinquency and adult criminality.

These observations encourage the study of the role of lead exposure, at levels experienced by children in school, as a risk factor in the genesis of antisocial behavior. To pursue this question, we studied a sample of 301 boys in primary schools. We measured their bone lead concentrations by in vivo x-ray fluorescence (XRF), a measure of cumulative exposure, and examined the relationship of bone lead burden to reports of antisocial behavior from three separate sources: parents, teachers, and the subjects themselves. We also evaluated attentional function, neurobehavioral, and academic performance in relation to bone lead. To minimize confounding by other factors, we controlled for nine relevant social and economic variables and compared outcome before and after covariate adjustment. To identify any development of lead-related dysfunctions over time, we tested the subjects at two periods separated by approximately 24 months, and we evaluated behavioral

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Table 1.—Characteristics of Included and Excluded Subjects*

No.	Status	Hollingshead Code, Mean±SD	Mother's Grade, Mean±SD	Mother's Age in y at Child's Birth, Mean±SD	Mother's IQ (Raven's), Mean±SD	No. of Children in Family, Mean±SD	Both Parents Present, %	High Risk Score, %	Subject's Full-Scale IQ, Mean±SD	Subject's Age in y, Mean±SD	Race, % White
503	Sample Pool	4.9±2.6	12.3±1.8	NA	NA	NA	NA	50.9	NA	12.5±.75	41.4
202	Excluded	5.0±2.7	12.3±1.8	NA	NA	NA	NA	44.1	NA	12.6±.76	45.5
301	Phase I	4.3±2.4	12.3±1.8	23.4±4.7	43.6±6.8	NA	NA	55.5	100.1±16.9	12.5±.74	38.5
69	Excluded	4.3±2.4	12.7±1.9	24.2±4.5	45.8±7.9	NA	NA	60.9	100.7±17.3	12.7±.76	55.1
232	Phase 2	3.7±2.0	12.7±1.7	23.2±4.8	42.9±8.9	3.1±1.4	33.6%	53.9	99.9±16.9	12.4±.73	32.3
20	Excluded	3.4±1.7	12.8±1.3	23.0±6.9	44.9±5.3	3.9±2.0	35.0%	30.0	95.2±19.9	12.5±.81	50.0
212	Analyzed	3.8±2.0	12.7±1.8	23.2±4.5	42.8±9.2	3.0±1.3	35.5%	56.1	100.3±16.5	12.4±.72	30.7

*IQ indicates intelligence quotient; NA, not available.

questionnaires obtained when the subjects were 7 and 11 years of age.

METHODS

Sample

Our sample was recruited from a cohort of students enrolled in the Pittsburgh Youth Study (PYS), a prospective, longitudinal study of the developmental course of delinquency.[10] The population was 850 first-grade boys in the Pittsburgh, Pa, public schools. From this group, subjects were selected to achieve a balanced sample at high and low risk of delinquency. Potential subjects were rated on an instrument composed of serious and potentially indictable behaviors extracted from the teachers' and parents' Child Behavior Checklist (CBCL) and the subjects' self-reports. All subjects who scored above the 30th percentile on the risk score (n=256) and an approximately equal number (n=247) randomly selected from the remainder of the distribution formed the sample. This method has been recommended in studies of delinquency to increase the number of potential offenders in the study.[11] Investigators and psychometricians for the study reported herein remained blind to the risk scores and to individual bone lead levels until data entry was completed.

Of the 503 eligible candidates, 202 families were not tested. Ninety-eight families refused to participate in our study; 17 families lived outside Allegheny County, Pennsylvania, and were not contacted; 33 families were not reachable after a minimum of three attempts by letter or telephone; 32 families repeatedly broke scheduled appointments. Recruitment efforts were dropped for 22 subjects without longitudinal data from the PYS.

Bone lead and psychological measures of subjects were obtained at two times: at mean subject age of 10.2 years (range, 9 to 13 years; n=301) and at mean subject age of 12.0 years (range, 11 to 14 years; n=232). Sixty-nine subjects either declined participation or were unable to be contacted at 12 years of age. Of the 232 subjects tested at 12 years of age, six were excluded from the data analysis because parents refused a repeat bone lead measurement. Fourteen subjects whose parental interview revealed a history of severe neurologic illness were excluded from data analysis. Table 1 describes the covariate structure, intelligence quotient (IQ), and risk scores in the included and excluded groups.

Measurement of Bone Lead

In vivo K XRF (KXRF) was used to determine subject bone (tibia) lead concentrations. Each subject sat in a low lead content ABS (acrylonitrile-butadiene-styrene terpolymer) chair with his target leg immobilized in a plastic restraint. In this technique, 88.035 keV photons from a ^{109}Cd source induce characteristic lead K x-rays, which are measured with a backscatter counting geometry. Bone lead concentrations were estimated from the lead $K\beta_{1+3}$ x-rays (84.94 and 84.45 keV).

The effective dose for a 10-year-old subject from a 30-minute exposure to our source was less than 200 nSv.[12] This procedure was approved by the University of Pittsburgh Institutional Review Board for Psychosocial Research and the Radiation Safety Committee. We modified the commercial bone lead analyzer by replacing the vendor-supplied data acquisition system with an Aptec model 3008 multichannel analyzer that improved signal processing threefold (Aptec Engineering Ltd, Concord, Ontario).

KXRF spectra from tibia phantoms (plaster of paris doped with lead acetate to concentrations ranging from 10 to 110 mg of lead per gram of plaster, with surrounding soft tissue simulated by water) were used to develop optimal peak-fitting routines, calibrate the instrument, and assess the precision of low lead concentration measurements. Plaster lead concentration was confirmed by inductively coupled plasma spectrometry.

Lead K x-ray and coherent scatter peak areas were obtained with a nonlinear minimization algorithm (SYSTAT Inc, Evanston, Ill). We fit gaussian peaks superimposed on monotonic background functions to model the functions. The signal was fit to two models: a monotonic background function as a "null hypothesis" (no lead signal) model and a peak-signal model. The net residual spectra (data-fitted model) of both models were examined for serial correlations that indicate the presence of detectable lead x-rays. The converged sum of squares (and reduced χ^2) values for the null model were then compared with those obtained from the peak-fit model values. In the presence of a significant lead peak, the net residuals for the fitted peak model were lower in magnitude and increased in randomness compared with the corresponding null hypothesis model. For virtually every subject, the lead $K\alpha$ signal was not detectable. In contrast, the $K\beta_{1+3}$ x-rays were routinely discerned and were thus used to estimate bone lead concentrations. For 57 subjects, the coherent scatter was great enough compared with the lead signal to yield negative bone lead values.

At the beginning of our study, the activity of the ^{109}Cd excitation source was 4.5 GBq (120 mCi). This activity proved to be too intense, and the resulting background continuum obscured the lead x-rays from even high-lead phantoms. As a result, many spectra were difficult to analyze. Two years later, when the source strength was 1.5 GBq (40 mCi), the $K\beta_{1+3}$ lines were more readily detectable. Consequently, we report herein the bone lead measurements from the second testing period, when the subjects were 12 years of age. The neuropsychologic data are from the first testing period.

Measures of Antisocial Behavior

The PYS interviewed the parents and children at 6-month intervals in the home. They provided us with the following structured interview data: the Self-reported Antisocial Behavior scale[13] (SRA) (given at subjects' mean age of 7.4 years), the Self-reported Delinquency scale[14] (SRD) (subjects' mean age, 10.9 years), and the parents' and teachers' version of the CBCL (also administered at these ages).[15] The SRA is an inventory of violent and nonviolent antisocial behavior

(scored "never, once, twice, more often"). Eight questions were not understood by many of the subjects and were dropped. We computed a linear sum score from the remaining 22 items. We used 30 items to compute a sum score for the SRD (scored "never, N times"). The CBCL is a 112-item, three-point (scored "never, some, often") scale inventory of child behavior used widely in diagnosis and assessment of psychopathology.[16]

Neurobehavioral Measures

We also surveyed the neurobehavioral function of our subjects. Following the XRF measurement, subjects received a shortened form of the Wechsler Intelligence Scale for Children–Revised (WISC-R),[17] the noncomputerized subtests of the Mirsky attention battery (Stroop color-word test, trail-making test, letter cancellation test, Wisconsin card sort),[18] elements of the Neurobehavioral Evaluation System,[19] and Lanthony's desaturated hue test.[20] To reduce the length of the testing session, a split-half form of the WISC-R was used. The Neurobehavioral Evaluation System subtests given were finger tapping, simple reaction time, serial digit learning, pattern recognition, associate learning, and associate recall.

Covariates

To evaluate and minimize confounding from social and familial factors, we evaluated nine covariates spanning three areas: maternal intelligence, socioeconomic status, and quality of child rearing. The measures were chosen based on a priori knowledge of factors known to influence child development or that could be correlated with lead. The biological mother's IQ was measured with Raven's standard progressive matrices test.[21] Socioeconomic status was estimated by measuring the mother's occupation and education.[22] Family function was estimated by scoring the presence of both parents in the home, mothers' age at subjects' birth, and number of children in the family. In addition, subjects' race and history of noteworthy medical problems were obtained by structured questionnaire. Age was entered into the analyses except in the analysis of the WISC-R, which is age adjusted when scored.

Quality Assurance

Data entry accuracy for the neurobehavioral assessment and WISC-R was checked by entering all data twice into a separate file and counting discrepancies. The error rate for data entry for these instruments was 0.0035. All discrepancies were checked against the primary record and corrected.

To estimate data entry error rates for PYS files, a randomly selected 5% of the PYS sample were examined, and each entry in the computer file was compared to the original hard-copy records. The rate for the CBCL (parent and teacher) ranged between 0.0000 and 0.0046.

Two psychometricians independently scored the written subtests of the attention battery and the WISC-R. The two primary raters agreed on 92.5% of the WISC-R items and 87.6% of the attention battery items. For each item, any discrepancies were evaluated by a third psychometrician, who, after reviewing the original record, made a final decision and recorded it in the database.

Data Analysis

To deal with the large SD in the individual XRF $K\beta_{1+3}$ measures and 57 resultant net negative lead values, we first treated the bone lead estimates categorically in six groups. All negative XRF values were assigned to class 1, the lowest. The positive values were then grouped into quintiles. This grouping produced six ordered classes. A plot of the unadjusted scores on a number of our primary outcome variables vs the six classes of bone lead burden indicated a steep inflection in unadjusted scores beginning after the middle grouping of lead burdens (Figure 1). Responding to the shape of the relationships displayed, we then treated our data dichotomously, splitting the subjects at the upper bound of class 3, and used analysis of covariance (ANCOVA), adjusting for the covariates listed earlier. After analyzing the CBCL data adjusted for nine covariates, we added CBCL scores at 7 years to the model as a covariate and examined the association between lead and CBCL scores at 11 years.

All variables were checked for outliers. The CBCL cluster scores were calculated according to the 1991 scoring manual.[15] Linear sum scores of the selected SRA and SRD items were calculated for each subject. To reduce the effect of influential outliers, CBCL, SRA, and SRD outcome data were transformed by taking square roots of each scaled or summed score.

We also calculated the proportion of subjects at 11 years of age who scored in the clinical ranges (the range within which psychiatrists will make a clinical diagnosis on that behavior) (T score ≥70) on the CBCL attention, aggression, and delinquency scales and cross-tabulated them against dichotomized bone lead category.

The Mirsky attention battery items were scored and factor analyzed. The optimal solution consisted of four factors. Factor 1 loaded primarily on Stroop, coding, trails, and letter cancellation. This factor corresponded to Mirsky's "focus/execute" factor. Factor 2 loaded on continuous performance test reaction time. This factor corresponds to Mirsky's "vigilance" factor. Factor 3 loaded on the continuous performance test errors. Factor 4 loaded on the perseveration item, arithmetic and digit span, and corresponded to Mirsky's "shift" factor. The relationship of the factors to bone lead were then analyzed by ANCOVA.

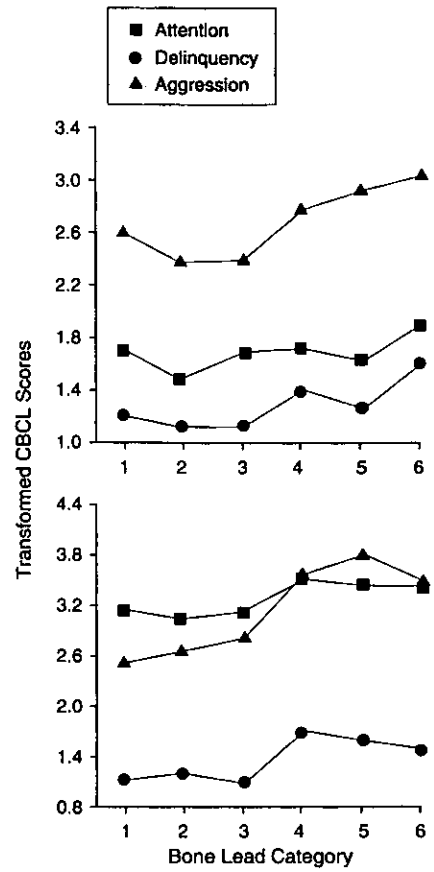

Figure 1.—The relationship between bone lead levels (in hextiles) and Child Behavior Checklist (CBCL) scores. Top, Parents' scores; bottom, teachers' scores. Three outcomes were examined: attention, delinquency, and aggression. Cluster scores were transformed by taking square roots. Group 1 contains all the negative bone lead measurements. The subjects with positive measurements were divided into quintiles.

RESULTS

Table 2 gives the ANCOVA analyses for both parents' and teachers' reports at 7 years of age. Tables 3 and 4 give the ANCOVA for CBCL at 11 years of age. Three models are presented in Tables 3 and 4: the unadjusted bivariate association of bone lead and CBCL cluster, adjustment for nine covariates, and adjustment for nine covariates and CBCL score at 7 years of age. *P* values are given for the third model. Table 5 presents the subjects' reports of their behavior at 7

and 11 years of age. Outcomes are reported with and without covariate adjustment.

The outcomes from all three informant groups were concordant and followed a developmental course. At subjects' age of 7 years (Table 2), parents reported no lead-related difficulties on the CBCL and subjects' SRA scores were not significant. Teachers reported borderline associations at 7 years between lead and somatic complaints, social problems, and delinquent, aggressive, and externalizing behaviors. At subjects' age of 11 years (Table 3), parents of high-lead subjects reported significantly more somatic complaints, more delinquent and aggressive behavior, and higher internalizing and externalizing scores. At 11 years of age, teachers reported significant increases in scores associated with bone lead on the following clusters: somatic complaints, anxious/depressed, social problems, attention problems, delinquent behavior, aggressive behavior, internalizing, and externalizing (Table 4). Adjustment for 7-year CBCL scores had practically no impact on the size of the lead effect.

Subjects' SRD at 11 years (Table 5) was significantly related to bone lead without covariate adjustment (P=.04). This finding was slightly altered by entering covariates (P=.07).

Table 6 gives the WISC-R, attention battery, and neurobehavioral outcome results. Lead level was positively related to verbal and full-scale IQ. This association was found in African-American subjects only. African Americans with high bone lead levels and IQ scores higher than 105 had mothers with higher Raven's scores, had more education and higher socioeconomic status, were more likely to come from two-parent families, and had fewer siblings, while African Americans with low bone lead levels and low IQs (<90) had mothers with lower Raven's scores, had less education and lower socioeconomic status, and had fewer fathers in the home and larger sibships. None of the Neurobehavioral Evaluation System items were related to lead.

When CBCL scores were compared over time, both parents and teachers reported that high-lead subjects were more likely to worsen between 7 and 11 years of age than low-lead subjects (Figures 2 and 3). More high-lead subjects had CBCL scores in the clinical range (T scores ≥70) than low-lead subjects. When we cross-tabulated bone lead split at the median against numbers of subjects with clinically defined scores of attention, aggression, and delinquency, the high bone lead subjects had a higher percentage of scores in the clinical range on every scale (Figure 4). The odds ratios for the outcomes ranged from 1.5 (parents' report of aggression) to 19.7 (parents' report of attention). The lower boundary of the 95% confidence interval was less than 1 on four of six scores (Table 7).

Table 2.—The Relationship of Bone Lead Concentration to Child Behavior Checklist (CBCL) Scores at Subject Age 7 Years*

CBCL Cluster Ratings at Child's Age 7 y	Unadjusted Scores: Low-Lead Group	Unadjusted Scores: High-Lead Group	Adjusted Scores: Low-Lead Group	Adjusted Scores: High-Lead Group	P
Parents' scores					
Withdrawn	1.30	1.39	1.27	1.38	.32
Somatic complaint	0.79	0.75	0.80	0.74	.62
Anxious/depressed	1.64	1.70	1.62	1.69	.59
Social problems	1.53	1.49	1.52	1.48	.65
Thought problems	0.40	0.33	0.40	0.32	.41
Attention problems	2.04	2.06	2.03	2.05	.82
Delinquent behavior	1.55	1.58	1.54	1.58	.84
Aggressive behavior	3.04	3.10	3.01	3.10	.58
Internalizing	2.42	2.48	2.39	2.47	.57
Externalizing	3.46	3.52	3.43	3.52	.66
Teachers' scores					
Withdrawn	0.89	0.97	0.86	0.98	.51
Somatic complaint	0.14	0.26	0.14	0.26	.14
Anxious/depressed	1.04	1.13	1.03	1.15	.49
Social problems	0.93	1.16	0.95	1.17	.10
Thought problems	0.22	0.32	0.23	0.33	.22
Attention problems	2.79	2.87	2.77	2.88	.67
Delinquent behavior	0.82	1.06	0.83	1.08	.06
Aggressive behavior	2.02	2.49	2.07	2.52	.08
Internalizing	1.51	1.65	1.49	1.67	.40
Externalizing	2.28	2.77	2.32	2.81	.08

*Scores were transformed by square root. Covariates in the model were mother's intelligence quotient, mother's highest grade achieved, age at subject's birth, presence of father, child's age, Hollingshead code, family size, race, and health status. P values are given for covariate-adjusted analysis of covariance.

COMMENT

These findings are congruent with each other and in agreement with long-held clinical observations of disturbed social

Table 3.—The Relationship of Bone Lead Concentration to Parents' Child Behavior Checklist (CBCL) Scores at Subject Age 11 Years*

Parents' CBCL Cluster Ratings at Child's Age 11 y	Unadjusted Scores: Low-Lead Group	Unadjusted Scores: High-Lead Group	Adjusted Scores: Low-Lead Group	Adjusted Scores: High-Lead Group	Adjusted Plus 7-y CBCL Scores: Low-Lead Group	Adjusted Plus 7-y CBCL Scores: High-Lead Group	P
Withdrawn	1.02	1.15	1.02	1.16	1.02	1.16	.26
Somatic complaint	0.52	0.83	0.52	0.85	0.52	0.85	.008
Anxious/depressed	1.10	1.34	1.08	1.35	1.08	1.35	.09
Social problems	1.16	1.32	1.16	1.32	1.16	1.32	.12
Thought problems	0.28	0.31	0.28	0.31	0.28	0.31	.54
Attention problems	1.66	1.76	1.65	1.76	1.65	1.76	.45
Delinquent behavior	1.19	1.44	1.18	1.45	1.18	1.45	.04
Aggressive behavior	2.48	2.90	2.43	2.9	2.43	2.98	.009
Internalizing	1.76	2.13	1.74	2.15	1.74	2.15	.03
Externalizing	2.82	3.31	2.78	3.31	2.78	3.31	.005

*Mean scores for each cluster are given. Test scores were transformed by square root before analysis of covariance. Covariates adjusted for in the model were mother's intelligence quotient (Raven's score), mother's highest grade achieved, mother's age at child's birth, both parents present in the home, child's age, caregiver's job code, number of siblings, race, and child's health status. Three models are given: unadjusted for covariates, adjusted for covariates, and adjusted for covariates plus 7-year CBCL score. P values are given for the final model.

