Fetal and Infant Lead Exposure: Effects on Growth in Stature

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ABSTRACT. The growth of a cohort of 260 infants was prospectively followed up from birth. Blood lead and stature measurements were obtained every 3 months until 15 months of age. Fetal lead exposure was indexed by measuring lead in maternal blood during pregnancy. A longitudinal analysis revealed that covariate adjusted growth rates in stature were negatively related to the infants' postnatal blood lead concentration, as indexed by increase in average blood lead values from 3 to 15 months. However, this relationship between growth rate and change in blood lead concentration was evidenced only among those infants whose mothers had prenatal blood lead levels greater than the maternal cohort median of 7.7 μg/dL ($P = .01$). The expected stature of a child born to a mother with a prenatal blood lead concentration more than 7.7 μg/dL is about 2 cm shorter at 15 months of age if, postnatally, the infant incurred a 10-μg/dL blood lead increase during the 3- to 15-month interval of life, compared with an infant who has no increase. *Pediatrics* 1989;84:604–612; *lead, growth, stature, infant.*

The objective of this analysis was to assess the possible association of lead exposure as indexed by maternal and/or infant blood lead concentration with the infants' growth in stature during the first 15 months of life. As early as 1930, stunted growth was reported in children who survived lead-induced intoxication.[1] More recently, asymptomatic lead exposure has been linked to short stature.[2,3] These studies dealt with effects of relatively high (50 μg/dL and greater) lead exposure on physical size. Most recently, results of an analysis of data derived from the National Health and Nutrition Examination Survey showed a negative relationship between "low to moderate" levels of lead exposure (as indexed by blood lead concentration) and stature, in 2695 children, aged 6 months through 7 years.[4] The results were based on a large cross-sectional data set.

Longitudinal study of the effects of low level prenatal and postnatal lead exposure on physical growth of children is a logical extension of this work because it permits better assessment of both toxic "dose" and associated "effect." Furthermore, changes in lead exposure and physical growth can be temporally linked. This, in turn, strengthens subsequent causal inferences. Repeated assessment of both prenatal and postnatal exposure also helps to identify critical times when a fetus or infant may be particularly sensitive to the insult. The Cincinnati lead study,[5] being prospective in nature, has provided the opportunity to assess the effects of fetal and infant lead exposure on physical growth in stature.

There is growing evidence that fetal lead exposure, as indexed by prenatal maternal and early infant postnatal blood lead levels, is negatively correlated with the infant's physical size (particularly weight) at birth.[6–8] Given these findings and the results of National Health and Nutrition Examination Survey II relating postnatal blood lead concentration and stature,[4] we postulated that there would be an interaction between prenatal lead exposure and infant's postnatal lead exposure to produce an effect of lead on early growth rate. Specifically, we hypothesized that the effect of lead on growth would be most pronounced among those infants experiencing both "high" prenatal lead exposure and "high" postnatal lead exposure. Given the relatively modest levels of lead exposure during the first 15 months of life, neither high prenatal maternal blood lead concentration nor high post-

Received for publication Feb 2, 1988; accepted Oct 5, 1988.
Presented, in part, in the proceedings of the International Conference on Heavy Metals in the Environment, New Orleans, LA, Sep 15–18, 1987.
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natal infant blood lead concentration, alone, were hypothesized to sufficiently perturb the system to produce both a biologically and statistically significant negative effect on growth.

MATERIALS AND METHODS

Subjects

The general design of the Cincinnati lead study has been reported elsewhere.[5] Briefly, pregnant women residing in a predesignated hazardous area for lead exposure of Cincinnati, Ohio, were asked to participate in the study between 1980 and 1985. City health department data showed that this geographical area had a history of producing many cases of childhood lead poisoning. This area has generally poor housing facilities, with paint of high lead content and lead-contaminated street dust and house dust.[9] A large majority of the included women were single (87%) and receiving public assistance (87%). Based upon a set of exclusion criteria for the newborn, 76 neonates were excluded from postnatal recruitment. Furthermore, 129 families refused to participate in a long-term postnatal follow-up (5 years). Descriptive statistics were obtained concerning mothers and infants who were excluded from the study either by prenatal/postnatal criteria or refusal to participate. They were compared to those who actually participated. Included and excluded subjects were similar with respect to key demographic variables.[6]

In prospective follow-up studies, data are often missing for one or more key independent variables. This proved to be the case for prenatal (maternal) blood lead measurement. Forty-five mothers of the study cohort did not provide prenatal blood lead values. They were usually missing because a sample was not obtained at the time of their recruitment. Analyses were conducted to determine whether cohort subjects with missing maternal blood lead data differed in any systematic way from the others in the cohort. Results indicated that there were no statistically significant ($P > .10$) differences between the two groups on the study covariates.

