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TO: ILZRO Lead Environmental Health Technical Committee
Members of the Sydney Cohort Study Steering Committee

FROM: Craig J. Boreiko, Ph.D.
Manager, Environmental Health

DATE: November 4, 1992

SUBJECT: Lead and Child Development

Enclosed you will find a variety of items that may be of interest to you. The Port Pirie Child Development study has just published their seven-year follow-up in the New England Journal of Medicine. A copy of the publication is enclosed, along with an editorial by Katherine Mahaffey which appeared in the same issue of the journal. The Port Pirie Child Development study reports that there is a small, but statistically significant, effect of lead upon the intellectual development of children. The deficits reported are related to the lifetime average blood lead concentration in the study cohort. In essence, this mode of data expression suggests that prolonged elevated exposure to lead, as opposed to transient increases, are those which should be attributed greater significance from a public health perspective. The Port Pirie findings are difficult to interpret in isolation - results from the other prospective studies will greatly facilitate our interpretation of the newly emerging data base.

The Boston and Cincinnati Prospective studies will be publishing their findings in the journal Pediatrics over the next several months. The Boston study will be reporting similar results from their ten-year follow-up with a dose-response that may be similar to that of Port Pirie. The Cincinnati Prospective study will also be reporting effects of lead upon intellectual development. In the Cincinnati study, we anticipate that the dose-response curves will suggest that the effects of lead are minimal below 20 µg/dl cumulative exposure. This 20 µg/dl "threshold" is interesting in light of the Port Pirie findings that there may be a discontinuity in the dose-response curve at approximately 17.5 µg/dl (figure 1). Although effects on IQ shall be reported by all studies, careful attention should be paid to the level of consistency observed (e.g. verbal vs. performance, male vs. female, etc.) in the outcome measures reported to be impacted by lead exposure.

I have also enclosed a copy of a review article produced by researchers at the Center for Disease Control. This article by Thacker et al. reviews the previously published data of the five prospective studies, discusses the limitations of meta-analysis in the analysis of the prospective study data, and concludes that a weight of evidence approach is optimal for interpretation of the data. In essence, this review concludes that definitive statements regarding the effects of low-lead lead exposure on IQ cannot be derived from the existing longitudinal data. However, using a weight of evidence approach which factors in the

results of other studies, the authors suggest that there is an adverse effect of lead upon intellectual development in children. I would like to draw your attention to Table 3 of the Thacker et al. paper. The Sydney cohort study has consistently reported the absense of lead effects. A variety of individuals have criticized the study for "methodological weaknesses" and cite this as a reason for the failure of the study to detect a lead effect. The CDC researchers conducted an interesting exercise during the course of their review. The methodologies employed during the course of the various prospective studies were stripped of all identifiers and sent to an independent panel of scientific experts for review. The Sydney study was judged to be the study with the strongest design characteristics by all reviewers. The Port Pirie and Cleveland studies "tied" for second. Boston was next, followed by Cincinnati.

I hope you find the enclosures to be of interest. Please do not hesitate to contact me should you have any questions or comments.

Best regards,

Craig J. Boreiko, Ph.D.
Manager, Environmental Health

CJB/mf

ENVIRONMENTAL EXPOSURE TO LEAD AND CHILDREN'S INTELLIGENCE AT THE AGE OF SEVEN YEARS

The Port Pirie Cohort Study

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Abstract *Background.* Exposure to lead in early childhood is thought to result in delayed neuropsychological development. As yet there is little longitudinal evidence to establish whether these effects persist into later childhood.

Methods. We measured IQ scores in 494 seven-year-old children from the lead-smelting community of Port Pirie, Australia, in whom developmental deficits associated with elevated blood lead concentrations had already been reported at the ages of two and four years. Exposure to lead was estimated from the lead concentrations in maternal blood samples drawn antenatally and at delivery and from blood samples drawn from the children at birth (umbilical-cord blood), at the ages of 6 and 15 months and 2 years, and annually thereafter. Data relating to known covariates of child development were collected systematically for each child throughout the first seven years of life.

Results. We found inverse relations between IQ at the age of seven years and both antenatal and postnatal blood lead concentrations. After adjustment by multiple regression for sex, parents' level of education, maternal age at delivery, parents' smoking status, socioeconomic status, quality of the home environment, maternal IQ, birth weight, birth order, feeding method (breast, bottle, or both), duration of breast-feeding, and whether the child's natural parents were living together, the relation with lead exposure was still evident for postnatal blood samples, particularly within the age range of 15 months to 4 years. For an increase in blood lead concentration from 10 μg per deciliter (0.48 μmol per liter) to 30 μg per deciliter (1.45 μmol per liter), expressed as the average of the concentrations at 15 months and 2, 3, and 4 years, the estimated reduction in the IQ of the children was in the range of 4.4 points (95 percent confidence interval, 2.2 to 6.6) to 5.3 points (95 percent confidence interval, 2.8 to 7.8). This reduction represents an approximate deficit in IQ of 4 to 5 percent.

Conclusions. Low-level exposure to lead during early childhood is inversely associated with neuropsychological development through the first seven years of life. (N Engl J Med 1992;327:1279-84.)

EXPOSURE to low levels of lead in childhood may result in impaired neuropsychological development and classroom performance.[1] The extent of this relation, however, after adjustment for the confounding effects of socioeconomic and environmental covariates, has been debated.[2-17] Taken together, the epidemiologic studies indicate a moderate inverse relation between the body burden of lead (measured as blood or tooth lead concentrations) and the neuropsychological or cognitive performance of children.[18-22] Whether the effects disappear once lead exposure ceases or whether early exposure to lead has effects on neuropsychological development that persist into later life is uncertain. Longitudinal studies are clearly the best way to address this question.

The Port Pirie Cohort Study began in 1979. Early results showed considerable interindividual variation in blood lead concentrations during early childhood,[23-25] with approximately one third of the children in this lead-smelting community having concentrations above 25 μg per deciliter (1.21 μmol per liter) on one or more occasions. Mental development was found to be inversely associated with postnatal blood lead concentrations at the ages of two and four years, after adjustment for confounding factors.[6,7] It was estimated that a child with a blood lead concentration of 30 μg per deciliter (1.45 μmol per liter) had a deficit of 3.3 points (approximately 3.2 percent) on the Bayley Mental Development Index at the age of two years, and of 7.2 points (approximately 6.7 percent) on the McCarthy General Cognitive Index at the age of four years, as compared with a child with a blood lead concentration of 10 μg per deciliter (0.48 μmol per liter). The cohort has now been followed into the primary-school age range. This paper examines intelligence at the age of seven years in relation to lifetime exposure to lead.

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METHODS

The Cohort

The original study population comprised 723 singleton infants born in and around Port Pirie, South Australia, during the three-year period from 1979 to 1982. These infants represented an estimated 90 percent of all singleton live births in the community during this period. Of the 516 children who remained in the study through the age of seven years, developmental status (including intelligence) was assessed in 494 within the specified age range of seven to eight years.

Data Collection

Four trained nurse-interviewers collected up to three venous-blood samples from each mother before delivery, a sample from the umbilical cord at birth, and capillary-blood samples from each child at the ages of 6 and 15 months and 2 years, and annually thereafter.[23,24] A pilot study demonstrated that the lead concentrations in

capillary-blood samples, collected according to a strict protocol, were highly correlated ($r = 0.97$) with the lead concentrations determined in venous-blood samples taken from 47 children who were two to four years of age.

At the time of each blood sampling, the nurse-interviewer also conducted a structured interview to obtain information on a range of demographic, psychosocial, medical, and environmental factors.

Measurement of Blood Lead Concentrations

Blood lead concentrations were measured by electrothermal atomization atomic-absorption spectrometry.[26] The analyses were subject to internal and external quality-control procedures, with consistently satisfactory results.[24] The results were standardized to a packed-cell volume of 35 percent for all samples except cord blood, for which a value of 50 percent was used.

Developmental Assessment

The IQ of each child was measured under uniform conditions by means of the revised version of the Wechsler Intelligence Scale for Children (WISC-R).[27] The WISC-R comprises 10 sequentially administered subscales. Although they do not in themselves measure discrete neuropsychological functions, the first five subscales (information, similarities, arithmetic, vocabulary, and comprehension) are used to estimate a verbal IQ, and the remaining subscales (picture completion, picture arrangement, block design, object assembly, and coding) are used to estimate a performance IQ. All children were evaluated by the same research psychologist, who was unaware of each child's lead-exposure status. Although the psychologist had also assessed the child's abilities at the ages of two and four years, he was not formally aware of the earlier results. The median age of the children on the day of testing was 186 days after their seventh birthday (the 25th and 75th percentiles were 132 and 246 days, respectively).

Covariate Measures

Other factors likely to confound the relation between lead exposure and IQ, and for which ancillary information was collected, included socioeconomic status (established with use of Daniel's Scale of Prestige of Occupations in Australia[28]), the care-giving environment (assessed by the Home Observation for the Measurement of the Environment [HOME] inventory[29]), maternal intelligence (measured with the Wechsler Adult Intelligence Scale[30]), parental smoking habits and years of secondary education, whether the parents were living together, the birth weight and birth order of the child, and the duration of breast-feeding during infancy.

