Pediatric Exposures to Lead, Arsenic, Cadmium, and Methyl Mercury

J. Julian Chisolm Jr.

John F. Kennedy Institute (Baltimore), Baltimore, Maryland 21205

Lead, arsenic, cadmium, and methyl mercury are nonessential and potentially highly toxic metals. They may be found in minute and variable but measurable amounts in food, drinking water, and/or ambient air. Because each of the metals has been identified as a serious environmental contaminant in various parts of the world, much research effort has been devoted to them, especially during the past two decades. This review focuses on the pediatric aspects of overexposure to lead, arsenic, cadmium, and methyl mercury in food, drinking water, ambient air, soil, and dust.

LEAD

Lead (Pb) has been mined, smelted, and refined virtually throughout recorded history. Indeed, it must have been used for about 6,000 years as evidenced by the fact that there is a lead figure in the British Museum which was made before 3800 BC. Phoenicians mined it in Spain about 2000 BC. Lead's malleability, ductility, and resistance to corrosion facilitates its wide variety of uses. Cerussite (PbCO$_3$) and red lead (Pb$_3$O$_4$) have been used as pigments for at least 2,000 years (1). Determinations of the concentrations of Pb in bone and teeth from ancient skeletons and modern autopsy material show that there has been a very substantial increase in human Pb exposure and body burden in modern industrialized countries. For example, Nubian bones dated from 3300 to 2900 BC and contemporary Danish autopsy data show lead levels of 0.6 and 5.5 μg Pb/g dry weight, respectively (2). Sharp contrasts in blood Pb concentrations (PbB; measured as micrograms of Pb per deciliter of whole blood) are found even today between remote and industrialized populations. For example, Piomelli et al. (3) reported in 1982 an average PbB of 3.4 μg/dl in Nepal. By contrast, NHANES II data show an average PbB in the United States of 15.8 μg/dl (4). These data reflect sharp differences in exposure. Core samples from the Greenland ice cap indicate a sharp increase in general atmospheric dissemination of Pb dating from the start of the industrial revolution (ca. 1750 AD) with a further sharp acceleration dating from 1950 AD (5). The increase during the past three decades appears clearly associated with the coincident vast increase in the use of Pb additives in motor fuels. These and other studies
have led during the past 15 years to a great increase in Pb research as well as steps to regulate the two major nonrecycled uses of Pb which disseminate it into the environment, i.e., Pb additives in petrol and lead-based paints. Extensive review of the many aspects of the environmental Pb problem is beyond the scope of this presentation and may be found elsewhere (1,6-12). This presentation concentrates on recent epidemiological data and the relative contributions from diet, drinking water, ambient air, and nondietary environmental sources to total body Pb burden in children.

Prevalence

The second National Health and Nutrition Examination Survey (NHANES II) conducted between 1976 and 1980 has provided the most comprehensive epidemiological assessment of Pb absorption in the general population ever made in the United States (4). Table 1 shows the percentages of children aged 6 months to 5 years with venous PbB $\geq 30 \mu g/dl$, according to race, sex, and family income. A PbB of $\leq 30 \mu g$ is the currently proposed upper limit of acceptable concentration (10,12) and is the action level proposed in the United States Centers for Disease Control (CDC) guidelines for the prevention of Pb poisoning in children (13) (which are soon to be revised). Data in Table 1 indicate that an estimated 4.0% of children, or approximately 675,000 children, aged 6 months to 5 years have blood Pb concentrations $\geq 30 \mu g/dl$. Owing to the higher prevalence among black children, an estimated 325,000 of these 675,000 young children are black. Prevalence is higher in both black and white children whose families fall in the lowest income range. Table 2 shows the distribution of PbB levels by race and sex in children aged 6 months to 5 years. The mean PbB in white children is approximately 15 $\mu g$, but it is approximately 21 $\mu g$ in black children. Only in black children is there a substantial proportion with PbB $\geq 40 \mu g$, i.e., an estimated 53,000 children.

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>Children (%)</th>
<th>All</th>
<th>White</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both sexes</td>
<td>4.0</td>
<td>2.0</td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>4.4</td>
<td>2.1</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td>Girls</td>
<td>3.5</td>
<td>1.8</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>Annual family income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under $6,000</td>
<td>10.9</td>
<td>5.9</td>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td>$6,000-14,999</td>
<td>4.2</td>
<td>2.2</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>$15,000 or more</td>
<td>1.2</td>
<td>0.7</td>
<td>2.8</td>
<td></td>
</tr>
</tbody>
</table>

*From National Center for Health Statistics, Advance Data, No. 79, May 12, 1982.

*Includes data for races not shown separately.
TABLE 2. Distribution of blood lead levels by race and sex in children aged 6 months to 5 years: United States, 1976–1980*

<table>
<thead>
<tr>
<th>Population</th>
<th>Estimated population in thousands</th>
<th>Percent distribution at blood lead levels of &lt;10 to 69 μg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>&lt;10</td>
</tr>
<tr>
<td>All races</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>8,621</td>
<td>16.3</td>
</tr>
<tr>
<td>Girls</td>
<td>8,241</td>
<td>15.8</td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>6,910</td>
<td>15.2</td>
</tr>
<tr>
<td>Girls</td>
<td>6,732</td>
<td>14.7</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>1,307</td>
<td>20.7</td>
</tr>
<tr>
<td>Girls</td>
<td>1,277</td>
<td>21.0</td>
</tr>
</tbody>
</table>

*aAdapted from National Center for Health Statistics. Advance Data, No. 79, May 12, 1982.
*bIncludes data for races not shown separately.
*cAt the midpoint of the survey, March 1, 1978.
*dNumbers may not add to totals due to rounding.

TABLE 3. Percent of children aged 6 months to 5 years with PbB levels of 30.0 μg/dl or more: United States, 1976–1980*

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>All</th>
<th>White</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of urbanization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban (1,000,000 persons or more)</td>
<td>7.2</td>
<td>4.0</td>
<td>15.2</td>
</tr>
<tr>
<td>Central city</td>
<td>11.5</td>
<td>4.5</td>
<td>18.6</td>
</tr>
<tr>
<td>Noncentral city</td>
<td>3.7</td>
<td>3.8</td>
<td>3.3c</td>
</tr>
<tr>
<td>Urban (≤1,000,000 persons)</td>
<td>3.5</td>
<td>1.6</td>
<td>10.2</td>
</tr>
<tr>
<td>Rural</td>
<td>2.1</td>
<td>1.2</td>
<td>10.3c</td>
</tr>
</tbody>
</table>

*aFrom National Center for Health Statistics. Advance Data, No. 79, May 12, 1982.
*bIncludes data for races not shown separately.
*cNumber of sample persons in cell is less than 50.

The NHANES II study was designed as a descriptive cross-sectional epidemiological study. Further analyses of these data indicate that average PbB may have decreased from 15.8 μg to 9.6 μg Pb/dl whole blood between 1978 and 1980 (14). Simultaneously, there was a substantial decrease in the usage of Pb additives in gasoline in the United States. In the absence of any evidence of sharp reduction in other exposures to Pb, the data are compatible with the hypothesis that the decrease in PbB in the United States is most likely related to the concurrent decrease in the use of Pb additives in automotive fuels. This trend, if confirmed in epidemiological studies designed to measure temporal trends, suggests that old deteriorated, Pb-painted housing is likely to remain as the primary environmental source of Pb for young children in the United States. Table 3 using NHANES II data, shows the
striking influence of residence on PbB in children. Increased Pb absorption is highest among low income urban black children (18.6%) and lowest among rural white children (1.2%). In the United Kingdom in 1979 selected screening surveys of 39 groups of children thought to be at high risk for increased Pb absorption were conducted (15). Increased Pb absorption, defined as PbB > 35 μg, was found only in three groups: in Glasgow, Scotland where the high Pb content of household drinking water has been a major source of overexposure; in one of several groups of children of Pb workers; and in one group of children living near a Pb-processing factory.

**Diet, Drinking Water, Air**

Assimilation of Pb from normal diet, drinking water, and ambient air has been estimated in a number of ways, including analyses of individual foods, composite diets, water and air, market-basket surveys, 24-hr dietary recall in large population samples, and metabolic balance studies in small groups. Not surprisingly, there are abundant data in adults but rather limited data in infants and children. What follows is based on studies of infants and children without undue exposure to Pb from nondietary sources. Among diet, water, and air, diet provides by far the largest source of Pb. The WHO/FAO recommended daily dietary intake of Pb for adults is up to 490 μg Pb/day, or 7 μg/kg/day (16). There is no comparable standard for infants and children. It is of interest in regard to the adult standard of 7 μg Pb/kg/day that Ziegler et al. (17) have found in metabolic balance studies in infants up to 24 months of age that a daily intake in excess of 5 μg Pb/kg/day is associated with positive lead balance. The work of Ziegler et al. (17) and others has demonstrated that infants and young children absorb approximately 50% of dietary Pb, of which about one-half is retained. By contrast, balance studies in adults show that 5 to 10% of dietary Pb is absorbed, and that retention is quite small (18). Autopsy data in English children show that the concentration of Pb in both bone and soft tissues increases during the first 12 months and then stays constant throughout the remainder of the first two decades of life, even though total body Pb burden increases in proportion to growth (19).