For the present analysis, 13 additional study infants were excluded. They were four sets of twins, two infants with serious illness during infancy, and three with insufficient growth data. Thus, the present report is based on a study cohort of 260 infants followed up for the first 15 months of life. Some descriptive statistics for this sample are given in Table 1.

Assessment of Lead Exposure

Maternal blood samples were collected by venipuncture at the first prenatal visit. Forty-three percent of these samples were collected during the first trimester, and 49% and 8% were collected in the second and third trimesters, respectively. Infant blood samples were collected 10 days postparturition (corrected for gestational age) and 3, 6, 9, 12, and 15 months thereafter. Blood was drawn by heel stick, finger stick, or venipuncture, depending upon the physical characteristics of the infant, with venipuncture being the method of choice. The mean concentrations of lead in whole blood at 3 and 15 months were 5.3 and 14.6 μg/dL, respectively. Approximately 10% of the sample had at least one postnatal blood lead determination in excess of 25 μg/dL during the first year of life. Prenatal blood lead measurements were conducted by Environmental Sciences Associates using a model 2014 Anodic Stripping Voltameter. All postnatal blood samples were analyzed in our laboratory using a model 3010 ESA instrument. Details of our laboratory's quality assurance and quality control program have been published elsewhere.[10] All prenatal and postnatal blood lead values were corrected for hematocrit and transformed to their natural logarithm. Maternal hematocrit declines during pregnancy with a resultant decline in blood lead concentration. It is for this reason that the value was adjusted for hematocrit. Hematocrit-adjusted prenatal blood lead values were not significantly different among the three trimester registrants ($F = .96$, $df = 2$, $P = .39$).

In these analyses, we focused on two lead exposure indices. Prenatal (maternal) blood lead concentration as an index of in utero exposure and an index of postnatal lead exposure. Early infant blood lead indices (cord blood lead and 10-day blood lead concentration) largely reflect fetal exposures or residual thereof. Correlations between maternal prenatal blood lead, cord blood lead and 10-day postnatal blood lead values ranged from 0.21 to 0.30 ($P < .05$). We chose maternal blood lead rather than cord blood lead as an index of in utero exposure, mainly for pragmatic reasons. Occasional clotting or contamination of the cord blood frequently resulted in poor quality samples. Elimination of subjects with poor quality samples resulted in a substantial reduction in the sample size. Moreover, maternal blood lead concentration has been used as an index of fetal lead exposure and has been found to be related to fetal growth[7] as well as fetal maturation.[6] For these reasons, maternal blood lead values appeared to be a reasonable choice instead of cord blood lead. The index of postnatal lead exposure chosen for this analysis was: postnatal exposure (postnatal blood lead concentration) = average postnatal blood lead concentration (10 days to 15 months) − average postnatal blood lead concentration (10 days to 3 months).

This index represents the change in an infant's average blood lead concentration during the interval from 3 to 15 months of life. For instance, if a child had an average of 4.0 μg/dL during the first 3 months of life and 12.0 μg/dL during the first 15 months, his or her postnatal exposure index would be (12 − 4) = 8 μg/dL. A summary of lead exposure indices for the study sample is given in Table 2. Infants had an average 3.7-μg/dL increase in their postnatal blood lead concentration during the 3- to 15-month interval, with a maximum increase of 17.6 μg/dL, and a few children had a net decrease relative to the first 3 months of life. Other indices of postnatal lead exposure such as blood lead concentration at 15 months or cumulative blood lead values were less strongly associated with the outcome measure.

