LEAD TOXICITY: SUSCEPTIBILITY AND TOLERANCE

The recognition of factors, which influence the toxicity of lead, is essential to effective control of the influence of environmental lead on human health. Such understanding must, of course, be predicated on knowledge of the mechanisms of lead toxicity. The immense body of literature already written about lead contains many clues and impressions of various factors, both adverse and beneficial, which influence the toxicity of lead. This brief discussion will review a number of such factors, few of which have been subjected to the rigors of experimental confirmation. A consideration of possible antagonisms and synergisms must be based on certain assumptions with regard to the metabolism of lead, particularly concerning events at the cellular level.

Lead is present in the body in two forms, a nondiffusible or fixed fraction and a diffusible or transportable form of lead. Lead in bone is probably in the form of bone mineral and is nondiffusible. Also, 95 percent or more of lead in whole blood is bound to red blood cells and is nondiffusible. Only the small plasma fraction bound to organic ligands is diffusible and, in a sense, is the only portion of lead that is biologically active. Only the diffusible fraction passes in and out of capillaries, permeates cell membranes, and enters the parenchymal cells of the central nervous system, liver, kidneys, and other organs. Lead within soft tissues may also become nondiffusible by forming insoluble complexes. Lead-protein

complexes appear as morphologically dense inclusion bodies in the nuclei of liver parenchymal cells and renal tubular lining cells of lead intoxicated people and animals. The inclusion body may serve to reduce the level of diffusible lead within the cell. Experimental studies suggest that any correlation between lead exposure and toxicity must be related to the soft tissue content of diffusible or ligand-bound lead (1).

Clinical Susceptibility

Age - The children brought to out-patient clinics and emergency rooms of large metropolitan medical centers with acute lead poisoning are usually between the ages of 2 and 5 years. Recent screening studies suggest that many times this number of urban children have evidence of subclinical lead poisoning. (Rennert et al., 1970; Blankma, et al.,1969). These numbers are in contrast to only sporadic occurrence of lead poisoning in adults and the latter are usually associated with identifiable episodes of exposure to large amounts of lead.

This difference in incidence of lead poisoning between children and adults is not, however, proof of greater biological susceptibility of children to the toxicity of lead. It may only mean that children are more prone to over-exposure to lead or the relation of their small body-size to dose. Pica and similar factors which contribute to the relatively more frequent high exposure of lead by young children probably accounts for the increased incidence of lead poisoning in early childhood. Greater incidence of lead poisoning must, however, be distinguished from greater biological susceptibility. There are, nevertheless, many reasons why the young might

be expected to be more susceptible to lead. Many of these have been reviewed by Harriet Hardy[4/] and include speculations that there may be greater vulnerability of young growing tissue, as evidenced by the "lead line" of arrested growth of long bone; the possibility that in children, lead may stay in the soft tissues in an active form; and greater variation in intestinal acidity or alkalinity into pH ranges that may tend to dissolve lead compounds and hence, increase the absorption of lead. Also, shifts of lead into and out of the growing bone of a child may be less predictable (5). If lead dosage in the child is considered on a weight basis, the greater susceptibility of children becomes less startling. Kehoe showed some years ago that young adults ingesting 0.3 to 0.4 mg/day of dietary lead excreted nearly the same amount, but if the diet was supplemented with 1 to 3 mg/ day, excretion was incomplete and accompanied over a period of months by progressively rising blood levels but without evidence of clinical lead toxicity (6). On the other hand Barltrop has documented clinical lead intoxication in a 2-year-old child from ingestion of only 1 mg/ day during a six month period (7). If the quantity of ingested lead is corrected for body weight the 1 mg/day ingested by the 2-year-old child becomes equivalent to 6 mg/day by a 180 lb. adult, a dose almost certain to result in clinical toxicity in the adult.

Clinical manifestation of acute lead poisoning also appears to differ between the child and adult. A large percentage of children with acute lead poisoning are seen by clinicians with central nervous system disease, even coma, whereas in adults, anemia is the predominanting complaint in

patients that have been exposed to a higher dose than children. Encephalopathy in the adults is rare except as the result of very large exposure to lead vapors or organic forms of lead. This difference may reflect inherent sensitivity of the central nervous system of the child to lead, or to a less effective blood-brain barrier. Alternatively it may simply refelct the relatively greater capacity of the adult to store lead in an inactive form, in bone or in lead-protein complexes, which appear as nuclear inclusion bodies.