In 1975 the Canadian FDA conducted a national survey to determine trace elements, including Pb, in Canadian foods. They used 24-hr dietary recall (11). These data were used to estimate dietary Pb intakes in infants (Table 4) and young children (Table 5). These data show mean intakes of approximately 5 μg Pb/kg/day and 90th percentile intakes in excess of 7 μg Pb/kg/day during the first year of life. Similar data based on market-basket surveys were reported by the U.S. FDA. There is a substantial difference between the Pb content of raw agricultural products (Pb rarely > 0.1 ppm) and that of processed foods in which the concentration of Pb may be increased by a factor of 10 or more. Foods may become contaminated during handling, transportation, preparation for packaging, preparation in the kitchen, and storage.

The single most important contributor is the Pb leached into canned foods, particularly liquids, from the Pb-soldered seam of three-piece cans. In infants in
TABLE 4. Dietary lead intake of infants (estimated from Canadian data)*

<table>
<thead>
<tr>
<th>Age group (months)</th>
<th>No. in sample</th>
<th>Mean intake ± SE</th>
<th>90th Percentile intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>μg/day</td>
<td>μg/kg/day</td>
</tr>
<tr>
<td>&lt;1</td>
<td>6</td>
<td>15.5 ± 10.8</td>
<td>3.9 ± 2.6</td>
</tr>
<tr>
<td>1-2</td>
<td>39</td>
<td>33.4 ± 7.1</td>
<td>5.3 ± 1.1</td>
</tr>
<tr>
<td>3-5</td>
<td>66</td>
<td>34.5 ± 3.4</td>
<td>4.7 ± 0.5</td>
</tr>
<tr>
<td>6-8</td>
<td>75</td>
<td>40.3 ± 5.0</td>
<td>4.8 ± 0.6</td>
</tr>
<tr>
<td>9-11</td>
<td>71</td>
<td>51.1 ± 4.7</td>
<td>5.0 ± 0.5</td>
</tr>
</tbody>
</table>

*From Nutrition Foundation (11).
Age ranges are inclusive of upper limits cited.
°SE, standard error.

TABLE 5. Dietary lead intake of children (estimated from Canadian data)*

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>No. in sample</th>
<th>Mean intake ± SE</th>
<th>90th Percentile intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>μg/day</td>
<td>μg/kg/day</td>
</tr>
<tr>
<td>1</td>
<td>257</td>
<td>61.4 ± 6.5</td>
<td>5.4 ± 0.5</td>
</tr>
<tr>
<td>2</td>
<td>272</td>
<td>61.2 ± 5.5</td>
<td>4.5 ± 0.4</td>
</tr>
<tr>
<td>3</td>
<td>264</td>
<td>64.1 ± 5.6</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>4</td>
<td>280</td>
<td>73.4 ± 6.4</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>5</td>
<td>2,086</td>
<td>83.2 ± 2.8</td>
<td>3.1 ± 0.1</td>
</tr>
</tbody>
</table>

*From Nutrition Foundation (11).
Age ranges are inclusive of upper limits cited.
°SE, standard error.

In the United States it has been estimated that this source may contribute anywhere from 13 to 40% of dietary Pb intake depending on the proportion of canned foods in the diet. Of particular importance is the leaching of Pb by acidic foods and beverages. The U.S. FDA has undertaken an active program to reduce dietary Pb. It has been estimated that mean daily Pb intake for the period 1973 to 1978 was 15 μg Pb/day for infants up to 5 months of age, 59 μg Pb/day for children 6 to 23 months, and 82 μg Pb/day for children 2 to 5 years of age (20). According to the U.S. FDA there had been a 47% reduction in Pb consumption by 1980 in infants less than 5 months of age and 7% reduction for the 6- to 23-month-old group. Most of this reduction was due to discontinuation of the use of Pb-soldered cans for infant formula. Meanwhile, a switchover from the use of Pb-soldered cans by the food canning industry to the use of cans free of Pb solder is in progress. It is hoped that they will be phased down to a minimum within the next 2 years.

The importance of Pb solder in increasing dietary Pb and PbB in infants is graphically illustrated by the studies of Ryu et al. (21). They performed metabolic balance studies on 4 breast-fed infants and 25 formula-fed infants 8 to 196 days of age. After 112 days the formula-fed infants were separated into two groups. One received milk in cardboard cartons, and the other received canned liquid formula
or heat-treated liquid milk in cans. Average daily intake of Pb in infants receiving milk from cans was 61 \( \mu g \) Pb/day and 16 \( \mu g \) Pb/day in those receiving milk in cartons. PbB in the low-Pb group was 7.2 \( \mu g/dl \), and it was 14.4 \( \mu g/dl \) after 196 days in infants receiving canned formula or heat-treated milk (Table 6). When infant formula is distributed in powder form, contamination with Pb does not present the problem that it does when formula is distributed in liquid form in Pb-soldered cans.

The concentration of Pb in human breast milk obtained from white middle-class donors with "normal" Pb exposure is quite low (mean 26 \( \mu g/liter \); range 10 to 59 \( \mu g/liter \)) (22). No data are available for lactating women with excessive exposure to Pb. In Glasgow, Scotland, where drinking water Pb may substantially exceed the WHO standard (100 \( \mu g \) Pb/liter), it has been shown that dietary Pb intake is much lower in wholly or partially breast-fed infants than in formula-fed infants for whom formula and other foods were prepared with tap water (23).

The U.S. Public Health Service (USPHS) primary drinking water standard for Pb is 50 \( \mu g \) Pb/liter and the WHO standard is 100 \( \mu g \) Pb/liter. It has been recommended that the USPHS drinking water standard be lowered, perhaps, to 25 \( \mu g \) Pb/liter (8). In the United States extensive studies during the 1970s indicated that the median concentration of Pb in drinking water is 10 \( \mu g \) Pb/liter, which in a child would provide a daily intake of \( \leq 4 \mu g \) Pb. It has long been known that soft acidic waters (pH<6.5) are plumbosolvent and leach Pb when conveyed in Pb pipes, which are found in many old distribution systems. With the exception of a few areas in the United States, e.g., Boston and Seattle, drinking water does not present a public health problem. Where the drinking water supply is known to be acidic, the problem can usually be resolved by adding lime at the water treatment plant in amounts sufficient to raise the pH above 6.5. By contrast, the great plumbosolvency of ground waters in Scotland and Northern England has presented a serious problem. Sherlock et al. (24) studied dietary and drinking water Pb exposures in mothers and infants living in Ayr, Scotland. Among the study popu-

<table>
<thead>
<tr>
<th>Age (days)</th>
<th>PbB of combined group (( \mu g/dl ))</th>
<th>Average Pb intake of combined group (( \mu g/day ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>8.9</td>
<td>17</td>
</tr>
<tr>
<td>56</td>
<td>5.1</td>
<td>17</td>
</tr>
<tr>
<td>112</td>
<td>6.1</td>
<td>17</td>
</tr>
<tr>
<td>Low Pb(^b)</td>
<td>6.2</td>
<td>16</td>
</tr>
<tr>
<td>High Pb(^c)</td>
<td>9.3</td>
<td>16</td>
</tr>
<tr>
<td>Low Pb</td>
<td>7.0</td>
<td>16</td>
</tr>
<tr>
<td>High Pb</td>
<td>7.2</td>
<td>16</td>
</tr>
</tbody>
</table>

\(^a\)Adapted from Ryu et al. (21).

\(^b\)Low Pb, liquid milk in cardboard cartons.

\(^c\)High Pb, liquid milk in cans (Pb-soldered seams).
lation of 114 women, 82 were exposed to a water Pb in excess of 100 μg Pb/liter, including 16 whose water supply had a Pb concentration greater than 1,000 μg Pb/liter. They concluded that water Pb in Ayr contributed more to total Pb intake than did dietary Pb. Among the infants, all had PbB > 20 μg/dl and 36% had PbB > 35 μg/dl.

Total atmospheric Pb emissions for the United States during 1981 have been estimated as 40,739 tons/year (25). Of this, 35,000 tons/year, or 85.9%, is due to combustion of leaded gasoline. The remainder is from a variety of sources including but not limited to waste oil combustion (6.2%), coal combustion (2.3%), secondary Pb smelting (1.3%), and primary Pb smelting (2.3%). The total for the United States does not include emissions from the burning of Pb-painted surfaces, welding of Pb-painted steel structures, or the weathering of painted surfaces. Nriagu (26) estimated annual global Pb emissions in 1979 at 449,170 tons/year, of which 273,000 tons/year was from the combustion of leaded gasoline. The use of leaded gasoline has decreased by more than 80% over the past decade in the United States. Coincident with this decrease has been a substantial reduction in ambient air Pb levels from 2 to 3 μg Pb/m³ of air to recent values. Now even in urban areas the vast preponderance of air-monitoring stations report values of approximately 0.5 μg Pb/m³ of air.

