LEAD POISONING

Herbert Needleman

Professor of Psychiatry and Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213; email: hlnlead@pitt.edu

■ **Abstract**   Understanding of lead toxicity has advanced substantially over the past three decades, and focus has shifted from high-dose effects in clinically symptomatic individuals to the consequences of exposure at lower doses that cause no symptoms, particularly in children and fetuses. The availability of more sensitive analytic methods has made it possible to measure lead at much lower concentrations. This advance, along with more refined epidemiological techniques and better outcome measures, has lowered the least observable effect level until it approaches zero. As a consequence, the segment of the population who are diagnosed with exposure to toxic levels has expanded. At the same time, environmental efforts, most importantly the removal of lead from gasoline, have dramatically reduced the amount of lead in the biosphere. The remaining major source of lead is older housing stock. Although the cost of lead paint abatement is measured in billions of dollars, the monetized benefits of such a Herculean task have been shown to far outweigh the costs.

INTRODUCTION

In recent years, the focus in lead poisoning has shifted away from adults exposed to high doses in industrial settings to the larger population of asymptomatic children with lesser exposures. This chapter surveys the past three decades of lead research and reviews the evolving knowledge of the distribution, toxicology, and remediation of lead toxicity.

EARLY HISTORY

Warnings of lead's poisonous properties extend at least as far back as the second century B.C., when Nikander, a Greek physician, described the colic and paralysis that followed lead ingestion. The early victims of lead toxicity were mainly lead workers and wine drinkers. Lead's sweet flavor made it useful in winemaking, to counteract the astringent flavor of tannic acid in grapes. Lead-sweetened wine, containing as much as 20 mg of lead per liter, was an important part of the diet of upper-class Romans. The synchronous decrease in fertility and increase in psychosis among the Roman aristocracy has raised speculation implicating lead poisoning in the fall of Rome (1).

Widespread outbreaks of lead colic continued in Europe until as late as the sixteenth century, when Eberhard Gockel, a German physician, traced a colic epidemic to lead-adulterated wine. Duke Ludwig of Würrtemberg, upon learning of an epidemic of lead colic in his duchy, banned its use in winemaking, imposing the death penalty for violators.

Workers in the metals trades remain an important risk group; lead exposure remains one of the leading causes of workplace illness. In the United States, more than 320,000 American workers were occupationally exposed to lead in 1998.

DISCOVERY OF CHILDHOOD LEAD POISONING

It was only a century ago that childhood lead poisoning was recognized. The rapid growth of scientific understanding can be divided into four stages. The first reports of lead-poisoned children in Brisbane, Australia, in 1892 were greeted with widespread disbelief that lead toxicity could afflict children (2). Although the disease had reached epidemic proportions, there was considerable doubt that lead was the cause. Many of the homes in Brisbane were raised on piles, with large wooden-enclosed verandas that served as play areas for children. The rails were painted with white lead, which chalked and powdered in the hot Brisbane sun. The cause of the epidemic, lead-containing paint, was established in 1904, and lead paint was banned for household use in Brisbane in 1920.

Childhood lead poisoning was first described in the United States in 1914 (3). The prevailing belief in the second stage of knowledge was that acute poisoning had only two outcomes: death or complete recovery without any residua. This misconception was discarded in 1943 with the first follow-up of children who had recovered from acute toxicity. Nineteen of 20 survivors had significant deficits: behavioral disorders, learning difficulties, and school failure (4). In this third stage, it was generally accepted that lead toxicity caused long-term deficits, but these deficits were thought to occur only in those children who had displayed clinical signs of encephalopathy during the acute episode. The fourth stage began in the 1970s, when studies of children with no clinical signs of toxicity showed deficits in IQ scores, attention, and language (see below).

TOXICOLOGY OF LEAD

Lead is a divalent cation, and it binds strongly to sulfhydryl groups on proteins. Of the many organs affected by lead, the most important is the central nervous system (CNS). Much of lead's toxicity can be attributed to distortion of enzymes and structural proteins, but this versatile toxicant has many other targets. Lead interferes with the development of the endogenous opiate system (5). It efficiently cleaves the ribophosphate backbone of tRNA catalytically at specific sites, with no evidence of a threshold (6). Many of lead's toxic properties are due to its ability to mimic or compete with calcium. At picomolar concentrations, lead competes

successfully with calcium for binding sites on cerebellar phosphokinase C and thereby affects neuronal signaling (7). It inhibits calcium entry into cells (8). Lead is picked up by mitochondria and produces swelling and distortion of mitochondrial cristae. Uncoupled energy metabolism, inhibited cellular respiration, and altered calcium kinetics follow (9). Lead has a binary impact on neurotransmitter release: Spontaneous neurotransmitter release is enhanced, whereas stimulated release is inhibited (10).

