

# THE HEALTH EFFECTS OF LOW LEVEL EXPOSURE TO LEAD

*Herbert L. Needleman*

School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania 15213

*David Bellinger*

Neuroepidemiology Unit, Children's Hospital and Harvard Medical School, Boston, Massachusetts 02115

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## INTRODUCTION

Eight years ago, the problem of low level lead exposure in children was reviewed in the *Annual Review of Public Health* (65). (The term "low level" refers to exposure that is below those at which clinical signs of lead poisoning are apparent.) Since that time, knowledge about lead's health effects, biochemical toxicology, and sources and routes to people has grown exponentially. Real progress in lowering environmental levels of lead has been achieved, notably through the virtual ban on leaded gasoline. In some sectors, particularly housing, efforts to abate lead have failed completely. But, despite increased recognition of the widespread distribution of lead, islands of ignorance about its effects at low dose persist. Many modern pediatric textbooks contain discussions of the diagnosis and treatment of frank lead poisoning, but do not mention effects of lead at lesser dose.

In this review, we examine some of the newer biomedical and epidemiological information about lead at low dose and evaluate the recent studies. We then suggest some policy actions to redress the imbalance between the broad knowledge of lead's dangers and the limited steps to eliminate them.

At the time of the earlier review, the most prominent question under study was whether there were substantial health effects at doses below those that produce symptoms. That question, once a focus of considerable controversy, has been effectively settled by a substantial group of newer studies. The newer data on lead's effects have revised the threshold for effect downward. As more sensitive measurement techniques have been used, the recognized effect level has dropped steadily in response.

Once held to be solely an American problem, low dose exposure has become a worldwide issue in the past decade. Except for a few British studies, in the 1970s almost all the data came from American investigations. In the 1980s, good epidemiological and toxicological studies were reported from England (110), Scotland (30), Denmark (33), Germany (108), Italy (13), Greece (36), Australia (59), and New Zealand (28). Studies of human health effects have extended backward in time to examine the impact of intrauterine exposure on birth outcome (67) and subsequent growth and neurobehavioral development of infants (8, 23, 27, 59). Some ongoing studies have followed individuals from birth up to ten years of age, and one has followed a school age cohort for 11 years into young adulthood. Experimental investigations have employed the newest tools of modern biology, pharmacology, and psychology to study the effects of lead on receptor development, subcellular systems, and animal behavior.

## SOURCES OF LEAD AND PATHWAYS TO HUMANS

Paint is the major source of high dose lead for American children today. Although the Lead Paint Poisoning Prevention Act was passed in 1971, many homes still have high amounts of lead in them. The recent Agency for Toxic Substances and Disease Registry (ATSDR) Report to Congress (1) estimates that there are 5 million tons of lead in household paint in the US. Of all houses built before 1960, 70% have leaded surfaces. More disturbing is the ATSDR estimate that 6 million homes, which house 2 million young children, are decayed and deteriorated with leaded surfaces. These houses are the critically dangerous dwelling units.

Lead is a natural constituent of soil and dust; it migrates only minimally in soil. Typical concentrations in uncontaminated soil range from 10–50 ppm. Human activity can raise these levels by a factor of 10–200. Within 25 meters of major roadways, concentrations in soil as high as 2000 ppm are found; these concentrations fall off exponentially with distance. Levels as high as 60,000 ppm have been measured in soil near smelters. In urban soils, the lead found is a mixture of powdered paint and atmospheric fallout of lead particles. The Environmental Protection Agency (EPA) is currently funding three demonstration projects to assess the efficiency of removing lead-contaminated soil in reducing the blood lead levels of inner-city children.

Dust is composed predominantly of the windblown, fine particle derivative of soil. Lead in dust may exceed that in soil because the smaller soil particles that become part of the dust mixture tend to have higher concentrations of lead. Indoor dust may have elevated lead concentrations because of weathering of paint, carry-in of soil, or fallout from airborne sources. Household dust lead level appears to be the strongest predictor of blood lead level among nonpoisoned children (6). Removing paint by sanding, scraping, or burning can raise dust lead levels into the hazardous range. The abatement of lead in homes can be dangerous. Lead abatement should only be done by trained workers in unoccupied dwellings; thorough cleanup is essential before residents may return.

Airborne lead derives from mobile and stationary sources. With the reduced amounts of lead added to gasoline, blood lead levels have declined (24, 78). Corresponding reductions in blood lead levels have been measured in children and in the umbilical cord blood of newborns (79).

Standing water contains only trace amounts of lead. The major source of lead in drinking water is household plumbing. There are three major contributors: the pipe from the street main (known as the "gooseneck"), lead pipes, and solder joints. Plumbosolvent water—water that is acidic and soft—can leach out large amounts of lead from the plumbing. This problem is especially true if the water has been standing in the pipes for an extended period of time. An estimated 16% of household water supplies have concentrations of lead over the proposed standard of 20  $\mu\text{g}/\text{dl}$  (25). Despite the undisputed fact that lead is added to drinking water downstream from the source, the EPA's recommended surveillance method calls for measuring lead at the source, and then sampling a small number of households. This method is inadequate to protect consumers and can miss communities that have an unacceptable proportion of homes over the standard.

Food can be an important source of lead. Some lead is taken up by crops, particularly root vegetables, such as radishes, potatoes, and carrots. Some crops near heavily traveled roads can accumulate atmospheric lead deposited on them. The meat of foraging animals does not present a risk because lead is not concentrated in muscle. Most lead contamination of food occurs during processing. Food from soldered cans has much higher levels of lead than unprocessed food or food from seamless, aluminum cans. The lead comes from microdots of spattered solder and is leached from the seam. Although fired chinaware is generally safe, many ceramic products contain glazes or are made from clays that have leachable lead in them. Foreign tableware is not subject to the same control as US-made goods. Some bone meals sold in health food stores for calcium replenishment have dangerous amounts of lead.

Other, rarer sources that can be clinically significant are cosmetics and folk medicines. Some hair dye preparations for men contain lead acetate. The darkening pigment results from the reaction of lead acetate with sulfides in the

air to produce lead sulfide. Kohl, an eye cosmetic used by Moslems, and surma, one used by Hindus, may have large concentrations of lead. These cosmetics may be applied directly to babies. Or, infants get the cosmetics on their hands by touching their mother's faces. The infants then put their hands in their mouths. The folk remedies *Azarcon* and *Greta* which are used by some Hispanic people for abdominal distress, may contain toxic amounts of lead.

## EXPERIMENTAL DATA ON THE BIOLOGICAL EFFECTS OF LEAD

In this section, we limit discussion to studies that direct attention to three heretofore undescribed toxic mechanisms of lead. For a complete review of recent biochemical data on lead's effects, consult EPA's Air Lead Criteria Document (24).

Most of lead's toxicity is ascribed to its action on proteins, where it binds to sulfhydryl groups. Brown et al (15), in a provocative study, suggest another mechanism of equal importance. The investigators measured lead binding to yeast tRNA, and compared binding at pH5 and pH7.4. At pH7.4, they observed site-specific cleavage of the ribophosphate backbone. This cleavage took place between sites D17 and G18 and was catalytic, rather than stoichiometric, which may account for lead's ability to rapidly depolymerize tRNA. The authors suggest that this cleavage may be a toxic mechanism of at least as much generalized importance as sulfhydryl binding, and may have no apparent threshold.

Marcovac and Goldstein (58) demonstrated another potentially important toxic mechanism. They studied protein kinase c, a calcium and phospholipid enzyme involved in growth, differentiation, and many other cellular functions. Of all metals tested, only lead activated phosphokinase c at picomolar concentrations. Phosphokinase c, which is a central part of the second messenger system, may be a fundamental route for lead toxicity in the central nervous system (CNS) and other organs.

