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LEAD POISONING — MENACE OR MYTH?
AN UPDATED REVIEW OF EVIDENCE

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Introduction

"Lead poisoning is a serious disease, developing from entirely man-made hazards, which should be controlled by appropriate legislation." Byers and Lord, 1943.[1]

Few rational people would argue with the concluding statement of Byers and Lord's classic description of the long-term sequelae of lead poisoning in childhood. There has long been an awareness of the potential for high doses of ingested lead to cause severe clinical illness leading to death or chronic neuro-developmental impairment. There is serious speculation that the fall of the Roman Empire owed more than a little to the effects of lead thought to have been leached out of the cooking utensils used to prepare foods and wines for the aristocracy.[2] In the early 1970's lead screening programs for preselected high-risk children in older core areas of many American cities revealed that up to 40% of these children had blood-lead (PbB) levels of >40 μg/dl.[3] In a 1979 paper, Chisolm and Barltrop[4] refer to 40,000 American children a year showing "undue lead absorption."

Recent Canadian data suggest that the situation in this country may be rather different. In the 1978 Canada Health Survey[5] none of the 1,950 children assessed between ages three and nine years had PbB >20 μg/dl, although another 490 children in this age group (20%) missed being sampled. The 1984 Ontario Ministry of Health Survey[6] of PbB in children under age six found 4.2% of 1,269 children with levels >19 μg/dl, of whom 1.4% were >24 μg/dl. Based upon fragmentary Canadian data over the past 13 years, there is an impression that blood lead levels of Canadians living outside of "hot spots" are decreasing.[7]

But whatever the pattern of blood-lead levels in the pediatric population, a fierce debate now rages over a new dimension of the "lead issue." There are probably few issues in contemporary child health as controversial,[8,9] complex,[10] and politically charged[11] as the question of the impact of "subclinical" lead burden on the health, development, and behaviour of children. For each study "proving" that subtoxic doses of lead impair brain function in childhood,[12,13] another paper can be cited purporting to show that differences in the health and development of exposed and unexposed populations of children can be accounted for by factors other than body lead burden.[14-16]

It is the aim of this Update to tease out some of the complexities of this controversy, and to draw conclusions about what is known and should be done when children are found to have an undue body lead burden. In this exploration, I shall also try to illustrate the limitations of simplistic cause-effect reasoning about etiology when applied to complex phenomena, such as child development and function, and to highlight some methodological problems confronting the investigator exploring these questions.

Lead Poisoning

It has been noted frequently in the recent pediatric literature on lead that classical childhood plumbism with encephalopathy is relatively rare now (and perhaps for this reason might be missed by physicians no longer ranking lead poisoning high on their differential diagnosis). Lead in high concentrations exerts its major toxic influences on the central nervous system (CNS), hematopoietic system, and the kidney.[17] Most serious in

terms of morbidity and mortality are the CNS signs and symptoms. These are generally nonspecific and include ataxia, clumsiness, weakness, altered sensorium, coma, and convulsions, probably due to cerebral vasculopathy and severe edema.[4] Inhibition of heme synthesis by high concentrations of lead leads to a microcytic hypochromic anemia, morphologically identical to the findings of iron deficiency anemia, with which it often co-exists. Renal dysfunction associated with acute lead intoxication may mimic the Fanconi triad of hyperaminoaciduria, glycosuria, and hyperphosphaturia, all of which are thought to be reversible.

