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COMMENTARY

A Higher Level of Analysis: Bellinger's, Interpreting the Literature on Lead and Child Development

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THE LEAD DEBATE

WHEN the international prospective studies of lead and child development were launched some 14 years ago, their charge was to address the question of how much lead exposure, if any, during the prenatal and postnatal periods of development is reasonably safe for fetuses and young children. In part, the impetus for the initiation of these longitudinal studies came from earlier cross sectional investigations. One notable example is Professor Needleman's study of children attending schools in Chelsea and Somerville Massachusetts where it was demonstrated that asymptomatic lead exposure is associated with small but measurable declines in IQ (11).

When these forward studies commenced, exposure to lead was virtually inescapable owing to the continued use of tetraethyl lead as an additive to gasoline. Lead paint in older homes and industrial activity also contributed significantly to exposure at several sites. In carrying out this research, the prospective studies documented lead exposure, neurobehavioral development and associated co-factors in a more comprehensive manner than ever before. As the results of these studies began to be published in the midst of the last decade, the lead debate was resurrected. The ensuing dialogue among scientists, clinicians, public health officials and representatives of industry has not always led to enlightenment.

Scientific advancement in the area of lead neuroepidemiology has been circumscribed by the practice of adhering to one absolutist viewpoint or another of the effects of lead on child development. In marked contrast to the character of some of the scientific debate which has occurred over the last decade, Dr. Bellinger has provided us with a thoughtfully conceived integration of the available pediatric data that draws sustenance from the principles of the basic and clinical epidemiologic sciences, and eschews both acrimony and hyperbole. In doing so, he has brought the ongoing exchange of ideas on pediatric lead toxicity to a higher level.

While reading Dr. Bellinger's paper, one gets the sense that we have reached an important milestone in the history of pediatric lead research as well as the debate that has accompanied it. Following years of disputation over whether or not lead-neurobehavior associations are merely the result of the under-assessment of confounding or chance, we now have a large number of epidemiologic studies of high quality that provide reasonably sound support for current public health policy (14,16), as well as an impressive quantity of sophisticated animal studies that reinforce the human findings with astounding consistency (16).

It is particularly significant that, among those prospective studies which have published reports out to school age, three out of four have observed an association between earlier postnatal lead exposure and intellectual attainment (1,2,7). The investigation reported out of Sydney has been the only negative study of school age children thus far (4).

The results of these studies demonstrate that the impact of postnatal lead exposure on neurobehavioral development can be detected in both low and high risk populations since the sociodemographic features of the cohorts ranged from the socially disadvantaged (e.g., Cincinnati) to the middle and upper social classes (Port Pirie, Boston). Although, as Dr. Bellinger points out, it may be more difficult under some circumstances to detect health effects of lead in groups with accompanying and correlated risk factors such as undernutrition, substance abuse, and inadequate caretaking. Thus, for example, results of the psychometric testing of Cincinnati subjects during later infancy and the preschool years were inconclusive (6). However, at school age when psychometric evaluations tend to become more reliable as well as more precise, a significant association between postnatal lead exposure and Performance IQ was observed (7). In this regard, it is also worth noting that we have observed significant associations between postnatal lead exposure and vestibular and neuromotor performance using measures that tend to be less correlated

with social disadvantage than traditional assessments of psychometric intelligence (3,8). In any event, the finding of adverse effects of postnatal lead exposure on the intellectual and neuromotor performance of school-age children is of special importance as measures of attainment and behavior taken after school entry are likely to be predictive of later academic and vocational success.

The Contexts of Development

The principal thesis of Dr. Bellinger's paper is that contextual factors need to be taken into account when evaluating the epidemiological evidence. For lead, he argues that the decline in neurobehavioral performance that is observed in response to increasing body burden will be different between studies depending upon the unique social and physiological conditions that pertain in a particular investigation. In certain respects, it is remarkable that this level of analysis has not already been applied in quantitative and qualitative reviews of the lead literature. Although this author has previously argued strongly for the application of more sophisticated developmental models in analyses of the data from the prospective studies (5,12).

The underlying problem may be found in the perspective that chemical exposures are somehow immune from the moderating influences of social and other factors. The other extreme position is that factors like social class, caretaking habits, nutrition, etc. must merely serve to confound associations between lead and behavior and should not be studied as buffering or exacerbating influences.

As Bellinger points out, a model which takes little or no account of the experimental milieu is untenable to researchers who work with animal models of human toxic effects. Moreover, a simplistic "additive" model of neurobehavioral maturation is not supported by studies of other biological hazards to normal development such as, for example, low birth weight (15). Such an elementary view of the growth of infants and children was largely abandoned by developmental psychology years ago (13). Even in the area of occupational health there has been a longstanding appreciation that chemical exposures can interact with contextual factors that could be regarded as both potential confounders as well as effect-modifiers. An example sometimes cited is the impact of cigarette smoking on the development of pulmonary fibrosis secondary to exposure to natural mineral fibers (10).

Seeking Sensitive Periods and Specific Effects

Lead is without a doubt the most widely studied pediatric neurotoxicant. Yet, as Dr. Bellinger points out, there remain a number of unresolved issues. The results of the international prospective studies have been disappointing in that they were unable to identify a stage of brain development or age span where exposure would produce either the most severe effects, or some specific effect (what is referred to in the paper as a "behavioral signature"). In the most highly exposed cohorts the historical blood Pb profiles were too homogenous to address hypotheses predicting that exposure during a particular period of central nervous system development would produce more severe or specific neurobehavioral deficits (1,7). In these studies it was also the case that age and peak blood lead concentration were confounded, with the vast majority of children presenting with their highest lifetime blood lead level somewhere between approximately 18 and 27 months of age.

