LOW LEVEL LEAD EXPOSURE AND THE DEVELOPMENT OF CHILDREN

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INTRODUCTION

The clinical picture of childhood lead poisoning has changed dramatically over the past 20 years. Acute symptomatic lead poisoning, once a common problem, is now a rare event. Lead encephalopathy is even rarer. Most pediatric residents will not see a case of acute plumbism during their training; few will encounter the problem in their career. At the same time, epidemiologic studies from around the world of the effects of lead on children have demonstrated behavioral and cognitive deficits in the absence of symptoms, at levels of blood lead once considered harmless. Traditional treatments with chelating agents are ineffective at these levels of lead in blood. As a result the principal domain of lead toxicity has shifted from the clinic and hospital to the public health arena, where the effects of lead at clinically silent doses on child development remains a major issue.

Lead poisoning is a man-made disease. The metal's neurotoxic properties were recognized as least as far back as the first century AD, when Dioscerides, the author of *Materia Medica*, wrote that 'Lead makes the mind give way'. For centuries plumbism was thought to be exclusively a disease of workers and drinkers of adulterated wine. Even though the Romans were aware of lead's toxic properties, they used it to counteract the astringent flavor of tannic acid in grapes and thus sweeten wine. The decrease in fecundity and simultaneous rise in madness in upper class Romans has attracted speculation that the metal played a role in the downfall of the empire.

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Childhood lead poisoning was first reported in 1892 at the Brisbane Children's Hospital in Australia (Gibson, 1892). In 1914, the first American report of a poisoned child was published. For decades thereafter, acute childhood lead poisoning was believed to have only two outcomes: death or complete recovery without any residua. The first follow-up study of children who had recovered from acute poisoning was published in 1943, and reported that 19 of 20 recovered cases had severe school problems, behavior disorders and impaired cognition (Byers and Lord, 1943). This paper established the long-term consequences of acute intoxication, and speculated that undiagnosed lead exposure was among the prominent causes of school and behavior problems.

The removal of lead from gasoline in the United States, begun in the 1970s and completed by 1991, resulted in dramatic lowering of blood levels. The mean blood lead level in 1975 was 15.5 μg/dl. At the time this is being written, the mean blood lead level is 2 μg/dl, robust testimony to the benefits of sound public health policy.

Lead is taken into the body through the lungs and the gastrointestinal tract. Absorption of inorganic lead through the skin is negligible. Children absorb more lead from the gut (40-50%), while adults absorb 20 to 24%. Absorption of respired lead is a function of particle size and respiratory rate. Because children are more active, and have a higher respiratory rate, they tend to respire and absorb more airborne lead.

Symptoms may be observed at blood lead levels of 40 μg/dl, although some children with much higher blood levels may display no apparent signs. Because of this, a prudent rule that should be followed is that any child with anemia, behavioral change, hyperactivity, weight loss, abdominal pain or the symptoms listed above should have a blood lead test.

THE CHANGING PICTURE OF LEAD TOXICITY

Cognitive deficits in children with no visible signs of lead toxicity first were reported in the 1970s. Since then, over 30 studies of children, conducted around the world have demonstrated deficits in cognition as measured in IQ tests (Needleman and Gatsonis, 1990). As blood lead levels have declined, effects of lead on the CNS have been demonstrated at lesser doses. In the 1970s, when the mean blood lead level was 15 μg/dl, the lack of a true low lead referent group prevented detection of effects at the lowest concentrations. The general reduction of blood lead levels has now permitted contrasts with subjects bearing very low amounts of lead in blood and tissues. The application of more sensitive measures of outcome, more sensitive and precise analytical methods for measuring lead in body tissues, and better epidemiological and biostatistical techniques have combined to demonstrate effects of lead at lower and lower concentrations. Investigators can now compare children to referent groups with blood lead as low as 1 μg/dl. When forward studies of children from birth onward showed effects on IQ at blood lead levels between 10 and 25 μg/dl, and one study showed effects below 10 μg/dl (Bellinger *et al*, 1987), the Centers for Disease Control (CDC) reset the defined toxic threshold at 10 μg/dl. There were many hints that lesser levels were neurotoxic, and recently (Lanfear *et al*, 2000; Canfield *et al*, 2003) two studies have shown deficits in subjects with lead levels below 10. The slope of the inverse lead/IQ association is steeper at levels below 7 μg/dl, raising interesting speculations about the underlying mechanism. The evidence that there is no threshold for lead is becoming more persuasive as more sensitive studies are published. Unlike most metals, lead has no function in human metabolism, and interference with biochemical and physiological mechanisms has been demonstrated at micromolar concentrations. A recent study examining neurite growth in rodent brain cell cultures showed decrease in neurite length at lead concentrations of 0.2 μg/dl (0.01 μM) (Schneider *et al*, 2003).