The Centers for Disease Control (CDC) have recently revised and reissued their guidelines for lead screening and the management of children with elevated body lead burden.[18] The authors define several categories of risk (low, moderate, high, urgent) based upon a combination of erythrocyte protoporphyrin (EP) and blood-lead obtained by venous sampling. In their schema, any child with an EP >34 μg/dl should have a blood-lead and repeat EP by the extraction method. Any child with a PbB >24 μg/dl should also be carefully assessed, particularly if EP is >34 μg/dl. Management will then depend upon the risk levels as defined in tables in the paper. The appendix to the report is a reprint of a contemporary paper on the treatment of childhood lead poisoning.[19]

Unfortunately, symptoms of undue body lead may correlate poorly with actual blood-lead levels. For example, Kline[20] describes a 22-month-old child with a blood-lead level of 110 μg/dl who was virtually asymptomatic before admission to hospital for chelation therapy. Nonetheless, the index of suspicion should be high for certain groups of children.[21,22] Inner-city children are exposed to the cumulative aggregations of lead-based paints in older houses.[3] In this group, children aged one to three are specially vulnerable because of their developmentally normal habits of mouthing objects, sucking fingers, and spending a large amount of time on the floor and ground. Children with pica are the group classically associated with lead intoxication from repeated ingestion of non-food substances. Based on evidence from animal studies, children with nutritional inadequacies, such as iron, protein or calcium deficiency, may be more prone to absorb and retain lead than well nourished children.[3,4,18]

Lead is everywhere in our environment, and some degree of absorption is probably unavoidable; however, excessive contamination can easily occur for both common and unusual reasons. Common sources of lead are water (especially soft water running in old lead pipes), soil and air (particularly near industrial sites using lead in manufacturing). The lead-based glaze on pottery caused the death of a child drinking (acidic) juice from a jug from which the lead had been leached out.[23] Lead is present in the usual diets of children, prompting investigators to attempt to define "tolerable" levels of lead ingestion.[4,17] These are based on the realization that lead is a ubiquitous element and the recommended levels appear to be consistent with an absence of health effects now recognized to be associated with lead at low levels. However, these decisions are in effect a post hoc acceptance of the existence of lead in the environment and do not constitute an "endorsement" of lead as a desirable constituent of the diet.

Sources of Controversy

In the past decade there has been intense study (and argument) concerning the importance, if any, of elevated lead levels in children who do not show any typical signs and symptoms of toxicity. The issue is polarized between those who are convinced that the evidence of an inverse association between lead and intelligence quotient (IQ) is incontrovertible,[9] and those who remain cautious in interpreting data they feel to be highly confounded.[13] Editorialists in prestigious journals[24-26] recommend care and coolness in trying to resolve this important problem. It is instructive to examine some of the sources of difficulty in reaching clear answers.

Lead and Child Development

Among the most fascinating dimensions of the lead story in childhood are the assumptions about child development, and the etiology of childhood behavioural and intellectual problems. Until recently, questions have been framed and arguments produced in an effort to prove or disprove a direct causal link between lead and lowered IQ or behavioural aberrations in children. There is an assumption of a linearity of cause and effect, which is out of date with contemporary "transactional" concepts of child development.[27]

Thus, for instance, while it has been acknowledged that pica can be a "cause" of lead poisoning, investigators have rarely explored lesser degrees of behavioural or developmental abnormality as potential factors initiating increased ingestion of ambient lead. As an illustration, if a child were developmentally retarded, mouthing of hands and toys might persist beyond the developmentally appropriate age of two or three years. If such a child acquires a high lead burden as a result of continual oral lead ingestion and is later ascertained to be retarded, one might draw a false conclusion about the direction of association between body lead and developmental abnormality. In a paper reporting elevated lead and cadmium levels in the hair of borderline and retarded children, Marlow et al[28] were careful to note that their observations do not constitute evidence of an etiological relationship.

Investigations of the "micro-environmental" influences on children's body lead burden have begun to illuminate the possible interrelationships between lead, behaviour, and intelligence in young children in new and important ways. Milar et al[29] compared aspects of the caretaking environment of 26 children with increased lead burdens with a demographically matched group of low lead children. Among the younger children (aged 12 to 30 months), they found significant deficits in both maternal IQ and qualities of the home environment associated with increased lead burden. In particular, measures of emotional and verbal responsivity of mothers, and maternal involvement with the child, were significantly

lower for the children with elevated blood-lead. One of their conclusions was: "In studies in which maternal intelligence is controlled, deficits in the care-giving environment could still contribute to poorer outcomes found in lead exposed children. Maternal IQ is not necessarily the only determinant of the care-giving environment" (page 343). Hunt et al[30] report similar findings, noting in particular that both inadequate physical care and limited cognitive-emotional care were highly correlated with EP and PbB levels in children hospitalized with a first episode of lead poisoning.