Attention has also focused on the heme synthetic pathway, where many sites for lead activity are found. Delta aminolevulinic acid dehydratase is extremely sensitive to lead. Inhibition of this enzyme results in increased circulating aminolevulinic acid (ALA). ALA is a weak gamma-aminobutyric acid (GABA) agonist that decreases GABA release by presynaptic inhibition. Increased circulating ALA may account for some of the behavioral disorders seen in patients with porphyria and perhaps in lead toxicity.

Lead has diverse impacts on the CNS. Immature astrocytes are sensitive to lead, and lead interferes with myelin formation and the integrity of the blood-brain barrier (11). Lead interferes with the synthesis of collagen and affects vascular permeability. At high enough doses, this results in brain edema and hemorrhage (12). At lower doses, lead given to lactating rats interferes with synaptogenesis in their pups (13). Lead's interference with brain development has been demonstrated using the rodent barrel field cortex as a model (14).

Behavioral alterations secondary to lead exposure in rodents and primates are analogous to changes in humans. In one study, monkeys received lead acetate in their food from birth to 200 days of age and achieved blood lead levels ranging from 3 μg/dl to 25 μg/dl. At 7 to 8 years, they were given a delayed alternation test, in which the critical positive stimulus was alternated. Treated monkeys showed impaired ability to learn, particularly at longer intervals of delay (15). Lead-exposed primates also demonstrate impaired social function (16). Rodents given lead show deficits in learning mediated by dopaminergic and glutamatergic systems (17). In one interesting report, untreated rats found 15% solutions of alcohol aversive in a free-choice situation, but when their blood lead levels were raised to 61 μg/dl, they increased their alcohol intake in both free- and forced-choice paradigms (18). The author speculated that lead increased the irritability of the rats and that they sought alcohol as a tranquilizer.

CLINICAL ASPECTS OF TOXICITY

Although adult lead poisoning is mainly of occupational origin, cases of acute lead poisoning from leaded dishware, bootlegged moonshine liquor, certain cosmetics, and folk remedies continue to be reported. Lead is still mined and smelted, although this has declined with the removal of lead from gasoline.

Lead poisoning in adults can affect the peripheral and central nervous systems, the kidneys, and blood pressure. Classical descriptions of occupational toxicity

depict peripheral neuropathy with wrist or foot drop. At lesser exposures, slowed peripheral nerve conduction has been reported (19). Patients with high blood lead levels may present with severe, intractable colic, motor clumsiness, clouded consciousness, weakness, and paralysis. Lead has adverse effects on both male and female reproduction. The fetotoxic properties of lead were known to British factory inspectors at the end of the nineteenth century; they found a high incidence of stillbirths (60%), neonatal deaths, and a decreased fertility rate in women employed in the ceramic industry (20). Males may manifest decreased sperm counts and teratospermia (21).

Hypertension has been associated with acute lead poisoning, along with renal failure. At lesser exposures, both experimental and epidemiological evidence of interference with renal function and elevations in blood pressure have been reported. Using data from the third National Health and Nutrition Examination Survey (NHANES III), a recent reevaluation of blood pressure in relation to contemporary blood lead levels found that black men and women had higher blood lead levels (5.4 μg/dl, 3.4 μg/dl) than their white counterparts (4.4 μg/dl, 3.0 μg/dl). Black subjects, both men and women, had a statistically significant association of blood lead with blood pressure after covariate adjustment. The association was not seen in whites (22).

In its alkyl form, lead is a powerful neurotoxin. When tetraethyl lead (TEL) was first produced for use as a motor fuel additive in 1925, workers at all three operating plants began to die. After a brief moratorium imposed by the Surgeon General, production resumed and continued until the 1980s. TEL is fat-soluble; absorption through the skin and uptake by the brain is rapid. Because of growing evidence of neurotoxic effects at low doses, TEL was removed from gasoline in stepwise fashion beginning in 1978.

Lead has been classified as an animal carcinogen, but the data on human carcinogenesis are considered inadequate. Some recent studies of cancer rates in lead trade workers (e.g., smelters, painters, body and fender repairmen) have shown an increase in standard mortality rates, but others have not (23).

CHILDHOOD LEAD TOXICITY

Children are more sensitive to lead than adults for several reasons: Their exposure is increased by their universal hand-to-mouth activity; their gut absorbs lead more readily than an adult's; and the developing CNS is more vulnerable to toxicants than the mature CNS.

At high doses, generally blood lead levels >60 μg/dl, clinical symptoms become visible in children. Abdominal pain and arthralgia are common early complaints. Clumsiness and staggering may be seen, followed by headache and behavioral changes, which are signs of early encephalopathy. This may progress to alterations of consciousness, stupor, and convulsions. Encephalopathy, fortunately, has become rare in the United States. A high percentage of those children who recover

from clinical encephalopathy have severe cognitive, attentional, and behavioral impairments.

