

What Happens in Lead Poisoning?

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This article deals with some of the features of clinical lead poisoning. The subject is confusing, as much has been written, particularly in the occupational medicine journals, about the effects of increased lead absorption without the development of clinical symptoms. Quite a small intake of lead may produce detectable biochemical or even neurophysiological changes and it is difficult, if not impossible, to decide when these changes are simply an adaptation to an increased intake of lead and when they indicate early poisoning. Sometimes this distinction between the two becomes a matter of semantics[1].

One may start, as it were, from the other end, by considering the clinical presentation of lead poisoning—for lead poisoning, or alleged lead poisoning, is still one of the commonest diseases we see at our occupational medicine out-patients—and then discussing the mechanisms underlying some of these changes.

Clinical Picture

When a patient moves from symptomless 'increased lead absorption' to lead poisoning, his symptoms generally follow in a certain sequence.

Lassitude usually comes first, although the patient often does not present with it, delaying going to the doctor until more striking symptoms occur. In that case, a carefully taken history will always disclose the early symptom of tiredness, noticed at first in the evenings. Although many people may have a short nap in the evening, they generally wake up quite refreshed and may have difficulty in going to sleep at bed-time. However, the patient with early lead poisoning will often sleep through the evening and have no difficulty in getting a night's sleep in bed. One of our patients, a semi-skilled worker on building sites, whose job was to cut through lead-painted steel, observed as an early manifestation of this lassitude that he was unable to complete *The Times* crossword when he got home. (He had received the same education as his brother, a university don, but had decided to follow what he considered a more free and lucrative calling.) If the condition progresses, the patient may develop lassitude during the day as well. This symptom is so common as to be almost invariable and may be explained by some of the biochemical abnormalities produced by lead.

Aching in joints and in limb muscles is also very common, but not always mentioned spontaneously by the

patient. It is, of course, unaffected by movement and although it may wax and wane, never goes completely. Occasionally, this symptom is more marked and in one of our patients aching pains in his legs dominated the clinical picture.

Abdominal colic is well known and for hundreds of years terms like 'Painters' Colic' and 'Devonshire Colic' have described lead colic from different sources. In our experience the picture is more complex. Lower abdominal colic, frequently with constipation, may occur with an excessive lead intake lasting over several months. There is a different picture in patients who have had a rapid intake of lead, what we might regard as acute or subacute lead poisoning. Here the symptoms may start within a few weeks of exposure and be dominated by attacks of vomiting and upper abdominal pain. This is generally unrelated to food intake, but we have seen one or two patients in whom the symptoms closely simulated those of duodenal ulcer. On the other hand, we have seen lead workers with high blood lead levels and a radiologically demonstrated peptic ulcer. Although the literature of occupational medicine has cautionary tales about surgeons opening abdomens of patients with lead colic, the converse is equally true; lead does not protect from the common, or even uncommon, causes of abdominal pain.

Nerve palsy and wrist drop are mentioned in many textbooks and in all examination answers, yet we have seen several hundred patients over the last 20 years and found only one case of wrist drop, the only patient with detectable weakness of the wrist extensors. However, reduced nerve conduction velocity has been demonstrated in patients with lead poisoning[2] and even in symptomless lead workers[3,4].

Biochemical Changes

In lead poisoning there is an increased urinary excretion of amino-levulinic acid and of coproporphyrin III. The amount of erythrocyte protoporphyrin may also be considerably increased. Consideration of the metabolic pathway of haem formation shows that some of the enzymes are present in the mitochondria while others are cytosolic (Fig. 1). Because mitochondria are not present in mature erythrocytes, leucocytes were used in a series of investigations on lead poisoned subjects to demonstrate that three enzymes are depressed by lead[5]. They are amino-

