

LEAD: A REVIEW OF THE RECENT LITERATURE

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INTRODUCTION

There is no evidence that lead is involved in any of the physiological or biochemical functions of the organism and, therefore, it is a purely toxic element. Thus, in theory, the normal lead level in any body fluid should be zero although it has become customary to accept the normal blood levels observed in industrialised society as “normal”. The main aim among clinical biochemists has been to establish “safe values”, “safety limits” or “maximum allowable concentrations”, if, indeed, such exist at all. Lead has been known for about 5000 years. During the Roman Empire, production was about 80,000 tons per year and has risen, very much more rapidly this century, to about three million tons annually. Half a million tons of this ends up in the atmosphere, 70% of which originates from the combustion of petrol which contains tetraethyllead, an additive which is used to improve its anti-knock characteristics.¹ The average American absorbs about 21 ug/day of lead from food¹ and between 1976 and 1980 there has been a drop of 36.7% in blood lead levels in U.S.A. due mainly to the introduction of unleaded petrol.² Lead inspired as small particulate matter is absorbed through the lungs and a proportion of that in the diet, about 10% in adults³ and up to 53% in young children,⁴ is absorbed by the gas-trointestinal tract and taken up predominantly by the red blood cells. Over 94% in adults but only about 64% in children is deposited in the bones,⁵ where it accumulates. The toxic effects of lead are given by that in the soft tissues of which the brain is the main target organ.⁵ Excretion is principally by the liver into the bile, part of which is lost in the faeces and part is reabsorbed into the general circulation and excreted by the kidneys. Blood levels rise rapidly after an exposure to lead but as the half life in blood is only about 18 days, blood levels are a measure of recent exposure only whereas lead is retained in the brain for far longer.⁶ However, a blood lead estimation is the most convenient biochemical method for the determination of lead status although urinary γ -aminolaevulinic acid is often estimated, as the activity of γ -aminolaevulinic acid dehydratase, involved in the biosynthesis of haem, is inhibited by lead. Unfortunately the latter estimation sometimes fails to indicate the presence of toxic levels of lead,⁷ especially in children.⁸ Lead poisoning was known to the ancient Greeks, was common among the Romans who used lead water pipes and stored their wine in lead-glazed containers, caused the insanity of some of the Roman emperors and was a contributory factor towards the downfall of their empire. In the modern literature, the neurotoxic effects were first reported in 1839,⁹ with encephalopathy noted in 1910.¹⁰ A massive single dose of lead may cause death or severe brain damage but a lesser not necessarily toxic dose over a long period may cause minimal brain damage and one or more of many subtle effects on the central nervous system, less easily linked by the clinician to lead exposure. These are now the focus of recent research and will be discussed later.

LEAD TOXICITY

Acute lead toxicity apparent by a blood lead level of 120 ug/dl or over, in the case of adults, or 80 ug/dl in children may give rise irreversibly to increased cerebrospinal pressure, convulsions, memory loss, acute encephalopathy and death.¹¹ The onset may be sudden,¹¹ especially of encephalopathy in children¹² which is often an early manifestation, whereas in adults it is late, and permanent neurological damage especially of the brain often results. The younger the child, the greater is the risk. The progress of acute exposure to tetraethyl-lead has been described as follows. After a latent period of

a few hours to ten days, anorexia, vomiting, insomnia, tremor, weakness, fatigue, headache, aggression, depression, irritability, body pains, hyperactivity, confusion or memory loss may occur. Hours or days later: acute mania, convulsions, delirium, fever or coma is possible. Death may occur in serious cases after 36 hours to several days. Even after acute psychosis, there is often complete recovery 2-6 months later although minor signs may be there for some time.¹³ However, often intellectual impairment or decreased working ability results.¹⁴ Chronic exposure may result in any of the above disturbances, hallucinations, encephalopathy¹⁵ as well as ?reduced sexual potency in men,¹⁶ psychomotor excitation, depression, E.E.G. changes,¹⁷ hypotension, bradycardia, hypothermia,¹⁸ or congestion and oedema of the brain.¹⁹

SAFETY LIMIT

Clearly blood lead levels of 120 ug/dl in adults and 80 ug/dl in children can be critical,¹¹ while those above 100 and 60 ug/dl respectively are toxic. Those below 60 ug/dl for lead industrial workers were previously regarded as acceptable and the safety limits for adults and children were set at 40 and 30 ug/dl respectively.²⁰ These last two figures are still often quoted in the literature but the European Community in 1978 decided on a mean acceptable value of 20 ug/dl,²¹ with 25 ug/dl being regarded as elevated in U.S.A.²² Lately, research into the more subtle mostly subclinical neurological, physiological, biochemical and psychological effects of lead has indicated strongly that there should be a downwards revision of these values; if, indeed, there is a safety limit at all.