Estimation of Growth Rate

Although many complicated curves, including exponential, Gompertz, or polynomial, can be used to express growth vs time, a simple linear relationship was found to be adequate for this analysis. Given the age span (12 months) and limited number of stature measurements, we first determined whether adequate fit, evidenced by acceptably small error, could be estimated by the slope of the least-squares regression line fitted to each subject's data. A logarithmic model did not improve the fits over and above the linear model. The reliability of the fit of a least-squares line estimated by coefficient of determination (R^2) exceeded .90 in all cases. Therefore, the slope of the least-squares regression line fitted to each subject's length measurements from 3 to 15 months was deemed to be an adequate estimate of growth rate. Obtaining good linear fits was the main reason for calculating growth rates from 3 to 15 months instead of birth to 15 months. Inclusion of length measurements before 3 months distorted the linearity of growth curves. Descriptive statistics concerning stature measurements for the study cohort are given in Table 3.

Assessment of Potential Confounders and Covariates

In epidemiologic cohort studies, such as the present one, a wide range of potentially confounding variables need to be measured and statistically controlled for. Therefore, a substantial amount of medical and social background data were collected from all subjects. In Table 4 are listed the candidate confounders and covariates which were chosen a priori based upon their theoretical and/or known empirical association with both the target independent variable (lead exposure) and/or target dependent variable (growth in stature).

Obstetrical history and pertinent perinatal data were recorded from the mother's and neonate's charts. These data were coded using the Littman-Parmelee Obstetrical and Postnatal Complications Scales.[11] One of the exclusion criteria for pregnant women's participation in the study was evidence of drug or alcohol addiction during pregnancy. Alcohol consumption per se was recorded as a yes-/no-type response to a question pertaining to any use of alcohol by the mothers during pregnancy. In our

TABLE 1. Descriptive Statistics on Study Sample (N = 260)

Variable	Mean	SD	Minimum	Maximum
Maternal age at delivery (y)	23.0	4.5	15	39
Social class[12]	17.0	5.0	8	44
Home Observation for Measurement of the Environment score[13]	31.3	4.6	17	42
% unmarried	87.0			
Birth wt (g)	3164.0	464.0	1850	4680
Gestational age (wk)*	39.7	1.5	35	43
% black	84			
% girls	51			

* As assessed by standardized physical examination of the neonate.

TABLE 2. Measures for Lead Exposure (n = 260)

	Blood Lead Concentration (μg/dL)			
	Mean	SD	Minimum	Maximum
Prenatal (maternal)*	7.5	1.6	1	27
3 mo*	5.3	1.8	1	22
15 mo*	14.6	1.6	3	56
Average* (birth to 3 mo)	4.7	1.8	0.2	15.7
Average* (birth to 15 mo)	8.3	1.5	2.4	27.1
Change in average* (3 to 15 mo)	3.7	3.0	−5.8	17.6

* Geometric mean and geometric standard deviation.

sample, only 37 of 260 women reported alcohol use during pregnancy (of these, 11 were using alcohol but no cigarettes, and the other 26 were alcohol and cigarette users). Cigarette consumption during pregnancy was quantified and recorded as packs per day and was used as a potential confounder. The socioeconomic status of the infant's family was assessed with the Hollingshead 4-Factor Index of Social Status.[12] The mean socioeconomic status for families in this sample was 17.0 (SD 5.0), reflecting the preponderance of single-parent, low-income households. The quality of the infant's domestic environment was assessed with Caldwell and Bradley's Home Observation for Measurement of the Environment (HOME).[13] The HOME combines inteviewer's questions with direct observations to yield subscale and total HOME scores. In general, the HOME measures the mother's responsivity and personal involvement with her infant and the extent to which the physical and temporal environment is stimulating and safe. The mean of the 6- and 12-month HOME scores was calculated for each subject and tested as a potential developmental covariate or confounder in regression analyses. Significant correlates of exposure and response measures are given in Table 5.