The search for the biological substrate of lead-associated behavioral alterations has focused on changes in capillary permeability (69), neuronal development (2, 16), myelination (44), and catecholamine metabolism. Recent studies from Surrey pointed in a different direction: opioid receptor development and function. Winder et al (107) found that administration of low doses of lead to nursing rodent dams produced decreased development of pro-enkephalin, an endogenous opioid precursor in offspring pups. This observation spawned many related studies. Using heat as the pain stimulus, Kitchen et al (41) found that the antinociceptive action of morphine was strongly diminished by low levels of lead in young rodents. They inferred that altered

development of the  $\mu$  opioid receptor was responsible for the observed effect. With similar blunting of the analgesic action of ketocyclazocine, Kitchen et al (41) reported a  $\delta$  opioid receptor agonist. Bailey and Kitchen (3) then showed that the four putative peptide products of proencephalin were markedly depressed by small doses of lead in rodents at ten days of age.

Studies of rodent consumption of alcohol in relation to lead exposure suggest that these intriguing findings may have relevance for human behavior. Nation et al (61) have shown that naive rats find 15% solutions of alcohol aversive, but when given lead in their diet sufficient to raise their blood leads to 61  $\mu\text{g}/\text{dl}$ , the rats increase their alcohol intake in both forced choice and free choice paradigms. Lead-fed rodents were also more responsive in the avoidance training period. The authors infer that lead increases emotionality, and that the rodents seek alcohol for its anxiolytic properties.

## NEUROBEHAVIORAL EFFECTS ON INFANTS AND CHILDREN

### *Recent Studies of School Age Children*

Childhood lead poisoning was first described in Brisbane, Australia, almost a century ago. The pioneering work of A. J. Turner (102) and J. Lockhart Gibson (31) established the environmental cause: paint on the porch railings of the dwellings. The first Australian lead paint legislation was enacted 20 years later. Fifty years after the Australian law, the first Lead Paint Poisoning Act was passed in the United States. In the early part of the twentieth century, lead paint poisoning was a frequent cause of death in city pediatric wards. As late as the 1940s, it was widely believed that a child who survived the acute phase of the illness was left without sequelae. In 1943, Byers reported on the follow-up of 20 children who had recovered from acute intoxication (17); of the group, 19 were behavior disordered or learning disabled. Byers asked how many cases of school failure or behavior disorder were in fact cases of missed lead poisoning. The pursuit of this question marked the beginning of the modern age of lead intoxication studies.

Growing interest in public health and inner-city populations stimulated screening studies of lead in asymptomatic children. Studies in the 1960s showed that as many as 20% of all children bore elevations of blood lead as high as two thirds that considered toxic ( $>60 \mu\text{g}/\text{dl}$ ). Byer's conjecture that silent lead exposure may be a frequent cause of cognitive deficit in children was raised for reexamination. Some early studies of low level lead exposure showed a lead-related deficit (21, 45, 70); others did not (43, 46). Many reviews of studies from this period have been published (9, 65, 86). In this review, we focus instead on our own work, on more recent studies by other investigators, and on forward studies of exposure that begin with the fetus.

In interpreting these studies, there are often problems with small sample size, difficulties in measuring some of the variables, and "overcontrol" for confounding factors. There is no doubt of the effect of lead at high exposure levels; that matter is settled. What is not settled is at how low a concentration lead continues to produce harmful effects. Estimating the effect of a toxicant at low concentrations is difficult, precisely because the effects are likely to be subtle. The section *Issues in Drawing Inferences from Observational Studies* explores the difficulties in interpreting the literature and shows why an authors' conclusions cannot always be relied upon.

In 1979, Needleman and colleagues attempted to confront the common problems in design that challenge investigators of lead (64). The problems were inadequate markers of exposure, weak measures of outcome, insufficient attention to potential confounders, and selection bias. They studied a sample of 2335 children who were attending ordinary first and second grade in Massachusetts schools. Shed deciduous teeth were collected and analyzed for lead. The tooth, which is a long-term storage system, may reflect early exposure even after blood lead level has returned to normal. Of the 2335 children, those with dentine lead levels in the highest decile and lowest decile were identified; 270 were brought into the neurobehavioral laboratory for an intensive four-hour assessment. The children were given a panel of measures that examined psychometric intelligence, speech and language ability, attention, and classroom behavior. The researchers measured and compared 39 covariates that could affect child development between the high and low lead groups. Those covariates that differed between groups were controlled as potential confounders. Children with a history of clinical plumbism, head injury, or seizures were eliminated from the data analysis. After adjustment for confounders, the high lead group ( $>20$  ppm,  $N=58$ ) scored significantly lower than the reference group ( $<10$  ppm,  $N=100$ ) on intelligence quotient (IQ), speech and language processing, and attention (Table 1). For 2146 students, a tooth lead level and a teacher-completed questionnaire that sampled classroom behavior were obtained. The prevalence of nonadaptive classroom behavior has related in a dose-response fashion to tooth lead levels (Figure 1). Lead exposure disrupted the usual relationship between maternal and child exposure (10).

This study proved to be the springboard for a group of investigations using similar designs. Yule et al (110) studied British school children classified by blood lead. They reported significantly lower IQ, reading, and spelling scores in children with elevated blood lead levels, after control of age, social class, and gender. Another study by this group failed to observe an association between lead and IQ, achievement, or behavior in a group of middle-class children (48).

In another British investigation, Smith et al (98) examined 402 London

**Table 1** Comparison of test outcomes between students with high and low lead levels: Analysis of Covariance (64)

Test	Mean Score in Low Lead Group	Mean Score in High Lead Group	P Value
Full scale IQ	106.6	102.1	0.03
Verbal IQ	103.9	99.3	0.03
Performance IQ	108.7	104.9	0.08
Seashore rhythm test			
Sum	21.6	19.4	0.002
Token test			
Sum	24.8	23.6	0.09
Sentence repetition test	12.6	11.3	0.04

[From Needleman et al (64)]

six-year olds who were classified by tooth lead level. The exposure of these children was lower than that of the children in the Needleman et al study (64). The Smith group administered an extensive battery of outcome measures. They adjusted for covariates related to tooth lead to evaluate the association between tooth lead and outcome. In some cases, this may have resulted in overcontrol. For instance, developmental delay, a possible effect of lead, was controlled in assessing IQ, reading level, and the Seashore rhythm test. The bivariate regression showed a statistically significant ( $P < .05$ ) relationship between lead and IQ. With the adjustment for covariates, the effect size was diminished, although a consistent decrease in performance related to tooth lead was reported. Pocock et al (74) reanalyzed the Smith study. They used regression techniques and measured the interaction between lead and gender. For boys, the lead effect was statistically significant. Although Pocock et al interpret this as an explanatory finding, there is abundant evidence that males are more sensitive to many toxicants, including lead.

Winneke et al conducted two studies in the German cities Duisburg and Stohlburg. In the Duisburg study (108), they found a marginally significant decrease in IQ (5–7 points) across lead groups and a significant association between lead and perceptual-motor function. In the Stohlburg study (109), they found significant associations between tooth lead and perceptual motor integration, reaction time performance, and mothers' behavioral ratings.

