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Pre- and Postnatal Lead Exposure and Behavior Problems in School-Aged Children[1]

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The association between early lead exposure and later problem behaviors was evaluated prospectively in a cohort of 8-year-old children born during a 12-month period at one hospital. Lead levels in umbilical cord blood ($\bar{X}$ = 6.8 μg/dl, SD = 3.1) and the dentin of a shed deciduous tooth ($\bar{X}$ = 3.4 μg/g, SD = 2.4) provided measures of prenatal and postnatal exposure, respectively. Ratings on the Teacher Report Form of the Child Behavior Profile provided information about children's problem behaviors. Cord blood lead level was not associated with the overall prevalence or nature of problem behaviors. In both crude and adjusted analyses, tooth lead level was significantly associated with total problem behavior scores (approximately 2 points in *T* score per log unit increase in tooth lead). Significant tooth lead-associated increases in both internalizing and externalizing scores were also observed (approximately 1.5 points in *T* score per log unit increase). Weaker associations were noted between tooth lead level and the prevalence of "extreme" problem behavior scores. The extent to which these associations reflect residual confounding is uncertain. These data suggest, however, that social and emotional dysfunctions are correlates and may be expressions of increased lead exposure. © 1994 Academic Press, Inc.

INTRODUCTION

Mental and behavioral disorders in children, characterized as "the new hidden morbidity" (Haggerty, 1988), are now recognized as a major public health problem, with recent studies suggesting an overall prevalence of approximately 20% among U.S. children and adolescents (IOM–NAS, 1989; Costello, 1989). To develop more effective primary and secondary prevention strategies, greater efforts are needed to identify the determinants of these disorders (Hamburg, 1989).

Only recently has serious consideration been given to the possibility that some fraction of childhood psychopathology reflects the impact of environmental pollutants on CNS function (Weiss, 1985). Lead is a likely candidate for study because it is ubiquitous and has documented developmental neurotoxicity (CDC, 1991). Although a broad spectrum of adverse health outcomes have been linked to low-level lead exposure (Needleman and Bellinger, 1991), social and emotional dysfunctions have received very little attention as a potential expression of lead toxicity. Four lines of evidence provide a rationale for investigating this link.

Animal studies. Lead exposure affects early mother–infant interaction and early social play in several animal models, including the rat, mouse, and rhesus mon-

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key. In general, lead exposure is associated with altered social investigation, aggression, rough-and-tumble play, and sexual behavior (Laughlin, 1986; Laughlin *et al.*, 1991).

Lead exposure and psychiatric status. Case reports indicate that individuals exposed to lead at high dose may display the clinical features of depression (Balestra, 1991) and affective or schizophreniform-like psychosis (Schottenfeld and Cullen, 1984; McCracken, 1987; Dumont, 1989). Lead levels are elevated in autistic children (Cohen *et al.*, 1976; Campbell *et al.*, 1980; Accardo *et al.*, 1988), although this may be secondary to increased hand-to-mouth activity or other behavioral abnormalities. Chelation appears to produce some improvement in the clinical status of psychiatric patients (Oliver, 1967; Romano and Grossi-Bianchi, 1968; Balestra, 1991).

Mood disturbances in adults occupationally exposed to lead. On self-report symptom checklists and rating scales, adult lead workers report significantly greater depression, irritability, decreased libido, fatigue, anger, tension, interpersonal conflict, and other indicators of affective disturbance than do controls (e.g., Baker *et al.*, 1983, 1985; Haenninen *et al.*, 1979; Bleeker *et al.*, 1983; Hogstedt *et al.*, 1983; Parkinson *et al.*, 1986; Pasternak *et al.*, 1989). These disturbances occur at blood lead levels lower than those associated with psychologic deficits (Baker *et al.*, 1985). Environmental or pharmacologic interventions that reduce workers' blood lead levels appear to reduce the severity of mood disturbances (Baker *et al.*, 1985; Cullen *et al.*, 1983).

Low-level lead exposure and behavior problems in children. In 1943, Byers and Lord reported a high prevalence of serious school problems among a series of clinically lead-poisoned children, who were characterized as distractible, impulsive, and aggressive (Byers and Lord, 1943). A small number of case-control studies then suggested that children with the clinical diagnosis of hyperactivity (or Attention Deficit Disorder) have histories of somewhat higher lead exposure (David *et al.*, 1972, 1977; Gittelman and Eskenazi, 1983). Subclinical elevations of blood or tooth lead levels have been associated with teachers' ratings of children's hyperactivity or activity levels on the Connors or Rutter teachers' rating scales (Yule *et al.*, 1984; Fergusson *et al.*, 1988, 1993; Silva *et al.*, 1988; Thomson *et al.*, 1989). Objective measures of activity level or "on task" behavior, however, have not been consistently associated with indices of lead burden (Milar *et al.*, 1981; Harvey *et al.*, 1984; Bellinger *et al.*, 1984; Hansen *et al.*, 1989).

Epidemiologic studies provide support for the hypothesis that teachers view children with higher lead burdens as having reduced ability to sustain attention. In the study of Needleman and colleagues (1979) children with high dentin lead levels were rated unfavorably on the following dimensions: distractibility, persistence, dependence, organization, impulsivity, frustration tolerance, daydreaming, and ability to follow directions (simple or a sequence). Using the same rating scale, investigators in the United Kingdom (Yule *et al.*, 1984) and Greece (Hatzakis *et al.*, 1985) generally replicated these findings. The results of the eight-country European Multicenter Study did not, however (Winneke *et al.*, 1990).

The possible associations between lead and other expressions of social and emotional dysfunction have received little attention. Two studies from the United

Kingdom reported lead-associated increases in teacher-reported "acting out" behavior (Yule *et al.*, 1984; Thomson *et al.*, 1989). Neither study reported significant associations between lead and problems that might be characterized as more "internalized" (i.e., neurotic). Among Taiwanese children, tooth lead level was not associated with either neurotic or antisocial behavior (Rabinowitz *et al.*, 1993). In a recent study (Sciarillo *et al.*, 1992), 2- to 5-year-old children with blood lead levels persistently above 15 μg/dl had total problem behavior scores on the parent-completed Child Behavior Checklist that were 5 points higher than the scores of children with lower blood lead levels. The children with higher levels were almost three times more likely to be assigned total problem behavior scores in the "clinical" range (95% CI: 1.2, 5.7).

The goal of this study was to contribute additional information about the association between "low-level" prenatal and postnatal lead exposure and childhood behavior problems by collecting teachers' ratings of a population-based sample of 8-year-old children.

METHODS

Sample

Children born at the Lying-In Division of the Boston Hospital for Women (now Brigham and Women's Hospital) between April 1979 and March 1980 were eligible for this study. Mothers were recruited shortly after delivery. As described elsewhere (Leviton *et al.*, 1993a), 3814 of the 4354 children born during this period were eligible for future follow-up. Parents of 177 infants had refused to grant consent to be contacted about future studies. Reasons for exclusion of the other 363 infants included death, adoption or custody change, location unknown, medical record not found, or participation in an ongoing study of this birth cohort. Of the 3814 eligible children, 605 could not be located and the parents of 552 either declined to participate or failed to respond to repeated mailed requests for consent. Thus, 2657 infants were enrolled. When each child was 6 years old, parents were asked to send us one of their child's shed deciduous teeth, complete a brief questionnaire, and to grant permission for us to send two questionnaires to the child's teacher, the Boston Teacher Questionnaire (Leviton *et al.*, 1993b,c) and the Teacher Report Form (Achenbach and Edelbrock, 1986).

