Susceptibility to Lead Toxicity

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Adverse effects of lead on human health have been recognized for centuries. Nevertheless, current public health measures require a greater understanding of the pathobiology of chronic low level exposure (*1-3*). Such considerations are related to the question of what level of lead intake is harmful and why specific clinical manifestations of lead poisoning are encountered under particular circumstances. The recognition of factors, both synergistic and antagonistic, which influence the toxicity of lead is essential for adequate understanding of the effects of environmental lead on human health. The immense body of literature already written about lead contains many clues to and impressions of such factors, both adverse and beneficial, modifying the toxicity of lead. This brief review will discuss a number of such factors. Few of these have as yet been subjected to rigorous experimental confirmation. A consideration of antagonisms and synergisms is based on certain assumptions with regard to the metabolism of lead; that is, the daily intake and excretion of lead as well as the movement of lead between various tissues and effects on cells and subcellular organelles.

Metabolism of Lead

The principle route of entry of lead into the body is oral. Net absorption of lead by the gastro-intestinal tract is about 5 to 15 per cent; the rest is excreted in the feces. Even inhaled lead particles with an average diameter above 0.5 μ are cleared by ciliary action of respiratory epithelial cells and swallowed into the gastro-intestinal tract. The daily intake of lead by adults probably varies from 0.10 mg/day to more than 2 mg but averages between 200 and 500 μg per day (*4-5*).

Most information about lead metabolism is related to levels of intake and excretion; we know even less about how lead moves about in the body or how it is handled at the cellular level. It is here that more knowledge is very much needed. Inside the body lead must exist in two forms: a diffusible or mobile form and a non-diffusible or fixed form. Lead must be in a diffusible form in tissues which transport it from one part of the body to another as in red blood cells and plasma, and in organs where lead is transported across cell membranes as in the liver and kidneys. Diffusible lead is sometimes equated with "biologically active" lead but this term may be more appropriately reserved for forms of lead which bind to membranes, enzymes, or other proteins.

Most lead in blood is fixed to the red blood cell in a non-diffusible fraction but it is thought that approximately 5% is chelated in the plasma to small diffusible ligands (*6*). The nature of these microligands is not known but may be small organic acids or peptides.

The liver is an important organ in the metabolism of lead. From experimental studies in dogs and rats it has been learned that lead is excreted from the liver mainly in bile (*7, 8*). A portion of ingested lead may be absorbed from the upper gastro-intestinal tract, transported across liver cells and ex-

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creted into the gut by way of the biliary system. The role of the entero-hepatic circulation in lead metabolism has not been quantitatively studied in man.

Lead is excreted by the kidney in two ways; by glomerular filtration and transtubular flow. Teisinger (*9*) has shown that urine lead levels correlate with blood lead levels when blood lead is in the normal range and Selander and Cramer (*10*) have shown a similar correlation for elevated blood lead levels. These correlations, however, are only statistically valid relationships, true for a large number of samples, but an individual urine sample cannot serve in predicting blood lead levels unless, of course, the urine lead level is very high, ie. over 150 μg/day. In other organs of the body, lead is nearly completely non-diffusible or bound lead. Over 90% of the total amount of lead in the body is in bone. The organs with the least concentrations are skeletal or cardiac muscle.

There has long been debate whether lead content of various tissues increases with age. Early studies suggested not, but recent reports which are conducted more precisely show that lead does in fact, accumulate in the body with age, especially in bone. Soft tissue lead concentrations, particularly after the second decade, are realtively constant so that the lead which is retained is for the most part fixed lead or non-diffusible lead.

Total body burden of lead has been variously estimated to range from 150 to 400 or more mg for average adults in the Western World. In the recent study by Barry and Mossman (*11*), lead content of tissues obtained at autopsy show a mean lead body burden of 175 mg for a 70 kg male without history of abnormal exposure to lead. Body burden of lead may be less than 2 mg for children under 10 years of age to over 200 mg for persons in their eighth and ninth decades. Hair may be an easily accessible tissue from which to obtain estimates of body stores of lead and other tracemetals, but caution is suggested in this estimation (*12*).

