

Diet and lead toxicity

By M. R. MOORE, *University of Glasgow, Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow G11 6NT*

Introduction

There is no known biological function for lead and any lead absorbed by man or by animal may be classified as potentially toxic. These toxic effects are many, ranging from morphological damage to tissues at higher concentrations, to lesser biochemical effects at lower concentrations. In biochemical systems lead will generally inhibit enzyme activity and result in clinical effects such as the development of anaemia, which is mediated in part through inhibition of haem biosynthesis. Pb has been associated with mental retardation in children and with hypertension and renal effects in adults (Moore, 1977). The potentially most hazardous effects to man are upon the central and peripheral nervous systems where the malign effects of Pb are seldom reversible.

The sources of Pb are many, but the principal absorptive routes are from the diet, from water that is drunk and used in cooking and from the air that we breathe. There may also be secondary and limited absorption by the percutaneous route (Fig. 1). Following absorption, Pb is bound principally in bone (greater than 90%). This Pb is fortunately not readily bio-available. The principal source of Pb exposure is through the diet and therefore any component of the diet that will alter the absorption of Pb, or following absorption, alter the distribution of Pb within the body, (such as by redistribution from the bone) or which influences the normal rate of excretion of Pb, is potentially hazardous.

Absorption

Since Pb must be absorbed to become toxic, the actual rate of absorption and retention is of considerable interest. Most studies to date have examined the effects in laboratory rodents and in general it might be assumed that qualitative effects found in these animals may be extrapolated to man, although quantitatively the effects are quite different. Rats are very much more resistant to the toxic effects of Pb than man. There is a tenfold difference in the rate of Pb absorption from the gut between the laboratory rat and man. Rats will only absorb around 1% of ingested Pb, where man has been shown to absorb in excess of 10% of an ingested dose (Rabinowitz *et al.* 1976). In rats and mice absorption of Pb from the intestine does not appear to be dose-dependent (Garber & Wei, 1974; Conrad & Barton, 1978) until the concentration of Pb is relatively high. Feeding decreases lead absorption (Garber & Wei, 1974) and following food restriction, Quarterman *et al.* (1976) noted that the retention of Pb was increased although there was not always an increase of the Pb content of the animal. However, Conrad & Barton (1978)