Perino and Ernhart (70) were among the first to report an association between lead and children's intelligence. They studied black preschoolers who differed on blood lead level (high  $>40$ ; low  $<30$ ). Controlling for maternal IQ and gender, they reported that lead was inversely related to General Cognitive Index (GCI) of the McCarthy Scales. At follow-up in the first grade, early exposure was no longer significantly related to outcome

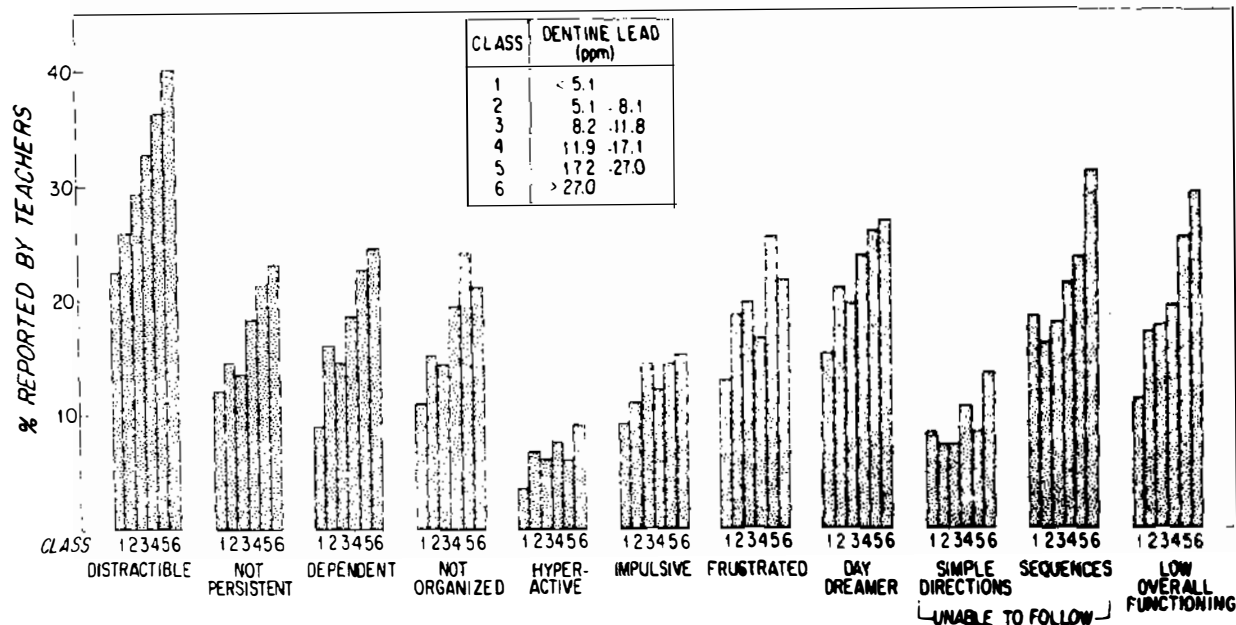


Figure 1 Teachers' ratings of 2146 students on 11-item forced-choice questionnaire. Proportion of negative comments within each dentine lead group are plotted. Teachers were blind to students' dentine lead levels, but knew each student for at least two months. (Reprinted by permission of the *New England Journal of Medicine*; see Ref. 64.)



(26). Ernhart interpreted this to mean that any effect had disappeared. But the sample size, originally 80, was reduced to 63 and then 40 because of loss-to-follow-up and missing data; the power to find an effect decreased correspondingly. Inferring no effect from studies of insufficient power is a frequent error encountered in lead studies. It and other Type II errors are discussed further in a later section of this review.

Schroeder et al (90) and Hawk et al (37) studied poor black children in North Carolina. Schroeder et al studied 104 children with blood levels between 6–59  $\mu\text{g}/\text{dl}$ . Adjusting for several covariates, the authors reported that lead was significantly associated with IQ ( $P < .01$ ). Five years later, with a reduced sample group, the association was weaker, but the slope of the regression of IQ on blood lead remained negative. Hawk et al (37) evaluated 80 children aged 3–7 years. The mean blood lead was 21.8  $\mu\text{g}/\text{dl}$ ; the highest was 26.7  $\mu\text{g}/\text{dl}$ . Lead was significantly associated with IQ score after adjustment for socioeconomic status (SES), maternal IQ, and home environment.

The most recent studies have larger samples and children of higher socioeconomic status. Silva et al (97) studied 579 New Zealand children at age 11. The mean blood lead was 11.1  $\mu\text{g}/\text{dl}$ . Only two children had blood leads in excess of 30  $\mu\text{g}/\text{dl}$ . Significant associations were found between log blood lead and children's reading, spelling, and behavior (as reported by both parents and teachers). Although the relationship between blood lead and IQ was inverse, it did not reach the  $P = .05$  criterion. Fergusson et al (28) studied 724 children in the Christchurch New Zealand child development project and found that high tooth lead levels were strongly related to lower reading scores, poorer spelling, lower mathematics scores, and poorer handwriting. The association between lead and IQ was inverse, but did not reach statistical significance at  $P = .05$ .

Fulton et al (30) studied 501 middle class school children in Edinburgh. They adjusted for many covariates and, using multiple regression, found a highly significant ( $P = .003$ ) inverse relationship between lead and IQ. In a more recent report, lead was also related to classroom performance (101). The effects of lead in this study extended down to 10  $\mu\text{g}/\text{dl}$ . Hatzakis et al (36) studied 509 Greek children from Lavrion, a smelter site. Controlling for 17 covariates, they also found a highly significant inverse association between lead and IQ ( $P = .00007$ ). Lead was also related to teachers' ratings of children's classroom behavior and reaction time.

Hansen et al (33) studied 162 middle class children from Aarhus, Denmark, using multivariate linear regression. They found significant associations between lead and IQ and scores on the Bender-Gestalt Test. They found no significant difference on the Seashore Rhythm Test or on the Trail-Making Test. They also found a significant increase in the risk for learning disabili-

ties, as measured by need for remedial education in reading, speech, or math (51).

Bergomi et al (13) studied 216 children from northern Italy. Controlling for gender and SES, they evaluated the relationship between lead exposure and outcome. Outcome was measured by the Weschler Intelligence Scale for Children-Revised (WISC-R), Bender-gestalt, Trail Making, the Toulouse Pieron Test, and delayed reaction time. After adjustment for covariates, tooth lead was significantly related to WISC-R scores and performance on the Toulouse Pieron Test (a measure of attention).

### *Forward Studies of Lead and Infant Development*

Lead crosses the placenta (89), and infant umbilical cord blood lead concentrations are correlated with maternal concentrations. In many studies, surveillance of children's exposure began during pregnancy and continued through the postnatal period. The forward nature of these investigations offers an opportunity to determine the direction of causality and to settle whether lead is a marker or a cause of cognitive deficit.

We and our colleagues identified a two-year cohort of children born at the Boston Hospital for Women (N=11, 837). We capitalized on an ongoing study of risk factors and birth outcome conducted by Linn and colleagues (50). For 5000 births, we estimated the relationship between lead and outcome at birth. Adjusting for covariates, lead was related, in dose-dependent fashion, to the rate of minor malformations (skin tags, herniae, hydrocoeles, hemangiomata). Lead was not related to birth weight or major malformations (67). In addition, infants' cord blood lead levels were associated with mothers' systolic blood pressure during labor and the prevalence of pregnancy hypertension (77).

We followed 249 of the children, from three exposure groups: low (PbB <3  $\mu\text{g}/\text{dl}$ ), middle (PbB= 6–7  $\mu\text{g}/\text{dl}$ ), and high (PbB= > 10  $\mu\text{g}/\text{dl}$ ). We evaluated the children at 1, 6, 12, 18, 24 and 57 months of age (6), which enabled us to plot the time course of exposure and to collect environmental data at several periods. In later analyses, we evaluated the impact of exposure at each epoch on concurrent and subsequent outcome.