ASYMPTOMATIC LEAD TOXICITY

In the 1960s, the accepted toxic threshold for lead in children was 60 μg/dl. Screening studies in eastern U.S. cities found that 10%–20% of inner-city children had blood lead levels over 40 μg/dl. This finding raised the conjecture, first made by Byers & Lord in 1943, that a proportion of school failure and behavioral disorder resulted from unrecognized lead toxicity. Five studies of lead levels and behavior in children without signs or symptoms of classical lead toxicity were undertaken in the early 1970s. Three reported an association between lead and IQ (24–26); two did not (27, 28). These early studies were constrained by design flaws: The number of subjects in each study was small, and each relied on blood lead levels to rank exposure. Blood lead, a short-term marker, may misclassify earlier exposure. Lead in blood has a half-life of 35 days. Exposure peaks at two years, then drops. Most studies enrolled children at about age 6 or later. There are no data on the validity of blood lead measurements four years after exposure has ended. Some studies used relatively insensitive outcome measures, such as group or screening tests. Control of confounders and statistical procedures was limited. Some investigators studied clinic samples and their data may thus have suffered selection bias.

In 1979, we conducted a study that attempted to address these design issues. Lead concentration in deciduous teeth was selected as the marker of exposure. The sample comprised asymptomatic primary school students from the public schools of Chelsea and Somerville, Massachusetts. Subjects were classified on a large number of covariates, and these were controlled in the analysis by Analysis of Covariance (ANCOVA). Excluded were children with a history of lead exposure or toxicity. Children with elevated lead levels (in the ninetieth percentile for lead concentration) in their teeth were found, after covariate control, to be significantly impaired on the Wechsler Intelligence Scale for Children—Revised (WISC-R) IQ test, on language processing, and on reaction time under varying conditions of delay, a measure of attention. When teachers' ratings of 2146 children on an 11-item forced-choice scale were classified by dentine lead level, we found a dose-dependent increase in bad classroom behavior in direct relation to tooth lead level (Figure 1) (29).

In the 1980s, following the removal of lead from gasoline, the blood lead levels in the referent group dropped. This enabled well-designed studies, employing larger samples, better measures of outcome and lead burden, and more sophisticated statistical analyses, to discover effects of lower blood lead levels (30–33). Three meta-analyses confirmed that low-level lead exposure was associated with IQ deficits (34–36). In response to the new data, in 1991, the Centers for Disease Control revised its limit of acceptable blood lead level downward in steps, from 60 μg/dl in the 1970s to its current status of 10 μg/dl.
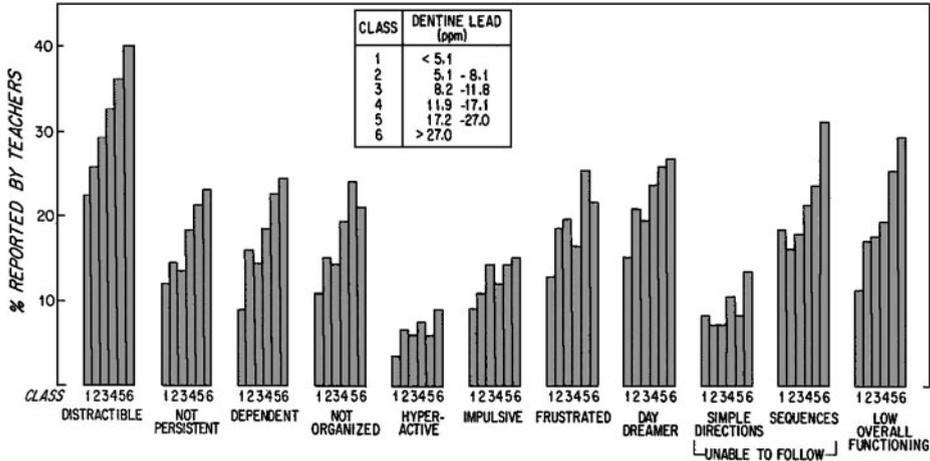
Figure 1   Distribution of negative teachers' ratings in relation to dentine lead concentrations.

