Relationship Between Childhood Blood Lead Levels and Stature

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ABSTRACT. The second National Health and Nutrition Examination Survey, 1976 to 1980, incorporated medical history, physical examination, anthropometric measurements, dietary information (24-hour recall and food frequency), laboratory tests, and radiographs. In linear regressions of adjusted data from 2,695 children aged 7 years and younger, 91% of the variance in height, 72% of the variance in weight, and 58% of the variance in chest circumference were explained by six variables: age, race, sex, blood lead level, total calories or protein, and hematocrit or transferrin saturation level. Variables that did not significantly improve the models predicting growth included family income, degree of urbanization, serum albumin, copper, iron, and zinc levels, dietary carbohydrate, fat, calcium, potassium, phosphorus, vitamin A, vitamin C, niacin, riboflavin, and thiamine. The highly significant correlation of blood lead level with growth does not contradict the established association of childhood deprivation with increased lead exposure and with nutritional deficiences known to enhance lead absorption. Blood lead level may also represent a composite marker for unidentified genetic, ethnic, environmental, and sociocultural variables, other than race, sex, and nutrition, that affect growth. However, the correlation of stature, particularly height, with blood lead levels in the range of 5 to 35 μg/dL is so statistically significant that it merits investigation in other surveys and consideration of the multiple biologic mechanisms by which low-level lead exposure could impair the growth of children. *Pediatrics* 1986;77:281–288; *growth, blood lead level, nutrition, stature.*

Runting, squint, foot drop, and albuminuria were considered a diagnostic criterion for chronic lead poisoning in Australian children of the 1920s.[1] Short stature in children with asymptomatic lead poisoning has been documented more recently and more definitively,[2,3] but the small number of studies are outnumbered by the intensive search for the threshold for neurologic and hematologic effects of low-level lead exposure. Similarly, there has been almost no investigation of an effect on growth of the known biotoxic interaction of lead with calcium messengers,[4–6] heme-dependent enzymes,[7–11] and neuroendocrine function.[12–19]

Impaired growth in children with increased blood lead levels is generally attributed to the association of childhood deprivation with both malnutrition and increased lead exposure; nutritional deficiencies, particularly iron, zinc, copper, calcium, and phosphorus, are known to enhance the absorption of lead.[20,21] Despite this consensus, there are no broad scale surveys of growth in children as related to low blood levels of lead, nutritional status, and major demographic variables. Under the Lead Based Paint Poisoning Prevention Act of 1971, more than 3 million children, primarily those at innercity health clinics, have been screened for lead poisoning with no systematic recording of their height and weight as related to anemia, erythrocyte protoporphyrins, or blood lead levels.[22]

The Second National Health and Nutrition Examination Survey (NHANES II)[23,24] provides a unique opportunity to examine the correlation of a comprehensive set of nutritional, demographic, and health data, including blood lead levels in the range of 5 to 35 μg/dL, with the height, weight, and chest circumference of 2,695 children 6 months through 7 years of age. The representative geographic and socioeconomic participation in the NHANES II survey permits analysis of the critical demographic and nutritional variables affecting blood lead level.

Contemporary calculations of the risk of environmental lead recognize the triple jeopardy of the urban poor: (1) the exposure to lead from multiple sources is highest in low income areas; (2) in high

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lead environments, the amount ingested increases with deficiencies in child care and household cleanliness;[25,26] (3) the intestinal absorption of lead increases with nutritional deficits.[20]

The interaction of sociocultural and nutritional deprivation with both environmental exposure and absorption of lead has long confounded the delineation of the threshold for behavorial and cognitive effects of low-level lead.[27] Equally rigorous analysis is required of any apparent correlation of childhood blood lead level and stature.

Analysis of the NHANES II data shows a significant negative correlation of height, weight, and chest circumference with childhood blood lead level. This is independent of the significant effects on growth of sex, race, total dietary protein or calories, and hematocrit or transferrin saturation levels. There were no significant correlations of the three measures of stature with dietary carbohydrate, fat, calcium, potassium, phosphorus, vitamin A, vitamin C, niacin, thiamine, or riboflavin or with serum albumin, copper, iron, or zinc levels.