This cohort was unusual in comparison to most studies: The majority of children were from middle and upper middle class families, and the exposure to lead was higher in the higher classes. This latter observation was probably due to the patterns of residence; many of our more favored children lived in older homes in heavily trafficked neighborhoods. This relationship enabled us to disentangle the usually encountered collinearity between SES and lead exposure. When we adjusted for SES, the size of the lead effect became larger. When we controlled for covariates, we found that higher umbilical cord blood lead levels were associated with lower scores on the Bayley Scales

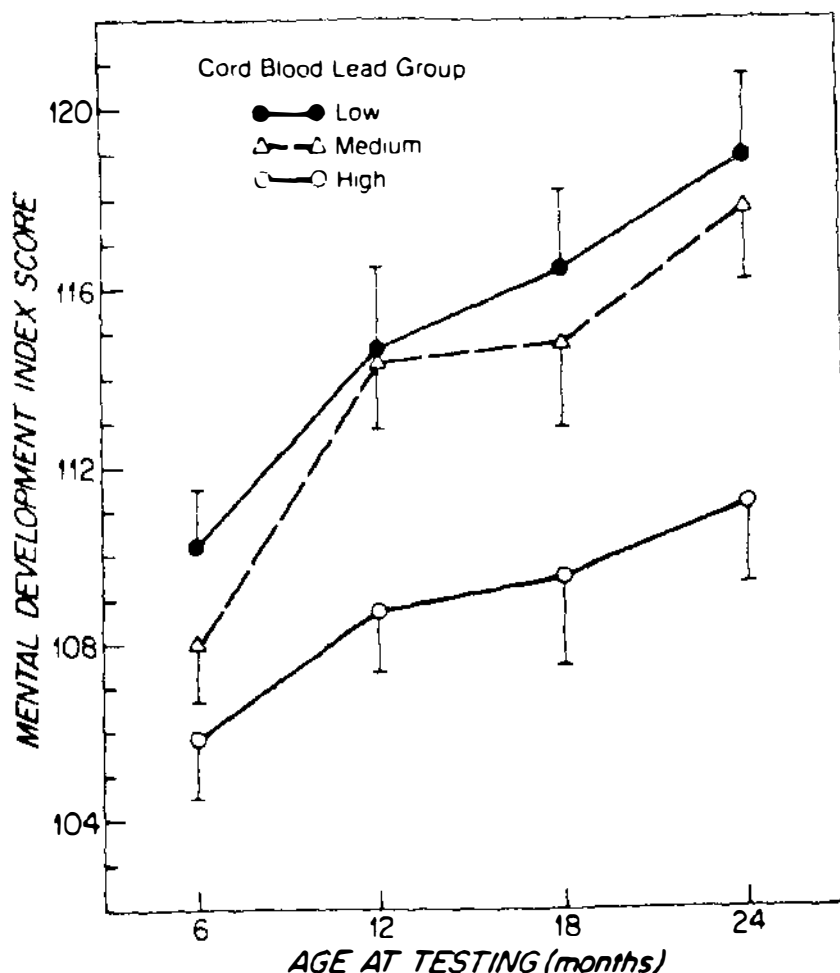


Figure 2 Mean Mental Development Index Scores at four ages in infants according to the lead level in umbilical-cord blood. (Reprinted by permission of *New England Journal of Medicine*; see Ref. 8.)

of Infant Development at all epochs between 6 and 24 months of age (Figure 2). None of the measures of postnatal exposure were associated with infants' development over this period. At 57 months of age, exposure at 24 months was significantly related to the GCI score on the McCarthy Scales, which decreased by approximately three points for each natural log unit increase in blood lead level. An increase in blood level at age 24 months from 3 to 20

$\mu\text{g/dl}$  was associated with a six point decrease in GCI. The high blood lead group was bounded on the lower side by 10  $\mu\text{g/dl}$ , far below the current Centers for Disease Control (CDC) screening target guideline of 25  $\mu\text{g/dl}$ . Although the effect of prenatal exposure was attenuated at 57 months, it continued to be significant for children who were of lower SES, for boys, and for children whose exposure at 24 months was high (7, 12).

Dietrich et al (23) have followed forward a cohort of 300 infants born in Cincinnati. As in the Boston cohort, prenatal exposure to lead was associated with later decrements in performance on the Bayley Scales of Infant Development. At six months of age, boys showed an 8.7 point decrease in the Mental Development Index for every 10  $\mu\text{g/dl}$  increase in blood lead. At 24 months, the deficits due to lead were no longer significant on the Bayley Scales. Language development at age 39 months was inversely associated with level of prenatal exposure (23). Many studies from this project have documented an association between lead at low dose and physical growth. A decrease of 114 g in birth weight for each natural log unit increase in maternal blood lead level during pregnancy was found (14), and linear growth was inhibited among infants with high exposure in both the prenatal and postnatal periods (95).

Ernhart et al (27) conducted a forward study of infants in Cleveland. This group found an association between cord blood lead levels and abnormal reflexes, and between prenatal exposure and developmental scores at age six months on the Bayley Scales and the Kent Infant Development Scale. No associations were apparent at later ages. Interpretation of this study is difficult because half the mothers in the sample were chosen because of their alcohol abuse.

Vimpani et al (104) and McMichael et al (59) reported on the relationship between lead exposure during pregnancy and postnatally in a large cohort of infants in proximity to a smelter. At 24 months of age, a significant relationship between six months blood lead levels and Bayley MDI scores was found. At 48 months, a significant association was found between GCI scores on the McCarthy Scales and an index of cumulative postnatal exposure.

## FOLLOW UP STUDIES OF LOW LEVEL LEAD EXPOSURE

A few studies have been undertaken to determine whether the effects of lead exposure are lasting. Bellinger et al (11) followed 141 of the children from the Needleman et al study (64) into the fourth and fifth grades. After covariate adjustment, performance on a school administered IQ test was inversely associated with past dentine lead levels ( $P=.1$ ,  $n=101$ ). They also found an inverse association between teachers' rating of children's abilities and dentine lead ( $P=.1$ ). High lead students had a greater need for special services.

Prevalence of grade retention was significantly related to lead level ( $P=.025$ ). Direct observation of systematically sampled classroom behavior did not reveal any association with lead.

Schroeder et al (90) were able to locate 50 of their 104 original subjects after five years. Although the bivariate correlation between lead and IQ was similar, the association was not statistically significant after covariate adjustment. The reduced power to find an effect may have produced this result.

Ernhart (26) followed 63 of her original sample of 80 children five years after initial assessment. As measured by McCarthy Scales, IQ was related to contemporary blood lead level, but not past level. This study also had low statistical power.