TABLE 3. Measures for Stature (N = 260)

	Infants' Height			
	Mean	SD	Minimum	Maximum
At birth (cm)	49.3	2.4	42.0	54.0
At 3 mo (cm)	60.4	2.7	53.0	68.5
At 15 mo (cm)	78.5	2.9	69.8	88.0
Growth rate (cm/mo)	1.5	0.2	0.8	2.1

Statistical Approaches

One of the strongest correlates of growth rate in our sample was the infant's length at 3 months (Pearson's $r = -.50$, $P < .0001$) indicating that shorter subjects at 3 months tended to have higher growth rates than did relatively larger infants. Given that the infant's stature at 3 months was a strong predictor of the subsequent growth in our sample, our initial working hypothesis was as follows: If postnatal lead exposure has any deleterious effect on the expected growth of an infant during 3 to 15 months of life, it should be evidenced predominantly among those infants whose measurements are less than expected (as predicted by their stature at 3 months of age).

To explore this hypothesis, growth rates were regressed on individual lengths at 3 months, separately for boys and girls. Based upon the sign and magnitude of the residuals, all infants were classified as follows: slow growing, those having large negative (more than 1 SD) residuals, ie, infants whose observed growth rates were lower than expected; fast growing, those having large positive (more than 1 SD) residuals, ie, infants whose growth rates were higher than expected; and average growing, those within ±1 SD of the expected growth rates, ie, infants whose growth rates were not deviating much from the predicted growth rates, based on their stature, at 3 months of age. The

TABLE 4. Candidate Confounders and/or Covariates

Perinatal Variables	Infant Variables	Sociohereditary Variables
Birth length	Iron status	Socioeconomic status
Gestational age by examination	Hemoglobin	Developmental stimulation
Postnatal complications scale	Total iron-binding capacity	Maternal race
No. of cigarettes smoked per day during pregnancy	Sex of infant	Maternal height
Maternal age at birth of child		

TABLE 5. Correlates of Lead Exposure and Response Variables*

Variables	Prenatal Lead Concentration	Postnatal Lead Concentration	Birth Length	Length at 3 mo	Growth Rate
Race	−.15 (.01)	NS	−.11 (.08)	−.11 (.08)	.12 (.06)
Cigarette use	.21 (.0006)	NS	−.21 (.0006)	−.14 (.03)	NS
Sex	NS	NS	−.11 (.08)	−.24 (.0001)	.13 (.04)
Gestational age	NS	NS	.22 (.0004)	.10 (.10)	NS
Maternal height	NS	NS	.17 (.006)	.26 (.0001)	.10 (.10)
Postnatal complications scale	NS	NS	.13 (.04)	.14 (.02)	NS
Socioeconomic status	NS	−.19 (.002)	NS	NS	NS
Home Observation for Measurement of the Environment	NS	−.18 (.008)	NS	NS	NS

* Race and cigarette use were bonafied confounders, based upon our definition. They were forced to remain in the models, irrespective of their significance levels. Not significant, $P > .10$. Entries are correlation coefficients; P values are in parentheses.

purpose of this classification was to permit a qualitative evaluation of important descriptors of each growth class. Analysis was also done using simultaneous equations' modeling (also known as structural equations' modeling).