The possibility of composite environmental and nutritional factors affecting in the statistical correlation of growth and blood lead level is discussed as is the need to consider the possibility of direct biologic effects of low-level lead exposure on the growth of children.

MATERIALS AND METHODS

Description of Data

The NHANES II was conducted from February 1976 until February 1980 on samples selected by the National Center for Health Statistics and Bureau of the Census to be representative of the civilian noninstitutionalized US population, aged 6 months to 74 years. A total of 20,322 people were examined, and blood lead determinations were obtained for 9,932. The probability of selection for each individual was determined, and the observations were weighed accordingly. Details of the complex survey design, the examination procedures, and the laboratory measurements have been published.[23,24] The medical evaluations included medical history, physical examination, anthropometric measurements, dietary information (24-hour recall and food frequency), laboratory tests, ECGs, and radiographs. Special interview and examination protocols and specifically trained interviewers and examiners were used to ensure the standardized conduct of the survey at each site. The nutrient intake from the 24-hour recall was quantified for each individual using a current nutrient data bank.

Blood samples were analyzed by the Clinical Chemistry Divison, Center for Environmental Health, Centers for Disease Control. Details of the methodology and the quality control for the various analyses have been published.[24] Blood lead concentrations were determined by atomic absorption spectrophotometry, using a modified Delves cup micromethod,[28,29] and both bench and blind quality controls were used.

Statistical Procedures

Multiple weighted linear regressions were performed on data from 2,695 children aged 7 years and younger to determine the relationship between their height, weight, and chest circumference and variables suspected of being related to growth and development. In addition to obvious factors, such as age in months, sex, and race, numerous variables were considered for selection as representative of nutritional status. These included blood concentrations of essential nutrients and dietary intake measures. Hematocrit and hemoglobin concentrations were included as indirectly representative of both iron status and general nutritional status. Family income (<$6,000, $6,000 to $15,000, and >$15,000) and degree of urbanization (eight categories from rural to an urbanized area with population of more than 3 million) were also included as variables, enabling them to account for general health, environmental, and nutritional factors that might not be adequately controlled for by the nutrient and blood measurements.

To assure that blood lead level was not found to be significantly associated with growth and development because of the correlation between blood lead level and nutritional status, we used a stepwise regression procedure employing the variables listed in Table 1. We used the Statistical Analysis System (SAS) procedures for stepwise and MAXR.[30]

TABLE 1. Variables Considered in the Regression

Age (mo)	Blood lead level
Age squared	Dietary niacin
Serum albumin level	Dietary potassium
Dietary caicium	Dietary phosphorus
Dietary calories	Dietary protein
Dietary carbohydrates	Race
Serum copper level	Dietary riboflavin
Dietary fat	Sex
Hematocrit concentration	Dietary thiamine
Hemoglobin level	Transferrin saturation level
Family income	Degree of urbanization
Free erythrocyte protoporphyrin (FEP)*	Dietary vitamin A
Serum iron level	Dietary vitamin C
	Serum zinc level

* Stepwise regression was run without FEP to avoid confounding of lead and iron and then repeated with FEP to determine whether its presence disturbed the lead relationship.

MAXR selects the set of variables having the largest explanatory power (R^2) with all variables still significant at the 95% confidence level. Both lead and its natural log were used as variables in the stepwise procedure to allow the regression to choose the functional form with the best fit to the data.

The stepwise regressions were then rerun without lead. This increased the chance for other potentially confounding variables to enter significantly without having to compete with lead. The largest statistically significant model was determined for each outcome, and then lead was reinserted into the model and the regression was run again to test whether lead was still significant. Finally, the stepwise regression was run to include the ten variables giving the largest R^2 for each outcome, regardless of significance levels, to determine whether the lead relationship was affected by including insignificant terms.