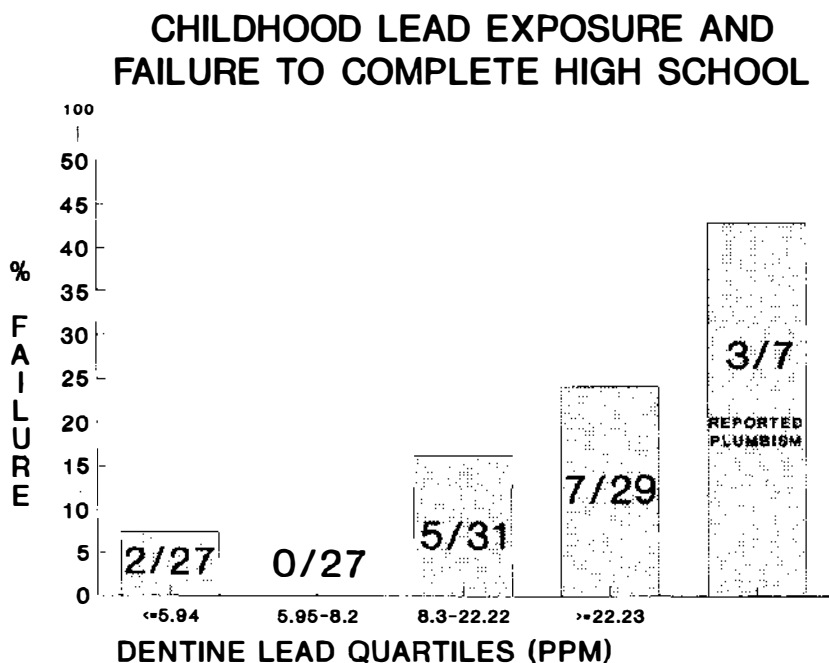
We recently followed up 132 subjects of our 1979 sample, now young adults (mean age 18.3 years) (68). We found that high dentine lead levels in 1979 were associated with a covariate adjusted sevenfold increased risk of failure to graduate from high school, and a sixfold increased risk for reading disability, (defined as a reading score two grades below expected). Students with high levels of lead had more absenteeism in their final year of school, lower class rank, poorer vocabulary and grammatical reasoning scores, longer reaction times, poorer hand-eye coordination, and slower finger tapping. We conclude that the effects of lead are enduring and are likely to be predictors of life success (Figure 3, Figure 4).

## OTHER HEALTH EFFECTS OF LEAD

### *Growth*

Schwartz et al (92) used data on 2695 children between 6 months and 7 years of age from the National Health and Nutrition Examination Survey (NHANES) II health survey to examine the relationship between lead and several outcomes. Blood lead levels were significantly related to stature after controlling for SES and 15 nutritional variables, including hematocrit and transferrin saturation. A blood lead level increase of  $26 \mu\text{g}/\text{dl}$  was associated with a 3% reduction in height. There was no apparent threshold.

In the Cincinnati prospective study, Dietrich et al (23) found that maternal blood lead levels were inversely associated with birth weight. They suggested that this association was partly responsible for the reduced development scores of infants with higher prenatal exposure. Shukla et al (95) showed that, among children with high prenatal exposure ( $>8 \mu\text{g}/\text{dl}$ ), growth in the first year of life was inversely related to postnatal exposure. Ward et al (105) reported an inverse association between birth weight and head circumference and placental lead levels. McMichael et al studied the birth weights of infants in the Australian forward study (59) and found that the incidence of low birth weight ( $<2500 \text{ g}$ ) was greater in the high lead group. Blood leads tended to be



*Figure 3* The proportion of students who failed to graduate high school classified by past exposure to lead. Asymptomatic individuals are classified by lead quartile. Seven of ten who were reported to have had clinical plumbism are also displayed. (Reprinted by permission of *The New England Journal of Medicine*; see Ref. 68.)

somewhat lower in the low birth weight group. Not all studies have reported a lead-associated decrement in birth weight, however (60, 67).

Lead's effects on growth might be an expression of its action on thyroid function. Sandstead (87) showed that lead interfered with the uptake and concentration of iodine in the thyroid gland of rats and of men poisoned by bootleg whiskey (88). Huseman (39) reported that two lead-poisoned children had impaired release of thyroid stimulating hormone after thyroid releasing hormone stimulation. Another potential mechanism is lead's inhibition of the production of the active form of vitamin D and the cascade of effects on calcium metabolism (54, 83).

### *Hearing*

Robinson et al (81) found a linear increase in the 2000 Hz pure tone hearing threshold in children whose blood lead levels ranged from 6 to 47  $\mu\text{g}/\text{dl}$ , with no sign of a threshold. Robinson et al (82) also studied 117 children, aged 39–66 months, from the Cincinnati study using brainstem auditory-evoked

## CHILDHOOD LEAD EXPOSURE AND READING DISABILITY IN YOUNG ADULTHOOD

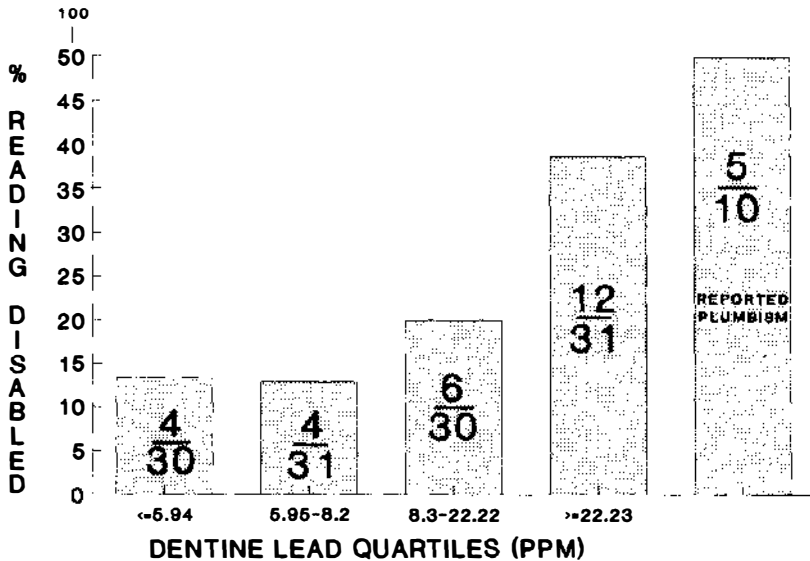


Figure 4 The proportion of reading disabled children classified by past exposure to lead. Asymptomatic children are classified by lead quartile, and ten children with a past history of clinical plumbism are displayed. The disability is defined as reading at two or more grades below expected. (Reprinted by permission of *The New England Journal of Medicine*; see Ref. 68.)

potential. They found increased latencies in the interpeak latencies III-V in relation to the prenatal blood lead level. Schwartz & Otto (93), again using data from the NHANES II study, found that lead was positively associated with hearing loss at 500, 1000, 2000, and 4000 Hz, with no evidence of a threshold.

### *Blood Pressure*

Many recent studies have shown a positive relationship between lead exposure and blood pressure. Harlan et al (34) and Pirkle et al (72) examined data from the NHANES II study. Harlan's paper dealt with persons aged 12-74, whereas Pirkle restricted the sample to 40-59 year-olds. Both groups reported significant associations in male subjects. Schwartz (91) reported significant associations in both men and women aged 20-74 years. Pocock et al (75) examined data from the British Regional Heart Study, (N=7371 men, 40-59 years) and found significant associations between blood lead levels and both systolic and diastolic blood pressure.

## ISSUES IN DRAWING INFERENCES FROM OBSERVATIONAL STUDIES

The question of whether low levels of lead are associated with deficit has provoked considerable controversy in the past. There are several reasons for this controversy: The possibility that many children have been damaged by lead, but have not been recognized, is disquieting: The effects of lead are modest in magnitude and often coexist with other risk factors that afflict the poor or minorities. And, because the financial stakes are high, vested interests have weighed in on the argument. Industry has exerted considerable energy and funds to persuade regulators and the public that lead is innocuous at lesser doses.

In making causal inferences from nonexperimental studies, the investigator must balance two opposing risks: the risk of Type I errors (accepting spurious associations as causal and the risk of Type II errors (missing true causal associations). Considerable attention has been given to avoiding Type I errors; scientific rigor is felt to be defended by focusing on this type of risk. Less attention has been given to avoiding Type II errors. Scientists must attempt to reduce the volume of spurious claims in the literature; it is time-consuming to correct false claims. But it is also important, particularly when evaluating the threats of widespread environmental pollutants, not to overlook true associations between exposures and deficits. In reviewing the literature on lead and IQ, we have encountered six flaws in design or interpretation that have systematically reduced the risk of Type I errors, but at the cost of increased risk of Type II errors:

1. OVERVALUING THE STATUS OF THE P VALUE AS A CRITERION. Many investigators have dismissed the possibility of a causal association because the statistical significance did not reach the criterion of  $P < .05$ . Studies that report statistical significance of  $P = .09$ , or  $P = .1$  are interpreted to mean that no association has been shown, or indeed, that none exists in nature (26, 98). This criterion is simply a threshold of convenience and is dependent on the sample size, as well as the effect size. R. A. Fisher (29), who is credited with introducing the criterion, was more modest in describing its use:

It is convenient to take this point [ $P = .05$ ] as a limit in judging whether a deviation is to be considered significant or not. Deviations exceeding twice the standard deviation are thus formally regarded as significant.