Structural Equations' Modeling and Analysis

In a longitudinal prospective study like this, in which subjects are repeatedly assessed throughout time for both "exposure" and "response," one could possibly treat the data as a multivariate-repeated measures problem. If the data are time structured (ie, data for all subjects are available at prespecified times), we may use multivariate analysis of variance or covariance. However, a conceptual problem sometimes may arise, namely, that an outcome measured early in life could theoretically be affected by exposures occurring later in life. For example, birth length and/or length at 3 months may get modeled as being affected by postnatal lead exposures occurring after 3 months of life. Simultaneous regression modeling allows us to overcome such a difficulty. Basically, structural equations' modeling is a collection of several regression equations in which the distinction between dependent and independent variables is not explicitly made. A variable (eg, birth length) may behave as an outcome or dependent variable in one of the regression equations and it may be treated as an independent variable in another regression equation. The variables serving as an outcome in any of the equations are termed endogenous and the others as exogenous. There are as many equations in a system as there are endogenous variables. Thus, for the present analysis, we essentially have three regression equations (one each for birth length, length at 3 months, and subsequent growth rate). Instead of treating the statistical problem as three separate multiple regressions, the structural equations' analyses permits separate modeling of each equation and, more important, simultaneous estimation of the model parameters (ie, regression coefficients). Simultaneous estimation provides an extra degree of control over obtaining false-positive results (ie, a spuriously significant lead effect). Structural equations' modeling was undertaken to confirm the qualitative findings after taking into account all relevant explanatory variables (covariates and confounders). Our strategy to control for various confounders and arriving at the final structural equations' model can be summarized in the following steps. Step 1: Identification of potential confounders and covariates (see Table 4 for the list of candidate variables). Step 2: Based on bivariate correlations, identify covariates and confounders ($P < .10$). Step 3: Execute three stepwise regressions (one each for birth length, length at 3 months, and growth rate). At this step, lead exposure variables are not included. The relevant confounders are forced to remain in the model. This series of stepwise regressions provided us with variables to be included in each of the equations for structural equations' modeling. Those variables that were deleted in this process were later checked statistically for possible reentry after including the lead exposure indices in the model. This permits any variable that was eliminated as a result of stepwise regression (because of the absence of lead variables from the models) to again be added to the model. Step 4: Structural equations' analysis was executed with all the relevant variables (from step 3) along with relevant lead exposure variables plus all two-factor lead exposure by explanatory variable interactions. A series of backward elimination of nonsignificant ($P > .05$) interactions from the structural equations' model was performed. The structural equations' analysis was carried out on a statistical software package called SAS (Statistical Analysis System) using the procedure SYSREG which is described in the supplement called ETS-Manual of SAS.[33]

RESULTS

The mean characteristics of the three types of growth patterns are given in Table 6. These growth classes do not differ with respect to various non-

TABLE 6. Descriptive Statistics for Various Nonlead-Related Variables by Type of Growth*

Variable	Growth		
	Slow (n = 38)	Average (n = 180)	Fast (n = 42)
Gestational age (wk)	39.4	39.7	39.8
Birth length (cm)	60.6	60.3	60.8
Cigarette use (packs/d)	0.8	0.8	0.6
Home Observation for Measurement of the Environment score	28.8	31.5	32.1
% girls	52	52	48
% blacks	79	84	90

* Results are mean values.

lead-related variables, although there appears to be a gradient for race and HOME scores. The frequency distribution of these three types of growth classes for various combinations of both maternal and postnatal infant lead exposure histories is given in Table 7. Based on a median split (7.7 μg/dL for prenatal blood lead concentration and 3.4 μg/dL for postnatal blood lead concentration), subjects with both maternal and postnatal blood lead values were divided into low/high groups, giving four combinations of the entire lead exposure history (low-low, low-high, high-low, high-high). Distribution of the infants within each type of growth category in each of the four lead exposure combinations is noteworthy. If lead exposure histories were unrelated to growth, one would expect 25% of the cases to occur in each of the exposure history categories. However, a larger percentage of the slow-growing infants (42%) belonged to that combination of exposures, which reflects high prenatal and high postnatal blood lead exposure (n = 16) and few (10%) belonged to the low-low exposure category (n = 4). Furthermore, most of the so-called fast-growing infants (38%, n = 16) were those infants whose mothers had high blood lead concentrations during pregnancy and low postnatal blood lead value increases during 3 to 15 months. This suggests that high maternal lead exposure suppressed normal growth early in life. However, if the infant escaped continued high postnatal exposure, then these infants tended to have higher than expected growth rates, indicating a growth catch-up.[14,15] Infants in the average growth category were evenly distributed across all four lead exposure combinations. The type of growth category was significantly associated with the lead exposure categorization (χ^2 = 15.9, 6 *df*, P = .014). Some tentative qualitative conclusions can be formulated from these results. Infants' postnatal lead exposure (as indexed by the increase in the average blood lead concentration from 3 to 15 months) in conjunction with high prenatal lead exposure appears to be associated with growth reductions in those infants exhibiting growth rates slower than predicted by their stature at 3 months of age.

To statistically confirm the preceding observation, structural equations' modeling was undertaken. The structural equations' analyses resulted in a significant negative interaction (prenatal blood lead × postnatal blood lead) (P =.006), even after controlling for relevant confounders, namely, race and number of cigarettes smoked during pregnancy. A qualitative description of the results of the structural equations' analysis is given in Fig 1.