Statistical Analysis

Statistical analyses were performed on the natural logarithm of the blood lead concentration, and all reported mean values are geometric. For each child, a curve plotting the blood lead concentration against age was constructed. The lifetime average blood lead concentration up to a particular age was estimated by dividing the appropriate area under the curve by the specified age.

The effects of potential confounding factors were investigated by multiple regression analysis with (log) blood lead concentration as a continuous explanatory variable. The covariates used in the final models included sex, birth weight, birth order, feeding method (breast, bottle, or both), duration of breast-feeding, parents' level of education, maternal age at delivery, parents' smoking status, socioeconomic status, quality of the home environment, maternal IQ, and whether the child's natural parents were living together.

Results

Loss to Follow-up

The 207 children born into the cohort but subsequently lost to follow-up were similar to the 516 who remained in the study with respect to 12 of the 15 variables studied. The socioeconomic status of the children lost to follow-up was slightly lower, more of their mothers smoked (35 percent vs. 27 percent), and fewer were breast-fed during infancy (32 percent vs. 37 percent). The mean umbilical-cord blood lead concentrations for the two groups were almost identical (9.3 vs. 8.9 μg per deciliter [0.45 vs. 0.43 μmol per liter]).

Blood Lead Concentrations

The geometric mean lead concentrations in maternal blood collected both antenatally and at delivery, in cord blood, and in capillary samples collected throughout childhood are shown (according to quartile) in Table 1. The blood lead concentrations were highest at the age of two years; by the age of seven years the mean values had fallen by over 40 percent. Lifetime averages at each age are also shown.

Age-Specific Blood Lead Concentration and Children's IQ

The mean scores for verbal IQ, performance IQ, and full-scale IQ were 103.1 (95 percent confidence interval, 101.8 to 104.4), 105.9 (95 percent confidence interval, 104.6 to 107.1), and 104.7 (95 percent confidence interval, 103.5 to 106.0), respectively. There was a consistent inverse relation between the blood lead concentrations and scores on all IQ scales (Table 2). The mean IQ scores differed by 2.7 to 12 percent between the children with values in the highest and lowest quartiles for blood lead concentration.

The unadjusted relation between IQ and lifetime average blood lead concentration at the age of seven years is shown in Figure 1. For each IQ scale, there was an inverse gradient across most of the range of blood lead concentration. There is a suggestion that this gradient was less steep at higher exposures (>20.0 μg per deciliter [>0.97 μmol per liter]), but because of the paucity of children with such exposure levels, there is greater statistical variability associated with these higher exposures. The gradient is steeper for verbal IQ than for performance IQ. The proportion of the variance of full-scale IQ that could be accounted for by the blood lead concentration at different ages (without consideration of the covariates) varied from 1.4 to 6.1 percent.

Other Covariates and Children's IQ

The unadjusted mean IQ scores for subgroups divided according to covariates that may confound the relation between lead exposure and IQ are shown in Table 3. Many sociodemographic factors and neonatal or infant characteristics were strongly related to the child's IQ, in the anticipated direction. Socioeconomic status, the quality of the home environment, and maternal intelligence were the variables most strongly associated with IQ and in simple regression analysis accounted for 8.4, 12.0, and 13.3 percent, respectively, of the variance of the full-scale IQ. Sex and birth order of the child were not significant correlates of IQ.

In simple regression analyses all measures of blood lead concentration (antenatal, delivery, and postnatal averages) were significantly inversely associated with

verbal, performance, and full-scale IQ. The inverse relation of the blood lead concentration to verbal IQ was consistently stronger than its relation to performance IQ. In multiple regression analyses (Table 4), the effect of adjusting for the covariates in Table 3 was to attenuate markedly the apparent association of the child's IQ with the various measures of blood lead concentration. In particular, the regression coefficients associated with the lead concentrations in antenatal, delivery, and cord-blood samples became insignificant. The covariates contributing most to this attenuating effect were those identified as being most closely related to IQ: socioeconomic status, HOME score, and maternal IQ. However, for lifetime average blood lead concentrations ranging from birth through 15 months to birth through 4 years, there were statistically significant inverse associations with verbal IQ and full-scale IQ. On the basis of regression analysis, an increase in blood lead concentration from 10 to 30 μg per deciliter (0.48 to 1.45 μmol per liter) was associated with a deficit in verbal IQ that varied according to age from 5.5 to 6.4 points (5.6 to 6.2 percent), and in full-scale IQ the estimated deficit was 4.4 to 5.3 points (4.2 to 5.1 percent). The largest changes in response to adjustment for covariates were in the relation of blood lead concentration to performance IQ.

The estimated linear inverse relation between log average blood lead concentration and full-scale IQ, determined with use of the covariate-adjusted coefficients at the age of 3 years in Table 4, is shown in Figure 2 (there are similar relations at other ages, but the age of 3 is centrally located in the range of apparently maximal sensitivity — 15 months to 4 years of age). The girls were more sensitive to the effects of lead than were the boys. For an increase in blood lead concentration from 10 μg per deciliter (0.48 μmol per liter) to 30 μg per deciliter (1.45 μmol per liter), the expected covariate-adjusted decrement in full-scale IQ was 7.8 points for the girls and 2.6 points for the boys.

Simple and Multivariable Analyses of Subscale Scores

Simple and multivariable analyses of WISC-R subscale scores showed that the mean subscale scores varied inversely with the lifetime average blood lead concentrations. However, the apparent sensitivity of the components of the WISC-R to the blood lead concentration differed. The associations between lifetime average blood lead concentration and the information and block-design subscales were stronger than those for any other subscales (Table 5).

Table 1. Mean Blood Lead Concentration (within Quartiles) in Maternal Samples Taken Antenatally and in Children's Samples at Various Ages.

Quartile	Blood Lead Concentration*								
	Average Antenatal	Umbilical Cord	Age						
			6 mo	15 mo	2 yr	3 yr	4 yr	5 yr	6 yr	7 yr
			micrograms per deciliter							
Mean concentration										
I (low)	6.2	4.3	8.3	11.8	13.0	11.6	9.5	8.3	7.2	6.6
II	8.7	7.4	12.6	18.6	18.6	17.4	14.7	12.6	11.2	10.1
III	10.6	9.9	16.8	24.4	24.2	22.4	19.0	17.2	14.7	13.7
IV (high)	14.3	15.0	24.2	34.4	33.5	30.2	26.5	23.6	20.5	20.0
Mean lifetime average concentration										
I (low)	—	—	7.4	9.9	11.6	12.2	12.2	11.8	11.2	10.8
II	—	—	10.6	14.3	16.6	17.4	17.6	17.0	16.4	15.7
III	—	—	13.5	18.0	20.5	21.7	21.5	21.1	20.3	19.7
IV (high)	—	—	18.4	23.8	27.1	28.2	27.7	26.9	25.9	24.8

*To convert values for lead to micromoles per liter, divide by 20.7.

Discussion

These results indicate that the inverse associations between blood lead concentration and indexes of development reported earlier for this cohort[6,7] persist into the primary-school years. The strong correlation ($r = 0.65$, $P<0.001$) of the full-scale IQ at the age of seven years with the McCarthy General Cognitive Index at the age of four years[6] indicates that many of the children who scored poorly initially have not had great improvements in their overall ranking by the age of seven years.

Two prospective studies have found that the lead concentration in the umbilical-cord blood is predictive of developmental progress in early childhood.[2,3] How-

Table 2. Mean Verbal, Performance, and Full-Scale IQ Scores of the Seven-Year-Old Subjects, According to the Quartile for Blood Lead Concentration at Various Ages.*

Quartile	Average Antenatal	Umbilical Cord	Age				
			6 mo	15 mo	3 yr	5 yr	7 yr
Verbal IQ score							
I (low)	107.3	106.9	107.9	107.9	109.0	108.4	108.2
II	103.9	104.6	102.8	105.4	104.4	104.5	106.4
III	102.8	99.4	101.7	101.0	100.7	102.2	100.5
IV (high)	98.6	101.7	98.0	99.8	98.5	96.8	97.1
Performance IQ score							
I (low)	108.2	108.7	109.5	109.2	109.6	108.7	109.4
II	107.0	106.1	106.0	106.7	107.8	106.8	107.9
III	107.0	103.4	104.1	104.7	103.8	105.6	105.0
IV (high)	101.4	105.8	102.4	102.9	101.8	101.6	100.9
Full-scale IQ score							
I (low)	108.5	108.4	109.4	109.3	110.2	109.3	109.6
II	105.7	105.8	104.7	106.5	106.5	106.1	107.7
III	105.1	101.3	102.9	102.9	102.2	104.1	102.7
IV (high)	99.8	103.9	100.0	101.3	100.0	98.8	98.7

*Differences between quartiles were statistically significant ($P<0.01$) in every instance except for the variation of performance IQ scores with cord-blood lead concentrations ($P = 0.05$).

ever, in a subsequent report from one of these study groups, the scores of the children on the McCarthy Scales of Children's Abilities at the age of 57 months were inversely related to the blood lead concentration at 24 months of age, but not to the umbilical-cord blood lead concentration.[12] This result is compatible with our overall finding of no significant relation between IQ and antenatal or perinatal blood lead concentration after other covariates are taken into account.

