LEAD POISONING:
A Pathophysiological Overview

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Environmental lead

During the last century, there has been a steep decline in the incidence of industrial lead poisoning and a similar decrease, in the number of deaths due to lead poisoning. However, many people are chronically exposed to high atmospheric lead concentrations, which although not causing lead poisoning, may cause subclinical effects, i.e. metabolic disturbances undetectable by usual clinical procedures. Table 1 compares the lead concentrations in an uncontaminated environment with today's levels and their effects on body lead. The 'safe' upper limit is considered to be about 70ug of lead per decilitre of blood.

Acute lead poisoning is commonest in children who ingest flakes of paint or other lead-containing materials. Food contaminated with lead may also cause acute lead poisoning. More commonly, the disease develops gradually, especially in factory workers exposed to excessively high atmospheric lead concentrations, notably those working in battery manufacture.

The commonest source of lead in the general environment is tetraethyllead $(Pb(C_2H_5)_4)$, an antiknock additive in petrol. Thus, the greater the amount of traffic in a city, the higher is its atmospheric lead content.

Lead absorption

For lead to exert its toxic effects, it must first enter the body and the general circulation. The two common-est routes of entry are the respiratory and gastro intestinal tracks.

About 30 to 60% of inhaled lead is deposited in the lungs, according to particle size. This is either absorbed into the blood or phagocytosed by macrophages. The smaller the particles and the greater their solubility, the more is the amount entering the circulation.

Only about 5 to 10% of ingested lead is absorbed by the adult gut. This value may be as great as 50% in growing children. Dietary calcium and vitamin D levels effect the amount of lead absorbed by the gut. Vitamin D — induced calcium binding proteins bind lead with a greater affinity than calcium, with both ions competitively competing for the calcium-binding sites. This explains why a high dietary calcium content decreases the amount of lead absorbed by the gut, while vitamin D increases it. Similarly dietary zinc and iron also decrease lead absorption.
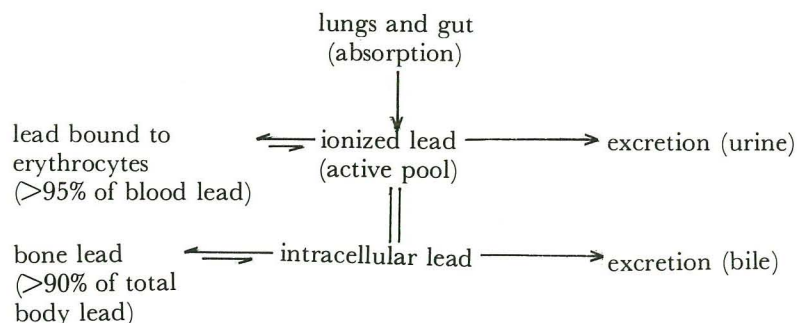
Body lead and its excretion

Absorbed lead enters the circulation, so that blood lead levels are usually indicative of recent exposure. Only minute quantities are present in the ionized form, most of the lead rapidly binding to the erythrocyte cell membranes, blood lead is also bound to plasma proteins. Part of this binding of lead to erythrocytes and proteins occurs by the same mechanism with which it exerts its pathological effects in lead poisoning, as will be explained later.

There is a dynamic equilibrium between the free plasma lead and the portion bound to the erythrocytres; a similar equilibrium exists between blood lead and extracellular lead, the ionized fraction comprising the 'active pool', (Fig. 1). Lead enters tissues and cells through the same routes taken by calcium, and binds particularly strongly to mitochondria. Bone is the commonest site of lead deposition, comprising over 90% of total body lead. It is laid down, together with calcium, at sites of active bone formation and it may also displace calcium in the bone apatite crystals. This provides a method of removal of blood lead, which may otherwise cause more severe effects. However bone is not static and when there is an increased demand for calcium, some of the lead is also

TABLE 1
Comparison of lead concentrations in different environments; all values are approximative and vary widely.

	Uncontaminated Sites	Preindustural Sites	Industrial Sites
Atmospheric lead (ug/m³)	0.0005	0.05	2
Blood lead (ug/dl)	0.25	5	20
Total body lead (mg)	2	60	120

lungs and gut
(absorption)

lead bound to erythrocytes (>95% of blood lead) ⇌ ionized lead (active pool) → excretion (urine)

bone lead (>90% of total body lead) ⇌ intracellular lead → excretion (bile)

Figure 1: Relationship between lead in various body compartments and its excretion.

mobilized. In fact, blood lead may double during pregnancy due to this fact.