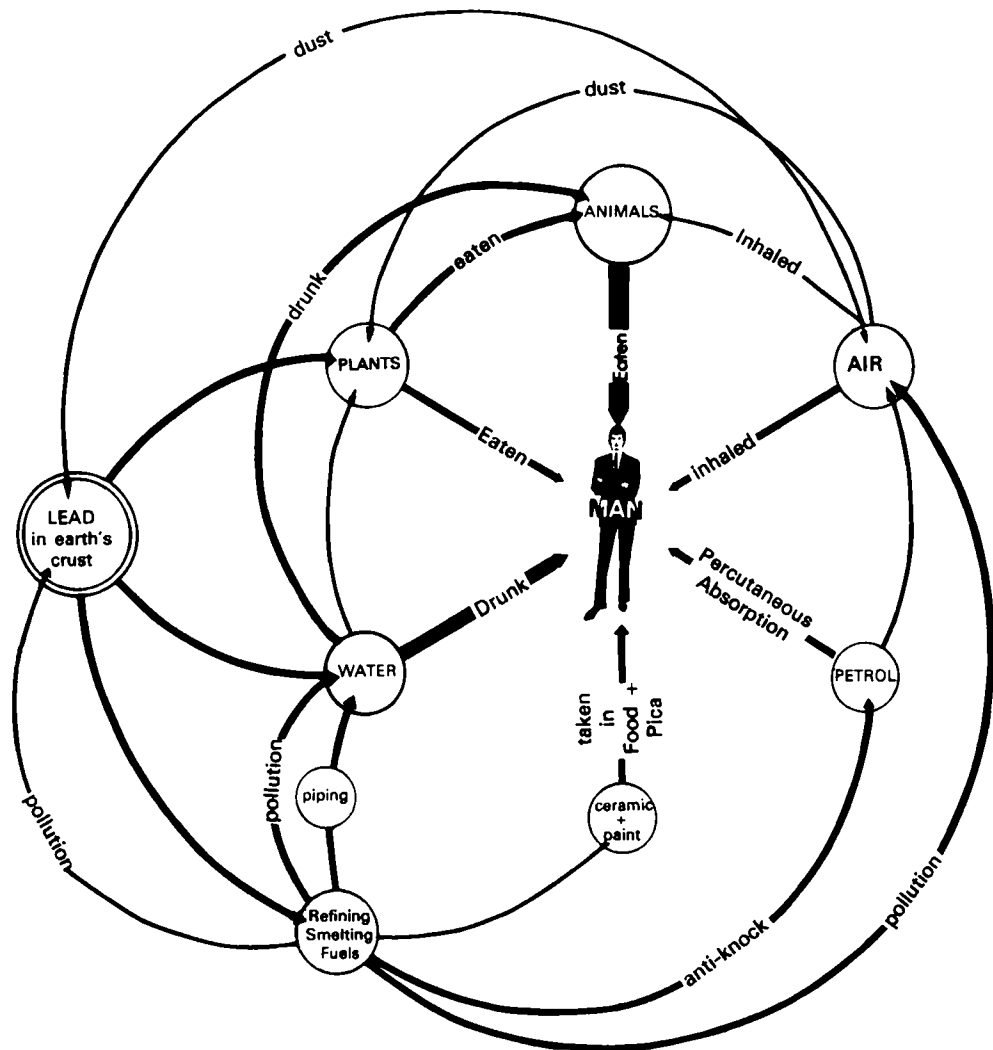


Fig. 1. The various vectors of lead exposure in man. Although other sources may play a variable role in total Pb exposure, the intake of Pb in diet is consistently the major source of the body Pb burden.

found that starvation lowered Pb absorption and there clearly is the possibility of adaptation of absorptive or excretory processes where consistent administration of high concentrations of Pb over long time periods will result in maxima of Pb absorption followed by decreases in the concentrations of Pb in various tissues (Moore *et al.* 1974; Morrison *et al.* 1974; Kelliher *et al.* 1973). Equally, animals given purified diets show increased susceptibility to Pb toxicity probably because of increased absorption from such diets (Myloie *et al.* 1978). Age will also influence the rate of absorption of Pb from the gut. Both young rats (Kostial *et al.* 1971; Forbes & Reina, 1972; Quarterman & Morrison, 1978) and human infants

(Alexander *et al.* 1973; Zeigler, Edwards *et al.* 1978) show increased absorption and retention of Pb.

An additional interesting feature of the effect of diet upon absorption arises during the cooking of foods. It is accepted that washing with water will remove topical Pb from foods such as vegetables. It is not, however, generally known that most foods show a positive uptake of Pb from aqueous cooking media (Moore *et al.* 1979). This can markedly alter the quantity of Pb available for absorption.