In summary, there is now a substantial body of data which indicate that human exposures to Pb in diet, drinking water, and ambient air have decreased substantially during the past decade. Further reductions in dietary Pb and ambient air are to be expected in relation to a continued phase-down in the use of Pb solder in food cans as well as Pb additives in gasoline. A variety of data indicate that the contribution to PbB from these sources would provide a mean PbB of about 10 μg/dl of whole blood in the general population. This is in close agreement with the NHANES II data, which indicate that PbB in the general U.S. population had decreased in 1980 to 9.6 μg/dl. Of these various sources, approximately 80% is attributable to food Pb at the present time (11). At a PbB level of 10 μg/dl, no adverse health affects are attributable to Pb. There are data which show statistically significant relationships between PbB and in vitro ALAD activity in peripheral erythrocytes, erythrocyte 5-pyrimidine nucleotidase activity, and serum levels of 1,25-dihydroxyvitamin D as PbB rises above approximately 10 to 15 μg/dl. The data of Ryu et al. (21) suggested that the only dietary situation likely to be associated with PbB > 10 μg/dl is to be found in infants receiving liquid infant formula or heat-treated milk from Pb-soldered cans.

Foods and beverages can be seriously contaminated with Pb in the home (27). Serious Pb poisoning, including fatal cases, have been traced to the contamination of food through preparation and/or storage in improperly Pb-glazed ceramic ware. Likewise, cases have been traced to the use of electric kettles, in which the heating element in contact with the water is soldered with Pb where it enters the kettle. Storage or cooking of foods in opened old Pb-soldered food cans may also increase the concentration of Pb in the contained food. In general, acidic substances such
as fruits, fruit juices, cola drinks, alcoholic beverages, and tomatoes cause much greater leaching of Pb than neutral or alkaline foodstuffs.

Environmental Sources

There are two major nonrecycled uses of Pb. Several million tons of Pb have been disseminated widely as inorganic lead oxide and lead sulfate through automotive exhausts for the past 30 to 40 years. This use of Pb has been sharply and substantially reduced particularly during the past 5 years. Lead paint pigments, particularly white lead (basic lead carbonate), have been used in residential paints in some of the industrialized countries for the past 300 years (1). In the United States the use of Pb-pigment paints peaked in 1935 at an estimated 80,000 tons/annum, slowly declined over the next 30 years, and rapidly decreased thereafter, so that in 1973 the estimated usage was 3,000 tons of white lead per annum (28). The use of Pb pigments and Pb additives in residential paints was finally banned under the Consumer Product Safety Act by the U.S. Consumer Products Safety Commission in September 1977 (29). This applies to the sale of new paints but not to old paints already applied in the past to old housing still in use. It is therefore of interest to look at the age and condition of the existing U.S. housing stock. As of 1978 (Table 7) there were 27 million occupied dwelling units built prior to 1940 (30). Studies have shown that 98% of such old houses would be found to have Pb paint in areas accessible to children if every surface was sampled (31). Furthermore, the CDC reported nationally that Pb paint hazards were identified for 90% of 14,481 children under pediatric follow-up for increased Pb absorption in 1980 (32). The percentage of rental units in 1978 (Table 7) with peeling paint, i.e., 9%, is of particular interest, as it is strongly suspected that the vast majority of cases of increased Pb absorption and clinical Pb poisoning occur in children who live in poorly maintained rental property (30). Table 8 shows the relationship between PbB in children and the type of housing in which they reside in Baltimore. Lead-based paints have not been used in public housing in Baltimore since the inception of the public housing program in 1938, and today Pb is still not found in such housing. In the “Pb-free” public housing, the mean PbB in a group of 1-year-old black children was 16.8 μg/dl, close to the national average for white children in 1978. On the other hand, 78% of 155 black children in an old housing area in Baltimore showed increased Pb absorption as defined by PbB ≥ 30 μg/dl. A study

<table>
<thead>
<tr>
<th>No. of units occupied in 1978</th>
<th>Built before 1940: 27,000,000</th>
<th>Built 1940–1960: 22,000,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of rental units in 1978 with peeling paint (U.S. Census 1979)</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

*From Lin-Fu (30).
### Table 8. Childhood screening data, Baltimore, 1978*

<table>
<thead>
<tr>
<th>Housing</th>
<th>No. tested</th>
<th>Mean</th>
<th>% &gt; 30</th>
<th>% &gt; 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public (&quot;lead-free&quot;)</td>
<td>447</td>
<td>16.5 ± 5.3</td>
<td>0.67</td>
<td>0</td>
</tr>
<tr>
<td>Old</td>
<td>155</td>
<td>38</td>
<td>78</td>
<td>18.7</td>
</tr>
</tbody>
</table>

*Adapted from Chisolm, 1975 and 1978 (unpublished data).

---

**FIG. 1.** Serial changes in geometric mean PbB in infants from birth to 18 months of age in Cincinnati according to type and condition of their dwelling; (●) public housing; (○) Rehabilitation housing; (■) pre-World War II (satisfactory); (▲) pre-World War II (deteriorated). Numbers in parentheses indicate numbers of homes evaluated for lead hazards. (From Hammond et al., ref. 33.)

In Cincinnati showed the effect of housing on PbB on infants (Fig. 1) and that PbB begins to rise by 6 months of age in children in old substandard housing (33). Once Pb-bearing dust has infiltrated an old dwelling, it is extremely difficult to remove. The data of Milar and Mushak (34) suggested that repeated cleanings of the interior of homes with high phosphate detergents is necessary if any substantial amount of Pb is to be removed. Charney et al. (35) have reported that frequent thorough scrubblings in old dilapidated homes may achieve an average reduction of PbB in children from 38 to 32 μg/dl.
Although it was thought by some a decade ago that direct inhalation of respirable, Pb-bearing, airborne particulates was responsible for much of the increased Pb absorption in children, more recent studies indicate that the major route of entry of Pb into the bodies of young children is through hand-to-mouth activity, the hands being contaminated with Pb-bearing dust and soils. The primary source of Pb in soils and dust may vary from place to place. In the vicinity of primary Pb smelters the source is fallout from smelter emissions. In old housing areas it appears that Pb falling in the soil from weathering and deterioration of Pb-painted surfaces is the major source. The study of Roels et al. (36) is of interest in this regard. The relationship between hand Pb and blood Pb is shown in Fig. 2 for four groups of school-age children. It shows two points of interest. First, the regression line intersects the PbB axis at a PbB of about 10 μg/dl, the average PbB attributable to the Pb content of current food, drinking water, and air. Second, above this level there is a close association between hand Pb and PbB. Taken together the data suggest that higher PbB levels are probably primarily attributable to ingestion of environmental Pb in dust and soil through the normal hand-to-mouth activity of children.

The ingestion of Pb-based house paint is without doubt the main source of serious pediatric Pb poisoning in the United States, United Kingdom, Australia, and New Zealand, where Pb-pigment paints have long been used and cases continue to be reported. On the other hand, residential Pb-based paints have long been prohibited in Germany and Scandinavia, and cases from this source are unheard of. The extent to which Pb paint may play a role in pediatric Pb poisoning elsewhere in the world is unknown. The occurrence of significantly increased Pb absorption

![FIG. 2. Relationship between mean concentrations of lead in blood (PbB) and on hands (PbH) in eight groups of school-age boys and girls residing at various distances from a primary lead smelter. For the PbB-PbH relationship in the eight groups, \( r = 0.976, p < 0.001 \). For individual subjects, \( N = 141, r = 0.711, p < 0.05 \) for the PbB-PbH relationships. (From Roels et al. ref. 36. Reproduced with permission.)](image-url)
EXPOSURE TO NONESSENTIAL METALS

in children residing in close proximity to primary Pb smelters in several countries has been reported (27,37). Similarly, the children of Pb workers who wear their contaminated work clothing home are at increased risk. Removal of old Pb paint by burning and sanding also places children in the home at greatly increased risk. Sporadic cases of poisoning have also occurred because of ingestion of Pb fishing weights, Pb curtain weights, Pb shot, as well as jewelry painted with Pb to simulate pearl, inhalation of fumes of leaded gasoline, cosmetics (surma), decals on cocktail glasses, hobbies that use ceramics or leaded-stained glass, and folk medicines from Asia and Central America (27,38).

Screening for the Prevention of Childhood Pb Poisoning

By 1970 it had become apparent that current methods of chelation therapy, which were introduced during the early 1960s, were effective in reducing substantially the mortality of acute Pb encephalopathy (39). On the other hand, chelation therapy started after the appearance of classical clinical symptoms of plumbism was ineffectual in reducing CNS sequelae among survivors (40). Only a preventive approach afforded any hope of improving the outlook for overexposed children.