Jerome Cornfield commented (19) on this point:

The prespecification of a significance level, e.g. .05 or .01, has no sound logical basis and remains unjustified.

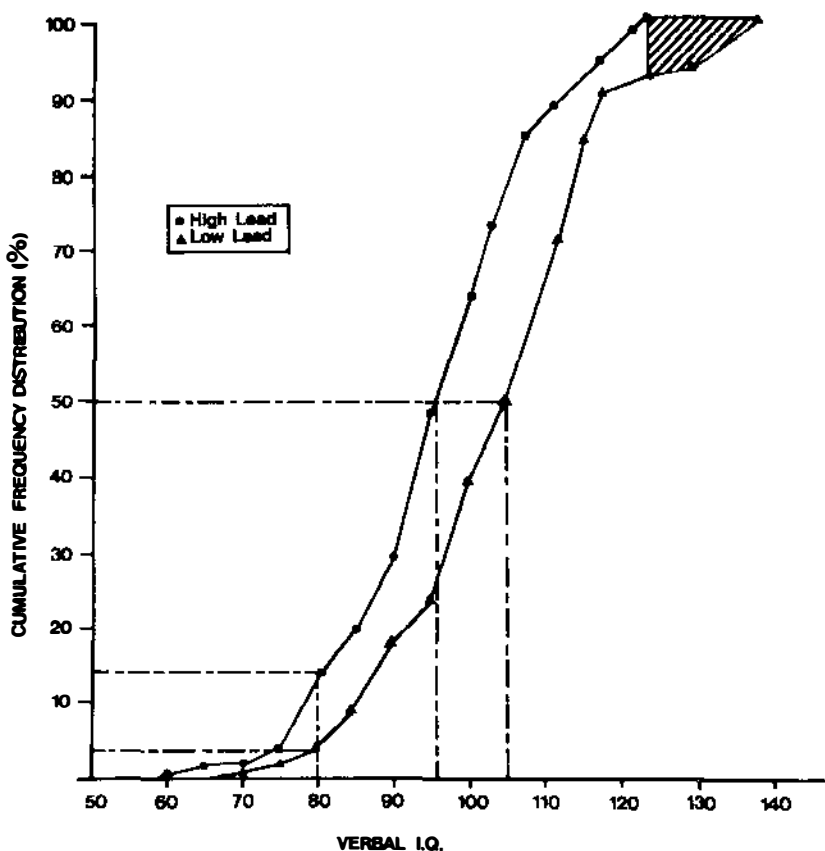


2. **POSTULATING PHANTOM COVARIATES.** Many factors affect child development and IQ, and careful investigators attempt to identify these factors and adjust for them in their analyses. In many, but not all cases, adjustment for confounders reduces the size of the effect of lead. Some investigators have argued from this reduced effect size: If the proper unidentified covariate had been measured or if identified covariates were measured more precisely, the effect size would drop to zero. For a variate to be a confounder, it must independently affect the outcome under examination and be associated with lead. There is a considerable, if not exhaustive, body of information on those factors that affect child development. Although the possibility of an undiscovered, lead-correlated influence on development exists, it is a tenuous reach to attribute a lead effect to residual confounding unless the variable responsible has been identified and measured.

3. **BUILDING NONVERIDICAL CAUSAL MODELS.** It is an oversimplification to classify variates into three groups: independent variables, dependent variables, and covariates. A variate may have more than one position in a causal chain. It could be an effect modifier, or it could be both an outcome (dependent) variable and an independent variable. The position of a variable in a causal chain requires knowledge about the biology of the disease. In ordinary, least squares regression, attempting to control for all variates, without regard for their position in the causal nexus, risks removing variance that truly belongs to lead. For example, controlling for hyperactivity (35), developmental delay (98), or school placement (108) clearly overcontrols; such control reduces the estimate of the true effect size. The same argument applies to the hypothesis that because mothers of children with high lead and deficit tend to score lower on the IQ tests, the cause of the child's deficits is the mother's rearing competence. A mother's rearing skill might be a product of her own lead exposure as a child, a hypothesis consistent with findings in animal studies (4).

4. **INADEQUATE SAMPLE SIZE AND STATISTICAL POWER.** The statistical power of a study (the probability of finding a true effect) is determined by the number of subjects, the effect size being sought, and the alpha level set by the investigator. Most studies of lead at low dose have used samples of fewer than 300 subjects. A recent review of 12 studies of lead and IQ, revealed that only four had power greater than .70 (63). One study (35) that claimed to show no lead effect had a sample size of 48 and evaluated 17 covariates. The statistical power in that study was between 0 and .30.

5. **UNDERESTIMATING THE BIOLOGICAL SIGNIFICANCE OF A "SMALL" EFFECT SIZE.** In most studies, the difference between the mean IQ scores of



*Figure 5* The distribution of IQ scores shows the effects of lead in first and second graders. The median IQ difference between groups is six points. At the low end of the scale, severe deficits occurred four times more often among children with high-lead levels. The highest score in the high-lead group was 125; among the low-lead children, 5% scored above 125. If these results are generally applicable, many children may be damaged intellectually, and others may fall short of their potential because of low-level lead exposure. (Reprinted by permission of *New England Journal of Medicine*; see Ref. 66.)

the exposed and unexposed groups studied is about 4–7 IQ points, and the partial  $r$  for lead in multiple regressions is about .14. Some researchers interpret these differences to be inconsequential. Figure 5 plots the actual cumulative frequency of IQ scores in high and low lead subjects from one of our studies (66). Although the median difference in IQ is six points, the rate of severe deficit, i.e. IQ < 80, is four times greater in the high lead group (16% vs. 4%). In addition, the shift of the curve to the left that occurs among children with higher lead exposure affects the top of the distribution severely.

This shift demonstrates a previously ignored effect of major public consequence: Lead exposure may prevent about 5% of the population from achieving truly superior function. No attention has been given to lead's effects at the high end of the scale.

6. EXPECTING PROOF OF CAUSALITY. Critics of the lead-IQ hypothesis often state that the data do not "prove" that lead caused the deficits. This assertion is true. Causality is a construct not subject to empirical proof (38, 49). The task of epidemiologists is to assemble data in a careful and rigorous fashion and then to draw the most veridical picture of nature from it. In asserting that a study has failed to prove a causal effect, the issue of possibly uncontrolled (and sometimes unidentified) covariates is often raised. But in the real world, multivariate space is infinite. There are a limitless number of factors that could influence cognition, and a finite number of subjects that can be studied. (The modal cost for a lead-IQ study is greater than \$1000/subject). Thus, investigators are always dealing with unsaturated structural models, and a variety of regression lines can be drawn through the data points. In addition, both independent and outcome variables are subject to errors in measurement, and the former tends to bias the estimated coefficients, toward zero.

Epidemiologists recognize the formal and practical barriers to causal proof. They accept, instead, certain canons that permit the drawing of causal inferences (40). These canons include time precedence of the putative cause; biological plausibility; nonspuriousness, or control of appropriate confounders; and consistency.