Because the NHANES II data were obtained from a complex, multistage probability sample, final hypothesis testing in the multiple regression analysis must incorporate the complex design effects. Special computer programs are available (SURREGR,[31,32] REPERR[33]) that allow these design effects to be incorporated into the variance estimates. SURREGR, which runs in the SAS environment, was used in this analysis. SURREGR corrects the estimates of the standard error of the regression coefficients to account for the fact that all persons sampled had different, but known, probabilities of being sampled. Because SURREGR does not incorporate stepwise analysis, and because SURREGR generally yields higher estimates of the standard errors of regression coefficients, we used a two-step process. First, weighted stepwise regression was used to determine the model with the largest R^2 with all variables significantly ($P < .05$) related to the outcomes; then, those models were rerun in SURREGR. In one case (chest circumference), a single variable was no longer significant, and it was deleted.

The absolute or categorical values for stature, nutritional status, race, and sex were used rather than percentile rank because of the population-adjusted data base.[34]

To account for the curvilinear dependence of growth on age, a quadratic age term was inserted into the final model. It was significant only in the regression for height. The lack of significance in the weight and chest circumference regressions may be due to colinearity with the linear age term but may also reflect the fact that, after 6 months of age, the rate of weight gain is more nearly linear than that of height. The quadratic age term had little effect on the size or significance of the other variables; the coefficient of lead changed by about 1%, with no change in its P value.

To define a quantitative index of the effect of multicolinearity on the regression, the variance inflation factors (VIF) were computed. The VIF for lead is the total variance explained by the simultaneous total correlation (ξR^2) of all other variables with lead: $\text{VIF} = 1/(1 - \xi R^2)$. If the total variance due to intercorrelations with lead is, for example, .05, then VIF = 1.052 and only 5.2% of the correlation is attributed to multicolinearity.

To determine whether a threshold existed for the effect of lead on these development outcomes, segmented regression models[35] were used. These models fit two regression lines to the data. One, independent of lead, is fit to the regression points with blood lead levels below the assumed threshold value T. Another, dependent on lead, is fit for blood lead levels above T. An iterative process, using the procedure NLIN in SAS, was used to find the value of T that minimizes the sum of the squares of the error terms over the full range of blood lead values.

RESULTS

Blood lead levels were a statistically significant predictor of children's height ($P < .0001$), weight ($P < .001$), and chest circumference ($P < .026$), after controlling for age in months (and months squared), race, sex, and nutritional covariates. The R^2 was highest for height and, at 0.905, indicated that age, sex, nutrition, and blood lead level accounted for 91% of the variance in height. The results of the final regression model are in Tables 2 to 4.

The regression coefficients indicate that protein intake was a significant predictor of chest circumference and weight but marginally insignificant in the regression for height, where total caloric intake was selected instead. If calories were deleted, protein was selected and gave only a slightly lower R^2. Thus, protein appears to be an important correlate of height, weight, and chest circumference.

Hematocrit concentration was significant in the height and weight regressions and appeared to be a more relevant variable than transferrin saturation or serum iron levels. Because free erythrocyte protoporphyrin (FEP) is an indicator of both lead and iron status, its inclusion in a model could make it difficult to interpret the significant and relative contribution of lead and iron to growth, and it was not included in our base line analysis. We then repeated the stepwise regressions with FEP included. FEP was selected only in the chest circumference regression and lead maintained its significance.

TABLE 2. Final Regression Model for Height*

Variable	Coefficient	SE	*F* Ratio	Probability
Intercept (cm)	60.06	4.11		
Age (mo)	0.8043	0.0006	1,038.20	.0000
Age (mo^2)	−0.00204	6.4^{-8}	64.30	.0000
Race†	2.106	0.183	24.20	.0000
Sex‡	−1.399	0.055	35.21	.0000
Blood lead level (μg/dL)	−0.119	0.0005	29.87	.0000
Calories (kcal/d)	0.0013	6.7^{-8}	24.77	.0000
Hematocrit concentration	0.0217	0.00004	11.61	.0018

* N = 2,695; R^2 = .905.
† White = 0; black = 1.
‡ Male = 0; female = 1.

TABLE 3. Final Regression Model for Weight*

Variable	Coefficient	SE	*F* Ratio	Probability
Intercept (kg)	5.03	2.81		
Age (mo)	0.1745	0.00002	14.91	.0000
Race†	0.8695	0.078	9.70	.0039
Sex‡	−0.6585	0.027	16.17	.0003
Protein (g/d)	0.0184	0.00002	14.91	.0005
Hematocrit concentration	0.0151	0.00002	10.00	.0034
Log blood lead level	−1.0217	0.08	13.03	.0010
Transferrin saturation level	−0.0024	9.0^{-7}	6.32	.0172

* N = 1,967; R^2 = .72.
† White = 0; black = 1.
‡ Male = 0; female = 1.