Excretion of lead takes place mainly via faeces, lead being secreted in the bite as salts with other compounds such as fatty acids. The kidneys also play a part in lead exretion, most of this occuring simply through glomerular filtration.

Figure 1 summarizes the distribution of lead in the body.

The Pathological Effects of Lead

Besides sharing some properties with calcium, lead also has other properties which enable it to inhibit certain enzymes. Like other heavy metals, lead has an affinity for sulphydryl groups. It may also bind to other ligands containing electron donors, such as carboxyl, hydroxy, phosphate, amino and imidazole groups, although less avidly than to sulphydryl groups. Dithiol groups are particularly susceptible to attack by lead. If the protein is an enzyme, it is usually inhibited due to irreversible denaturation and hence loss of its active site. The biochemical pathway most sensitive to inhibition by lead is that of haem biosynthesis.

Haem biosynthesis

Before stating the effects of lead on haem biosynthesis, it is important to consider the synthesis and regulation of porphyrins (see Fig. 2). This occurs in virtually every metabolically active cell, but is most active in red bone marrow and liver tissue, where the porphyrins are used primarily for haemoglobin production.

The first step in the pathway involves the condensation of glycine and succinyl coenzyme A into delta-amino-levulinate. This is the rate-limiting and regulatory step for haem biosynthesis and is catalysed by the mitchondrial-bound enzyme delta-aminolevulinate synthase (succinyl coenzyme A: glycine C — succinyltransferase). This enzyme is very specific and will not accept other aminoacids or acyl coenzyme A compounds as substrates. It is controlled primarily by negative feedback inhibition by haem, the end-product of this pathway. Thus, anything that depletes haem, inhibits its synthesis or increases its metabolism, will cause an increased activity of delta-aminolevulinate synthase.
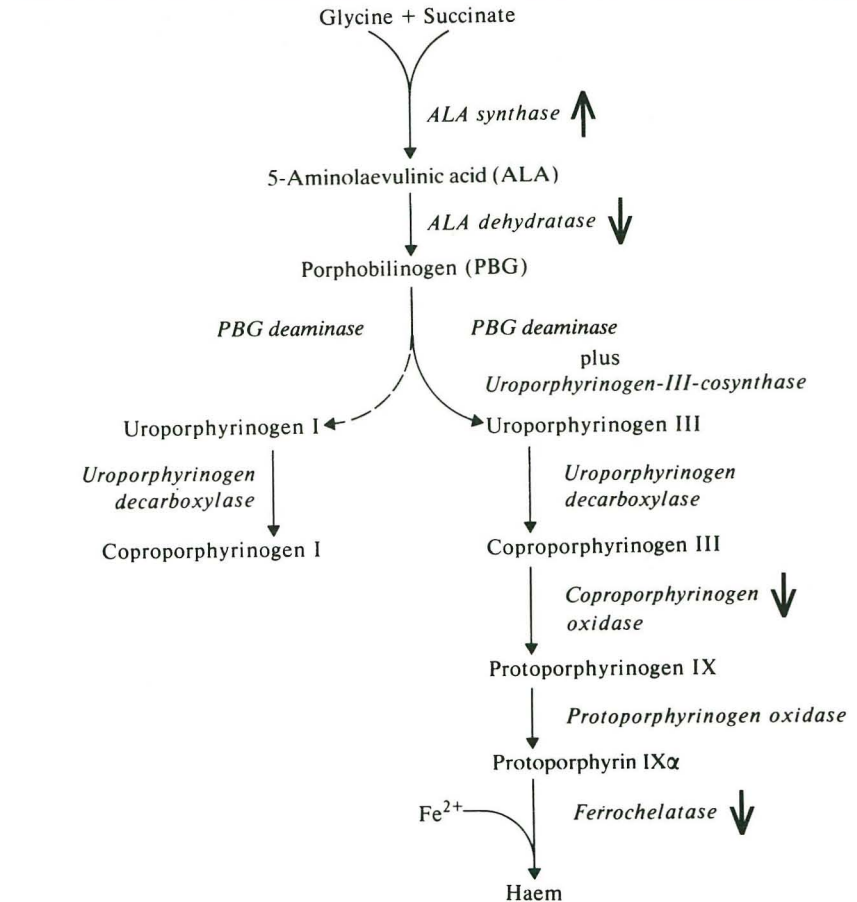
Lead particularly inhibits delta-

Figure 2: The biosysthesis of haem showing the enzymes that are inhibited (↓) by lead and the resultant induction (↑) of ALA synthase.

aminolevulinate dehydratase, copro-porphyrinogen oxidase and ferrochelatase. These contain exposed sulphydryl groups (of cysteine residues) with which lead can combine easily. The active site of these enzymes is thus irreversibly blocked, with a greater amount of these enzymes inhibited at higher lead concentrations. The lead does not have to bind necessarily to the active site, for a change in the three-dimensional configuration of the enzyme will still denature it. Thus, inhibition here is of the noncompetitive type, with an increase in substrate concentration being virtually useless. Inhibition of these enzymes causes increased activity of delta-amino-levulinate synthase with accumulation of delta-aminolevulinate and other intermediates. (See Fig. 2).