When the Lead Paint Poison Prevention Act was first enacted by the U.S. Congress in 1970, there were no micro blood Pb or micro free-erythrocyte protoporphyrin (FEP) screening tests in existence. During the early 1970s intensive effort was devoted to the development of micro procedures that are now taken for granted. Overall, an operational national screening program has been in place in the United States since about 1975. Currently, the FEP screening test is incorporated widely into primary pediatric care programs. The clinical rationale for this approach is apparent; that is, detection at a preclinical stage followed by appropriate intervention should prevent the more serious forms of the disease. The theoretical rationale for the use of the FEP test is based on the critical effect concept as proposed in 1974 by the Subcommittee on the Toxicology of Metals of the Permanent Commission and International Association of Occupational Health (41). Figure 3 depicts this concept in its simplest form. Toxic metals may have effects A, B, and C, with effect A occurring at the lowest internal dose of Pb. There is a substantial body of dose-effect and dose-response data in man on the relationship between PbB, the indicator of internal dose of Pb, and the indicators of its biochemical effects on heme synthesis (FEP, δ-aminolevulinic acid dehydrase activity and the excretion of δ-aminolevulinic acid and coproporphyrin in urine). There was a consensus that the erythroid cells in the bone marrow are the cells affected at the lowest PbB level, and that FEP is the most sensitive and practical biochemical marker of this effect (12,41). Effect B in Fig. 3 is presumed to be Pb's effect in the nervous system. However, the relative sensitivity of the hemopoietic and nervous system to Pb is not known. Effects on A (heme synthesis) and B (nervous system) might, in fact, take the form shown in Fig. 4. Indeed, more recent studies employing sensitive biochemical and electrophysiological techniques suggest that measurable changes in some kidney and nervous system functions may be occurring at very
FIG. 3. Theoretical form of relationship between an increasing dose of a nonessential metal, e.g., lead, and an increasing degree of adverse effect where the law of biological random variation applies. When the metal has several adverse effects, separate dose-effect curves are needed for each effect. As shown above, effect A is the first, or "critical," effect, occurring at a lower dose than either effect B or C. The relationship among effects A, B, and C have important implications for preventive medicine: Intervention based on detection of effect A, the first effect, at an early reversible stage should serve to prevent effects B and C, which may have more serious consequences. This shows the possible relationship among effects A, B, and C in their simplest form. (Adapted from Nordberg, ref. 41.)

FIG. 4. Another theoretical form of relationship between the increasing dose of a nonessential metal, e.g., lead, and increasing degree of adverse effect, where a law of biological random variation applies. Here the slopes of the regression curves for effects A, B, and C differ. In this case effect A has the lowest threshold, but effect B has a much steeper slope. Under these conditions, the slopes of effects of A and B may cross over at a rather low dosage interval. Other combinations are also theoretically possible. (From Chisolm, ref. 46. Reproduced with permission.)

low PbB levels, and that heme synthesis may not necessarily be the system most sensitive to Pb's various inhibitory biochemical effects. Thus statistically significant relationships have been found between PbB 10 to 15 µg and reduction in serum 1,25-dihydroxyvitamin D (42,43), reduction in 5-pyrimidine nucleotidase activity in erythrocytes (44), and slow-wave-evoked cortical potential (45).

Nevertheless, the FEP test (or EP test) remains the only practical screening test for detection of increased Pb absorption. The limitations in the sensitivity and specificity of the FEP test may not be generally appreciated. Data in Fig. 5 may be taken as representative of a number of studies in children on the relationship between PbB and FEP (46). These data show that about 10% of children with
EXPOSURE TO NONSENSIBLE METALS

FIG. 5. Dose–response relationship between blood lead concentration and erythrocyte protoporphyrin, as determined prospectively in 155 children (1 to 5 years of age) in an old housing area in Baltimore. The response rate in this particular population is plotted as the percentage of children in each blood lead group showing an erythrocyte protoporphyrin level which is elevated beyond the range of “normal” physiological variation. (From Chisolm, ref. 46. Reproduced with permission.)

PbB ≥ 30 μg react positively. A raised FEP is a highly sensitive indicator of iron deficiency, so that this probably reflects the prevalence of iron deficiency in the population being sampled (47,48). Only about 20% of the children with PbB in the range of 30 to 39 μg react positively, and approximately 45% of children with PbB in the range of 40 to 49 μg react positively. Only when the PbB level is ≥ 50 μg do 95% or more react positively. If, in fact, unwanted outcomes occur only when PbB during early childhood is sustained above 50 μg, the FEP test is of adequate sensitivity. If, on the other hand, such outcomes are associated with lower PbB during early childhood, it is clear that a large proportion of such children escape detection when the FEP test is used alone as a primary screening test. Because blood obtained from a fingerprick is satisfactory for the FEP test, it is the only practical primary micro screening test. For reliable data, samples of blood for Pb must be obtained by venipuncture. For the past 5 years the CDC has recommended an FEP cutoff value of 50 μg/dl of whole blood, a value which is clearly above the upper limit of normal. It is anticipated that this cutoff value will be lowered soon to 35 μg/dl whole blood as determined by extraction techniques.

Studies of CNS Sequelae of Increased Pb Absorption Without Clinical Symptoms During Early Childhood

Forty years ago Byers and Lord (49) followed 20 children through the early school years who had sustained recurrent episodes of clinical Pb poisoning during the preschool years. They were struck by the fact that 19 of the 20 were eventually excluded from school despite the fact that 15 of the 20 had normal IQs on standard intelligence tests. They attributed these failures to shortened attention span, antisocial behavior, perseveration, and impaired visual-motor coordination. The types of deficits being attributed to increased Pb absorption without clinical symptoms today are qualitatively the same as those described by Byers and Lord 40 years
EXPOSURE TO NONESSENTIAL METALS

ago (49). Three major critical reviews of the more than two dozen recent human studies on the postnatal neurobehavioral and developmental effects of Pb have appeared since 1976 (15,50,51). With the exception of the prospective study of De la Burde and Choate (52), all recent published studies have been cross-sectional or retrospective. Most reviewers are agreed that the human studies so far reported have methodological deficiencies, although the deficiencies vary in type and severity from one study to another. Nevertheless, review groups, charged with providing scientific evaluations upon which policy decisions rest, must do so on the basis of the data at hand. Among such groups there is general agreement that PbB persistently elevated above 60 μg/dl during the early preschool years carries an unacceptable risk of permanent CNS injury. This may also occur in the PbB range of 40 to 60 μg, but this conclusion rests on less firm data (11,50).

More recent retrospective, cross-sectional studies have used Pb in shed deciduous teeth as an index of body Pb burden together with a wide battery of cognitive and neurobehavioral tests in an attempt to assess the possible adverse effects of Pb in those with low level Pb exposure. Although only limited PbB data are available in these studies, it has been presumed by the investigators that they probably were dealing with children with PbB levels of about 35 to 40 μg. However, the occurrence of higher PbB levels during early childhood cannot be excluded in these studies. An independent committee assembled by the U.S. EPA to evaluate these studies concluded that the studies of Needleman et al. (53) and Ernhart et al. (54) neither confirm nor refute the hypothesis that low-level Pb exposure in children causes permanent neuropsychological deficits (55). English and German studies, in which confounding variables were adequately controlled, found no residual effect of Pb after control for confounding variables (56,57). There is also a general consensus that further retrospective cross-sectional studies should be discouraged. Only through careful prospective studies, several of which are now in progress, is it likely that dose (serial PbB levels) can be reliably estimated and confounding variables adequately controlled, so that the role of Pb can be more reliably defined.

ARSENIC

Humans are exposed to many chemical forms of both inorganic and organic arsenic (As). This discussion is limited to certain aspects of human exposure to inorganic As, which can occur in trivalent or pentavalent form. The relative toxicity of these two forms of inorganic As in man is not known, in part because the specific species of As has not been determined in most human studies. Furthermore, because of limitations in the analysis of biological materials for As, only total As is determined. Data from experimental animals show that the acute toxicity of trivalent As is greater than that of pentavalent As. The abundance of As in the earth's crust is generally given as 1.5 to 2 ppm. Higher concentrations are found in mineral deposits, particularly in sulfide deposits, in which it is often found in combination with lead, copper, silver, or thallium. Arsenic is present in all soils. The natural As content of virgin soils ranges from 0.1 to 40 ppm, with an average
EXPOSURE TO NONESSENTIAL METALS

of about 5 to 6 ppm. Among samples of ground water, 97% have been reported to contain As at no more than 50 ppb. In areas of high thermal activity (volcanoes, hot springs) very high levels of As may be found. For example, in Searles County, California, where hot springs are located, As is found in a concentration of 198,000 to 243,000 μg/liter. Ground water in regions of Chile, Argentina, and Taiwan have naturally high As contents.

With the exception of seafoods, the As content of food is generally less than 1 mg/kg. Marine fish usually contain 1 to 10 mg/kg, and certain crustaceans and shellfish can contain up to 100 mg/kg. Thus the total dietary exposure to As is substantially influenced by the amount of seafood in the diet. Total dietary intake of As in Canada, France, the United Kingdom, and the United States has been estimated at 0.5 to 4.2 mg/day in standard man (58). Arsenic in seafood is present in highly stable but unidentified organic forms which are apparently nontoxic and rapidly excreted, mainly in the urine. The burning of coal and smelting of metals, particularly copper, are the major sources of airborne As pollution. To this should be added tobacco smoking. The estimated total daily exposure of the general population to inorganic As may be summarized as follows: Normally, total exposure is 10 to 50 μg/day, primarily from food, and the total absorbed dose is less than 40 to 50 μg/day. In smokers the internal dose may be further increased by 5 to 20 μg/day. Certain seafoods may lead to absorption of more than 1 mg As, but this is organic As.