TABLE 4. Final Regression Model for Chest Circumference*

Variable	Coefficient	SE	*F* Ratio	Probability
Intercept	47.36	0.706		
Age (mo)	0.1530	2.8^{-5}	827.3	.0000
Sex†	−1.230	0.029	51.72	.0000
Protein (g/d)	0.0137	2.7^{-5}	6.95	.0128
Log blood lead level	−0.6476	0.077	5.42	.0263

*N = 2,671; R^2 = .58.
† Male = 0; female = 1.

Neither income nor urbanization were significant when protein or calories and hematocrit or transferrin saturation were included in the stepwise regression, indicating that direct measures of nutritional status override the correlation of stature with socioeconomic status.[36] The prediction of stature by family income may have been obscured by the upper limit of $15,000 per year used throughout 1976 to 1980, a period of rapid fiscal inflation.

When the stepwise regressions were run without lead, and lead was then inserted into the largest significant model that was obtained, lead was always significant. Moreover, the R^2 for the largest significant model with lead always exceeded the R^2 for the largest significant model that excluded lead as a variable, indicating that less of the variation in height, weight, and chest circumference is explained by models that ignore blood lead level. The ten variable regressions reached down to covariates significant at only the P = .28 level (chest circumference), P = .58 level (height), and P = .17 level (weight). Lead remained significant (P = .01, .0003, and .002, respectively) for all three outcomes, after including these insignificant terms, which included income.

The relationship of stature with blood lead level, after controlling for all of the other covariates is shown in Figs 1 to 3. The threshold regressions indicated that there was no identified threshold for the relationship down to the lowest observed blood lead level of 4 μg/dl.

At the average age (59 months), the mean blood lead level of the children appears to be associated with a reduction of about 1.5% in the height that would be expected if their blood lead level had been zero. The relative impact on weight and chest circumference is of the same magnitude.

To test whether colinearity between lead and any of the other significant variables could account for the significance of blood lead level, we computed VIF. For the height, weight, and chest regressions, the VIFs for lead were 1.02, 1.14, and 1.12, respectively. These VIFs indicate that interaction of lead with all other variables explains about 2%, 14%, and 12% of the outcome variances attributed to lead. This makes it unlikely that the correlation of lead with outcome is due to the intercorrelation of lead with other variables.