The time precedence of exposure to developmental deficit has been demonstrated in the forward studies of lead in infants and in the elegant animal studies of Rice & Gilbert (80) and Cory-Slechta et al (20). The plausibility of the low lead-developmental deficit association is strongly supported by the resemblance of the findings at low dose to the more striking outcomes long observed in clinical plumbism. The meticulous efforts to control covariates in epidemiological investigations (and the parallel findings in experimental animal studies) satisfy the canon of nonspuriousness. Consistency is discussed in the next section.

## METAANALYSIS OF THE LEAD IQ STUDIES

Individual studies of childhood lead exposure have differed in their conclusions, and review articles of the same group of studies have differed in their interpretations (9, 65, 73, 86). Narrative review articles have certain unavoidable constraints: They are subject to bias in selection of included papers. The reviewer's judgments of the papers may be biased. And, the

overall conclusion may be based on simple tallies of papers that find an association and those that do not. Such an approach to research synthesis badly degrades the data.

A relatively new alternative to narrative reviews is metaanalysis, by which each study is treated as a data point in a sample of the universe of studies. Joint estimates of probability or effect size can be made with various mathematical techniques. There are three published metaanalyses of lead at low dose and IQ.

Schwartz et al (94) first summarized the data from six studies. Using Fisher's technique for aggregating probabilities, he found that the joint probability of finding the pattern of reported results by chance under the null hypothesis was .004.

Needleman & Bellinger (62) extended Schwartz's analysis to 13 studies. Using Fisher's technique, they calculated a joint probability of  $3 \times 10^{-12}$  for the hypothesis that lead and IQ are not associated.

Needleman & Gatsonis (63) reviewed 24 studies on lead and IQ. They excluded those studies that did not control for covariates and did not use multivariate analysis. The 12 included studies were then classified by tissue (blood or tooth) and metaanalyses conducted within groups. This study went further than its predecessors; it tested samples for homogeneity, estimated the range of effect sizes, and calculated joint probabilities on the basis of weighted and unweighted samples (weighting by subject number). To test for influential studies, probabilities were recalculated for each group after leaving out each study. The sign of the lead coefficient was negative in 11 of the 12 studies, the partial  $r$  ranged from  $-.27$  to  $-.003$ . The joint  $P$  values for the seven blood lead studies were less than .0001 for both methods of analysis; for the tooth lead studies, the joint probabilities were .0005 and .004. The effect was robust to the removal of any study. The three metaanalyses taken together permit a strong inference that lead is causally related to IQ deficits.

## INTERPRETATION OF FINDINGS

The evidence summarized above draws us to conclude that lead is a potent toxicant that acts on many organ systems. The lower limit of its "no effect" level has yet to be plumbed. Indeed, with the development of more sensitive measures of function and more rigorous experimental and quasiexperimental designs, definition of undue lead exposure has regularly been reduced. It was set at  $60 \mu\text{g/dl}$  only three decades ago, and was  $40 \mu\text{g/dl}$  only 15 years ago. It certainly will be lowered to acknowledge the most recent studies of effects on IQ, hearing, and growth.

There is no shortage of toxic mechanisms to explain the epidemiologic findings. Understanding of lead's toxic properties has deepened with the

**Table 2** Summaries of estimated numbers of children 6 months to 5 years old in all SMSAs who are projected to exceed selected levels of blood lead, by urban status, 1984 (1)

Characteristic	Base Population	Blood Level ( $\mu\text{g}/\text{dl}$ )		
		>15	>20	>25
In SMSAs >1,000,000	7,251,000	1,493,400	459,500	128,200
In central city	2,886,200	901,800	301,700	86,200
Not in central city	4,364,800	591,600	157,800	42,000
In SMSAs <1,000,000	3,536,400	483,000	142,400	40,300
In central city	1,504,800	301,100	93,800	27,500
Not in central city	2,031,600	181,900	48,600	12,800
In small SMSAs	3,052,600 <sup>a</sup>	404,200	113,600	31,200
National total	13,840,000	2,380,600	715,500	200,700

<sup>a</sup> Total includes 6800 children who could not be stratified by income and were not included in estimates for three Pb-B levels.

application of new methods of analysis. Lead affects receptors, calcium channels, dendritic complexity, cortical connectivity during maturation, migration of cells, and the opiate system. Recent studies suggest that lead may affect RNA transcription and activate protein kinase at concentrations in the range of calcium concentrations. There is a plethora of demonstrated toxic effects; in the human host, it is reasonable that more than one phenomenon is operating at a time. Each mechanism has its own threshold and its own time constant.

In the child, the direct toxicologic expression of lead interacts with many other variables. Nutritional status and social stimulation are two of the more obvious operative factors. Iron, protein, calcium, and zinc deficiency all are associated with increased lead uptake. Lead enhances calciuria and zincuria (103). This effect provides a potential positive feedback loop, in which lead exposure results in depleted calcium and zinc stores, which in turn result in enhanced lead uptake. In those households where the parents are verbal and more inclined to stimulate the children, the toxic expression of lead at very low doses might be, to some extent, meliorated. This protective effect of highest socioeconomic status is overridden at blood lead levels greater than 10  $\mu\text{g}/\text{dl}$  (5). In those homes where the possibilities for a child's enrichment are constrained, the toxic effects of lead are allowed full expression.

The newest estimates of the prevalence of elevated lead exposure are troubling (1). Table 2 displays the numbers of children exceeding 15, 20, and 25  $\mu\text{g}/\text{dl}$  by area of residence. Table 3 displays the distribution of blood lead levels for children classified by race and class. There are 2.4 million children in the US with blood leads greater than 15  $\mu\text{g}/\text{dl}$  (standard metropolitan statistical areas only), and there is a distinct class and race bias to the exposure patterns. An estimated 1.9 million children live in deteriorated homes with

**Table 3** Projected percentages of children 0.5-5 years old estimated to exceed selected Pb-B criterion values ( $\mu\text{g}/\text{dl}$ ) by family income, race, and urban status, who live "inside central city" of SMSAs, 1984 (1)<sup>a</sup>

Family Income/Race	> 15 $\mu\text{g}/\text{dl}$	
	<1 M	>1 M
<\$6,000		
White	25.7	36.0
Black	55.5	67.8
\$6,000–14,999		
White	15.2	22.9
Black	41.1	53.6
$\geq$ \$15,000		
White	7.1	11.9
Black	26.6	38.2

<sup>a</sup>SMSA with population <1 million (<1 M) and SMSA with population >1 Million (>1 M)

leaded surfaces. The social costs of problem of this magnitude can only be estimated. Provenzano (76) attempted to calculate the costs of acute and convalescent care and remedial education in 1980. Based on CDC prevalence data for blood leads greater than 35  $\mu\text{g}/\text{dl}$  and 1979 costs for health care and remedial education, he set the annual costs at \$429 million to \$1 billion in 1979 dollars. The estimate requires upward revision to reflect current prevalence data, inflated health and educational costs, and lost wages.

## AREAS FOR FUTURE RESEARCH

### *Measurement of Lead Burden*

Recent research has dramatic implications for issues such as lead screening protocols and case definition. Since the early 1970s, most screening programs have relied on a hematofluorometric method to measure the concentration of erythrocyte protoporphyrin in capillary blood, an index of heme synthesis derangement (71). According to the current CDC screening guidelines, a child with a blood erythrocyte protoporphyrin (EP) level greater than 35  $\mu\text{g}/\text{dl}$  should be referred for follow-up evaluation of blood lead level and classified in terms of risk (18). Lead toxicity, or lead poisoning, is defined as a blood lead level greater than 25  $\mu\text{g}/\text{dl}$  and a blood EP level greater than 35  $\mu\text{g}/\text{dl}$ .