SUBTLE EFFECTS

It has been reported that anaemia may be caused in children at lead levels of 37 ug/dl or below in blood²³ and in adults at 60 ug/dl or above.²⁴ G.I.T. problems may occur at above 40 ug/dl and chronic long term exposure can give rise to renal problems at above 35 ug/dl.²⁴ An irreversible loss of 1.0. (especially in children) can occur at 25 ug/dl.¹¹ Although this may amount to only 2 to 5 units,²⁵ it means that three times as many children with an I.Q. of less than 80 will occur and only one-third as many with an I.Q. above 125.²⁶ Even definite differences in I.Q. and reading ability in children have been found at 14.4, 11.9 and 11.4 ug/dl.²⁷ Irreversible chronic nephropathy may occur at 25 ug/dl,¹¹ or a reversible decrease in haemoglobin production.¹¹ Neurotoxic effects may occur: irreversible changes in brainstem audi-evoked potentials at 7 ug/dl, irreversible slow wave voltage changes at 15 ug/dl and peripheral nerve velocity changes at 25 ug/dl (reversible or irreversible ?).¹¹ Blood pressure increases may occur at 8 ug/dl¹¹ and it has been estimated that in the reduction of the mean blood lead level of 17 ug/dl in U.S.A. to 10 ug/dl, 50,000 myocardial infarctions, 70,000 strokes, and 25,000 predicted deaths should be saved over a ten year period.²⁸ Higher blood lead levels have been found in children with failure to thrive (mean 22.67 ug/dl) than in normals (14.33)²⁹ and in hyperactive children, mean SD, 26.23 ± 8.41; normals 22.16 ± 9.59. Enzymes, whose activities are known to be inhibited by lead, include haem synthetase and monoamine oxidase (in the rate determining step of serotonin synthesis) at 15-20 ug/dl,³⁰ ferrochelatase at 15 ug/dl in children,³¹ and -aminolaevulinic acid dehydratase at 10 ug/dl.³² The last of these increases -aminolaevulinic acid in the tissues, which is a known neurotoxin and causes hyperactivity.¹² Other effects which have been found include chromosomal alterations in lead workers³³ reduced fidelity of DNA synthesis in vitro,³⁴ and reduced neuroendocrine function.³⁵ Lead also causes inhibition of glucose metabolism in the brain, demyelination (also caused by copper deficiency) and the antagonisation of calcium in the utilization of ATP and in the biosynthesis of the

myelin sheath.³⁶ Lead inhibits the flux of calcium to the presynaptic nerve terminals and in the release of neurotransmitters, and inhibits GABA metabolism causing hyperexcitability.³⁶ Reduced sperm count and an increase in the incidence of oligospermia have been detected in the blood of battery workers in Italy (61 ± 20 ug/dl; controls 18 ± 8).³⁷ Two prison populations in Switzerland, many of whose members were hyperactive, had mean blood lead levels of 43.5 and 40.5 ug/dl (controls 22.4 and 21.7). Similar results were found among violent criminals in Switzerland, Australia and Canada.¹²

EFFECTS IN CHILDREN

Children are more sensitive to lead than adults. For example, anaemia was found to occur at or below a blood level of 37 ug/dl,²³ whereas it did not occur in adult lead workers below 60 ug/dl.²⁴ It has been established that children under 6 years of age are more prone to the neurological effects of lead than older children,³⁸ presumably, at least partly, for reasons stated at the beginning of this discussion. In addition, their exposure is also greater because of crawling, mouthing, pica, etc.³⁹ for example the younger children of workers exposed to lead borosilicate dust at a capacitor factory in U.S.A., had higher blood lead levels than the older children.⁴⁰

CHILDREN AND ELEVATED AND ACCEPTABLE LEVELS

Around 1974, it was estimated that about 85% (12,840,000) of the mentally retarded population under 13 years of age in U.S.A. were mildly or borderline retarded.⁴¹ About 50% of these (6,420,000) were diagnosed as "cause unknown or uncertain"⁴² which included those whose retardation was probably due to having "elevated" blood lead levels of 25-55 ug/dl. Against this, it was estimated that about 15% (7,550,000) of all U.S. children had blood lead levels of 25-55 ug/dl⁴³. In New York City it was 41%⁴⁴. It should be pointed out that there is no evidence that mentally retarded or hyperactive children eat or chew more lead containing materials than normals⁴⁵ and that only in those who owed their condition to lead did their condition improve or was cured after EDTA chelation therapy.⁴⁶ Before the introduction of lead free petrol, between 10 and 30% of U.S. children below the age of 5 years had levels of at least 40 ug/dl (1972)⁴⁷ but since then, only 4% had levels of over 30 ug/dl (1982).⁴⁸ However, in 1982, 40% of all children and 60% of black children in the cities had levels above the "acceptable" of 20 ug/dl.⁴⁸

