The Epidemiologic Conquest of Childhood Lead Poisoning

A Pyrrhic Victory

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Pyrrhic victory - A victory that is offset by staggering losses.

In 281, Pyrrhus, a Greek general, defeated the Romans in two battles, but suffered bitterly heavy losses.

The devastation led to his famous statement, "One more such victory and I am lost".
Evolution of Epidemiologic Studies

• First Generation (Case Series or Cross-Sectional)
• Second Generation (Prospective Cohorts)
• Third Generation (Representative Samples and RCTs)

“Prevention is easy. Paint containing lead should never be employed ... where children, especially young children, are accustomed to play.”

A.J. Turner, 1908
## Countries Banning Lead-based Paints

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>1909</td>
</tr>
<tr>
<td>Belgium</td>
<td>1909</td>
</tr>
<tr>
<td>Austria</td>
<td>1909</td>
</tr>
<tr>
<td>Tunisia</td>
<td>1922</td>
</tr>
<tr>
<td>Greece</td>
<td>1922</td>
</tr>
<tr>
<td>Czechoslovakia</td>
<td>1924</td>
</tr>
<tr>
<td>Great Britain</td>
<td>1926</td>
</tr>
<tr>
<td>Sweden</td>
<td>1926</td>
</tr>
<tr>
<td>Belgium</td>
<td>1926</td>
</tr>
<tr>
<td>Poland</td>
<td>1927</td>
</tr>
<tr>
<td>Spain</td>
<td>1931</td>
</tr>
<tr>
<td>Yugoslavia</td>
<td>1931</td>
</tr>
<tr>
<td>Cuba</td>
<td>1934</td>
</tr>
</tbody>
</table>

## Lead-associated Behavioral and Emotional Problems in Children

Lead-associated IQ deficit linked with a blood lead increase from $10\mu g/dL$ to $20\mu g/dL$

<table>
<thead>
<tr>
<th>Study</th>
<th>Estimated Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawk (1986)</td>
<td>2.6</td>
</tr>
<tr>
<td>Hatzakis (1987)</td>
<td>2.7</td>
</tr>
<tr>
<td>Fulton (1987)</td>
<td>2.6</td>
</tr>
<tr>
<td>Yule (1981)</td>
<td>5.6</td>
</tr>
<tr>
<td>Bellinger (1992)</td>
<td>5.8</td>
</tr>
<tr>
<td>Dietrich (1992)</td>
<td>1.3</td>
</tr>
<tr>
<td>Baghurst (1992)</td>
<td>3.3</td>
</tr>
<tr>
<td>Silva (1988)</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Percent of U.S. Preschool Children Exceeding Selected Blood Lead Levels, NHANES II - III


Low-Level Lead Toxicity
Assessment of IQ and Children’s Blood Lead Levels at 60 Months of Age

Relationship of Lead-IQ Scores among Children for Seven Prospective Lead-Exposed Cohorts

Relationship of Concurrent Blood Lead Concentration with Children’s Intellectual Function

Estimated Lead-associated IQ Deficits by Concurrent Blood Lead Concentration

<table>
<thead>
<tr>
<th>Range of Blood Lead</th>
<th>Estimated IQ Deficit (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 to 30 μg/dL</td>
<td>9.2 (5.7, 13.1)</td>
</tr>
<tr>
<td>&lt;1 to 10 μg/dL</td>
<td>6.2 (3.8, 8.6)</td>
</tr>
<tr>
<td>10 to 20 μg/dL</td>
<td>1.9 (1.2, 2.6)</td>
</tr>
<tr>
<td>20 to 30 μg/dL</td>
<td>1.1 (0.7, 1.5)</td>
</tr>
</tbody>
</table>
Research Supporting Adverse Effects at Blood Lead Concentrations <10 µg/dL


Health Outcomes and Measures of the Environment Study

Enroll Women < 16 weeks gestation (n= 400)

Conduct prenatal surveys, collect maternal urine and blood samples for assessing fetal exposure to toxicants

Collection of Biomarkers and exposure assessment in early childhood

Randomization

Injury Control Group (n = 200)
12 - month visit
24 - month visit
36 - month visit

Lead Hazard Group (n = 200)
12 - month visit
24 - month visit
36 - month visit

Meconium Collection

12, 24 and 36-Month Outcomes
Exposures and Biomarkers for Pesticides, Lead and Cotinine
Behavior, Cognition and Executive Function
Hearing and Growth
Evolution of Exposure Measurement

Figure 1. Source to exposure to health effects pathway.