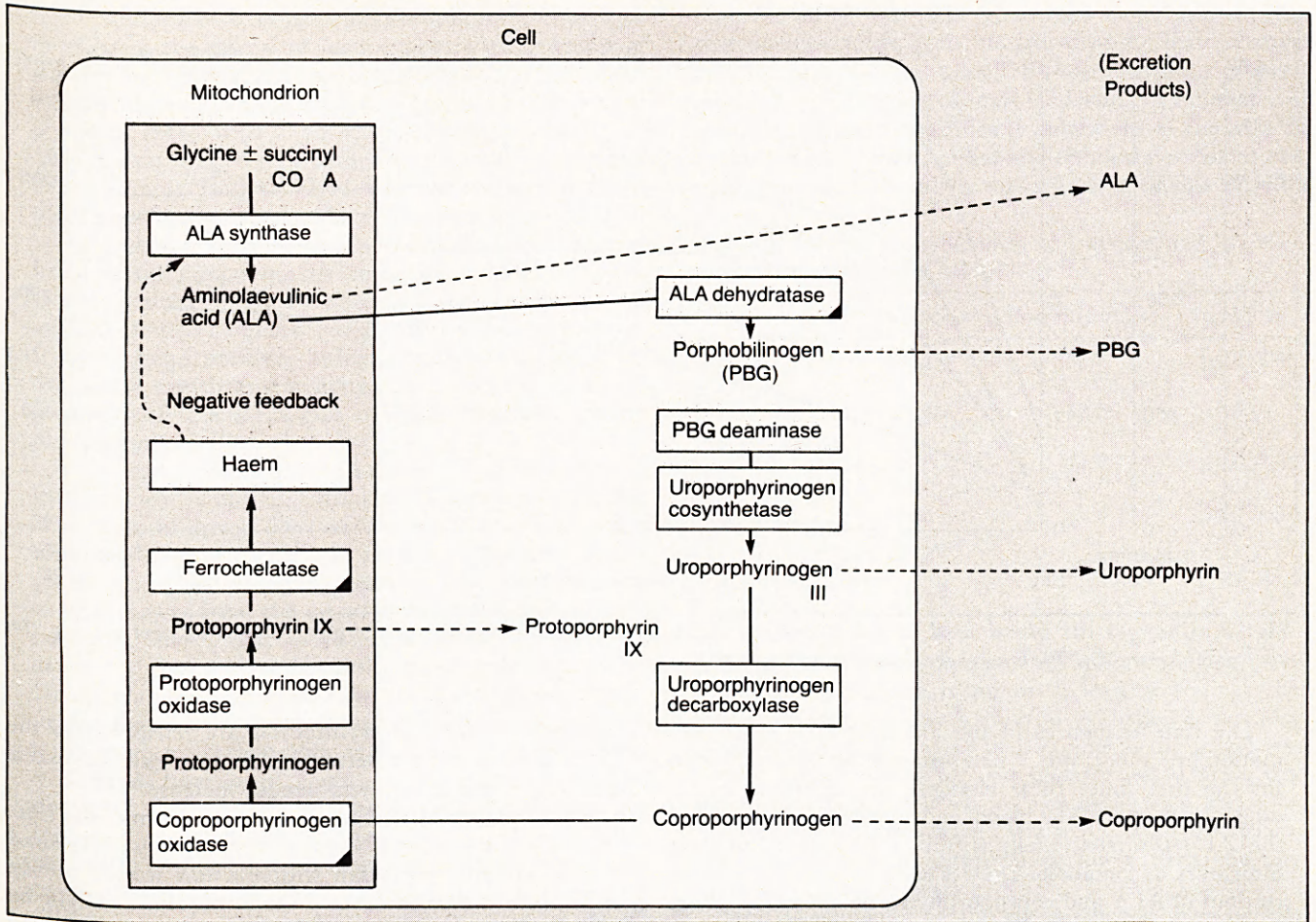


Fig. 1. Haem biosynthesis. (After Campbell et al.[5]) Enzymes not depressed by lead. Enzymes depressed by lead.

levulinic acid dehydrase (ALA-D), coproporphyrinogen oxidase, and ferrochelatase.

It was also shown that the activity of amino-levulinic acid synthase (ALA-S), the rate-limiting enzyme for the system, is increased, almost certainly due to release of haem suppression which provides the negative feedback. Incidentally, this observation has led to the use of haematin infusion to control acute episodes in acute intermittent porphyria[6].