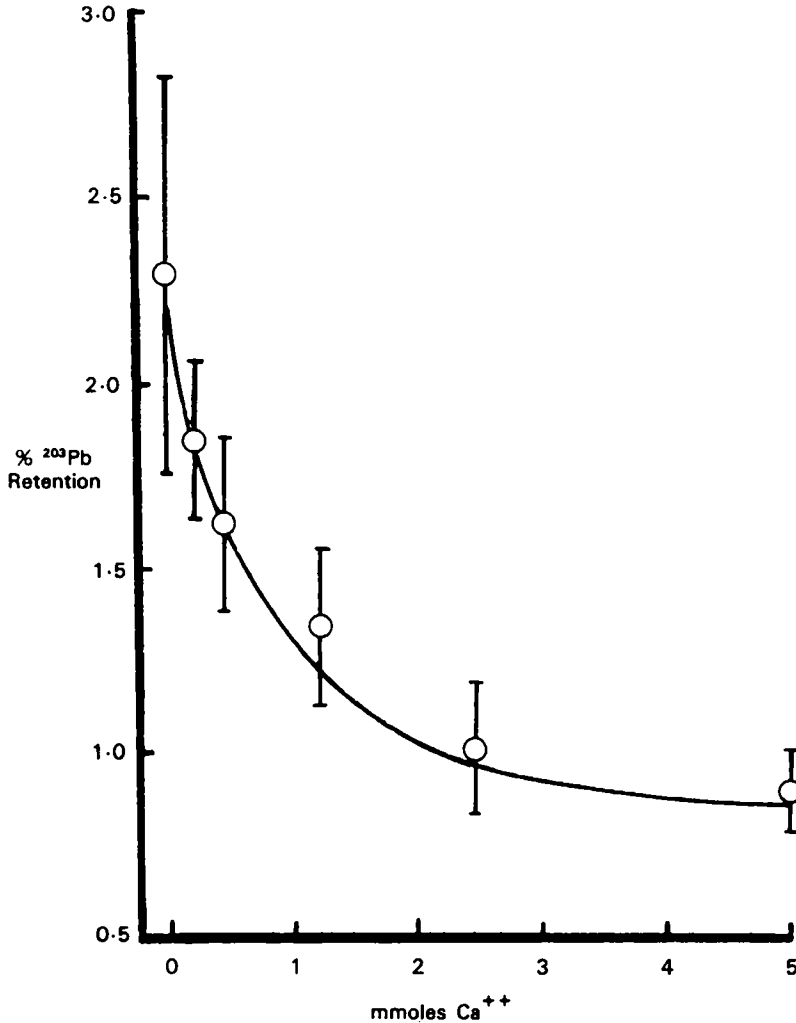


Fig. 2. The influence of varying concentrations of calcium salts (calcium chloride) on the whole body retention of ²⁰³lead chloride in rats. Six groups of rats were intubated with varying amounts of CaCl₂ solution followed after 10 min with an oral solution of 5 μmol ²⁰³Pb Cl₂ (25μCi). Whole body counts were monitored after 120 h. Each point represents the mean ± SD for each group at 120 h.

Of all dietary components most likely to influence Pb absorption, minerals have been most extensively examined. Various studies have shown that the retention of Pb varies inversely with dietary calcium content (Fig. 2). There is a residual quantity of Pb that may be absorbed which is unaffected by the concentration of Ca within the gut. This would suggest that there are two mechanisms for transport of Pb from the lumen of the gastrointestinal tract across the gut wall, only one of which is influenced by Ca (Meredith *et al.* 1977). Equally, systemic Ca concentrations do not appear to influence Pb retention (Quarterman & Morrison, 1974; Meredith *et al.* 1977). It has been postulated that Ca and Pb share binding sites on absorptive protein to cause this effect (Barton *et al.* 1978a) and indeed that iron will act similarly (Barton *et al.* 1978b). It has indeed been suggested that there may be a basis in mineral deficiency for the production of Pb pica in infants (Snowdon, 1976). Gruden *et al.* (1974) found that Pb inhibited the transport of Ca across the duodenal wall of rats *in vitro*. Like calcium, most other minerals, such as Fe (Six & Goyer, 1972), zinc (Conrad & Barton, 1978), copper (Klauder & Petering, 1975) and magnesium (Fine *et al.* 1976), will diminish Pb absorption from the gut. Unlike Ca, Fe absorption is apparently not influenced by increased Pb concentrations (Dobbins *et al.* 1978).

The mode of action of Ca on Pb absorption is not clear. Studies using everted intestinal sack preparations have suggested that Pb transport into the serosal compartment is related to water movement. Ionic Pb utilizes the extra-cellular route to transverse the intestinal barrier. Results have suggested that any process which opens up the tight junctions between cells will increase absorption. (Blair *et al.* 1979; Coleman *et al.* 1978). Factors known to cause such changes are depleted concentrations of Ca^{2+} and increased acidity. These studies have also shown that Pb interacts with tissue phosphate ions which removes the Pb from the available transport pool. Thus Pb transport across the intestinal wall has two separate rate processes, one being the binding of the Pb to the cell surface and the second the transport of Pb across the intestinal membrane and subsequent accumulation in the serosal compartment.