A recent study from New Haven[21] found evidence to support these observations. They noted that factors which tended to impair the ability of a family to provide necessary care and supervision for a young child (high mobility, single parent family, unemployed parents, absence of a telephone, four or more children under age seven) were all statistically associated with higher blood-lead levels.

Charney et al[31] showed that home environments of children with elevated blood-lead levels contained significantly more lead in household dust than the environments of children with low lead levels living in the same inner-city environment. There was also more lead on the hands of children in the high blood-lead group than in the low lead group. These observations contribute to the recognition of the importance of specific environmental factors (e.g., variations in lead burden from one home to another), which might otherwise be assumed to be uniform across a sector of the community (in this case, a stratum of social class).

The relevance of these studies is that they have refocused the inquiry about the lead-development relationship. In addition to questioning the directionality of association between lead and behaviour or lead and IQ, they have begun to take account of the influence of confounding variables on the outcomes of interest. Three recent studies from Great Britain[13,16,32] illustrate the emerging complexity of study methods and statistical analyses in the investigation of the lead-development issue. In these studies, varying attention was paid to sociodemographic and environmental as well as developmental and behavioural factors in drawing inferences about the role of body lead on cognitive and emotional function.

The conclusions reached by Yule et al[13] suggested that there was a real but modest correlation between blood-lead and several aspects of intellectual performance, although they cautioned that their study did not adequately assess social factors. In a subsequent and more detailed study[32] controlling for relevant social factors and parental intelligence, these same investigators found no association between PbB and IQ or several tests of educational attainment. In the study of Smith et al,[16] a broad-based evaluation of parental and social factors was made. The results suggested that when social factors and other influences on IQ were controlled, differences between groups of children with different levels of dentine lead become non-significant on all tests. In other words, social factors appear to explain the largest component of differences in test performances, leaving little (if any) contribution to outcome attributable to body lead.

Methodologic Problems

As in any research endeavour, problems of measurement are legion in the study of the lead-IQ relationship. Blood-lead has traditionally been used as the criterion for ascertainment of children's body lead burden. There is evidence, however, that blood-lead reflects only recent exposure and does not correlate well with cumulative body lead burden, duration of exposure or timing of exposure in the child's past.[4] Depending on one's view of the possible pathophysiology of lead poisoning timing, peak dose, length of exposure or total body accumulation of lead (or some combination of these factors) may be the critical variable(s).[33] Unfortunately, no reliable and valid methods of measuring these types of exposure are known.

More recently, investigators have begun to use tooth-lead levels in children as the criterion of cumulative lead exposure.[12,16] Even here, however, there are both technical and biological problems. Smith et al[16] found important differences in lead content between upper and lower central or lateral incisors of the same children, with variations of up to 30% more lead in upper incisors. In addition, they determined blood-lead to tooth-lead correlation co-efficients as strong as 0.58 (though most values ranged from 0.38 to 0.50). These observations show both that the "gold standard" ("lead standard") measure of tooth-lead can be variable in the same child, and that there is on average only a relatively modest correlation between tooth- and blood-lead values.

Deciding what aspects of child performance to measure poses more problems. Whereas some earlier investigators used standard IQ measures,[34,35] more recent studies have attempted to assess additional aspects of children's functions thought to underlie the "performance" components of standard tests. For example, the Institute of Child Health/Southampton group[16] added observations of visual and auditory processing, attention and memory, and studies of reaction time to the usual intelligence testing, while Needleman et al[12] used in addition a teacher behaviour rating scale to evaluate social performance at school.