Indices of Lead Exposure

Umbilical cord blood lead level. The level of lead in umbilical cord blood was measured in duplicate by anodic stripping voltammetry (ESA Model 2014, Bedford, MA). QA/QC procedures included participation in the quarterly blind interlaboratory comparisons then sponsored by the Blood Reference Program of the Centers for Disease Control and use of the bovine liver standard furnished by the National Bureau of Standards. Details of the measurements are described elsewhere (Rabinowitz and Needleman, 1982). The mean cord blood lead level of the children who participated in this follow-up study was 6.8 μg/dl (SD = 3.1; range 0.1–35.1 μg/dl; 95th percentile, 12.2).

Tooth lead level. One or more teeth were received from 1982 children. Lead in the dentin of these teeth was measured by anodic stripping voltammetry (ESA Model 3010A) using methods described by Rabinowitz *et al.* (1989). Briefly, tooth lead was determined in two portions of dentin taken from the zone considered to represent cumulative postnatal deposition. Values for the two specimens were averaged if they differed by 2.5 μg/g or less. Otherwise, two additional portions of the tooth were analyzed and the three closest values averaged. (This was necessary for less than 15% of the teeth.) The concentrations of lead in the internal standards used to monitor the analytical system were determined by the reference method of isotope dilution mass spectrometry.

A total of 2528 teeth were submitted. When a child submitted more than one tooth, only the first was considered. The mean tooth lead level was 3.4 μg/g (SD = 2.4; range, 0.1–28.9; 95th percentile, 7.4).

Outcome Measure

Teachers rated the children's behavior using the Teacher Report Form (TRF) of the Child Behavior Profile (Achenbach and Edelbrock, 1986). This instrument was modeled after the parent-completed Child Behavior Checklist (Achenbach and Edelbrock, 1983) and includes items pertaining to behavior in the school setting. The teacher is asked to judge whether a child manifests any of 118 "problem behaviors" using a 3-point scale (0 = not true, 1 = somewhat or sometimes true, 2 = very true or often true). Examples include: "acts too young for his/her age," "defiant, talks back to staff," "confused, seems to be in a fog," "nervous, high-strung, tense," "likes to be alone," "stubborn, irritable, sullen." The TRF was sent to each teacher in March of the school year to ensure that his or her judgments were based on sufficient experience with the child. A child's ratings were not included in the analyses if the teacher reported having known the child for less than 6 months. Teachers were blind to children's blood and tooth lead levels. A total of 1782 completed TRFs were received and computer-scored using the TR-SCORE program (version 2.2).

The TRF yields scores on 9 "narrow-band" scales, 2 "broad-band" scales, and a total problem behavior (TPB) score. For 6 to 11 year olds, the age range relevant to the present study, the narrow-band scales are anxious, social withdrawal, unpopular, self-destructive, aggressive, nervous–overactive, inattentive, obsessive–compulsive (boys only), and depressed (girls only). The broad-band scales are "internalizing" (consisting of anxious and social withdrawal scores), and "externalizing" (consisting of inattentive, nervous–overactive, and aggressive scores). These broad-band scales distinguish overcontrolled (inhibited/fearful) behavior from undercontrolled (aggressive/antisocial) behavior.

Potential Confounding Variables

Two sources provided information about factors that might confound an estimate of the association between lead exposure and behavior problems. A 150-item in-hospital interview conducted with each mother in the postdelivery period and an obstetric/pediatric record review provided information about the family's sociodemographic characteristics, the mother's general medical and reproductive history, the course of the index pregnancy, labor, and delivery, and the child's neonatal status. When children were 6 years old, their parents were sent a questionnaire intended to provide information about current sociodemographic status, as well as medical and behavioral histories of the children (e.g., child care arrangements, parental separation/divorce, birth of siblings, childhood illnesses and injuries).

Statistical Analyses

Because both cord blood and tooth lead levels were positively skewed, the natural log transformation was applied to each. In analyses of the association between children's lead levels and their behavior, TRF ratings were expressed in several ways:

(1) TPB and broad-band scores were analyzed as both continuous and dichotomous variables. The recommended cutoff for identifying TPB and broad-band scores "in the clinical range" is the 89th percentile (Achenbach and Edelbrock, 1986). An "extreme" score was defined as a T score of 60 or higher. In our cohort, this identified 12.2, 11.1, and 12.5% of children as having extreme scores on the TPB, internalizing, and externalizing scales, respectively.

(2) Scores on the narrow-band scales were not analyzed as continuous variables due to extreme skew. For most scales, 75 to 80% of children had the lowest T score possible (55). Scores were analyzed as dichotomous variables only, using empirically derived cutoffs corresponding as closely as possible to the 89th percentiles: anxious ($\geq$61, 11.8%), social withdrawal ($\geq$63, 10.8%), depressed ($\geq$60, 11.9%), unpopular ($>$61, 13.2%), self-destructive ($\geq$63, 14.1%), obsessive–compulsive ($\geq$63, 10.4%), inattentive ($\geq$62, 10.6%), nervous–overactive ($\geq$61, 13.2%), and aggressive ($\geq$60, 11.1%).

Identification of potential confounders and model selection. Spearman rank-order correlations and bivariate regressions were computed to identify prenatal, perinatal, and postnatal medical and social factors that were associated with indices of childhood lead exposure and with childhood behavior problems. Different covariate models were derived for different combinations of exposure (i.e., umbilical cord blood lead level, tooth lead level) and outcome (i.e., TPB, internalizing, externalizing) by identifying variables that were associated with both exposure and outcome at $P < 0.25$. In addition to variables selected using this empirical criterion, other variables were added to models on the basis of their plausibility as confounders (e.g., child sex, maternal marital status, care-taking arrangements, sibship size). We did not include variables judged to be potential indicators of increased lead exposure (e.g., bed wetting, maternal blood pressure during labor, child height, premature rupture of the membranes). The number of variables included in the multiple linear regression models fitted initially was generally large (up to 31). Models were reduced by backward elimination regression using $P < 0.10$ as the criterion for retention. The variables in these "trimmed" models are presented in Table 1.

To assess the nature of any dose–effect relationships, least-squares adjusted means, calculated on the basis of the trimmed models, were computed for children categorized into eight groups according to 1 μg/g increments in tooth lead or 2 μg/dl increments in cord blood lead level.

TABLE 1

"TRIMMED" REGRESSION MODELS FOR SUMMARY SCORES AND TWO INDICES OF LEAD BURDEN

Cord blood lead

Total problem behavior scale: prepregnant weight, birth weight, black (Y/N), cesarean section (Y/N), paternal education (years), sex, parents living together during child's first year (Y/N)

Internalizing scale: prepregnant weight, aspirin use during week before delivery (Y/N), black (Y/N), cesarean section (Y/N), maternal education (5–11, 12, 13–15, 16+ years), sex, birth weight

Externalizing scale: prepregnant weight, birth weight, black (Y/N), cesarean section (Y/N), urinary tract infection during pregnancy (Y/N), sex, paternal education (years), current medication use by child (Y/N), parents living together during child's first year (Y/N)

Tooth lead

Total problem behavior scale: prepregnant weight, black (Y/N), cesarean section (Y/N), mother married at time of delivery (Y/N), paternal education (years), sex, birth weight, mother smoking during pregnancy (never, current, stopped during pregnancy, stopped before pregnancy), maternal education (5–11, 12, 13–15, 16+ years)

Internalizing scale: prepregnant weight, cesarean section (Y/N), mother married at time of delivery (Y/N), mother on public assistance at time of delivery (Y/N), white (Y/N), maternal education (5–11, 12, 13–15, 16+ years), birth weight, sex

Externalizing scale: prepregnant weight, black (Y/N), cesarean section (Y/N), mother married at time of delivery (Y/N), prenatal care begun after first trimester (Y/N), paternal education (years), colic (Y/N), current medication use by child (Y/N), sibship size, sex, birth weight

The multiple logistic regression analyses evaluating the association between lead exposure indices and narrow-band scale scores were adjusted for the following factors: prepregnant weight, black (yes/no), delivery by cesarean section (yes/no), marital status at time of delivery (married/unmarried), paternal education (father's highest grade), maternal education (mother's highest grade), sex, birth weight, maternal smoking during pregnancy (yes/no), prenatal care began after the first trimester (yes/no), recipient of public assistance at time of delivery (yes/no), number of children in family at time of follow-up, child currently on medication (yes/no).

