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Environmental Lead Toxicity: Nutrition As a Component of Intervention

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The influence of nutritional status on susceptibility to the toxicity of lead is discussed. Emphasis is given to dietary factors of substantial clinical importance. Subtle changes in susceptibility are difficult to evaluate under conditions of overwhelming lead exposure. It is clear that subtle effects of lead exposure on neurobehavioral and cognitive development are a major concern. The role of nutrition is considered to be an adjunct to reduction of environmental lead exposure, which is the primary means of reducing adverse health effects of lead. Nutrition should be evaluated as a component of strategies to address this broad societal issue.

Nutrition and Environmental Lead Toxicity

Prenatal exposures to lead at concentrations lower than recognized a decade ago adversely affect cognitive, neurobehavioral, and neurophysiological development. The preponderance of results from the published prospective epidemiological studies (*1-3*) demonstrate that exposure to quantities of lead typically present in the environment have an adverse effect on very early neurobehavioral development.

Advances in lead research over the past decade have demonstrated that a very narrow margin of safety exists between typical environmental exposures to lead and the external dose of lead associated with long-term, adverse health effects. Because the margin of safety between exposures and effects is either very narrow or nonexistent, other factors that modify biokinetics of lead or modify susceptibility to lead toxicity assume added importance.

The role of nutritional status in altering susceptibility to lead toxicity has been recognized during most of this century. The topic has been intensely investigated using a variety of techniques (Table 1), particularly with laboratory investigations. The purpose of the following discussion is to provide an overview of the topic, taking a closer look at consistencies, inconsistencies, and future directions for use of nutritional intervention as a component of prevention of lead toxicity.

The extent of understanding how nutritional factors affect susceptibility to lead vary from nutrient to nutrient. For some nutrient-toxicant interactions, the cellular bases of the interactions are well understood. For example, iron deficiency and lead affect the enzyme kinetics in the heme biosynthetic pathway (*4,5*). However, when evaluating the whole animal, the effects of multiple organ systems are combined. In the whole animal, the effects of adding quantities of nutrients above physiologically required concentrations are not consistent. Possibly, the inconsistencies occur because of numerous physiological mechanisms that control concentrations of nutritionally required minerals. Control of tissue concentrations of nutrients will influence the responsiveness of organ systems to environmental manipulation.

Table 1. Sources of information on susceptibility to lead toxicity.

Investigative studies with laboratory animals
Human studies
Epidemiology
Environmental surveys
Health assessment surveys
Dietary surveys
Clinical observations
Metabolic balance studies
In vitro studies of isolated organelles

A number of different nutrients influence susceptibility to lead toxicity. These nutrients include those listed in Table 2. Techniques used to investigate nutrient/lead interactions include isolated cells studied *in vitro, in situ-in vivo* methods, whole animal studies, cross-sectional and longitudinal studies with humans, and clinical trials with nutrient therapy. The latter have typically been poorly controlled with respect to other variables.

Consistency of effects of nutritional status based on this

Table 2. Nutritional factors known to influence susceptibility to lead effects.

Total food intake
Source of dietary calories (e.g., percent of calories from fat)
Calcium
Phosphorus
Iron
Zinc
Various vitamins (e.g., thiamin, ascorbic acid, vitamin E)

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array of techniques differs from study to study for specific nutrients. For example, most investigations of food restriction on absorption and toxicity of lead indicate that diminished food intake increases lead absorption (*6–9*). By contrast, multiple types of investigation of effects of iron deficiency on lead toxicity show much more variability between studies (*9–11*). For example, experimental data have shown consistently that long-term iron deficiency in animals maintained under controlled conditions for a period of months increased the absorption and biotoxicity of lead (*12–14*).

Likewise, *in vitro* studies appear to demonstrate effects of iron and iron status on indicators of lead toxicity. However, clinical investigation of gastrointestinal absorption of lead by adults has produced inconsistent results from study to study (*9–11*). Some investigators find increased lead absorption in at least half of the iron deficient subjects (*11*), while other groups report no change from normal subjects (*9*). Possible reasons for these inconsistencies include measurement techniques, the timing or severity of iron deficiency, other dietary factors, and whether or not the mechanism is direct or related to compensatory responses secondary to nutrient deficiency.