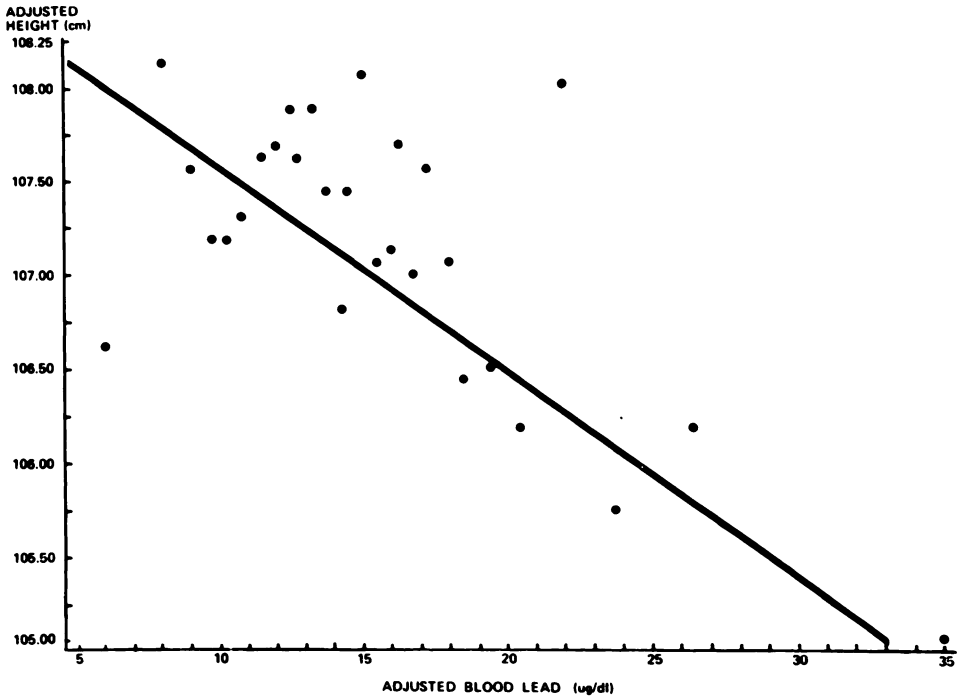

Fig 1. Adjusted height and adjusted blood lead levels for children aged 7 years and younger in Second National Health and Nutrition Examination Survey. Both height and blood lead level have been adjusted by regression for effects of age, race, sex, and all other variables significant at .05 level. Each point is mean height and mean blood lead level of approximately 100 consecutive observations, ordered by blood lead levels. Regression line reflects slope of coefficient obtained from multiple regression analysis of all 2,695 observations.

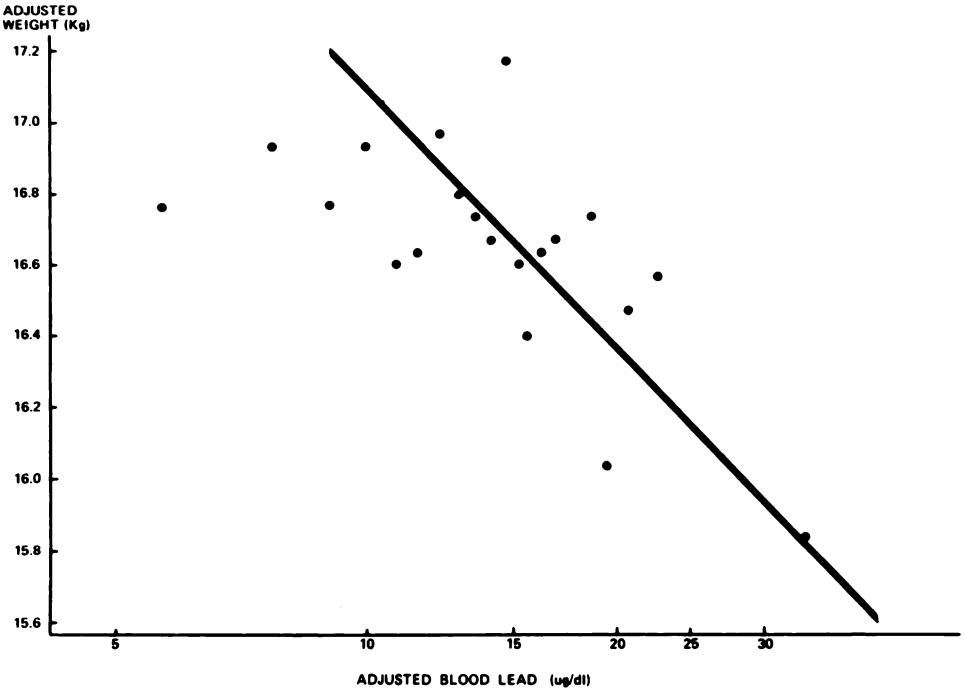

Fig 2. Adjusted weight and adjusted blood lead levels for children aged 7 years and younger in Second National Health and Nutrition Examination Survey. Both weight and blood lead level have been adjusted by regression for effects of age, race, sex, and all other variables significant at .05 level. Each point is mean weight and mean blood lead level of approximately 70 consecutive observations, ordered by blood lead levels. Regression line reflects slope of coefficient obtained from multiple regression analysis of all 1,967 observations with no missing data.

