Legacy of lead exposure: Consequences for the central nervous system

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The central nervous system appears to be the primary target organ for lead. Children in particular remain at risk for the central nervous system effects of lead, not only in many American cities but also in numerous developing countries where the use of leaded gasoline continues. Those same children, moreover, may sustain many of the risk factors, such as low socioeconomic status and calcium and iron insufficiencies, known to exacerbate the manifestations of lead exposure, including its central nervous system effects. Physiologic conditions associated with bone resorption, including pregnancy, lactation, and aging can also potentiate the central nervous system effects of lead and enhance exposure of adults. Questions regarding safe and efficacious diagnosis and treatment of elevated lead burden, particularly as they relate to central nervous system–based effects of lead have recently been raised. Clearly, greater education of and awareness in the medical community are needed for recognition of problems accruing from lead exposure. (OTOLARYNGOL HEAD NECK SURG 1996; 114:224-6.)

The enactment of laws requiring removal of lead from paint and particularly from gasoline in the United States has resulted in a decline in air lead levels and, concurrently, in blood lead levels of the population. Despite the apparent success of such efforts, the problem of lead neurotoxicity remains for two reasons. First, even with removal of these exposure sources, the residual lead contamination that has accumulated during years of unrestricted use persists. In some areas, especially urban areas, levels of lead exposure remain unacceptably high. Many urban dwellings have layers of lead-based paint that, as they disintegrate or are purposely removed, provide additional and substantial contributions to sources of lead contamination. Lead so incorporated in dust and dirt remains the major source of exposure of pediatric populations. Millions of U.S. residences are still known to contain lead-based paint and thus serve as potential exposure sources for U.S. children.

Another basis for the continued problem of lead neurotoxicity is that research during the past 10 years has provided accumulating evidence showing that the levels of lead exposure associated with central nervous system (CNS) effects, particularly as manifest in behavioral changes, are far lower than ever previously realized. Fifteen years ago, blood lead concentrations in children were not considered problematic until they exceeded levels of 30 to 40 μg/dl. Increasingly, sophisticated prospective epidemiologic studies carried out since that time have resulted in demonstrations of changes in cognitive function, at least on the basis of shifts in population IQ and other psychometric indexes, at blood lead concentrations as low as 10 to 15 μg/dl. Moreover, these effects are corroborated by findings of analogous behavioral manifestations in experimental animals, both rodents and nonhuman primates, at equivalent blood lead concentrations. Such findings are of particular concern given that the CNS appears to be the primary target organ for lead.

Lead neurotoxicity is an even more significant problem in many other countries of the world where leaded gasoline remains in widespread use. As elaborated in a recent *New York Times* article, Dr. David Bates, professor emeritus of medicine at the University of British Columbia, said that no third-world country is even close to mandating unleaded gasoline and catalytic converters. In fact, since the

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mid-1970s, when unleaded gasoline was introduced in the United States and airborne lead levels consequently declined by 95%, airborne lead levels have actually risen in developing-world cities where only leaded gasoline is used. That same article stated that airborne lead levels are so high in Mexico City that parents are advised to keep young children indoors as much as possible.

SUSCEPTIBLE SUBPOPULATIONS

Some have claimed that lead is only a minor contribution to the problems of disadvantaged children in relation to issues of cognitive development and that resources should, instead, be devoted to educational and other deficiencies of such disadvantaged groups. Such arguments, however, ignore the fact that it is these very children, not only in third-world developing countries but also in many inner cities of the United States, who sustain many of the risk factors now known to potentiate the toxicity of lead, including its behavioral toxicity.

Low socioeconomic status is one such factor and in fact has been shown to potentiate the effects of lead exposure on population IQ decrements. In one prospective longitudinal study carried out in a population that was not maximally disadvantaged, scores on the Bayley scales of infant development were inversely related to blood lead concentration. As these scores increased, as would be expected with age, the rate and magnitude of that increase was less pronounced in children of lower socioeconomic status. That is, lower socioeconomic status children continued to sustain greater decrements in developmental progress than did more advantaged children.

Dietary deficiencies and insufficiencies are well known to enhance uptake of lead and to alter its distribution as well. This has been shown for both calcium and iron, two metals that compete with lead for absorption from the gastrointestinal tract. Calcium and iron insufficiency are common in many of these same U.S. children of lower socioeconomic status. Such deficiencies are of course prevalent in third-world countries as well, where nutritional problems are widespread. Thus, together, lead exposure, particularly when combined with the numerous other risk factors that accompany low socioeconomic status, keeps children of the world from achieving their full intellectual potential.

