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Age and Sensitivity to Lead Toxicity: A Review

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During the past 20 years considerable attention has been focused on the epidemiologic features of childhood lead poisoning in the United States. Large numbers of children with symptomatic intoxication, as well as those with incipient symptoms, were commonplace a decade ago for physicians working in inner-city hospitals. With the recent availability of improved screening techniques, as well as a variety of environmental control measures, the incidence of symptomatic lead poisoning in children has diminished significantly in recent years.

With the focus shifting from children with dangerously elevated body lead burdens to those with less significant exposures, increased attention has been directed to the various inherent metabolic and physical characteristics of the young that may influence the toxic effects of lead exposure. A number of differences with respect to lead exposure, absorption and retention, and varying nutritional conditions between children and older individuals are discussed. Experimental studies dealing with age differences of lead-treated animals are examined, and relevant human studies are reviewed.

Introduction

The overall clinical picture of acute childhood lead intoxication has changed in the United States in the past 20 years. Until approximately 15 years ago, the majority of clinical interest was focused on children who presented with the acute signs and symptoms of lead poisoning (*1*, *2*). These ranged from vague complaints such as nausea, colicky abdominal pain, and headache, to those symptoms characteristic of acute encephalopathy, including coma and convulsions, often resulting in death. In the mid-1960's it became increasingly apparent that a significant proportion of those children who experienced central nervous system symptoms as a result of lead exposure exhibited irreversible neurologic impairments. Perlstein and Attala noted that 82% of the children they followed who survived an episode of lead encephalopathy experienced recurrent seizures and/or were judged to be mentally deficient (*3*).

As additional follow-up studies of children who experienced symptomatic lead intoxication continued to confirm the observations of Perstein and Attala, the efforts for a number of communities became focused on identifying children prior to the onset of symptoms. Lin Fu has summarized a number of these earliest screening programs from such cities as Chicago, New Haven, Philadelphia, and New York (*1*). The majority of children screened were in the age range of 1-5 and were selected for a number of high risk factors, such as socioeconomic status and residence in deteriorated housing areas. The percentage of children with blood lead levels exceeding 40 μg/dl of whole blood ranged from 20% to more than 40% in a number of these earliest large-scale screening projects.

Fortunately, interest in the early detection of children with increased body burdens of lead has continued. The Federal government began providing extensive funds in 1971 supporting childhood lead screening and environmental hazard reduction projects, and during the past 6 years there has been a dramatic reduction in the morbidity and mortality of lead poisoning in children in the United States. Klein has recently noted that only three children with symptomatic lead poisoning were seen at Children's Hospital of Boston in 1974 and 1975, a marked decrease from the number of cases seen ten years ago at the same institution (*4*). The same trend has also been noted in Baltimore, as is summarized in Table 1.

The trends noted above involving the epidemiology of childhood lead exposure have resulted in a shift of medical attention from those children with

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Table 1. Incidence of symptomatic lead poisoning.[a]

Year	No. of clinical cases	No. of deaths
1959	66	2
1960	53	4
1961	48	1
1962	44	1
1963	42	3
1964	45	1
1965	32	0
1966	32	1
1967	15	1
1968	13	0
1969	19	0
1970	20	1
1971	11	0
1972	8	0

[a] Data of Klein (4) from Baltimore City Health Department.

markedly increased body burdens of lead to those with less significant exposures. Increased interest has developed in defining and understanding any particular inherent metabolic, physical or behavioral characteristics that render the young more vulnerable to the toxic effects of lead (5, 6). For a number of years the incidence of acute lead intoxication has been noted to be more prevalent for children than for adults. However, until recently it was commonly suggested that this facet of Pb toxicity was not necessarily the result of a greater biological susceptibility of children, but rather that children were much more likely to experience conditions of excessive lead exposure (7). Children indeed may well be exposed to greater amounts of environmental lead due to age specific behavioral patterns, but recent evidence indicates that there may also be age-specific differences regarding other variables affecting lead toxicity such as lead absorption through the gastrointestinal tract, nutritional deficiences of the young, and specific biologic differences involving the effects of lead on the hematopoietic and nervous systems.