Table 4.—The Relationship of Bone Lead Concentration to Teachers' Child Behavior Checklist (CBCL) Scores at Subject Age 11 Years*

Teachers' CBCL Cluster Ratings at Child's Age 11 y*	Unadjusted Scores		Adjusted Scores		Adjusted Scores		
	Low-Lead Group	High-Lead Group	Low-Lead Group	High-Lead Group	Low-Lead Group	High-Lead Group	P
Withdrawn	1.28	1.53	1.25	1.53	1.25	1.53	.08
Somatic complaint	0.27	0.64	0.24	0.65	0.24	0.65	<.001
Anxious/depressed	1.37	1.94	1.35	1.95	1.35	1.95	<.001
Social problems	1.19	1.71	1.18	1.71	1.18	1.71	.001
Thought problems	0.35	0.55	0.35	0.56	0.35	0.56	.06
Attention problems	3.08	3.50	3.07	3.51	3.07	3.51	.05
Delinquent behavior	1.09	1.64	1.04	1.63	1.04	1.63	<.001
Aggressive behavior	2.60	3.69	2.56	3.71	2.56	3.71	<.001
Internalizing	2.04	2.68	1.99	2.69	1.99	2.69	.004
Externalizing	2.88	4.09	2.82	4.10	2.82	4.1	<.001

*Mean scores for each cluster are given. Test scores were transformed by square root before analysis of covariance. Covariates adjusted for in the model were mother's intelligence quotient (Raven's score), mother's highest grade achieved, mother's age at child's birth, both parents present in the home, child's age, caregiver's job code, number of siblings, race, and child's health status. Three models are given: unadjusted for covariates, adjusted for covariates, and adjusted for covariates plus 7-year CBCL score. P values are given for the final model.

Table 5.—Analysis of Covariance (ANCOVA) of Self-report of Delinquency at Ages 7 and 11 Years*

Self-report	Unadjusted Scores			Adjusted Scores		
	Low-Lead Group	High-Lead Group	P	Low-Lead Group	High-Lead Group	P
Antisocial behavior at age 7 y	2.08	2.35	.56	2.12	2.40	.51
Delinquency at age 11 y	1.51	2.39	.04	1.50	2.44	.07

*Test scores were transformed by square root before ANCOVA. Covariates adjusted for in the model were Mother's intelligence quotient (Raven's score), mother's highest grade achieved, mother's age at child's birth, both parents present in the home, child's age, caregiver's job code, number of siblings, race, and child's health status.

Table 6.—Bone Lead Concentrations and Intelligence Quotient (IQ), Attention, and Neurobehavioral Evaluation System Scores*

Test	Mean Low-Lead Level	Mean High-Lead Level	P
Wechsler Intelligence Scale for Children–Revised			
Verbal IQ	96.54	101.08	.006
Performance IQ	102.18	103.14	.68
Full-scale IQ	99.14	102.15	.07
Attention Battery			
Factor 1			
Focus/execute	−.043	−.017	.71
Factor 2			
Reaction time/vigilance	.112	−.143	.09
Factor 3			
Continuous Performance Test errors	−.018	.068	.62
Factor 4			
Shift	.002	.079	.55
Neurobehavioral Evaluation System			
Finger tapping, No. of taps	122.96	122.79	.96
Reaction time, mean ms†	351.73	356.54	.68
Reaction time SD, ms†	138.87	139.56	.94
Serial digit learning†	3.11	2.68	.26
Pattern recognition, mean latency, on correct trials	5.27	5.08	.30
Associate learning across three trials, No. correct per trial	3.41	3.29	.46
Associate recall, No. correct	3.44	3.30	.55

*Covariate-adjusted mean scores are given. Covariates in the model are the same as in Tables 2, 3, and 4. IQ score analyses are not adjusted for age.
†Lower scores indicate better performance.

behavior in children who recovered from clinical lead poisoning. They extend the relationship downward in dose to asymptomatic youths with elevated body burdens. In this study, male children considered asymptomatic for lead toxicity with elevated bone lead levels at 11 years of age were judged by both parents and teachers to be more aggressive, have higher delinquent scores, and have more somatic complaints than their low-lead counterparts. The subjects themselves reported lead-related increases in antisocial acts at the same age. High-lead subjects were more likely than low-lead subjects to worsen on all scores of parents' and teachers' CBCL during the 4-year observation period. These results were not altered by control for nine social and familial covariates, indicating that confounding was not influential in our sample.

Other investigators have reported lead-related increases in CBCL scores. Sciarillo[5] found similar effects in African-American children aged 2 to 5 years using parents' ratings alone. Subjects with blood lead levels greater than 0.73 μmol/L (15 μg/dL) had higher scores on the internalizing and externalizing scales and higher total behavior problem scores. Males had higher rates of scores in the clinical range on aggression, delinquency, sex problems, and immaturity. Bellinger et al[23] evaluated teachers' CBCL ratings in a large sample of 8-year-olds. Dentine lead levels were related to total behavioral problem scores, internalizing scores, and externalizing scores. Our study extends these earlier reports by measuring both teachers' and parents' scores and adding the subjects' own ratings of their behavior.

The validity of stuctured behavioral inventories in the measurement of conduct disorder and prediction of future outcome has been shown in many studies, and the CBCL has found wide acceptance since its publication. Children with CBCL T scores above 70, the clinical cutoff, have much higher referral rates to psychiatric clinics than those who score below the cutoff.[15] A follow-up study of 1613 subjects who had received the CBCL scales demonstrated that scores on the delinquency cluster were the best predictor of later adjustment difficulty, as measured by academic failure, behavior problems, police contacts, need for mental health services, or substance abuse. The best predictor of suicidal threats or attempts was high aggression scores on the CBCL.[24]

Early reports of conduct disorder or aggression, demonstrated in these subjects, are strong predictors of later criminality. These behaviors, when displayed early in early childhood, are stable. Farrington studied 411 males in London and

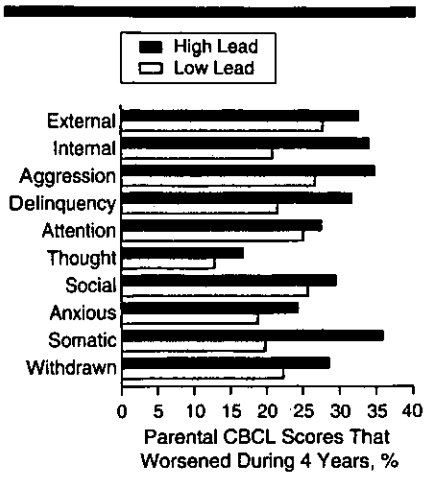

Figure 2.—The change in parental Child Behavior Checklist (CBCL) scores during 4 years in relation to bone lead concentrations. Subjects are classified as "high lead" (above the median) and "low lead" (below the median).

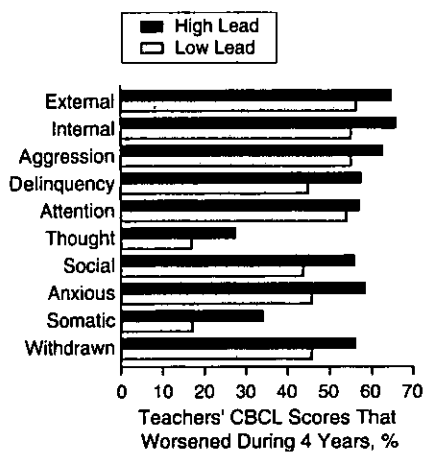

Figure 3.—The change in teachers' Child Behavior Checklist (CBCL) scores during 4 years in relation to bone lead concentrations. Subjects are classified as "high lead" (above the median) and "low lead" (below the median).

found that children reported to be "troublesome" on a rating scale by their teachers at 8 years of age were significantly more likely to be adjudicated as delinquent at 18 years of age, to rate themselves as aggressive at 32 years of age, and to have been convicted of a violent crime by 32 years of age.[25]

Any study of lead must confront the fact that lead exposure is higher in samples who have more nonlead risk factors. Lead levels are higher in minorities and in subjects with low income. Delinquency is associated with minority status, poverty, and disorganized families. In this study, adjusting for nine covariates did not substantially alter the strength of the association. While we did not control for all nonlead covariates, the

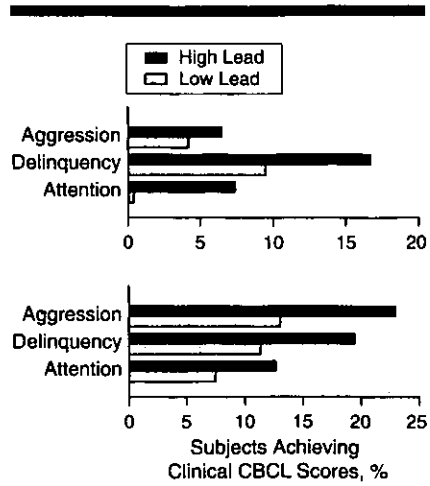

Figure 4.—The association between bone lead concentation and clinical Child Behavior Checklist (CBCL) (T>70) scores for aggression, delinquency, and attention. Subjects are classified as "high lead" (above the median) and "low lead" (below the median). Both parents' CBCL scores (top) and teachers' scores (bottom) are displayed.

Table 7.—The Relationship Between Bone Lead and Clinical Child Behavior Checklist (CBCL) Scores

CBCL Cluster/Rater	OR	95% CI
Attention		
Parent	19.35	8.9-41.6
Teacher	1.71	0.57-5.1
Delinquency		
Parent	1.89	0.83-4.3
Teacher	2.16	0.96-4.6
Aggression		
Parent	1.49	0.45-4.9
Teacher	2.18	1.03-4.6

*OR indicates odds ratio; CI; confidence interval.

factors we entered into the model did capture parental education and occupation (an index of socioeconomic status), race, mother's age at subject's birth, and presence of father in the home (indexes of family intactness and support). The small alteration in effect size when the covariates were entered into the model suggest that confounding is not great in this sample. It is possible, of course, that some unmeasured socioeconomic factor is influencing outcome and is associated with lead. It is unlikely that such a factor would not be correlated with any of the nine socioeconomic variates for which we controlled.

The positive association between bone lead and IQ that we encountered was limited to African-American subjects. High-IQ, high-lead subjects were favored on all nonlead factors when compared with low-IQ, low-lead subjects, who were disfavored on the same factors. This finding suggests that at these low levels of internal dose, social rearing factors were more influential than lead on IQ and that imperfect control of covariates or error in measuring them may explain the positive association. When we stratified subjects by IQ (<90, 91 to 104, >104) and examined the effect of lead on CBCL scores, we found that within each IQ stratum, high-lead subjects had higher CBCL scores. This finding was true for both races.

Through what mechanisms could a toxic metal influence a child's social adjustment? A number of neurochemical alterations offer potential explanatory mechanisms. For example, lead has been shown to interfere with norepinephrine-mediated inhibition in the rodent.[26] By disrupting inhibitory processes, lead could result in unmediated rapid responses to stimuli, which could be expressed as impulsivity. Lead exposure peaks between 2 and 3 years of life in children, the time of pruning back neuronal fibers. Goldstein suggests that by increasing the response to a given stimulus, lead could disturb the orderly pruning and result in later overresponsiveness.[27] Studies of teachers' reports of classroom behavior[2,3,28] have shown a lead-related increase in impulsivity, hyperactivity, and frustratibility.

Experimental studies in subhuman primates report similar effects of lead on behavior. Infant rhesus monkeys given low doses of lead that raised their blood lead levels to 3.39 μmol/L (70 μg/dL) showed disruptions in social behavior that lasted well past the time of administration, when blood lead levels had declined to 1.45 μmol/L (30 μg/dL).[29]

In children, attentional impairment[30] is a strong risk factor for delinquent behavior. Lead has been shown in a number of studies to affect attention: signaled reaction time,[2] teachers' ratings of classroom behavior,[2,3] and scores on structured behavioral inventories.[3] Monkeys dosed with lead from birth onward to reach a mean blood lead level of 0.73 μmol/L (15 μg/dL) showed perseveration, increased distractibility, inability to inhibit inappropriate responding, and difficulty in changing response strategy.[31] In our subjects, scores on the vigilance factor of the attention battery and clinical scores on the attention cluster of the CBCL were related to bone lead level.

Lead exposure is associated with reduced verbal competence, increased rates of reading disabilities, frustration, and increased academic failure. Reduced verbal skills could interfere with the use of internal language to mediate behavior and to delay immediate responding. Another factor that may be an intervening variable in the causal chain between lead and delinquency is academic failure, a demonstrated consequence of lead exposure. Subjects with elevated tooth lead levels in childhood, when followed into adulthood, had a sevenfold increase in the rate of high school failure and a sixfold increase in reading disability.[32] Stu-

dents who fail to graduate from high school and have poor reading skills have dim employment prospects, which could readily increase the risk of antisocial behavior. The sample reported herein is too young for this mechanism to express itself. Bone lead burden was not associated with inferior school performance in this study.

We cannot readily relate our XRF data to current or past blood lead standards. Our subjects were considered asymptomatic for lead and were attending ordinary public school. This circumstance suggests that the distribution of lead levels in our sample was in the range of community exposures in 1982, when the estimated prevalence of blood lead levels of greater than 0.73 μmol/L (15 μg/dL) of all US children was 16%.[33] The appearance of lead-related effects at the median bone lead level suggests that in some samples lead may contribute to dysfunction in an appreciable proportion of the community. Further work is needed to define the relationship between XRF measures and past blood lead concentrations.

If the findings reported herein are found to extend to the population of US children, the contribution of lead to delinquent behavior would be substantial. Large numbers of US children continue to have lead burdens in the neurotoxic range. Between 1976 and 1991, mean blood lead levels in children have decreased 77%, from 0.66 μmol/L (13.7 μg/dL) to 0.15 μmol/L (3.2 μg/dL). But many thousands of children continue to have toxic lead burdens, especially in minority urban communities. The prevalence of blood lead levels greater than 0.48 μmol/L (10 μg/dL), the current Centers for Disease Control and Prevention effect level, in non-Hispanic blacks is 21%.[34]

Delinquent behavior is a complex and multifaceted problem in which the search for causes has centered on two groups of determinants: social or experiential factors and those that are subsumed under the class of biological causes. In *Crime and Human Nature*,[35] Wilson and Herrnstein, arguing that criminality is primarily constitutional in origin, observed the following correlates with criminal behavior: criminality is more common in males, the rate of criminality is higher in African Americans, criminals have lower verbal IQ scores, and criminals frequently have histories of hyperactivity. It is intriguing that these factors are also associated with lead, either as risks for lead exposure or as effects of lead.

The interrelations between biological and experiential roots are tightly interwoven and difficult to disentangle. Among the biological factors, brain injury is recognized to impair social adjustment and occasionally to lead to violence or criminality.[9,10,36] The role of brain damage due to neurotoxins in eliciting antisocial behavior has, with the exception of alcohol, been largely ignored. The convergent findings in this report from three separate sources, parents, teachers, and the subjects themselves, in the absence of consistent psychometric or neurobehavioral effects, suggest that altered social behavior may be among the earliest expressions of lead toxicity. These data argue that environmental lead exposure, a preventable occurrence, should be included when considering the many factors contributing to delinquent behavior.

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LONGITUDINAL ANALYSES OF PRENATAL AND POSTNATAL LEAD EXPOSURE AND EARLY COGNITIVE DEVELOPMENT

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Abstract In a prospective cohort study of 249 children from birth to two years of age, we assessed the relation between prenatal and postnatal lead exposure and early cognitive development. On the basis of lead levels in umbilical-cord blood, children were assigned to one of three prenatal-exposure groups: low (<3 μg per deciliter), medium (6 to 7 μg per deciliter), or high (≥10 μg per deciliter). Development was assessed semiannually, beginning at the age of six months, with use of the Mental Development Index of the Bayley Scales of Infant Development (mean ±SD, 100±16). Capillary-blood samples obtained at the same times provided measures of postnatal lead exposure.

Regression methods for longitudinal data were used to evaluate the association between infants' lead levels and their development scores after adjustment for potential confounders. At all ages, infants in the high-prenatal-exposure group scored lower than infants in the other two groups. The estimated difference between the overall performance of the low-exposure and high-exposure groups was 4.8 points (95 percent confidence interval, 2.3 to 7.3). Between the medium- and high-exposure groups, the estimated difference was 3.8 points (95 percent confidence interval, 1.3 to 6.3). Scores were not related to infants' postnatal blood lead levels.

It appears that the fetus may be adversely affected at blood lead concentrations well below 25 μg per deciliter, the level currently defined by the Centers for Disease Control as the highest acceptable level for young children. (N Engl J Med 1987; 316:1037-43.)

IN a national survey conducted in the late 1970s,[1] 40 percent of U.S. children under five years of age had blood lead levels above 20 μg per deciliter. Among city-dwelling black children, the figure approached 60 percent. A variety of enzymatic and neurophysiologic processes are impaired at this concentration.[2-6] Debate persists, however, regarding the blood lead level at which deficits in children's learning and behavior become apparent.[7,8] Limitations inherent in retrospective study designs may account for some of the controversy.[9] Detailed histories of children's exposure to lead and their development are rarely available, but both are necessary to determine whether lead exposure precedes or follows the appearance of a developmental deficit. Elevated lead exposure may be a marker of a preexisting handicap rather than its cause, resulting from the tendency of impaired children to have pica.[10]

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Some investigators have attempted to determine a child's cumulative exposure by measuring the lead content of shed deciduous teeth.[11-14] The usefulness of this tissue as a basis for reconstructing the details of exposure history has not been established, however. At present, there is no satisfactory way to obtain an adequate developmental history retrospectively.

Some of the methodologic limitations of retrospective studies can be avoided with a longitudinal design in which both children's lead exposure and their development are periodically measured, starting at birth. This design allows investigators to measure the temporal relations between changes in lead exposure and changes in behavior. Besides suggesting which of the competing causal models accounts best for the data, a longitudinal design permits assessment of various exposure variables (e.g., dose, timing, and duration). Few studies in humans have addressed such issues as the threshold for lead's developmental toxicity, the age or ages at which children are most vulnerable, and the relative effects of long-term and short-term exposures.

Using a longitudinal design, we obtained repeated measures of blood lead levels, development, and the correlates of both in a group of urban children followed from birth to the age of two years. Lead levels in umbilical-cord blood between 10 and 25 μg per deciliter were associated with worse performance on tests of

infant development administered at six-month intervals through the second year of life.

Methods

Sample Selection

Between April 1979 and April 1981, umbilical-cord blood samples were collected from the placentas of 11,837 babies born at the Brigham and Women's Hospital in Boston. The mean (±SD) lead concentration was 6.6±3.2 μg per deciliter (range, 0 to 37).[15] In recruiting our longitudinal sample from this population, our goal was to select three groups of infants defined by their position within the distribution of values: below the 10th percentile (low), at approximately the 50th percentile (middle, or medium exposure), and above the 90th percentile (high). On the basis of the cord-blood lead concentrations of the infants born between April and July 1979 (approximately 2500), the criteria for eligibility in the three exposure groups were established at <3 μg per deciliter, 6 to 7 μg per deciliter, and ≥10 μg per deciliter, respectively. (At the beginning of the study, only infants with lead levels >15 μg per deciliter were eligible for the high-exposure group. A 20 percent decline in the mean cord-blood lead level over the period of sample collection,[15] as well as different degrees of success in enrolling infants in the three exposure groups, led us to modify the eligibility criteria over the course of the study.[16]) We obtained umbilical-cord blood samples for 9489 infants born during the subsequent 21 months (August 1979 to April 1981), representing 97 percent of the available population. Those with a blood lead level in one of the three target ranges were provisionally eligible for enrollment (n = 1207). To be included in the study, infants also had to satisfy the following criteria: (1) absence of a medical condition considered to be a risk factor for developmental difficulty (e.g., Down's syndrome, cleft palate, gestational age <34 weeks, and retinoblastoma); (2) birth into an English-speaking family; (3) residence near the Children's Hospital (<19 km) in an area considered safe for home visitors, and (4) maternal consent to be contacted. Families meeting these criteria were sent letters introducing the study and then telephoned to request their participation. Those reporting an intention to move from our catchment area in the immediate future were excluded. Some families refused our request, and others could not be contacted by either letter or telephone. The final sample consisted of 249 families (Table 1). No infant in the longitudinal sample had a lead level exceeding 25 μg per deciliter, which is the current definition of an "elevated" blood lead level.[17] Two thirds of the infants in the high-lead group (50 of 76) had cord-blood lead levels between 10 and 15 μg per deciliter.

Table 1. Reasons for Excluding Infants Whose Lead Levels in Umbilical-Cord Blood Were in One of the Target Ranges.