In 2002 and 2003, two new studies found effects at levels below 10 μg/dl, further lowering the observed threshold for effect. Lanphear et al. examined psychological performance and blood lead levels in 4853 children who were NHANES III subjects. The mean blood lead in this sample was 1.9 μg/dl; 2.1% of the sample had blood lead levels in excess of 10 μg/dl. After adjustment for covariates, significant inverse relationships between blood lead and math and reading subtests and the Block Design and Digit Span of the WISC-III were reported down to 2.5 μg/dl (37). Canfield et al. (38) studied 166 36-month-old children whose mean blood lead level was 7.9 μg/dl. Seventy-three percent of the subjects had blood lead levels under 10 μg/dl. Significant inverse relationships were found between IQ scores and lead after covariate adjustment. The slope of the effect was greater at the lower blood levels of lead (38). The import of the recent studies is that a threshold for lead and neurobehavioral function has not yet been demonstrated.

FOLLOW-UP STUDIES OF CHILDREN

The late effects of early-childhood lead exposure have been examined by several investigators, who found persistence of deficits over time. Our subjects, first examined in 1979, were seen again 12 years later at mean age of 18.7 years. Subjects whose dentine lead levels were in the high-lead group (ninetieth percentile) had more school failure, reading disabilities, lower class standing in their final year of high school, and disturbances in fine motor function (39) (Figure 2).

Fergusson et al. followed a sample of New Zealand children into their eighteenth year and reported that elevated lead levels were associated with poorer reading
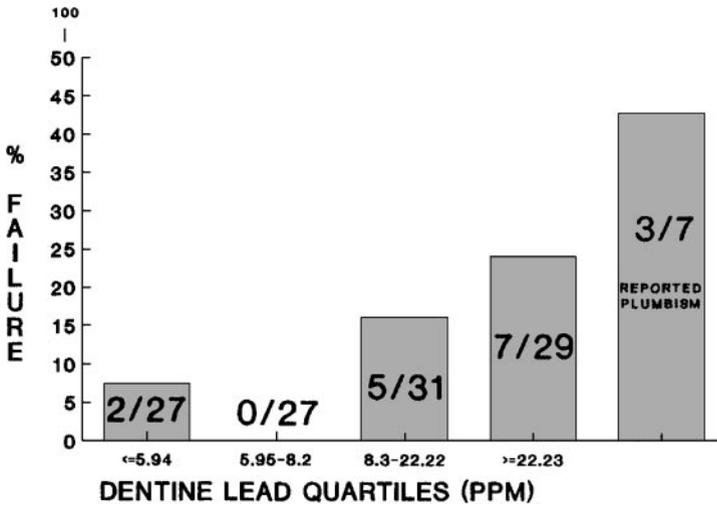
Figure 2 Rate of failure to graduate from high school in relation to dentine lead levels.

scores, more failure to graduate from high school, and poorer examination scores (40).

FORWARD STUDIES OF PRENATAL AND INFANT LEAD EXPOSURE

Bellinger et al. found significant associations between umbilical blood lead levels and neurodevelopmental scores at 2 years of age (41). At later ages, the association between umbilical cord blood lead and outcome was attenuated. The 2-year blood lead concentrations, however, were significantly related to scores at 10 years of age. Exposure at 2 years had no observable threshold, demonstrating neurotoxic effects at blood lead levels below 10 μg/dl.

Dietrich et al. followed a group of 253 children from birth until 6 years of age. Blood lead levels at age 6 were associated with deficits in performance scores of the WISC, after covariate adjustment, and in motor function (42).

LEAD AND BEHAVIOR

Cognitive function, measured by psychometric IQ tests, has been the major focus of most studies of lead exposure in childhood. There are persuasive reasons to believe that cognitive dysfunction may not be the most important effect of lead, and that we may be entering a fifth stage of understanding of lead's effects, in which lead is recognized to adversely affect social behavior.

This is not an entirely new notion. Parents have frequently reported that after recovery from an episode of acute lead poisoning, their child's behavior changed dramatically, and they became restless, inattentive, and aggressive. In 1943, Byers & Lord reported attentional dysfunction and aggression in a sample of lead-poisoned children on follow-up (4).

We studied 301 primary-school students and found that children with elevated bone lead levels scored higher on the attention deficit, aggression, and delinquency clusters of the Child Behavior Checklist after adjustment of covariates (43). Dietrich et al. found that prenatal lead exposure was associated with parents' reports of delinquency and aggression, and postnatal lead exposure was associated with self reports of delinquent acts (44). A recent case-control study of 195 arrested and convicted delinquent youths found an increased risk of delinquency associated with bone lead concentrations measured by X-ray fluorescence. The covariate-adjusted odds ratio was 4 (95% CL 1.4–11.1). The population-attributable risk for delinquency due to lead exposure ranged from 11% to 38% in this sample (45).

