

## DOSE-RESPONSE RELATIONSHIP FOR LEAD

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I think it is very important that we put the problem of lead poisoning in its proper context, and the proper context really is dose-response relationship as applies to all toxins in our environment. The remarks that I shall make this morning are really based on information which all of you can obtain in a rather bulky document of some 500 pages, entitled "Air-Borne Lead in Perspective," recently published by the National Academy of Science. While the main information today will be on children, I will refer to data obtained on adults where necessary.

If physicians are to deal effectively with the biologic effects of ubiquitous chemical agents such as lead, a working knowledge of the pertinent time-dose-response relationships is essential. Lead is currently considered a nonessential trace element and is detectable in minute amounts in food and water and in the blood, tissues, and excreta of virtually all healthy persons. Apparently, the biologic effects of the usual daily intake from uncontaminated food and water (approximately 0.2 to 0.3 mg lead/day in adults) is negligible, so that this small "dose" of lead has no known adverse effect on the health of people, but as the chronic "dose" of lead increases, adverse responses of increasing severity become evident. While initial increments in "dose" may be associated with undesirable subclinical effects for which the body may compensate, at least temporarily, further increments in "dose" (and absorption) produce obvious alterations in function and clinical symptoms of illness. Still higher "doses" will be fatal. Thus, as may seem

self-evident, a continuum of increasingly severe adverse responses are apparently associated with increasing doses of lead. The time factor adds yet another important dimension to the problem.

Elsewhere in this issue, a statement by the U. S. Public Health Service entitled "Medical Aspects of Childhood Lead Poisoning," sets forth rather detailed guidelines for the management of children with increased lead absorption, with emphasis on preservation of health and prevention of overt plumbism. An examination of some of the risk factors involved and of our scanty knowledge of the dose-response relationships to lead in children may help to place these rather detailed recommendations in perspective.

In the U. S. Public Health Service statement, great emphasis is placed on blood lead levels, which, in adults, reflect increases in the level of current and recent exposure to inorganic lead salts. In particular, the work of Kehoe in which human adult volunteers were fed supplemental amounts of lead (0.3, 1.0, 2.0 and 3.0 mg lead/day) has shown that blood lead levels increase in proportion to the dose and that the higher doses are associated with a more rapid rate of rise. While the relationship between blood lead levels and current exposure cannot be precisely defined, exponential increases in "dose" appear to be reflected by arithmetic increases in blood lead concentration.

Clinical observations in children are consistent with this observation. The "dose" of lead associated with the repetitive ingestion of a few lead-containing paint chips (or of putty) or lead-contaminated acidic juices may contain 10 to 500 times or more the quantity of lead found in normal diet--a truly enormous dose by comparison. Review of the basic data from previously published

cases indicates that blood lead levels in children with pica for leaded paint may rise from the 40 to 60 mg lead range to well above the 100 mg lead range within a period of one to two months. How frequently this occurs is, of course, unknown, but clearly it can occur. Finally, the blood lead level does not appear to be in equilibrium with the total body lead burden, most of which is apparently rather tightly bound in bone; rather, the limited data available suggest that blood lead levels provide an index of the small but "mobile" pool of lead situated primarily in the soft tissues. It would further appear that this is the fraction of the total body lead burden responsible for the known acute toxic effects of lead.

Both in children and adults with lead poisoning, important interrelationships have been found between blood lead levels, "chelatable" lead, and quantitative daily outputs of aminolevulinic acid (ALA) and coproporphrin (UCP) in urine. Again, arithmetic increases in blood lead levels appear to be associated with exponential increases in these other parameters. Increased excretion of ALA and UCP indicates interference in biosynthesis of heme. The "chelatable" lead (i.e., response to a standardized parenteral dose of CaEDTA) correlates most closely with the daily output of ALA and UCP in urine.

Clinical risk factors may also be defined in terms of accurately determined blood lead levels. Epidemiologic surveys in "normal" adults indicate that mean blood lead levels are approximately 20 mg lead/100 gm whole blood (range 5 to 40 mg lead/100 gm whole blood) in populations without undue exposure to lead. Persons in close daily occupational contact with motor vehicular exhausts in

confined spaces may exhibit blood lead levels in the 40 to 50 mg lead range, but rarely higher. Comparable data are not available in young children, since most of the published data are derived from populations in which pica, exposure to old housing and to air, dust and dirt-borne lead cannot be excluded.