Arsenic causes a wide variety of adverse health effects in humans. Acute poisoning after ingestion of inorganic As results in severe vomiting, excruciating abdominal pain and profuse diarrhea (rice-water stools), cardiac abnormalities, shock, and death. Among survivors, anemia, upper respiratory tract irritation, skin lesions, and, as late sequelae, peripheral neuropathy and brain dysfunction have been reported. Long-term subacute exposure has been associated with hyperkeratosis, hyperpigmentation of the skin, skin cancer, and peripheral vascular disorders. In other studies impairment of hearing, hematopoietic disturbances including anemia and leukopenia, and portal hypertension have been reported. Exposure to airborne As, particularly in smelter workers, can cause irritation of the upper respiratory tract, perforation of the nasal septum, and dermatitis. A dose-response relationship has been demonstrated in workers at a copper smelter between excess mortality from lung cancer and mean arsenic exposure, calculated as As (μg/liter of urine) × years of exposure. The workers were exposed mainly to airborne As₂O₃. Among chronically exposed workers there is apparently a latency period of 30 to 40 years prior to the appearance of lung cancer. Drugs containing both inorganic and organic As, although declining in usage, were still available in Europe in 1978. These and other aspects of the chemistry, toxicology, exposure, and metabolism of As are discussed in considerable detail elsewhere (8,59,60). The remainder of this brief presentation is limited to outbreaks of acute and chronic inorganic As poisoning involving children and resulting from contamination of food or drinking water.
During the early 1960s physicians in Antofagasta, Chile noted dermatological manifestations and some deaths, especially in children, that were traced to a water supply containing As, 800 ppb, which had been placed in operation in 1958. In 1971 Borgono and Greiber (61) reported a series of studies in the inhabitants of this city, most of whom were less than 10 years of age. They compared 180 subjects from Antofagasta with 98 controls who lived in a nearby city (Iquique) with a normal water supply. Their findings are summarized in Tables 9 and 10. Most prominent among the findings were abnormal skin pigmentation, hyperkeratosis, and peripheral vascular disease. It is clear (Table 10) that the more serious toxic effects were far more prevalent in those with abnormal skin pigmentation than in those with normal skin. Among 21 children referred from Antofagasta to Santiago for evaluation and treatment after 1962, 16 had recurrent bronchopneumonia during the first year of life, and all had bronchiectasis. All 21 were referred because of abnormal skin color and hyperkeratosis. In a survey of 27,088 schoolchildren, 12% were found to have cutaneous changes of arsenism, and one-fourth to one-third of these had suggestive systemic symptoms. In another study, Zaldivar (62) reported 457 patients (208 males, 249 females) with cutaneous lesions (leukoderma, melanoderma, hyperkeratosis, squamous cell carcinoma). Children between birth and 15 years of age accounted for 69.2% of the male cases and for 77.5% of the female cases. All exhibited high As content in the hair. The finding of lip herpes (Tables 9 and 10) is of interest inasmuch as there are some experimental data suggesting that As may interfere with immune function. During 1968 and 1969 the mean concentration of As in the drinking water in Antofagasta was 580 ppb. After installation of a new filtration plant, the As content was reduced to 80 ppb in May 1970. Coincident with this change in the As content of the drinking water, the average incidence of cutaneous lesions per 100,000 population decreased in males from 145.5 to 9.1 and in females from 168.0 to 10.0. The very rapid decrease in cutaneous lesions has raised questions because it seemed to be too rapid and thus suggested that other factors may have been involved. Even so, the data suggest that the current USPHS drinking water standard for As of $\leq 50$ ppb may not provide a sufficient margin of safety.

The Raynaud's phenomenon and acrocyanosis in these Chilean children are in agreement with the report of Tseng et al. (63), who surveyed a group of 40,421 people in southwestern Taiwan where the concentration of As in the wells of various villages ranged from 17 to 1,097 ppb. Epidemiological data revealed a dose-response relationship between blackfoot disease and the concentration of As in well water. It is of interest that the earliest ages at which specific findings were noted were 3 years for the characteristic hyperpigmentation and 4 years for hyperkeratosis. This study was also well controlled. Other, smaller outbreaks have produced findings ranging from acute to less severe subacute arsenism in the Cordoba Province of Argentina. A brief outbreak of acute As poisoning with predominantly gastrointestinal symptoms in the United States was traced to the contamination of a small well near a buried deposit of arsenical pesticide (64).
TABLE 9. Clinical manifestations among 180 Antofagasta and 98 Iquique inhabitants*  

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Incidence in Antofagasta (%)</th>
<th>Incidence in Iquique (%)</th>
<th>Manifestation</th>
<th>Incidence in Antofagasta (%)</th>
<th>Incidence in Iquique (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchopulmonary disease history</td>
<td>14.9</td>
<td>5.3</td>
<td>Cardiovascular manifestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal skin pigmentation</td>
<td>80.0</td>
<td>0.0</td>
<td>Raynaud's syndrome</td>
<td>30.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>36.1</td>
<td>0.0</td>
<td>Acrocyanosis</td>
<td>22.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Chronic coryza</td>
<td>59.7</td>
<td>1.0</td>
<td>Angina pectoris</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Lip herpes</td>
<td>12.7</td>
<td>0.0</td>
<td>Hypertension</td>
<td>5.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Chronic cough</td>
<td>28.3</td>
<td>4.0</td>
<td>Chronic diarrhea</td>
<td>7.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

*Derived from Borgono and Greiber (61).
There have also been outbreaks traced to the contamination of food. Mizuta et al. (65) studied 220 patients of all ages who had been poisoned by As-contaminated soy sauce. Average daily ingestion was estimated at approximately 3 mg of As (probably as calcium arsenate) for 2 to 3 weeks. In this group 85% had facial edema and anorexia. About 20% had peripheral neuropathy, and less than 10% had exanthema, desquamation, and hyperpigmentation. Although most of the patients had enlarged livers, few abnormalities were found in liver function tests, and histopathological examination of five liver biopsies did not reveal severe degenerative changes. Although there were no findings suggestive of congestive heart failure, electrocardiograms (ECGs) were abnormal in 16 of 20 patients. In none of the above studies of children has the question of possible disturbance of neurodevelopment in young children been addressed.

A follow-up study of the Morinaga As-tainted powdered milk epidemic in western Japan has provided the only evidence that overexposure to As during infancy may have long-lasting, detrimental effects on neurodevelopment (66). An estimated 12,159 babies were exposed for periods of 1 to 3 months during the summer of 1955 to a powdered milk formula contaminated with arsenic trioxide (67). This powdered infant milk formula had been stabilized with sodium bisphosphate of inferior grade from industrial waste containing As and vanadium. The estimated daily average intake of arsenic trioxide was 1 to 7 mg. Most of the infants involved were less than 1 year of age. It is thought that the infants who became clinically ill had consumed the formula for at least 10 days. Several thousand infants became clinically ill, and 131 deaths were reported (68). When As was identified in the tissue of fatal cases, more than 500,000 cans of the contaminated lot of Morinaga powdered milk were recalled. This terminated the epidemic. Acute symptoms included cough, rhinorrhea, conjunctivitis, vomiting, diarrhea, melanosis, fever, hepatomegaly, anemia, granulocytopenia, and abnormal ECGs. A strik-
ing finding was that of increased density at the metaphyseal ends of the long bones, indistinguishable from the familiar "lead line." A small group of affected children were followed for approximately 6 months. These follow-up examinations were concentrated on ECG abnormalities and hepatic and renal function tests. Although a few electroencephalograms (EEGs) were done and found to be normal, there was no mention of further neurobehavioral assessments. Except for some retardation of growth in the ulnar bone, all of the features of this syndrome disappeared within 6 months, so that follow-up was dropped (69).

Some 16 years after the original episode, groups of affected children were reevaluated at the insistence of the Japanese Pediatric Society. Among 554 affected children in Kyoto Prefecture, complete examinations, including psychometric testing, were carried out in 241 (67). Of these children, 73% had been exposed when they were less than 1 year of age, and the remaining children were less than 23 months of age when exposed. The results in these children were compared with age-specific norms for the entire Kyoto Prefecture and with a small control group. Results were as follows: (a) Persistent dermatological abnormalities were still found in approximately 65% of affected adolescents. (b) Average height was reduced, but weight was not. (c) Abnormal EEGs were found in 4%; 6% had persistent seizure disorders, and 12% were mentally retarded. (d) The percentage of affected children with an IQ of 85 or less (21.6%) was substantially higher than that found in the general population (2%). (e) Significant hearing loss was found in 18%. Follow-up studies in other prefectures gave similar results (66,70).

The hearing loss is of interest, as Bencko and Symon (71) reported significant hearing loss in 50 ten-year-old Czechoslovakian children who had both air and bone conduction loss and who lived near a power plant burning coal of high As content. On the other hand, a small group of children in the western United States exposed to almost similar concentrations of airborne As showed no impairment of hearing (72). Despite the long interval in the Japanese outbreak between the original episode and the follow-up studies during adolescence and other limitations which are inherent in retrospective studies, the Japanese follow-up data strongly suggest that arsenic trioxide in amounts sufficient to produce acute clinical illness during infancy may cause subsequent appearance of permanent neurobehavioral deficits.