	Lead Level in Umbilical-Cord Blood			Total
	Low	Medium	High	
No. of infants provisionally eligible	434	380	393	1207
No. excluded	349	292	317	958
Reason for exclusion*				
Lack of maternal consent	69	64	63	196
Birth complication†	17	17	4	38
Family not English-speaking	23	18	24	65
Location of residence‡	150	107	108	365
Refusal§	52	54	61	167
Moving	20	12	10	42
Unreachable	18	20	47	85
No. enrolled	85	88	76	249

*Some infants were not acceptable for inclusion for two or more of the following reasons: lack of maternal consent, birth complication, family not English-speaking, and location of residence. Each child was counted only once, according to the first of these reasons. Therefore, except for "lack of maternal consent," the numbers in the table underestimate the incidence of the various reasons for exclusion.

†Complications included Down's syndrome, retinoblastoma, cleft palate, gestational age <34 weeks, and others.

‡Subjects were excluded if they lived >19 km from Boston, or in an area considered unsafe for home visitors.

§Mothers had two opportunities to refuse to participate. While still in the hospital, all the mothers were asked for permission to be contacted in the future about participating in a follow-up study. Some refused this request; some who gave consent at this time refused when subsequently contacted.

Sample Characteristics

The mean socioeconomic standing of the families contrasted sharply with that of families typically enrolled in research on the effects of lead exposure.[18-20] In general, the infants were healthy products of unremarkable pregnancies, with few of the characteristics of infants at increased risk of developmental handicap. Overall, 77 percent of the fathers and 70 percent of the mothers employed outside the home at the time of conception were in the top two social strata according to Hollingshead's index (combining occupational and educational achievement). Eighty-seven percent of the families were white, and 92 percent were intact. The differences in these and most other variables among the families with infants in the three cord-blood lead groups were slight and generally not in the direction expected on the basis of studies of the social correlates of childhood lead exposure[21] (Table 2). Infants with lead levels between 10 and 15 μg per deciliter were compared for this same set of variables with infants with levels above 15 μg per deciliter. The results were consistent with those in which all three exposure groups were compared, suggesting that infants already at higher risk of poor outcome for other reasons did not tend to have higher blood lead levels. Through our choice of delivery population and eligibility criteria, we were able to dissociate increased lead exposure from other risk factors. A more comprehensive comparison of the groups has been presented elsewhere.[16]

Collection of Developmental Data

Infants and their families were contacted five times after delivery, when the infants were 1, 6, 12, 18, and 24 months of age (SD <2 weeks at all ages). The assessment protocols at each age have been described elsewhere.[22] The principal outcome measures — the Bayley Scales of Infant Development[23] — were administered at all ages except one month. This assessment yields two scores: the Mental Development Index and the Psychomotor Development Index. In this report, we present longitudinal analyses of the infants' scores on the Mental Development Index, an age-corrected scale (mean ±SD, 100±16) that assesses infants' "sensory-perceptual acuities, discriminations, and the ability to respond to these; the early acquisition of 'object constancy,' memory, learning, and problem solving ability; vocalizations and the beginnings of verbal communication; and early evidence of the ability to form generalizations and classifications, which is the basis of abstract thinking."[23]

Five examiners blinded to the infants' lead levels administered the Bayley scales. Interexaminer reliability was assessed separately for each age at which the scales were administered. The mean correlation between the Mental Development Index scores assigned by two examiners observing a third administer the scales exceeded 0.95 at all ages.

Collection and Analysis of Blood Samples

Samples of umbilical-cord blood were collected at the time of delivery and analyzed according to procedures that have previously been described.[15] Specimens were sonicated and acid-digested in a microwave oven. The lead content was measured in duplicate by anodic stripping voltammetry (Environmental Sciences Associates [ESA] Model 2014, Bedford, Mass.).

Capillary blood samples, collected at 6, 12, 18, and 24 months, were assayed in duplicate or triplicate with an ESA Model 3010 anodic stripping voltammeter with use of an exchange reagent. The average difference between duplicate assays was 1 μg per deciliter, and there was a difference of 3.5 or more in 10 percent of the pairs. The analytic systems were calibrated with aqueous standards of known lead concentrations. No interference from varying copper concentrations was observed. Each batch of samples was accompanied by blood samples of known lead concentration so that intralaboratory variability could be quantified. In addition, several standardized blood samples, with lead concentrations measured to

three significant figures by isotope-dilution mass spectrophotometry, were included after they became available from the Centers for Disease Control in 1982. Further details about the blood lead measurements are available elsewhere.[21]

In the sample as a whole, the mean blood lead level was <8 μg per deciliter at all the ages sampled. The differences in exposure level among the three cord-blood groups did not carry over into the postnatal period (Table 1). Although the mean postnatal lead levels of infants in the high cord-lead group exceeded those of infants in the low cord-lead group at all ages, the difference was statistically significant only at 12 months. The means of the infants in the medium and high cord-lead groups did not differ significantly at any postnatal age. Most important, the correlation between cord and postnatal blood lead level did not exceed 0.20 at any age.[21] The equality of postnatal exposures in groups with widely discrepant prenatal exposures provided us the opportunity to assess the developmental effect of prenatal exposure in the absence of substantial confounding by postnatal exposure.

Sample Attrition

Forty-five infants were lost to follow-up at some point in the study — an attrition rate of approximately 10 percent per year. The likelihood of loss increased slightly with decreasing lead levels in umbilical-cord blood ($\chi^2_1 = 1.22$; $P>0.50$). The percentage of infants who did not complete all visits was 21.2, 18.2, and 14.5 percent for the low, medium, and high cord-lead groups, respectively. As compared with the mothers of the infants who remained in this study, the mothers who withdrew their children were more likely to be nonwhite or unmarried, and their mean age, educational level, IQ, and socioeconomic status were lower. They also had lower scores on a measure of the quality of the rearing environment they provided for their six-month-old infants.[23]

Cases Excluded from Analyses

Seven sets of twins enrolled in the study were not included in the statistical analyses because of their generally poorer performance relative to the nontwins in the sample. Earlier analyses of Mental Development Index scores at six months of age showed that restricting the sample to nontwins did not affect the results appreciably.[16] Another four infants were excluded because of the diagnosis of a serious medical condition known to be associated with developmental handicap (congenital heart defect, prenatal toxoplasmosis infection, myoclonic seizure disorder, and severe hypotonia).

The statistical analysis is described in the Appendix.

Results

Exploratory Analyses

Infants who had higher lead levels in umbilical-cord blood had lower crude Mental Development Index scores during the first two years of life. This relation was stronger when the 12 potential confounders were taken into account (Table 4). Despite a steady increase with age in the scores of infants in all three exposure groups, the least-squares mean Mental Development Index scores of the infants in the high cord-lead group were 4 to 8 points lower than those of the infants in the low cord-lead group at all ages (Fig. 1). The mean scores of the infants in the low and medium groups were similar throughout this age range.

The pattern of the adjusted Mental Development Index (MDIA) scores illustrates the consistency in the direction and magnitude of the relation between Mental Development Index and prenatal lead exposure (Table 5). A plus or minus sign indicates whether, on average, the infants within a group did better (+) or worse (−) than predicted at a given age on the basis of the 12 variables considered potential confounders. The average MDIA was increasingly negative with increasing prenatal exposure. The infants in the low cord-lead group averaged 1.9±0.4 points, those in the medium cord-lead group 1.2±0.8, and those in the high cord-lead group −3.4±1.1. The

Table 2. Characteristics of Families in the Three Cord-Blood Lead Groups.*

Characteristic	Cord-Blood Lead Group†			P Value‡
	Low	Medium	High	
Demographic				
Marital status (% single)	17.3	7.2	10.8	0.13
Maternal age (yr)	28.2±4.6	30.0±4.8	30.9±5.1	0.002
Race (% white)	79.0	95.2	85.1	0.015
Maternal education§	16.0±3.8	16.5±3.9	16.3±4.1	0.76
Paternal education§	17.3±3.5	18.0±3.6	17.7±3.6	0.51
Family social class§	2.3±1.7	2.2±1.8	2.3±2.0	0.94
Reproductive history¶				
Gravidity	2.3±1.2	2.1±1.6	2.3±2.0	0.57
Parity	0.6±0.5	0.5±0.5	0.4±0.5	0.14
Miscarriage (% with any)	18.5	10.8	24.3	0.08
Index pregnancy				
Month prenatal care began	2.5±1.0	2.2±0.9	2.1±0.7	0.021
Length of gestation (wk)	39.6±1.8	40.1±1.6	40.0±2.0	0.14
Weight gain (lb)	31.5±10.7	32.0±11.4	28.3±9.8	0.063
Hypertension (%)	11.1	8.4	12.3	0.72
Bleeding (%)	7.4	9.6	4.0	0.40
Cigarette smoking (%)‖	21.0	34.9	28.4	0.14
Smoking duration (yr)	2.2±3.6	5.2±5.8	6.7±6.6	0.0001
Alcohol consumption (%)**	25.9	41.0	50.0	0.008
Labor and delivery¶				
Duration of stage 1 (hr)	8.6±6.8	7.9±4.6	8.3±4.9	0.89
Vaginal delivery (%)	77.5	78.0	71.6	0.59
No or local anesthesia (%)	40.3	24.4	35.2	0.10
Neonatal status				
Birth weight (g)¶	3316±474	3478±521	3379±538	0.12
Apgar score: 5 min¶	8.9±0.6	8.8±0.5	8.8±0.5	0.60
Sex (% male)	59.3	56.6	50.0	0.49
Postnatal environment				
H.O.M.E. total score††				
6 Mo	34.4±3.8	35.1±3.5	35.3±3.4	0.33
24 Mo	36.8±3.2	37.2±3.0	37.0±3.1	0.76
Mother's IQ‡‡	119.0±20.9	123.3±17.1	121.7±18.4	0.38

*For dichotomous variables, differences between groups were evaluated by overall chi-square tests. For continuous variables, group differences were tested by one-way analyses of variance.

†Plus-minus values are means ±SD.

‡Indicates P value associated with the hypothesis that differences among infants in the three cord-blood lead groups were due to chance.

§Weighted scores were computed with use of Hollingshead's Four-Factor Index of Social Status.

¶The information was obtained from obstetrical or pediatric records; otherwise, it was obtained in an interview with the mother.

‖Values are the percentages of women who reported smoking during any portion of the index pregnancy.

**Values are the percentages of women who reported having consumed, on average, one or more drinks per week during the third trimester of the index pregnancy.

††H.O.M.E. denotes Home Observation for the Measurement of the Environment.

‡‡The mother's IQ was measured with the Peabody Picture Vocabulary Test.

number of positive MDIA scores was determined for each infant. This corresponds to the number of ages at which the infant had a Mental Development Index score that exceeded the predicted value. The percentage of infants who did not score higher than predicted at any of the four ages was three times higher in the high cord-lead group than in the low or medium groups (23.6 percent vs. 8.5 and 6.5 percent, respectively).

Infants' Mental Development Index scores were not associated with their prior postnatal or concurrent blood lead levels.

Longitudinal Analyses

In all the longitudinal models fitted, the lead variables most strongly associated with MDIA scores were those that compared the overall level of performance of infants in the low and high cord-lead groups or the medium and high cord-lead groups. The estimated deficit in the overall MDIA score of infants in the high cord-lead group was 4.8 points (95 percent confidence interval, 2.3 to 7.3; $P = 0.0001$) with respect to the infants in the low group, and 3.8 points (95 percent confidence interval, 1.3 to 6.3; $P = 0.004$) with respect to infants in the medium group.

Age trends in MDIA scores were not significantly related to cord-lead group (Model 2) or to early postnatal lead exposure (Model 5). Similarly, MDIA scores were not related significantly to the blood lead concentration at the time of developmental assessment (Model 3) or to cumulative postnatal lead exposure up to the time of assessment (Model 4). (Additional details about the models and their relative fit are available from the authors.)

Discussion

Infants with lead levels in umbilical-cord blood of 10 to 25 μg per deciliter — levels currently considered acceptable — had stable performance deficits of 0.25 to 0.5 SD during the first two years of life, relative to infants with levels under 10 μg per deciliter. Postnatal blood lead levels of comparable magnitude, measured during the first two years of life, were not associated with performance deficits.

This association between development and prenatal lead exposure but not between development and postnatal lead exposure may be interpreted in one of three ways. First, it may have been an artifact of study design. We selected for extremes of prenatal lead exposure but not for extremes of postnatal lead exposure. The mean lead level in the cord blood of the infants in the high group exceeded the mean level of the infants in the low group by a factor of 8, whereas the mean postnatal blood levels of lead in the two groups were much more comparable, never differing by more than 3 μg per deciliter. Although this design allowed us to appreciate an association between development and prenatal lead exposure, it may have limited our ability to perceive a small postnatal effect.

Second, early postnatal exposure corresponding to blood lead levels in the upper portion of the range from 0 to 25 μg per deciliter may not adversely affect infants' performances on the Bayley Scales.[26]

Third, adverse effects associated with postnatal exposures in this range may be discernible only at later ages or in infants who are at greater risk of poor outcome on the basis of socioenvironmental factors than those in our sample.

The performance deficits we observed were consistent with studies in primates in which learning deficits produced by the prenatal or early postnatal administration of lead persisted in some cases for several years after the blood lead levels of the exposed animals fell to the control level.[27-32] This may be attributable to the fact that brain lead levels remain elevated considerably longer after a short-term exposure than do blood lead levels.[33,34]

Like malnutrition and other developmental insults, lead's adverse effects may be expressed most dramatically when exposure occurs in conjunction with other factors that compromise a child's development. In-

Table 3. Blood Lead Levels in Infants Classified According to Cord-Blood Lead Group.

Cord-Blood Lead Group	Blood Lead Level (mean ±SD)				
	Birth*	6 mo	12 mo†	18 mo	24 mo
	micrograms per deciliter				
Low	1.8±0.6	4.6±3.9	5.8±5.1	6.7±5.5	5.4±4.8
Medium	6.5±0.3	7.0±7.8	8.5±7.6	9.3±5.8	7.2±5.0
High	14.6±3.0	7.0±8.7	8.8±6.4	7.6±5.8	7.7±8.5

*Each value is significantly different from the other two (Tukey's studentized range test: $\alpha = 0.05$).

†The value for the low-lead group is significantly different from the other two values (Tukey's studentized range test: $\alpha = 0.05$).

Table 4. Infants' Mental Development Index Scores According to Cord-Blood Lead Group.

Cord-Blood Lead Group	Mental Development Index Score			
	6 mo	12 mo	18 mo	24 mo
	mean ±SD			
Crude score				
Low	109.2±12.9	113.1±12.5	113.4±15.5	115.9±17.2
Medium	108.6±12.0	115.4±12.9	116.6±16.7	119.9±14.4
High	106.1±11.1	108.7±12.8	109.5±17.5	110.6±16.5
	mean ±SE			
Controlled for potential confounders*				
Low	110.2±1.3	114.7±1.6	116.2±1.9	118.9±1.8
Medium	108.0±1.3	114.4±1.5	114.8±1.9	117.8±1.7
High	105.9±1.4	108.9±1.6	109.5±2.0	111.1±1.8
P value†	0.095	0.020	0.049	0.006
No. of infants‡	201	199	187	182

*Least-squares mean ±SE, derived from regression equations that included 12 potential confounders (see text) and cord-blood lead group coded as two indicator variables.

†Indicates P value associated with the F ratio that evaluates whether the mean Mental Development Index for any cord-blood lead group differed significantly from the common mean after potential confounders were controlled for.

‡The numbers of infants at the four ages differ from one another and from those shown in Table 1 because of (1) loss to follow-up between Mental Development Index assessments and (2) the exclusion from the analyses of twins, infants with handicapping medical conditions, and infants for whom the Mental Development Index or confounder values were unavailable.

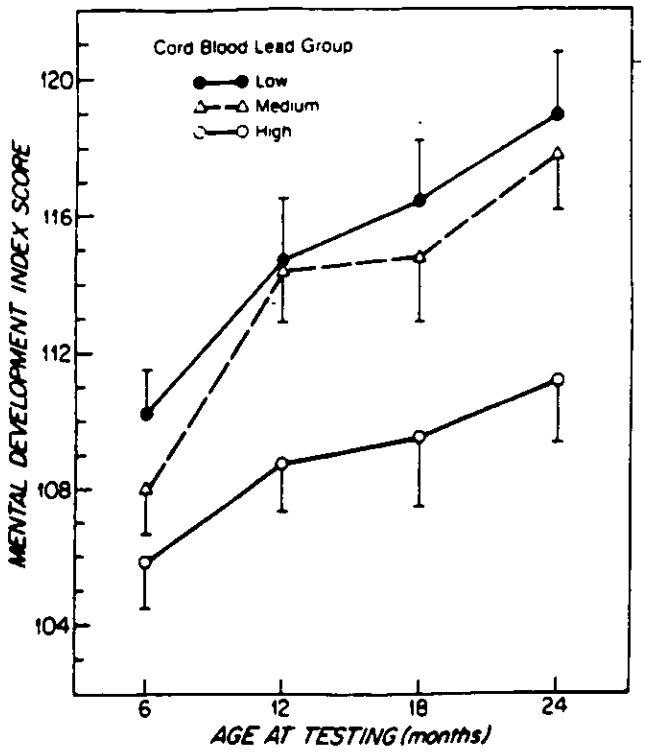

Figure 1. Mean Mental Development Index Scores at Four Ages in Infants According to the Lead Level in Umbilical-Cord Blood. Scores are least-squares means obtained by regressing Mental Development Index scores on the cord-blood lead group and 12 variables considered to be potential confounders. Error bars represent 1 SD. For clarity, bars extend only in one direction.

deed, in a German study of school-aged children, visual–motor integration and reaction-time performance were adversely affected only among the children exposed to lead who were also socially disadvantaged.[35] If this is also true for prenatal lead exposure and early infant development, our sample provides a conservative assessment of the association. The early results of another longitudinal study of the developmental effect of prenatal lead exposure, conducted in a less socially advantaged sample, support this interpretation.[36]

Our sample, a relatively homogeneous group of families willing to contribute substantial time and effort to participate in longitudinal research, cannot be considered representative of the population of U.S. infants. The increasingly high Mental Development Index scores over the 6- to 24-month period of infants in all the exposure groups are most likely due to the overrepresentation in this sample of infants from families in the higher socioeconomic strata. In addition, the mean blood lead level of the sample as a whole never exceeded half the mean level of U.S. preschool children,[1] and infants with serious handicaps or characteristics strongly associated with handicap were excluded from the sample. In addition, infants were not sampled in such a way that the distribution of levels of cord-blood lead matched the distribution in all infants.

Some of the design features of our study would be expected to reduce the likelihood that an effect of prenatal lead exposure would be perceived. Indeed, the association did not become significant until after adjustment for potential confounders. Moreover, the estimate of the prenatal effect became larger and its significance level more extreme the greater the number of potential confounders included in the regression equation.[17] This finding is unique among lead studies and can be attributed to the fact that the more socioeconomically advantaged infants in our sample tended to have higher levels of lead in umbilical-cord blood.[18] On the basis of a regression equation consisting of the 12 potential confounders, the predicted Mental Development Index scores of the infants in the high cord-lead group were higher than the predicted scores of the infants in the low cord-lead group at all four ages. As a result, adjusting for these variables enhanced rather than reduced the estimate of lead's association with Mental Development Index scores.

The adequacy of the lead level in umbilical-cord blood as an indicator of intrauterine lead exposure has not been studied in detail. The lead level in cord blood is strongly correlated with the concurrent lead level in the mother's venous blood.[39-42] The mother's lead level appears either to remain stable or to decline slightly over the course of pregnancy.[40,41,43,44] Nevertheless, we advise caution in extrapolating the lead exposure throughout pregnancy from just one blood measurement at the time of delivery.

The pattern of attrition in this study provides a striking example of the bias that can occur when loss to follow-up is related to the exposure or the outcome of interest and the statistical approach employed uses only subjects for whom complete data are available. Although the overall rate of attrition did not vary significantly among the prenatal-exposure groups, the relation between loss to follow-up and development did. The infants in the low cord-lead group who did not complete the study tended to have more improvement in performance over the period of their participation than did the infants in the low group who remained in the study. Those in the high cord-lead

Table 5. Infants' Mean Adjusted Mental Development Index Scores (MDIA) According to Cord-Blood Lead Group.*

Cord-Blood Lead Group	MDIA Scores			
	6 mo	12 mo	18 mo	24 mo
Low				
Mean score ±SE	1.72±1.20	1.46±1.46	2.12±1.75	2.28±1.58
No. of infants†	70	69	65	61
Medium				
Mean score ±SE	−0.06±1.25	1.60±1.38	1.22±1.76	1.82±1.60
No. of infants†	70	70	65	63
High				
Mean score ±SE	−1.90±1.21	−3.54±1.54	−3.81±1.97	−4.38±1.76
No. of infants†	61	60	57	58

*The MDIA score is the residual of the regression of Mental Development Index on the 12 variables considered potential confounders; MDIA scores are the dependent variables in the longitudinal analyses.