Review of the files of previously reported children show that blood lead exceeded 100 mg in 136 of 139 cases of acute symptomatic lead poisoning. In 98 fatal cases of acute lead encephalopathy reported to the Baltimore City Health Department, the range of blood lead levels at the time of acute illness was 138 to 750 (m=330) mg/100 gm blood. The range in 46 children considered asymptomatic was 55 to 300 mg lead/100 gm. While levels above 100 mg lead do not correlate well with the presence, absence, or severity of symptoms, virtually all such patients may be expected to show significant metabolic and functional abnormalities. Clearly, levels over 80 mg lead/100 gm whole blood in children signify a risk to health that is unacceptable. The biologic significance of sustained blood lead in the 50 to 80 mg lead/100 gm range is unclear: variations in metabolic responses are noted, but the usually mild and nonspecific nature of minimal symptoms precludes precise clinical diagnosis. Whether such children may sustain subtle but significant impairment of function particularly in the nervous system is not known. Nevertheless, such children clearly have a potentially hazardous increase in soft tissue lead and continued excessive intake at a high dose level can quickly cause severe illness. Prompt termination of their abnormal intake is the paramount consideration.

The recommendations of the U. S. Public Health Service statement for pediatric care vary according to the estimate of current risk provided by blood lead levels. Levels less than 40 mg lead are assumed to indicate a negligible risk with normal daily dietary intake probably accounting for most of the intake. (These assumptions remain to be documented satisfactorily in young children.) Blood lead levels of more than 40 mg lead signify some additional source of intake and hence "undue exposure to lead," which may result from airborne or dust-and dirt-borne lead, especially in congested urban areas. If so, current estimates indicate that blood lead levels, at least in adults, are not likely to rise much above the 50 mg lead range. These sources do, however, serve to increase the background level upon which further intake must be superimposed. If, on the other hand, the child's undue exposure to lead results from pica for high dose environmental sources such as leaded paint, putty, lead in dirt, or the use of improperly lead-glazed earthenware pottery, a rapid rise in blood and tissue lead levels may be expected. Only serial determinations will indicate the trend and separate these two groups of children when the initial level lies in the 40 to 50 mg lead range.

Levels from 50 to 79 mg/100 ml of blood indicate an accelerating risk, an increasing probability of demonstrable metabolic impairment in heme synthesis, and the possibility of ill-defined symptoms of illness. Levels above 80 mg appear to present an unacceptable risk, particularly if long sustained. Chelation therapy is clearly indicated in this group, but would be of

progressively decreasing benefit at lower levels of lead in the soft tissues. Because of the persistent and often clandestine nature of pica in some children, and the prevalence of deteriorated housing, serial testing of preschool age children in identified high risk areas would appear to be an essential part of regular health care. The trend of blood lead levels will help to determine the need for ancillary tests and indicated medical care in a given child.

The recommendations concerning ancillary tests are deemed by some as unrealistic in that they call for timed quantitative urine collection. This is a serious deficiency of the current "state of the art." Qualitative tests in random samples of urine for aminolevulinic acid or urinary coproporphyrin (ALA or UCP) are apparently inadequate in children, as they do not discriminate between normal and subclinical increased lead absorption. Since they become reliable indicators only as blood lead exceeds 80 to 100 mg lead, their usefulness is limited to children already at high risk. When reproducible simplified procedures adapted to capillary blood samples can be developed, the wider use of meaningful biochemical data, so often essential to good medical care, will be possible.

Perhaps the most serious limitation imposed upon good medical management of children (and adults) is the very limited availability to the general public of reliable lead analyses in blood and urine. A recent interlaboratory study revealed wide discrepancies in measurements from a number of laboratories. Reliable methods, quality control techniques, competent analysts, and continuous

experience are essential if accurate and reproducible results are to be obtained in any trace metal analysis. The "U.S. Public Health Service method" has served in recent years as a suitable reference method for other dithizone techniques. Criteria for evaluating other and newer ones may be found in the analytical literature.

In conclusion, some may deem the U. S. Public Health Service statement too idealistic. It is, however, aimed at the preservation of health with guidelines based on the limited data currently available. Careful attention to dose-response relationships in studies in experimental animal systems and in clinical investigation may, in the future, help to define more closely some of the thresholds for the various significant adverse toxicological effects of excessive absorption of lead. At the biochemical level, the main adverse effects appear to be in the area of heme synthesis, cellular respiration, and membrane function. At the action level, it is clear that sustained pediatric follow-up during the pre-school years, coupled with better environmental control techniques, especially for the high-dose types of exposure, are essential to minimize this particular hazard to the health of children.