Unfortunately, at least two important problems arise in considering this measurement dilemma. First, if one is seeking evidence of subtle dysfunctions in children with increased lead burden, one requires measures of great sensitivity. On the other hand, if the differences between groups are small but "real," based on the capacity of measures to detect minor alterations of function, one is left to ponder the "clinical" significance of these small distinctions between groups. Second, the more tests one does and the larger the sample sizes, the more likely one is to detect spurious statistical differences.

A second problem in lead research concerns the type of studies undertaken to assess etiological relationships.[26,36]

In the absence of any possibility of experimental study of the lead-development question, investigators must resort to descriptive analyses of groups of children with varying degrees of body lead burden. The lead burden may be ascertained early in life and the children then followed forward in time to measure developmental and behavioural outcomes, usually in comparison with a control group (cohort or prospective analytic survey). Attempts are made to match subjects with the abnormality of interest (increased blood-lead levels) to controls with similar socio-demographic characteristics (sex, age, place of residence, parental IQ), who differ with respect to blood-lead levels. The underlying assumption is that the factors on which the groups are matched are the potential confounding variables.

However, matching is often difficult, with resulting uncertainty about the validity of findings. One apparently "positive" study[34] purporting to link elevated body lead with later developmental problems studied children known to have ingested plaster and paint at ages one to three years, and to have elevated blood-lead levels (greater than 40 μg/dl) or radiologic abnormalities. The matched control children all had a negative history of ingestion, but no biochemical or radiological studies were done. Unfortunately, there is no report of any attempt to match children on behavioural characteristics at entry to the study. This leaves open the possibility that later abnormalities of behaviour or learning may have been secondary to earlier developmental or functional problems, which predisposed to abnormal ingestions, rather than the lead "causing" behavioural problems. Several other prospective studies[15,33,35] have failed to find evidence linking elevated lead to behavioural or developmental morbidity.

Cross-sectional analytic surveys assess simultaneously the exposure and outcomes of the population under study. Relatively little time passes between measurement of exposure and outcome, so that the rate of development of abnormality (incidence) cannot be adequately assessed. Therefore, cross-sectional designs usually yield only correlational data, and causality is difficult to infer.

It is essential to understand who was initially included in the study population and what proportion of the inclusion group was actually studied. Evidence abounds[37] that participants in studies differ importantly from refusers, so that complete or almost complete (greater than 80%) data on a sample is vital if the results are to be considered representative.[38]

In a recent highly publicized study reporting correlations between tooth-lead levels and both developmental and behavioural morbidity, outcomes were available for only 30% (154 out of 524) of the eligible children.[12] Exclusions for reasons of bilingual family, two working parents or "lack of interest" in the study could seriously distort the final results in either direction; in any case, one cannot be confident about the generalizability of these findings.[39]

In the study of Smith et al,[16] data was available for 93% of the children selected by previously stated inclusion criteria. This study failed to find evidence to link levels of tooth-lead with developmental or behavioural abnormalities. As the authors point out, however, this was essentially a volunteer study, dependent on school children donating teeth for measurement of lead before developmental assessment. Since there is a suspicion that altruism is linked to social factors, it is not surprising that tooth givers might have lower behavioural abnormality scores than non-givers. The volunteer bias might, therefore, account in part for the failure to find an association between body lead and behaviour, if one exists.

At the present time, evidence[14-16,32,33,35] and opinion[40-43] appear to support the interpretation that, when sociodemographic factors are adequately controlled for in methodologically sound investigations, there is no clear evidence of a statistically significant relationship between body lead burden and developmental and/or behavioural abnormalities in children. What is encouraging as one reviews this literature is that the quality of studies has improved in the past decade. While the problems of design and measurement persist, recent investigators have devised increasingly sophisticated approaches in an attempt to take account of the potential pitfalls in this rocky terrain. The results are occasionally studies of considerable elegance, detail, and complexity.[16]

Conclusions

Given the profusion of conflicting information and the problems of design and measurement, can one draw any firm conclusions about the threat to children posed by lead? Does any clarity emerge from available evidence? Two answers seem difficult to dispute on the basis of current knowledge.

