

Perspective

Neurological and Behavioral Consequences of Childhood Lead Exposure

David C. Bellinger

Among environmental chemicals, lead's reputation as a "bad actor" is confirmed in study after study. Over the past 30 years, we have learned that its toxicities are expressed in many forms, and, unfortunately, at levels of exposure that are still prevalent in the general population. The United States Centers for Disease Control and Prevention's current screening guidelines for preventing lead poisoning in young children suggest that screening should be targeted at identifying those with a blood lead level of 10 µg/dl or more [1]. However, this level has no special biological significance and certainly should not be interpreted as "safe." Indeed, a "safe" level has yet to be found. Two new studies published in this issue of *PLoS Medicine*, both from the long-running Cincinnati Lead Study (CLS), extend our knowledge of lead's effects and their societal implications [2,3].

Increased Lead Exposure and Changes in Brain Structure

A wealth of experimental data show, unequivocally, that lead causes neurological dysfunction in animals [4]. But in the context of environmental regulation and litigation, it remains contentious whether the observed associations between lead exposure and neurological dysfunction in humans, particularly children, reflect a causal or a secondary (epiphenomenal) role for lead. Some continue to argue that the associations observed merely reflect residual confounding, that is, the adverse effects of other known risk factors with which lead exposure often co-occurs. Such confounding seems highly unlikely to account completely for the associations, given the wide range of circumstances and settings in which they have been found. Evidence that so-called "subclinical" exposure

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Linked Research Articles

This Perspective discusses the following new studies published in *PLoS Medicine*:

Cecil KM, Brubaker CJ, Adler CM, Dietrich KN, Altaye M, et al. (2008) Decreased brain volume in adults with childhood lead exposure. *PLoS Med* 5(5): e112. doi:10.1371/journal.pmed.0050112

Using magnetic resonance imaging to assess brain volumes, Kim Cecil and colleagues find that inner-city children with higher blood lead levels showed regions of decreased gray matter as adults.

Wright JP, Dietrich KN, Ris MD, Hornung RW, Wessel SD, et al. (2008) Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. *PLoS Med* 5(5): e101. doi:10.1371/journal.pmed.0050101

Kim Dietrich and colleagues find an association between developmental exposure to lead and adult criminal behavior.

to lead not only alters behavior but brain structure as well would make the argument of confounding even less tenable. To date, clear neuropathological changes, including edema, herniation, and atrophy, have been reported in clinically lead-intoxicated children, and white matter degeneration and volume reductions in regions of cortical gray matter have been found in adult workers exposed to lead [5].

The new study by Kim Cecil and colleagues is the first population-based study of childhood lead exposure to include morphometric brain imaging [2]. The study's participants, now 19–24 years old, were recruited from areas of inner-city Cincinnati. Detailed blood lead histories were assembled prospectively, beginning before birth. Dose-dependent decreases were found in the volumes of gray matter in the ventrolateral prefrontal cortex, the anterior cingulate cortex, the postcentral gyri, the inferior parietal

lobule, and the cerebellum. Reduced volumes in the prefrontal cortical areas were particularly striking in males.

Being observational in design, this study cannot settle the issue of causality. One could still postulate that the relationships observed reflect residual confounding, but this seems unlikely in view of the socioeconomic homogeneity of the participants and the dose-dependence of the relationships. Cecil and colleagues attempted to discern the functional significance of the volume changes using data previously collected on the neuropsychological status of the participants. They were unable to identify clear structure–function correlates except in the case of motor skills. This is not entirely unexpected, however, given that complex neuropsychological functions almost certainly depend more on the integrity of distributed circuits than on the sizes of discrete brain regions. Correlations between volumes and neuropsychological test scores have been found in adults with occupational lead exposure [6]. Perhaps the absence of such relationships in the CLS reflects differences in the effects that lead has on a developing brain versus an adult brain.

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Abbreviations: CLS, Cincinnati Lead Study

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Nevertheless, the associations observed by Cecil and colleagues provide a clear warning sign that early lead exposure disrupts brain development in ways that are likely to be permanent, and that are robust enough to affect an index as gross as volume. It is important to note that in a previous study, using functional MRI on members of the CLS cohort, these investigators also reported lead effects on activation patterns during a verb generation task [7].

Increased Lead Exposure and Criminal Activity

The second new study [3], by Kim Dietrich and colleagues, adds to the literature indicating that lead produces psychosocial as well as cognitive morbidity. The existing studies implicating lead as a risk factor for antisocial behavior are provocative but limited by a variety of methodological factors, including use of an ecological design, indirect measures of lead exposure history, or parent- or self-reported outcome data, rendering them subject to a variety of alternative interpretations [8–15].

Exploiting the rich historical dataset available for the 19 to 24-year-olds in the CLS, Dietrich and colleagues evaluated the association between early blood lead history and arrests, since the age of 18 years, for violent offenses, drug offenses, theft or fraud, obstruction of justice, serious motor vehicle offenses, and disorderly conduct. The covariate-adjusted rate ratios for number of arrests associated with each 5 µg/dl increment were modest, but statistically significant, for prenatal childhood blood lead and blood lead at six years of age. The adjusted rate ratios for arrests for violent crimes were significant, and again modest, for average childhood blood lead and blood lead at age six. In other studies, increased lead exposure has also been linked to attention deficit hyperactivity disorder [16], teen pregnancy [17], and, in animals, to certain forms of substance abuse [18]. The underlying common pathway for all of these associations might be lead's adverse effects on executive functioning [19–21], resulting in poor impulse control.

The use of a county-wide database as the source of information on arrests and the prospective collection of data

on both blood lead levels and potential confounders prior to the occurrence of the outcomes of interest reduced the likelihood of information biases and effectively eliminated a role for selection bias as an explanation for these findings. The frequency of arrests in this group is startling, even among the participants with lower levels of childhood lead exposure. More than half (55%) had been arrested at least once after the age of 18 years, with means of 5.2 arrests for males and 1.1 arrests for females. Thus, although early lead exposure might increase a child's risk of being arrested after the age of 18 years, it is clearly only one of many factors. Even if the contribution of lead to arrest risk is small, however, it has a special status in that, in contrast to most other known risk factors for criminality, we know full well how to prevent it.

Public Health Implications

The studies by Cecil and colleagues and Dietrich and colleagues expand the range of outcomes linked to increased lead exposure in the “subclinical” range and help to place the problem in a larger public health context. Lead's detrimental effect on IQ, the outcome most often studied, is clearly only the “tip of the iceberg.”

The good news is that the blood lead levels at which reduced brain volumes and increased risk of arrest were observed are much less common among US children today than they were in the early 1980s, when the participants in the CLS were young children. The mean childhood blood lead level of CLS participants was 13 µg/dl, and ranged from 4 to 37 µg/dl. Currently, the median blood lead level among one to five-year-old US children is 1.5 µg/dl, and 5% have a level greater than 5.8 µg/dl [22]. In Ohio, where the CLS study is based, the percentage of children less than six years of age who had a blood lead level of more than 10 µg/dl was 16.55% in 1997, but only 2.30% in 2006 [23]. This is an impressive public health victory, but in light of clear evidence that a broad array of adverse effects occur at blood lead levels that are well below 10 µg/dl, it is a national disgrace that so many children continue to be exposed at levels known to be neurotoxic.

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