Nutrition As a Component of Intervention

Nutrients and their relation to lead toxicity can be viewed from a number of perspectives. If one is seeking intervention strategies to reduce the impact of lead exposure, three very common nutritional problems can influence susceptibility to lead toxicity.

Total Food Intake

Overall patterns of food consumption and frequency of food intake influence absorption of lead from the gastrointestinal tract, at least among adults (*7*). Although the mechanisms may be complex, the data are relatively straightforward. Lead that is ingested during fasting is absorbed to a much greater extent than if ingested with food. For example, Rabinowitz et al. (*7*) reported that among adult male subjects, lead without food was 35% absorbed; tracer lead ingested with food was absorbed to the extent of 8.2%, and lead in food was 10.3% absorbed. Similar results have been reported by Blake et al. (*8*) and Flanagan et al. (*9*).

Identifying the particular components of food intake that so dramatically reduce lead absorption largely remains to be done. However, some data are available. Possible components are shown in the data presented in Table 3. For example, addition of ferric iron during fasting reduced the percentage retention of the lead dose to that of nonfasted animals (*15*).

The practical role of this information depends on the reason people have limited food intake. Frequency of food intake is controlled by a number of cultural and economic factors. Certainly, shortages of food exist in many parts of the world. In addition, there are numerous individuals, who for various reasons that have little to do with the food supply or economics, have bizarre eating patterns. Many people reduce their frequency of food intake for weight reduction. In industrial situations, people may have odd eating patterns because of lack of food service facilities or work on irregular shift patterns.

Table 3. Influence of diet on lead absorption from the gastrointestinal tract in adult rats (*15*).

Diet	Number of rats	Supplement gavaged	Percent of gavaged ^{210}Pb does ±SEM	
			Liver	Kidney
Rat food	5		0.03 ± 0.01	0.1 ± 0.01
Fasted	13		0.2 ± 0.06	0.8 ± 0.2
Fasted	5	Fe^{3+}	0.04 ± 0.01	0.1 ± 0.03

Calcium Intake

Not only do nutritional factors increase overall lead absorption, nutrients can also have marked effects on patterns of tissue deposition of lead once absorbed from the environment. A striking example of this has been observed with calcium status. This pattern has been recognized since the 1920s (*16*).

The experimental literature on this topic is extensive and rather consistently supports the observations that ingestion of diets low in calcium increases lead absorption and toxicity. For example, rats raised on a low-calcium diet have much higher blood lead concentrations among the calcium-deficient animals (*17,18*), although lead ingestion did not differ (Fig. 1). Similar differences have also been observed in tissue lead concentrations (*18*) (Table 4). Diets low in calcium typically result in greater deposition of lead in nonosseous tissues as well as osseous tissues. This change is observed at both background as well as high lead exposures. Low-calcium diets increased femur and kidney lead concentrations for both the rats receiving distilled and high lead water. At high lead intakes, tissue lead concentrations were increased most in nonosseous tissues.

Although bone has predominantly been considered a storage site for sequestering absorbed lead, bone is not simply an inert storage site. Once deposited in bone, lead

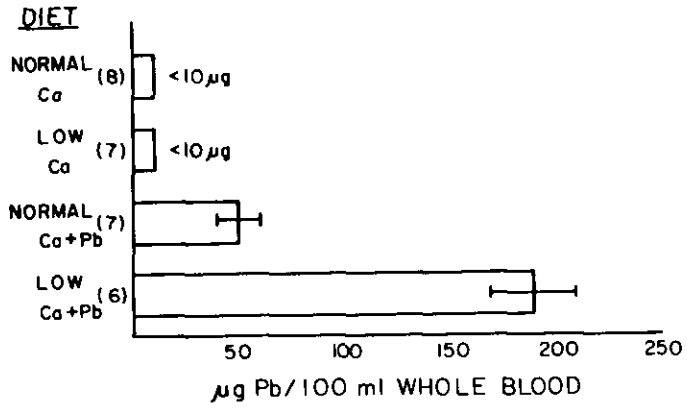

FIGURE 1. Blood lead concentrations of rats raised on a low-calcium diet.