Vitamin D administration influences Pb uptake in a manner similar to that it exercises on the absorption of Ca. Thus, in situations where high vitamin D concentrations are found, there is enhancement of Pb absorption (Smith *et al.* 1978). Surprisingly, however, it has been found that in Pb-burdened children a relative vitamin D deficiency rather than excess is associated with high blood lead levels (Sorrell *et al.* 1977).

There is then a catalogue of substances that might influence the absorption of Pb by various means. In general, substances influencing the intestinal barrier (such as ethanol) will increase Pb absorption (Mahaffey *et al.* 1974). Equally, substances that increase the solubility of Pb will also increase its absorption. Examples of this are by acidification, such as ascorbic or citric acid or combination with other compounds such as amino acids (Conrad & Barton, 1978) or chelating agents (Jugo *et al.* 1975). Tannic acid has been reported to exert a protective effect upon

animals given dietary Pb (Peaslee & Einhellig, 1977) which may well be related to its affinity to bind heavy metals.

Of other major dietary components likely to influence absorption, carbohydrates would appear to have little effect, whilst there are large increases in Pb uptake with increasing dietary fat content (Barltrop & Khoo, 1976). This increase with increasing fat content, has been associated with increased concentration of phospholipids and indeed, ultimately, with the possible stimulation of bile flow which will add phospholipids and bile salts to the gut lumen content (Quarterman *et al.* 1977). The effects of dietary protein have been shown to be complex but in general lowering of dietary protein lowers the uptake of Pb. This effect is screened by apparent increases in Pb absorption due to dietary restriction, which means that growth rate and Pb retention are inversely related (Quarterman *et al.* 1978).

Toxicity following absorption

In an analysis of the toxic interactions of Pb with other minerals on the haematological system, Thawley *et al.* (1977) found that toxic concentrations of other metals such as Zn or Cd caused a marked reduction in other toxic effects of Pb, such as reticulocytosis, and indeed administration of Zn caused a diminution of urinary delta-aminolaevulinic acid concentrations. Of all the effects of Pb upon biological systems, those on the haem biosynthetic pathway, and particularly upon the enzyme delta-aminolaevulinic acid (ALA) dehydratase, have been studied most extensively. Increasing concentrations of Zn decreases the toxic effects of Pb upon this enzyme (Meredith & Moore, 1978). Like Zn, ethanol exerts an antagonistic effect on ALA dehydratase, where raised ethanol concentrations reverse the decreases in enzyme activity caused by Pb (Moore, 1975). It has also been noted that high dietary Zn concentrations will reduce Pb levels in tissues, all of which would suggest that there is a protective role for Zn in Pb toxicity (Cerklewski & Forbes, 1976; El-Gazzar *et al.* 1978). Similar effects have been observed for aluminium, although in this case it is not certain that the diminution of effect occurs at concentrations within physiological levels (Meredith *et al.* 1977). Another element exhibiting a similar antagonistic toxic effect is selenium. Selenium and lead together, both at toxic concentrations, were found to result in normal activities of ALA dehydratase and cytochrome P-450 activity in rats, in which the activities of both compounds were depressed in animals treated either with Se or Pb alone (Rastogi *et al.* 1976).

The neurotoxic effects of Pb may be attributed to various aspects of Pb based biochemical alterations of physiological pathways. Amongst these, δ -aminolaevulinic acid has been shown to have neuroactive effects. (Moore & Meredith, 1976). In consequence, alteration of Zn availability and therefore of ALA dehydratase activity, could markedly affect the synthesis of ALA and therefore change its neurotoxic action. Similarly, Ca plays a central role in nerve transmission and Pb has been postulated to act at synaptic sites by increasing the Ca flux (Silbergeld & Adler, 1978). Again, the availability of Ca with changes in the Pb-Ca interaction must influence this effect.