Nordström et al. (73) studied the offspring of women who worked during pregnancy at a copper smelter in northern Sweden, where high levels of airborne As were found in some of the work places. He reported that the frequency of all malformations was twice as high among the offspring of women at the smelter as in the offspring of other women in the region, and that a five-fold increase was noted in multiple malformations. Data were based on study of 25,619 live births that occurred between 1955 and 1976. Although this is the only study suggesting that inorganic As may be teratogenic, the nonferrous smelter in which these women worked entailed exposure to many heavy metals, as well as sulfur dioxide. Thus no specific cause for the increase in malformations can be ascertained because of the complexity of the total exposure of these pregnant women.
Vigilant quality control in the production and processing of food as well as careful evaluation of public and other water supplies, before and after they are put into operation, could have prevented the serious outbreaks of arsenism just described. It seems curious that developmental and neurobehavioral assessments have not been included in the epidemiological studies just cited. The Japanese Morinaga powdered milk episode has demonstrated the clear need for such studies in the future. Research, particularly in regard to the question of the carcinogenicity of As and its dermatological effects, has been severely handicapped owing to the lack of suitable animal model. The rat has a unique As metabolism which is totally unlike that of man or other mammals. Therefore, the use of the rat as an experimental animal is to be strongly discouraged. Additional studies on the possible teratogenic, mutagenic, and immunological effects of As employing doses of As compounds comparable to those likely to be encountered by man are to be encouraged (60).

**CADMIUM**

The occurrence, exposure, metabolism, and effects of cadmium (Cd) have been most extensively reviewed by Friberg et al. (74) and Friberg and Kjellström (75). There is extensive literature on the toxic effects of Cd. On the other hand, no specific functional role for Cd has yet been found in any single species of plant or animal. Cadmium therefore is classed as a nonessential trace element. Most concentrated natural deposits of Cd are found in zinc and lead sulfide minerals, so that Cd is produced industrially as a by-product of the smelting of lead and zinc. Its major uses are as an anticorrosive agent for the galvanizing and electroplating of steel, as a color pigment, as a stabilizer in PVC plastics, and as a cathode material in alkaline batteries. In the United States 60% of consumption of Cd is for electroplating, 11% for pigments, 19% for stabilizers, and 3% for batteries. Cadmium-bearing minerals may contain 1,000 to 50,000 μg Cd/g. Cadmium concentrations in unpolluted soils range from 0.4 to 0.7 μg/g and in unpolluted waters from 0.04 to 0.5 ng/g. Long-term averages indicate that ambient air ranges from 1 to 120 ng Cd/m³. This may be contrasted with the air in Cd-processing factories, in which the range may be three to four orders of magnitude higher or from 5 to 7,000 μg/m³ (75).

Exposure to Cd fumes is a major industrial hazard. Concentrations greater than 1 mg Cd/m³ of air may cause chemical pneumonitis or pulmonary edema, and exposure to concentrations above 5 mg Cd/m³ for an 8-hr period may be lethal. Such high industrial exposure is most likely to occur when Cd-plated or other Cd-containing materials are smelted, welded, or soldered. In the general population ingestion of foods containing Cd at concentrations greater than 15 mg/liter can cause nausea, vomiting, abdominal cramps, and sometimes diarrhea. The risk of such acute poisoning is high, particularly when ice or acidic beverages are placed in Cd-plated pots or pans. This is now prohibited in most countries. Similar episodes have resulted from the storage of foods and beverages in pottery with Cd-containing
glazes. Also, release of Cd from silver solder in water faucets or in water containers of automatic vending machines for cold or hot beverages may be sufficient to cause poisoning.

Of greater concern from the public health viewpoint is chronic low-level increased exposure of the general population to Cd. This results from the fact that Cd has a very long biological half-life. In blood the half-life is about 80 days, in liver about 10 years, and in kidney about 20 to 30 years. Concentration of Cd in the renal cortex increases almost linearly from birth to 50 years of age. In adults 30 to 59 years of age, the Cd concentration in the renal cortex has been found to vary from 5 to 100 µg/g and in the liver from 1 to 10 µg/g (74). When the major port of entry is the gastrointestinal tract, the renal cortex is the critical organ, whereas emphysema is associated mainly with occupational airborne exposure to Cd.

The late renal effects of Cd have been studied extensively in workers and Japanese populations living in Cd-polluted areas where itai-itai (ouch-ouch) disease is well known. Cadmium-induced renal damage characterized by the adult Fanconi syndrome, including osteoporosis and osteomalacia, has been described. Friberg and Kjellström (75) have proposed that the probable mechanisms involved in the pathophysiology of Cd-induced bone disease are as follows: (a) High Cd concentration in food as occurs in Cd-polluted areas of Japan decreases the absorption of calcium in the intestine. (b) As the concentration of Cd in the kidney increases, an increasing number of renal tubular cells are damaged and the enzymes adenylcyclase and 1,25-hydroxylase are increasingly inhibited. (c) This leads to a decrease in PTH-stimulated production of 1,25-dihydroxyvitamin D. (d) Deficiency of 1,25-dihydroxyvitamin D impairs absorption of calcium from the gut. (e) To maintain plasma calcium, PTH continues to stimulate mobilization of calcium from bone. This situation may be further aggravated by diets deficient in calcium, protein, and/or vitamin D. To substantiate these proposed mechanisms, further studies are badly needed in Cd-poisoned workers and patients with itai-itai disease.

From studies on patients with itai-itai disease and Cd workers, metabolic models for Cd have been developed. From these data, dose-response relationships have been constructed, and it has been estimated that the critical concentration of Cd in the renal cortex for Cd-induced renal injury is about 200 µg/g (74). To reach this Cd level in the cortex, it has been calculated that the intake of Cd in food would require an average daily intake of 250 µg Cd for at least 25 years. Exposure in occupational air to approximately 10 µg Cd/m³ for 25 years or more would lead to the same result. At present, there are no biochemical indicators of overexposure to Cd which indicate rising renal cortical concentrations of Cd prior to renal injury. It seems likely that measures of renal tubular proteinuria, e.g., β₂-microglobulin or retinol-binding protein, become positive only after cellular damage has occurred. Thus some margin of safety must be arbitrarily calculated. Epidemiological data suggest that air concentrations of Cd should be maintained at less than 5 µg/m³ and that the daily intake of Cd from food should be less than 140 µg/day if less than 10% of chronically overexposed persons are to show renal damage (75).
Estimates based on analysis of food with reliable analytical techniques indicate that the usual daily intake varies between 4 and 60 \( \mu g \) Cd/day. This may be contrasted with the average intake in Cd-polluted areas of Japan, which has been estimated to vary between 100 and 600 \( \mu g \) Cd/day. Average intakes for 45-year-old males were about 35 \( \mu g \) Cd/day in Tokyo, 19 \( \mu g \) Cd/day in Dallas, and 17 \( \mu g \) Cd/day in Stockholm (76). The data indicate that there is no imminent hazard to the general public from current Cd contents of food and water. Nevertheless, it is clear that these sources require constant monitoring. In particular, great care is needed to monitor the results of the application of sewage sludge and superphosphate fertilizers to agricultural lands. There are no safe means of decorporating Cd from the body once an excess has accumulated. Assessment of human exposure to Cd is best monitored through measurement of urinary Cd excretion. However, stringent quality control must be incorporated into the procedures for collection and analysis of samples (77).

**METHYL MERCURY**

The toxicity of mercury (Hg)-containing compounds is highly dependent on their physical and chemical properties, which determine their absorption, distribution, metabolism, and rate and route of excretion (78–80). For example, metallic Hg readily vaporizes at ambient temperature, and Hg vapor, as an uncharged species, readily crosses cell membranes and can accumulate in the CNS. On the other hand, divalent Hg is largely excluded from the brain but rapidly accumulates in the kidney. Among alkyl and aryl mercury compounds, only methyl mercury (MeHg) is relatively resistant to rapid cleavage of the C–Hg bond. Among Hg compounds, MeHg has a unique pattern of distribution, binding, metabolism, and clearance. It is virtually completely absorbed from the gastrointestinal tract as a lipid-soluble compound. It is readily accumulated in the brain. Its half-life in the body is estimated as approximately 70 days. In this section, recent studies of the effects of human exposure to MeHg \textit{in utero} or in early life are reviewed.

Of historical interest are the reported effects of inorganic Hg compounds, particularly calomel (mercurous chloride) in infants (81). Until about 30 years ago, calomel was widely used in powders applied to the gingiva of teething infants. Some infants, so treated, developed acrodynia, a condition characterized by flushing, excessive sweating, photophobia, hypotonia, and the salaam position. When use of calomel teething powders was discontinued, acrodynia became rare (82). Such reports suggest that mercurials other than MeHg have the potential for producing multiorgan toxic effects in infants.