Table 4. Effect of dietary calcium deficiency on blood, kidney, and femur lead concentrations in rats (*17*).

Calcium level	Mean ± SEM Kidney Pb, μg/g[a]	Femur Pb, μg/g[a]
Normal Ca[b]	2.6 ± 1.2	2.2 ± 1.0
Low Ca[c]	4.4 ± 0.6	9.7 ± 2.2
Normal Ca + Pb	29.6 ± 7.0	202.0 ± 22.2
Low Ca + Pb	691.0 ± 203.0	225.0 ± 15.2

[a] Wet weight.
[b] 0.7% of diet.
[c] 0.1% of diet.

can be remobilized from bone in response to both physiological (e.g., pregnancy or lactation) (*19,20*) or pathological (e.g., osteoporosis) conditions (*21*). It has been shown that during the first few years after onset of menopause, there can be marked mobilization of calcium from bone matrix. Analysis of data from the Second National Health and Nutrition Survey (NHANES II) has demonstrated a highly significant increase in whole blood lead concentration after menopause.

Mobilization of long-term stores of lead from the maternal skeleton may be a major determinant in transfer of lead from mother to infant during pregnancy and lactation. Because of concern that maternal blood lead concentrations be maintained as low as possible during pregnancy, this remobilization of lead from bone has substantial public health interest.

Iron Intake

Extensive research has been carried out on various nutrient-lead interactions at the cellular level. One of the most well studied of these areas, in terms of both basic research and public health, has been the interaction of lead and iron. Overall, iron deficiency resulting from ingestion of diets low in iron increases susceptibility to lead toxicity in experimental animals (*12–14*). Unlike calcium deficiency, iron deficiency in rodents appears not to result in a redistribution of lead to nonbone tissues.

The physiological basis for increased susceptibility to lead accumulation and toxicity remains a topic of active research nearly two decades after the initial discovery of the influence of iron status on lead toxicity (*12*). The public health implications for enhanced lead toxicity among iron-deficient persons are substantial. Iron deficiency is recognized worldwide as one of the most prevalent nutritional problems.

In recent years, the impairment of cognitive function among iron-deficient children has been recognized (*22–25*). Lozoff et al. (*25*), using the Bayley Scales of Infant Development, found significant delays in language development among iron-deficient infants ages 19 to 24 months. Analysis of the particular items failed on the Bayley tests showed a pattern; the items failed were those that are most predictive of later intelligence. Additional studies include Oski et al. (*26*), who reported rapid improvement in the development scores of infants (as assessed by the Bayley Development Index) following iron therapy. Re-analyses of their own data did not suggest to Oski et al. that these improvements in cognitive function were due to changes in any particular elements of the Bayley test (*26*). However, the children in this study were younger (9 to 12 months of age) than the subjects (ages 19 to 24 months) for whom an effect on language development was identified by Lozoff et al. (*25*). In the age group under study (9- to 12-month-old infants) by Oski et al. (*26*), development of motor skills is a strong component of the entire testing procedures.

At this time, it is unclear what serves as the biochemical basis that links iron deficiency to behavioral alterations. To date there has been very limited investigation of whether or not neurobehavioral changes and cognitive impairment are more extreme in iron-deficient, lead-toxic children than in either condition alone. However, it is known that long-term iron deficiency, as can be created in experimental animals fed low-iron diets, increases absorption and retention of lead. Clearly, the timing and severity of iron deficiency, as is the case with timing and severity of lead exposures, greatly influence the extent of the cognitive deficit.

In contrast to our more limited understanding of the interaction of lead and iron in cognitive deficits, the effects of lead and iron on the heme biosynthetic pathways have been extensively investigated and characterized biochemically. Both iron and lead affect the heme biosynthetic process. Lead inhibits three major enzymes: δ-aminolevulinic acid synthetase, δ-aminolevulinic acid dehydratase, and ferrochelatase (*27*). Lead is known to interfere with mitochondrial energy metabolism that is necessary to reduce ferric iron to ferrous iron before insertion of iron into the porphyrin ring. When there is insufficient ferrous iron for incorporation by ferrochelatase into heme, protoporphyrin accumulates.