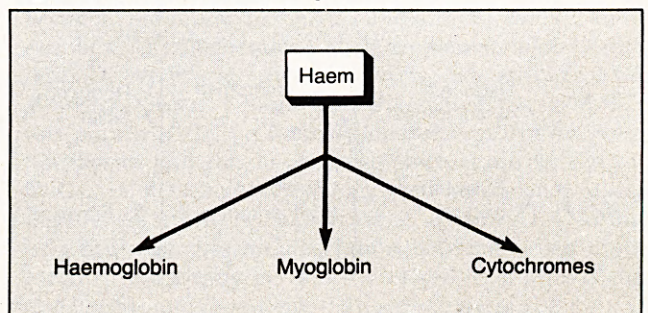
ALA-D is the only one of the three enzymes affected by lead that is cytosolic and, therefore, present in mature erythrocytes. Because of this relative ease of accessibility it is the enzyme most frequently investigated in studies of lead absorption.

Haem synthesis is, of course, not confined to the erythroid cells and is a necessary function of most, if not all, cells in the body. In rabbits, lead actively depresses haem synthesis in cells of brain, liver and kidney, as well as in the bone marrow[7]. Haem is used in the formation of haemoglobin and also myoglobin and the microsomal cytochromes (Fig. 2) such as P_{450} .

When lead is fed to rats the hepatic cytochrome P_{450} and the associated drug metabolising enzymes are reduced[8,9]. However, if lead is added to homogenates of rat liver *in vitro*, the contents of P_{450} and b_5 are

unaffected[10]. These observations suggest that lead does not have a direct toxic action on the cytochromes themselves but may exercise its effect by depression of haem formation, as a large proportion of haem synthesised in the liver is used as the prosthetic group in cytochrome P_{450} [9]. In an interesting investigation in lead poisoned subjects, Meredith and his colleagues[11] demonstrated an extension of the biological half-life of the antipyretic drug phenazone, which is metabolised by the liver cytochrome P_{450} .

Fig. 2. Some common uses of haem.