A number of recent ecological investigations correlating leaded gasoline sales or ambient lead levels with crime rates support an association between lead exposure and crime. Stretesky & Lynch compared homicide rates in 3311 counties in the United States (46) After adjustment for 15 covariates, they reported a fourfold increase in homicide rates in those counties with the highest air lead levels compared to controls. Nevin correlated sales of leaded gasoline with violent crime rates and, adjusting for unemployment and percent of population in the high-crime age group, found a statistically significant association (47). It has been speculated that one of the reasons for the recent decline in crime rates is decreased exposure to lead.

LEAD EFFECTS IN OLDER SUBJECTS

The greatest storage pool for lead is in bone, and the question of lead's fate in older subjects when bone demineralizes has attracted considerable speculation. It is estimated that 50% of trabecular bone in women is lost over a lifetime. Lead is mobilized when bone resorption begins; significantly higher blood lead levels have been measured in postmenopausal women than in premenopausal women (48). Elevated lead appears to adversely affect cognitive function in elderly subjects as well. Older women (mean age 70.5 years) with blood lead levels >8 μg/dl had poorer performance on cognitive measures and slower reaction times than women with blood lead levels <3 μg/dl after covariate adjustment (49).

Results of a large-cohort study of former TEL workers support a causal association between lead and dementia (50). The subjects ($n = 535$) were studied a mean of 16 years after their workplace exposure. The investigators report elevated bone lead levels and dose-related deficits in verbal and visual memory, executive ability, and manual dexterity. TEL workers exhibited a greater decline in function measured at yearly intervals than controls. The same investigators examined the interaction between APOE genotypes with bone lead levels. An interaction effect for bone lead $\times$ APOE genotype was found for 19 of 20 regression models, indicating that the toxic effect of lead is greater in subjects with at least one APOE allele (51).

Lead has induced apoptosis in a number of experimental systems, including rat midbrain (52), rat testis (53), rat fibroblasts (54), rodent lung (55), and rodent retinal rod cells (56, 57). These findings, and similarities in the distribution of lead exposure and the rates of Alzheimer's, make the topic of lead-related dementia worthy of further study.

Lead exposure may also decrease lifespan. This is borne out by a recent study of subjects from the second NHANES study (1976–1980), who were followed up in 1992. The mortality of 4292 subjects with blood lead levels of 20–29 μg/dl was compared to those with levels <10 μg/dl. Subjects with higher lead levels had a 46% increased all-cause mortality, 39% increased cardiovascular mortality, and 68% increased cancer mortality (58).

DIAGNOSIS AND MANAGEMENT OF CLINICAL LEAD POISONING

In adults, lead toxicity should be considered in the differential diagnosis of abdominal pain, arthralgia, hypertension, severe headache, increased intracranial pressure, CNS dysfunction, anemia, and renal dysfunction. An occupational history and an inventory of possible sources of exposure are useful. A blood lead level >10 μg/dl should be considered elevated, even though clinical symptoms are rarely seen below 60 μg/dl.

Any child with growth failure, abdominal pain, behavior change, hyperactivity, language delay, or anemia should have a blood lead test to rule out lead toxicity.

The cornerstone of lead toxicity management is the termination of exposure. For children, this means inspection of the home, and if this does not reveal lead, a survey of other possible sources. For lead levels >40 μg/dl, chelation therapy is effective in lowering the blood lead level. Calcium disodium edathamil (EDTA) was the preferred method until recently, when dimercaptosuccinic acid (succimer), an oral agent, was found to have equal efficacy. Both agents will reduce an elevated blood lead level to 40%–50% of its baseline. After treatment is concluded (5 days for EDTA, 19 days for succimer), body pools tend to equilibrate, and blood lead levels begin to rise, often requiring repeated courses.

EDTA has drastically reduced the mortality rate from encephalopathy, but its efficacy at lower exposures has never been systematically studied. As a result, whether it conveys any benefit to children without encephalopathy remains unknown.

After succimer had been in use for a few years, a multicenter study evaluated its efficacy in children with moderate elevations of lead (25–44 μg/dl). Blood lead levels in the treatment group were reduced to significantly lower levels than controls at the completion of treatment, but two years later, there were no differences between the two groups. At the conclusion of the study, no significant differences were found between treatment subjects and controls in cognitive, behavioral, or neuropsychological function (59). The only remedy at this time for low-level lead exposure is therefore primary prevention.

PRIMARY PREVENTION

In the early 1970s, the question of silent lead toxicity became the focus of intense controversy because of its regulatory implications. In 1973, when the Environmental Protection Agency began examining the health effects of TEL, industrial representatives claimed that the associations between lead and IQ were spurious, and that removing lead from gasoline would have no impact on body lead burdens. In 1977, after review of the health effects, the Environmental Protection Agency established an air lead standard of 1.5 μg/M^3. The stepwise removal of lead from gasoline, based on the new air standard, began in the late 1970s. Figure 3 shows the effect of removing lead from gasoline on blood lead levels in the United States between 1975 and 1980.