Because of the relatively low prevalence of extreme scores, the assessment of dose–response relationships was based on the stratification of children into four rather than eight exposure groups. The children were grouped by 4 μg/dl increments for cord blood lead and 2 μg/g increments for tooth lead. For both exposure indices, separate odds ratios were calculated for each of the three higher exposure groups, using the least-exposed group as the reference.

Statistical analyses were carried out using PC-SAS (SAS, 1988) and STATA (Computing Resource Center, 1992).

RESULTS

Sample

The children for whom completed Teacher Report Forms were available had lower cord blood lead levels than children for whom forms were not available (Table 2). These children also enjoyed better neonatal health, as they had higher birth weights and longer gestations, and fewer required placement in the special care nursery. A higher percentage of participating families was white. Mothers of participants had more years of education and were more often married at the time

TABLE 2
SAMPLE CHARACTERISTICS

	Teacher Report Form[a]		
	Present	Absent	*P* value
Sex (% male)	50.4	52.0	0.29
Birth weight[b] (g)	3397 ± 563	3258 ± 728	<0.001
Length of gestation[b] (weeks)	39.8 ± 2.1	39.5 ± 2.5	<0.001
Delivery by cesarean section (%)	23.0	21.0	0.11
Placement in special care nursery (%)	17.1	21.2	0.001
Race (% white)	90.7	59.7	<0.001
Maternal age at child's birth[b] (years)	29.4 ± 4.3	26.5 ± 5.8	<0.001
Maternal education (at delivery)			
% Grade 5–11	3.2	21.1	<0.001
% College graduate	55.7	31.5	
Married at time of delivery (%)	95.2	73.5	<0.001
Paternal education[b] (grade)	16.2 ± 2.9	*[c]	
Number of children in family[b]	2.4 ± 0.9	*	
Child cared for full-time by a parent (%)			
First year of life	90.2	*	
Second year of life	81.2	*	
Third year of life	74.3	*	
Child living with both parents (%)			
First year of life	95.4	*	
Second year of life	94.5	*	
Third year of life	92.8	*	
Log cord blood lead level[a] (μg/dl)	1.98 ± 0.38	2.02 ± 0.40	0.001
Dentin lead level[a] (ppm)	3.4 ± 2.4	*	

[a] *N* for Teacher Report Form "present" was a maximum of 1782; "absent" category represents the rest of the children in the original cohort.
[b] Mean ± SD.
[c] Information is not available on nonparticipants since it was collected at the time ratings on teacher report forms were obtained.

of delivery. Thus, the children for whom Teacher Report Forms were available are not representative of the original population and appear to be at lower risk for poor outcome. This is likely to have restricted the range of behavior scores in this cohort, especially the prevalence of scores reflecting problematic behaviors, reducing the likelihood of observing an association with lead level.

Overall Ratings on the Teacher Report Form

The mean *T* scores on the TPB scale, the broad-band scales and the narrow-band scales were similar for girls and boys (Table 3), as expected from the sex-specific procedures used to calculate standard scores. Regression analyses including sex × lead (cord or tooth level) interaction terms indicated that the associations between lead and behavior ratings did not differ significantly for boys and girls.

Total and Broad-Band Scores as Continuous Variables

Cord blood lead level was not significantly associated with TPB, internalizing,

TABLE 3
MEANS AND STANDARD DEVIATIONS OF SUMMARY AND SUBSCALE T SCORES ON THE TEACHER'S REPORT FORM

	Girls (N = 884)	Boys (N = 898)	Combined (N = 1782)
Summary scales			
Total problem behaviors	47.1 ± 8.8	47.9 ± 10.2	47.5 ± 9.5
Internalizing	49.6 ± 7.7	51.1 ± 8.5	50.3 ± 8.1
Externalizing	49.1 ± 7.3	49.1 ± 8.7	49.1 ± 8.0
Narrow-band scales			
Anxious	56.2 ± 3.3	56.9 ± 3.9	56.6 ± 3.6
Social withdrawal	57.1 ± 5.0	57.3 ± 4.8	57.2 ± 4.9
Depressed	56.7 ± 4.4	[a]	[a]
Unpopular	58.2 ± 3.8	56.8 ± 4.4	57.5 ± 4.1
Self-destructive	59.0 ± 2.9	57.0 ± 4.1	58.0 ± 3.7
Obsessive–compulsive	[a]	57.2 ± 4.7	[a]
Inattentive	56.3 ± 3.7	56.9 ± 4.2	56.6 ± 4.0
Nervous–overactive	56.5 ± 4.0	57.1 ± 4.5	56.8 ± 4.3
Aggressive	56.2 ± 3.4	56.5 ± 4.3	56.4 ± 3.9

[a] Scores on the "depressed" and "obsessive–compulsive" subscales are assigned only to girls and boys, respectively.

or externalizing scores, either in crude analyses or after adjustment (Table 4). Adjusted TPB scores for children classified by cord blood lead level showed virtually no trend (Fig. 1A). In contrast, the relationship between ratings and tooth lead level was modest but statistically significant for all three summary scales (Table 4). In crude analyses, an increase of one log unit in tooth lead level was associated with a 2.8 point increase in TPB score, and a 2 point increase in internalizing and externalizing score. After adjustment, the effect sizes were reduced to approximately 2 points per log unit for TPB score and approximately 1.5 points per log unit for both internalizing and externalizing scores. For all summary scales, adjusted scores increased systematically according to tooth lead level (Figs. 1B, 2A, and 2B). The mean TPB score of children in the highest tooth lead category (≥ 7 μg/g) was 3.4 points greater than the mean score of children in the lowest group (<1 μg/g). This represents a difference of approximately 0.35 standard deviation units on this scale.

As a check on the extent to which the trimmed model selected by backward elimination controlled for confounding, a "change-in-estimate" strategy was applied to determine if any variables omitted from the full model had an appreciable effect on the tooth lead coefficient. Using TPB as the outcome, the only variable not selected by backward elimination which produced more than a 10% change in the tooth lead coefficient was "vertex presentation at birth" (yes/no). Adding this variable to the trimmed model reduced the tooth lead coefficient by 6%, to 1.93 (SE = 0.62). Standard regression influence diagnostics indicated a satisfactory fit for the trimmed model of TPB.

In bivariate analyses, log tooth lead accounted for 1.8, 1.3, and 1.5% of the variance in TPB, internalizing, and externalizing scores, respectively. After ad-

TABLE 4
REGRESSION OF SUMMARY *T* SCORES ON LOG CORD BLOOD LEAD AND LOG TOOTH LEAD LEVEL

Scale	Crude	Adjusted	
		Full model	Trimmed model[a]
Cord blood lead			
TPB[b]	0.06[c] (−0.08, 0.20)[d] 1781, 0.38[e]	−0.31 (−1.69, 1.07) 1228, 0.66	−0.02 (−1.21, 1.17) 1515, 0.98
Int	−0.04 (−0.16, 0.08) 1781, 0.49	−0.43 (−1.51, 0.64) 1439, 0.43	−0.27 (−1.30, 0.75) 1567, 0.60
Ext	0.08 (−0.03, 0.20) 1781, 0.16	−0.28 (−1.35, 0.78) 1420, 0.61	0.08 (−0.92, 1.09) 1515, 0.87
Tooth lead			
TPB	2.81 (1.73, 3.89) 1410, .0001	1.79 (0.49, 3.09) 1000, 0.007	2.06 (0.93, 3.18) 1250, 0.0003
Int	2.07 (1.12, 3.02) 1410, 0.0001	1.33 (0.28, 2.37) 1176, 0.013	1.61 (0.62, 2.60) 1273, 0.002
Ext	2.15 (1.26, 3.05) 1410, 0.0001	1.58 (0.59, 2.57) 1160, 0.002	1.57 (0.64, 2.50) 1243, 0.001

[a] Variables in trimmed models are listed in Table 1.
[b] TPB, total problem behavior *T* score; Int, internalizing *T* score; Ext, externalizing *T* score.
[c] Regression coefficient represents the change in score for each natural log unit change in lead level.
[d] 95% confidence interval for the regression coefficient.
[e] *N*, *P* value associated with regression coefficient for lead.

justment for the variables in the trimmed models, the amounts of additional variance in TPB, internalizing, and externalizing scores that tooth lead accounted for were 0.7% (out of a total of 7.2% variance accounted for), 0.8% (out of 5.6%), and 0.8% (out of 7.6%), respectively.