The conclusions reached in this study are likely to be conservative for several reasons. First, the children remaining in the cohort had slightly more advantaged backgrounds than those lost to follow-up. Since children from disadvantaged families may be more vulnerable to the effects of lead than those from more favorable backgrounds,[3,31] the inverse relation of lead to IQ might have been stronger among the children lost to follow-up than among those remaining in the cohort. Second, the use of certain covariates in multivariate analyses may result in an overadjustment in studies of the association between lead and IQ.[6,31,32] Parental smoking status, the quality of the home environment, and maternal IQ may themselves contribute to a child's lead burden,[2,3,6,7,25] in which case some of the true effect of lead would have been removed by controlling for these factors. Third, randomly distributed imprecision or misclassification in the measurement of lead exposure (or its confounders) will bias the estimate of the effect toward the null value.[33]

Although the estimates presented here are likely to be conservative for the reasons described above, the possibility that we did not completely control for positive confounding variables and subsequently overestimated the true effect cannot be completely eliminated. For example, the developmental effects of anemia could bias the study.[34,35] After the exclusion of the 10 children who had a packed-cell volume of less than 34 percent at the age of seven years, however, the estimated regression coefficients for the blood lead concentrations changed little.

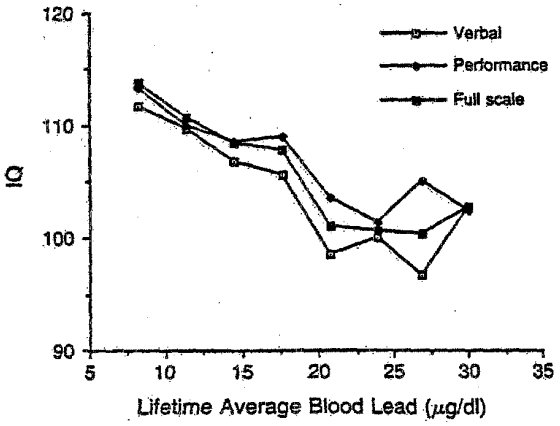

Figure 1. Lifetime Average Blood Lead Concentration and IQ at the Age of Seven Years.

To convert blood lead concentrations to micromoles per liter, divide by 20.7.

Table 3. Effect of Potential Confounding Variables on Mean IQ Scores at the Age of Seven Years.*

Covariate	Blood Lead†	Verbal IQ	Performance IQ	Full-Scale IQ
	μg/dl			
Sex				
Male	17.2	104.4±0.9	105.9±1.0	105.4±0.9
Female	17.0	102.1±0.9	106.0±0.9	104.3±0.9
Mother's education level‡				
≤3 yr	18.2	100.0±0.8	103.4±0.9	101.7±0.8
>3 yr	15.5	106.7±0.9	108.8±0.9	108.4±0.9
Father's education level‡				
≤3 yr	17.2	101.2±1.0	104.8±1.0	103.0±0.9
>3 yr	16.1	106.6±0.9	108.6±0.9	108.3±0.9
Mother's age at child's birth (yr)				
<23	19.2	101.0±1.2	104.5±1.2	102.8±1.2
23–28	16.2	102.9±1.1	106.1±1.0	104.8±1.0
>28	16.4	105.6±1.1	107.1±1.1	106.8±1.1
No. of parents smoking				
None	15.9	105.5±0.9	107.6±0.8	107.1±0.8
One	17.4	101.3±1.1	104.1±1.2	102.7±1.1
Both	19.2	99.7±1.8	104.3±1.6	102.0±1.7
Socioeconomic status				
Lower	20.7	98.0±1.1	102.4±1.2	99.9±1.1
Middle	16.6	102.9±1.3	104.2±1.2	103.8±1.3
Higher	15.1	106.6±0.9	109.1±1.0	108.5±0.9
HOME scores				
<40	19.7	96.5±1.1	100.3±1.1	98.0±1.1
40–45	17.4	105.7±1.0	108.5±0.9	107.6±0.9
>45	14.1	107.5±1.2	108.9±1.3	108.9±1.2
Mother's IQ				
<85	20.7	97.1±1.4	99.6±1.6	97.8±1.3
85–95	17.0	101.0±1.2	106.1±1.3	103.6±1.2
>95	15.5	110.6±1.0	111.5±1.0	112.1±1.0
Birth weight (g)				
<2500	19.2	99.2±3.4	102.1±3.7	100.5±3.6
2500–3500	17.6	102.4±0.9	104.7±0.9	103.7±0.9
>3500	16.2	104.6±0.9	107.9±1.0	106.7±0.9
Birth order				
1st	17.4	103.2±0.9	105.8±1.0	104.8±0.9
2nd	16.6	102.7±1.2	106.8±1.1	105.0±1.1
≥3rd	16.4	103.4±1.4	105.0±1.4	104.4±1.4
Feeding style				
Breast	15.7	106.6±1.0	108.4±1.0	108.1±1.0
Mixed	14.7	105.4±2.3	105.0±2.7	105.6±2.6
Bottle	18.4	100.3±0.9	104.2±0.9	102.2±0.8
Months of breast-feeding				
0	19.0	98.3±1.3	103.0±1.4	100.4±1.3
1–6	17.4	102.7±0.9	105.2±0.9	104.2±0.9
>6	15.5	106.6±1.1	108.8±1.1	108.3±1.1
Parents living together				
Yes	16.6	103.5±0.7	106.4±0.7	105.3±0.7
No	20.3	100.8±1.8	102.4±1.9	101.5±1.8

*Plus–minus values are means ±SE.

†Values are the lifetime average blood lead concentrations at the age of seven years. To convert values for lead to micromoles per liter, divide by 20.7.

‡Years refer to the number of years of high school completed.

Because a child with a high blood lead concentration at one age is likely to have high concentrations at other ages (a phenomenon referred to as "tracking"), it is difficult to determine critical or sensitive periods for the effects of lead. However, the maximal effect of lead on IQ was found for lifetime average blood lead concentrations from birth to any age between 15 months and 4 years. This sug-

gests that exposure to lead in the preschool age range has a maximal effect on IQ.

Among the WISC-R subscales, the information and the block-design subscales were the most sensitive to the effects of lead. Since the information subscale may be culturally dependent, its effects on the relation of the more objective block-design scores to the blood lead concentration were tested by including the information score as an additional covariate in the regression model. The association between log blood lead concentration and the block-design scores was only partially attenuated (regression coefficient, −1.00; 95 percent confidence interval, −0.42 to −1.58), which dispels the notion that the results are an artifact of the cultural environment. The block-design subscale tests a person's perceptual organization and synthesis, spatial visualization, nonverbal concept formation, and

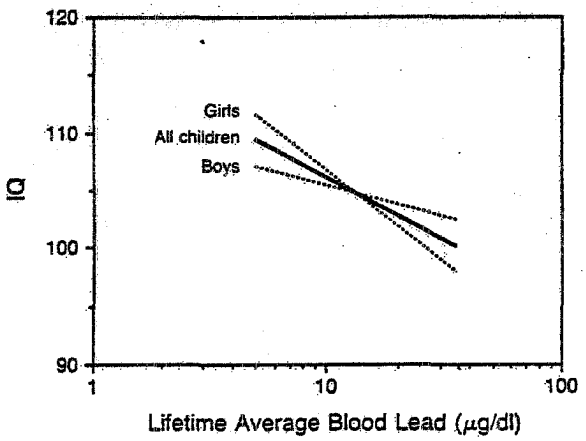

Figure 2. Estimated Relation between Full-Scale IQ at the Age of Seven Years and the Lifetime Average Blood Lead Concentration up to the Age of Three Years.

The line of best fit is shown, as estimated by multiple regression analysis. To convert blood lead concentrations to micromoles per liter, divide by 20.7.

visual motor coordination. It also reflects the degree to which right and left cerebral functioning is integrated.[36] Impaired spatial discrimination has also been reported in adult monkeys exposed to low levels of lead for long periods.[37]

The results indicate that the deleterious effects of environmental lead are not large, and that only a small fraction of the overall variation in IQ can be attributed to lead exposure. Nevertheless, the social consequences of such an effect are not negligible. If a child with an IQ of less than 80 requires educational assistance, then the number of children requiring assistance in a community whose children are expected to have a mean IQ of 105 will be doubled if the mean is reduced by approximately 5 percent as a result of lead exposure. Health authorities in the United States have recently estimated that for each reduction of 1 μg per deciliter (0.05 μmol per liter) in the blood lead concentration due to lead-exposure–abatement programs, there would be a net saving to society of approximately $2,000 per child, because the need for clinical attention and remedial education and the expense of lost productivity could be avoided.[38]

The fact that an inverse association between the blood lead concentrations and abilities has been observed longitudinally at the ages of two, four, and seven years within this cohort suggests that even a low level of exposure to lead has an independent and enduring effect on neuropsychological development in childhood. From a public health perspective, the early detection and abatement of lead in the environment are highly desirable.