Lead Exposure in Children

Young children, especially those who live in deteriorated housing, have been known for years to be susceptible to the hazards of lead poisoning by virtue of their exposure to lead based paint. In previous years the "classic" case of lead poisoning occurred in a child who exhibited pica for flaking lead-based paint chips (2, 8). Lead-based paint, widely used for interior surfaces of homes and apartments prior to World War II, commonly contained 10% or more lead by dry weight (100,000 ppm). Habitual ingestion or mouthing of paint chips with this concentration of lead often resulted in a massive lead exposure for the young child. As large-scale screening projects were developed, however, a sizable proportion of inner city children were often discovered who had asymptomatic blood level elevations and in whom the habit of pica could not always be documented (5). Furthermore, parents of children living in the same houses seldom exhibited similar blood lead elevations. Sayre et al. noted in a study of inner city children that those children living in older homes consistently have more lead on their hands than children of similar age living in newer homes or in the suburbs (9). (Fig.1) This study also revealed a definite correlation between the lead recovered from children's hands and the amount of lead in interior dust samples of their homes. They also noted a significantly higher concentration of lead in floor smears of older inner city homes than in newer homes, or those found in the suburbs.

Sayre's findings suggest that a significant amount of lead can be easily recovered from the hands of children who live in the presence of lead-based paint. Furthermore, it is suggested that the normal hand-to-mouth activities so common in preschool children might constitute an inherent increased risk for this age group for exposure to and ingestion of lead from their environment. This mechanism is also likely responsible for the significantly in-

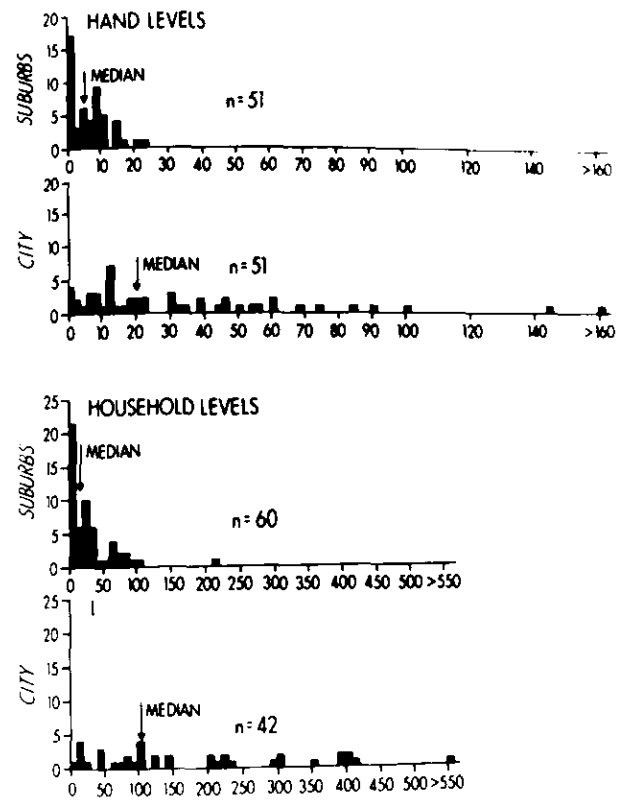

FIGURE 1. Hand and household Pb levels from Rochester, New York. From Sayre et al. (9), with permission.

creased elevations of blood lead values recently noted in children living near lead smelters (*10*). Landrigon et al. reported that 42.5% of preschool children who lived near the El Paso, Texas smelter had blood levels of 40 μg/dl whole blood compared to 5.0% of adults with similar elevations.