Toxic Effects of Lead

The most prominent signs and symptoms of lead intoxication may be related to three organ systems: the central nervous system, the hematopoietic system and the kidney. The clinical signs and diagnosis of lead toxicity has been reviewed in detail elsewhere but for the purpose of this review it is important to recognize that in most instances the onset of lead poisoning is a slowly progressive process accompanied by a variable continuum of biochemical and clinical manifestations.

These effects may be divided into several categories, metabolic, functional and histological. The anemia of lead poisoning results from impaired heme synthesis and shortened red blood cell life span. Renal effects include tubular dysfunction and perhaps a form of chronic nephropathy, and central nervous system effects extend from non-specific behavioral abnormalities to encephalopathy, coma and death (*13*). It is difficult, therefore, to establish a definitive clinical symptom or value for one laboratory test above which a person has lead poisoning. Instead, the effects form a spectrum from no effect to definite, clear-cut toxicity.

Blood lead values are probably the most useful parameter to establish whether or not one has excessive level of lead absorption.

Among lead industry workers the acceptable upper limit of blood lead concentration is set at 70 μg per 100 ml (*10*) but many reports claim that 60 μg per 100 ml is the upper limit that should be tolerated in persons without a known source of excessive exposure to lead. In a recent review of blood lead values in various segments of the population, particularly children, it has been emphasized that 40 μg per 100 ml. should be the maximum upper limit of "normal" (*1*).

Factors Influencing Susceptibility

Whether exposure to a particular dosage of lead results in overt clinical toxicity or not may depend on a number of factors both constitutional and environmental which either enhance or reduce susceptibility to the toxic effects of lead. A number of such factors are:

Age
Season of the Year
Calcium, Phosphorus

Iron Deficiency
Dietary Protein
Vitamin D
Ascorbic Acid
Nicotinic Acid
Alcohol
Other Metals
Co-existent Disease
Intracellular Complexing of Lead (inclusion bodies)

Age: Acute lead poisoning is most common in children between the ages of 2 and 5 years (*14-16*). Blood lead levels above 40 μg/100 ml in children may be associated with non-specific clinical effects sometimes referred to as subclinical lead toxicity whereas recognizable symptoms of lead toxicity in adults are uncommon with blood lead levels below 60 μg/100 ml. Persons with continued occupational exposure to lead may have blood levels of 80 to 100μg/100 ml with few or no overt symptoms whereas a young child with this level of blood lead may already have convulsions and coma. There are many reasons why the young might be expected to be more susceptible to lead. Some of these have been reviewed by Hardy (*17*) and include the greater vulnerability of young growing tissue and greater variation in gastro-intestinal acidity or alkalinity to include pH ranges that may be more likely to dissolve and hence, increase absorption of lead. Also, shifts of lead into and out of the growing bone of a child may influence biologic effects. Whether comparable doses of lead based on body weight will produce similar symptoms in children and adults is difficult to answer. Children with acute lead intoxication develop lead encephalopathy but encephalopathy in adults is rare except as the result of a very large exposure to lead vapors or organic forms of lead. Dose-response relationships to large amounts of lead in humans are not documented well enough to answer this question. Also, the greater incidence of lead encephalopathy in the child may reflect inherent sensitivity of the nervous system of the child to lead. Alternatively, the adult may have a greater capacity to store lead in an inactive form in bone. On the other hand, Hardy (*17*) has suggested that the worker in a lead industry may be more vulnerable to clinical lead toxicity following a particular dose of lead at any time because of the likelihood of a high level of stored lead or non-diffusible lead in such persons.

Seasonal Variation: Clinical lead toxicity is more common among children in summer months. Also, Kehoe's data (*5*) suggest that urinary lead excretion in a person voluntarily ingesting supplemental lead is greater in the summer. It would seem, therefore, that this phenomenon must result from some seasonal metabolic difference. Two explanations cited by Baetjer (*18*) include increased vitamin D formation from the sun's ultraviolet irradiation 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 rabbits kept at room temperature survive. Mice exposed to high temperature and injected intraperitoneally with lead nitrite have 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 (*18*) although it is unlikely that dehydration is clinically relevant in lead poisoned children. It has been suggested that seasonal metabolic cycles might explain not only increased susceptibility to infectious disease but may influence nutritional and metabolic abnormalities (Horton, R.J.M., Personal communication). These ideas have been reviewed by Sargent and Sargent (*19*) but have not been related to the problems of lead toxicity.