LEAD AND PREGNANCY

Maternal versus cord blood and foetal blood lead levels⁵⁰ are highly correlated, $r = 0.80$ and 0.81 respectively. Excessive lead exposure during pregnancy has been found to give rise to neurological damage to infants, to intrauterine and postnatal growth retardation,⁵¹ and to a high proportion of retarded infants.⁵² Subtoxic material levels are associated with an increased risk of premature delivery,⁵³ miscarriage,¹² and reduction in birth weight⁵⁴ and raised placental lead levels have been shown to give rise to stillbirths and congenital abnormalities.⁵⁵ Although inconclusive evidence was found by one group of researchers trying to link low maternal blood and cord blood lead levels with deformities,⁴⁹ maternal levels down to 10 ug/dl (but not postnatal exposure) have been found by others to retard development from 6 months to 2 years of age.⁵⁶ Hence the foetus is probably affected by lead

levels well below 20 ug/dl. Lead concentrations of around 40 p.p.m. have been found in the bones of stillborn infants.¹² At 2 p.p.m of lead birth is normal. The question has been asked: What are the affects on the foetus of lead exposure which causes a concentration in bone of, say, 20 p.p.m. ? Such exposure postnatally would not be recognised as being dangerous. However, such exposure may be dangerous to the foetus, the effects appearing later in life, untreatable, and the connection with lead exposure going unrecognised.

IS THERE REALLY A SAFETY LIMIT?

In recent years, the safety limit of lead in blood has been gradually reduced and the evidence is. that it should be reduced still further below the now acceptable level of 20 ug/dl especially as children are more sensitive to lead than adults and the foetus most probably even more so. Is there, in fact, a safe limit at all? - a level below which lead has no effect - a threshold, or conversely, a continuum?. Early signs and symptoms of lead toxicity are vague and non- specific: abdominal pain, loss of appetite, headache, listlessness, vague personality changes etc. They are usually not associated in the clinician's mind with lead toxicity, and lead levels are rarely measured at this stage, until the disease has progressed to an acute or nearly catastrophic encephalopathic incident. Hence, a continuum of illness⁴³ prevails from the non-specific CNS symptomatology to the acutely dramatic catastrophe. The generally accepted. threshold view thus does not apply. In starting at the vague non-specific end of the spectrum and considering chronic cases of lower and lower blood lead level, CNS symptomatology - learning disability, mental.retardation, hyperactivity, perceptual motor disability, conduct disturbances etc. becomes more and more vague, but is there a threshold below which there is no effect? Although there seems to be a threshold level of 11.5 ug/dl above which the age at which children first sit up or speak is increased, the age at which children first start walking seems to be affected at lower and lower levels on investigation,⁵⁷ 1.0. differences at 14.4 and 11.4 ug/dl have been found,²⁷ the elevation of hearing thresholds in young people continue down to at least 5 ug/dl⁵⁷ and growth in children is certainly affected down to 4 ug/dl.⁵⁸ These authors,^{57,58} show statistically that these last two factors should be influenced at still lower levels of lead, theoretically down to zero and it thus appears that there is a continuum: no true safe Level i.e. any lead level has an effect. Blood lead levels in ancient man were estimated to be around 0.2 ug/dl and in the remote Yanomama Indians a mean level of 0.83 ug/dl was found. Even in the Himalayan foothills of Nepal a mean level of 3.4 ug/dl was found in the population and it seems that global pollution is almost so complete that mankind is living at 10-200 times the norm for lead or even more.

BLOOD LEAD: SOURCE AND FACTORS

The main sources are environmental, occupational and, in Pakistan, cosmetical; important factors are nutritional status and socioeconomic factors. Apart from contamination of the water supply and fish and other food sources by industrial effluents and of land and vegetables by the use of sewage sludge as fertilizer, the use of leaded petrol and of lead paints, solders, pipes etc. and contamination by certain industries of their surroundings, must, in general, be the most important environmental sources of lead in the body. Evidence for the importance of lead emitted in the exhaust of petrol driven vehicles is legion, for example, trainers for a marathon in South Africa in rural areas had levels 4.2-42.8 (mean 20.1 ug/dl) and in urban areas 19.9-77.7 (51.9) whereas controls in remote areas had 3.0- 16.0 (9.7): Competitors pre-race had 25-93(45.8) and afterwards 25-105(53 ug/dl).⁶⁰ Blood lead levels as high as 97 ug/dl were reported in traffic constables in Alexandria, Egypt.⁶¹ Between 1976 and 1980, a drop of 36.7% in the mean blood lead level was reported in U.S.A. due mainly to the introduction of lead free petrol² Since the clean up of local industries, the abandonment of lead based paints and varnishes and the replacement of lead-soldered food and drinks cans by seamless welded containers, mean blood lead levels fell by 42-46% in Christchurch, New Zealand although petrol and water consumption remained approximately constant and the lead content of both did not vary.⁶² Workers and their families in the