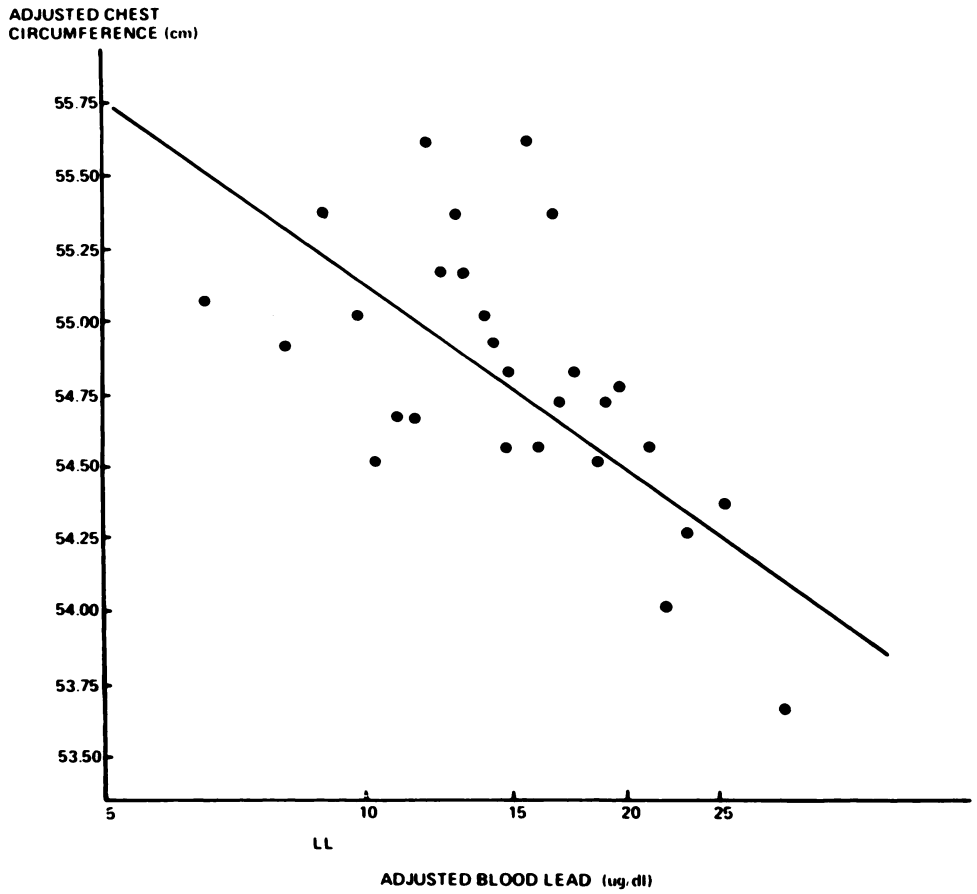

Fig 3. Adjusted chest circumference and adjusted blood lead levels for children aged 7 years and younger in Second National Health and Nutrition Examination Survey. Both chest circumference and blood lead level have been adjusted by regression for effects of age, sex, and all other variables significant at .05 level. Each point is mean chest circumference and mean blood lead level for approximately 95 consecutive observations, ordered by blood lead levels. Regression line reflects slope of coefficient obtained from multiple regression analysis of all 2,671 points with no missing data.

DISCUSSION

The initial and obvious explanation for the inverse correlation of blood lead level and growth in US children is that blood lead level is a composite factor for genetic, ethnic, nutritional, environmental, and sociocultural factors that are insufficiently delineated by age, race, sex, and nutrition or by family income, urban residence, and the 15 nutritional indices deleted because of insignificant contribution. An environment that favors a higher blood lead level may supercede all of the established predictors such as socioeconomic status and other demographic characteristics.[36]

Spurious correlation due to the distinctive curvilinear relations of stature and of blood lead level with age requires careful evaluation. The mean blood lead level for ages 6 to 8 years is approximately 2 μg/dL lower than for younger than 6 years[34] but is stable from 6 months through 5 years,[34] whereas height and weight are curvilinear for younger than 1 year and almost linear from 1 to 8 years.[36] A subcalculation was made of the regression coefficients predicting height for ages 6 months to 5 years of age. This showed no change in the rank order of significant contributing factors. Similarly, the entry of age squared improved the total R^2 for height but did not decrease the contribution of blood lead level.