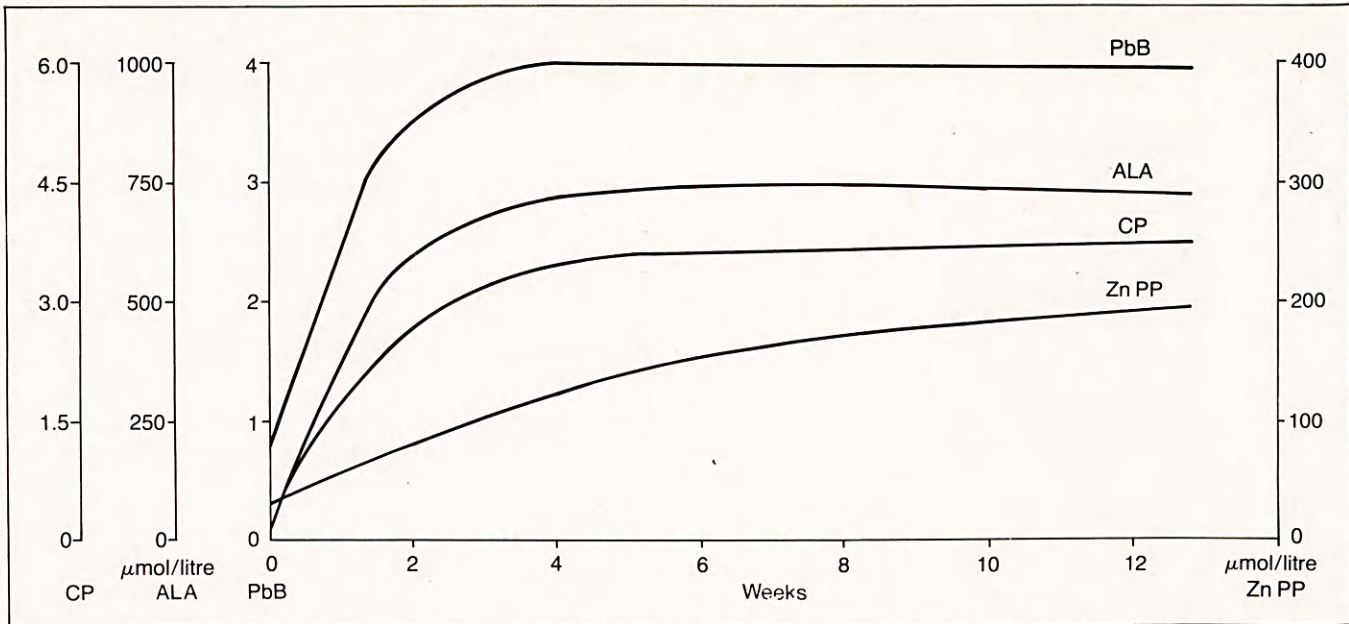


Fig. 3. Changes in: blood lead (Pb-B), urinary ALA (ALA), urinary coproporphyrin (CP) and erythrocyte zinc protoporphyrin (ZnPP) in workers first exposed to lead.

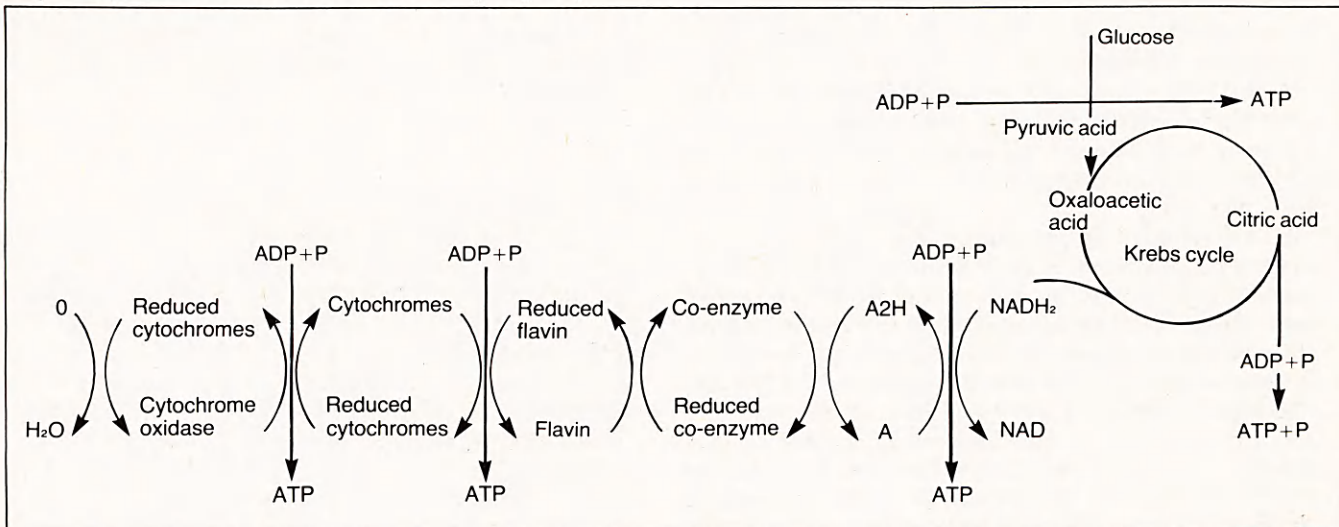
The time sequences of the alterations in haem formation are important. When someone is exposed to lead for the first time, these changes do not occur simultaneously (Fig. 3). The blood lead concentration rises and the ALA-D activity falls within a few days, whereas indicators of metabolic activity such as urinary concentrations of ALA and coproporphyrin do not usually start to rise for about two weeks[12,13]. The rise of erythrocyte protoporphyrin is much slower, taking some 2 to 4 months, and it may continue to rise more slowly for even longer[14]. Because mitochondria, the site of haem formation, are absent from adult erythrocytes, the concentration of protoporphyrins in a circulating red cell may reflect the state of affairs when it was a blast cell. As

successive cohorts of erythrocytes are released into the circulation so will the percentage of them carrying excess amounts of protoporphyrin steadily increase.