TABLE 7. Distribution of Infants: Lead History By Type of Growth

Prenatal/Postnatal Lead Exposure*	Growth		
	Slow	Average	Fast
Low/low (n = 66)	4	51	11
High/low (n = 65)	12	37	16
Low/high (n = 59)	6	47	6
High/high (n = 70)	16	45	9

* Based on median split (7.7 μg/dL for prenatal, 3.4 μg/dL for postnatal).

To understand the nature of the interaction between postnatal and prenatal blood lead exposure, partial regressions between postnatal blood lead index and growth rate (after controlling for relevant variables, namely, the length at 3 months, maternal height, race, and cigarette use), were obtained for each prenatal maternal blood lead category (low or high). No relationship was found between postnatal blood lead concentration increase and growth rate of those infants whose mothers had low (≤7.7 μg/dL) prenatal blood lead values during pregnancy (slope = .007, P = .19), whereas a significant negative regression was obtained for those infants whose mothers had high prenatal blood lead concentrations (slope = −.015, P = .013) (Fig 2). This lends support to our initial hypothesis that the increase in postnatal blood lead concentration was negatively correlated with growth rate but for only those infants whose mothers had high prenatal values during pregnancy.

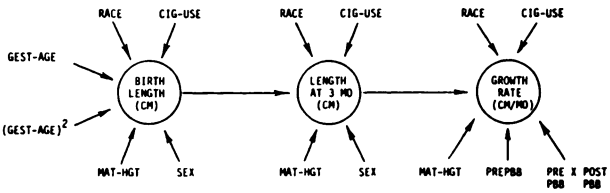

Fig 1. Qualitative description of structural equations' model. Abbreviations: GEST-AGE, gestational age; (GEST-AGE)², square of gestational age; MAT-HGT, maternal height PREPBB, prenatal blood lead concentration; POSTPBB, postnatal blood lead concentration; CIG-USE, cigarette use.

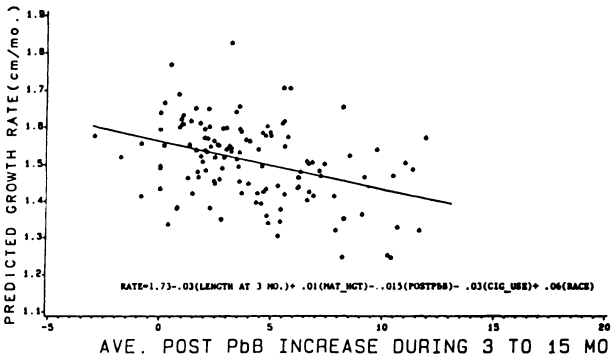

Fig 2. Influence of postnatal lead exposure on growth rate of infants with prenatal lead exposure greater than cohort median (7.7 μg/dL) (n = 129). Abbreviations: MAT-HGT, maternal height POSTPBB, postnatal blood lead concentration; CIG-USE, cigarette use; AVE, average.

The expected growth of an infant whose mother had high (more than 7.7 μg/dL) prenatal blood lead concentrations is shown in Fig 3. Then estimates were based on the estimated model after controlling for relevant covariates and confounders. There was, on average, 2.0 cm difference in predicted stature at 15 months of age between those infants who had no additional increase in postnatal blood lead concentration during 3 to 15 months vs those who had an increase of approximately 10 μg/dL. This difference of 2 cm at 15 months of age could shift an infant, for example, from the 50th percentile to about the 25th percentile, which is a considerable decrease.

DISCUSSION

This is the first longitudinal study of the effects of low to moderate levels of lead exposure on infants' growth in stature. The results of this study are consistent with previous cross-sectional studies in which lead exposure was found to be negatively associated with stature of young children. A distinct advantage of the prospective study design and analysis is borne out in the present study. Because of the availability of information about in utero exposure to lead (as indexed by maternal prenatal blood lead concentration) as well as infants' postnatal lead exposure, it was possible to assess the interaction between the two exposure periods. The results suggest that postnatal lead exposure is negatively associated with growth rates in stature at levels that are well below those associated with overt lead poisoning. However, this inverse relationship is evidenced only among those infants whose mothers had higher than average (>7.7 μg/dL) prenatal blood lead values. These results emphasize the importance of in utero exposure to lead.