Gastrointestinal Absorption of Lead

Kehoe's metabolic balance studies involving healthy adult male volunteers indicated that approximately 10% of ingested lead is absorbed by the gastrointestinal tract (*11*). Until recently, it was assumed that children and infants absorbed a similar proportion of their ingested lead, although similar balance studies with children were not available. Forbes and Reina recently noted that young rats absorb a much greater percentage of ingested lead (^{212}Pb), and at the time of weaning, the absorption suddenly changes and is similar to that observed in adult rats (*12*). They noted a similar pattern with Fe and Sr and postulated that the maturation process is not element-specific, but rather probably is indicative of developmental changes in the intestine. Alexander et al. recently reported the results of metabolic balance studies in eight healthy children whose ages ranged from 3 months to 8 years (*13*). The results of these 72-hr balance studies indicated that approximately 50% of dietary lead was absorbed, and that 18% was retained. Ziegler et al. has also performed balance studies in nine children whose ages ranged from 2 months to 2 years (*14*). Multiple 3-day balance studies were carried out. When dietary lead intake exceeded 5 μg/kg-day, net absorption averaged 41%, and net retention was 32%. The children included in this study had a mean dietary intake of 9.4 μg/kg-day, a figure that is thought to be consistent with the normal child's dietary intake of lead (*6*). Gastrointestinal absorption at higher lead intake was not investigated. Thus from both experimental studies as well as from these two balance studies with healthy children, it appears the young absorb more lead through the gastrointestinal tract than do adults.

Factors Relating Nutritional State and Lead Toxicity

It has been noted previously that the nutritional status of a population may play a significant role in determining the overall toxicity of environmental contaminants (*15*). Iron deficiency is probably the most widespread nutritional deficiency in preschool children in the United States (*16*). An association between lead poisoning and iron deficiency in children has been noted for years, and a synergism has been suspected. Six and Goyer reported a definite increased retention of Pb in both soft tissue as well as bone in rats maintained on an Fe-deficient diet (*17*). Excretion of δ-aminolevulinic acid (ALA-d) was also increased in these rats compared to their controls.

Mahaffey has also recently demonstrated that by reducing the recommended daily calcium allowance for laboratory rats by 20%, gastrointestinal absorption of lead is enhanced (*18*). In addition, the influence of low dietary calcium directly affected the metabolic parameters of lead toxicity such as the urinary excretion of ALA-d. The increased lead retention of animals on calcium deficient diets suggests a competition between the two elements for gastrointestinal absorption. Additionally, recent evidence involving bone organ culture studies indicates that low calcium concentration of extracellular fluid enhances the release of Pb from bone (*19*). This finding may have particular relevance to inner city children with increased body burdens of lead. Sorrell et al. have recently reported a significant difference in serum calcium concentrations between a control group of children and a group whose blood lead levels were extremely elevated (*20*). The control group had a mean blood lead concentration of 23 μg/dl and a mean calcium concentration of 9.85 mg/dl, whereas the lead-exposed group had a mean blood lead concentration of 84 μg/dl and a mean calcium level of 9.08 mg/dl. These authors suggested that some children, by virtue of their calcium-deficient state, were at particular risk for the toxic effects of lead.

The majority of studies relating nutritional deficiency states to lead toxicity have involved experimental animals. The relevance of these studies to human health is speculative. Nonetheless, it is well known that the population at greatest risk for a number of nutritional deficiencies that may potentiate the toxicity of lead is also at greatest risk for increased lead exposure, that is, young children from the lower socioeconomic background (*5, 6*). Hence, by virtue of this association, certain subgroups of children may be more vulnerable to the toxic effects of lead.

Physiologic Vulnerability of the Young

The toxic effects of lead on the hematopoietic and central nervous system has been extensively studied in both laboratory animals and humans. The effects of lead exposure on the heme biosynthetic

pathway is well known, and it has been shown to interfere with a number of specific steps in the production of hemoglobin (*7, 21*). Diminished activity of ALA-d and an accumulation of protoporphyrin in erythrocytes (FEP) are among the earliest hematologic changes resulting from lead exposure. Roels et al. recently studied a population of children that lived near a lead smelter. In this group there was a direct correlation between the elevation of FEP values and blood lead levels (*22*), a finding noted by others (*23*). They also noted that children exhibited higher FEP values for a given blood lead level than did adults, and concluded that children were at a greater risk for the lead effect on the heme biosynthetic pathway. They noted the threshold value for elevated FEP occurred at a blood lead level of 20 μg/dl, whereas that for adults was 25–30 μg/dl.