Table 4. Adjusted Coefficients of Log Lifetime Average Blood Lead Concentration from Multiple Regression Analyses of IQ Scores at the Age of Seven Years.*

Time Blood Sample Obtained	Verbal IQ	Performance IQ	Full-Scale IQ
Before birth†	−1.5±2.0 (0.46)	−1.0±2.1 (0.62)	−1.4±2.0 (0.48)
After birth (cord blood)	−0.1±1.4 (0.94)	1.0±1.5 (0.50)	0.6±1.4 (0.68)
0–15 Mo of age	−5.0±2.1 (0.03)	−2.3±2.2 (0.30)	−4.0±2.0 (0.04)
0–2 Yr of age	−5.8±2.2 (<0.01)	−2.4±2.2 (0.28)	−4.6±2.1 (0.03)
0–3 Yr of age	−5.7±2.4 (0.03)	−2.8±2.4 (0.24)	−4.8±2.3‡ (0.04)
0–4 Yr of age	−5.0±2.5 (0.04)	−3.3±2.5 (0.18)	−4.6±2.4 (0.05)
0–7 Yr of age	−4.3±2.6 (0.10)	−2.3±2.6 (0.37)	−3.7±2.5 (0.14)

*The coefficients were adjusted for all covariates shown in Table 3. Plus–minus values are means ±SE. P values are shown in parentheses.

†Blood samples were obtained antenatally from the mother.

‡This means that the expected decrement in full-scale IQ associated with an increase in average blood lead concentration from 10 to 30 μg per deciliter (0.48 to 1.45 μmol per liter) during the first three years of life is 5.3 points: 4.8 × (log[30] − log[10]) = 5.3.

Table 5. Mean Age-Adjusted Subscale Scores and Estimated Regression Coefficients for Lifetime Average Blood Lead Concentration up to the Age of Three Years.*

Subscale	Blood Lead Quartile†				Coefficient	
	I	II	III	IV	Estimate	P value
Information	11.7	12.2	11.2	10.5	−1.45±0.57	0.01
Similarities	10.0	10.8	10.2	9.2	−0.90±0.62	0.14
Arithmetic	9.6	9.7	9.2	8.5	−0.51±0.63	0.42
Vocabulary	12.5	12.7	12.0	12.3	−0.44±0.51	0.40
Comprehension	10.0	9.6	9.6	9.2	−0.88±0.54	0.10
Picture completion	11.2	11.4	11.0	10.6	−0.15±0.45	0.74
Picture arrangement	10.2	10.7	10.2	9.9	−0.34±0.60	0.56
Block design	11.6	12.0	10.8	10.2	−1.61±0.62‡	0.01
Object assembly	11.4	11.7	11.4	10.9	−0.08±0.50	0.86
Coding	10.8	10.1	10.9	9.9	−0.22±0.53	0.66

*The coefficients were adjusted for school year, age at testing, and the covariates listed in Table 3. Plus–minus values are means ±SE.

†The lowest values are in the first quartile, and the highest values are in the fourth quartile.

‡This means that the expected decrement in the block-design score for an increase in average blood lead concentration from 10 to 30 μg per deciliter (0.48 to 1.45 μmol per liter) during the first three years of life is 1.8 points: 1.61 × (log[30] − log[10]) = 1.8.

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unknown. Amyloid is formed in the patient's brain because of changes in the proteolytic processing of APP, and not because of alterations of genetic or molecular properties. There are two known pathways for processing APP — constitutive secretion and internal processing within the endosomal–lysosomal system.[10] In constitutive secretion a membrane-associated endoprotease cleaves the β/A4 peptide into nontoxic fragments, whereas amyloidogenic fragments are likely to accumulate as a result of APP metabolism in the lysosomal pathway. APP processing appears to be regulated by neurotransmitter-receptor–coupled activation. In the resting state the lysosomal pathway is dominant, whereas cholinergic stimulation of protein kinase C–linked muscarinic receptors preferentially increases the release of nontoxic fragments.[11] With better understanding of factors that influence APP processing, it may be possible to develop pharmacologic treatments designed to enhance constitutive secretion or block the lysosomal pathway. Either approach would decrease β/A4 deposition and, if started early enough, might prevent neuronal degeneration and the evolution of clinical dementia.

To date, there are no safe and effective treatments that improve cognition in Alzheimer's disease. There are reasons, however, to be optimistic about the future. Compounds embodying restorative, protective, and preventive strategies are under development. The pace of research into the causes and mechanisms of neuronal degeneration in Alzheimer's disease is quickening, and the investigations will yield additional drugs. Finally, as the Tacrine Collaborative Study showed, patients with Alzheimer's disease, their families, and their physicians stand ready to test promising drugs in rigorous clinical trials.

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EXPOSURE TO LEAD IN CHILDHOOD

The Importance of Prevention

BAGHURST et al.[1] are to be congratulated for continuing their long-term studies of intellectual deficits in children who were exposed to lead in early childhood. These investigators have identified deficits in intelligence, not just delays in neurobehavioral or motor development, among school-age children that are associated with exposure to lead in early childhood. That children's intellectual performance can be diminished by environmental exposure to a chemical as common as lead appears to startle many. This association has been attacked in both the popular press and the scientific literature. The principal counterassertion is that such deficits are due to other factors common among children with the highest prevalence of exposure to lead, such as poverty, urban environments, lower social class, having a mother with too few resources to cope with multiple problems, and deteriorating housing. Even when these social factors have been considered, whether through the type of population studied or through the use of statistical techniques, the assertion has persisted that not all the covariables have been considered or that the cohort studied has another as yet unidentified problem.[2]

The assertion that the effects of lead are limited to socially and economically disadvantaged children is repudiated by the findings of Baghurst et al. reported in this issue of the *Journal*,[1] as well as by the results of another longitudinal cohort study of an affluent population in Boston.[3] Child-development experts have predicted that the adverse effects of exposure to lead on intellectual development will be greatest among disadvantaged children.[4] The results of a longitudinal study of a cohort of severely disadvantaged children in Cincinnati verify this prediction.[5-7] Taken together, the results of three longitudinal studies[1,3,5-7] demonstrate that the lead-associated decrements in intelligence are persistent across cultures, racial and ethnic groups, and social and economic classes.

Although the results of cross-sectional studies of lead-associated effects on IQ are inconsistent, longitudinal studies have permitted a more thorough consideration of the covariables that might interact with lead exposure. The higher social and economic status of the children studied by Baghurst et al.[1] is in marked contrast to the traditional image of lead-exposed children as those from poor and medically underserved communities. The intellectual deficits associated with exposure to lead that were identified by Baghurst et

al.[1] seem especially compelling because the cohort was drawn from families of skilled workers as well as from middle-class families, the testing instrument — the revised version of the Wechsler Intelligence Scales for Children (WISC-R) — has been widely used and well standardized, and the children's integrated blood lead concentrations were comparable to those often encountered in the United States. In addressing the importance of social and familial covariables, it is critical to recognize that the reduction in intellectual scores attributed to exposure to lead in early childhood was present after statistical adjustment for the covariables known to influence intellectual development.

The longitudinal evaluation of severely disadvantaged children in Cincinnati identified central auditory-processing deficits and an eight-point decrement (from 91 to 83) in the performance IQ (based on the WISC-R scores after adjustment for covariables) as the lifetime average blood lead concentration increased from 10 to 35 μg per deciliter (from 0.48 to 1.45 μmol per liter).[5,6] These children also had decreased fine-motor skills[7] after adjustment for covariables reflecting such factors as mothering skills and socioeconomic status. A cohort of children from affluent families in Boston[3] had a six-point decline in the WISC-R full-scale IQ when tested at the age of 10 years that was associated with an increase in the blood lead concentration of 10 μg per deciliter (0.48 μmol per liter), within the range of 0 to 25 μg per deciliter (0 to 1.21 μmol per liter), at the age of 24 months. Both cohorts of children, therefore, had adverse intellectual outcomes associated with exposure to lead in early childhood. However, in the most disadvantaged children the lead-associated intellectual deficits represented not only a greater fractional loss of IQ points, but also a decrease to a level associated with clinically evident dysfunction (e.g., IQ scores in the low 80s).

Blood lead concentrations (reflecting the degree of lead exposure) are higher among disadvantaged children in the United States.[8] The approximate magnitude of the decrement in IQ associated with exposure to low-to-moderate levels of lead during early childhood appears to range from 5 to 10 percent of the IQ scores determined early in elementary school with the WISC-R.[1,4,5] A downward shift of 5 to 10 points is comparable to that produced by other environmental variables traditionally recognized as affecting children's development.[9] The magnitude of the decrement associated with lead exposure may be greater because a number of covariables considered may share variance with lead. Attributing the fraction of the variance to the covariable rather than to lead is likely to cause one to underestimate the magnitude of the effect of lead.[1]

The U.S. government has launched a major campaign to reduce childhood exposure to lead.[10] Since our 1982 report[8] on the prevalence of elevated blood lead concentrations in the United States, the concentrations have decreased. This decrease reflects the virtual elimination of lead solder from the seams of food and beverage cans produced in the United States and marked decreases in the use of leaded gasoline. Although these changes have helped the general population, children continue to be exposed to lead. Lead-based paint and dust containing high levels of lead remain a health menace in an estimated 3.8 million U.S. homes housing children seven years of age or younger.[11] The high cost of removing environmental sources of lead, however, has often been cited as a reason for delaying the removal of lead-based paint.

The problem of excessive exposure to lead is certainly not unique to the United States, although this country has been in the forefront of attempts to reduce lead exposure. International programs for chemical safety and the control of exposure to chemicals have lagged behind those of the United States. Clinical lead poisoning remains an internationally recognized problem.