Total and Broad-Band Scores Expressed as Dichotomous Variables

The adjusted odds ratios associated with cord blood lead level were approximately 1 for all three summary scores (Table 5). Calculation of separate odds ratios for different cord blood lead categories provided no indication of a dose–response relationship (Table 6).

As Fig. 1B suggests, the overall association between tooth lead level and children's TPB scores was not due solely to an increased risk of extreme scores among children with higher exposures. The adjusted risk (trimmed model) of having an extreme score on any of the three summary scales increased by approximately 40% with each log unit increase in tooth lead level (Table 5). For all three scales, the 95% CI's extended from slightly below 1 (0.94–0.98) to approximately 2 (1.97 to 2.13). The results were substantially the same when tooth lead level was fitted as a set of four categories (Table 6). Although the risk of an extreme score on any of the three scales was increased among children in the higher exposure categories, the elevations were modest, ranging from 1.1 to 1.5, and in no case did the 95% CI exclude 1.

Narrow-Band Scales

The percentages of children in different cord or tooth lead groups who were

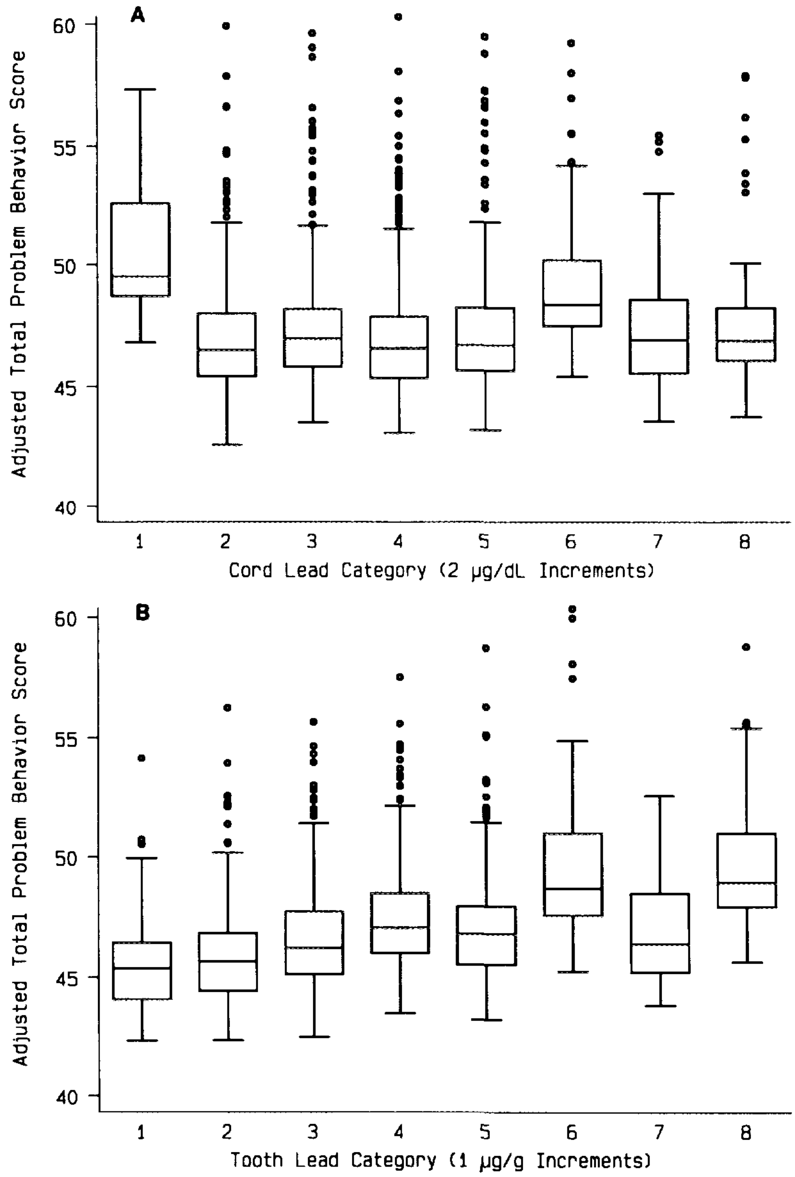

FIG. 1. Box plots of adjusted total problem behavior scores of children classified by umbilical cord blood lead level (A) or tooth lead level (B). Scores are adjusted for the variables in the trimmed models (Table 1). Boxes extend from the 25th to the 75th percentiles (the interquartile range). The "whiskers" extend to 1.5 times the interquartile range. Values exceeding this are plotted individually.

assigned extreme scores on the narrow-band scales are presented in Table 7. For cord blood lead level, the prevalence increased in a monotonic fashion for only the "unpopular" scale. The adjusted odds ratios for cord blood lead level derived from logistic regression analyses were approximately 1 for all scales (Table 8).

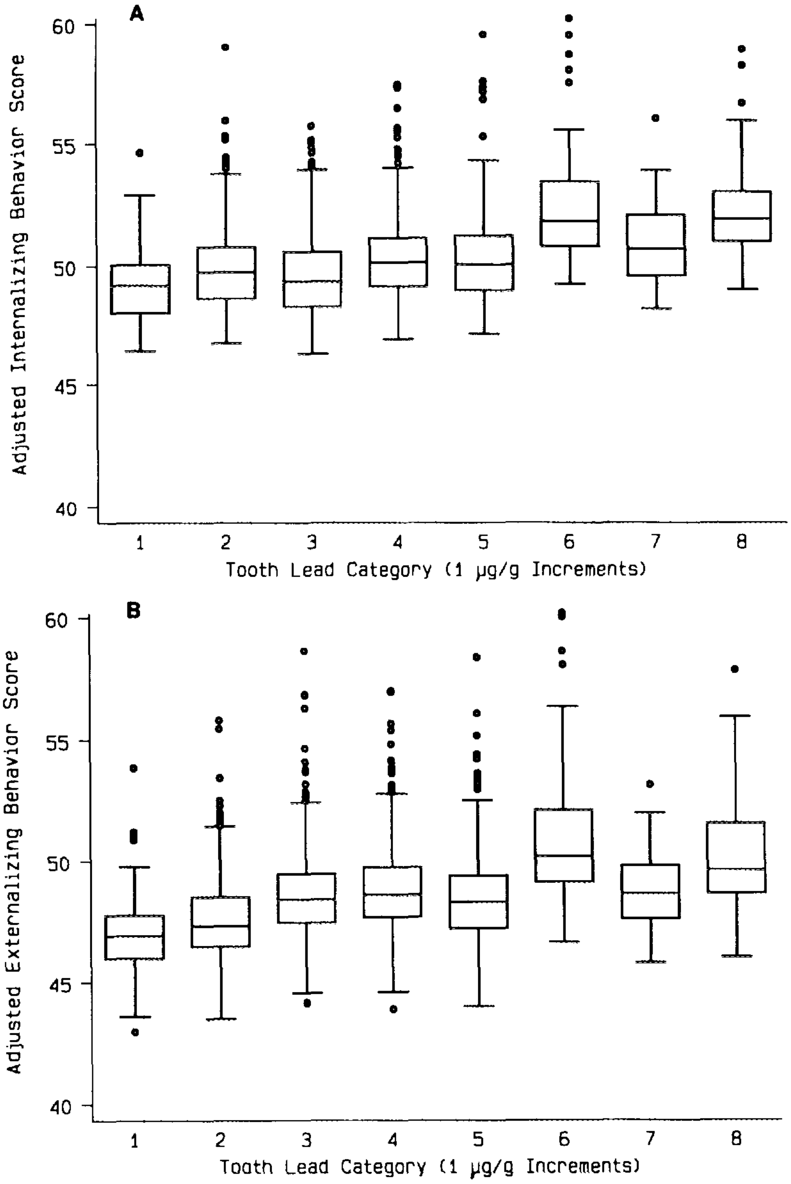

FIG. 2. Box plots of adjusted internalizing (A) and externalizing (B) broad-band scores for children classified by tooth lead level. Scores are adjusted for the variables in trimmed models (Table 1).