Ferrochelatase activity is sensitive to both lead and iron. Kapoor et al. (*4*) have reported that the enzyme kinetics of ferrochelatase in isolated human reticulocytes change with both iron and lead concentrations. When iron deficiency is present, ferrochelatase is more sensitive to lead effects. The cellular basis for greater susceptibility of iron-deficient animals to lead is that limited iron in the mitochondria apparently enhances the impairment by lead of iron utilization for heme synthesis.

Iron deficiency is common among the same populations of children known to be at greatest risk of lead exposure. The heme synthesis intermediate, protoporphyrin, has been used to determine both lead exposure and iron status. Many programs have measured erythrocyte protoporphyrin concentrations to determine lead exposure. Many others have used erythrocyte protoporphyrin to assess iron nutrition. Analysis of data from NHANES II illustrates that erythrocyte protoporphyrin concentrations reflect both iron status and lead exposures (Fig. 2).

Conclusions

Over the past decade there have been a number of significant changes in how lead exposures are viewed. First, adverse subtle effects of lead have been identified at progressively lower lead exposures. Second, there is virtually no, possibly not any, remaining margin of safety between typical lead exposures and those producing subtle, adverse effects in people.

Progressively lower lead exposures have become of in-

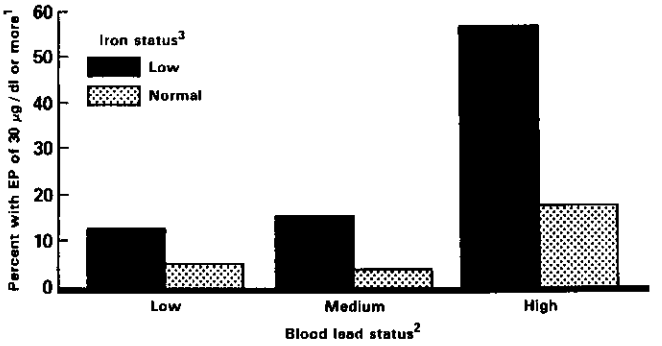

FIGURE 2. Percent of persons aged 6 months to 74 years with erythrocyte protoporphyrin (EP) values of 30 μg/dL whole blood or more by blood lead level (PbB) and iron status, United States, 1976–1980. [1]Predicted from logit analysis. [2]Low, medium and high refer to blood lead concentrations of < 20 μg/dL, 20–30 μg/dL, and > 30 μg/dL, respectively. [3]Low iron status is indicated by a transferrin saturation of ≤ 16%, or a total iron-binding capacity of ≥ 450 μg/dL; normal iron status by a transferrin saturation of > 16%, or an iron-binding capacity of < μg/dL. From Mahaffey and Annest (*5*).

terest from a public health perspective. When lead exposures are overwhelming, nutritional factors do not prevent lead intoxication. However, far lower exposures are of concern in efforts to prevent subtle, adverse effects of lead; the importance of nutrition as a component of a preventive strategy is much greater.

To date, there is information on how certain nutrients and lead interact to increase susceptibility to adverse effects of lead. Evaluation of such intervention very likely requires long-term study. Still missing are the longitudinal, prospective studies to evaluate the potential effectiveness of nutrition as an intervention strategy.

Fortunately, the dietary changes that are favorable, in terms of bioavailability and biotoxicity of lead, are very consistent with general recommendations for consuming a healthful diet (*28*). The type of diets that appear most effective in reducing lead toxicity are very consistent with general recommendations for health-promoting nutrition. Unusual, imbalanced, or bizarre diets are not needed to reduce susceptibility to lead.

Subtle changes in susceptibility are difficult to evaluate under conditions of overwhelming lead exposure. However, based on information presented in this conference, it is clear that subtle effects of lead exposure on neurobehavioral and cognitive development are a major concern. Nutrition should be evaluated as a component of strategies to address this broad societal issue.

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