In coming decades, maximizing the intellectual and educational capacity of our population will be critical to our success in dealing with many social and economic challenges. The importance of safeguarding the intellectual and educational development of our children against preventable disease is difficult to overestimate. Childhood exposure to lead is preventable. The data of Baghurst et al.[1] emphasize the intellectual cost of not preventing it.

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Effect of Low-level Body Burdens of Lead on the Mental Development of Children: Limitations of Meta-analysis in a Review of Longitudinal Data

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ABSTRACT. The effect of low-level body burdens of lead on the intelligence of children, as measured by intelligence quotient (IQ), was assessed. We reviewed 35 reports from five longitudinal studies conducted in the United States and Australia. In each of these studies, infants were followed for 58 mo or less. The study populations consisted of low- and middle-socioeconomic-class infants who had low-level exposure to environmental lead. Blood-lead levels were measured in a standard fashion at various times, beginning in the prenatal period, and intelligence was first measured at 6 mo of age and was followed by subsequent assessments. Studies were assessed for quality by a review panel blinded to the identity of the investigators and their affiliations. Efforts were made to pool the data with meta-analytic techniques, but efforts were unsuccessful because the methods used to analyze and report data were inconsistent. Inconsistencies were as follows: (a) there were few instances in which IQ and blood-lead levels were measured at comparable times in different studies; (b) incompatibilities existed among the studies, including differences in independent variables, data transformations, and statistical parameters reported; (c) results conflicted when measurement intervals were comparable (i.e., heterogeneity); (d) patterns of regression and correlation coefficients were inconsistent; and (e) data were insufficient to interconvert the parameters reported. Consequently, definitive conclusions regarding the effect of low-level body burdens of lead on IQ could not be determined from the longitudinal data. Examination of the weight of the evidence from this and other studies, however, suggests an adverse relationship of lead on the intelligence of children.

LEAD is absorbed readily by humans and affects the central nervous system, peripheral nerves, red blood cells, liver, and bone.[1] The absorption of high doses of lead has adverse health effects on children and adults.[1-3] Since the clinical description in 1943 of the effects of very high lead levels in children without encephalopa-

thy, the existence of more subtle effects of lower levels of lead has been hypothesized and studied.[4] In 1965, Patterson's observations of the distribution of high levels of lead within the population of the United States caused attention to be directed at determining a "safe" threshold for lead in humans.[5] In 1985, the Centers for Disease Control (CDC) established a threshold of intervention for children at 25 μg/dl (× 0.04826 = mmol/l).[6] Whether a threshold of effect for lead exists in children is a matter of current debate. In particular, the potential impact of low blood-lead levels (i.e., < 25 μg/dl) on early neurodevelopment is of increasing concern. In a recent meta-analysis (i.e., systematic method used to compare results quantitatively across studies[7]), a statistically significant inverse correlation was found between exposure to low levels of lead in the teeth of children (PbT) and their intelligence quotient (IQ) levels.[8] Controversy centers on defining the exposure levels that produce these effects, the duration of these effects, and the role of concomitant factors such as parental IQ, home environment, and other types of exposures.

Although literature is extensive regarding the relationship between asymptomatic exposure and neurodevelopmental effects, most published reports are either retrospective or are limited to research in which blood lead (PbB) and neurodevelopmental outcomes are measured at one time (i.e., cross-sectional studies). Longitudinal studies of children, beginning before birth (i.e., in utero), offer several advantages. The population at risk is defined at the outset, which enables investigators to estimate the magnitude of potential selection bias associated with children lost to follow-up. Prospective data collection can minimize recall and other types of information bias, and it allows investigators to measure temporal changes in outcome relative to prior levels of exposure. Finally, repeated measures of PbB enable investigators to analyze the effects of lead in a child at different times and to estimate cumulative exposure. Considerations of cost and effort have limited the size and numbers of such studies, the effect of which has limited both the power of studies to detect small differences and the generalizability of results to other populations.

Materials and methods

We reviewed 40 reports from five longitudinal studies in which the relationship between PbB and mental development in children was examined.[9-49] These reports were identified in a search of the MEDLINE database for the period 1966 through 1988, in a review of major literature summaries, and in bibliographies from identified articles. We included all studies for which data were published prior to September 1, 1989. We created a database that contained all relevant quantitative statistical information from the five studies, which enabled us to evaluate the potential for a meta-analysis.

An epidemiologist, a statistician, and a laboratorian—all of whom were unfamiliar with the five longitudinal studies—made up a panel that assigned quality scores to the five studies. They read only the methods sections of the relevant publications for which all study identifiers had been removed. The panel scored the studies independently on a scale from 0 to 100 in accordance with the criteria provided in Table 1. The panel met and discussed the strengths and weaknesses of each study and adjusted their individual scores. The final score for each study was the arithmetic mean of the score assigned by each reviewer. Studies were scored higher if (a) the source population was a defined, representative population; (b) exclusion criteria were defined; (c) completeness of follow-up was described; (d) examiners were blinded and interexaminer variation was addressed; (e) selection and detection bias were addressed; (f) appropriate covariates were included; (g) laboratory quality control was adequate; and (h) statistical analyses addressed issues such as multiple comparisons, distributional assumptions, colinearity, bivariate screening, dose-response approach to data analysis, and outliers. After we reviewed these scores, one of us—who had read the publications in their entirety but had not served on the panel—suggested that pertinent methodologic information given in sections other than the results sections of publications should be considered. The panel, still blinded to identifiers and outcomes, reviewed the added information and adjusted scores as appropriate.

In this review, we addressed study design, data-collection methods, laboratory methods, and statistical analyses, and we placed particular emphasis on the elimination of bias and on confounding. The results of these studies, a discussion of methodological concerns, and an attempt to reconcile apparent discrepancies in the data follow. Also presented is an examination of the strength of the evidence for a causal association between lead and decreased mental development. Finally, the implications of our findings for current public policy are discussed.

Results

Analyses were limited to five longitudinal studies in which pregnant women were identified, and serial PbB levels in their infants were measured for 2-5 y after birth (Table 2). These studies varied in size, i.e., from 249 births[11] to 745 births in the most recently reported study.[41] Three of the studies were conducted in predominantly middle-class and working-class white populations (Boston,[9-16] Port Pirie,[37-44] and Sydney,[45-49] respectively); two were conducted in low-income populations in Cincinnati[17-28] and Cleveland[29-36]; and one study included many blacks in Cincinnati.[24] Typically, a maternal and/or cord-blood sample was obtained, and during many years, PbB samples were obtained at various intervals after birth. PbB levels in all these studies tended to be low (mean PbB, < 25 μg/dl).

The investigators of the five studies examined the relationship between PbB and mental development through the first 2 y of life with Bayley's mental development index (MDI). This index was designed to assess "sensory-perceptual acuities, discriminations, and the ability to respond to these: the early acquisition of 'ob-

Table 1.—Assessment of Data from Five Longitudinal Studies That Evaluated the Association between Asymptomatic Childhood Lead Exposure and Intelligence

	Longitudinal studies				
	Boston	Cincinnati	Cleveland	Port Pirie	Sydney
Prior hypotheses	I	I	Y	Y	I
Power calculation	N	N	*N(Y)	N	N
Eligibility criteria	Y	Y	Y	Y	U
Exclusion criteria	Y	Y	Y	N	Y
Drop-out assessment	Y	Y	Y	Y	Y
Laboratory quality control	Y	Y	Y	Y	Y
Blinding					
Interviewers	Y	Y	Y	Y	Y
Statisticians	U	U	U	U	U
Laboratorians	U	U	U	U	U
Assessment of interexaminer variability					
IQ measure	Y	Y	N	N	Y
Standardized	Y	Y	Y	Y	Y
Quality control	Y	U	U	U	Y
Appropriate statistics					
Main effects	Y	Y	Y	Y	Y
Subgroups	Y	Y	Y	Y	Y
Multiple comparisons	N	N	Y	U	N
Multivariate adjustment for confounding					
Age	Y	Y	Y	Y	Y
Sex	Y	Y	Y	Y	Y
Parental IQ	Y	N	Y	Y	Y
Socioeconomic status	Y	Y	Y	Y	Y
Caregiving	Y	Y	Y	Y	Y
Maternal smoking	Y	N	Y	Y	Y
Effect modification assessed	Y	Y	Y	Y	N

Notes: I = implicit, Y = yes, N = no, U = unknown, and NA = not applicable.
*No power calculations were reported in the initial studies, but a later study included power calculations.

ject constancy' and 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."[50,51] The test evaluates developmental status and consists of mental, motor, and behavioral ratings scales. The MDI measures mental ability, whereas the psychomotor development index (PDI) measures gross- and fine-motor abilities. Investigators from the Boston, Port Pirie, and Sydney studies used the McCarthy scales to assess mental development in older children. The Cleveland study used the Stanford-Binet intelligence scale for children 3 y of age and used the Wechsler preschool and primary scale of intelligence (WPPSI) for children 58 mo old. The Cincinnati investigators used the Kaufman assessment battery for children 4 y of age. Each study included data on various combinations of potential confounding variables, including socioeconomic status, caregiving at home, parental IQ (except the Cincinnati study), and material smoking, as well as other potentially important variables such as age, sex, race, and obstetrical factors. Data from the entire population were used in three of the studies; the Boston investigators focused their analysis on the highest, lowest, and central PbB groups of the population; and the Sydney investigators examined the children at the highest and lowest PbB deciles of the population.