Some of the effects of lead on the central nervous system also appear to be age-dependent. During the rapid growth phase, the mammalian brain appears to be susceptible to a wide variety of insults (*5, 6*). Dobbing has noted that there are wide species variations for the rapid brain growth phase, and that these differences must be kept in mind in order to make valid animal data interpretations (*24*) (Fig. 2). The vulnerability of the developing central nervous system may derive from a number of factors, including inherent physical differences of the immature brain and incomplete development of the blood brain barrier (*25*). Pentschew and Garro first demonstrated the development of experimental encephalopathy in suckling rats of mothers who were fed lead in their diet (*26*). More recently, Brown has showed that suckling rats of dams who received lead in their diet on days 1-10 demonstrated decreased learning ability, but not those when the dam received lead on days 11–20 (*27*).

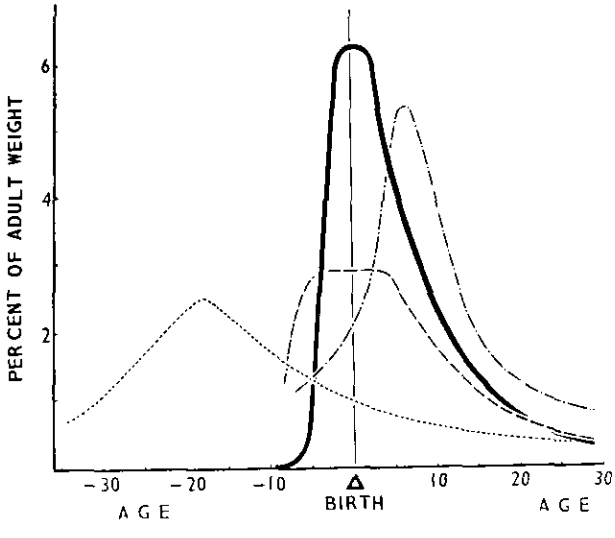

FIGURE 2. Velocity of human brain growth (wet weight) compared to that in other species, with prenatal and postnatal age expressed as follows: (——) human, in months; (--) guinea pig, in days; (— —) pig, in weeks; (— ·—) rat. From Dobbing (*24*), with permission.

Table 2. Age differences with excess lead exposure.

	Children	Adults
Dose	Pica, "normal" hand-to-mouth activity provide greater risk from Pb in paint, paint-dust, dirt	Less likely to ingest Pb from hand-to-mouth activities except in industrial exposure
GI absorption	30-50%	10%
Fe deficiency enhances Pb retention	Common in many (10-40%)	Less common (<10%)
Ca deficiency enhances Pb retention	Common among disadvantaged	Uncommon
FEP elevation (threshold value, blood, Pb)	20 μg/dl	25-30 μg/dl
CNS effect	Encephalopathy	Peripheral neuropathy
Onset of CNS effect	Often sudden	Gradual

Differences in the clinical manifestations of lead poisoning in humans has also been shown to vary with age (*5, 28*). Clinical signs and symptoms, especially those involving the gastrointestinal and central nervous system, generally appear at somewhat lower blood lead levels in children compared to adults. Moreover, clinical symptoms often occur suddenly in children, especially those characteristic of encephalopathy, whereas there is often an insidious onset of symptoms in adults, and signs of encephalopathy are unusual (*5*). Peripheral neuropathy, on the other hand, is relatively rare in children but is known to occur commonly among adults who experience prolonged lead exposure (*28*).

In summary, there appear to be a number of inherent differences of children when compared to adults, that render them more vulnerable to the toxic effects of lead (Table 2). In addition to the child's likelihood of greater exposure to lead under certain conditions, a number of other factors contribute to this risk, including a greater gastrointestinal absorption, an increased incidence of nutritional Fe and Ca deficiency states which enhance the effects of lead, and physiologic differences involving the hematopoietic and central nervous systems.

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