Deficits in speech and language, attention, and classroom behavior have also been reported in relation to low level lead exposure (Fig 1). Early studies were cross-sectional in nature, but later, forward studies from birth onward confirmed the association between lead and deficit and supported the causal nature of the association. Follow-up of lead-exposed but asymptomatic subjects into young adulthood found that the high lead group had a 7-fold increase in high school graduation failure and a 6-fold increase in reading disabilities. This indicates that the effects of childhood lead exposure are permanent, and affect life success and adjustment (Fig 2).

Most studies of lead at low dose have concentrated on IQ. Behavioral dyscontrol is among the more important and largely ignored expressions of lead neurotoxicity. Parents of lead poisoned children have frequently reported behavioral changes after recovery, and complained that previously placid children became fidgety, irritable, oppositional and aggressive. The first fol-

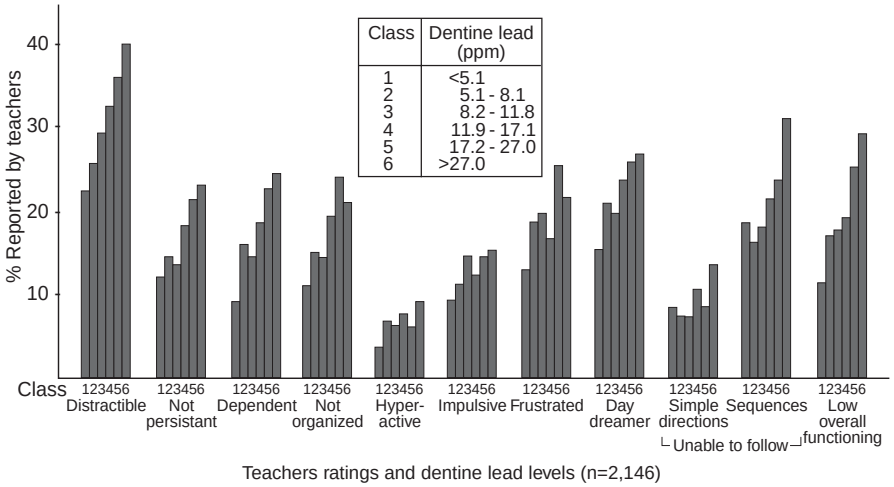

Fig 1–Teacher' ratings of classroom behavior in ralation to dentine lead levels. From: Needleman *et al* (1979).

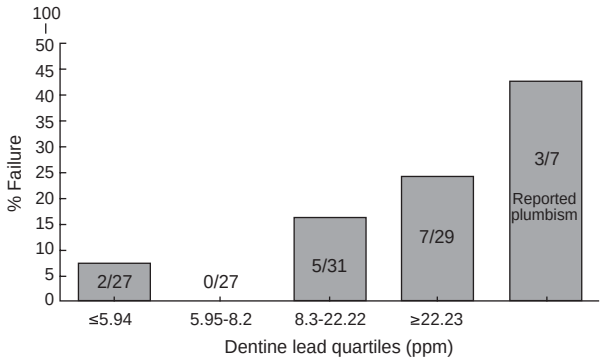

Fig 2–Failure to graduate from high school in relation to earlier dentine lead levels.

low-up study of lead poisoning, conducted in 1943 by Byers and Lord, was triggered by the observation that two children referred to his clinic for violent behavior had been patients treated earlier for lead poisoning.

This question of lead and antisocial behavior has only recently received attention. Four studies of children report associations between lead exposure and delinquent behavior, In Philadelphia children formerly enrolled in the Collaborative Perinatal study, the most influential predictor of arrest in adolescence was a prior history of lead poisoning. A cohort study of children with elevated bone lead levels measured by x-ray fluorescence found higher scores for aggression, attentional disorders and delinquent behavior (Needleman *et al,* 2002). Another study using self reports of delinquency found elevated scores to be associated with cumulative blood lead levels. A case-control study of arrested and adjudicated delinquents found that delinquents had significantly higher bone lead levels, and the odds ratio for elevated bone lead levels was 4 (Needleman *et al,* 1996). The population- attributable risk estimated for this sample ranged between 11% and 38%. These findings are supported by a number of ecological studies that report correlations between air lead concentrations or sales of leaded gasoline and crime rates after adjustment for potential confounders.

Lead exposure has been reported to be associated with attentional disturbances. A number of investigators have found associations of blood and dentine lead levels with scores on the Connors ADHD instrument, the Rutter Behavioral Inventory, and the Child Behavior Checklist, strongly supporting the reports of parents about adverse changes in their children's conduct after recovery. The essential public health task is to take lead out of the environment before it enters children's bodies. Earlier in this paper, it was said that lead poisoning is a man-made disease. Given then, the proper motivation, man should be able to extract this disorder from the textbooks of pediatrics and enter it into the histories of medicine.

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