†Values are the numbers of infants for whom MDIA scores were available.

group who did not complete the study tended to have a greater decline in performance over the period of their participation than did the infants in the high group who remained in the study. Basing the longitudinal-modeling analyses only on the infants for whom Mental Development Index scores were available at all four ages would have biased the result toward underestimation of the relation between prenatal lead exposure and development.[15,16]

Recent estimates of lead levels in umbilical-cord blood in subjects in urban areas are typically 7 to 9 μg per deciliter, with an SD of 3 to 4.[15,39,47-50] Thus, more than one fourth of all newborns in these areas may have lead levels comparable to those of the infants in our high-exposure group (i.e., ≥10 μg per deciliter). If replicated in other samples, our findings suggest that the current standard of the Centers for Disease Control for acceptable blood lead levels in young children (<25 μg per deciliter) should not be applied to fetuses.

We are indebted to the families participating in this research; to Molly Nichols (project coordinator), Joan Hargrave, M.S., Paula Weiss, M.A., and Judy Clouston, who conducted the developmental assessments; to Stephen Schoenbaum, M.D., Sharon Taitz, R.N., Kathy Finn Sullivan, R.N., Linda Stone, R.N., and the delivery staff of the Brigham and Women's Hospital, who helped collect umbilical-cord blood samples; to Marie Betts and Michael Burley, who collected the postnatal blood samples; to Elizabeth Allred, M.S., who assisted with data management, programming, and statistical analyses; to Jone Sloman, Ph.D., and Angelos Hatzakis, M.D., who provided many helpful comments on the manuscript; and to several *Journal* reviewers for their suggestions.

Appendix: Statistical Methods

Data analyses were conducted in two stages. First, the associations between the various lead measures and Mental Development Index scores were examined separately for each age. The goal was to suggest hypotheses to investigate in the second stage. These exploratory analyses consisted of ordinary least-squares multiple regressions in which Mental Development Index scores were regressed on the cord-blood lead category and a set of 12 factors generally associated with infant development: the mother's age, race (white or nonwhite), IQ,[51] education, number of years of cigarette smoking, and number of alcoholic drinks per week in the third trimester of pregnancy; the mean family social class over the period of the study (according to the Hollingshead Four-Factor Index); the quality of the care-giving environment[25]; and the infant's sex, birth weight, gestational age, and birth order.

In the second stage, longitudinal analyses were carried out with use of weighted regression.[52] This was considered more appropriate than ordinary least-squares regression, because it takes into account the correlation between an infant's Mental Development Index scores at different ages. In these analyses, adjustment for potential confounders preceded evaluation of lead's contributions to Mental Development Index scores. The dependent variables — the adjusted Mental Development Index (MDIA) scores — are the residuals of the regression of Mental Development Index scores on the 12 potential confounders listed above. Because the relation between a potential confounder and infant performance may change with time, Mental Development Index scores were adjusted in four separate regression analyses, one for each age. In both exploratory and longitudinal analyses, the cord-lead group was represented as two indicator variables, with the high group as the reference group. Postnatal blood lead levels, transformed to their natural logarithms, were treated as continuous variables.

Five models were fitted, each postulating specific relations between MDIA and lead exposure during different periods. These models were chosen to assess the effect of prenatal and postnatal lead exposure on the overall level of performance and rate of change in the MDIA score. All five included a term relating prenatal exposure (cord-lead group) to the mean MDIA score. The simplest model (Model 1) considered no other influences. Other models included terms representing more complex relations: Model 2, prenatal lead exposure affects the temporal change in MDIA score; Model 3, blood lead level at the time of assessment affects the MDIA score; Model 4, cumulative lead exposure up to the time of assessment affects the MDIA score; and Model 5, the blood lead level at the age of six months interacts with the cord-lead group to affect a subsequent temporal change in the MDIA score.

In all the models, MDIA scores for an individual child at the jth visit were expressed as the sum of the mean μ_j and a random component e_j:

$$MDIA_j = \mu_j + e_j,$$

where the e_js for a child have a multivariate normal distribution, with a mean of 0 and an arbitrary covariance matrix Σ, assumed to be the same for all children for whom data were complete (i.e., MDIA scores were available for each age). For children with incomplete data, the appropriate rows and columns were deleted from the covariance matrix.

The covariance matrix was estimated from the data with use of an iterative algorithm. In a first step, Σ was estimated by computing the sample covariance matrix of the residuals of the ordinary (unweighted) least-squares estimate of the regression of the MDIA score against the lead-exposure variables. The inverse of the estimated Σ provided the weights given to the observations made in a child. These were then used to compute the weighted least-squares estimates of the coefficients and their standard errors.

Parallel analyses were conducted in which two features of the method were varied. In one set (Waternaux C, Laird NM, Ware JH: unpublished data), adjustment was made for potential confounders selected empirically (viz., those determined to be responsible for any differences between crude and adjusted estimates of lead's association with Mental Development Index scores.[38] In the other set, unadjusted Mental Development Index scores were subjected to regression, in a one-stage analysis, on the 12 confounders and the lead terms specified in the various models. These alternative approaches produced results equivalent to those obtained in the two-stage analysis that involved adjustment for the 12 confounders listed above. Only the results of the latter sets of analyses are presented.

The algorithm for iterative weighted least-squares regression was programmed with use of the Statistical Analysis System.[53] All P values are two-tailed.

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Low-Level Lead Exposure, Intelligence and Academic Achievement: A Long-term Follow-up Study

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ABSTRACT. The implications of low-level lead exposure for children's intellectual and academic performance at school age are uncertain. This issue was investigated in a prospective study of middle-class and upper-middle-class children with low lifetime exposures to lead. A battery of neuropsychological tests was administered at age 10 years to 148 children whose lead exposure and cognitive function had been previously assessed at ages 6, 12, 18, 24, and 57 months. Primary endpoints were Wechsler Intelligence Scale for Children-Revised (WISC-R) and the Kaufman Test of Educational Achievement (K-TEA). Higher levels of blood lead at age 24 months, but not at other ages, were significantly associated with lower global scores on both the WISC-R and the K-TEA after adjustment for potential confounders. Over the range of approximately 0 to 25 μg/dL, a 0.48-μmol/L (10 μg/dL) increase in blood lead at 24 months was associated with a 5.8-point decline in WISC-R Full-Scale IQ (95% confidence interval: 1.7 to 9.9, $P = .007$) and an 8.9-point decline in K-TEA Battery Composite score (95% confidence interval: 4.2 to 13.6, $P = .0003$). Mean blood lead level at age 24 months was 0.31 μmol/L (6.5 μg/dL; SD: 4.9, 90% percentile: 12.5). Slightly elevated blood lead levels around the age of 24 months are associated with intellectual and academic performance deficits at age 10 years. *Pediatrics* 1992;90:855–861; *lead, intelligence, achievement, neuropsychological toxicology, environmental epidemiology.*

ABBREVIATIONS. WISC-R, Wechsler Intelligence Scale for Children-Revised; K-TEA, Kaufman Test of Educational Achievement-Brief Form; HOME, Home Observation for Measurement of the Environment; GCI, General Cognitive Index; pb24, 24-month blood lead level; CI, confidence interval.

Lead poisoning is considered the most important pediatric environmental health problem in the United States.[1] Blood lead levels in the range of 0.48 to 0.97 μmol/L (10 to 20 μg/dL) have been linked to a variety of adverse health effects[2] and serve as reference points for recent revisions in the screening and treatment protocols recommended by the Centers for Disease Control.[1] The long-term implications of exposures producing blood lead levels in this range remain uncertain, however. In primates, early exposures producing peak blood lead levels of 1.21 μmol/L (25 μg/dL) and steady-state levels of 0.63 μmol/L (13 μg/dL) impair performance up to 10 years later on a variety of cognitive tasks.[3] Some ongoing prospective studies,[4,5] but not all,[6,7] report cognitive deficits at preschool age among children with similar early exposures. The results of another study are mixed.[8] No prospective study has yet reported to what extent any early deficits persist to school age. We report here on the association between early lead exposure and children's intellectual functioning and academic achievement at age 10 years.

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METHODS

Sample

Infants born at the Brigham and Women's Hospital (Boston, MA) between August 1979 and April 1981 were provisionally eligible if the umbilical cord blood lead level was below the 10th percentile (<0.15 μmol/L or 3 μg/dL), approximately at the 50th percentile (0.31 μmol/L or 6.5 μg/dL), or greater than the 90th percentile (≥0.48 μmol/L or 10 μg/dL) ("low," "medium," and "high" prenatal exposure, respectively). Other eligibility criteria included (1) absence of medical conditions associated with developmental handicap, (2) English as the first language, (3) residence in the Boston area (<19 km from The Children's Hospital but not in certain public housing projects), and (4) maternal consent to be contacted.[9] A total of 249 infants were enrolled. Postnatal blood lead levels and development were assessed at ages 6, 12, 18, 24, and 57 months. The base population for the 10-year follow-up assessment was the 169 children from the original sample who were tested at age 57 months.[5] Assessments were completed on 148 children (87.6% of those considered eligible; 59.4% of the original cohort). Nine families refused or repeatedly failed to keep appointments (5.3%), 4 had moved from the area (2.4%), and 8 could not be located (4.7%). The cohort generally consisted of white, intact families with college-educated parents and relatively high-functioning children with low lifetime exposures to lead (Table 1). Compared with eligible families that did not participate in the 10-year assessment, participants tended to be of relatively higher socioeconomic status and to provide slightly more optimal developmental environments for their children.

Neuropsychological Assessment

The children were administered a battery of tests by a psychologist (K.M.S.) who was "blind" to all aspects of a child's developmental and lead exposure histories. In most cases, testing was conducted at The Children's Hospital (Boston) in a single session lasting approximately 3 hours. A second session was required to complete the testing of two children, and seven children were tested in their homes. The mean age (SD, range) of the children at testing was 9 years 9 months (41 days, 9 years 7 months to 10 years 2 months).

Children's Full-Scale IQ scores on the Wechsler Intelligence Scale for Children-Revised (WISC-R)[14] and Battery Composite scores on the Kaufman Test of Educational Achievement-Brief Form (K-TEA)[15] are considered the primary endpoints. The other tests in the battery are considered secondary endpoints, which may shed light on the bases for any exposure-related performance differences on the WISC-R or K-TEA. Analyses of these secondary endpoints will be presented in a separate report.

Measurement of Potential Confounders

Parents completed several questionnaires: medical and educational history of the child, family structure and sociodemographic characteristics, Family Adaptability and Cohesion Evaluation Scales,[16] Social Readjustment Rating Scale,[12] Parenting Stress Index,[17] Children's Life Events Inventory-Revised (modified),[18] and Social Support Network.[19] Based on a brief interview with the parent, the psychologist completed Scales V (Provision for Active Stimulation) and VI (Family Participation in Developmentally Stimulating Experiences) of the Home Observation for Measurement of the Environment (HOME) Inventory (Elementary).[11] Information about many other potential confounders was available in records from previous assessments (eg, maternal IQ, birth weight, HOME scores).

Blood Sampling and Analysis

A Children's Hospital phlebotomist drew 5-mL venous blood samples from 116 children on the day of testing. Samples were not obtained from 32 children because of refusal or because the assessment was conducted at home. A portion of each sample was sent to the Clinical Laboratories of the Children's Hospital for serum ferritin measurement by an immunoenzymatic assay using monoclonal antibodies. The remainder of the sample was sent to ESA Laboratories (Bedford, MA), where blood lead concentration was measured in duplicate using graphite furnace atomic absorption spectrophotometry with Zeeman Background correction using a Hitachi model Z-9000.[20] Quality control samples (low and high bench samples and low and high blind samples provided by the Centers for Disease Control) were included among sample batches to monitor performance of the analytical system.

Mean blood lead level was 0.14 μmol/L (2.9 μg/dL, SD: 2.4, range: 0.5 to 16). Seven additional measures of the children's lead exposure were available: blood lead levels at birth (cord blood), 6, 12, 18, 24, and 57 months, and for 78 children, tooth lead level. Due to the limited data available, no analyses involving tooth lead level are reported. The median correlation among the various blood lead levels was 0.24 (range 0.66 to 0.02).

TABLE 1. Characteristics of Families Participating in 10-Year Assessment

Family social class,* % class 1	58.1
Maternal education, % college graduate	64.9
Paternal education, % college graduate	66.2
Maternal IQ†	125.0 (15.7)¶
HOME‡ total (57 mo)	51.4 (3.7)¶
Sex, % male	50.7
Race, % white	94.6
Birth order, % firstborn	56.1
Life events§	123.2 (107.7)¶
General Cognitive Index‖ (57 mo)	116.0 (14.9)¶
Blood lead history, μg/dL	
57 mo	6.3 (3.8)¶
24 mo	6.5 (4.9)¶
18 mo	7.8 (5.7)¶
12 mo	7.7 (6.5)¶
6 mo	6.7 (7.0)¶
Cord blood, %≥10 μg/dL	28.6

* Hollingshead Four-Factor Index of Social Class.
† Peabody Picture Vocabulary Test.[10]
‡ Home Observation for Measurement of the Environment.[11]
§ Social Readjustment Rating Scale.[12]
‖ McCarthy Scales of Children's Abilities.[13]
¶ Mean (SD).

Statistical Methods

The association between children's lead exposure and their neuropsychological performance was evaluated by multiple regression, adjusting for potential confounders. Because the correlates of a child's blood lead level may change over time, a separate confounder selection process was carried out for each age at which blood lead level was measured. As the endpoint of highest priority, WISC-R Full-Scale IQ score was used to identify correlates of test performance.

The process by which covariates were selected for inclusion in the regression models was based on a combination of empirical and subject matter considerations. The primary goal was to include the variables necessary to obtain an unbiased estimate of the association between lead exposure and performance. Following the recommendation of Dales and Ury[21] and Mickey and Greenland,[22] we considered variables associated with both Full-Scale IQ and a particular blood lead measurement at a P value of .25 or less to be potential confounders. The secondary goal was to increase the precision of the estimate. To this end, we also included factors generally acknowledged to be important antecedents or correlates of cognitive development but which did not necessarily meet the empirical criteria for a confounder[23] (eg, maternal IQ, birth order, sex). The result was a unique set of 8 to 13 variables for each of the seven blood lead measurements. For a given blood lead measurement, the model derived for Full-Scale IQ was employed in the analyses of other endpoints.

To assess the impact of confounder selection strategy, additional regression analyses were conducted, including as confounders factors selected using a change-in-estimate criterion,[24] ie, variables whose addition to the bivariate regression of Full-Scale IQ on lead produced more than a 10% change in the lead coefficient.

Coefficients associated with postnatal blood lead levels represent the estimated change in outcome score (eg, IQ) for each increase of 0.05 μmol/L (1 μg/dL) in blood lead level. Umbilical cord blood lead level was fitted as two indicator variables representing membership in the "low" and "medium" exposure groups. Coefficients represent the estimated differences between the scores of children in these groups and children in the "high" exposure group.

The sensitivity of the models was evaluated in several ways. Standard regression diagnostics were used to identify influential observations,[25] and models were refitted, deleting observations with large residuals or with large impact on either the regression coefficients or fitted values. Various model reduction strategies were explored, including stepwise backward elimination and all subsets (optimal) regression. Model specification was evaluated by examining the impact of including additional variables: terms representing a child's average blood lead level across various age intervals; maximum blood lead level in the first year, the second year, or over the course of the study; interaction terms combining blood lead level and each of the other predictors; measures of marital and maternal psychiatric factors; serum ferritin level; and General Cognitive Index (GCI) score achieved at age 57 months on the McCarthy Scales of Children's Abilities.[5]

All analysis were carried out using PC-SAS.[25] All P values are two-tailed.

RESULTS

Overall Performance

Children's WISC-R and K-TEA scores were approximately 1 SD above the population average. Mean (SD, range) Full-Scale, Verbal, and Performance IQ scores were 119.1 (14.8, 71 to 147), 118.1 (14.9, 67 to 146), and 115.9 (14.2, 78 to 146), respectively. Mean (SD, range) Battery Composite, Mathematics Composite, Reading Composite, and Spelling scores were 118.8 (16.3, 69 to 160), 122.1 (18.7, 70 to 160), 117.0 (14.0, 71 to 140), and 113.5 (17.1, 68 to 153), respectively.

Wechsler Intelligence Scale for Children-Revised

Crude Analyses. All postnatal blood lead levels were inversely associated with Full-Scale IQ measured at 10 years of age, although only the associations in-

volving blood lead levels at age 10 years, 57 months, and 24 months were statistically significant (Table 2). This was also true for both Verbal and Performance IQ scores.

Adjusted Analyses. Adjustment for confounding reduced the magnitude of the coefficients associated with all blood lead levels. The coefficient associated with 24-month blood lead level (pb24) remained significant (Table 2). The decline in children's Full-Scale IQ corresponds to 5.8 points per 0.48 μmol/L (10 μg/dL) increase in pb24 (95% confidence interval [CI]: 1.7 to 9.9 points). Adding pb24 to the covariate model accounted for an additional 3.2% of the variance in Full-Scale IQ scores. The partial regression residual plot indicated that this association was linear across the range of pb24 levels in this cohort. Adjusted mean Full-Scale IQ scores are shown for children in pb24 categories corresponding to 0.24-μmol/L (5-μg/dL) increments (Figure).

Coefficients associated with a child's average blood lead level between 24 and 57 months or between 24 months and 10 years were greater (although less precise) than the coefficient associated with pb24 alone (−0.82, SE = 0.28, P = .004 and −0.86, SE = 0.34, P = .013, respectively, vs −0.58, SE = 0.21, P = .007). The timing of exposure appeared to be more important than magnitude alone. No index of a child's maximum blood lead level during various age intervals (first year, second year, or lifetime) was significantly associated with Full-Scale IQ (coefficients of −0.13, −0.35, −0.20, respectively).

At the 57-month assessment, higher levels of pb24 were associated with lower GCI scores.[5] To evaluate whether the association between pb24 and 10-year Full-Scale IQ was due simply to the high correlation between GCI and IQ in this cohort (r = .71), IQ was adjusted for GCI in addition to the other 11 variables. The pb24 coefficient in this model was −0.42 (SE = .17, P = .018).

The sensitivity analyses indicated that the association between pb24 and Full-Scale IQ was robust to different specifications of the model, to different

TABLE 2. Regression Coefficients Associated With Blood Lead Levels and Children's Wechsler Intelligence Scale for Children-Revised IQ Scores at 10 Years of Age

Blood Lead Measurement*	Crude: Full-Scale IQ	Adjusted†		
		Full-Scale IQ	Verbal IQ	Performance IQ
10 y	−1.53 (0.56)‡	−0.46 (0.52)	−0.59 (0.53)	−0.17 (0.55)
	.008§	.38	.27	.76
57 mo	−0.90 (0.33)	−0.26 (0.29)	−0.07 (0.30)	−0.44 (0.31)
	.008	.37	.80	.16
24 mo	−0.71 (0.25)	−0.58 (0.21)	−0.63 (0.22)	−0.39 (0.23)
	.005	.007	.004	.091
18 mo	−0.28 (0.21)	−0.12 (0.18)	−0.20 (0.19)	−0.00 (0.20)
	.20	.53	.30	.99
12 mo	−0.20 (0.19)	−0.00 (0.16)	−0.13 (0.16)	0.14 (0.17)
	.28	.99	.42	.39
6 mo	−0.20 (0.18)	−0.13 (0.15)	−0.24 (0.16)	0.03 (0.16)
	.29	.39	.14	.83
Cord				
Low‖	−1.29 (3.03)	−0.48 (2.65)	−0.98 (2.69)	0.23 (2.83)
Med¶	−1.52 (3.01)	−2.55 (2.56)	−3.31 (2.61)	−1.21 (2.74)
	.86#	.57	.43	.85

* Age at which blood lead level was measured.