Haem synthesis is depressed with blood lead levels over 15ug/dl leading to anaemia. At lower lead concentra-tions, the increased activity of delta-aminolevulinate synthase is enough to maintain a normal haemoglobin level.

The anaemia of lead poisoning is rarely severe and is a normocytic, hypochromic type of anaemia,

although macrocytosis may develop if it is prolonged. Decreased activity of cytochrome P450 in the liver has been observed in lead poisoning and other systems requiring porphyrins may also be affected.

It is the increased levels of inter-mediates in the haem biosynthetic pathway that are responsible for most of the toxic manifestations in lead poisoning.

Lead neuropathy
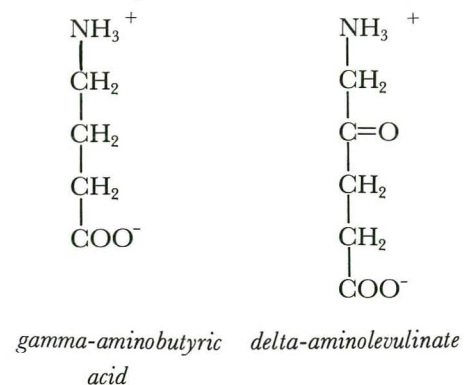
Probably the worst effect of lead

NH_3^+ NH_3^+

CH_2 CH_2

CH_2 $C=O$

CH_2 CH_2

COO^- CH_2

             COO^-

gamma-aminobutyric acid   *delta-aminolevulinate*

Figure 3.

poisoning is the development of associated neuropathy. Both central nervous system and peripheral nerve abnormalities occur in lead poisoning, CNS impairment occuring earlier. This is detectable at blod lead levels over 40ug/dl, even in the absence of clinical lead poisoning.

The main cause for lead encephalopathy is probably the result of delta-aminolevulinate competing with the neurotransmitter gamma-aminobutyric acid for its receptor sites on post-synaptic membranes. Figure 3 shows the similarity in structure betwen these two compounds.

Other Mechanisms for lead encephalopathy have been proposed. The inhibition of essential enzyme systems in nervous tissue as well as the blockade of dopamine D_2 receptors may play a role.

Lead poisoning in children usually causes a more severe encephalopathy, with cerebral oedema, due to the fact that the blood-brain barrier is still not fully developed. Inhibition of brain sodium-potassium adenosine triphosphatase by lead is probably one of the main factors causing the oedema. The electroencephalogram is normal in lead poisoning and is thus of no use in diagnosis of this condition.

Peripheral nerves in lead-poisoned patients show signs of segmental demyelination and remyelination and also axonal degeneration in some cases. Motor nerves are especially affected, with a reduction in their mean maximum conduction velocity, while sensory nerves remain unaffected. These changes are present even in people with subclinical lead poisoning. The exact cause of these features is unknown. It is important to stress that the effects of lead on the nervous system and their consequences may remain even after complete disappearance of other symptoms, although some improvment always occurs after reduction of exposure.

Inhibition of the pentose phosphate shunt

The pentose phosphate shunt is the source of reduced nicotinamide dinucleotide phosphate (NADPH + H$^+$). This provides a reducing atmosphere in cells and is especially important in erythrocytes. NADPH is used to produce reduced glutathione; which is an important reducing agent, and also plays a part in maintaining the integrity of the red cell membrane. (See Fig. 4).

Lead inhibits glucose — 6 — phosphate dehydrogenase, the first enzyme in the pentose phosphate shunt. This results in a lower concentration of reduced glutathione within the red blood cell. The loss of reducing power makes the cell sensitive to oxidant stress, leading to haemolysis and a shortened red cell life-span. Thus the anaemia of lead poisoning also has a haemolytic component.

Lead Nephropathy

The proximal tubules are mainly affected in lead poisoning. The epithelial cells show structural abnormalities with the mitchondria showing the greatest changes. The characteristic finding here is intranuclear inclusion bodies. These occur in all cases of lead poisoning and appear soon after exposure to lead. Their number is proportional to the degree of exposure.