With the removal of lead from gasoline, a single major source remains for American children: leaded paint. Although it has been banned in household paint since 1971, 80% of the houses built before 1950, or 23,000,000 units, contain leaded paint. A cost-benefit analysis by the Public Health Service estimated the cost of abatement in these houses over a 30-year period at $33.7 billion in 1991. The estimated benefit from avoided health care costs and increased income due to raised IQ was $61.7 billion. This cost analysis may be conservative; it does not include avoided delinquency and cardiovascular disease, both demonstrated effects of lead exposure, among the health effects (60).
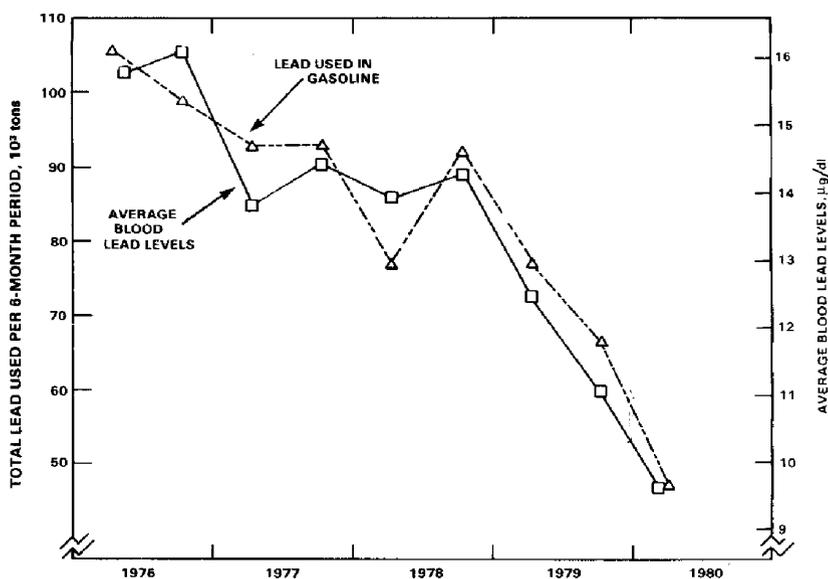

Figure 3   Parallel decreases in blood lead values observed in the NHANES II study and amounts of lead used in gasoline during 1976–1980.

Current analyses also demonstrate that primary prevention yields large economic benefits. Grosse et al. calculated that each present-day preschool child's IQ was increased by 2.2–4.7 points over what it would have been had the reduction in leaded gasoline and blood lead not taken place (61). From this, they calculated the IQ-related increase in income and estimated the economic benefit for each year's birth cohort of 3.8 million children. The benefit range for the 1998 birth cohort was between $110 billion and $319 billion (61). Landrigan et al., assuming no threshold for the lead-IQ association, estimated the loss of future earnings for the one-year cohort of children aged 5 in 1997 at $43.4 billion (62).

The evidence that lead toxicity extends down to the lowest measurable levels, that pharmacological therapies are ineffective at preventing sequelae in those with low levels, and that reduction of exposure yields huge economic as well as health benefits are strong warrants for a systematic program of abatement of lead from the single remaining major source: lead in older homes.

The *Annual Review of Medicine* is online at http://med.annualreviews.org

LITERATURE CITED

1. Gilfillan SC. 1965. Lead poisoning and the fall of Rome. *J. Occup. Med.* 7:53–60
2. Gibson JL. 1892. Notes on lead-poisoning as observed among children in Brisbane. *Proc. Intercolonial Med. Congr. Austr.* 3:76–83
3. Blackfan KD. 1917. Lead poisoning in children with especial reference to lead as a cause of convulsions. *Am. J. Med. Sci.* 53:877–87
4. Byers RK, Lord EE. 1943. Late effects of lead poisoning on mental development. *Am. J. Dis. Child.* 66:471–83
5. Bailey C, Kitchen I. 1985. Ontogenesis of proenkephalin products in rat striatum and the inhibitory effects of low-level lead exposure. *Dev. Brain Res.* 22:75–79
6. Brown RS, Hingerty BE, Dewan JC, et al. 1983. Pb(II)-catalysed cleavage of the sugar-phosphate backbone of yeast tRNA(Phe)—implications for lead toxicity and self-splicing RNA. *Nature* 303:543–46
7. Markovac J, Goldstein GW. 1988. Picomolar concentrations of lead stumulate brain protein kinase C. *Nature* 334:71–73
8. Simons T. 1993. Lead-calcium interactions in cellular lead toxicity. *Neurotoxicology* 14:77–85
9. Holtzman D, DeVries C, Nguyen H, Bensch K. 1984. Maturation of resistance to lead encephalopathy: cellular and subcellular mechanisms. *Neurotoxicology* 5:97–124
10. Bressler J, Goldstein G. 1991. Mechanisms of lead neurotoxicity. *Biochem. Pharnacol.* 41:479–84
11. Krigman MR. 1978. Neuropathology of heavy metal intoxication. *Environ. Health Persp.* 26:117–20
12. Pentschew A. 1965. Morphology and morphogenesis of lead encephalopathy. *Acta Neuropathol.* 5:133–60
13. Averill D, Needleman HL. 1980. Neonatal lead exposure retards cortical synaptogenesis in the rat. In *Low Level Lead Exposure: The Clinical Implications of Current Research*, ed. HL Needleman, pp. 201–10. New York: Raven
14. Wilson MA, Johnston MV, Goldstein GW, et al. 2000. Neonatal lead exposure impairs development of rodent barrel field