Seasonal Variation - It is clear that clinical lead toxicity is more common in summer months although affected children are exposed to lead from indoor paint and it is not believed that such exposure varies seasonally. Studies by Kehoe [6] have shown that urinary lead excretion in a person subjected to increased dietary lead is also increased in the summer. It would seem, therefore, that this phenomenon must result from some seasonal metabolic difference. Two explanations, cited by Baetjer (8), include increased vitamin D from the sun's ultraviolet radiation and increased environmental temperature. This latter notion is supported by experimental studies showing that lead-poisoned rabbits subjected to 37° C die in about 4 days, whereas lead poisoned rats kept at room temperature survive. Mice exposed to high temperature and injected intraperitoneally with lead nitrate had a more rapid and higher mortality rate than similarly injected mice kept at room temperature. The added burden of dehydration further lessens the survival of lead-injected mice (8) although it is unlikely that dehydration is clinically relevant in lead poisoned children (9). Seasonal metabolic cycles might explain not only increased susceptibility to infectious disease but may influence nutritional and metabolic abnormalities, ideas that have been reviewed by Sargent (10) but have not been related to the

problems of lead toxicity.

DIETARY FACTORS

Calcium, phosphorus and vitamin D - The absorption of lead from the gastrointestinal tract as well as the partitioning of lead in various body compartments appears to be regulated by some of the same physiological mechanisms that control the metabolism of calcium and phosphorus and the Ca: P ratio. Interest in the relationship of these minerals to lead metabolism has been directed toward their usefulness in the treatment of lead poisoning. Many of the early studies are summarized in papers by Lederer and Bing (11) and Shields and Mitchell (12). Absorption of lead from the gastrointestinal tract is impaired by amounts of dietary calcium and phosphorus above certain low limits. The drinking of large amounts of milk has been practiced as prophylaxis to lead poisoning but the effectiveness of this custom has been questioned (13).

Shields and Mitchell[12] conclude that low dietary calcium or phosphorus or both, does induce a higher retention of lead in the body in comparison with diets containing higher levels of these minerals. Attempts to partition the enhanced retention of lead between bone and soft tissues were limited to a few experiments. More recently, the studies of Six and Goyer (14) have been directed toward determining the effect of a low-calcium, normal phosphorus diet on the adverse or pathological effects of lead and the partitioning of lead between bone and specific tissue compartments.* In rats given the same amount of lead

* Low calcium diets were specifically chosen for these studies because low dietary calcium (low milk ingestion) is thought to be clinically relevant. Nutritional studies (49), (50), (51) suggest that significant populations of urban children do ingest diets low in calcium, but it should be pointed out that some diets contain

in their drinking water (200 ppm) as the controls, low dietary calcium greatly enhanced the severity of anemia and biochemical parameters of lead poisoning including blood lead levels, urinary delta-aminolevulinic acid excretion, and aminoaciduria. The bone lead was higher and bone calcium lower than that found in rats given the same amount of lead and normal dietary calcium. These studies emphasize the correlation between soft tissue lead and severity of clinical toxicity. The conclusion of Shields and Mitchell[12/] that an adequate intake of calcium protects against unwarranted increases in the body burden of lead is also strengthened. In this sense, therefore, dietary calcium is antagonistic to the toxic effects of lead.

Vitamin D, on the other hand, appears to worsen lead poisoning in experimental animals. Lead concentration in blood and bones is greater in animals receiving this vitamin than in those not receiving this addition (15). Presumably, vitamin D enhances gastrointestinal absorption of lead as it does calcium. Whether increased bone deposition of lead during vitamin D administration reflects a specific effect on bone metabolism or merely reflects increased blood levels of lead is not clear, although the authors cited believe the evidence is in favor of the views that the major effect is on absorption, and hence higher blood levels.

Protein:-Dietary protein is another factor that may influence lead intoxication. An early paper on this subject is that of Baernstein and Grand (16). Young rats were fed diets containing 1.5% lead chloride and 6, 13 or 20% casein. Decrease in rate of weight gain and mortality associated with lead toxicity diminished with diets containing higher protein levels. Addition

of cystine or methionine to the 6% casein diet decreased mortality and improved weight gain in the lead-fed as well as in the control rats. Gontzea and coworkers (17) observed that pair-fed rats on a 9% casein diet showed greater susceptibility to lead intoxication (shown by the lead content of liver, kidney, and blood) as compared to rats fed diet containing 18% casein. Recently, DeBarreiro[52/] found that cysteine protected the depression of SALA dehydratase activity by $Pb(CH_3COO)_2$ in rabbit liver.

Ascorbic Acid: The addition of large amounts of ascorbic acid to the diet of industrial workers was suggested as a means of alleviating such symptoms of lead intoxication as basophilic stippling of the erythrocyte (18). Pillemer and coworkers (19)

found that lead-poisoned guinea pigs treated with a scorbutic diet developed neurological symptoms more readily than did lead-poisoned animals fed ascorbic acid adequate diets. A number of other investigators have found ascorbic acid to be without effect in lead toxicity (20,21).