† Variables included in models:

10 years: HOME120 (sum of Scales V and VI of the Home Observation for Measurement of the Environment at age 10 years), family stress, child stress, maternal age, race (white/nonwhite), birth weight, maternal IQ, number of day-care situations through 57 months, HOME57 (total score at 57 months), socioeconomic status (SES), sex, birth order (first, second, third or later), marital status (married/not married)

57 months: HOME120, family stress, child stress, race, maternal IQ, HOME57, SES, sex, birth order, marital status

24 months: HOME120, child stress, maternal age, race, maternal IQ, HOME57, SES, sex, birth order, marital status, number of residence changes prior to age 57 months

18 months: HOME120, family stress, child stress, maternal age, race, maternal IQ, HOME57, SES, sex, birth order, marital status, number of residence changes prior to age 57 months

12 months: HOME120, child stress, race, maternal IQ, HOME57, SES, sex, birth order, marital status, family balance (Family Adaptability and Cohesion Evaluation Scales-III), parent's sense of competence

6 months: HOME120, child stress, race, maternal IQ, HOME57, SES, sex, birth order, marital status

Cord blood: child stress, maternal age, maternal IQ, HOME57, SES, sex, birth order, number of residence changes prior to age 57 months, race.

‡ Regression coefficient (SE), representing the estimated change in score associated with each 0.48-μmol/L (1-μg/dL) increase in blood lead level.

§ Two-sided P value associated with the hypothesis that the coefficient is zero.

‖ Coefficient (SE) associated with membership in the "low" cord blood lead group (<3 μg/dL); reference group is children in the "high" cord blood lead group.

¶ Coefficient (SE) associated with membership in the "medium" cord blood lead group (6 to 7 μg/dL); reference group is children in the "high" cord blood lead group.

Two-sided P value associated with the hypothesis that there are no differences among the scores of children in the three cord blood lead groups.

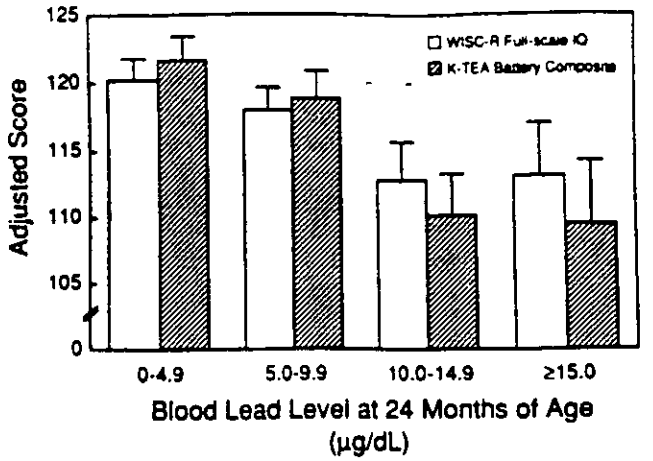

Figure. Mean (± SE) adjusted Wechsler Intelligence Scale for Children-Revised (WISC-R) Full-Scale IQ scores and Kaufman Test of Educational Achievement-Brief Form (K-TEA) Battery Composite scores for children classified by blood lead concentration at age 24 months (pb24). Scores are adjusted for Home Observation for Measurement of the Environment (HOME) score at 10 years (Scales V and VI), total HOME score at 57 months, child stress, maternal age, race, maternal IQ, socioeconomic status, sex, birth order, maternal martial status, and number of family residence changes prior to age 57 months. The number of observations by pb24 stratum are 58 (57 for K-TEA score), 47, 18, and 10 for 0 to 4.9, 5.0 to 9.9, 10.0 to 14.9, and ≥15 μg/dL, respectively.

model reduction or confounder selection strategies, and to the deletion of influential observations. In most analyses, the change in the pb24 coefficient was less than 15%. The largest change was a 40% reduction (−0.58 to −0.34) when observations with large impact on fitted values were deleted.

Pb24 was also significantly associated at $P < .05$ with Verbal IQ and five WISC-R subtest scores (Arithmetic, Comprehension, Similarities, Picture Completion, Block Design) and at $P < .10$ with two others (Vocabulary, Digit Span). It was not significantly associated with Performance IQ. Children with pb24 levels greater than 10 μg/dL were less likely than children with lower levels to have Verbal IQs that were significantly higher (≥ 12 points) than their Performance IQs.[26] No distinct pattern of relative strengths and weaknesses was apparent in subtest scores, however, nor was the amount of scatter in subtest scores (defined as the number of subtest scores deviating from the overall mean subtest score by at least 1 SD)[26] associated with pb24.

Kaufman Test of Educational Achievement

Crude Analyses. Blood lead levels measured at ages 10 years, 24, 18, and 12 months were significantly related to children's Battery Composite scores (Table 3). Each of these blood lead levels was also significantly associated with one or more of the subtest scores (data not shown).

Adjusted Analyses. Only blood lead levels at 24 months of age were significantly associated with adjusted K-TEA scores. Battery Composite score declined 8.9 points for each 0.48-μmol/L (10-μg/dL) increase in pb24 (95% CI: 4.2 to 13.6) (Table 3) (Figure). Including Full-Scale IQ in the model reduced but did not eliminate the association (coefficient = −.51; SE = 0.20, $P = .013$). Exposure-related decreases were also noted in Spelling scores (95% CI: 4.2 to 15.3 points per 0.48-μmol/L increase) and Mathematics Composite scores (95% CI: 3.4 to 14.8 points per 0.48-μmol/L increase). Pb24 was more strongly associated with performance on the more advanced Concepts/Applications items (coefficient = −.24, SE = .08, $P = .004$) than on the Computation items (coefficient = −.08, SE = .05, $P = .099$).

DISCUSSION

The most striking finding in this long-term follow-up study is the continued presence at age 10 years of an association noted at age 5 years between a child's blood lead level at 24 months of age and cognitive function. Terms integrating blood lead level over various intervals beginning at 24 months of age were also associated with children's performance. These associations were evident in broad-based assessments of both intelligence and academic achievement. Because the association between pb24 and IQ was apparent even with adjustment for GCI scores achieved at 57 months, the underlying process may involve more than simple persistence of the performance deficits noted at that time. One possibility is that lead exposure around the age of 24 months has adverse impact on cognition that is not yet fully expressed at age 5 years. A second possibility, not supported by additional analyses, is that different subsets of children were responsible for the associations at the two ages. A third possibility is that this is a measurement artifact stemming from differences in the functional domains assessed by the WISC-R and the McCarthy Scales of Children's Abilities. The associations between pb24 and K-TEA scores were still evident after we adjusted for IQ, suggesting that lead-sensitive behavioral or neuropsychological factors not reflected in WISC-R IQ scores may contribute to reduced performance on academic tasks.

At 24 months of age, children in this cohort had a mean blood lead level of less than 0.34 μmol/L (7 μg/dL), 90% had levels below 0.63 μmol/L (13 μg/dL), and all had levels below 1.21 μmol/L (25 μg/dL). The exposure-related performance differences are approximately twice the size of that observed at 57 months, corresponding to declines of 5.8 and 8.9 points in Full-Scale IQ and K-TEA Battery Composite scores, respectively, for each 0.48-μmol/L (10-μg/dL) increase in pb24. To provide a context for evaluating the relative importance of lead as a predictor of IQ, children whose mothers achieved IQ scores in the top quartile (in this cohort) had IQ scores that averaged 13.4 points higher than those of children whose mothers' IQ scores were in the bottom quartile. IQ scores of firstborn children averaged 9.0 points higher than those of children born third or later.

Children's performance was much more strongly associated with pb24 than with blood lead levels at other ages. It is unclear whether this reflects a special vulnerability of the nervous system during this period[27] or simply the fact that blood lead level tends to peak in the second year.[4,6–8] Our finding that pb24 was more predictive of performance than was maxi-

TABLE 3. Regression Coefficients Associated With Blood Lead Levels and Children's Kaufman Test of Educational Achievement-Brief Form Scores at 10 Years of Age

Blood Lead Measurement*	Crude: Battery Composite	Adjusted†			
		Battery Composite	Mathematics Composite	Reading Composite	Spelling
10 y	−1.43 (0.63)‡ .025§	−0.44 (0.61) .47	−0.46 (0.71) .52	−0.71 (0.54) .19	−0.24 (0.73) .74
57 mo	−0.80 (0.37) .033	−0.16 (0.34) .64	0.00 (0.41) .99	−0.15 (0.31) .62	−0.35 (0.41) .40
24 mo	−1.09 (0.27) .0001	−0.89 (0.24) .0003	−0.91 (0.29) .002	−0.38 (0.21) .078	−0.97 (0.28) .0008
18 mo	−0.47 (0.24) .050	−0.28 (0.21) .19	−0.31 (0.25) .22	0.08 (0.19) .65	−0.44 (0.25) .077
12 mo	−0.50 (0.21) .018	−0.34 (0.19) .076	−0.40 (0.23) .083	0.08 (.17) .65	−0.41 (0.22) .067
6 mo	−0.14 (0.21) .50	−0.00 (0.18) .99	−0.11 (0.22) .61	0.02 (0.16) .89	0.09 (0.21) .67
Cord					
Low‖	−0.43 (3.32)	0.76 (3.06)	−0.88 (3.62)	−0.35 (2.69)	1.72 (3.58)
Med¶	0.65 (3.36) .95#	−1.55 (2.99) .74	−2.16 (3.55) .83	−3.34 (2.64) .38	−0.44 (3.51) .81

* Age at which blood lead level was measured.
† Adjustment made for the same variables listed in footnote † of Table 2.
‡ Regression coefficient (SE), representing the estimated change in score associated with each 0.48-μmol/L (1-μg/dL) increase in blood lead level.
§ Two-sided *P* value associated with the hypothesis that the coefficient is zero.
‖ Coefficient (SE) associated with membership in the "low" cord blood lead group; reference group is children in the "high" cord blood lead group.
¶ Coefficient (SE) associated with membership in the "medium" cord blood lead group; reference group is children in the "high" cord blood lead group.
# Two-sided *P* value associated with the hypothesis that there are no differences among the scores of children in the three cord blood lead groups.

mum blood lead level supports the hypothesis of an age-specific vulnerability.

Alternatively, the apparent importance of pb24 as a predictor may be due to methodological factors such as differences in the power of hypothesis tests involving blood lead levels measured at different ages. The extremely low levels, restricted range, and smaller number of 10-year blood lead values reduced the likelihood of finding an association between current exposure and performance. Analyses involving all other postnatal blood lead levels had about 80% power to detect roughly the same effect size (f^2 = .065 to .073 in Cohen's[28] terminology). Other considerations are relevant to this issue, however. The coefficient of variation was substantially greater for pb24 than pb57 (75.0 vs 60.4), suggesting that a greater proportion of the observed variation in pb24 than pb57 reflects differences in children's exposures rather than analytical variation, which was relatively constant over time. Moreover, unlike blood lead levels at 57 months and 10 years, pb24 was not strongly associated with sociodemographic characteristics and psychosocial environment.[29] Nevertheless, our finding that, after adjustment for confounding, only blood lead level measured at 24 months was significantly associated with children's function should be interpreted cautiously until confirmed by other studies.

The association was robust to changes in analytical strategy and model composition. Although we cannot exclude the possibility that confounding by some unmeasured or inadequately measured variables produced a spurious association, the estimated decline in children's scores with increasing pb24 was relatively unaffected by adjustment for a variety of factors germane to the psychological, emotional, and intellectual climate within a family. Nevertheless, measures of such factors are fallible. To the extent that these factors are true confounders and the instruments failed to measure them accurately, our adjustment for confounding bias is incomplete.

Another factor to be weighed in evaluating these results is the possibility of bias in terms of the children available for follow-up. The key issue is whether the associations we observed between lead exposure and development among participants are similar to those we would have observed had we been able to evaluate the entire cohort. We determined that the estimated associations noted at earlier assessments between cord blood lead level and Mental Development Index Scores at 6, 12, 18, and 24 months of age were comparable among children who participated in the 10-year follow-up and those who did not. The degree of similarity in the relationship between pb24 and GCI scores at 57 months is more uncertain because of the relatively small number of children lost to follow-up between 57 months and 10 years. Although the coefficients for participants and nonparticipants were not significantly different, the association between pb24 and performance at 10 years may have been somewhat diminished had we achieved 100% follow-up.

Analyses of WISC-R subtest scores indicated that pb24 was most strongly related to children's scores on verbally mediated tasks. In contrast, at age 57

months pb24 was more strongly associated with nonverbal skills. Verbal deficits among children with higher pb24 levels may not have been apparent at 57 months because of the relative insensitivity of the language assessments available for evaluating children at that age, greater compensatory effects of environmental stimulation on language performance at younger ages, or both. Alternatively, a common underlying neurological substrate (eg, attention, state) that affects performance on psychometric tests may be expressed differently over time. This hypothesis is speculative, although, other follow-up studies have reported that the behavioral and developmental correlates of early biological insult may change over time.[30]

There is little evidence that lead exposure has a distinctive "behavioral signature." Measures of lead exposure have been significantly related to both Verbal and Performance IQ,[31] only Verbal IQ,[32-36] only Performance IQ,[37,38] or neither.[39-43] Findings are also inconsistent with respect to lead and academic achievement.[33,34,39,41-44] The explanation for this is not clear, although differences in study power may be contributory.[45] In addition, the manner in which toxicity is expressed may depend on a number of factors, including the timing and level of exposure, its chronicity, and other aspects of a child's developmental context.[46] Retrospective and cross-sectional studies provide only limited opportunities to discern associations between specific characteristics of exposure history and neuropsychological outcome.

At present, other prospective studies provide only partial support for our findings.[4-8,47] It is unclear whether this reflects instability of the association between lead exposure and development, methodological differences among studies, or both. The cohorts being followed differ substantially in terms of exposure characteristics. On the basis of toxicokinetic principles, different patterns of associations between exposure and function should be expected.[48] Functional deficits have consistently been noted at lower blood lead levels in our cohort than in the others. We attribute this, at least in part, to the low background risk of intellectual handicap in this cohort relative to others.[49] Most US lead studies focus on poor inner-city children for whom lead exposure is only one of many developmental risk factors. The high socioeconomic standing of our cohort may have provided us greater opportunity to perceive lead-related variance in cognitive function. It may also restrict the population to which our findings may be generalized. Early insults tend to be expressed more severely among populations at high socioeconomic risk.[50] The associations we observed may underestimate those that, with adequate control of confounding, would be observed in a group more representative of children with higher levels of lead exposure.

In summary, this follow-up study of socioeconomically advantaged children with relatively low lifetime exposures to lead suggests that slight elevations of blood lead at around the age of 2 years are associated, without an apparent threshold, with significant decrements in intellectual and academic performance at 10 years of age.

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FAT FACTS

McDonald's merits praise for introducing a lower-fat version of its large hamburger. But by promoting its new "McLean Deluxe" as "91% fat free," it reinforces the trend of using misleading fat-free claims.

Such claims, expressing fat content as a percentage of weight, are a powerful selling tool in a health-conscious market. But much of the weight may be water, so the implication that a product is low in fat can be deceptive. The McLean's 9 percent fat content, for example, though only about half that of standard burgers, still packs 10 grams of fat—five times the FDA definition of low fat.

McDonald's is hardly the only offender. Misleading percentage claims are a marketing ploy for fat-laden products ranging from frozen sausages and french fries to ice cream. The FDA could help consumers by immediately calling for a moratorium on such claims, even while the agency prepares new restrictions to carry out last year's Federal nutrition labeling reform.

Fat facts. *The New York Times.* April 23, 1991.

Submitted by Kurt Metzl, MD

COMMENTARY

Opinions expressed in this commentary are those of the authors and not necessarily those of the American Academy of Pediatrics or its Committees.

Lead Toxicity in the 21st Century: Will We Still Be Treating It?

Clinical pediatric practice has not kept pace with the explosive growth in scientific understanding of lead poisoning during the past decade. The report by Glotzer and Bauchner in this issue[1] demonstrates the widely differing approaches to treatment of lead toxicity found at many centers. Primary prevention of lead poisoning, the most effective response, continues at a pedestrian pace, even though in the United States we now possess both the knowledge and means to eradicate the disease permanently.

Our understanding of lead's role in human health has changed profoundly during the past five decades. In that period, pediatricians have discarded the once widely held belief that affected children either died or recovered completely from lead poisoning. They now are confronted with data demonstrating that 3 to 4 million lead-exposed children, most of whom have no symptoms, may have impaired neurobehavioral function.[2] This new information has drawn the Public Health Service to declare that "Lead Poisoning remains the most common and societally devastating environmental disease of young children."[3]

In 1988, the Agency for Toxic Substances and Disease Registry issued "The Nature and Extent of Lead Poisoning in Children in the United States: A report to Congress."[2] This historic report estimated that 16% of *all* American children have blood lead levels in the neurotoxic range. Being well off does not protect children against lead hazards; 7% of economically favored white children were estimated to have blood lead levels greater than 15 μg/dL. But being poor radically increases the risk; 55% of African American children in poverty have blood lead levels greater than 15 μg/dL. There is no other serious disease with this prevalence. It is a disgrace that more than half of the Black children in poverty in the United States enter the first grade with this preventable handicapping condition. It is also a real danger to the polity.

As a result of these data, the announced federal strategy has shifted from finding cases and then treating them, to finding the toxicant in the environment, removing it, and breaking the exposure link. On February 21, 1991, Dr James Mason, the Assistant Secretary of Health, issued the "Strategic Plan to Eliminate Childhood Lead Poisoning."[4] This initiative represents the first authentic step toward primary prevention.

As recently as 1969, a blood lead less than 60 μg/dL was thought to be safe. In 1970, the Surgeon General reset the definition of toxicity from 60 μg/dL to 40 μg/dL. Many studies, beginning early in the 1970s, showed that lead at "silent" levels was associated with deficits in psychometric intelligence.[5] Once thought to be exclusively a disease of inner city African-American children, the impact of lead exposure on intelligence came under international study. As a result, in the 1980s, well-designed and well-executed investigations from Scotland, Denmark, Greece, Italy, Germany, England, Australia, and New Zealand reported effects of lead on children's IQ, academic achievement, and behavior.[6–13] These studies, which capitalized on previous work, tended to use larger samples, better outcome measures, better covariate control, and more sophisticated multivariate models.

Not all studies report an effect; some reviewers, after counting the number of positive and negative reports, have concluded that the issue of silent lead neurotoxicity is still a matter of controversy. It is important to recognize that simple tallies of studies are weak and unsatisfactory ways to draw conclusions from a group of investigations. If there were no effect of lead on children's IQs, one would expect about one study in 20 to report an association on the basis of chance. In fact, more than half of the published studies show an effect at $P < .05$. Meta-analysis, a quantitative approach to synthesis, offers a stronger method to draw conclusions from a group of studies. Three recent meta-analyses all showed a strong effect of lead on IQ.[14–16]

Do children have elevated blood lead levels because of preexisting intellectual deficit? Is lead an effect rather than a cause? These questions were answered by prospective studies of children from birth onward. These showed that prenatal lead levels, or early infancy lead levels, were related to latter psychologic scores,[12,17,18] after adjustment for other variables such as maternal IQ and socioeconomic status.

These findings prompted the Centers for Disease Control to lower the definition of lead toxicity to 30 μg/dL in 1978, and then to 25 μg/dL in 1985.[19] This was a contentious process, and on both occasions the lead industry attempted to retard the decision making.[20] The Centers for Disease Control Advisory Committee now has reviewed the latest data and has concluded that lead toxicity is found at levels of 10 μg/dL and that the effect may occur at levels below this.[21]

This new standard raises difficult questions for the clinician. The first is how to implement lead screening

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in practice. Many pediatricians serving middle class patients believe that lead exposure has too low a prevalence to warrant the expense. Yet tuberculosis tine tests, phenylketouria, and galactosemia screening are conducted routinely in busy practices, even though the prevalence of these diseases is less than 1/10 000. In the average pediatric practice of 3000 children, if the prevalence of blood lead levels greater than 25 μg/dL is 0.5% and those greater than 10 μg/dL is 3%, 15 children with blood leads greater than 25 μg/dL and 90 children with blood lead levels greater than 10 μg/dL can be expected. This may be a conservative scenario. A random survey of a racially and economically diverse private practice in a midwestern city recently showed that 22% of the patients had blood lead levels greater than 15 μg/dL, and 3% had blood lead levels greater than 25 μg/dL (T. Schlenker, MD, personal communication, Dec 16, 1991).

Clinicians are reluctant to screen because, at levels of lead less than 25 μg/dL, no pharmacologic treatment is currently available. Management of lead exposure is not limited to prescribing drugs. The pediatrician has much to offer: testing siblings; finding the source; detection of risky behaviors such as pica, nail biting, or finger sucking; education about the hazards and control of lead in paint, dirt, dust, and water; nutritional counseling; and finally, systematic follow-up. A child with a blood lead level between 10 and 14 μg/dL should be retested at 3-month intervals to determine if the level is rising.