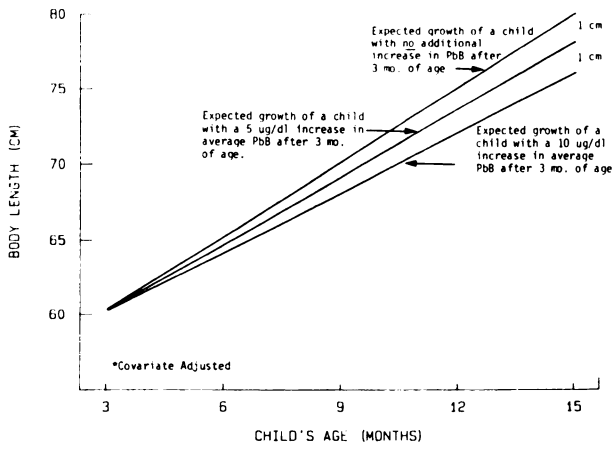

Fig 3. Predicted growth as a function of increase in average postnatal blood lead concentration (PbB) during 3 to 15 months for infants born to mothers with prenatal blood lead levels greater than cohort median (7.7 μg/dL).

They suggest that in utero growth is affected by lead, such that continued elevated postnatal exposure results in suppressed growth in stature. On the other hand, infants with increased in utero exposure but not increased postnatal exposure tended to have faster growth rates, implying catch up.[14,15] Because only the high (>7.7 μg/dL) prenatal blood lead group exhibited a significant negative relationship between growth rate and postnatal blood lead values, one must not infer that 7.7 μg/dL is a well-defined threshold for the prenatal blood lead effect. This value was simply the median prenatal blood lead concentration for our sample.

Indicators of iron status, such as hemoglobin level, serum iron concentration, and total iron-binding capacity were not found to be associated with growth rates in the present sample. Approximately 95% of this cohort of children participated in the Women, Infant, and Children program. Approximately 40% of this study cohort was interviewed regarding frequency of food intake per week. Calcium and phosphorus intakes were greater than recommended daily intakes, whereas vitamin D was slightly less. Serum calcium, phosphorus, and 1,25-vitamin D levels were normal. Therefore, the reduced growth rate should not be ascribed to grossly inadequate diet. Father's height was not a candidate covariate for the present analysis (although mother's height was included). Data concerning father's height was unavailable for this analysis. However, father's height is not as good a predictor of infant's height, during the first 2 years of life, as is the mother's. There is no a priori reason to suspect that paternal height is related to both maternal blood lead level and/or infant blood lead level as well as infant growth rate. If, in fact, paternal height is not a confounder, then the effect size on the lead growth relationship is less likely to be affected by whether or not paternal height is included in the analyses. Inclusion of maternal height in the analysis did not diminish the lead-growth relationship.

It is worthwhile to point out that, in an observational study like the present one (in which treatments of interest are not randomly assigned), the evidence of a relationship between exposure (ie, lead) and effect (ie, growth) is, by itself, not proof of a causal relationship. Nevertheless, this study does identify lead exposure as an important effect modifier (risk factor) for growth in stature in our study cohort. Analysis was carried out to assess the sensitivity of the magnitude of the lead effect to the inclusion or exclusion of the various covariates/confounders. For example, exclusion of all those women who reported use of alcohol during pregnancy did not affect the blood lead concentration-growth relationship. The sensitivity analysis revealed

that the magnitude of the regression coefficient for postnatal blood lead index, in fact, increased as the covariates/confounders were gradually included in the model. It increased from −.0126 (with no other variable in the model) to −.0148 (with all significant covariates and confounders included in the model).

An interesting possibility remains. Let us speculate for a moment that, for a given level of lead exposure, infants who are intrinsically growing at a reduced rate have a total body lead distribution such that they have higher blood lead values vs those who are inherently growing faster, even if both have similar lead intake and total body burdens. If such were the case, then the present results would be obtained, namely, larger increases in blood lead concentration would be associated with lower rates of growth in stature. To explore such a possibility, other estimates of body burden (such as lead in bone) would need to be obtained.