**In Utero Exposure**

The profound toxic effects of MeHg in the human fetus and newborn were first recognized in Minamata Bay in Japan during the early 1950s. After prolonged investigation, it was determined that an alkyl plant was discharging MeHg into the bay, where it accumulated in large quantity in fish. Local fish lovers (cats, birds,
and heavy fish-eating people, particularly fishermen and their families) developed severe neurotoxic manifestations which have come to be known as Minamata disease. Some pregnant women who consumed MeHg-containing seafood remained symptom-free but delivered infants with congenital Minamata disease. Murakami (83) described the clinical and pathological findings in 26 cases of fetal Minamata disease. Common morphological findings included skull deformities (11 of 26), strabismus (13 of 26), nystagmus (4 of 26), malocclusion (14 of 26), and irregular tooth size (5 of 26). Torticollis, atresia of the auditory canal, defects of the chorioretinal membrane, and auricular deformity were less commonly described. The brains of two fetal Minimata cases, which were examined by Takeuchi (84) showed developmental arrest and atrophy, hypoplasia and dysplasia of neurons with poor myelination, decreased neuronal density in the cerebrum, and loss of cerebellar granule cells. In the United States in 1969 a woman consumed MeHg-contaminated pork from the third to sixth month of her pregnancy. Although her urinary Hg output was high, she manifested no signs or symptoms of MeHg intoxication. At term a male infant was delivered who developed intermittent gross tremors within 1 min of birth, a persistently abnormal EEG at 3 months of age, myoclonic jerks at 6 months of age, and nystagmoid eye movements and absence of visual fixation at 8 months of age. By 16 months of age, it was evident that the child’s development was arrested at the 3-month level; thus it is quite clear that this is yet another instance in which severe neurotoxic injury to the fetus can occur without any clinical evidence of toxicity in the pregnant female (80).

In the late autumn of 1971 and early winter of 1972, a severe epidemic of MeHg poisoning occurred in Iraq (85). It has been estimated that there were more than 5,000 fatal cases. This brief epidemic was traced to the consumption of MeHg-treated seed wheat not intended for human consumption; however, the affected population used this wheat to make bread. This outbreak has been rather extensively studied. The placental transfer of MeHg from mother to fetus was confirmed by measuring organic Hg in the blood of the newborn. The data demonstrated a rough dose-effect relationship between the concentration of organic Hg in the blood of the neonate and the mother. Postmortem examination of the brains of two Iraqi infants exposed in utero to MeHg, who died within 1 month of birth, showed shortening of the frontal lobe and simplification of the gyri. The cerebellum and brainstem appeared grossly normal. Large numbers of heterotropic neurons were found in the white matter of the cerebrum and cerebellum. The cerebral cortex, neuronal alignment, and organization were disordered. The findings indicated that abnormal neuronal migration with resultant deranged cortical organization appeared to be the major effect of in utero exposure to MeHg.

Follow-up studies of those infants exposed in utero to MeHg are continuing in order to determine the long-term effects of such exposure. Among 15 mother–infant pairs exposed to MeHg during pregnancy, 6 mothers and 6 infants were found to have signs and symptoms of MeHg poisoning (86). These children were nursed by their mothers so that continuing exposure to MeHg via the maternal milk was a confounding factor in determining the effects of purely fetal exposure
to MeHg. Among the 6 affected infants, common findings during the first year of life were microcephaly (3 of 6), fretfulness, irritability and excessive crying (6 of 6), total blindness (4 of 6), nystagmus (1 of 6), strabismus (2 of 6), severe hearing impairment (4 of 6), increased muscle tone (3 of 6), decreased muscle tone (2 of 6), severe generalized paralysis (4 of 6), and hyperactive deep tendon reflexes (5 of 6). No congenital anatomical malformations were observed. In the mothers the lowest concentration of Hg in blood associated with signs and symptoms of MeHg poisoning was 300 ppb, and all mothers with blood Hg concentrations of >400 ppb had clinical signs and symptoms of poisoning. In infants the lowest blood Hg concentration associated with clinical signs and symptoms was 546 ppb, and all infants with blood Hg concentrations of >3,000 ppb were severely affected.

A relatively constant relationship between concentrations of Hg in hair and blood has been established (87). This permits one to estimate blood Hg concentrations in the past from segmental hair analysis. Marsh et al. (88) used the concentration of Hg in maternal hair to estimate fetal exposure. Twenty-nine infants exposed in utero to MeHg were examined at 3 to 3.5 and 4.5 to 5 years of age. These children were classified according to peak Hg concentration in maternal hair. Neurological abnormalities, short stature, small head circumference, mental retardation, delayed speech, and convulsive disorders were all more common in children born of mothers with peak hair Hg concentrations of >100 ppm than among the children of women with peak hair Hg concentrations of <25 ppm during pregnancy. These and other studies on Iraqi mother–infant pairs indicated that the critical maternal peak hair Hg concentration associated with developmental delay in the offspring was <67.7 ppm (89). Based on the apparent hair/blood ratio of about 300, the data correspond to a peak maternal blood Hg concentration during pregnancy of approximately 230 ppb. Data indicate that exposure in utero to relatively small amounts of MeHg may produce significant developmental delay.

Postnatal Exposure

Amin-Zaki et al. (90) studied Iraqi infants exposed by consumption of breast milk produced by mothers who ate MeHg-contaminated bread as well as infants who directly consumed MeHg-contaminated bread. Infants exposed postnatally to MeHg had blood Hg concentrations exceeding 200 ppb, although they remained free of clinical signs and symptoms of MeHg poisoning. This is of interest in view of the observation in Minimata, Japan, that a blood Hg level of 200 ppb was considered the minimum concentration associated with clinical signs and symptoms of MeHg poisoning in adults (91). These results suggest either that infants are less susceptible to MeHg poisoning than adults, or that the signs and symptoms of MeHg poisoning, which can be used for diagnosis in adults, are either insensitive or inappropriate in infants. Long-term follow-up studies of these postnatally exposed Iraqi infants are awaited.
Reproductive Status and MeHg Kinetics

Studies of the Iraqi episode of MeHg poisoning suggest that there may be a higher susceptibility of pregnant women to the lethal effects of this agent. Bakir et al. (85) reported case-fatality rates for pregnant women 20 to 29 years of age as 70.5% and for pregnant women 30 to 39 years of age as 16%. Corresponding case-fatality rates for nonpregnant women 20 to 29 years of age and 30 to 39 years of age were 8.3 and 5.2%, respectively. Whether this difference in mortality reflects a biological effect of pregnancy on susceptibility to MeHg intoxication is uncertain, as bias in selection of cases cannot be ruled out. Because the case-fatality rates were based on hospital admissions and many affected individuals lived in remote villages in Iraq, it is possible that a higher proportion of pregnant women than nonpregnant women were referred to hospital. Greenwood et al. (92) have found that the average half-life for clearance of Hg from blood is faster in lactating women (42.2 days) than in nonlactating women or men (75.7 days). These differences were not accounted for by loss of Hg via the milk. These human data are supported by studies in MeHg-exposed mice and rats (93) which show that lactation does reduce the half-life of Hg in the whole body and may protect against signs and symptoms of MeHg poisoning. The physiological bases for these lactation-dependent differences in Hg clearance remain unknown. Chelation therapy with Hg-binding agents can substantially reduce the half-life of Hg in blood. Among agents studied by Clarkson et al. (94) in Iraq, 2,3-dimercapto-1-propane sulfonate (DMPS) was the most effective in accelerating elimination of Hg from the body and was well tolerated without serious side effects.

SUMMARY

During the past 5 years in the United States there has been a substantial reduction in the use of leaded gasoline. Air Pb levels, even in urban areas, have decreased, and there appears to have been a concurrent decrease in PbB. Steps to replace cans that have Pb-soldered seams with cans free of Pb by the food canning industry are in progress, which will further reduce the Pb content of foods. Except in small scattered areas where acidic plumbosolvent waters are conveyed in old Pb pipes, insignificant amounts of Pb are found in public drinking water. At the present time, the contribution of Pb in foods, drinking water, and ambient air produces on average PbB of 8 to 10 μg/dl in urban areas and lower values in rural or remote areas. No adverse health effects are associated with such exposure. The major identified high-risk group today are young children residing in old, deteriorated, poorly maintained dwellings with old Pb paints that have never been removed. The major route of entry of Pb into the body in such children is through hand-to-mouth activity, which is common in young children. This problem is chronic and severe in the United States, where PbB = 38 to 40 μg/dl and cases of Pb encephalopathy, although rare, still occur in children in old houses. Smaller groups of children in close proximity to Pb smelters and the children of Pb workers who wear their dusty work clothing home are similarly at risk. Prospective longitudinal studies will be
required to ascertain whether sustained PbB levels of \(<40 \mu g/dl\) during infancy and early childhood are associated with long-lasting, detrimental neurobehavioral effects. As PbB rises above this level, the risk of such effects becomes increasingly unacceptable.

Chronic overexposure to inorganic As has caused profound adverse dermatological, cardiovascular, and, in infants, probably CNS effects. Studies in workers chronically exposed to As support the hypothesis that As is carcinogenic. The amounts of As to which the general population is exposed through food, water, and air do not pose significant risks to health, although the current drinking water standard of \(50 \mu g\) As/liter may not provide an adequate margin of safety. Epidemics of acute and subacute As poisoning in infants and children have been traced to serious contamination of food (Japan) and drinking water (Chile, Argentina, and Taiwan). An increase in the burning of coal with high As content in power plants could, in the absence of effective control measures, significantly increase the levels of As in ambient air.

Present exposures of the general population to Cd do not pose any documented risks to health. Certain grains grown in soils rich in Cd accumulate Cd in the edible portions of the plant. Because of the extensive use of superphosphate fertilizers, which contain Cd, and because of the proposed increase in the use of sewage sludge on agricultural lands, monitoring must be maintained on a long-term basis if dangerous increases in exposure to Cd are to be prevented. When exposure is via the alimentary tract, the critical organ for Cd is the renal cortex, in which Cd concentration steadily increases from birth to at least 50 years of age. Its biological half-life in the renal cortex is about 20 to 30 years.