First, as long as lead continues to be part of our environment, children remain vulnerable to clinical intoxication, with the potential disastrous long-term results of permanent CNS damage. Children at special risk are those exposed to contamination from industrial, commercial, food, and water sources; children with a family history of lead poisoning; those with pica; and inner-city children in lead polluted surroundings. For these children in particular, a high index of suspicion about vague clinical symptoms or the finding of microcytic hypochromic anemia should alert the clinician to the possibility of excess body lead and should improve case-finding. Biochemical assessment should be done using the CDC guidelines[18] followed by appropriate clinical management with chelation therapy.[19]

Less clear are the potential clinical and economic benefits of widespread community screening programs, such as those advocated by the CDC.[18] Cadman et al[44] have recently outlined seven guidelines for determining whether community screening programs are likely to be effective. Several questions posed by these authors remain unanswered. First, no randomized clinical trial has been found showing the effectiveness of a lead screening program. Second, doubt remains about the "burden of

suffering" of asymptomatic children with elevated body lead. Third, the problems of measurement of blood-lead have not been solved. Furthermore, in its recommendations concerning the use of erythrocyte protoporphyrin as a screening test, the CDC acknowledges that this biochemical marker is usually elevated in iron deficiency anemia. One must, therefore, rule out this disorder before interpreting the elevated erythrocyte protoporphyrin level as being related to excess body lead. Finally, because negative results at one time reflect only the current lead burden, repeated testing of children age 12 to 36 months would be required for a screening program to be effective.

For all of these reasons, community screening, as opposed to case-finding, remains to be proved of benefit for children.

The second conclusion to be drawn from these data concerns the social, as distinct from the medical implications of the lead problem in childhood. It would seem appropriate to agree that "to a certain extent, lead does act as a marker for social disadvantage."[16] This social disadvantage includes a probable combination of undesirable environmental influences (location, age, and quality of housing) and impaired caretaking capacity (care, nurturance, safety, stimulation), which can easily conspire against the optimal psychosocial development of the youngster irrespective of any putative noxious effects of lead on development. Under these circumstances, intervention for children with lead poisoning must include appropriate assessments of the physical and familial environments of the child, with interventions broadly based to offer improved nurture with a new and cleaner (less lead-ridden) environment. These interventions go beyond "medical" management to include environmental manipulation, long-term support to parents, and appropriate long-term surveillance of both child and family by medical and community agencies.

Finally, it must be recognized that the full answer to questions about the relationship between body lead burden and impaired child development is not yet available. Gloag[25] argues that there is a strong enough possibility of risk to justify energetic measures of all types. And Rutter[10] reminds us that even an apparently small (3 to 5 points average) IQ decrement in children (if such is shown to be the "effect" of lead on development) will result statistically in a doubling of the proportion of individuals in that population with an IQ less than 70. As Rutter expresses it, "Lead has no known benefits to health and it would seem not only reasonable, but highly desirable to reduce the risks of lead exposure as far as possible" (page 21). At both the clinical and community levels, it would seem prudent to support efforts at surveillance, detection, intervention, and particularly, prevention of exposure of our children to lead.

Summary

Lead poisoning is well recognized as a cause of morbidity and mortality in the pediatric population. Although acute toxicity is relatively rare, concern has been raised about the possible association of "sub-toxic" body lead burden, and developmental and behavioural abnormalities in children. After an overview of lead intoxication, this Update addresses the controversial issues. It is argued that the development of children is multi-determined and that if lead plays a role in childhood morbidity, it is probably a relatively small one. The methodologic complexities of studying the relationships between lead and behaviour are reviewed to indicate where current research is being directed to answer these questions. Finally, conclusions are drawn about case-finding, screening, and the social implications of excess body lead in children.

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