All five studies appeared to have been carefully designed and executed. In each study, the investigators described eligibility and exclusion criteria; analyzed to varying degrees data on persons who dropped out or who were removed from the study; reported careful quality-assessment and quality-control procedures in the laboratory; "blinded" both interviewers and persons who administered the intelligence tests; and used appropriate statistical methods for main effects, subgroup analysis, and assessment of interactions (Table 2). Investigators from the Boston, Sydney, and Cincinnati studies reported analysis of interobserver variability in psychological tests. In Port Pirie, almost all the tests were conducted by the same person. Only the Sydney investigators, however, reported quality-control procedures for the psychological tests. None of the investigators reported power calculations in the initial publication of their study methods, and none "blinded" the statisticians, laboratorians, or persons who evaluated caregiving at home. Only the Cleveland investigators expressed concern regarding statistical problems with multiple comparisons of data, and only in that study's latest publications were power calculations reported.[32,33]

Table 2.—Results of Five Longitudinal Studies That Evaluated the Impact of Low-dose Human Exposure to Environmental Lead (United States and Australia, 1979–1988)

	Boston (1979–1983)	Cincinnati (1979–1983)	Cleveland (1971–1981)	Port Pirie (1979–1988)	Sydney (1982–present)
No. of subjects:					
In original sample*	11 837	1 073	543	831	318
Birth	249	305	359	745	298
6 mo	216	305	127	652	274
12 mo	204	NA	145	619	259
24 mo	188	NA	142	601	234
36 mo	NA	NA	138	NA	215
48 mo	NA	258	NA	438	207
58 mo	170	NA	234	NA	NA
Race (% White/Black)	85/15	15/85	65/35	100/0	100/0
Socioeconomic status	Middle/high	Low	Low	Middle/low	Middle
Child lead:					
Type of measure	Capillary	Mainly venous	venous	Capillary	Venous, capillary
Exposure level (μg/dl)					
Pb, maternal (mean)	NA	8.1	6.5	9.5	9.1
Pb, cord (mean)	6.6	6.3	6.0	8.3	8.1
Pb, postnatal (mean-range)	6.2–7.7	4.8–21.1	6.5–16.7	9.3–24.3	10.1–16.4
Pb, postnatal (peak-range)	24.9–48.9	26.0–85.0	11.0–41.8	14.7–67.0	5.0–79.0
MDI change (points)‡					
6 mo	↓5.8§	↓22.7#	↓//	↓7.1**	↓††
12 mo	↓7.3§	NA	↓//	↓6.5**‡‡	↓†††
24 mo	↓4.8§	NA	↓//	↓10.0**	↓†††
IQ change (points)					
36 mo	NA	NA	↓//	↓10.1**	†††
48 mo	NA	↓§§	NA	↓4.5**	↓††
58 mo	↓1.8##	NA	↓//	NA	NA

Notes: MDI = Mental Development Index of the Bayley developmental tests (measures obtained after adjustment for confounding); WPPSSI = Wechsler Preschool and Primary Scale of Intelligence; PbB = blood lead level; NA = not available; and SC = study completed.

*Differences between the number of subjects in the original sample and the number included for follow-up at birth varied in each cohort. In Boston, the birth cohort was a sample of eligible children available after exclusion. In Cincinnati, the difference between the initial sample and those followed at birth resulted solely from exclusion whereas that difference in the Cleveland study included both exclusions and some pregnant women lost to follow-up. In Port Pirie, reported numbers in the original cohort of pregnant women varied, but the difference between the original sample and the birth cohort presumably included both exclusions and those lost to follow-up. The Sydney cohort was apparently selected at birth, and the number excluded was not available in papers published.

†All 6-mo blood samples were capillary; up to 24 mo, approximately half the samples were capillary; almost all subsequent samples were venous.

‡Related to maternal or cord PbB, adjusted for confounding.

§Adjusted difference in means of upper and lower umbilical cord PbB exposure deciles.

#Decrement across the range of prenatal PbB for males. Each log unit of prenatal PbB is associated with a covariate-adjusted decrease of 5.7 MDI points.

//Whereas the coefficients for the association between PbB and MDI (Stanford-Binet at 3 y and verbal scaale of the Wechsler Preschool and Primary Scales of Intelligence at 58 mo) were negative, MDI changes were not quantitated. These decreases were statistically significant at 6 mo only, and none remained significant after adjustment for confounding.

**Difference in means of upper and lower exposure quartiles of average or antenatal PbB based on McCarthy Scales of Children's Abilities.

††Reports of correlations varied in different reports;[44,46] adjusted analyses at 48 mo were not published for maternal or cord PbB.

‡‡15 mo, rather than 12 mo.

§§At 48 mo, there was no statistically significant association between prenatal or neonatal PbB and mental development (Kaufmann), although postnatal PbB at 2 y was significantly associated with a decrease in mental development.

##AT 57 mo, the inverse association between cord PbB and IQ (McCarthy) was not statistically significant.

The review panel agreed in their assignments of highest and lowest quality scores: in all cases, the Sydney study scored the highest and the Cincinnati study scored the lowest (Table 3). Even though the ranks of the three remaining studies varied among the reviewers, quality scores did not vary more than 15 points among the three studies for any one of the three reviewers. Information provided in additional to the methods sections of the papers did not affect the panel's relative rankings of the studies.

Table 3.—Quality Scores, Assessed by Panel of Three "Blinded" Reviewers, of Five Longitudinal Studies That Evaluated the Input of Low-dose, Asymptomatic Human Exposure to Environmental Lead (United States and Australia, 1979–1988)

Study	Reviewer 1	2	3	Mean	Median
Boston	60	50	55	55.0	55
Cincinnati	43	35	45	41.0	43
Cleveland	53	65	60	59.3	60
Port Pirie	60	65	54	59.7	60
Sydney	83	70	65	72.7	70

Table 4.—Reported Parameters in Blood-Lead Studies

	Boston	Cincinnati	Cleveland	Port Pirie	Sydney
Regression coefficient	Yes*	Yes†		Yes‡	
Change in standardized scores	Yes§				
Correlation	Yes#		Yes		Yes//

*Coefficients given, where (1) independent variable represents three lead concentration groups and dependent variable is MDI, adjusted for covariates; (2) independent variable is change in Pb concentration, dependent variable is change in standardized scores for MDI and McCarthy tests. Ages at mental tests were 6, 12, 18, 24, and 57 mo.
†Coefficients are adjusted for confounders; and dependent variable is MDI. Ages at mental test were 3, 6, and 24 mo. The Kaufman Assessment Battery for Children was administered at 48 mo.
‡Coefficients are adjusted for confounders, dependent variables are MDI, and McCarthy measures of mental development. Ages at which mental tests were conducted were 24 and 48 mo.
§Change in standardized scores for MDI (24 mo) and McCarthy tests (57 mo).
#Correlation between MDI (6–24 mo) cord PbB in three categories.
//Correlation between MDI (6–36 mo) and maternal and cord PbB.

More than 250 reported statistical parameter values were obtained from the five studies. These parameters were examined for feasibility of meta-analysis so that the magnitude of the effect of increased blood lead levels on intelligence could be estimated from all studies. The statistical measures reported most frequently in each of the five studies included regression coefficients, correlations, and changes in standardized scores (Tables 4-6). Although the Boston, Cincinnati, and Port Pirie investigators reported regression coefficients, PbB was collapsed into three categories in the Boston study, which made estimates of regression coefficients unsuitable for potential pooling with coefficients from continuous PbB values. Also, the Boston study used changes in Z-scores as a dependent variable—a measure incompatible with that used in other studies. The Boston, Cincinnati, and Port Pirie investigators reported the regression on mental development of PbB at the same age only once, i.e., 24 mo. The regression coefficient was positive in the Cincinnati study only. When mental ability was measured at 24 mo and was related to PbB measured at 6 mo, the Boston and Port Pirie studies obtained regression coefficients of opposite sign. Although the Boston, Cleveland, and Sydney studies reported correlations, the Boston study again computed its value, based on collapsed PbB categories, which prevented pooling of its correlation coefficient with those of the other two studies. On six occasions, the Cleveland and Sydney investigators correlated mental development or IQ with PbB at the same time. In three of the six occasions, quite different correlations were obtained.

A quantitative estimate of the common effect of PbB on mental development from these five studies was not made because there were different statistical parameters, PbB was treated differently in the analyses, and conditions under which results were obtained (age at mental development test and blood lead measurements) differed. In the few instances of similar reporting conditions, the results were not comparable; however, in three instances, similar negative coefficients were obtained for the Cleveland and Sydney studies.