They consist of proteins rich in sulphydryl groups and have a high lead content. The protein p32/6.3 is unique to these inclusions. They seem to act as protective devices to reduce the amount of circulating lead by binding it in an inactive form. This is even safer than the deposition of lead in bone, as bone lead is mobilized with calcium, when the latter is required. Lead itself probably induces the formation of these proteins, limiting its harmful effects. Chronic renal damage however does not seem to follow lead poisoning.

Lead also reduces the ability of the kidneys to excrete uric acid, causing saturnine gout. However, this does not occur in all cases of lead poisoning.

Other effects of lead

Theoretically, any enzyme containing exposed sulphydryl groups can be inhibited by lead.

Thyroid dysfunction may occur in lead-poisoned patients. They seem to have impaired uptake of iodine by the thyroid. Lead may cause this by binding to sulphydryl groups on a protein sulphonyl iodine carrier or by displacing the iodine in the protein.

Muscular weakness is another common feature of lead poisoning. Essential enzyme systems may be partially inhibited by lead. Besides enzyme inhibition through sulphydryl groups, lead can also bind to troponin C, with even greater affinity than calcium. This may contribute to the muscle weakness by directly interfering with the mechanism of contraction.

The activity of other enzymes, such as alkaline phosphatase and cholinesterase, has been found to be reduced in lead poisoning. Lead in the nucleus has the ability to alter nucleic acid conformation, degrade RNA, increase misincorporation in DNA synthesis and stimulate chain initiation by magnesium-activated RNA polymerase. It may affect cell proliferation, producing chromosomal abnormalities and therefore lead to neoplastic transformation.

Lead can also affect the cardio-vascular system. Myocardites, ECG abnormalities, increased cardiac arrhythmogenicity and altered myocardial contractility have all been observed in certain cases. Alterations in blood pressure-regulating mechanisms (renin secretion, vagal and sympathetic tone), together with lead nephropathy, may contribute to the development of hypertension.
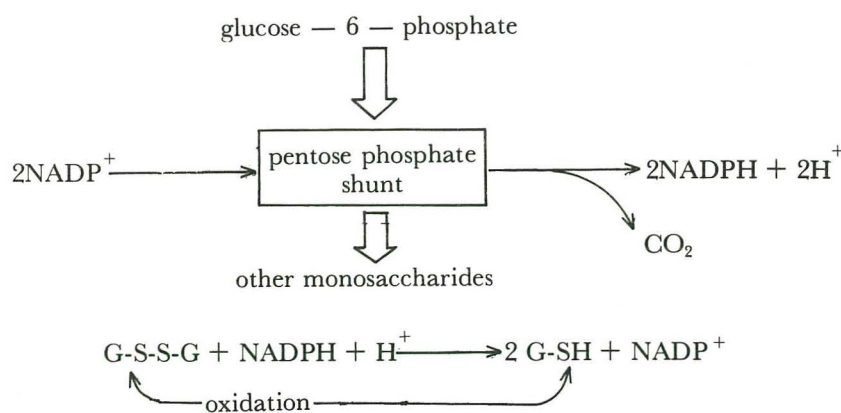
glucose — 6 — phosphate

2NADP$^+$ → pentose phosphate shunt → 2NADPH + 2H$^+$

other monosaccharides

CO$_2$

G-S-S-G + NADPH + H$^+$ → 2 G-SH + NADP$^+$

— oxidation —

Figure 4: Features of the pentose phosphate shunt; G represents glutathione (a tripeptide: yglu - cys - gly).

Diagnosis and Treatment of Lead poisoning

There are no symptoms particular to lead poisoning and this may lead to difficulty in diagnosing the condition. A history of exposure to lead (or its ingestion) is probably the most useful diagnostic tool. The features of organic and inorganic lead poisoning exhibit some differences. Table 2 lists the various symptoms of the disease.

Encephalopathy is common in children and peripheral neuropathy may be obvious in some cases. Burton's blue line (deposits of lead on the gingival margin) may be present in chronic cases. Radiography of the long bones may show "lead lines" at their

contain electron-donating groups that enable them to bind with lead and are subsequently excreted in the urine. The three agents in common use are BAL, EDTA and D-penicillamine, the latter being the one of choice. A high enough dietary calcium is required during treatment, for the chelates are not specific for lead and will bind other divalent metal ions such as calcium. DMSA (2,3-dimercaptoniccinic acid) is more specific for lead and causes less side-effects.

An excess of chelate over lead is required, otherwise this may have the effect of simply redistributing the lead in the body. If insoluble lead is still present in the gut, chelating agents may have the adverse effect of solubil-

TABLE 2
Symptoms of lead poisoning listed in their order of frequency as presenting symptoms, depending on state (organic lead is mainly T.E.L.)