When someone is removed from lead work, the time relationships are somewhat different. Urinary ALA and coproporphyrin levels fall within a few weeks. In our experience the erythrocyte protoporphyrin, as might be expected, takes several months to return to normal. The biological half-life of lead, as measured by the blood lead, is several months[15], although the half-life of skeletal lead may be more than two years[15,16]. The activity of ALA-D may remain depressed for many years after removal from lead work[17].

These changes over a period of time may be important

Fig. 4. Glucose metabolism and oxidative phosphorylation.



for a number of reasons. The occupational physician, monitoring the effects of lead exposure on a group of workers by looking at some of the abnormalities, must consider the duration of exposure. Similarly, the general physician faced with a patient with lead poisoning or asked for an opinion on whether or not a patient has had lead poisoning, is well advised, when reviewing the results of his investigations, to consider these time relationships.

More interesting is the way in which this disturbance of haem metabolism, with its consequent effect on cytochrome activity, might explain the fatigue which is such an early and pronounced feature of the clinical picture. It seems quite possible, although not proven, that reduction in cytochrome activity might result in an interference with the formation of ATP during oxidative phosphorylation (Fig. 4).

Two related observations on the biochemical effects of lead are worth noting, although no practical use has been made of them. They were made at about the same time, in different centres. It has been known for many years that, in lead poisoning, there is accelerated removal of erythrocytes from the circulation[18,19]. Recently, it has been shown that in rat liver, lead increases the activity of haem oxygenase[20], the enzyme responsible for opening the porphyrin ring at the α -methine bridge during haem breakdown. The carbon atom so released is oxidised to carbon monoxide, one mole of which is formed from each mole of haemoglobin broken down[21]. Consequently, the blood carboxyhaemoglobin increases in increased haemoglobin breakdown. We showed[22] that in non-smoking lead workers the carboxyhaemoglobin levels are significantly increased (Table 1).

Table 1. Blood lead (Pb-B) and carboxyhaemoglobin (CO Hb) concentrations in lead workers and controls[22].

	Pb-B (nmol/litre)	CO Hb %
Non-smoking lead workers (n = 23)	2.29 (± 0.84)	2.47 (± 0.90)
Non-smoking controls (n = 20)	1.15 (± 0.18)	1.12 (± 0.22)

Studies on Nerve Conduction

Nerve palsy, as we have seen, is now extremely uncommon in clinical lead poisoning although motor nerve conduction velocity is often reduced even in symptomless lead workers[3,4]. There has been some disagreement among different investigators over the results of measurement of maximum motor conduction velocity (MMCV), some claiming to find it significantly decreased[23-25] and others being unable to demonstrate any change in persons exposed to lead[26,27].

One explanation is that the changes resulting from exposure to lead are small compared with the wide range of published normal values. If the results from lead workers are compared with these 'normal' values no statistically significant differences may emerge. However, if they are compared with results obtained by the same

observer under the same controlled conditions and on matched control subjects, statistically significant changes may be found. Thus, Ashby[28], working in our department, studied 94 pairs of male lead workers and matched controls and found significant reductions of the MMCV in the ulnar, median, radial and femoral nerves but not, interestingly, in the ulnar sensory nerve (Table 2). This

Table 2. MMCV in symptomless lead workers and in control subjects ($m \text{ sec}^{-1}$). (After Ashby[28].)

	Lead Workers	Control Subjects	Significance
Ulnar n (n = 94)	53.4	55.6	$p < 0.0005$
Median n (n = 94)	55.9	57.3	$p < 0.01$
Radial n (n = 91)	63.9	71.7	$p < 0.0005$
Peroneal n (n = 91)	46.1	47.6	$p < 0.005$
Ulnar sens n (n = 96)	57.5	57.9	N.S.

conforms with the observations of earlier clinicians, when wrist drop was more common in lead poisoning, that sensory changes were very unusual. A further observation by Ashby[28] was that 13 of the men in the group had been exposed to lead for two years or less. During that time their blood lead levels, on 3-monthly tests, had never risen above $3.8 \mu\text{mol/litre}$ ($80 \mu\text{g}/100 \text{ ml}$), nevertheless their MMCVs were significantly lower than the age-matched control subjects.