A well-accepted explanation of the observed correlation is that nutritional deficits that retard growth also increase lead absorption.[20] Iron deficiency enhances lead absorption,[20,21] and preliminary analyses of NHANES II show the expected association of anemia and increased blood lead level. Black males 3 to 5 years old have a median hematocrit concentration of 35.3 ± 1.98 *v* 36.0 ± 2.33 for white males with a difference of 0.4 at ages 6 to 8 years.[36] At all ages, they are taller than white males[36] despite higher blood lead levels.[34] The inverse correlation of stature with blood lead and hematocrit levels would not be anticipated from

racial differences. The contribution of hematocrit to height is a provocative, although quantitatively minor, observation since growth impairment has not been defined in mild anemia.[37,38]

A fourth consideration is a direct effect of low-level lead on growth in children. There are only two contemporary studies of growth in childhood lead poisoning[2,3] plus a report by Henderson[39] that there were no residual effects on stature 5 to 10 years after symptomatic lead poisoning. Mooty and colleagues[2] reported that 21 children with a blood lead level of 50 to 80 μg/dL had an average height at the 32nd percentile as compared with a mean height at the 41st percentile for 25 comparably anemic children with a blood lead level of 10 to 25 μg/dL. There were no significant differences in weight or caloric intake. Johnson and Tenuta[3] noted that 12 children with blood lead levels of 50 to 67 μg/dL had a mean height at the 26th percentile, although their weight at the 42nd percentile was comparable to control subjects. The only dietary difference was a decrease in calcium intake in the high lead group.[3]

The lack of attention to growth in children with increased lead exposure may relate to the absence of data defining a low level effect on growth in rats and mice, the primary experimental animals. Michaelson[40] concludes that the malnutrition and growth impairment of rat and mice pups suckled to lead-poisoned dams, which has confounded hundreds of experimental studies, is related to the dams' conditioned aversion to lead-treated water, resulting in a decrease in the milk supply. There are species as well as strain differences in susceptibility to growth failure,[41] but most studies are limited to measurements of weight alone, not length, with inadequate documentation of either caloric intake or the tissue levels of lead.

Grant et al[42] provide the only complete study to relate the long-term dose to blood and tissue lead levels and to both weight and length. Rats were exposed to lead in the form of the drinking water of the dams and of the postweanling animals from conception through 180 days. At blood lead levels of 18 to 48 μg/dL, females were shorter from days 7 through 180 but decreased length was transient in males. The threshold for decreased body weight, with no change in food consumption per unit of body weight, was a blood lead level of 40 to 60 μg/dL, whereas neurobehavioral deficits and organ pathology were evident at blood lead level of 20 to 40 μg/dL.

Although the threshold for growth failure in animals appears to be higher than that for effects on the neural, renal, and heme systems, the correlation of stature with blood lead levels in 2,695 US children of NHANES II merits serious consideration of one or more toxic effects on growth.

At least three general mechanisms exist by which low-level blood lead might alter growth: an interaction of lead with reactions mediated by calcium as a second messenger;[4-6] heme-dependent enzymes decreased by either lead or iron deficiency;[7-11] and neuroendocrine toxicity possibly related to inhibition of dopaminergic and α-adrenergic receptors in the hypothalamus.[12-19]

RELEVANCE

The analysis of the NHANES II data indicates a highly significant association of the height, weight, and chest circumference of US children with blood lead levels in the so-called normal range of 5 to 35 μg/dL. Blood lead level is correlated with stature and not through its colinearity with the other demographic and nutritional variables. It is probable that multiple nutritional and socioeconomic variables are compressed within the overall nutritional indices of total protein intake and iron status that also predicted stature. This requires similar consideration of blood lead level as a surrogate for a multiplicity of environmental factors. Comprehensive data evaluation of NHANES II did not, however, identify any additional significant correlates, and the inclusion of insignificant variables did not disturb the relationship of blood lead level and stature.

These observations amplify, but do not contradict, the contemporary paradigm defining children at risk for lead toxicity. The higher lead exposure of the urban poor, the increased lead ingestion in dustier, less well-supervised households, and the enhanced lead absorption of nutritional deficits continue to be primary predictors of an excessive lead burden.

Association does not imply causability, but this statistically significant association of decreased stature with increased blood lead level merits additional investigation as well as consideration of a biologic effect of low-level lead on growth. Evidence of impaired growth would consolidate the cumulative medical evidence that there may be no "zero effect" level of childhood blood lead level.

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