The prevalence of extreme scores on all subscales tended to increase across tooth lead categories (Table 7). For most scales, the adjusted risk of an extreme score increased from 30 to 60% for each log unit increase in tooth lead level (Table 8), although only for the nervous–overactive subscale did the increase reach statistical significance. The lower bounds of the 95% CI's were generally 0.8 to 0.9, while the upper bounds were 1.7 to 2.7.

TABLE 5
ADJUSTED ODDS RATIOS (95% CIs) FOR EXTREME SUMMARY SCORES ASSOCIATED WITH EACH LOG UNIT INCREASE IN CORD AND TOOTH LEAD LEVELS

	Crude	Adjusted[a]
Cord blood lead		
Total problem behaviors[b]	1.24 (0.85, 1.79) 1781, 0.27[c]	0.94 (0.63, 1.42) 1515, 0.78
Internalizing	0.95 (0.68, 1.32) 1781, 0.76	1.06 (0.74, 1.53) 1567, 0.74
Externalizing	1.32 (0.92, 1.91) 1781, 0.14	0.95 (0.63, 1.43) 1515, 0.79
Tooth lead		
Total problem behaviors	1.82 (1.26, 2.61) 1410, 0.001	1.42 (0.95, 2.13) 1250, 0.092
Internalizing	1.53 (1.11, 2.11) 1410, 0.009	1.39 (0.98, 1.97) 1273, 0.064
Externalizing	1.82 (1.27, 2.61) 1410, 0.001	1.41 (0.94, 2.12) 1243, 0.099

[a] Odds ratios were adjusted using trimmed models (Table 1).
[b] *T* scores for all three summary scores are categorized as greater than or less than 60.
[c] *N*, *P* value associated with regression coefficient for lead.

Children with an extreme score on one scale were at increased risk of an extreme score on another. The adjusted number of narrow-band scales on which a child's score was considered extreme increased significantly as tooth lead increased (0.24 scales for each log unit increase, SE = 0.10, $P = 0.018$). The percentages of children in the four tooth lead groups (defined by 2 μg/g increments) who were assigned extreme scores on four or more of the eight narrow-band scales were 7.2, 9.2, 10.3, and 14.1%, moving from lowest to highest tooth lead group.

Item Analysis

To provide a more concrete picture of the specific types of problem behaviors reported among children with increased tooth lead levels, separate multiple logistic regression analyses were conducted on the individual items of the TRF, adjusting for the same set of variables used in analyses of the narrow-band scores. Ratings of 1 (i.e., somewhat or sometimes true) and 2 (i.e., very true or often true) were combined to create a dichotomous score for each item. A total of 30 problem behaviors were associated with log tooth lead level at $P < 0.05$ (Table 9).

DISCUSSION

The risk of behavior problems was unrelated to children's prenatal lead exposure, at least as reflected by umbilical cord blood lead levels that were nearly all below 15 μg/dl. This is consistent with other evidence that prenatal exposures of this magnitude are less likely than postnatal exposures to have adverse effects that are detectable at school-age (Baghurst *et al.*, 1992; Bellinger *et al.*, 1992; Dietrich *et al.*, 1993).

TABLE 6

ADJUSTED ODDS RATIOS (95% CIs) FOR EXTREME SUMMARY SCORES ASSOCIATED WITH CATEGORIES OF CORD AND TOOTH LEAD[a,b]

Category	Total problem behaviors	Internalizing	Externalizing
Cord blood lead			
≤4.0 μg/dl	1.00	1.00	1.00
4.0–7.9 μg/dl	0.71 (0.46, 1.10)	1.16 (0.77, 1.76)	0.87 (0.55, 1.38)
	0.13[c]	0.48	0.55
8.0–11.9 μg/dl	0.90 (0.55, 1.46)	1.07 (0.67, 1.71)	1.14 (0.68, 1.89)
	0.66	0.78	0.62
≥12.0 μg/dl	0.53 (0.23, 1.24)	1.24 (0.63, 2.45)	0.49 (0.20, 1.22)
	0.14	0.54	0.12
Tooth lead			
≤2 μg/g	1.00	1.00	1.00
2.0–3.9 μg/g	1.22 (0.76, 1.96)	1.05 (0.71, 1.56)	1.12 (0.70, 1.80)
	0.41	0.82	0.63
4.0–5.9 μg/g	1.21 (0.68, 2.16)	1.11 (0.69, 1.80)	1.16 (0.65, 2.06)
	0.51	0.67	0.61
≥6.0 μg/g	1.31 (0.66, 2.60)	1.49 (0.85, 2.60)	1.26 (0.63, 2.50)
	0.44	0.16	0.51

[a] Odds ratios are interpreted as the increase in risk of extreme score associated with membership in lead category; lowest lead group is the reference category; odds ratios were adjusted using trimmed models (Table 1).

[b] *N* for total problem behavior scale analyses is 1515 for cord and 1250 for tooth; *N* for internalizing scale analyses is 1567 for cord and 1273 for tooth; *N* for externalizing scale analyses is 1515 for cord and 1243 for tooth.

[c] *P* value associated with the difference from the odds ratio of the reference group.

Our data are consistent with a modest association between children's postnatal lead exposure, as reflected by tooth lead levels, and the risk of teacher-reported behavior problems. Most tooth lead values were in the range of 0 to 10 μg/g, with behavior problem scores increasing by approximately 0.25 standard deviations for

TABLE 7

PERCENTAGE OF CHILDREN IN EACH LEAD CATEGORY WITH EXTREME SUBSCALE SCORES

	Cord blood lead (μg/dl), *N* = 1781				Tooth lead (μg/g), *N* = 1410			
Subscale	≤4	4.0–7.9	8–11.9	≥12	≤2	2–3.9	4–5.9	≥6
Anxious	11.0	12.6	11.0	10.9	11.3	10.6	11.8	16.3
Social withdrawal	11.4	10.6	10.5	12.9	8.8	10.2	10.3	15.6
Depressed	14.3	11.2	11.2	14.6	8.0	11.6	11.9	16.7
Unpopular	12.5	12.8	13.8	16.8	9.1	12.5	12.9	12.6
Self-destructive	14.7	13.4	16.1	10.9	11.0	13.5	12.2	19.3
Obsessive–compulsive	14.3	7.3	13.8	13.2	5.9	11.5	11.6	13.0
Inattentive	11.7	9.0	13.8	9.9	6.9	10.5	8.4	15.6
Nervous–overactive	13.9	11.7	15.9	14.9	9.4	12.8	12.9	18.5
Aggressive	12.5	10.1	12.4	10.9	9.1	10.3	9.5	12.6

TABLE 8

ODDS RATIOS (95% CIs, *P*) FOR EXTREME SUBSCALE SCORES ASSOCIATED WITH EACH LOG UNIT INCREASE IN CORD AND TOOTH LEAD LEVELS[a]