MMCV may not be the most sensitive investigation because, even if many nerve fibres are damaged, it remains normal so long as even a few fast fibres remain intact. Two methods have been employed to get around this, antidromic blocking of the fast fibres[4,25] and measurement of the percentage amplitude. The latter, used by Ashby whose results are cited above, is based on the suggestion that if slowing of conduction occurred in only a proportion of the motor nerve fibres, the muscle action potential would become dispersed. The amplitude of the proximally produced muscle action potential is expressed as a percentage of the amplitude of the distally produced action potential[29]. This method only indicates change and does not show absolute values.

The changes in motor nerve conduction velocity found in symptomless lead workers do not appear to have any clinical significance. Furthermore, Ashby[28] and others[23,25] have failed to demonstrate any correlation between reduction in nerve conduction velocity and a number of biochemical measurements: blood lead, ALA-D, erythrocyte protoporphyrin, Hb, urinary ALA. However, Sessa[2] found that decreased ulnar MMCV was paralleled by an increase in free erythrocyte protoporphyrins and this has recently been confirmed in rats by Carter[30] who also demonstrated an association, but slightly less strong, with increase of urinary ALA. It may be significant that an association between raised erythrocyte protoporphyrin values and reduced MMCV has also been found in patients on haemodialysis[31].

Histological Changes and Pathogenesis

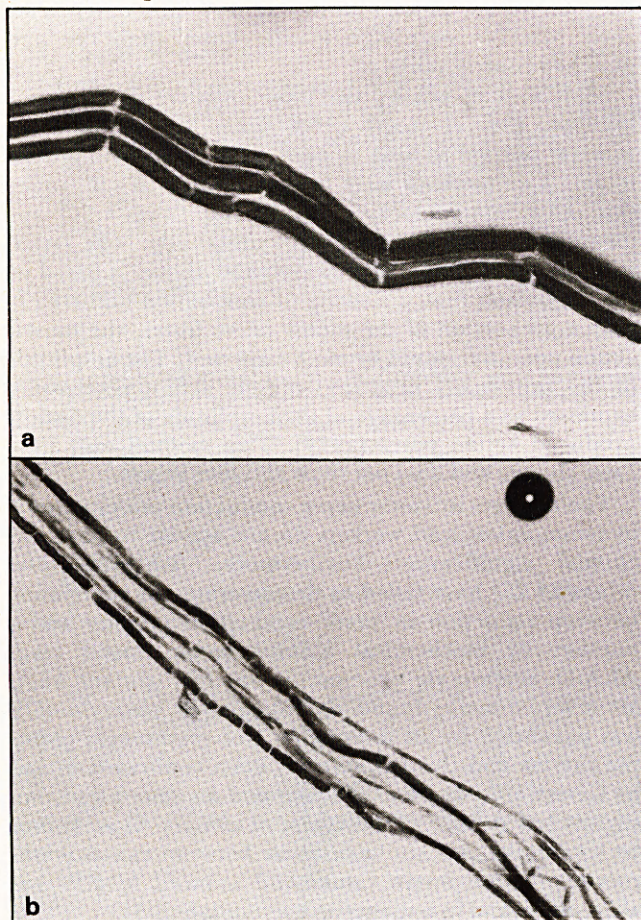
Before the biochemical mechanisms that might explain these neurophysiological changes are considered, we should look at the nature of the histological changes in the peripheral nerves. These vary from one species to another (Table 3)[32]. This marked variation does not

Table 3. Histological effects of lead on peripheral nerves (after Hopkins[32]).

Species	Segmental demyelination	Axonal degeneration
Man	0	+
Baboon	0	0
Guinea-pig	+	Slight
Rabbit	0	+
Cat	0	0
Rat	+	+

help to shed light on which metabolic lesions may be responsible for the changes in nerve conduction velocity. In rats there is a mixture of axonal degeneration and segmental demyelination (Fig. 5a, b).