lead industry are at risk. For example, levels of up to 280 ug/dl were reported in workers at a lead smelting plant in U.S.A.,²⁴ amongst whom some had G.I.t problems, extensor muscle weakness (at above 40 ug/dl) and anaemia (above 60 ug/dl) and all with levels of 35 ug/dl upwards and a minimum of seven years exposure had renal problems. The homes of workers exposed to lead borosilicate dust at a capacitor factory in U.S.A. were contaminated with more lead and the children had higher blood lead levels, than those of unexposed workers, due to the dust carried home on clothing.⁴⁰ Surma in Pakistan, which in the past contained antimony, now contains up to 89% lead as lead sulphide. Its use has recently been reported (1988) as being responsible for causing blood lead levels of up to 80 ug/ dl. Fortunately there appeared to be no clinical ill- effects⁶³ as was reported earlier among a group of surma-using Punjabi immigrants in U.K., who were using material obtained mostly from abroad. Levels of up to 70 ug/dl were found.⁶⁴ However, death due to encephalopathy of a surma user has been reported in U.K.⁶⁵ Clearly, its use should be forbidden bylaw. Nutritional deficiencies of iron, zinc, copper, calcium and phosphorus enhance the absorption of lead from the diet.⁶⁶ Lead absorption is higher in iron deficiency anaemia in humans⁶⁷ and also in protein deficiency in rats.⁶⁸ A high lead diet in rats produces copper deficiency,⁶⁹ and lead in humans competes with zinc, iron, and calcium and thus interferes with embryonic nutrition.⁷⁰ Childhood exposure to lead in general is higher in low income areas owing to the environment, peeling paint in houses etc., and to deficiencies in child care and household cleanliness⁷¹ Neurological effects of such exposure are also greater.⁷² One can assume that nutritional factors are at least partly the cause and that these facts apply to adults in socially disadvantaged groups also. Increased blood lead levels have been found in smokers, probably lead is present in the tobacco.⁷³ Alcohol intake results in higher blood lead levels especially among wine drinkers and it has been found that the lead content of wines is greater than that of spirits or beers.⁷⁴ Those with liver disease without cirrhosis had higher levels than cirrhotics.⁷⁴ Possibly lead accumulates in the livers of cirrbotics and acute liver damage induced by alcohol releases the lead.⁷⁵

RACIAL AND INDIVIDUAL VARIATIONS IN THE EFFECTS OF LEAD

A series of studies has been carried out in various population groups in Karachi and blood lead levels, mostly, are alarmingly high. The obvious question is why is the incidence of neurological disease not higher even than it is? Admittedly, a blood lead level is not a good indicator of lead status, for reasons mentioned earlier, but short of going around doing brain biopsies ad lib., there is no other satisfactory method, as enzyme estimations are even less reliable indicators.^{7,8} Could the effects of lead be less serious than among Westerners? Many differences in biochemistry occur between Pakistanis and Westerners as differences in normal ranges indicate. It cannot yet be known if this applies to the effects of lead but certainly American negroes are less affected than white Americans, hence a racial difference. Although higher blood lead levels are found among black American children than among white,^{48,76,77} the former have better hearing abilities than the latter⁷⁶ and they develop quicker during the first year of life.⁷⁷ (Lead is detrimental to both these factors^{57,58}). Individuals vary greatly in their response to lead. A blood lead level of 100 ug/dl can literally kill one person and have no effect on another.⁴² A worker at a lead smelting plant in U.S.A. had a lead level of 280 ug/dl which was toxic but not fatal²⁴ At a levels 48.4-95.4 ug/dl yet only 50% suffered from insomnia, 44.6% with fatigue, 41.4% with abdominal colic, 37.6% with weakness, 29.0% with drowsiness and 2% only had a blue gum line.⁷⁸ In November 1988 it was reported from U.K. concerning evidence for the existence of, what has simply been described as, a low molecular weight protein in red blood cells, which chelates with lead and supposedly prevents its toxic action. This protein was absent in those with low blood lead levels, is present in low concentration in those with high lead levels exhibiting signs of lead toxicity, and is present in higher concentration in those with high lead levels with no symptoms of lead toxicity.

⁷⁹ So, perhaps, all is not doom and gloom!

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