	Crude	Adjusted[b]
Cord blood lead		
Anxious	0.91 (0.63, 1.32, 0.62)	1.10 (0.73, 1.67, 0.65)
Social withdrawal	1.01 (0.68, 1.49, 0.97)	0.93 (0.60, 1.45, 0.75)
Depressed	0.84 (0.49, 1.45, 0.53)	0.78 (0.42, 1.46, 0.44)
Unpopular	1.09 (0.76, 1.56, 0.64)	0.94 (0.63, 1.40, 0.75)
Self-destructive	0.94 (0.67, 1.33, 0.73)	0.79 (0.54, 1.17, 0.24)
Obsessive–compulsive	1.23 (0.71, 2.15, 0.46)	1.16 (0.65, 2.06, 0.62)
Inattentive	1.33 (0.89, 1.97, 0.16)	1.13 (0.73, 1.76, 0.57)
Nervous–overactive	1.25 (0.87, 1.79, 0.22)	1.09 (0.74, 1.63, 0.66)
Aggressive	0.97 (0.66, 1.42, 0.86)	0.76 (0.50, 1.17, 0.21)
Tooth lead		
Anxious	1.52 (1.06, 2.17, 0.022)	1.41 (0.94, 2.10, 0.094)
Social withdrawal	1.61 (1.11, 2.34, 0.012)	1.36 (0.89, 2.07, 0.16)
Depressed	2.08 (1.26, 3.46, 0.004)	1.44 (0.77, 2.67, 0.25)
Unpopular	1.44 (1.01, 2.05, 0.045)	1.35 (0.91, 2.02, 0.14)
Self-destructive	1.56 (1.11, 2.19, 0.010)	1.17 (0.80, 1.71, 0.42)
Obsessive–compulsive	1.87 (1.10, 3.17, 0.021)	1.55 (0.88, 2.74, 0.13)
Inattentive	1.91 (1.30, 2.79, 0.001)	1.31 (0.85, 2.03, 0.22)
Nervous–overactive	1.93 (1.37, 2.72, 0.000)	1.61 (1.09, 2.38, 0.017)
Aggressive	1.37 (0.94, 2.00, 0.11)	1.18 (0.77, 1.80, 0.45)

[a] *N* is 1781 for crude analyses and 1511 for adjusted analyses, except for sex-specific scales of depressed (N = 884 and 742) and obsessive–compulsive (N = 897 and 769); N is 1410 for crude analyses and 1239 for adjusted analyses, except for sex-specific scales of depressed (N = 695 and 608) and obsessive–compulsive (N = 715 and 631).

[b] Variables for which the odds ratios are adjusted are listed in the text.

each log unit increase in tooth lead. The association was not limited to children manifesting the most problems or the highest levels of tooth lead. As Figs. 1B and 2 show, the frequency of problem behaviors increased in a nearly monotonic fashion as tooth lead level increased. Analyses in which behaviors were categorized (extreme/not extreme) generally produced less striking results than analyses in which behavior scores were treated as continuous variables. This would be expected if tooth lead level were associated in a graded fashion with the number of behavior problems, even below the cutoff used to dichotomize behavior scores.

Somewhat surprisingly, lead exposure was not more strongly associated with externalizing (i.e., undercontrolled) behavior problems than with internalizing (i.e., overcontrolled) behavior problems, as suggested by prior clinical and epidemiological studies (e.g., Byers and Lord, 1943; Needleman *et al.*, 1979; Thomson *et al.*, 1989; Sciarillo *et al.*, 1992). Historically, more attention may have been accorded undercontrolled behaviors because they are more readily apparent and more likely than overcontrolled behaviors to disrupt structured settings such as a classroom. Internalizing behaviors may be part of the full spectrum of behaviors in which lead's behavioral toxicity is expressed in children.

Although tooth lead levels provide information about some aspects of a child's

TABLE 9

TEACHER REPORT FORM ITEMS SIGNIFICANTLY ASSOCIATED WITH TOOTH LEAD LEVEL

P value	Item	Adjusted odds ratio[a]
<0.01	Behaves like opposite sex	5.3 (1.8, 15.2, 1207)
	Unclean personal appearance	4.9 (2.1, 11.3, 1204)
	Fears going to school	3.3 (1.4, 7.8, 1223)
	Messy work	1.8 (1.3, 2.4, 1233)
	Underactive, slow moving, or lacks energy	1.8 (1.2, 2.7, 1230)
	Too fearful or anxious	1.7 (1.2, 2.5, 1232)
	Cannot concentrate, cannot pay attention for long	1.6 (1.2, 2.2, 1233)
	Fidgets	1.6 (1.2, 2.2, 1235)
<0.025	Problems with eyes	2.2 (1.2, 4.0, 1183)
	Complains of loneliness	2.1 (1.1, 4.0, 1208)
	Feels or complains that no one loves him/her	2.1 (1.1, 4.1, 1237)
	Overtired	1.8 (1.1, 2.9, 1234)
	Unhappy, sad, depressed	1.7 (1.1, 2.6, 1232)
	Cannot sit still, restless, hyperactive	1.5 (1.1, 2.2, 1234)
	Worries	1.5 (1.1, 2.0, 1229)
	Inattentive, easily distracted	1.4 (1.1, 2.0, 1234)
<0.05	Vomiting, throwing up	4.9 (1.2, 20.5, 1144)
	Fears certain animals, situations, or places	2.5 (1.1, 5.7, 1189)
	Tardy to school or class	2.2 (1.1, 4.4, 1191)
	Prefers being with younger children	1.9 (1.1, 3.5, 1189)
	Dislikes school	1.8 (1.0, 3.1, 1234)
	Lying or cheating	1.8 (1.0, 3.3, 1236)
	Has difficulty learning	1.5 (1.0, 2.1, 1235)
	Hums or makes odd noises in class	1.5 (1.0, 2.2, 1230)
	Stubborn, sullen, or irritable	1.5 (1.0, 2.3, 1233)
	Underachieving, not working up to potential	1.4 (1.0, 2.1, 1234)
	Fails to finish things he/she starts	1.4 (1.0, 1.8, 1230)
	Difficulty following directions	1.4 (1.0, 1.8, 1235)
	Acts too young for his/her age	1.4 (1.0, 2.0, 1232)
	Impulsive or acts without thinking	1.4 (1.0, 2.0, 1238)

[a] Increase in odds ratio (95% CI, *N*) associated with each log unit increase in tooth lead; ratings of 1 and 2 were combined; variables for which the odds ratios were adjusted are listed in the text.

exposure history, our study provides little basis for distinguishing alternative hypotheses about temporal features of the association between tooth lead and behavior problems. For instance, behavior problems among children with the highest tooth lead levels may be primary or secondary to lead-induced cognitive problems. Increased psychiatric comorbidity among children with learning difficulties is well-described (Spreen, 1989). Stress that accompanies, contributes to, or results from learning or behavioral problems might affect lead metabolism, creating the epiphenomenon of an association between lead level and problem behaviors. In animal studies, for example, confinement stress increases mobilization of lead from deep body pools (Bushnell *et al.*, 1979). Finally, certain behavioral problems might increase the likelihood of lead exposure (i.e., increased activity, nail biting, pica). Regardless of their origin, however, behavior problems might be part of the clinical presentation of the child with elevated lead exposure, requiring assessment and possible intervention.

Despite the statistical significance of the association between tooth lead and behavior problems, the change in score per unit change in lead was very small. Furthermore tooth lead accounted for less than 1% of the variance in TPB scores. Like other lead-associated changes in health that may not be clinically significant for an individual child, this change, if confirmed as causal, may have substantial implications on a population basis because of the high prevalence of the implicated exposure levels.