An inverse relationship between prenatal and postnatal exposure to lead and the MDI in unadjusted analyses was shown in all five studies. Even after adjustment was made for confounding, no statistically significant relationship was seen between PbB and the MDI in the Cleveland and Sydney studies (Table 2). Statistically significant differences remained only in the studies from Boston, Cincinnati (white infants), and Port Pirie. The Cincinnati investigators found no evidence of an adverse effect of prenatal or neonatal lead exposure by the time children reached 2 y of age, except for children from the poorest families. Blood-lead levels at 1, 2, 3, and 4 y of age were associated inversely with mental development at 4 y, but this association was not statistically significant when adjustment was made for confounding. In the Boston and Port Pirie studies, however, correction for confounding increased the magnitude of the inverse relationship. An analysis of Port Pirie children, based on the cumulative measure of postnatal exposure measure of children at 4 y of age, showed a 9.6-point decrement in mental development between the lowest and highest quartiles. The Port Pirie investigators concluded that, even after controlling for confounding, children with an average postnatal PbB of 31.3 μg/dl during the first 4 y of life had a mental development score 7.2 points lower than children who had an average PbB concentration of 10.4 μg/dl during the same period. The Boston follow-up at 57 mo determined that decreased lead exposure, as measured by PbB and sociodemographic characteristics previously associated with increased mental development, appeared to compensate for cognitive deficits attributed to prenatal lead exposure.[7] This same study demonstrated a statistically significant association between

Table 5.—Reported Regression Coefficients* for Age at Mental Development Test (MDI) versus Age at Blood Lead Concentration Measurement in Five Longitudinal Studies That Evaluated the Impact of Low-dose, Asymptomatic Human Exposure to Environmental Lead (United States and Australia, 1979–1988)

Age lead measured (mo)	Study	Age (mo) MDI or IQ measured					
		3	6	12	24	48	57
0	Boston†		−2.89 (0.92)				
	Cincinnati	−0.60	−0.66			−.63	
	Port Pirie				0.10		
3	Cincinnati	−0.23	−0.48	0.24			
6	Boston				0.28 (1.29)		
	Port Pirie				−0.16 (p = .09)		
12	Boston				−1.43 (1.25)		
	Cincinnati					.03	
15	Port Pirie				−0.03		
18	Boston				−1.62 (1.39)		
24	Boston				−2.95 (1.42)		
	Cincinnati				0.13	−.02	
	Port Pirie				−0.05		
36	Cincinnati					−.08	
48	Cincinnati					−.10	
57	Boston						−2.28 (1.88)

*Regression coefficients were not available in published reports from studies in Cleveland and Sydney. These data were not available beyond 24 mo in any of the studies. Standard errors or p values are given within parentheses.
†Categorized lead values were used to determine coefficients for the Boston study; continuous values were used in other studies.

Table 6.—Reported Correlation Coefficients* for Age at Mental Development Test (MDI or IQ) versus Age at Blood Lead Concentration Measurement (United States and Australia, 1979–1988)

Age lead measured (mo)	Study	Age (mo) at which MDI or IQ measured				
		6	12	24	36	58
0	Cleveland	−0.14	−0.24	−0.15	−0.21	
	Sydney	−0.16	0.15	0.05		
	Boston†	−0.11				
6	Cleveland	−0.09	0.08	−0.03	−0.04	−0.06
	Port Pirie			−0.12		
12	Sydney		0.11	0.09		
18	Sydney			−0.05		
24	Cleveland			−0.24	−0.31	−0.38
	Sydney			−0.02		−0.38
	Port Pirie			−0.18		
36	Cleveland				−0.29	−0.32
	Sydney					−0.32

*Correlation coefficients were not available in published reports from the Cincinnati study.
†Categorized lead values were used to determine coefficients for the Boston study; continuous values were used in other studies.

PbB at 24 mo and decreased mental development (McCarthy scale) at 57 mo. The negative association found in the Boston study between cord PbB and IQ at 57 mo was small (1.8 points) and was not statistically significant. In none of the studies, however, was an effect on the PDI demonstrated.

Data reported from the Sydney study differed from those in the other longitudinal studies in that, apart from unadjusted data for 6-mo-olds, PbB was not consistently related inversely to either MDI or IQ. Results at 12 mo and 24 mo differed in direction in various reports from this study, but PbB was generally directly

related to MDI or IQ through 48 mo in both adjusted and unadjusted analyses.

Methodological issues

Several methodological concerns affect the interpretation of studies regarding the health effects of low-dose exposure to environmental lead.[2] Each of the investigations reported here must be understood in light of these concerns.

Measures of body-lead burden. The transient nature of PbB levels necessitates repeated PbB testing to determine measures of PbB. Alternative methods for the development of summary measures from serial PbB measurements have not been validated as measures of exposure to lead, and PbT has been regarded as a more accurate measure of cumulative exposure/body burden. Moreover, the longitudinal study design requires that laboratory methods be stable over time. Serial PbB measurements, however, allow evaluation of the effects of varying exposure to environmental lead. Blood lead measurements that exceed 10 μg/dl have been quantified precisely, although at levels below this the precision decreases substantially. The relative accuracy of PbB, based on capillary ("finger-stick") samples that are possibly contaminated with external surface lead, also needs to be accounted for in the analysis and interpretation of data. The Port Pirie investigators examined this potential source of bias and found no effect. The possible effect of surface contamination in Boston, Cleveland, and Sydney cannot be assessed, although, in many instances, the Sydney investigators obtained duplicate venous samples.

Measures of mental development. The Bayley, WISC, Stanford-Binet, and McCarthy scales are reliable, well-standardized scales of mental development or intelligence. Their use facilitates comparison of results from the several studies. Whereas the best available measure of infant development is the MDI on the Bayley scale, it does not correlate well with the Stanford-Binet Form L-M.[51] Similarly, although concurrent validity of the McCarthy scale is satisfactory, large differences have been reported between it and either Stanford-Binet Form L-M or the WISC-R IQ measures. The Kaufman assessment battery for children is standardized adequately and has high reliability. The correlations with Stanford-Binet Form L-M and the WISC-R are moderate, but no verbal comprehension component is contained in the mental-processing section of the test. Overall, this test is not a good measure of intellectual abilities.

Sample size. None of the studies reported to date are sufficiently large to evaluate the impact of environmental lead on these outcomes. This lack of power is also a function of the low levels of exposure measured and the minimal changes in expected neuropsychological outcomes.

Bias. Selection bias could easily account for apparent differences among children with different PbB levels or could mask true differences between groups. In prospective studies, e.g., those that examine PbB over time, children excluded or lost to follow-up must be studied carefully to ascertain the impact of their absence on analysis and interpretation (e.g., the exclusion of children with low birth weight who tend to have elevated levels of PbB). If the possibility of transgenerational effects is ignored, true relationships between exposure and adverse outcomes may be obscured. Mothers (or fathers), whose IQs were lowered by exposure to lead, may have parented children with postnatal lead exposure. Control for parental IQ in this setting may overcontrol for lead exposure and possibly obscure a true relationship between PbB and lowered mental development. All five longitudinal studies are at risk of selection bias because of loss of subjects from the original samples (Table 2). The effects of such bias are difficult to assess, however, because the two Australian studies with the fewest children lost to follow-up showed opposite effects of lead exposure on mental development.

Information bias occurs when measurement of exposure (i.e., PbB) or outcome (i.e., mental development and behavior) is incorrect. Increased accuracy and precision in measurement, standardization of study instruments, and "blinding" of interviewers to study hypotheses and of laboratorians and statisticians to the identities of cases and controls will help to reduce this bias. All five studies included laboratory quality-control activities, and investigators also made efforts to blind interviewers to the study hypotheses in all the studies (Table 1). None of the studies, however, blinded the laboratorians or the statisticians to the study hypotheses, which potentially introduced biases that could obscure an association between exposure and outcome.

Confounding. In these studies, one cannot adjust analytically for confounding of the effect exposure to low levels of lead has on mental development without encountering risk of overadjustment or underadjustment. It is necessary, therefore, to review the efforts of control for confounding and to assess the overall effect of confounding on the postulated relationship in the context of all the evidence for causation, as discussed below.

Although evidence is consistent concerning a crude inverse relationship between lead levels in the body and decreased mental development, skeptics argue that this relationship results primarily from social deprivation, poverty, and parental intelligence, especially if PbB levels are < 25 μg/dl. All of the investigators who authored the five studies reviewed in this report controlled for confounding in their analyses, but the cofactors and methods used varied (Table 1). In three studies, control of these variables diminished the association between PbB and IQ, and, in Cleveland and Sydney, control of the variables accounted for most of the association. In Boston and Port Pirie, however, correction for confounding strengthened the inverse association between PbB levels and intelligence.

Although analysts must account for such confounding, they must also be aware of potential interactions among variables and be careful not to overadjust and obscure an exposure-outcome relationship by controlling for a variable either intermediate in the causal

pathway or proxy for an exposure.[52] In this situation, a child's social class might convey some information about lead contamination in the environment and thus about a child's PbB level. The association between social class and mental development includes two components, one of which is dependent on lead and the other not. Simulation demonstrated how the association between lead and mental development can be obscured (or exaggerated) by the way in which social class is handled in the analysis.[53] Multiple comparisons of data will, on the other hand, tend to produce statistical associations that have little or no biological plausibility.

Comparability. Differences exist in populations (e.g., nationality, socioeconomic status, and race), and measures of exposure (e.g., PbT versus PbB) and analytic approaches also differ; therefore, studies may not be comparable. Longitudinal studies, on the other hand, are remarkably similar in design and implementation, and, except for the Sydney study, the findings are consistent.