Dust Lead Loading vs Dust Lead Concentration

Contribution of Lead-Contaminated Floor Dust to Children’s Blood Lead

## Biomarkers

Comparison of Biomarkers for Prenatal Lead Exposure

<table>
<thead>
<tr>
<th>Sample</th>
<th>Blood</th>
<th>Plasma</th>
<th>Bone</th>
<th>Meconium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validated</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Invasive</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ease of Collection</td>
<td>+/-</td>
<td>+/-</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Detection Limit</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Cumulative Measure</td>
<td>+/-</td>
<td>+/-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Window of Susceptibility</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cost</td>
<td>$</td>
<td>$$</td>
<td>$$$</td>
<td>$</td>
</tr>
</tbody>
</table>

The table compares different biomarkers for prenatal lead exposure, including their validation status, invasiveness, ease of collection, detection limit, cumulative measure, window of susceptibility, and cost. Each biomarker is evaluated across blood, plasma, bone, and meconium samples.


Plasma Lead Levels by MDI Scores at 24 Months of Age

Figure 2. Plasma lead levels in the first trimester of pregnancy versus MDI scores at 24 months of age. CI, confidence interval. Curve indicates the best-fit model for the association between plasma lead levels and MDI scores, adjusting for plasma lead levels in the second and third trimesters, mother's age and IQ, child's blood lead levels at 24 months of age, sex and height-for-age Z-score. Vertical line marks average plasma lead concentration when whole blood lead equals 100 μg/L.


Mean Adjusted Full-Scale IQ Scores by Quartiles for Tibial Bone Lead and Average Lifetime Blood Lead Levels

Mean Adjusted Full-Scale IQ Scores by Quartiles for Tibial Bone Lead and Average Lifetime Blood Lead Levels – Combined Analysis


Linkage of Lead Exposure with Lead-associated Disease and Disability
Traditional Epidemiology

Exposure → Black Box → Clinical Disease

Linkage of Biomarkers of Exposure, Effect and Susceptibility with Disease or Disability

Biomarker of Exposure

- Internal Dose
- Biologically Effective Dose

Biomarker of Effects

- Early Biological Effect
- Altered Structure/Function

Biomarker of Susceptibility

Exposure → Clinical Disease

Association of Blood Lead Levels and Delinquency in Adolescents


Number of Arrests by Childhood Lead Exposure: The Cincinnati Lead Study

* Accounting for birthweight, age, prenatal tobacco exposure, maternal age at delivery, maternal IQ, maternal arrest history, HOME Inventory.
Grey Matter Loss by Childhood Lead Exposure (n=157)

Adjusted for child’s age, birth weight, sex, gestational age, prenatal tobacco, prenatal alcohol, prenatal marijuana, total intracranial volume, SES and HOME Inventory did not alter results (Cecil K, Dietrich KN, et al. in preparation.)

Grey Matter Loss Associated with Childhood Lead Exposure by Sex

Males (n=83)  Females (n=74)

Adjusted for child’s age, birth weight, sex, gestational age, prenatal tobacco, prenatal alcohol, prenatal marijuana, total intracranial volume, SES and HOME Inventory did not alter results (Cecil K, Dietrich KN, et al. in preparation.)
Linking Putative Biomarkers of Lead Exposure and Effect with Criminal Behavior

Conclusions

- Expand research and validation for environmental exposure and biomarkers of internal dose
- RFA to target priorities vs reliance on investigator-initiated proposals (e.g., Children's Centers)
- Lengthen funding cycle for cohort studies
- Ensure National Children's Study is funded
- Expand NHANES to include exposure assessment and relevant measures of disease and disability
- Require pre-market DNT testing to ensure products are safe before dissemination in the environment
"All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."

Austin Bradford Hill