Although children are indeed more susceptible to the CNS effects of lead, adults exhibit similar types of deficits (i.e., in learning and memory) at slightly higher blood lead levels (i.e., 30 to 40 μg/dl), as has been shown in studies of occupationally exposed individuals. Advances during the past 10 or so years in our understanding of the kinetics of lead exposure have shown that physiologic processes associated with calcium mobilization may result in elevated exposure of adults and, hence, enhanced vulnerability to CNS toxicity as well as other effects of lead. These processes include pregnancy, lactation, and aging.

The first two, pregnancy and lactation, impose calcium requirements that, if not met by increased calcium intake, many result in bone resorption as a source of calcium. Bone resorption likewise increases with advancing age, as does a slow down in the rate of bone growth. Because greater than 90% of the total body burden of lead is stored in bone, processes that enhance bone resorption mobilize bone lead stores and make this toxicant available to target organs such as the CNS through the plasma lead compartment. A decline in the rate of bone growth, moreover, means that absorbed lead will not be taken up into bone but may be diverted to soft tissue target organs.

Calcium requirements during lactation are in fact believed to be even greater than those during pregnancy. It is well known that lead can be excreted in breast milk, and thus breast milk may serve as an additional source of lead exposure to nursing babies, an exposure that occurs during critical periods of brain growth and development and at a time when the blood-brain barrier is not fully in place.

Aging represents a period when enhanced vulnerability to the toxic effects of lead might already be predicted. It is a time during which virtually all physiologic systems including the CNS, undergo degeneration. A large study carried out in Germany documented an age-related decline in bone lead concentrations with advancing age. This effect was more pronounced in women than in men, no doubt reflecting postmenopausal processes in women that contribute to bone resorption. Such effects have been noted in experimental animal studies as well, where the decline in bone lead was accompanied by increased levels of lead in brain and in kidney.

Bone resorption during this period of advancing age, with an accompanying mobilization of lead, means in effect that lead exposure is actually increased during a period of already heightened susceptibility because of concurrent degeneration of other physiologic functions, including both CNS and renal functions. Whether this additional exposure to lead actually hastens the rate of decline of any physiologic systems is as yet unknown. It is not

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difficult to imagine how it might contribute to dementias also associated with aging or to renal problems likewise common during later stages of the life cycle. In many instances, the causes of such dementias or renal problems may be unknown.

PROBLEMS OF TREATMENT

Compounding the problems described above are the current uncertainties associated with both the diagnosis and treatment of elevated lead burden. CaEDTA had been the agent of choice for both the diagnosis and treatment of elevated lead burden for pediatric and adult populations since the mid 1950s in the United States. However, a study in lead-exposed rats showing that a single injection of CaEDTA, the analog of the CaEDTA diagnostic test, mobilized lead from bone and increased levels of lead in brain and liver raised serious concerns about the use of this agent. Moreover, injections of CaEDTA during a 5-day period, as in treatment for elevated lead burden, did not result in any net loss of lead from brain. Although early studies suggested a beneficial effect of CaEDTA chelation in reversing cognitive deficits associated with exposure to lead, more recent efforts that include more appropriate control procedures for the interventions per se do not substantiate those findings, nor do experimental animal studies.

New, orally effective chelating agents are in the wings. DMSA (2,3-dimercaptosuccinic acid) and DMPS (dimercaptopropane sulfonate) are currently being evaluated for efficacy in both pediatric and adult populations. Whether these compounds likewise result in mobilization and redistribution of lead to soft tissue target organs remains to be fully determined. Such agents would clearly be beneficial in developing countries where more involved treatment protocols such as are required with CaEDTA would be less feasible because of limited medical resources.

As with all diseases, prevention of lead exposure remains the best medicine and argues for screening programs for young children. Such efforts are particularly important for several reasons. Given the diffuseness of its effects, lead exposure is often a delayed or even overlooked diagnosis in children. Moreover, as the former implies, the problem of lead exposure is generally not recognized in children until signs and symptoms have been manifest. For very young children, such an event may be further delayed by the fact that the verbal behavior needed to report any feelings of illness is not yet in place. An additional argument in support of screening is that as of yet there is little understanding of the reversibility of lead's behavioral toxicity, but those studies that have been carried out suggest prolonged consequences.

CONCLUSIONS

Although great strides have been made in addressing the problems associated with lead exposure in most Western countries, it remains a significant public health problem not only in many urban areas of the United States but also in many third-world developing countries where the use of leaded gasoline continues. Education and screening programs need further promotion in such environments. More precise diagnostic and treatment capabilities are also needed, particularly those that can be effectively used in environments with limited medical resources. In addition, a more informed medical community must be in place for accurate and rapid diagnosis of lead-based problems.

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