INORGANIC		ORGANIC
Adults	*Children*	disturbances in sleep pattern
abdominal pain	drowsiness	nausea
constipation	irritability	anorexia
vomiting	vomiting	vomiting
non-abdominal pain	gastrointestinal	vertigo and headache
asthenia	symptoms	muscular weakness
paraesthesiae	ataxia	weight loss
psychological	stupor	tremor
symptoms		diarrhaea
diarrhea	fatigue	abdominal pain
		hyperexcitability
		mania

epiphyses. It is thought that this "lead line" is not necessarily lead but is caused by lead interfering with the normal deposition of calcium at these sites.

Tests for lead **absorption** are based on the lead content of blood, urine, teeth, hair and bones. For lead **poisoning**, urine aminolevulinate and coproporphyrin levels are the most useful tests. Erythrocyte aminolevulinate and protoporphyrin also give very useful information. Porphobilinogen may be excreted in the urine in severe cases.

Treatment

Chelating agents are used to treat lead poisoning. These compounds

izing it, worsening the situation.

Conclusion: differential diagnosis

Being an uncommon disease with no specific symptoms, lead poisoning should be considered in the differential diagnosis of patients presenting with anemia, psychogenic disorders (seizures, mental retardation, behavioral disorders, pica), abdominal pain, growth retardation and other development problems.

References

1. Baker, E.L. et al. 1985. Occupational lead neurotoxicity: improvement in hehavioural effects after reduction to exposure, British Journal of Industrial Medicine 42(8): 507-516.

2. Bascolo, P. et al. 1988, Neurohormonal blood pressure regulation in lead exposure. Environ. Health Perect. 78:101-6.

3. Campbell, B.C. et al. 1977. Alterations in the activity of enzymes of haem biosynthesis in lead poisoning and acute hepatic prophyria Clinical Science and Molecular Medicine 53:335-340.

5. Fournier et al. 1988. DMSA treatment of heavy metal poisoning in humans. Med. Toxical. Adv. Ding. Exp.; 3(6):499-504.

6. Fullmer, C.S. et al. 1985. Lead-binding properties of intestinal calcium-binding proteins, Journal of Biological Chemistry 260(11):6816-6819.

7. Goldberg, A. et al. 1980, Clinics in Haematology, Vol. 9 no. 2 — The Porphyrias.

8. Hernberg, et al. 1970. Enzyme inhibition by lead under normal urban conditions, Lancet 1:63-66.

9. Jeyaratnam, J. et al. 1985, Neurophysiological studies on workers exposed to lead, British Journal of Industrial Medicine 42(3):173-177.

10. Kopp, S.J. et al. 1988. Cardiovascular actions of lead and relationship to hypertension: a Review. Eviron. Health Perspect. 78:91-99.

11. Lachant, N.A. et al. 1984. Inhibition of the pentose phosphate shunt by lead: a potential mechanism for haemolysis in lead poisoning Blood 63(3):518-524.

12. Lefauconnier, J.M. et al. 1983. Regressive or lethal lead encephalopathy in the suckling rat, Journal of Neuropathology and Experimental Neurology 42(2):177-190.

13. Manton, W.I. 1985, Total contribution of airborne lead to blood lead, British Journal of Industrial Medicine 42(3):168-172.

14. Moel, D.A. et al. 1985, Renal function 9 to 17 years after childhood lead poisoning, Journal of Paediatrics 106(5):729-733.

15. Montgomery, R. et al. 1980. Biochemistry – a case-oriented approach (3rd ed.).

16. Moresco, R.M. et al. 1988. Lead neurotoxicity: A role for dopamine receptors. Toxicology 53(2-3):315-322.

17. Pocock, S.J. et al. 1984. Blood lead concentration, blood pressure and rental function, British Medical Journal 289(6449):872-874.

18. Purser, D.A. et al. 1983. Effects of lead exposure on peripheral nerve in the cynomolgus monkey, British Journal of Industrial Medicine 40(4):402-412.

19. Schottenfeld, R.S. et al. 1984. Organic affective illness associated with lead intoxication, American Journal of Psychiatry 141(11):1423-1426.

20. Shelton, K.R. et al. 1982. The proteins of lead-induced intranuclear inclusion bodies Journal of Biological Chemistry 2(10):11802-11807.

21. Simons, T.J.B. 1986. Cellular interactions between lead and calcium, British Medical Bulletin 42(4):431-434.

22. Waldron, et al. 1974. Subclinical lead poisoning.