Another reason is the nature of the screening test for lead. The Free Erythrocytic Protoporphyrin test has no screening value for blood lead levels less than 25 μg/dL. Venous blood lead levels are reliable in reflecting actual body burdens, but phlebotomy of 1-year-olds is difficult. Capillary blood lead tests using a finger stick require scrupulous quality control; contamination must be avoided, and venous blood follow-up is needed to eliminate false positive results. X-ray fluorescence of bone lead, as well as micromethods for detecting erythrocyte lead levels, are on the research horizon and should enhance the ease of lead screening.

Some clinicians cite the lack of environmental health and housing resources as reasons not to screen. When no children are screened, no cases are found, and the myth that there is no lead problem becomes fixed. When screening is put in place, community lead problems have been identified consistently.

Glotzer and Bauchner[1] show that the choice of treatment and the criteria for instituting it vary widely across institutions. There are many reasons for this. Most prominent is the lack of data about the efficacy of chelation at levels of lead, that while toxic, are not associated with severe symptoms. It is startling to realize that 48 years after the introduction of chelation therapy with edathamil ($CaNa_2EDTA$),[22] we still do not know if it conveys any benefits to children with moderate elevations of blood lead. Nor do we know the long-term consequences of penicillamine therapy. A new oral chelating agent, succimer, chemically related to British anti-lewisite, has been released by the Food and Drug Administration. It is a safe bet that unless a multicenter trial of all three agents, with a rigorous randomized design and standard set of outcome measures is conducted, the current *Laissez faire* intuitive approach to chelation will continue, and that our successors will know as little about the benefits and hazards of these drugs as we do today. There are no data on the long-term effects of succimer on blood lead levels.

Succimer has been approved for use in children with blood lead levels greater than 45 μg/dL, but many pediatricians are already using it at lesser concentrations. Administration of succimer should not be considered a substitute for environmental control; the drug must not be administered until the patient has been separated from the source of lead. Because the drug is administered orally, many physicians will be tempted to give it on an outpatient basis, and there is already some evidence that insurance carriers are encouraging this. It is dangerous to give an oral chelating agent while the child continues to reside in the presence of lead.

The current experience with this agent is less than 200 cases, and the postmarket surveillance protocol issued by the manufacturer cannot be described as rigorous. In the face of limited experience, statements about the lack of side effects must be considered tentative and subject to revision. To rely on physicians' reports of untoward effects of any agent is to accept a notoriously weak scheme of detection. Physicians who employ succimer should inquire carefully for allergic reactions, neutropenia, and test renal and kidney function at regular intervals.

Treatment begins and ends with removing lead from the child's environment, and the most important source is old leaded paint. Removing lead safely from houses takes time and trained workers. The residents should not be on the premises while the work is carried out.

Finding and treating patients can only be thought of as a temporary response to a problem of such dimensions. The Centers for Disease Control Strategic Plan to Eliminate Childhood Lead Poisoning[4] outlines the first 5 years of a 15-year effort to reduce the prevalence rate to zero. But at this time the Plan is merely an important document, and will remain so until the required steps to implement it have been put in place. The costs of such an effort are formidable, and will be counted in billions of dollars. There are four lead bills in congress requesting additional funds for lead control. It is critical that the Administration, having declared that it considers lead at the top of the list of serious environmentally related childhood diseases, provide the federal funds to match its rhetoric.

We will not end this man-made epidemic until we understand the reasons for its curious persistence in the face of considerable data about what lead does, and what is needed to rid ourselves of it. Among the reasons for desultory attention to this epidemic is the stubborn belief that this is an affliction of only poor minority children. Related is the tendency on the part of some to blame the mother's rearing style for the elevated blood lead. Many people believe that with the passage of the Lead Paint Poisoning Prevention

Acts, and the removal of lead from gasoline, the problem somehow disappeared. Academic pediatrics, with some exceptions, has not found this commonplace low technology malady as fascinating as molecular disorders. Most academic pediatric departments give more attention, resources, and urgency to much rarer diseases. Private pediatric practitioners generally believe that this is not a problem for their patients. The lead industry since at least as early as 1939 has worked to obscure the effects of lead on human health; this practice continues today. Finally, the size of the problem and the amount of dollars and effort involved result in a reflex wave of pessimism. Self-styled realists, when confronted with a 10-billion-dollar estimate to delead and improve the 2 million dangerous houses in which children live and the paint is peeling, shrug and turn away.

The Centers for Disease Control Strategic Plan[4] contains an econometric analysis of the costs and benefits of lead prevention. The Plan estimates the costs for deleading homes and the benefits that accrue from reduced need for medical care, for special education and the increase in wages that goes with having a higher IQ. The model does not include other potentially related benefits such as increased tax returns, reduced spending for delinquency, and reduced medical costs for hypertension and cardiovascular disease. The conclusion of the analysis, described as conservative by Centers for Disease Control, is that the net return to our society for deleading the housing stock in the United States would be $28 billion more than the costs of the abatement.

It should not be necessary to place a price tag on the eradication of a serious childhood illness; the presence of the disease and owning the means to eliminate it should be enough. But this is the era of self-satisfied pragmatism, and metrics are often required to justify undertaking moral actions. The eradication of lead, this blunter of children's cognition and silent thief of their futures, meets the pragmatic test. The numbers are clear; it makes unequivocal fiscal sense to make this investment in human capital, and in achieving this end, we might learn something important about our ability to control our personal destinies.

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Childhood Lead Poisoning: A Disease for the History Texts

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Editorials

Childhood Lead Poisoning: A Disease for the History Texts

The sources of lead are both manifold and ubiquitous. Wiesel et al. in their brief paper published in this issue of the journal,[1] identify a previously unrecognized source to add to the list. They report that the amount of lead in the pigment of bread wrappers taken from store shelves ranges from 0 to 84 mg per bag, with a mean of 23 mg. For environmental or economic reasons, some families recycle these bags as food containers; some consumers turn the bags inside out when they reuse them. Diluted acetic acid applied to the wrappers in the laboratory leaches lead rather rapidly. Even so, bread wrappers are probably not a noteworthy health risk; bread is considerably less aggressive than vinegar. A more serious issue is the insertion of lead into the ecosystem through this source. The estimated contribution to the waste stream from bread bags is about 0.8 metric tons of lead per day. Some of this will find its way into incinerators and enter the atmosphere. This is an incremental dose that we do not need. Lead pigments for food container labels should be banned. We strongly assert that this toxin should not be employed in any activity where complete recovery is not possible or where an adequate substitute exists.

Of all the sources of lead for children, paint remains the most important. There are 30 million homes in the United States that have leaded paint surfaces. Young children live in 3 million homes that have peeling deteriorated leaded surfaces. These houses are the equivalent of the pest houses of Dickens' England. Each child in one of these homes must be considered at immediate risk for lead-engendered brain poisoning.

In recent months federal policy regarding lead has undergone a historic change. This is because the current body of scientific data about lead—where it is, what it does, and what is needed to eliminate it—has become too vast and convincing to be disregarded. The USEPA Air Lead Criteria Document of 1977 is 200 pages long. The same document for 1986 is four times that size and has two separate lengthy appendixes.

Many well-conducted epidemiologic studies of low-level lead exposure in children have been reported in recent years. Almost all conclude that lead is associated with disturbances in cognition, behavior, and attention at levels below those that cause frank symptoms. A recent meta-analysis of all 24 modern studies[2] showed that the joint *P* value of the included studies was well below .0001. This joint probability was not influenced by any single study. When an analysis of whether unpublished negative studies could change the inference was done, this question, known as the "file drawer problem," was effectively dismissed. To dilute the joint probability, there would have to be 93 unpublished (and unknown) negative studies languishing in the files of investigators somewhere.

The experimental literature on low-level lead intoxication is huge and continues to show lead effects at lower and lower doses in systems previously not recognized as lead targets. A few recent examples suffice to demonstrate the span of lead effects: Lead affects tRNA structure,[3] the development of the endogenous opioid system,[4] and brain protein kinase C at extremely low concentrations.[5] Studies of immature monkeys that were given lead at doses congruent with human exposure

Editor's Note: See also related article on page 756 of this issue.

have shown behavioral changes closely modeling the human findings.[6]

The Agency for Toxic Substances and Disease Registry reviewed the newer data on lead toxicity as well as the National Center for Health Statistics exposure data. The agency updated the data to reflect secular changes in blood lead levels and estimated that 3 to 4 million children have toxic levels of lead in their blood.[7]

The federal definition of lead toxicity is now 10 μg/dl. The new definition puts an extraordinary number of children at neurotoxic risk. These data indicate that 17% of all children, regardless of race or socioeconomic status, have blood lead levels in the toxic range. Being white and well off does not shield a child; but being poor or black radically increases the risk. Over 50% of black children in poverty enter the first grade with elevated blood lead levels considered neurotoxic. Our society will ignore this datum at peril to its survival.

In recognition of this rapidly changing but compelling picture of lead poisoning, the Department of Health and Human Services made a major departure from previous policy in its response to the problem. On February 21, 1991, in the United States Senate, Assistant Secretary of Health James Mason announced a plan to eradicate childhood lead poisoning.[8]

The plan has four essential elements: abatement of leaded paint in high-risk housing; expansion of prevention activities; reduction of exposure from food, water, air, soil, and the workplace; and finally, the establishment of a national surveillance for children. None of these measures are new; what is new is the federal commitment not to simply control the disease or to reduce the prevalence, but to drive the rate close to zero. This kind of vision could only have come from a Centers for Disease Control veteran. The CDC has known success in disease eradication; in 1963 this agency directed the World Health Organization program that erased smallpox from the face of the earth.

The CDC strategic plan anticipated critics' arguments that this was too expensive an enterprise. The plan examined the monetized benefits of lead prevention in these areas: reduction in medical care costs, reduction in special education costs, reduction in lost productivity due to cognitive deficits, and reduction in neonatal mortality due to lead exposure. Other important effects of lead not entered into the model were effects on stature and renal function and the effects of hypertension and anemia. Nor were the monetized benefits of increased employment and improved housing estimated.

By CDC's own accounting, the estimates staff members made are conservative. They estimate that the avoided medical costs from preventing a child's blood lead level from reaching 25μg/dl are $1300. The avoided special education costs per child are $3331. The econometricians then calculated the change in wage rate for a 1μg/dl in blood lead level at 0.125%. This was predicated on a .25 point IQ decrement per μg/dl blood lead increase and a 0.5% decrease in wage rate for each IQ point decrease. Using similar techniques, they estimated the decline in wage rate for decreased educational attainment (0.197%) and for decreased labor force participation for failure to graduate from high school (0.118%). The monetary benefit for decreased infant mortality was calculated to be $300 per μg/dl decrease in blood lead level. Using these data, they then estimated the total benefits for abatement of a single dwelling over its lifetime at $4323 per unit. The analysis reaches a startling conclusion: the net benefit in dollars gained over costs from abatement is $2098 per unit abated. This meticulous analysis is a powerful counter to those who argue that the effective abatement of leaded houses is too expensive for our society to support.

Given that lead toxicity is no secret and that more data documenting this toxicity are available than for any other neurotoxin, one is compelled to ask why so little real prevention has occurred until now. There are many factors that have retarded progress in eliminating this disease. They continue to operate. First is the enduring belief that this is a problem only for poor inner city black children. Related to this is the assertion that the mother's inferior care is responsible for the child's lead exposure and poor learning ability. Society has always been myopic about the problems of poor minorities, and once the mother has been blamed for the problem, official consciences can rest. In addition, academic medicine has not been charmed by the problem of plumbism; it does not carry the intrigue of molecular biology or the drama of major organ transplantation. There are no airlines taking lead-poisoned children to Disney World or corporate jets taking them to hospitals to save their lives.

Some authorities believe that the passage of the Lead Paint Poisoning Prevention Acts and the removal of lead from gasoline eliminated the disease. This is, of course, not true. The lead industry and its academic spokespersons have labored mightily to obscure the health effects of lead. This is not a new phenomenon: Rosner and Markowitz[9] and Rabin[10] detailed in this journal the influence of the industry in camouflaging the toxic properties of lead.

The inactivity of some government agencies—and here CDC is notably excepted—has contributed to the sluggish pace of official action. In the past, the Department of Housing and Urban Development (HUD) has been the worst offender. After HUD was assigned the task of estimating the size and nature of the lead problem in 1972, its staff discovered that meeting the agency's responsibility to remove lead from houses would cost $30 billion. This launched HUD onto a furious effort to assign the blame for lead poisoning to any source but paint. Their attempts to obscure the risks of leaded housing were so egregious that they became the subject of a GAO report entitled "HUD Not Fulfilling Responsibility to Eliminate Lead Based Paint Hazard in Federal Housing."[11] HUD has continued to run from its responsibility to reduce lead poisoning in its properties. In response to the announcement of the Strategic Plan, an assistant secretary for research at HUD was quoted as saying that more money to abate housing was not needed, that funds were available for home rehabilitation, but that people had simply not applied for them.[12] This is not a new refrain; many readers will remember a president who, when asked about urban homelessness and unemployment, held up the help wanted pages of the *Washington Post* in rebuttal.

The final reason for the lack of action over lead is perhaps the most intractable. Whereas many think the disease has been eradicated, a perhaps even larger number think the problem is too large to handle. The idea that millions of children may suffer lead intoxication and that millions of houses are in need of abatement produces a reflex wave of pessimism. Self-styled realists will argue that this is too expensive and that society could never find the money for such an enterprise.

But the eradication of lead poisoning presents a unique opportunity to address many of the other urban pathologies that afflict our nation. To abate the 3 million houses that house children will require a large labor force, and there is no shortage of men who cannot find work, men living in precisely those areas where lead is in excess. The removal of this toxin could provide an opportunity to put people back to work restoring houses while creating

decent living conditions for people. It is reasonable to ask whether we can afford *not* to mount this effort.

In 1963, when the executive secretary of the World Health Organization was approached with a plan to eradicate smallpox, he scoffed. Because he believed such an attempt would be doomed to failure, he requested that an American be asked to direct the project and thus take the heat for its failure. Dr. Donald Henderson and CDC accepted the challenge, and today smallpox is a disease for the history books. Lead poisoning, this silent, relentless destroyer of brain cells, can have the same fate if we have the same kind of vision. □

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Low-Level Lead Exposure and the IQ of Children

A Meta-analysis of Modern Studies

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We identified 24 modern studies of childhood exposures to lead in relation to IQ. From this population, 12 that employed multiple regression analysis with IQ as the dependent variable and lead as the main effect and that controlled for nonlead covariates were selected for a quantitative, integrated review or meta-analysis. The studies were grouped according to type of tissue analyzed for lead. There were 7 blood and 5 tooth lead studies. Within each group, we obtained joint *P* values by two different methods and average effect sizes as measured by the partial correlation coefficients. We also investigated the sensitivity of the results to any single study. The sample sizes ranged from 75 to 724. The sign of the regression coefficient for lead was negative in 11 of 12 studies. The negative partial *r*'s for lead ranged from −.27 to −.003. The power to find an effect was limited, below 0.6 in 7 of 12 studies. The joint *P* values for the blood lead studies were <.0001 for both methods of analysis (95% confidence interval for group partial *r*, −.15 ± .05), while for the tooth lead studies they were .0005 and .004, respectively (95% confidence interval for group partial *r*, −.08 ± .05). The hypothesis that lead impairs children's IQ at low dose is strongly supported by this quantitative review. The effect is robust to the impact of any single study.

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THE NEUROTOXIC properties of lead at high doses have been recognized for at least a century and are not a matter of dispute. In 1943, Byers and Lord[1] first suggested that childhood exposure to doses of lead insufficient to produce clinical encephalopathy was associated with deficits in psychological function. The question of low-level lead exposure has been studied widely over the past two decades and, in contrast to high-dose lead exposure, has been the source of considerable contention. Several methodological difficulties encountered in the conduct of these studies have contributed to the controversy. Among them are (1) selecting adequate markers of exposure or internal dose, (2) measuring outcome with instruments of adequate sensitivity, (3) identifying, measuring, and controlling for factors that might confound the lead effect, (4) recruiting and testing a sample large enough to provide adequate statistical power to detect a small effect, and (5) designing a study that avoids biases in sample selection.

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A number of reviews of studies on the effects of low-level lead exposure on the neuropsychological function of children have been published.[2-5] The outcome of major focus in these reviews has been psychometric intelligence. The general approach was to provide narrative summaries in which the epidemiologic and statistical issues often received limited critical attention. Where quantitative synthesis was attempted, it consisted of a simple tally of those studies showing statistically significant effects (at the .05 level) vs those that did not. This approach gives undue emphasis to the individual study's *P* value and attaches equal weight to all studies without regard to their specific merits or flaws. The size of the effect measured in each study is generally ignored in the process.

The statistical techniques that have been subsumed recently under the rubric of meta-analysis offer a framework within which formal research synthesis can be conducted with more clearly defined methods and criteria.[6-9] In this approach, individual studies are treated as data points in a larger "meta-study." Summary measures from each study are pooled by one of a number of techniques, and quantitative inferences are drawn about the research questions of interest. The difficulties entailed in combining dissimilar studies ("apples and oranges") is a concern for any meta-analysis.[6,8] It points to the need for some measure of commonality in the studies that are being combined. At the same time, the usefulness and novelty of meta-analysis lies in the fact that it enables the investigator to combine the results of studies that *differ* in several respects, while addressing the same research questions.

The first meta-analysis of six lead-IQ studies was reported by Schwartz et al[10] in 1985. They used Fisher's aggregation technique to calculate a joint *P* value of .004 for the effect of lead on IQ in the six studies. Needleman and Bellinger[11] extended the analysis by Schwartz et al and also used Fisher's technique on pooled tooth and blood lead studies.

In the last few years, a substantial number of new epidemiologic studies from various nations, using more refined designs, larger sample sizes, and more sophisticated statistical techniques, have been reported. This presents an opportunity for a more comprehensive meta-analysis. Herein, 12 recent studies are reviewed and a quantitative synthesis of their results is presented. The major outcome of interest is full-scale IQ, although many studies also examined the effects of lead exposure on important functions such as school performance, reading ability, and classroom behavior. All studies reviewed employed multiple regression analysis in which the dependent variable (IQ) was treated as continuous. Lead exposure was classified by one of two methods: blood or tooth lead level. In contrast to earlier attempts, this analysis divides the studies by tissue analyzed and combines inferences within tissue groups. The question of possible bias in the obtained sample of studies (known as the "file drawer" problem) is addressed. Moreover, the aggregate effect of the exclusion criteria is assessed by performing an analysis that combines all of the initial 24 studies. The sensitivity of the results of this meta-analysis is further investigated by eliminating each of the included studies, one at a time, from the analysis and observing how this affects the conclusions. The statistical power of each study to find an effect is also computed.

This article presents a discussion of some methodological difficulties encountered in the studies reviewed, examines the critical question of effect assessment in pollutant studies, and concludes with comments on the difficulties entailed in drawing causal inferences from observational studies of lead exposure and intellectual development.