cortex. *Proc. Natl. Acad. Sci. USA* 97: 5540–45

15. Rice DC. 1992. Behavioral impairment produced by developmental lead exposure: evidence from primate reseach. In *Human Lead Exposure*, ed. HL Needleman, pp. 137–54. Boca Raton, FL: CRC

16. Bushnell PJ, Bowman RE. 1979. Effects of chronic lead ingestion on social development in infant rhesus monkeys. *Neurobehav. Tox.* 1:207–19

17. Cory-Slechta DA. 1997. Relationships between Pb-induced changes in neurotransmitter system function and behavioral toxicity. *Neurotox.* 18:673–88

18. Nation JR, Baker DM, Taylor B, et al. 1986. Dietary lead increases ethanol consumption in the rat. *Behav. Neurosci.* 100:525–30

19. Seppalainen A, Hernberg S. 1980. Subclinical lead neuropathy. *Am. J. Ind. Med.* 1:413–20

20. Oliver ST. 1911. A lecture on lead poisoning and the race. *BMJ.* 1:1096–98

21. Lancrajan, Popescu JL, Gavenescu O, et al. 1975. Reproductive ability of workmen occupationally exposed to lead. *Arch. Environ. Health.* 30:396–401

22. Vuppurturi S, Muntner P, Bazzano LA, et al. 2003. Blood lead level is associated with elevated blood pessure in blacks. *Hypertension* 41:463–68

23. Landrigan PJ, Boffetta P, Apostoli P. 2000. The reproductive toxicity and carcinogenicity of lead: a critical review. *Am. J. Ind. Med.* 38:231–43

24. De la Burde B, NcLin S, Choate S, 1972. Does asymptomatic lead exposure in children have latent sequelae? *J. Pediatr.* 81:1088–91

25. Landrigan PJ, Baloh RW, Barthel WF, et al. 1975. Neuropsychological dysfunction in children with low level lead absorption. *Lancet*, pp. 708–12, March 29

26. Perino J, Ernhart CB. 1974. The relation of subclinical lead level to cognitive and sensorimotor impairment in black preschoolers. *J. Learn. Disabil.* 7:26–30

27. Kotok D. 1972. Development of children with elevated blood lead levels: a controlled study. *J. Pediatr.* 80:57–61

28. Lansdown RG, Shepherd J, Clayton BE, et al. 1974. Blood-lead levels, behaviour, and intelligence. A population study. *Lancet* 1:538–41

29. Needleman HL, Gunnoe C, Leviton A, et al. 1979. Deficits in psychological and classroom performance of children with elevated dentine lead levels. *N. Engl. J. Med.* 300:689–95

30. Fulton M, Raab G, Thomson G, et al. 1987. Influence of blood lead on the ability and attainment of children in Edinburgh. *Lancet* 1:1221–26

31. Lyngbye T, Hansen ON, Trillingsgaard A, et al. 1990. Learning disabilities in children: significance of low level lead exposure and confounding factors. *Acta Pedriatr. Scand.* 79:352–60

32. Fergusson DM, Horwood J, Lynskey MT. 1997. Early dentine lead levels and educational outcomes at 18 years. *J. Child Psychol. Psychiatry* 38:471–78

33. McMichael AJ, Baghurst PA, Wigg NR, et al. 1988. Port Pirie Cohort Study: environmental exposure to lead and children's abilities at the age of four years. *N. Engl. J. Med.* 319:468–75

34. Needleman HL, Gatsonis C. 1990. Low level lead exposure and the IQ of children. *J. Am. Med. Assoc.* 263(5):673–78

35. Schwartz J. 1993. Beyond LOEL's, p values and vote counting: methods for looking at the shapes and strengths of associations. *Neurotoxicology* 14:237–46

36. Pocock SJ, Smith M, Baghurst P. 1994. Environmental lead and children's intelligence: a systematic review of the epidemiological evidence. *BMJ* 309:11889–97