Calcium and Phosphorus: The absorption of lead from the gastro-intestinal tract as well as the partitioning of lead in various body compartments appears to be regulated by the same physiological mechanisms which control the metabolism of calcium and phosphorus. Early studies summarized in papers by Lederer and Bing (*20*) and Shields and Mitchell (*21*) show that absorption of lead from the gastro-intestinal 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 (22). However, Kostial and coworkers (23) have shown that calcium and phosphate additives to cow's milk reduce body burden of lead in newborn rats. Greater retention of trace amounts of dietary lead^{203} occurred in 5-7 day old rats fed cow's milk only, compared to cow's milk supplemented with calcium and phosphate.

Shields and Mitchell (*21*) conclude that low dietary calcium, phosphorus or both induce a higher retention of lead in the body in comparison with diets containing higher levels of these minerals. Attempts to partition the increase in retained lead between bone and soft tissues were limited to a few experiments. Six and Goyer (*24*) have shown that low dietary calcium greatly enhances the severity of anemia and biochemical parameters of lead poisoning including blood lead levels and urinary d-ALA excretion and aminoaciduria in rats given the same aount of lead in their drinking water (200 μg/ml).

Iron Deficiency: Children with lead poisoning often have iron deficiency anemia and either lead poisoning or iron deficiency results in a microcytic anemia. A synergism between the two conditions has been suspected. The tendency for children to have pica, a factor in childhood lead poisoning, may be one level of interaction between these two conditions. Experimental iron deficiency, however, does result in greater tissue concentrations of lead and toxicity in rats given subtoxic levels of lead than occurs in control rats (*25*).

The mechanisms by which calcium and iron deficiencies enhance susceptibility to lead toxicity appear different as shown in Table 1. In control animals without added lead, lowering the dietary levels of calcium or iron results in significantly increased levels of lead in bone. There is no elevation of soft tissue lead on the low iron diet and a slight elevation of soft tissue lead on the low calcium diet. This is without added lead. When lead is added to the drinking water at the level of 200 μg per ml, there is an increase in bone lead on a nutritionally adequate diet. Soft tissue lead is also increased. On a low iron diet, bone lead approximately triples in content but soft tissue lead remains approximately the same as on the nutritionally adequate diet.

Table 1. Comparison of Tissue Concentrations (μg/g wet tissue) of Lead in Rats Fed Diets Deficient in Calcium (LCa) and Iron (LFe) and Nutritionally Adequate Diets (NCa, NFe). Data is From Six and Goyer *(24, 25)*

DIET	BONE Pb	KIDNEY Pb
No Pb		
NCa, NFe	2.2 ± 1.0	2.6 ± 1.2
LFe	10.6 ± 3.0	1.9 ± 0.4
LCa	9.7 ± 2.2	4.4 ± 0.6
200 μg Pb/ml H_2O		
NCa, NFe	74 ± 12	22 ± 4.3
LFe	225 ± 15	28.7 ± 4.8
LCa	202 ± 22	691 ± 203

With the low calcium diet, bone lead is approximately equal to that found in rats fed the low iron diet. However, soft tissue lead is approximately 25 to 30 times that seen on either the nutritionally adequate or iron deficient diet. The changes in renal lead content on the low calcium diet are accompanied by indicators of renal dysfunction, such as elevated aminoaciduria and increased renal size. Therefore, low dietary calcium greatly alters the partitioning of lead from the fixed lead in bone to the diffusible lead in soft tissue. In general, the pathological effects of lead are associated with elevated soft tissue levels but partitioning of lead may be influenced by deficiencies of particular nutrients.

Protein: Dietary protein may influence lead intoxication. An early paper on this subject is that of Baernstein and Grand (*26*). Young rats were fed lead chloride (1.5%) in diets containing 6, 13 or 20% protein. Decrease in weight gain and mortality diminished on diets with 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 control rats. More recently Gontzea and coworkers (27) observed that pair-fed rats on a 9% protein diet showed greater susceptibility to lead intoxication as compared to rats fed an 18% casein diet as judged by the lead content of liver, kidney and blood.

Vitamin D: Vitamin D may enhance lead poisoning in the experimental animal. Lead concentration in blood and bones is greater in animals receiving this vitamin than in those not receiving this addition (*28*). Presumably, vitamin D enhances gastrointestinal absorption of lead as it does that of 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.