Table 1.—Candidate Studies for Meta-analysis*

Study	Year	No. of Subjects	Tissue	Lead Level†	Data Analysis	Included/Reason for Exclusion	Comments	Lead Effect, $P<.05$
Kotok[12]	1972	C = 25; E = 24	Blood	C = 38; E = 81	*t* test	No/G,D	A, B	No
Perino and Emhart[13]	1974	C = 50; E = 30	Blood	C<30; E = 40-70	Multiple regression	No/H	...	Yes
Rummo et al[14]	1979	C = 45; E = 45	Blood	C = 23; E = 61-88	ANOVA	No/G,D	A	Yes
de la Burde and Choate[15]	1975	C = 67; E = 70	Blood	R = 30-100	χ^2	No/D,E,G	C	Yes
Landrigan et al[16]	1975	C = 78; E = 46	Blood	C<40; E = 40-68	*t* test	No/D,E	...	Yes
McNeil et al[17]	1975	C = 37; E = 101	Blood	C = 29; E = 59	*t* test	No/D	E, G, H	No
Yamins[18]	1976	80	Blood	$PbB\bar{x} = 33.2 \pm 9.1$	Multiple regression	No/E	A, B	Yes
Kotok et al[19]	1977	C = 36; E = 24	Blood	C = 38; E = 81	*t* test	No/G,D	A, B	No
Ratcliffe[20]	1977	C = 23; E = 24	Blood	C = 28; E = 44	*t* test	No/E	A, B	No
Needleman et al[21]	1979	C = 100; E = 58	Tooth	PbC = 24; PbE = 36; PbTC≤10; PbTE≥20	ANCOVA	No/H	...	Yes
Yule et al[22]	1981	166	Blood	C≤13; E = 13-32	Multiple regression	Yes	...	Yes
Winneke et al[23]	1982	C = 26; E = 26	Tooth	$PbTC\bar{x} = 2.4$; $PbTE\bar{x} = 9$	*t* test	No/D	A	No
McBride et al[24]	1982	108	Blood	C = 2-9; E = 19-29	ANOVA	No/D,E	...	No
Smith et al[25]	1983	402	Tooth	$PbT\bar{x} = 5.1 \pm 2.8$	ANCOVA	No/H	...	No
Winneke et al[26]	1983	115	Tooth	$PbT\bar{x} = 6.2$; $PbB\bar{x} = 14$	Multiple regression	Yes	...	No
Harvey et al[27]	1984	48	Blood	R = 6.2-26.8	Multiple regression	No/F	A	No
Shapiro and Marecek[28]	1984	193	Tooth	R = 30-150	Multiple regression	No/E	...	Yes
Needleman et al[29]	1985	218	Tooth	$PbT\bar{x} = 12.7$	Multiple regression	Yes	...	Yes
Emhart et al[30]	1985	80	Blood	C = 30; E = 40-70	Multiple regression	Yes	A	No
Schroeder et al[31]	1985	104	Blood	Median = 30	Multiple regression	Yes	...	Yes
Hawk et al[32]	1986	75	Blood	$PbB\bar{x} = 21$; R = 6-47	Multiple regression	Yes	A	Yes
Lansdown et al[33]	1986	C = 80; E = 80	Blood	C = 7-12; E = 13-24	Multiple regression	Yes	...	No
Hatzakis et al[34]	1987	509	Blood	$PbB\bar{x} = 23$; R = 7-63	Multiple regression	Yes	...	Yes
Pocock et al[35]	1987	402	Tooth	$PbT\bar{x} = 5.1 = 2.8$	Multiple regression	Yes	...	Yes
Fergusson et al[36]	1987	724	Tooth	$PbT\bar{x} = 6.2 = 3.8$	Multiple regression	Yes	...	No
Fulton et al[37]	1987	501	Blood	GM = 11.5; R = 3-34	Multiple regression	Yes	...	Yes
Hansen et al[38]	1987	156	Tooth	$PbT\bar{x} = 10.7$; $PbB\bar{x} = 5$	Multiple regression	Yes	...	Yes

*A indicates small sample; B, weak outcome measures; C, poor exposure measures; D, inadequate data analysis or reporting; E, inadequate or no covariate control; F, overcontrol; G, clinical levels of lead exposure (blood lead level >3.86 μmol/L); H, later reanalysis substituted (Needleman et al[29] [1985] for Needleman et al[21] [1979], Pocock et al[35] [1987] for Smith et al[25] [1983], and Emhart et al[30] [1985] for Perino and Emhart[13] [1974]; $PbT\bar{x}$, mean tooth lead value; $PbB\bar{x}$, mean blood lead value; R, range; PbTC, values for control group; PbTE, values for high-lead group; GM, geometric mean; ANOVA, analysis of variance; and ANCOVA, analysis of covariance.

†All tooth studies are measured in parts per million and all blood studies are measured in micrograms per deciliter.

METHODS

Data Collection

All studies on lead exposure and children's neurobehavioral development that were published since 1972 were examined for eligibility. The sources of candidate studies were a computerized MEDLINE subject search and a search of programs of meetings on metals, neurotoxicology, lead, pediatrics, and public health. Dissertation abstracts were also searched. Table 1 lists the studies identified in the search[12-38] and presents summary data.

Studies were excluded for the following reasons: (1) Inadequate control of covariates reflecting socioeconomic and familial factors.[12,16-20,24,28] (2) Overcontrol of factors that reflect exposure to the independent variable, lead. One study[27] controlled for pica and peeling paint. (3) Inclusion of subjects with defined clinical lead poisoning (ie, blood lead levels >3.9 μmol/L).[12,14,19] (4) Reported data either did not permit any further quantification[15] or did not enable us to calculate the coefficient of lead in a multiple regression model.[12,14,16,17,23,24]

Some studies were excluded on the basis of more than one of the above criteria. The first criterion effectively excludes most of the early studies in this area since these simply compared high- and low-lead groups, with limited or no control for relevant covariates. The second criterion was selected to avoid overcontrol. The one study[27] that was excluded on this basis also involved a very small sample (multiple regression with 17 covariates and complete data on 48 subjects).

Two of the studies[21,25] originally analyzed the data by dichotomizing lead exposure. The data were later reanalyzed by regression, treating exposure as a continuous variable. We used the results reported in the reanalyses. Supplementary information about the regression analysis was obtained from the authors of two studies.[26,38]

Data Analysis

To achieve an acceptable level of homogeneity, the studies were divided into two groups according to the type of tissue analyzed for lead (blood or tooth). The P values within each group were compared for homogeneity using the technique of Rosenthal,[8(p76)] which is based on the sum of the squared deviations of the t values for lead from the group mean.

Joint P values for lead were calculated for each of the two groups using two different approaches proposed by Fisher and by Mosteller and Bush.[8(p94)] In Fisher's procedure, the logarithm of the product of the individual P values is multiplied by -2. The resulting quantity has a χ^2 distribution with $2N$ *df*. In the procedure by Mosteller and Bush, the weighted sum of the t values of the lead coefficient is computed, with each coefficient being weighted by its *df*. This method effectively weights each study by the number of subjects involved. It is particularly useful in this meta-analysis because of the wide range of sample sizes (75 to 724).

For each study, the partial correlation coefficient of lead was derived from the corresponding t value and was used as a measure of effect size. These coefficients were transformed to z scores using Fisher's transformation[8(p27)] and were then compared via a χ^2 statistic.[8(p77)] When the hypothesis of homogeneity was not rejected, the values of partial r from each study were treated as independent estimates of a common (group) partial correlation. Weighted z score averages were computed and were used to construct 95% confidence intervals

Table 2.—Studies Included in the Meta-analysis*

Study	Year	Exposure Measure	Outcome Measure	Publication Status	Subjects' Age, y	Country
Yule et al[22]	1981	Blood	WISC-R V, F	Journal	6-12	United Kingdom
Lansdown et al[33]	1986	Blood	WISC-R V, F	Journal	Preschool	United Kingdom
Winneke et al[28]	1983	Tooth	WISC-R V, F	Journal	7-12	Germany
Needleman et al[29]	1985	Tooth	WISC-R V, F	Journal	7-8	United States
Ernhart et al[30]	1985	Blood	McCarthy Scale	Journal	Preschool	United States
Schroeder et al[31]	1985	Blood	Bayley/Stanford Binet IQ Scale	Journal	1-6	United States
Hawk et al[32]	1986	Blood	Stanford Binet IQ Scale	Journal	3-7	United States
Fergusson et al[36]	1987	Tooth	WISC-R V, F	Journal	8-9	New Zealand
Fulton et al[37]	1987	Blood	British Ability Scale C	Journal	6-9	United Kingdom
Hatzakis et al[34]	1987	Blood	WISC-R V, F	PROC	7-12	Greece
Pocock et al[35]	1987	Tooth	WISC-R F	Journal	6	United Kingdom
Hansen et al[38]	1987	Tooth	WISC-R V, F	PROC	7-8	Denmark

*WISC-R indicates Wechsler Intelligence Scale for Children–Revised; V, verbal; F, full-scale; and PROC, proceedings of meeting.

Table 3.—Covariates Entered Into the Final Multiple Regression Model*

Study‡	SES	Parental Factors	Perinatal Factors	Physical Factors	Gender	Parent IQ	Parental Rearing	Lead Coefficients†	
								Unadjusted	Final Model
Yule et al[22] (2)	*	...	...	Age	...	...	...	NA	−8.08 (4.63)
Lansdown et al[33] (2)	*	...	...	Age	...	...	...	NA	2.15 (4.48)
Winneke et al[28] (52)	*	...	*	*	*	...	...	NA	−0.125 (466)
Needleman et al[29] (5)	*	*	...	...	...	*	...	NA	−0.21 (0.07)
Ernhart et al[30] (3)	...	*	*	Age	...	*	...	NA	NA
Schroeder et al[31] (7)	*	...	...	...	...	...	...	NA	−0.199 (0.07)
Hawk et al[32] (1)	*	...	...	...	*	*	*	−0.456	−0.255 (0.15)
Fergusson et al[36] (7)	*	*	*	...	*	...	...	NA	−1.46 (1.25)
Fulton et al[37] (21)§	*	*	...	*	*	*	*	−5.45 (1.5)	−3.70 (1.31)
Hatzakis et al[34] (10)	*	*	...	...	...	*	*	−0.376	−0.266 (0.07)
Smith et al[25] (18)	*	*	*	...	*	*	*	−2.66 (0.86)	−0.77 (0.63)
Hansen et al[38] (6)	*	...	*	...	...	...	...	NA	−4.27 (1.21)

*Asterisk (*) indicates those factors entered into the model; and SES, socioeconomic status.
†NA indicates not available. Where available, coefficients for lead are given for the unadjusted bivariate model and the final multivariate model.
‡The number of coefficients entered into the initial model is in parentheses.
§The SE of the coefficients was estimated from the data.

for the group partial correlation coefficient.[7(p227)]

Power for each study to find a "small" effect was computed using the method (and program) described in Gatsonis and Sampson.[39] We used the definition by Cohen[40] of a "small" effect (partial $r = .14$).

Finally, to assess whether the exclusion of 12 of the original 24 studies had a biasing effect on our conclusions, we used Fisher's aggregation technique in an analysis that included all 24 studies. For most of the early studies, P values were either given in the published reports or derived on the basis of the published data. In the few cases where a P value was not available, we followed a conservative approach and assumed it was .5.

RESULTS

All studies considered and reasons for exclusion are listed in Table 1. Of the 12 excluded studies, 5 reported an effect significant at the .05 level and 7 did not. Twelve studies were included in the meta-analysis; 7 of them measured exposure by blood lead and 5 by tooth lead values (Table 2). The two groups were analyzed separately. In 11 of the 12 studies reviewed, the t value of the regression coefficient for lead was negative, ranging from −3.86 to 0.48 in the blood lead group and from −3.0 to −0.03 in the tooth lead group. The partial correlation coefficient of lead ranged from −.27 to .05 and from −.2 to −.003, respectively, for the two groups.

The dependent variable (IQ) was measured by the Wechsler Intelligence Scale for Children–Revised in eight studies. Two studies employed the Stanford Binet IQ Scale, one employed the British Ability Scale, and one employed the McCarthy Scale. The comparison of the distributions of lead exposure was hindered by two difficulties: (1) methods for measuring lead level differed, particularly in the tooth lead group, and (2) summary descriptions of the distribution of lead exposure also differed. In the blood lead group, the lead exposure in the study by Landsdown et al[33] (mean, 0.62 μmol/L) was among the lowest, while the exposure in the study by Schroeder et al[31] (median, 1.46 μmol/L) was among the highest. In the tooth lead group, where analytic methods were different, the lead exposure in the study by Smith et al[25] was among the lowest (248 of 402 children had tooth lead concentration <5.5 ppm), while the exposure in the study by Needleman et al[21] (mean, 12.7 ppm) was among the highest. The sets of covariates included in the regression equations differed for each study, although most covariates purported to measure factors that were similar across studies. It is impractical to present herein a detailed list of the covariates for each study. A condensed form of this information is in Table 3, in which we classified the various covariates into groups on the basis of seven factors. Where available, the unadjusted coefficient of lead is also included in Table 3, along with the coefficient of lead in the final model. In some studies the logarithm of the lead measurement was used in the regression equations.

The P values for the common direc-

Table 4.—Results of Synthesis of 12 Studies

Study	Weighted t Values: z	Weighted t Values: P (One-Sided)	Fisher's Technique: χ^2	Fisher's Technique: P
Blood Lead Studies				
All studies	−5.46	<.0001	61.29	<.0001
Eliminating one study at a time (study eliminated)				
Hatzakis et al[34]	−3.88	<.0001	42.87	<.0001
Hawk et al[32]	−5.34	<.0001	55.3	<.0001
Schroeder et al[31]	−5.15	<.0001	49.68	<.0001
Fulton et al[37]	−4.87	<.0001	49.68	<.0001
Yule et al[22]	−5.25	<.0001	54.86	<.0001
Lansdown et al[33]	−5.56	<.0001	60.52	<.0001
Emhart et al[30]	−5.31	<.0001	54.86	<.0001
Combining studies using log-transformed values (Fulton et al,[37] Yule et al,[22] and Lansdown et al[33])	...	...	18.83	.005
Tooth Lead Studies				
All studies	−2.65	.004	33.11	<.0005
Eliminating one study at a time (study eliminated)				
Needleman et al[29]	−1.97	.024	19.29	<.025
Hansen et al[36]	−2.3	.011	23.9	<.005
Winneke et al[26]	−2.67	.004	31.68	<.0005
Smith et al[25]	−2.36	.009	28.69	<.0005
Fergusson et al[36]	−3.04	.001	28.88	<.0005
Combining studies using log-transformed values (Smith et al[25] and Fergusson et al[36])	−1.61	.001	8.66	<.0005

Table 5.—Lead Coefficients for Full-scale IQ Scores*

Study	Coefficient	SE	t	P (One-Sided)	Sample Size	Partial r	Total R^2
Blood Lead Studies							
Hatzakis et al[34]	−0.27	0.07†	−3.86†	.0001	509	−.17	0.25
Hawk et al[32]	−0.25	0.15	−1.67	.05	75	−.20	0.21
Schroeder et al[31]	−0.2	0.07†	−2.78	.003	104	−.27	NA
Fulton et al[37]‡	−3.7	1.37	−2.77	.003	501	−.12	0.46
Yule et al[22]‡	−8.08	4.63	−1.75	.04	129	−.16	NA
Lansdown et al[33]‡	2.15	4.48†	0.48	.68	86	.05	NA
Emhart et al[30]	NA	NA	−1.8†	.04	80	−.20	NA
(Average weighted partial r = −.152; 95% confidence interval, −.2 to −.1)							
Tooth Lead Studies							
Needleman et al[29]	−0.21	0.07	−3	.001	218	−.20	0.35
Hansen et al[36]	−4.27	1.91	−2.23§	.01	156	−.18	0.2
Winneke et al[26]	−0.13	4.66	−0.03§	.49	115	−.003	0.13
Pocock et al[35]‡	−0.77	0.63	−1.22	.11	388	−.06	NA
Fergusson et al[36]‡	−1.46	1.25	−1.17	.12	724	−.04	NA
Average weighted partial r = −.08; 95% confidence interval, −.13 to −.03)							

*NA indicates not available.
†Estimated from data in article.
‡Log transforms.
§Obtained from the author.

tional hypothesis that lead is negatively correlated with IQ were tabulated. Before combining the probabilities, the homogeneity of the P values was assessed. The χ^2 statistics were 11.02 ($df=6$, $P=.09$) and 5.13 ($df=4$, $P=.26$) for the blood lead and tooth lead group, respectively. Thus, the hypothesis of homogeneity cannot be rejected for either group.

Combined P values in the blood lead group were less than .0001 for both methods of combining probabilities. The corresponding combined P values for the tooth lead group were less than .0005 and .004, respectively.

Sensitivity Analysis

The sensitivity of the findings was examined by removing the studies one by one from the analysis and recalculating combined P values (Table 4). For the tooth lead group the highest combined P value was .025 and the lowest was .0001. The corresponding figures for the blood lead group were below .0001. The overall finding of a significant lead effect is supported by both methods of combining the data. No single study seems to be responsible for the significance of the final finding.

Effect Size

In the case of multiple regression/cor relation studies, the usual measure c effect size is the partial correlation coef ficient (partial r).[7,8,40] Derived partial r for the 12 studies under review are giv en in Table 5.

Each partial r was converted to a score using Fisher's z transform. The statistics for homogeneity were 5.7 ($df=6$, $P>.4$) for the blood lead grou and 6.44 ($df=4$, $P>.1$) for the tooth lea group. The hypothesis of homogeneit of the effect sizes cannot be rejected fc either of the two groups. The weighted score averages were −.152 (SE = .02 and −.08 (SE = .025), respectively. I the original scale, the approximate 95 confidence intervals for the group pa tial r were $-.15 \pm .05$ for the blood lea group and $-.08 \pm .05$ for the tooth lea group.

The results of the analysis in terms the partial r's support those obtaine from the analysis of the P values. Ne ther approach provides an overall est mate of the raw effect size, ie, of th average change in IQ units per un change in lead exposure. A meaningf attempt to arrive at such an overall est mate is precluded by the substantial di ferences in model specification amor the studies, as well as in units and met ods of measuring lead exposure ar outcome.

Selection Bias and the File Drawer Problem

There were two basic steps in th selection of studies for this meta-anal sis: (1) the retrieval of studies and (the formulation and application of excl sion criteria to the retrieved studie The possibility of bias in both steps w investigated. In particular with respe to the second step, calculations with the original 24 studies included show that Fisher's statistic was 93.8 ($df=8$ $P<.0001$) for the blood lead group, 42 ($df=14$, $P<.001$) for the tooth le group, and 136.4 ($df=48$, $P<.0001$) f all studies together. This is evider that the application of the exclusion c teria was not an important source of bi in this meta-analysis.

The possibility of bias resulting fr the first step has been termed the *f drawer problem.*[8(p107)] Such bias may sult from at least two sources (beyo faults in the retrieval process): the fa ure of all investigators to report th results or the failure of journals to pu lish all results submitted. Studies th show a statistically significant result tend to be published more frequently

We estimated the magnitude of t file drawer problem by calculating t number of unpublished nonsignific

Table 6.—Power Calculations for "Small" Effects of Lead ($\alpha = .05$; Partial $r = .14$)

Study	Sample Size	No. of Covariates (Final)	Power
Blood Lead Studies			
Fulton et al[37]	501	14	0.87
Hatzakis et al[34]	509	8	0.88
Hawk et al[32]	75	5	0.21
Schroeder et al[31]	104	7	0.28
Yule et al[22]	129	2	0.35
Lansdown et al[33]	86	2	0.25
Emhart et al[30]	45	4	0.23
Tooth Lead Studies			
Needleman et al[29]	218	5	0.53
Fergusson et al[35]	724	8	0.96
Smith et al[25]	388	10	0.78
Winneke et al[26]	115	4	0.31
Hansen et al[36]	156	7	0.40

studies that would be necessary to bring the overall P value to greater than .05. Using the procedure of Rosenthal,[8(p108)] we found that 26 null result studies would be necessary to dilute the finding for the tooth lead group and that 67 would be necessary for the blood lead group. This procedure assumes that the mean z score of the unseen studies is 0. A more stringent procedure is suggested by Iyengar and Greenhouse,[41] which assumes that all unseen studies simply are not significant at the .05 level. Under this assumption, it would require 16 and 35 studies to dilute the finding for the tooth lead group and the blood lead group, respectively. Given the expense of conducting human studies of lead exposure and the amount of attention directed to this question, it is unlikely that this number of negative studies have escaped notice.

Power Calculations

The studies included in this meta-analysis are observational. The values of the covariates cannot be fixed in advance by design but are themselves outcomes of the study. Any calculation of power must account for this extra variability.[39] Table 6 presents the a priori power of each study to detect a partial r of .14 (denoted as a "small" effect[40]). "Small" in this sense does not mean biologically unimportant, it means difficult to identify. Cohen[40] has pointed out that a result of this size "all too frequently in practice represents the true order of magnitude of the effects being tested." As can be seen from Table 5, a partial r equal to $-.14$ is near the center of the values for the partial correlation coefficient that were derived from the studies under review. Of the 12 studies, 8 had power below 60% to detect an effect of this magnitude.

The power figures given here are optimistic: they are calculated on the number of covariates present in the final model reported in each study. Most studies, however, initially controlled for many more covariates than those in the final model. As few articles gave information about missing values in the data, it is possible that some of the sample sizes used to calculate power are larger than the effective sample sizes of the studies.