As in all follow-up studies, the possibility of biased attrition should be considered. Although the sample size was relatively large, only 70% of the eligible population granted consent for this follow-up assessment and completed TRF forms were obtained for only 41%. This group of children had significantly lower cord blood lead levels and significantly better neonatal status, and their families were higher in socioeconomic status. Even among participants in this study, nonresponse on key variables was not always random with respect to exposure or outcome (Conaway *et al.*, 1992). Unfortunately, no information is available on the late status of nonparticipants and an assessment of follow-up bias should not be based solely on a comparison of starting characteristics (Vestbo and Rasmussen, 1992).

The poor fit of the multivariate models was quite striking. Models including as many as 30 sociodemographic and medical variables accounted for less than 10% of the variance in teachers' ratings. This is not unique to this study. The standard variables used in epidemiologic analysis, such as sex, age, and socioeconomic status, typically account for little of the variance in item scores (Achenbach and Edelbrock, 1986). Either the major determinants of childhood behavior problems have yet to be identified or they are measured poorly by the instruments available. This does, however, raise the possibility that the association observed between tooth lead and child behavior is attributable to residual confounding. One factor not measured in this study is family history of psychiatric illness. Children with a strong genetic predisposition toward behavior problems might tend to accumulate relatively high secondary lead burdens. On the other hand, complex models incorporating intergenerational direct and indirect effects of lead on the behavior of both parents and children can also be posited.

Another potentially important confounder that was not measured is the family microenvironment. In a previous study of the association between lead and TRF ratings in a small portion of this birth cohort, we assessed the importance of such factors as the home observation for measurement of the environment (HOME) (Caldwell and Bradley, 1984), the parenting stress index (PSI) (Abidin, 1986), and the family adaptability and cohesion evaluation scales (FACES) (Olson *et al.*, 1985). Adjustment for maternal IQ, HOME, PSI, and FACES scores as well as factors such as sex and SES reduced the coefficient for cumulative blood lead index by 48%. Thus, had we measured these family factors in the larger portion of the cohort, the difference between the crude and adjusted tooth lead coefficients might have been greater than the 25–30% reduction in magnitude that we observed, assuming that the pattern of covariance is similar in the two cohort subsamples. Finally, systematic information was not collected on life events that are sometimes associated with childhood behavior problems (e.g., deaths and illnesses in family, changes in employment and financial status, drug and alcohol use). If such events are also associated with a child's lead burden, they may confound an association between lead burden and behavior problems.

The potential impact of random misclassification in the teachers' ratings should also be considered. The children were distributed across a large number of classrooms, requiring us to seek the ratings assigned by many different teachers. Under the plausible hypothesis that all the teachers did not interpret and complete the TRF in exactly the same manner, variation in the ratings conveys information about interteacher differences as well as interchild differences. Being random, interteacher variability would produce bias toward the null hypothesis (i.e., toward finding no association between lead level and behavior).

In summary, teachers' ratings of children's problem behaviors are associated with lead levels in their shed teeth, presumably a reflection of postnatal exposure. Ratings are unrelated to children's blood lead levels measured at the time of birth. The lead-associated increase in problem behaviors is modest in magnitude and should be regarded as a preliminary finding because the possibility that it reflects residual confounding by unmeasured or poorly measured factors cannot be dismissed. The potential link between low-level lead exposure and behavior problems warrants additional study involving more detailed assessments of both childhood psychopathology and its risk factors.

REFERENCES

Abidin, R. (1986). "Parenting Stress Index—Manual" (PSI), 2nd ed, Pediatric Psychology Press, Charlottesville, VA.

Accardo, P., Whitman, B., Caul, J., and Rolfe, U. (1988). Autism and plumbism: A possible association. *Clin. Pediatr.* **27,** 41–44.

Achenbach, T., and Edelbrock, C. (1983). "Manual for the Child Behavior Checklist and Revised Child Behavior Profile," University of Vermont Department of Psychiatry, Burlington, VT.

Achenbach, T., and Edelbrock, C. (1986). "Manual for the Teacher's Report Form and Teacher Version of the Child Behavior Profile." University of Vermont Department of Psychiatry, Burlington, VT.

Baghurst, P., McMichael, A., Wigg, N., Vimpani, G., Robertson, E., Roberts, R., and Tong, S-L. (1992). Environmental exposure to lead and children's intelligence at the age of seven years. *N. Engl. J. Med.* **327,** 1279–1284.

Baker, E., Feldman, R., White, R., and Harley, J. (1983). The role of occupational lead exposure in the genesis of psychiatric and behavioral disturbances. *Acta Psychiatr. Scand. Suppl.* **67,** 38–48.

Baker, E., White, R., Pothier, L., *et al.* (1985). Occupational lead neurotoxicity: Improvement in behavioral effects after reduction of exposure. *Br. J. Ind. Med.* **42,** 507–516.

Balestra, D. (1991). Adult chronic lead intoxication: A clinical review. *Arch. Intern. Med.* **151,** 1718–1720.

Bellinger, D., Needleman, H., Bromfield, R., and Mintz, M. (1984). A follow-up study of the academic attainment and classroom behavior of children with elevated dentine lead levels. *Biol. Trace Elem. Res.* **6,** 207–223.

Bellinger, D., Stiles, K., and Needleman, H. (1992). Low-level lead exposure, intelligence, and academic attainment. *Pediatrics* **90,** 855–861.

Bleeker, M., Agnew, J., Keough, J., and Stetson, D. (1983). Neurobehavioral evaluation in workers following a brief exposure to lead. *In* "Neurobehavioral Methods in Occupational Health" (R. Gilioh, M. Cassitto and V. Foa, Eds.). Pergamon Press, Oxford.

Bushnell, P., Shelton, S., and Bowman, R. (1979). Elevation of blood lead concentration by confinement in the rhesus monkey. *Bull. Environ. Contam. Toxicol.* **22,** 819–826.

Byers, R., and Lord, E. (1943). Late effects of lead poisoning on mental development. *Am. J. Dis. Child.* **66**, 471–494.

Caldwell, B., and Bradley, R. (1984). "Administration Manual: Home Observation for Measurement of the Environment," rev. ed. Univ. of Arkansas at Little Rock.

Campbell, M., Petti, T., Green, W., *et al.* (1980). Some physical parameters of young autistic children. *J. Am. Acad. Child Psychiatr.* **19**, 193–212.

Centers for Disease Control (CDC) (1991). "Preventing Lead Poisoning in Young Children," U.S. DHHS, Atlanta, GA.

Cohen, D., Johnson, W., and Caparulo, B. (1976). Pica and elevated blood lead level in autistic and atypical children. *Am. J. Dis. Child.* **130**, 47–48.

Computing Resource Center (1992). "STATA Reference Manual: Release 3," 5th ed. Santa Monica, CA.

Conaway, M., Waternaux, C., Allred, E., Bellinger, D., and Leviton, A. (1992). Pre-natal blood lead levels and learning difficulties in children: An analysis of non-randomly missing categorical data. *Statistics in Medicine* **11**, 799–811.

Costello, E. (1989). Child psychiatric disorders and their correlates: A primary care pediatric sample. *J. Am. Acad. Child Adol. Psych.* **28**, 851–855.

Cullen, M., Robins, J., and Eskenazi, B. (1983). Adult lead intoxication. *Medicine* **62**, 221–247.

David, O., Clark, J., and Voeller, K. (1972). Lead and hyperactivity. *Lancet* **2**(7783), 900–903.

David, O., Hoffman, S., Sverd, J., and Clark, J. (1977). Lead and hyperactivity: Lead levels among hyperactive children. *J. Abn. Child Psychol.* **5**, 405–416.

Dietrich K., Berger, O., Succop, P., and Hammond, P. (1993). The developmental consequences of low to moderate prenatal and postnatal lead exposure: Intellectual attainment in the Cincinnati lead study cohort following school entry. *Neurotoxicol. Teratol.* **15**, 37–44.