Discussion

The understanding of the effects on humans of exposure to environmental lead is an important public health issue. Whereas childhood lead poisoning and occupational lead intoxication in adults are well-recognized clinical entities that result from high body burdens of lead, the effects that lower levels of lead have on humans continue to be controversial. In this review, we have focused on the effects that low levels of lead (< 25 μg/dl) may have on mental development.

At the outset of the overview, we intended to combine data from the longitudinal studies in a statistical meta-analysis; we were unable to pool the data for several reasons. First, the statistics used by the study authors (i.e., correlations, regression coefficients, and changes in standardized scores) were different and could not be interconverted because of a lack of supporting data. For example, correlations could not be converted to equivalent regression coefficients because standard deviations of the independent and dependent variables were not provided. Grouping values of an independent variable into categories and regressing the independent variables for these categories[1-3] will yield different regression coefficients from those based on continuous measurements of the variable of interest. Second, Pb-B values were treated differently in the various studies. Blood-lead values were categorized prior to statistical regression analysis in the Boston study, and either log-transformed or original values were used in other studies. Also, the ages at which mental tests were given and ages at which lead levels were measured were different for the studies. In the few instances where comparable measurement intervals were reported, the signs of the coefficients differed. In addition, the stated goals of the studies were not identical. For example, the Cleveland study was designed originally as a case-comparison study, and it investigated the impact of maternal lifestyle factors (e.g., alcoholism) on the occurrence of birth defects.[29] Finally, except for the Sydney study, any reported absence of PbB effect on mental development was apparent only when analyses were adjusted for confounding. For these reasons, we did not pool or stratify even the unadjusted data.

The authors of the Boston, Cincinnati, and Port Pirie studies concluded that increased exposure to lead at levels below the current threshold for intervention (25 μg/dl) slowed mental development in children and lowered IQ. But the Cleveland investigators concluded that their data did not show such an effect. Careful examination of their data, however, showed a consistent adverse effect of lead exposure on MDI and IQ, although the differences measured were not significant statistically. The Cleveland findings, therefore, are consistent with studies that have shown a statistically significant toxic effect of lead on mental development. Perhaps there was insufficient statistical power to detect such an effect.

The results of the Sydney study, however, are more difficult to reconcile with the findings of the other longitudinal studies. With the exception of the unadjusted results on the effect of maternal PbB on the MDI at 6 mo and results reported inconsistently at 12 mo and 24 mo in separate publications, the findings of the Sydney investigators are consistent either with no effect or with a direct (but not statistically significant) effect of PbB on MDI at all times of exposure up until 48 mo. Moreover, this finding was apparent in both adjusted and unadjusted analyses. Some methodologic concerns set this study apart from the others, e.g., inconsistently reported results noted above, inconsistency of reported PbB measurements within subgroups of the population, potential selection bias that resulted from the hospital-based nature of the populations, and the limited scope of reported analyses. In addition, the reported effect of environmental factors on mental development measures suggests that social factors in this middle-class population may have played a role in compensating for adverse effects of exposure to lead on the fetus and child. At the same time, it is not clear why this study, judged by blinded reviewers to be of the highest quality methodologically, showed results different from the other studies and other sources of evidence. Final judgment must await further publications from these investigators.

Whereas investigators from the five longitudinal studies exchanged ideas and results during a period of several years and agreed on certain aspects of study design and implementation, apparently no such consensus on the analyses and reporting of results occurred. Our inability to perform a meta-analysis should sensitize investigators to the need for publication of commonly reported statistical results or, at a minimum, sufficient information to allow interconversion of parameters. The alternative that the meta-analyst seek the primary data from authors is time-consuming, sometimes impractical, and may introduce serious bias from inconsistent efforts in the retrieval of old information and the inadequacy of old files.[54] The establishment of an international registry of longitudinal lead studies, analogous to registries proposed for randomized controlled trials,[54,55] would help to address concerns of

comparability and would facilitate meta-analysis. Recent studies in Yugoslavia, Mexico, and Scotland should be included in such a registry.[4,56,57]

The among-person variability should be reduced if the statistical modeling for longitudinal studies takes advantage of the longitudinal nature of the results for each person.[58] This variability could account for much of the observed variation. The slope of the mental development index versus elapsed time should be obtained for each person. The null hypothesis dictates that this slope should average zero if testing is consistent. These individual slopes should then be considered in a model versus their respective mean PbB values and potential confounding variables. The second slope would indicate the low-level effects of lead. If this approach were used, the power of the analysis to detect even low-level effects might be increased in longitudinal studies.

Assessment of the evidence for causation

Currently, efforts are being made to eliminate environmental lead as a risk factor for disease and disability; therefore, it is important to place these five longitudinal studies in the context of available scientific knowledge. There are issues described in this report that limit generalizations from these studies; therefore, the evidence for a causal association between low-dose exposure to lead and impaired mental development will be discussed. The evidence will be reviewed, using the following features proposed first by Hill, to evaluate observational data for the nature of a relationship between exposure and outcome:[59] strength of association, consistency, specificity, temporal relationship, biological gradient, biological plausibility, coherence of the evidence, experimental evidence, and reasoning by analogy.

Strength of association. Strength of association would be best measured by the change in mental development that results from a change in PbB. Unfortunately, this information is available from the Boston study only. Moreover, the relative risk of having a low IQ (e.g., < 90 on the WISC verbal) has not been calculated in any of the studies, and the published reports do not provide sufficient data on which to base such a calculation.

Consistency. Investigators who authored four of the five longitudinal studies from two countries demonstrated an inverse relationship between PbB and MDI, although adjustment for confounding reduced or removed the effect in two of the studies. The data from the PbT studies are consistent with an inverse association between PbT and mental development.[8]

Temporal relationship. Longitudinal studies provide the best evidence for a temporal relationship because exposure can be most clearly demonstrated to precede outcome.

Biological gradient. A dose-related effect of lead on mental development was seen in the Cleveland and Cincinnati studies, in which PbB was used as a continuous variable, and in the German and English PbT studies.[8] In the Boston and Port Pirie longitudinal studies, PbB was found to be correlated inversely with IQ. Similar results were noted for the Philadelphia and Boston PbT studies.[60,61] The well-recognized clinical syndrome of encephalopathy that is associated with elevated PbB is also consistent with a biological gradient.[1]

Biological plausibility. The evidence for biological plausibility has been documented independently of this review. The known neurologic effects of lead in humans on nerve conduction velocity and EEG patterns, the uptake of lead in human tissue—primarily in bone and teeth, at very low levels, and the experimental evidence in animals, are all consistent with a neurobiological effect of low PbB levels on intelligence and behavior.[1-3]

Experimental evidence. Although intentionally exposing children to environmental lead is unethical, studies that examine the effects of removing or reducing lead levels can be regarded, for the purpose of this discussion, as an experiment in lead removal, in which the child is his/her own control. The few rather small reports on PbB reduction do not clearly show improved neuropsychological performance.[4] This observation does not contradict a causal role for lead in inhibiting mental development, because it could indicate a long-lasting or perhaps irreversible effect of lead. As noted above, animal experiments support a causal role for lead in the inhibition of mental development. Lead exposure in rats leads to a reduction of axonal pathway development in the hippocampus, which affects neuronal development, and eventually effects a reduced intellectual potential.[62] Lead also competes with and displaces calcium in the neural membrane, which disrupts cholinergic functioning.[63] This effect was most apparent in the brain, especially in the hippocampus and developing cerebellum. These basic mechanisms of lead action at the neuronal level have reduced long-term memory in experimental animals. A reduction in long-term memory, resulting from lead exposure, could explain differences in mental development and educational attainment tests that reflect learning and retention over long periods.

Coherence of the evidence. Adverse effects of childhood lead exposure on mental development and behavior, seen with different types of research in a wide variety of settings, are consistent with a causal role for lead. The studies with experimental animals cited above are also consistent.

Reasoning by analogy. Lead is the prototypic heavy-metal toxicant in environmental health, and few substances can be compared with it. Although other metals such as mercury have known effects on the human nervous system, studies of low-dose chronic exposure are not available for them.

Conclusion

Although data from the longitudinal studies remain inconclusive, current evidence from all sources is consistent with a small (2-10 points), but biologically significant, effect on IQ of children exposed to low levels of lead (< 25 μg/dl). This significance stems from the dramatic effect that a shift in the mean in a population

distribution has on the tails of that distribution. For example, a decrease of 4 points in mean population intelligence increases the number of children with IQs of < 80 by threefold and decrease the percentage of children with IQ scores of > 125 from 5 to 0. This seemingly small effect on individuals can, therefore, have very dramatic effects on a population.[64]

We should continue to examine critically future data collected from the longitudinal studies reviewed in this article, as well as other studies that are planned or are under way. Nevertheless, the evidence for the existence of adverse health effects directly related to lead exposure is more consistent than some skeptics have argued, and this evidence has led some clinicians to recommend treatment for asymptomatic children who have low levels of PbB.[65] From a public health perspective, the argument for both primary and secondary prevention of lead exposure and its sequelae is compelling because lead has not been shown to benefit humans and efforts to reduce PbB levels in children by removing lead from urban dwellings can be successful. Lead poisoning is an entirely preventable environmental disease, the elimination of which should be one of the nation's public health goals. The nature and extent of public health programs that aim to reduce lead in the environment should reflect the continuing review of the best available scientific information, the costs to society of alternative interventions, and the social and economic costs of failure to intervene appropriately.

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