Bellinger suggests that exposure around 2 years of age may be critical. This speculation is based upon the Boston epidemiologic data where blood lead level at 2 years of age was most predictive of later deficits in IQ and academic achievement, as well as on some interesting work by Goldstein that described lead's influence on the action of three protein kinases (9). However, for the most part the data from the prospective studies do not speak clearly on this point. One example can be

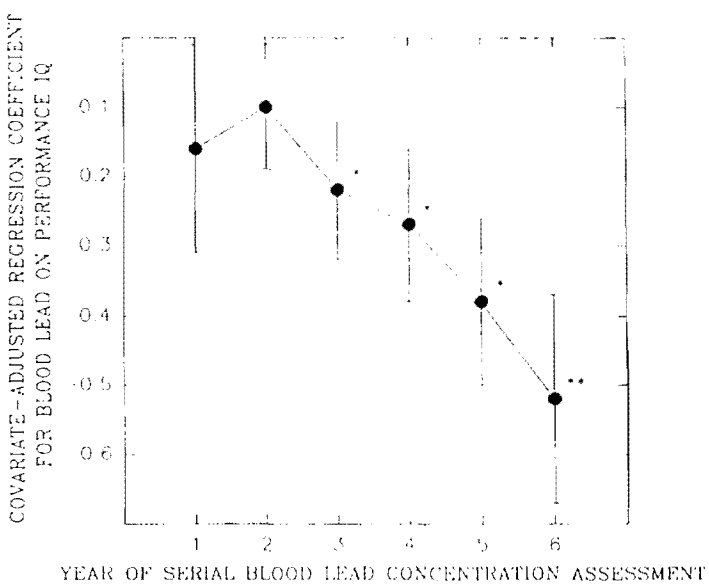

FIG. 1. Plot of covariate-adjusted regression coefficients (and SEs) for mean blood lead concentration by year of assessment and Performance IQ as measured by the Wechsler Intelligence Scale for Children-Revised. Data were previously presented in ref. 6. $^{*}p < 0.05$; $^{**}p < 0.001$.

found in the Cincinnati data. Figure 1 plots the covariate-adjusted regression coefficients for a child's average blood lead level in a given year (the mean of 4 quarterly determinations) and his or her Performance IQ assessed at approximately 6.5 years of age. The relationship between blood Pb concentration at 2 years of age and IQ, though negative, is statistically nonsignificant. Indeed, the general trend is for later measures of lead in blood to be more predictive of attainment. We have observed a similar trend in motor developmental studies at age 6 years. In Port Pirie, serial blood lead concentrations spanning 0-2, 0-3, and 0-4 years of age were nearly equally predictive of IQ measured at 7 years of age (1). At this point in time, specification of a critical or sensitive period for central nervous system damage remains a matter of neuromaturational theory and conjecture.

Bellinger provides a thoughtful discussion as to why more specific tests of neuropsychological domains do not appear to be as sensitive to lead effects as more global measures of development and IQ. If it is true, as Bellinger speculates, that lead may be disrupting the matching process whereby neurons are organized to meet "environmentally specified substrate needs," then considering the "experimental system" or the context in which lead exposure occurs becomes extremely critical. It also follows that more global and broad-based measures of central nervous system development and function are likely to be the most sensitive to toxic effects when evaluated across diverse studies because the net used to capture the variable and contextually specific effect of lead will be deep and wide.

Future Directions

Bellinger's article provides guidance for future research in lead neurotoxicology. It is almost certain that mechanistic studies will continue to be conducted and perhaps expand into investigations of individual genetic susceptibility. As far as epidemiologic investigations of children are concerned, it seems unlikely that we will witness the level of effort and expenditure represented by the international prospective studies. In our efforts to describe the developmental hazards of low level lead exposure, it seems that we have presently reached the limits of chemical analytical precision, neuropsychological estimation, and the epidemiologic method.

With better knowledge of the nature and scope of the public health problem of low to moderate lead exposure, researchers now seem to have shifted their focus toward finding efficient and economical methods of primary prevention such as parental education, nutrition and abatement of environmental sources. Other researchers are studying the developmental benefits of pharmacological treatment of toxicity using chelating agents to reduce the amount of lead sequestered in bone and soft tissue compartments. Succimer (meso 2,3-dimercaptosuccinic acid) was recently introduced as the first approved oral treatment for lead poisoning in children with blood lead concentrations above 45 μg/dL. It is not known if such treatment would also benefit children with lower blood lead concentrations (i.e., between 20 to 44 μg/dL). A multicenter randomized clinical trial of the developmental benefits of treatment with succimer at lower blood lead levels is now underway under the sponsorship and oversight of the National Institute of Environmental Health Sciences.

Future discussions are likely to focus on the lead problem in the context of other public health priorities. The final cost of "getting the lead out" will be substantial. One thing that we can surely depend on in the future is that the lead debate will continue. If this discussion rises to the level of Bellinger's article, we should look forward to a refreshing and productive exchange.

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