Dumont, M. (1989). Psychotoxicology. *Soc. Sci. Med.* **29**, 1077–1082.

Fergusson, D., Fergusson, J., Horwood, L., and Kinzett, N. (1988). A longitudinal study of dentine lead levels, intelligence, school performance, and behaviour. *J. Child Psychol. Psychiatr.* **29**, 811–824.

Fergusson, D., Horwood, L., and Lynskey, M. (1993). Early dentine lead levels and subsequent cognitive and behavioural development. *J. Child Psychol. Psychiatr.* **34**, 215–227.

Gittelman, R., and Eskenazi, B. (1983). Lead and hyperactivity revisited: An investigation of nondisadvantaged children. *Arch. Gen. Psychiatr.* **40**, 827–833.

Haenninen, M., Mantere, P., Hernberg, S., Seppalainen, A., and Koch, B. (1979). Subjective symptoms in low-level exposure to lead. *Neurotoxicology* **1**, 333–347.

Haggerty, R. (1988). Behavioral pediatrics: A time for research. *Pediatrics* **81**, 179–185.

Hamburg, B. (1989). Research on child and adolescent mental disorders. *Science* **246**, 738.

Hansen, O., Trillingsgaard, A., Beese, I., Lyngbye, T., and Grandjean, P. (1989). A neuropsychological study of children with elevated dentine lead level: Assessment of the effect of lead in different socioeconomic groups. *Neurotoxicol. Teratol.* **11**, 205–213.

Harvey, P., Hamlin, M., and Kumar, R. (1984). Blood lead, behaviour and intelligence test performance in preschool children. *Sci. Tot. Environ.* **40**, 45–60.

Hatzakis, A., Salaminios, F., Kokevi, A., *et al.* (1985). Blood lead and classroom behaviour of children in two communities with different degree of lead exposure: Evidence of a dose-related effect? *Int. Conf. Heavy Metals Environ.* **1**, 47.

Hogstedt, C., Hane, M., Agrell, A., and Bodin, L. (1983). Neuropsychological test results and symptoms among workers with well-defined long-term exposure to lead. *Br. J. Ind. Med.* **40**, 99–105.

Institute of Medicine–National Academy of Sciences (IOM–NAS) (1989). "Research on Children and Adolescents with Mental, Behavioral and Developmental Disorders: Mobilizing a National Initiative," NAS Press, Washington, DC.

Laughlin, N. (1986). Animal models of behavioral effects of early lead exposure. *In* "Handbook of Behavioral Teratology" (E. Riley and C. Vorhees, Eds.), pp. 291–319, Plenum, New York.

Laughlin, N., Bushnell, P., and Bowman, R. (1991). Lead exposure and diet: Differential effects on social development in the rhesus monkey. *Neurotoxicol. Teratol.* **13**, 429–440.

Leviton, A., Bellinger, D., Allred, E., Rabinowitz, M., Needleman, H., and Schoenbaum, S. (1993a).

Pre- and postnatal low-level lead exposure and children's dysfunction in school. *Environ. Res.* **60**, 30–43.

Leviton, A., Guild-Wilson, M., Neff, R., and Gambill, P. (1993b). The Boston teacher questionnaire. 1. Definition of syndromes. *J. Child Neurol.* **8**, 43–53.

Leviton, A., Kirby, C., Guild-Wilson, M., and Neff, R. (1993c). The Boston teacher questionnaire. 2. Assessments of validity. *J. Child Neurol.* **8**, 54–63.

Mailman, R., and DeHaven, D. (1984). Responses of neurotransmitter systems to toxicant exposure. *In* "Cellular and Molecular Neurotoxicity" (T. Narahasi, Ed.), pp. 207–224, Raven Press, New York.

McCracken, J. (1987). Lead intoxication psychosis in an adolescent. *J. Am. Acad. Child Adol. Psychiatr.* **26**, 274–276.

Milar, C., Schroeder, S., Mushak, P., and Boone, L. (1981). Failure to find hyperactivity in preschool children with moderately elevated lead burden. *J. Ped. Psychol.* **6**, 85–95.

Needleman, H., and Bellinger, D. (1991). The health effects of low level exposure to lead. *Annual Review of Public Health* **12**, 111–140.

Needleman, H., Gunnoe, C., Leviton, A., *et al.* (1979). Deficits in psychologic and classroom performance of children with elevated dentine lead levels. *N. Engl. J. Med.* **300**, 689–695.

Oliver, B. (1967). Aspects of lead absorption in hospitalised psychotic children. *J. Ment. Defic. Res.* **11**, 132–142.

Olson, D., Portner, L., and Lavee, Y. (1985). "Family Adaptability and Cohesion Evaluation Scales—III" University of Minnesota, Minneapolis, MN.

Parkinson, D., Ryan, C., Bromet, E., and Connell, M. (1986). A psychiatric epidemiologic study of occupational lead exposure. *Am. J. Epidemiol.* **123**, 261–269.

Pasternak, G., Becker, C., Lash, A., Bowler, R., Estrin, W., and Law, D. (1989). Cross-sectional neurotoxicology study of lead-exposed cohort. *Clin. Toxicol.* **27**, 37–51.

Rabinowitz, M., and Needleman, H. (1982). Temporal trends in the lead concentrations of umbilical cord blood. *Science* **216**, 1429–1431.

Rabinowitz, M., Leviton, A., and Bellinger, D. (1989). Blood lead–tooth lead relationship among Boston children. *Bull. Environ. Contam. Toxicol.* **43**, 485–492.

Rabinowitz, M., Wang, J-D., and Soong, W-T. (1993). Lead and classroom performance at seven primary schools in Taiwan. *In* "Research in Human Capital and Development," Vol. 7, pp. 253–272, JAI Press, London.

Romano, C., and Grossi-Bianchi, M. (1968). Aphasia and dementia in childhood chronic lead encephalopathy: A curable form of acquired mental impairment. *Panminerva Med.* **10**, 448–450.

SAS Institute Inc. (1988). "SAS/STAT User's Guide, Release 6.03." SAS Institute Inc., Cary, NC.

Schottenfeld, R., and Cullen, M. (1984). Organic affective illness associated with lead intoxication. *Am. J. Psychiatr.* **141**, 1423–1426.

Sciarillo, W., Alexander, G., and Farrell, K. (1992). Lead exposure and child behavior. *Am. J. Public Health* **82**, 1356–1360.

Silva, P., Hughes, P., Williams, S., and Faed, J. (1988). Blood lead, intelligence, reading attainment and behaviour in eleven year old children in Dunedin, New Zealand. *J. Child Psychol. Psychiatr.* **29**, 43–52.

Spreen, O. (1989). The relationship between learning disability, emotional disorders, and neuropsychology: Some results and observations. *J. Clin. Exp. Neuropsychol.* **11**, 117–140.

Thomson, G., Raab, G., Hepburn, W., Hunter, R., Fulton, M., and Laxen, D. (1989). Blood-lead levels and children's behaviour: Results from the Edinburgh lead study. *J. Child Psychol. Psychiatr.* **30**, 515–528.

Vestbo, J., and Rasmussen, F. (1992). Baseline characteristics are not sufficient indicators of non-response bias in follow-up studies. *J. Epidemiol. Comm. Health* **46**, 617–619.

Weiss, B. (1985). Intersections of psychiatry and toxicology. *Int. J. Ment. Health* **14**, 7–25.

Winneke, G., Brockhaus, A., Ewers, U., Kramer, U., and Neuf, M. (1990). Results from the European multicenter study on lead neurotoxicity in children: Implications for risk assessment. *Neurotoxicol. Teratol.* **12**, 553–559.

Yule, W., Urbanowicz, M., Lansdown, R., and Millar, I. (1984). Teachers' ratings of children's behaviour in relation to blood lead levels. *Br. J. Dev. Psychol.* **2**, 295–305.