Ascorbic Acid: The addition of large amounts of ascorbic acid to the diet of industrial workers was suggested as a means of alleviating symptoms of lead intoxication such as basophilic stippling of the erythrocyte (*29*). Pillemer and coworkers (*30*) found that lead poisoned guinea pigs on a scorbutic diet developed neurological symptoms more readily than did lead poisoned animals fed ascorbic acid adequate diets. Other investigators, however, have found ascorbic acid to be without effect in lead toxicity (*31*, *32*).

Nicotinic Acid: A number of experimental studies suggest that nicotinic acid synthesis from tryptophan is impaired in experimental lead poisoning. (*33-36*) However, using tryptophan load tests, Tenconi and Acocella (*37*) concluded that lead intoxication in rats did not cause changes in tryptophan metabolism similar to that seen in pyridoxine deficient states.

Alcohol: It has been suggested that persons who are alcoholic are more susceptible to the toxic effects of lead (*38*). 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. Each alone can produce mitochondrial injury. In vitro studies of mitrochondria from ethanol-treated rats show decreased oxidative capacity and increased membrane permeability (*39*). Another possible mechanism for 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 alreay been commented upon.

Other metals: It might be expected that the metabolism of different heavy metals is similar enough to have overlapping or similar toxic effects. 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 independent of other metals (*40*). It has been recently learned that cadmium is elevated along with lead in the blood of children with suspected lead poisoning and possible toxic synergism between these metals is being explored clinically (*41*). In addition synergism between lead and cadmium has recently been shown to cause teratogenic effects in experimental animals *(42).*

Influence of co-existent disease: Preexistent disease of major organ systems may enhance the vulnerability of affected persons to the toxic effects of lead but documentation of this type of synergism is limited. A report from Europe points out the increased susceptibility of persons with hemoglobin anomalies, such as hemoglobin S and C diseases and thalassemia, to toxins like lead which affect red blood cell metabolism (*43*). Carriers of such defects must be recognized and protected from lead exposure.

Glucose-6-phosphate dehydrogenase deficient individuals may also show increased susceptibility to lead and should be identified by a screening test to avoid 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 and 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*).

Intracellular complexing of lead (inclusion bodies): Partitioning of lead between subcellular organelles may influence the toxic

potential of a particular dose of lead. Lead has a strong affinity for mitochondrial membranes and mitochondria isolated from liver and kidneys of lead-intoxicated animals have impaired respiratory and phosphorylative abilities. The *in vivo* appearance of mitochondria in renal tubular cells of lead poisoned experimental animals and humans shows altered ultrastructure. Measurement of lead content of cell organelles, however, has demonstrated that the major fraction of lead in renal tubular lining cells is in the nucleus bound in a lead-protein complex in the form of an intranuclear inclusion body (*46*). These bodies are seen by microscopy of liver or renal tubular cells from lead poisoned subjects. The ultrastructure of a typical inclusion body in the nucleus of a renal tubular lining cell of a lead-intoxicated rat is shown in Fig. 1. The lead content of these bodies has been confirmed by autoradiography (*47*), electron probe microanalysis (*48*) and direct measurement following isolation and purification by differential centrifugation (*46*, *49*). It is suggested that the binding of lead that occurs in the inclusion body serves as an adaptive or protective mechanism during transcellular transport of lead (*50*). In the course of excretion of lead from capillaries to bile by hepatic cells, or by transtubular flow in renal tubular lining cells a portion of the lead enters the nucleus where it becomes bound into a lead-protein complex and is no longer diffusible. This mechanism has the effect of maintaining a relatively low cytoplasmic concentration of lead, and, therefore, reducing the toxic effects of lead on sensitive cellular functions, such as mitochondrial respiration and protein synthesis.