A positive correlation has been reported between concentrations of vitamin E and tissue Pb concentrations (Sleet & Soares, 1978). The effects of other vitamins and hormones cannot be neglected at this stage. Increased levels of Pb diminish thiamine content in rat liver (Tokarski & Reio, 1978), whilst other substances, such as ascorbic acid and other Pb-binding agents, (e.g. cysteine and methionine) may decrease Pb toxicity by increasing its excretion (MacNiff *et al.* 1978). In the circumstances where vitamin D will increase Pb absorption, it is also true that vitamin D will lower blood Pb concentrations in animals with established Pb poisoning. This is also associated with a decreased loss of Pb from bone (Sobel & Burger, 1955). Similarly, citric acid will decrease Pb toxicity by increasing its excretion in the urine. The possibility therefore exists that the presence of other compounds in the body will alter the over-all distribution of Pb within the body.

In studies of parathyroid hormone in rats, it was found that there was an increase in the renal accumulation of Pb and therefore presumably in the potential toxic effects of Pb on the kidney (Mouw *et al.* 1978). These effects were attributed to increased formation of insoluble Pb phosphate in renal cells following mitochondrial breakdown although it might also have been attributed to changes in tubular reabsorption in the kidney. These effects on the kidney are analogous to those found by Quarterman *et al.* (1977) who found increased Pb content in the kidneys of castrated rams, but surprisingly, a greater mortality in the normal rams than in the castrates. The result implied, together with the observations of others, that hormonal effects will influence the excretion of Pb (Alcroft & Blaxter, 1950; Kostial *et al.* 1974). In the same experiments, Quarterman *et al.* (1977) found diminished toxic effects of dietary Pb following sulphate addition to the diet of lambs. They attributed this effect to the formation of sulphhydryl compounds during rumen digestion which, by binding Pb, lowered its retention.

Excretion

From what has been said before various dietary components will considerably alter Pb excretion, for example, increased Ca levels decrease the rate of loss of Pb (Quarterman *et al.* 1978), although Fe apparently does not influence excretion (Barton *et al.* 1978). Chelating agents would appear to play a central role by increasing Pb excretion. These are frequently used as food additives (Furia, 1968). Amino acids, such as methionine and cysteine, will also facilitate the renal excretion of Pb. Therapeutically, penicillamine has been used for the treatment of Pb poisoning (Goldberg *et al.* 1963). This functions by increasing the urinary excretion of Pb as the chelated penicillamine complex. Although some chelating agents such as ethylenediaminetetraacetic acid are poorly absorbed from the intestine, if these are given to man or to animals by injection they rapidly result in the loss of Pb in the urine. Such an enhancement of urinary excretion of Pb is common to all chelating agents (Graziano *et al.* 1978). The effects of acidic compounds such as citric acid or ascorbic acid are more equivocal. In both cases the rate of metabolism may be so great following absorption as to have little effect on the subsequent urinary excretion of Pb. It has been shown, however, that

blockage of the citric acid cycle with mono fluoroacetic acid allowed modest doses of sodium citrate to provide animals with protection against Pb poisoning (Schubert & Lindenbaum, 1960).

Overview

The preceding review has clearly demonstrated the difficulty of assessing potential effects of certain diets on not only the absorption and excretion of Pb, but also upon the various effects of the dietary components following absorption and prior to excretion. Even when viewed individually it is not always clear whether the net effect of a single dietary component will be beneficial or otherwise. Ca, which would appear to be a useful compound in the prophylaxis of Pb poisoning, demonstrated this. In one study, Moore *et al.* (1978) showed that the use of calcium glycerophosphate as a prophylactic agent against Pb absorption produced only small, although significant, effects on the blood Pb status of a group of lead workers. The whole problem is perhaps best exemplified by the example of milk, the effects of which are well summarized by Stephens & Waldron (1975). In milk there are a number of different components, some of which will increase and some decrease Pb absorption. Some components which raise or lower toxic effects following absorption and finally some which will increase and some which will cause a diminution in the excretion of the absorbed Pb. The over-all conclusion was that the net effect would be an enhancement of Pb absorption by milk but it is by no means clear that such a conclusion can be made in all circumstances since other studies have shown that malnutrition will increase Pb absorption and in consequence a valuable food such as milk could potentially alter this. One may therefore conclude that only in circumstances where a single dietary component is found in great excess or in great deficiency will one be able to divine the likely outcome in terms of Pb toxicity.

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