Minamata disease was first recognized in about 1950 and was subsequently shown to be caused by chronic MeHg poisoning. MeHg was being discharged from a chloralkali plant into Minamata Bay, Japan. Those poisoned were heavy fish eaters (birds, cats, people). During the early 1970s an estimated 5,000 people in Iraq died after consumption of MeHg-treated seed grain. Surviving infants and fetuses showed permanent CNS injury. Inasmuch as certain aquatic organisms can convert inorganic Hg to MeHg, no Hg compounds should be discharged into water. There is a scientific consensus that the manufacture and use of MeHg should be totally banned on a worldwide basis. At present only heavy fish-eating populations (i.e., the Japanese) may be overexposed to MeHg, particularly if the preponderance of dietary protein is derived from fish.

ACKNOWLEDGMENTS

Supported by DHHS Maternal and Child Health Project 917 and Project MCJ 240458.

REFERENCES


258 EXPOSURE TO NONESSENTIAL METALS


DISCUSSION

*Dr. Mertz:* Dr. Chisolm, I appreciated your presentation and have two comments which do not in any way detract from anything you said. First, I appreciated very much that you did not use the term toxic elements even though this was suggested in your title. All elements are toxic, and therefore you chose not to single out lead or arsenic with this unpleasant name. One element for which we have very good information as to toxicity is iron because in the United States several hundred children come into hospitals with acute iron poisoning when they get hold of their mother's iron supplements. We are concerned here with metals to which we are exposed in excessive concentrations, and all of us take the problems very seriously. I would like to mention the work that is going on in Weihenstephan, just 25 miles from here. Kirchgessner and his group have demonstrated beneficial effects of lead in rats. I hasten to add that these beneficial effects occur only at extremely low concentrations— their results contradict in no way our concern for excessive exposure, but they do suggest that lead at extremely low concentrations, as well as arsenic, may have some essential role. The Environmental Protection Agency convened an Expert Committee on that question and the Committee came up with a statement that the evidence is compatible with a possible essential role even though it did not consider the present evidence strong enough to call lead unequivocally an essential element. I suggest that essentiality and toxicity are compatible, and our concern for either is determined by environmental exposure.
EXPOSURE TO NONESSENTIAL METALS

Dr. Chisolm: Just to reinforce what Dr. Mertz said, no one here is in any danger of being deficient in lead. There may be some remote populations with extraordinarily low exposure to lead, but even here deficiency is very doubtful because the experimental values that you cited are well below anything reported in humans.

Dr. Zlotkin: My first question has to do with peeling paint. I always have had a difficult time envisioning how children actually became intoxicated from peeling paint. It is my impression that in most circumstances children do not actually eat the paint that peels off the wall. Perhaps you could comment on whether it is actually the ingestion or the respiratory component of the peeling paint that is the important component. My second question is with respect to the transfer of lead from the mother’s milk to the infant. If a situation occurred where a mother was exposed to high lead concentrations, and the infant was being fed breast milk, would the infant be at increased risk? My final question: you mentioned the problems and some of the solutions to the problems of lead intoxication in North America and in Britain; what is the situation in developing countries?

Dr. Chisolm: Some mothers of children with lead poisoning do report that they have seen their child eating paint from the walls or woodwork of the home. We have found daily fecal outputs of 5 to 105 mg Pb in children with acute lead encephalopathy. In asymptomatic children with PbB in the range of 60 to 80 μg Pb/dl whole blood, fecal outputs of 1 mg Pb/day have been found (Chisolm, Barltrop. *Arch Dis Child* 1979;54:249–62). Hand-to-mouth activity (thumb- and finger-sucking, sucking on toys and other objects picked up from the floor, etc.) is highly prevalent among young children. Roels et al. (*Environ Res* 1980;22:81–94) showed that hand-to-mouth activity resulting in ingestion of lead-bearing particulates, and not the respiratory route, probably constitutes the main route of entry of lead into the bodies of children.

With regard to the transfer of lead to infants via breast milk, studies in both experimental animals and human infants show that this does occur. Under “normal” low exposure conditions (mean PbB = 10 μg/dl) the concentration of lead in human milk is quite low (mean = 2 μg Pb/liter) (Kovar et al. *Arch Dis Child* 1984;59:36–9). I know of no studies in which the lead content of breast milk has been determined in women with high blood lead levels.

With regard to lead exposure in developing countries, clinical reports indicate that lead poisoning in children from cosmetics (Surma, al Kohl), lead-glazed pottery, lead-containing folk medicines, and residence close to lead smelters may all be important public health problems. By contrast, I am unaware of any reports of childhood lead poisoning in developing countries which have been related to lead paints.

Dr. Bergmann: Lead concentration has been measured in Germany in foods for infants and children as well as in pipe water. On the basis of the results, average (2.5 μg/kg/day) and maximum (9 to 16 μg/kg/day) intakes during infancy have been estimated (Müller, Schmidt. Heavy metals in the infant diet. Bergmann, Bergmann. Impact on infant growth and physiology on heavy metal toxicity. In: Schmidt, Hildebrandt, eds. *Health evaluation of heavy metals in infant formula and junior food*. Berlin: Springer-Verlag, 1983). Rapid growth during infancy is a strong homeostatic factor with respect to total body burden of lead, as illustrated in Fig. D1. In a nongrowing infant fed the “maximum” lead intake, body lead burden would increase steeply, no matter whether the starting point was 1.73 ppm (adult value) or 0.3 ppm (estimated burden in a newborn). Growth retards the body lead burden significantly if the starting point is low and diminishes it if the starting point is high. Similar homeostatic effects of growth may be anticipated in other elements accumulating in the body.
Dr. Chisolm: Barry's autopsy data from the U.K. show values similar to your data for newborns and near-term stillborns. During the first year of life both bone and soft tissue Pb remain quite low. After 12 months of age soft tissue Pb increases slightly, shows no increase with age, and is comparable to levels found in the soft tissues of adult females. After 12 months of age, bone Pb increases by a factor of 2.5 to 5 in the 1- to 16-year age group, and still higher values are found in adult bone. Although growth may contribute somewhat to homeostasis in the soft tissues, sequestration of lead in bone probably is the main protective factor in maintaining low concentrations of lead in the soft tissues in which lead's major adverse effects occur. When the rate of assimilation of lead exceeds the rates of excretion and storage in bone, soft tissue concentrations of lead rise and toxicity may occur. Balance studies in infants indicate that intakes exceeding 5 \( \mu g \) Pb/kg body weight/day are associated with positive lead balance.

Dr. Haschke: Under normal circumstances the major environmental source of lead for young infants is food. Infant formulas in most European countries are sold as milk powders which must be reconstituted with boiled water before use. Therefore lead concentration of both the boiled water and the milk powder determine lead intake of young infants. Previous studies estimating lead intake from formulas utilized measured lead concentration in tap water instead of that in boiled water.

We studied the effect of 1 min of boiling on lead concentration in water. Water samples \( (N = 23) \) from households with lead plumbing from Vienna were analyzed for their lead concentration before and after boiling (Fig. D-2). Boiling for 1 min substantially reduced the lead concentration of water: Pb concentration in tap water samples \( (N = 23) \) was 28.3 ± 42.0 (mean ± SD; median 15.6) \( \mu g/ \)liter; and after boiling for 1 min it was 7.6 ± 6.0 (median 4.8) \( \mu g/ \)liter. The difference was statistically highly significant \( (p<0.0005; \) Kruskal-Wallis test). The cause of the reduction of lead concentration in water during boiling was coprecipitation of \( \text{PbCO}_3 \) during formation of boiler scale \( \text{(CaCO}_3\text{)} \). Therefore estimates of lead intake from formulas utilizing lead concentration in tap water may be too high. Our study indicated that even water with high lead concentration can be used safely if it is boiled for at least 1 min before use.

Dr. Chisolm: Dr. Haschke's data are most interesting for they indicate that the lead in hard water has coprecipitated with the salts in the boiler scale, thereby substantially reducing...
the amount of lead actually entering the formula. By contrast, in Scotland where very acidic soft plumbosolvent water conveyed in lead pipes has been an important problem, the studies of Michael Moore have shown that "kettle" water Pb content is highly correlated with blood lead. This, of course, is the water actually used to prepare an infant's formula, so it is not surprising that "kettle" water lead is a much better predictor of blood lead than tap water lead values. These two sets of data illustrate nicely the difference between soft and hard water. Wherever soft, acidic, plumbosolvent drinking water is conveyed in lead pipes in the distribution system, a problem may exist. Fortunately, drinking water lead can generally be corrected by adding salts at the water purification plant in an amount sufficient to raise the pH to approximately pH 8.0. Sometimes additional buffering is necessary to maintain a relatively uniform pH throughout an entire distribution system.

Dr. Golden: Dr. Bergmann's comments are very important. We have seen a high accumulation of lead in the hair of some malnourished children in rural Jamaica, with no heavy traffic and no obvious lead anywhere around the house. If we compare the lead level to the zinc level in the hair, we have found lead levels in hair up to 10 times the concentration of the zinc. I should emphasize that these children are not growing. When the children are growing normally, we do not find this.