Some Methodological Issues

The inclusion criteria ensured that the studies analyzed provided an acceptable minimum control for relevant covariates. In two studies,[22,33] control was done only for social class. Multiple regression analysis was employed in all studies, usually in stepwise form. No study reported any analysis of residuals, model checking, and detection of possible outliers in the data. Only two studies attempted to select an "optimal" regression model in a formal way. No study addressed the issue of errors in measurement of the independent variables. The question of errors in variables is particularly relevant when measuring exposure at low levels. Other covariates that represent arbitrary constructs (eg, marital relationships, parental interest, parental involvement in school, and so on) are also particularly vulnerable to errors-in-variables problems.

COMMENT

The overall evidence from our meta-analysis establishes a strong link between low-dose lead exposure and intellectual deficit in children. A natural question that arises at this point is whether the link is a causal one. The answer to this question goes beyond the formal meta-analytic method. Some of the epistemological issues encountered in making causal inferences are discussed below.

The effects of lead on the central nervous system are embedded in a complex process involving biologic, environmental, familial, and socioeconomic factors. Epidemiologic studies cannot, by themselves, establish causal relationships. Causality is not subject to empirical proof, whether in the field or in the laboratory.[42] Given that direct demonstration of proof of a low-dose lead effect in a naturalistic setting is not achievable, epidemiologists rely on canons[43] that, if satisfied, permit the conservative drawing of causal inferences. They are (1) time precedence of the putative cause, (2) biologic plausibility, (3) nonspuriousness, and (4) consistency.

Cross-sectional studies such as those reviewed herein cannot establish the time precedence of lead exposure; the level of lead was measured at the same time as IQ. The claim has been made that neurobehavioral deficits result in excess lead intake, ie, deficient children mouth more leaded substances. This assertion has been effectively refuted by forward studies of lead exposure beginning at birth. These studies have shown a clear relationship between umbilical cord blood lead levels and later development at 6 to 24 months.[44-46]

Biologic plausibility demands that mechanisms at a lower biologic level have been demonstrated to explain the phenomenon under examination. Lead is a thoroughly investigated neurotoxin.[47] Among many effects that have been demonstrated, lead has been shown to affect neurotransmitter activity, brain adenyl cyclase activity, and dendritic complexity.[48-50] Demonstration of dose-response relationships strengthens the plausibility of the relationships studied. Convincing demonstrations of dose-related behavioral effects have been made in animal studies.[51,52] Epidemiologic demonstrations of association between dose (blood or tooth lead levels) and response (teachers' ratings of classroom behavior and reaction time under varying intervals of delay) also have been published.[21,34]

Nonspuriousness means that the relationship put forth in the causal claim is not due to a confounder or a set of confounders. Complete confounder control is impossible in real world studies. In most studies reviewed, control of confounders has reduced the magnitude of the lead-IQ effect but has not obliterated it. The argument for nonspuriousness is further strengthened by the evidence provided by animal studies in rodents and subhuman primates, which produced cognate outcomes in cross-fostered litter mates.[51,52]

Finally, consistency requires that the phenomenon be demonstrated in different studies under similar but not identical circumstances. The statistical nature of these investigations requires an extended notion of consistency. Even if the effect under study exists in nature, the P values and effect sizes reported in investigations of the question will vary in magnitude, and not all studies will give a significant result.

A different type of evidence for consistency was offered in the study by Wallsten and Whitfield.[53] This evidence is based on the probabilistically encoded opinions of six lead experts of widely ranging viewpoints about the dose-response relation between lead exposure and IQ. Five of the six experts' estimates of the dose-response curve were convergent, leading the authors to state: "In view of the extensive debate concerning the effects of lead on IQ, the degree of consensus reflected in the

study's results is notable, especially since the experts were selected so as to span the full range of opinion."

The four previously cited reviews of the studies of lead at low dose differed in their evaluation of essentially the same evidence. One review came to a qualified negative conclusion,[5] one came to a positive conclusion,[4] and two found the evidence inconclusive.[2,3] This difference of opinion partly proceeds from a limitation inherent in the method of narrative reviewing; it essentially evaluates each study in isolation and is unable to achieve a systematic synthesis. Meta-analysis avoids this limitation and includes all studies in a joint inference. Using this method, and incorporating into our review a number of recent studies that were not available to the earlier reviewers, we found that although the sample of studies varied widely in their individual power to find an effect, and not all found an effect by the conventional rule of $P<.05$, 11 of 12 studies reviewed reported a negative coefficient for lead. The joint probability of the findings reported occurring by chance under the null hypothesis was quite small, and this was not materially influenced by any single study. The estimated effect sizes for the two groups were both significantly different from zero. These findings, taken in sum, permit a strong inference that low-dose lead exposure is causally associated with deficits in psychometric intelligence.

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The Relationship Between Prenatal Exposure to Lead and Congenital Anomalies

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• **We obtained umbilical cord blood from 5,183 consecutive deliveries of at least 20 weeks' gestation and analyzed them for lead concentration. Those demographic and socioeconomic variables, including lead, which were shown on univariate analysis to be associated with increased risk for congenital anomalies were evaluated and controlled by entering them into a stepwise logistic-regression model with malformation as the outcome. Coffee, alcohol, tobacco, and marijuana use, which were associated with lead level, but not risk of malformation, were also controlled. The model was reduced in steps by eliminating the variables with the highest *P* value, until the most parsimonious model was created. The relative risk for anomalies associated with lead was then calculated while holding other covariates constant. Lead was found to be associated, in a dose-related fashion, with an increased risk for minor anomalies.**

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SINCE the beginning of the 20th century, lead has been considered a potential human teratogen. British factory inspectors of that period reported an increase in the incidence of infertility, abortion, stillbirth, fetal death, and macrocephaly associated with industrial lead exposure.[1] It is surprising that for the next 50 years, little attention was given to the possible embryotoxic effects of lead. Lead crosses the placenta, and in the rat has been shown to be mobilized from maternal stores during pregnancy.[2] Studies in three rodent species have shown that lead readily produces neural tube lesions.[3]

Women who lived during pregnancy in homes where the drinking water had excessive amounts of lead, bore a significantly ($P<.01$) higher proportion of retarded infants.[4] Increased placental lead concentrations have been reported in stillbirths, and in infants with congenital anomalies.[5] Lead also affects the male gamete. Increased numbers of chromosomal alterations have been reported in lead workers, and abnormalities in sperm number, vigor, and morphologic features have been demonstrated in both experimental animals and in workers.[6]

We and others have shown a deleterious effect of exposure to lead at low dose on the neuropsychological function of school-age children.[7] Because younger, developing organisms may be most vulnerable to lead, the study of the effects of exposure on the human fetus is a matter of considerable interest. No epidemiologic studies of umbilical cord blood lead levels and their relationship to neonatal outcome have been reported.

To evaluate lead's impact during pregnancy, we measured the concentration of lead in umbilical cord blood in a large cohort of neonates from a single obstetrical hospital, and examined its relationship to a number of outcomes measured at birth, including congenital anomalies.

METHODS

Study Sample

Between April 1979 and March 1980, at the Boston Hospital for Women, 5,183 mothers delivered live-born neonates of at least 20 weeks' gestational age. In the delivery room, during the fourth stage of labor, 5-mL samples of umbilical cord blood were collected in metal-free tubes from 97% of the neonates. Mothers were interviewed by trained personnel on the first or second postnatal day, employing a structured questionnaire previously used in other studies of reproductive outcome.[8] In addition to standard demographic variables, the questionnaire focused on reproductive and medical history and on exposure to medicines, alcohol, tobacco, coffee, tea, and marijuana.

Permission for the interview was sought from 84% of the eligible mothers. Reasons for not contacting the mother were lack of interviewers (14%) and lack of consent of obstetrician (1.5%). Of those mothers approached, 90% were interviewed. Reasons for not being interviewed were early discharge (5%), refusal (3%), language barrier (1.6%), and maternal medical condition (0.1%).

From hospital records, data on each newborn's status, the pregnancy, and delivery were obtained. A small number of records (1.2%) could not be found after several systematic searches. These cases were excluded from the study.

Malformations were classified from the physicians' notes in the charts by employing the coding scheme developed by the Centers for Disease Control's Malformation Surveillance Program. The newborn examinations were done by pediatric house officers assigned to the neonatology service. Whenever a malformation could not be classified by this scheme, we used the criteria employed in the Collaborative Perinatal Project.

Lead determinations were obtained for 97% of the births during the period of the study. They were analyzed in duplicate by an anodic-stripping voltammetry to a precision of 2 ug/dL as previously reported.[9]

Statistical Analysis

Combined lead and maternal interview data were available for 4,354 births. Neonates were classified according to their blood lead levels into quartiles. To identify those maternal and neonate variables that were associated with lead level, we cross tabulated the variables with lead and evaluated whether the overall distribution of demographic, pregnancy, and delivery events differed across lead groups by χ^2. The univariate relationship between umbilical cord blood lead level and certain outcomes was then evaluated by testing for linear trends.

Logistic regression analysis was then used to determine the contribution of lead

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to risk of malformation while controlling for the effect of other potentially confounding variables. Those variables that previous univariate analyses had shown to be associated with anomalies at $P<.3$, were entered into the logistic regression model. These potentially confounding variables were gestational age, birth weight, history of either spontaneous or induced abortion, maternal parity, and age. Initially all variables and their interactions with lead were entered and the fitness of the model quantified in terms of its log likelihood. Continuous variables were not degraded. Lead was logarithmically transformed (base 10) to normalize its distribution. Maternal age was entered both as a linear and quadratic term. In sequential steps, the variable whose coefficient had the highest P value was dropped from the model. Priority was given to eliminating interaction terms. After each step a new model was recalculated. The new model was retained only if Wilk's criterion was met, ie, the change in the model's log likelihood was not significantly degraded ($P>.05$) by dropping a variable. This step-down iteration generated a set of increasingly parsimonious models. Each model was also calculated without including the term for lead to see if that step met Wilk's criterion for additional predictive information. Because this procedure excludes a subject if any single observation is missing, a minimum data set with complete interview data was required to count a subject. This limitation reduced the number of subjects by only 0.8%.

Coffee, alcohol, tobacco, and marijuana use, which were associated with lead level but not with malformation risk, were included in the initial model. Entering these variables, categorized either according to their associated risk of malformation or as continuous values, did not increase the predictability of the model.

The covariate-adjusted relative risk of malformations associated with lead level was then calculated while maintaining the other predictive variables constant.[11] As is customary with probit analysis, we assumed an exponential relationship between lead's β coefficient from the logistic model and the observed malformation rates.

Table 1.—Number of Mothers With Selected Demographic and Medical Characteristics Within Each Cord Blood Lead Category

Characteristic	Lead Category, µg/dL: Low 0-≤4.8	Mid-Low 4.9-≤6.5	Mid-High 6.6-≤8.6	High 8.7-≤35.1
Total No.	1,118	1,068	1,105	1,063
Demographic				
Age ≥35 yr	97	96	109	115
Age ≤16 yr	17	17	24	24
On welfare	139	176	184	237*
White	838	797	790	724†
Jewish	149	119	113	83*
College educated	772	691	684	599*
Divorced or cohabitating	22	45	54	55*
Habits				
Alcohol, third trimester, ≥7/wk	18	18	28	49*
Coffee, ≥3/day	72	84	118	134*
Tobacco, third trimester, ≥3/day	147	189	234	303*
History				
Gravidity >1	728	685	694	659
Parity >1	585	545	539	485†
Previous stillbirth(s)	26	29	30	30
Induced abortion(s)	169	189	202	220†
Miscarriage(s)	187	187	194	167
Ponderal index‡				
<18, thin	82	52	70	68
>30, obese	36	33	45	49

*$P<.01$, χ^2. †$P<.05$, χ^2. ‡Weight (kg)/height^2 (m).

Table 2.—Number of Selected Pregnancy Events and Delivery Characteristics Within Each Lead Category

Characteristic	Lead Category: Low	Mid-Low	Mid-High	High
Pregnancy events				
Bleeding in				
1st trimester	104	91	99	77*
2nd trimester	22	29	32	23
3rd trimester	29	34	36	32
Toxemia or eclampsia	39	33	37	48
Prepartum admissions	87	105	123	90†
Premature labor	44	37	32	26*
Delivery characteristics				
Breech presentation	38	47	47	46
Placenta previa	3	8	5	3
Premature rupture of membrane	55	47	50	36
Placenta abruptio	5	9	5	7
Fetal distress	40	34	34	40

*$P<.01$, χ^2. †$P<.05$, χ^2.

RESULTS

Women whose neonate's cord blood lead levels were elevated tended to be divorced, unmarried, on public assistance, to consume more alcohol, coffee, and tobacco, and to have had an induced abortion (Table 1). Decreased lead levels were associated with being white, Jewish, college educated, and having had full-term pregnancies in the past. Maternal characteristics not significantly related to lead included aspirin or acetaminophen use, venereal disease, diabetes or hypertension, maternal occupation, age of menarche, or contraceptive use. Bleeding during the first trimester and premature labor were more frequent in women with lower levels of lead (Table 2). In general, perinatal blood lead levels were not altered by late pregnancy events, presentation, or mode of delivery.

Low birth weight, short gestation, low Apgar score, jaundice, blood type, and neonate gender were unrelated to lead. The occurrence of respiratory distress varied inversely with lead level.

The incidence of minor malformations was associated with cord blood lead level (Table 3). Multiple or major malformations did not show this pattern. The commonest anomalies found were hemangiomas and lymphangiomas (14/1,000 births), hydrocele (27.6/1,000 males), minor skin anomalies such as skin tags and papillae (12.2/1,000 births), and undescended

Table 3.—Number of Infants With Selected Characteristics Grouped by Lead Category

Characteristic	Lead Category			
	Low	Mid-Low	Mid-High	High
Birth weight <2,500 g	84	76	86	83
Gestation <37 wk	86	73	76	76
Malformations				
Any	86	72	101	102*
≥2	9	8	17	11
Major	32	25	32	31
Minor	54	47	69	71*
Hydrocele or undescended testicle	21	11	23	27
1 minute Apgar <6	74	60	76	65
Respiratory distress	72	57	57	47*
Neonatal jaundice	290	238	284	261

*Significant ($P<.05$) linear trends across lead categories.

Table 4.—Logistic Models Predicting Malformations*

Variable	β, ±SE	
	With Lead	Without Lead
	Logistic Model	
Log_{10} lead, ug/dL	0.66±.27	. . .
Maternal age, yr	−.014±.010	−.013±.010
Birth weight, kg	.0036±.0021	.0036±.0021
Gestational age, wk	−.040±.025	−.037±.024
Race, B	0.31±.15	.33±.15
	Agreement of Model Fit to Data	
−2 log likelihood	2,457.25	2,463.14
Model χ^2	17.61	11.71
df	5	4
P	.004	.020

*Maternal age, gestational age, birth weight, race, and blood lead are the significant predictors in this most terse model, given with and without blood lead terms. Information about lead significantly ($P=.015$) improves the model's predictive power.

Table 5.—Covariate-Adjusted Relative Risk of Malformation at Selected Blood Lead Levels

Blood Lead, μg/dL	Relative Risk*	% of Neonates at Greater Lead Levels
0.7	1.0	98.7
6.3	1.87 (1.44-2.42)	50.0
15	2.39 (1.66-3.43)	1.7
24	2.73 (1.80-4.16)	0.2

*Mean±95% confidence interval, $\beta=0.655\pm0.273$ (SE).

testicles (11/1,000 males). No particular type of malformation was associated with lead.

The observed associations of malformations and lead with parity and past abortion, as well as the interactions of lead with other personal factors, required multivariate analysis to quantify the contribution of each variable to the risk of malformation. A variety of logistic regression analyses included different combinations of variables; increasingly terse models were achieved, both with and without lead as a covariate. Information about lead levels significantly improved the powers of prediction of these models ($P<.02$). Adding information about alcohol, tobacco, or coffee use changed the model log likelihood by only 0.5 ($P>.26$). Table 4 gives the most parsimonious model.

Of considerable interest are the calculations summarized in Table 5. The β coefficient for lead was determined by fitting the model with lead plus maternal age, birth weight, race, and gestational age. Holding the other factors constant, the relative risk of a child's demonstrating a malformation at birth increases by 50% as lead levels increase from 0.7 to the mean of 6.3 ug/dL, and increases another 50% at 24 ug/dL.

COMMENT

These data show a relationship between umbilical cord blood lead levels and the risk of minor congenital anomaly, while controlling for other covariates. No single characteristic anatomic defect was found; the overall incidence of many different anomalies was raised in newborns with high lead burdens. This suggests that lead may interact with other teratogenic risk factors to enhance the probability of abnormal outcome. Lead was not found to be associated with decreased birth weight, shortened gestation, Apgar score, respiratory distress, or the presence of jaundice.

The anomalies discovered in this study are in themselves of little health consequence, but may be important as markers of impaired development. Marden et al[11] examined 4,412 newborns, and reported that the risk of having a major anomaly was increased in those newborns with two or more minor anomalies. They suggest that the presence of minor anomalies may be a clue to the presence of more serious malformations.

This study may be considered a "level 2" study, that is, it employed preexisting records (hospital charts) to collect data, and cross tabulated these data with blood lead levels measured in our laboratory. Diagnosis of anomaly was made by clinicians (pediatric residents assigned to the neonatology service) in the conduct of their routine neonatologic duties, and observation was limited to the first days of life. We did not examine these newborns ourselves. A potential weakness of this study is that the surveillance was not carried out by specialists in teratology. It is quite likely then that a number of birth defects were missed, and some will be diagnosed at later ages. It is not likely, however, that these misclassifications were biased with regard to their lead exposure because exposure was ascertained separately and was not known by either mother or pediatrician.

Valid comparisons of the rates of anomalies reported by different observers are difficult because of variations in diagnostic criteria and other risk factors that may vary across groups. Our reported rate for major malformations, 3%, is somewhat higher than that reported by Heinonen et al[12] (1.8%), or Christianson et al[13] (1.2%). This may be because the

Boston Hospital for Women is a referral center for high-risk pregnancies. For technical reasons, we were unable to sample the mother's blood lead levels during the three trimesters of pregnancy, and cannot, therefore, report directly on the exposure of the fetuses in early development. Sequential blood levels have been measured in another study, however, and no significant change in concentration was observed during the period of gestation.[14]

Among the mechanisms through which teratogens act are germinal and somatic mutations, interference with mitosis, chromosomal alterations, membrane changes, and disturbances in nutrition or energy sources. Lead has been shown to act on many of these mechanisms. Lead can affect the fidelity of DNA synthesis in vitro,[15] and in vivo has been shown to perturb cell proliferation and DNA synthesis.[16] Lead has recently been shown to cleave the sugar-phosphate backbone of transfer RNA in catalytic fashion.[17] Mammalian cells exposed to lead in vitro have shown increases in dicentric chromosomes and defects in centralization.[18]

Lead inteferes with embryonic nutrition and energy supply at a number of sites. It competes with other cations such as zinc, iron, or calcium, and thereby limits their availability at critical sites.[19] Lead interferes with mitochondrial function,[20] depresses the synthesis of cytochromes, and thus alters the energy supply to a number of organs. Delayed appearance of cytochromes in developing rat brains have been reported at low tissue levels of lead. This has been paralleled by delayed synaptic development.[20,21]

Lead administered to mammals reliably produces fetal death, abortion, and retarded fetal and postnatal growth, CNS hemorrhage, and hydrocephalus.[22] Lead given at lower doses during neurogenesis produces no macroscopic alterations in structure, but inteferes with cortical connectivity as measured by synaptic number and maturity.[23] Behavioral studies of the offspring of mother and father rats exposed to lead before conception showed impaired learning,[24] suggesting that the gametoxic effects of lead can be expressed in behavioral deficit at doses well below those which produce macroscopic anatomic abnormality.

In this study we restricted our inquiry to the identification of growth retardation and structural abnormalities visible to the clinician during the first few days of the newborn's life. We were able to evaluate the contribution of a number of covariates, including coffee, alcohol, and tobacco use. These variables did not increase the predictive power of lead when added to the model. Indicators of nutritional status such as protein, zinc, and, calcium intake were not evaluated in this investigation. Because deficiency of these factors may affect outcome and be associated with increased lead absorption, they may represent potential confounders. The study was not designed to measure the impact of lead on fetal death, abortion, or other embryotoxic outcomes such as impaired postnatal growth or CNS development.

Whether children in this birth cohort found to be without anomaly will later demonstrate malformations, growth, or behavioral deficits remains to be determined. We are currently following a sample of these children in the high, middle, and low range of cord blood lead levels at regular intervals and evaluating both their physical and neuropsychological development.

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