Fig. 5. Teased out peripheral motor nerve: (a) control rat, (b) lead poisoned rat.



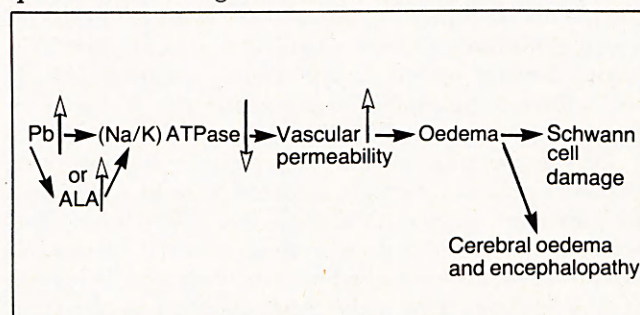
What is the pathogenesis of these effects? A tenable hypothesis, though at present it is no more, may be found by starting from observations of the changes in the brain in lead encephalopathy. Although, in the past, changes have been described in the nerve cells, the neuroglia, the meninges or as a consequence of hypertension, a recent careful study and review[33] has stressed the importance of cerebral oedema. This is in keeping with the observations on the brains of suckling rats[34,35]. In these animals, trypan blue injected into the circulation leaked into the cerebrum and the spinal cord[34], providing further support for the suggestion that cerebral oedema is an integral part of the condition and may be secondary to increased vascular permeability[35,36].

Recently, direct measurement of endoneural fluid pressure in peripheral nerves in lead poisoned rats has shown this to be increased in parallel with pathological changes of endoneural oedema. Such increases in pressure in lead poisoning are relatively small compared with externally applied pressure which produces segmental demyelination after only minutes or hours of application. However, the moderate increase in pressure in lead poisoning is sustained for weeks or months. The lesser but sustained increased pressure in lead poisoning will not cause ischaemia from capillary collapse, but might result in damage to Schwann cells[37].

By what means might the increased vascular permeability be produced? Acute intermittent porphyria (AIP) and lead poisoning display similarities in some of their clinical features, including the predominantly motor disorder[19]. In AIP, but not in lead poisoning, there is an increased excretion of porphobilinogen. This substance has no pharmacological effects[38]. Also, the uroporphyrins and coproporphyrins whose urinary excretion is increased in both acute porphyria and lead poisoning, are not pharmacologically active[38]. ALA, too, which is excreted in excess in porphyria and lead poisoning is, apart perhaps from some increase in photosensitivity, pharmacologically inactive[39]. However, it has been suggested that increase in vascular permeability might result from the inhibition of (Na/K) ATPase in brain tissue by ALA[40]. There is also evidence in humans that increased exposure to lead is associated with depression of (Na/K) ATPase activity[41,42] although activity of this enzyme was found to be normal in one study of suckling rats[35].

In summary, then, the suggested mechanism (Fig. 6),

Fig. 6. Suggested mechanism for development of peripheral nerve changes in lead intoxication.



and it is at present no more than a hypothesis, is that lead, either directly or by producing an increase in the circulating ALA, causes an inhibition of (Na/K) ATPase resulting in increased vascular permeability. In the nervous system the resulting oedema may lead to damage to Schwann cells and, in more extreme cases, to cerebral oedema and encephalopathy.

Control Measures

What should the occupational physician do? As with any hazard, he may advocate environmental control, which could include wet methods to dampen down the dust, increasing the general ventilation in the workplace to dilute the dust, local exhaust ventilation to get rid of this dust or, at times, the provision of respiratory protection such as masks. To monitor the effectiveness of such measures on the health of the worker, or in circumstances where environmental control is not readily applied, the occupational physician can select from a wide range of biochemical tests, most of which have their proponents.

Blood Lead

The test most frequently used in preventive and curative medicine for the basis of official comment and advice[1,43,44], and as the usual datum by which other tests are assessed, is the blood lead. So what do we mean by blood lead and how is the lead distributed among the different components of the blood? Only some 6 per cent is in the plasma and most of that is in the albumin fractions and, of the remaining 94 per cent, nearly all, over 90 per cent, is attached to the haemoglobin molecule[45]. Looking at this more closely, it was shown that the α -chains of haemoglobin have a very low affinity for lead and most of it becomes bound to the β -chains. Furthermore, the γ -chains of fetal haemoglobin have an even higher affinity for lead than do the β -chains.