There are a few statistical issues that need further elaboration. One is the approach of classifying infants into various growth categories. An arbitrary choice of 1 SD as a cutoff was chosen to be both reasonable and simple. One could actually construct confidence (prediction) bands for the regression line between growth rates and the 3 months' lengths. Then, one could use those bands to classify infants into various categories. For the purpose of this study, the classification of the infants into the growth categories was intended for an initial look at the distribution.

A second issue is the linear growth assumption, ie, that growth during 3 to 15 months can be summarized by the slope of the least-squares line fitted to each subject's data. One could postulate that lead exposure is not only related to reduced linear growth rate but may also be related to deviations from linear growth rates. We explored this question in a qualitative manner. One way to assess the goodness of linear fit is to compute and examine the R^2. The distributions of R^2 in each of the four lead exposure categories were similar and no evidence of trend in support of this postulate was found.

Another issue that emerged from this analysis involved the interaction between prenatal and postnatal lead exposure. Because we also measured infant blood lead 10 days after birth, we examined the data to determine whether additional light could be shed on the lead exposure-growth relationship by characterizing lead exposure as a three-way interaction, viz, prenatal, 10-day, and postnatal. The results of such a modification did not indicate existence of such a three-way interaction.

To recapitulate the main results of the study, we conclude that high in utero lead exposure (as indexed by the maternal blood lead concentration), followed by a relatively high postnatal lead exposure, does have a detrimental effect on growth in stature of infants. On the other hand, if this group of infants avoided high postnatal lead exposure, they tended to catch-up from the deleterious effects of in utero lead exposure. In other words, they tended to return to their genetically programmed path for growth in stature. The mechanisms by which lead exposure may affect growth early in development remain to be more fully delineated. At least three general mechanisms exist by which low-level blood lead might alter growth[4]: an interaction of lead with reactions mediated by calcium as a second messenger,[16–18] lead inhibition of heme-dependent enzymes,[19–23] and neuroendocrine toxicity possibly related to inhibition of dopaminergic and α-adrenergic receptors in the hypothalamus.[24–32] Whether these effects are transient or persist into later childhood will be explored further as and when the Cincinnati cohort matures.

ACKNOWLEDGMENTS

This research was supported by a program project grant from the National Institute of Environmental Health Sciences (grant ES-01566, Dr Paul B. Hammond, Project Director).

This study protocol was reviewed and approved by the Committee on Human Research, University of Cincinnati College of Medicine. We acknowledge the support of J. Grote and T. Mitchell for their contributions in this study. We thank Drs J. Chisolm and S. D. Walter for reviewing an earlier draft and for providing numerous suggestions which substantially improved the paper. We thank N. Knapp for typing this manuscript.

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Erratum

In the commentary, "Sunburns, Melanoma, and the Pediatrician," by Williams and Sagebiel (*Pediatrics* 1989;84:381–382), three lines were omitted from the bottom of p 381. The whole paragraph is reprinted here.

It is clear that a change is required in social perceptions in which a suntan is equated with health and beauty—not because suntans per se are unhealthy (the deleterious effects of ultraviolet light at suberythemogenic levels are not well-established), but because the persistent and often futile efforts of those who constitutionally have less pigment to achieve a tan have serious long-term health consequences. Ideally, there should be a social norm of beauty in which the natural differences in skin color are appreciated and black, tan, pink, and all shades in between are celebrated. Similarly, we need to change our thinking about freckles and solar lentigines. These are not "cute" but represent the ineffective efforts of melanocytes in genetically underpigmented skin to provide protective pigmentation in response to solar stress. Although pediatricians alone cannot change social concepts of beauty, we can instruct our patients and their families about sun protection and we can monitor them for early signs of excessive sun exposure. Weinstock et al[11] demonstrated an increased risk of melanoma for those who had blistering sunburns in adolescence. Although they did not address the risk associated with sunburning prior to ages 15 years, it seems likely that these data can be applied to children of all ages. Therefore, instruction and sun protection should begin in infancy. Moreover, teenagers are known to be both highly conditioned by peer concepts of beauty and relatively impervious to the counsel of their elders. It is essential, therefore, that they enter these years with skin that has been well protected and with minds well indoctrinated.