Nicotinic Acid - Several experimental studies suggested that nicotinic acid synthesis from tryptophan was impaired in experimental lead poisoning (22). Nicotinic acid may relieve some of the clinical manifestations of experimental lead poisoning and reduced porphyrinuria in lead poisoned rabbits (22,24). This finding was not confirmed by similar studies in the rat (25).

Other studies have found reduced nicotinic acid levels in blood and urine in lead poisoning along with increased urinary excretion of xanthurenic acid suggesting impaired tryptophan metabolism in lead poisoning (22). However, using tryptophan load tests, Tenconi and Acocella (26) concluded that lead intoxication in rats did not cause changes in tryptophan metabolism similar to that seen in pyridoxine deficient states.

Alcohol - It has long been believed that persons who are alcoholics are more susceptible to the toxic effects of lead. This relationship was clearly stated in Oliver's book on lead toxicity published more than 50 years ago and avoidance of alcoholic

beverages is still recommended for workmen in lead industries (27). Cramér found that Swedish workers who consumed more than 7.5 liters of alcoholic beverage per month experienced a significantly greater incidence of clinical lead intoxication than moderate drinkers (less than 3.7 liters per month) or non-drinkers (28).

Little is known about the basis for the apparent synergism between alcohol and lead, particularly at the molecular level. If the cellular pathology of lead and alcohol are compared, similarities are observed, for example, each produces mitochondrial injury. In vitro studies of mitochondria from ethanol-treated rats show decreased oxidative properties and increased membrane permeability (29). Lead also produces mitochondrial swelling, particularly in reticulocytes of the bone marrow (30), liver (31), and kidney (32), and also impairs respiratory abilities of mitochondria from these organs (33,34,35). Although the molecular mechanisms for the toxicity of alcohol and lead probably differ, effects on the same organelle, the mitochondrion, may result in a mutual enhancement of cellular injury.

Another probable mechanism for apparent synergism between lead and alcohol is through the introduction of nutritional deficiencies by alcoholism which enhance the toxicity of lead. These deficiencies include calcium, protein, and vitamins which have already been commented on.

Other aspects of the subject of lead poisoning from ingestion of illicit whiskey are discussed in detail elsewhere.

Synergism with Other Metals

It might be expected that the metabolism of different heavy metals is similar enough to have overlapping or similar toxic effects. There are few clear examples of such synergism. Several of the heavy metals bind in vivo to red blood cells. However, the attachment of lead to the red blood cell membrane is not influenced (in vitro) by the presence of other heavy metals including cadmium, mercury, zinc, and aluminum which suggests that lead may be metabolized independently of other metals (41). A recent study does demonstrate synergism between the teratogenic effects of lead and cadmium (43).

Influence of co-existant disease

It is reasonable to expect that pre-existant disease of major organ systems might enhance the vulnerability of affected persons to the toxic effects of lead. Documentation of this type of synergism is limited. Several reports from Europe point out the increased susceptibility of persons with hemoglobin anomalies, such as hemoglobin-S and C disease and thalessemia, to toxins like lead which affect red blood cell metabolism. Carriers of such defects must be recognized and protected from lead exposure (43).

Glucose-6-phosphate dehyrogenase-deficient individuals also may show increased susceptibility to lead and should be identified by a screening test before employment in a lead industry (44).

The kidney has a key role in lead metabolism and chronic renal disease from any cause must reduce the lead excretory capacity of an individual. Again, there is little documentation of the contribution reduced renal function has in increasing susceptibility to the toxic effects of lead but studies in rats suggest that the immature kidney is more susceptible than the adult kidney and reduced renal excretory function as occurs in unilateral nephrectomy enhances the toxicity of lead (45).

SUMMARY

Since many factors are suspected of influencing both the severity and clinical manifestations of lead toxicity, it would seem useful to be able to recognize common denominators. The common mode of action of a number of the factors discussed is the effect of mobilizing lead into a transportable or diffusible form. There is presently little known about the biochemical nature of diffusible lead.

Likewise, the toxicology of lead at the cellular or molecular level is ubiquitous, and probably entails a number of mechanisms, depending on the physiologic or biochemical process involved. Lead does interact with certain enzymes; those concerned with heme synthesis, particularly d-aminolevulinic acid dehydrase, are the best studied (46).

Lead ions also impair the oxidative and phosphorylative functions of mitochondria (35) and it is also suggested that lead interferes with transmission of impulses at preganglionic nerve endings by reducing the output of acetylcholine (47). In vitro studies have shown that lead may impair protein synthesis by polyribosome disaggregation (48). In spite of the sophistication of these studies, the present level of knowledge for any of these lead effects is not complete enough to identify a common physico-chemical property of the lead ion.

Understanding of synergistic and antagonistic factors in lead toxicity will be greatly enhanced when more basic knowledge of the metabolism of lead is known.

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