The fact that circulating lead is attached to the globin chains of the haemoglobin probably has little, if anything, to do with its effects on haem formation, which are probably exerted at the myeloid stage. The lead attached to the globin chains may be regarded, not as active lead, but rather as carried passively in a 'sink'. Thus, a particular blood lead level, while to some extent reflecting the amount of lead exposure, would also be influenced by the capacity of the 'sink'.

Put another way, instead of a 'bucket' hypothesis (Fig. 7), which appears to presume that the body burden of lead can be assessed simply by examining a sample of blood (even allowing that it may be in dynamic equilibrium with a sludge in the bottom of the bucket, i.e. stored in the bones) one could postulate an 'affinity' hypothesis in which the lead level in the circulating blood reflects not only the body burden of lead, but also the affinity for lead of the globin chains.

This 'affinity' model is fruitful. First, it provides a satisfactory explanation for the well-recognised clinical observation of the poor discriminatory value of blood lead in the diagnosis of lead poisoning. Some patients are seen with quite high blood lead levels, even of 24.2

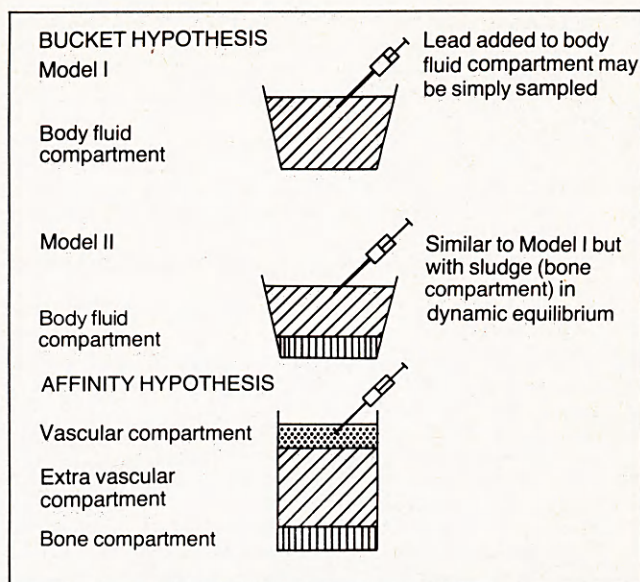


Fig. 7. Alternative hypotheses to illustrate the significance of 'blood lead'.

$\mu\text{mol/litre}$ (500 $\mu\text{g}/100\text{ ml}$) or more, but no clinical suggestion of lead poisoning[46,47], while other patients develop symptoms with blood lead levels below 3.9 $\mu\text{mol/litre}$ (80 $\mu\text{g}/100\text{ ml}$)[48]. Secondly, it might explain why some workers, although apparently clean and tidy in their working habits, rapidly develop a comparatively high blood lead, which their workmates do not, that seems to fall quite rapidly when they are removed from work. We are asked to see 3 or 4 such persons every year. Of course, such a suggestion would imply that some people have globin chains with differing affinities for lead. We have already seen that γ -chains have a higher affinity than β and it is worth exploring whether there are more subtle changes in the globin polypeptides which will alter their affinity for lead. That this is not too fanciful is shown by some recent observations that, as well as affecting haem formation, lead may also affect globin formation leading, at least in some persons, to disturbed haemoglobin synthesis. Some workers have described the appearance of globins that may normally be present only in small amounts such as A_3 [49], an increase in α -haemoglobin, an alteration in the α/β ratio[50] or an increase in HbF[51]. Others have described an increase in a ' γ -like' chain[52]. Whether these modified haemoglobins have an increased or a decreased capacity to serve as a lead 'sink' (that is, whether they have a protective effect or otherwise) is not known and will form an intriguing and perhaps useful subject for research.

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