37. Lanphear BP, Dietrich K, Auinger P, Cox C. 2000. Cognitive deficits associated with blood lead concentrations <10 microg/dL in US children and adolescents. *Public Health Rep.* 115(6):521–29

38. Canfield RL, Henderson CR, Cory-Slechta

DA, et al. 2003. Intellectual impairments in children with blood lead concentrations below 10 μg per deciliter. *N. Engl. J. Med.* 348:1517–26

39. Needleman HL, Schell A, Bellinger D, et al. 1990. The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report. *N. Engl. J. Med.* 11:83–88

40. Fergusson DM, Horwood J, Lynskey MT. 1997. Early dentine lead levels and educational outcomes at 18 years. *J. Child Psychol. Psychiatry* 38:471–78

41. Bellinger D, Leviton A, Waternaux C, et al. 1987. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *N. Engl. J. Med.* 316:1037–43

42. Dietrich KN, Krafft KM, Bornschein RL, et al. 1987. Low-level fetal lead exposure effect on neurobehavioral development in early infancy. *Pediatrics* 80:721–30

43. Needleman HL, Riess JA, Tobin MJ, et al. 1996. Bone lead levels and delinquent behavior. *J. Am. Med. Assoc.* 275:363–69

44. Dietrich KN, Ris MD, Succop PA, et al. 2001. Early exposure to lead and juvenile delinquency. *Neurotoxicol. Teratol.* 23:511–18

45. Needleman H, McFarland CE, Ness R, et al. 2002. Bone lead levels in adjudicated delinquency: a case-control study. *Neurotoxicol. Teratol.* 24:711–17

46. Stretesky PB, Lynch MJ. 2001. The relationship between lead exposure and homicide. *Pediatr. Adolesc. Med.* 155:579–82

47. Nevin R. 2000. How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. *Environ. Res.* 83:1–22

48. Silbergeld EK, Schwartz J, Mahaffey K. 1988. Lead and osteoporosis: mobilization of lead from bone in postmenopausal women. *Environ. Res.* 47:79–94

49. Muldoon SB, Cauley JA, Kuller LH, et al. 1996. Effects of blood lead levels on cognitive function of older women. *Neuroepidemiology* 15:62–72

50. Schwartz BS, Stewart WF, Bolla KI, et al. 2000. Past adult lead exposure is associated with longitudinal decline in cognitive function. *Neurology* 8:1144–50

51. Stewart WF, Schwartz BS, Simon D, et al. 2002. APOE genotype, past adult lead exposure, and neurobehavioral function. *Environ. Health Persp.* 110:501–5

52. Tavakili-Nezhad M, Barron AJ, Pitts DK. 2001. Postnatal inorganic lead exposure decreases the number of spontaniously acive midbrain dopamine neurons in the rat. *Neurotoxicology* 22:259–69

53. Adhikari N, Sinha N, Narayan R, et al. 2001. Lead induces cell death in testes of young rats. *J. Appl. Toxicol.* 21:275–77

54. Iavocoli I, Carelli G, Sgambato A, et al. 2001. Lead inhibits growth and induces apoptosis in normal rat fibroblasts. *Altern. Lab. Anim.* 29:461–69

55. Shabani A, Rabbani A. 2000. Lead nitrate induced apoptosis in alveolar macrophages from rat lung. *Toxicology* 149:109–14

56. He L, Poblenz AT, Medrano CJ, et al. 2000. Lead and calcium produce photoreceptor cell apoptosis by opening the mitochondria permeability pore. *J. Biol. Chem.* 275:12175–84

57. Fox DA, Campbell ML, Blocker YS. 1997. Functional alterations and apoptotic cell death in the retina following developmental or adult lead exposure . *Neurotoxicology* 18:645–64

58. Lustberg M, Silbergeld E. 2002. Blood lead levels and mortality. *Arch. Intern. Med.* 25:2443–49

59. Rogan WJ, Dietrich KN, Ware JH, et al. 2001. Treatment of Lead-Exposed Children Trial Group. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. *N. Engl. J. Med.* 344:1421–26

60. US Dep. Health Hum. Serv., Public Health Serv./Cent. Dis. Control. 1991. *Strategic plan for the elimination of childhood lead*

poisoning. Prepared for Risk Manag. Sub-comm. of Dep. Health Hum. Serv.

61. Grosse SD, Matte TD, Schwartz J, et al. 2002. Economic gains resulting from the reduction in children's exposure to lead in the United States. *Environ. Health Persp.* 110:563–70

62. Landrigan PJ, Schechter CB, Lipton JM, et al. 2002. Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and develop-mental disabilities. *Environ. Health Persp.* 110:721–28