Indirect support for this hypothesis is found in experimental studies of the relationship of the formation of intranuclear inclusion bodies and other renal effects of lead. Intranuclear inclusion bodies are observed at a lower dose levels of lead than any other renal effect of lead; in fact, at a lower dose of lead

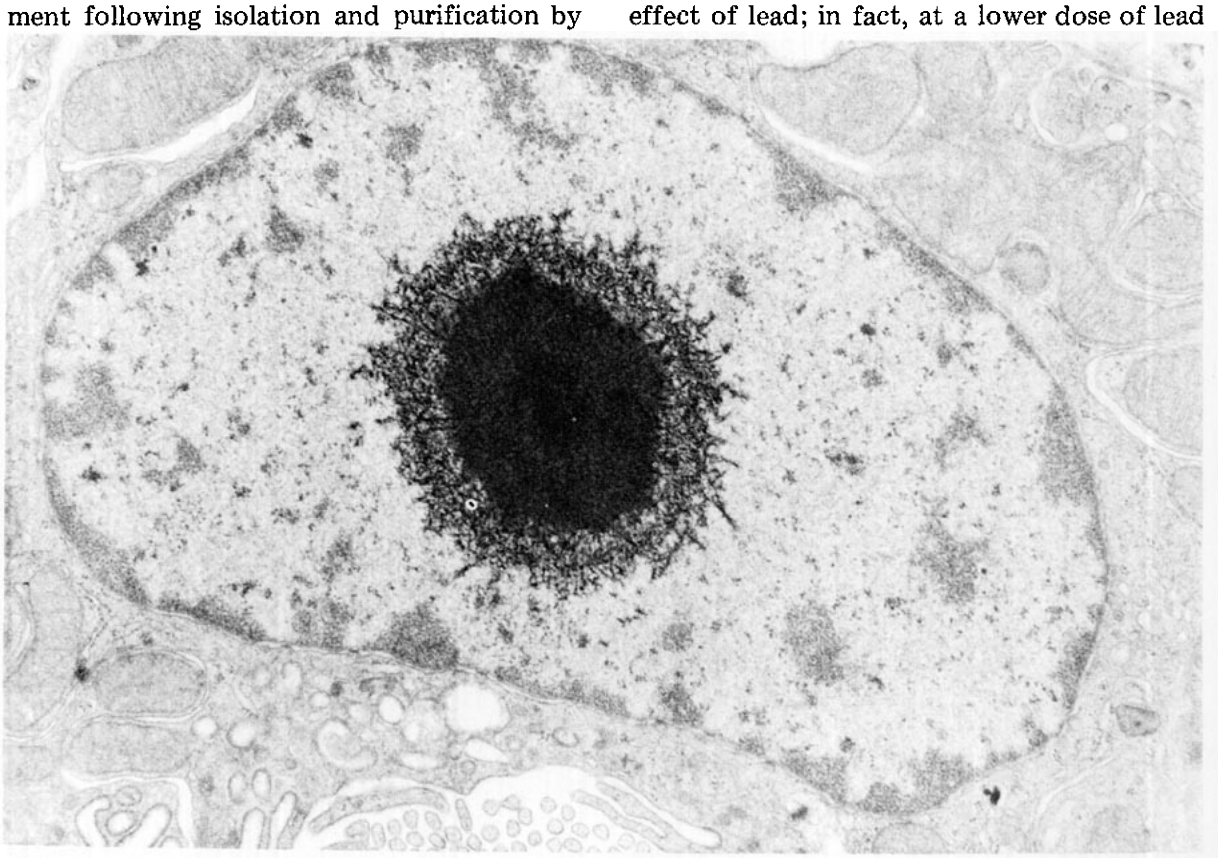

FIGURE 1. Intranuclear inclusion body of renal tubular lining cell consisting of a dense central core with fibrillary margins. X20,000

than that which produces any signs and symptoms of lead toxicity (*46*, *50*).

Summary

There is considerable variation in human susceptibility to lead toxicity and a number of factors have been identified as synergistic and antagonistic. The influence of deficiencies of dietary calcium and iron has been studied experimentally and found to increase soft tissue retention of a particular dose of lead. Synergism with other toxic metals, particularly cadmium, has been suggested but this relationship needs further study.

Genetic factors, such as hemoglobin S and C, and glucose-6-phosphate dehydrogenase deficiencies are also suspected of increasing susceptibility to lead but large scale clinical support of this relationship is not yet available.

Renal disease decreases excretion of lead, thus enhancing body stores and toxicity.

Also of importance are intrinsic metabolic factors which influence subcellular partitioning of lead. The binding of lead as a non-diffusible protein complex in the form of intranuclear inclusion bodies in liver and kidney may function as an intracellular detoxifying mechanism as well as facilitate renal excretion of lead.

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