The utility of EP as a marker of blood lead level is greatly reduced at the lower blood lead levels that recent research indicates are toxic. The blood lead level at which EP begins to increase in response to rising blood lead levels is 16–18  $\mu\text{g}/\text{dl}$  (71), although the point of inflection appears to depend on

children's iron status (57). Data from the NHANES II survey indicate that among children in the general population, reliance on EP alone as the basis for screening produces many false-negatives, even at blood lead levels that exceed the current "action level." For example, in the NHANES II survey, only 47% of children with a blood lead level greater than 30  $\mu\text{g}/\text{dl}$  had an EP level greater than 30  $\mu\text{g}/\text{dl}$  (53). The false-negative rate is dramatically higher if the target blood lead level is shifted to 15 or 20  $\mu\text{g}/\text{dl}$ .

At the time the CDC last redefined the screening guidelines, the decision was based on both biologic and practical considerations. Although the CDC acknowledged that the threshold for biologic toxicity is less than 25  $\mu\text{g}/\text{dl}$ , they also recognized that the EP test has relatively poor sensitivity and specificity at blood lead levels less than 25  $\mu\text{g}/\text{dl}$ . The decision to recommend reliance on the EP test was essentially a compromise. The decision balanced the deficiencies of EP concentration as a screening measure and the practical issues of analytical cost, acceptability of venous blood sampling, and laboratory proficiency required for lead analysis of micro blood samples. With a developing consensus that 25  $\mu\text{g}/\text{dl}$  is unacceptable as the intervention blood lead level, the goal of screening clearly will become the identification of children with considerably lower blood lead levels. The basis for screening will have to shift either to blood lead itself or a biologic marker that is considerably more sensitive to blood lead than EP is. At this time, the former alternative appears more likely.

### *In Vivo Bone Lead Measurement*

Efforts to identify dose-response and dose-effect relationships between lead burden and health indexes have been hampered by the shortcomings, in most circumstances, of blood lead as an index of an individual's total body lead burden. Until recently, the only way to obtain such information had been through somewhat invasive procedures, such as provocative chelation in which stored lead is mobilized and the amount excreted in urine over the subsequent 24 hours is measured. Recent progress in the development of noninvasive x-ray fluorescence-based methods for assessing bone lead stores in vivo has provided optimism that measures of total body lead burden that can be conveniently applied to the general population will be available in the near future. Currently, instruments based on K-XRF and L-XRF technology are being developed (84, 99). These instruments differ in many respects, but most significantly in the type of bone sampled (L: surface bone; K: full thickness of bone). At present, L-XRF may be especially appropriate for pediatric and K-XRF for adult populations, but ongoing research may reveal that this generalization is too simplistic. If realized, rapid, noninvasive XRF measurement of bone lead could provide the basis for screening large populations of children for lead toxicity. Before this goal will be realized,

however, more work is necessary to establish the sensitivity and validity of the method at the levels commonly encountered in the general population.

### *Other Effects of Lead*

Most studies of childhood lead exposure have focused on psychometric intelligence, i.e. reading and math achievement. Little attention has been paid to higher order behavior, such as ability to get along with peers and to accept the prevailing social mores. There is growing evidence that lead-exposed children have difficulty in attention (64); some evidence suggests that exposure is associated with aggressiveness (48). Attention deficit with hyperactivity, coupled with antisocial behavior, is a strong predictor of criminality (52, 55). Criminal behavior has been found to be higher in males, blacks, and urban dwellers. It displays itself early in life; criminals are more likely to have been hyperactive as young children and to have come from disorderly homes with poor housekeeping (106). All of these factors are associated with lead exposure. Carefully designed case control and forward studies of the association of lead exposure with antisocial behavior are clearly warranted.

The studies of Kitchen et al (42, 41) and Nation et al (61) suggest that studies of lead exposure in drug and alcohol abusers are worth pursuit. Case control studies of older individuals who are past the ages of peak exposure should benefit from new advances in the technology of in vivo lead measurement.

Almost all studies of lead toxicity have focused on young children, and more recently on fetuses in utero. Because the fetus clearly is not protected from lead, maternal exposure has become a subject of considerable interest. Hormonal changes associated with pregnancy might mobilize lead stores, which would create an endogenous source of fetal exposure, even if external exposure during pregnancy is low (56, 100). Less attention has been paid to paternal exposure and its consequences for the father and his potential offspring, despite evidence that suggests that lead is a gametotoxin. Studies of male reproductive function and fetal consequences of paternal exposure are needed.

Another ignored issue is the effect of early lead exposure on the aged. Most lead is deposited in bone, where it is relatively inert. But with aging, bone demineralizes, which possibly provides an endogenous source of ongoing exposure (96). No information on the sites of redistribution of bone lead is available. Does some of this lead get to the CNS? Is lead one factor in the disordered memory and cognition found in some older patients?

## CONTROL STRATEGIES

The major sources of lead for American children are paint, dust, soil, and drinking water. What should the response of society be to this problem? To



develop an informed strategy, we need to examine the forces that have impeded action in face of a large and growing body of knowledge. Activity directed at the removal of lead from the human environment has been slowed by the following factors:

1. **THE BELIEF THAT THE DISEASE IS LIMITED TO POOR MINORITIES.** Related to this belief is the conviction that the disease is a product of poor mothering and unsanitary habits. The widespread tendency to assign the primary cause to human, rather than environmental, factors has relieved authorities from the obligation to act.

2. **THE BELIEF THAT REDUCING THE AMOUNT OF LEAD ADDED TO GASOLINE AND LEAD PAINT LEGISLATION HAS ALREADY SOLVED THE PROBLEM.** The removal of lead from gasoline has resulted in a decrease in blood lead levels of about 10% per year. Although it has been impossible to purchase lead-containing paint for household use legally since 1976, half the homes in this country were built before the passage of the lead paint legislation. The ATSDR report estimates that 2 million homes in which young children live are leaded and have deteriorated surfaces.

3. **THE OBDURATE OBSTRUCTIONISM OF THE LEAD INDUSTRY.** Since the 1920s the industry has worked to diminish and obscure the hazards of lead to human health and to impede legislation or regulation (32, 85). Recently mounted lawsuits, which state that knowledge of the dangers of lead paint to children were known and hidden by the industry, have added the lead industry to the list of defendants.

4. **THE LACK OF MEDICAL INTEREST IN THE PROBLEM.** Lead poisoning is a low technology disease. It does not possess the drama of transplant surgery or molecular biology. Many pediatric centers have stopped screening for lead, and many house officers complete their training without having seen a case of plumbism. As a result, they do not think of the disease when constructing a differential diagnosis of developmental delay, growth failure, or behavior disorder.

To address these misplaced beliefs, we need to develop firm and repeated educational efforts for the public, regulators, educators, and pediatricians. Lead poisoning is not a disease of poor minorities alone. The ATSDR report indicates that 16% of all American children have blood lead levels in the neurotoxic range. Clearly, the poor and minorities receive a disproportionate dose of lead. For black children in poverty, the prevalence of blood lead levels greater than 15  $\mu\text{g}/\text{dl}$  is 55%! Lead exists in dangerous overabundance in precisely the same areas in which there are two shameful and threatening shortages: decent housing and jobs. A rational way to manage this imbalance

would be to train and then hire the unemployed in the safe deleading of houses. Lead control can be readily seen as a health program, a housing program, and an employment program. No one has spelled out the dilemma (and the hope) of lead poisoning more pointedly than the late Rene Dubos (quoted in Ref. 68a):

The problem is so well defined, so neatly packaged, with both causes and cures known, that if we don't eliminate this social crime, our society deserves all the disasters that have been forecast for it.

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