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Toxicity of lead: a review

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Introduction

Lead is widely distributed in nature; the metal and its compounds are potentially toxic. Its gross effects on health have been known for decades and measures to deal with this over the past 50 years have greatly reduced the number of cases of frank poisoning. Exposure to small amounts can also, however, give rise to adverse effects.

Uses

Industrial uses

The main use of lead is in the manufacture of storage batteries, the production of alkyllead petrol additives, and as alloys combined with various metals that provide certain qualities suitable for the particular use. Lead alloys with antimony are used to insulate cables from moisture, and alloys that contain arsenic, bismuth and tin are used for power cables.[1] Lead and antimony alloys are used in grids in acid-storage batteries. Type metals are lead alloys which contain antimony and tin. Solders contain lead composition with antimony. Lead is used in bullets and shot, as its high density makes it ideal for this purpose.

Lead is also used extensively in the chemical industry, and is widely used in the manufacture and handling of sulphuric acid. It is also used in the protection of pipelines, bridges, and ships. Because of its excellent sound attenuation property, lead is used in construction to keep within prescribed noise and vibration levels. Lead asbestos pads are used to isolate heavy machinery. Because of its radiation-absorbing property, lead is used as a protective shielding for Xray machines and protective aprons, and wherever glass windows

are needed in radiation equipment.[1] Lead combined with chromate and molybdate forms paint pigments, and its silicate is used in ceramics and in fireproofing fabrics, and the lead arsenate has been used as an insecticide.[1]

Medicinal uses

Lead salts have an astringent action, which is due to the formation of lead proteinate. They were once used as soothing astringent applications, such as 10% lead carbonate ointment or lead subacetate solution in a variety of external preparations.[2] The medicinal use of preparations containing lead is no longer recommended. The use of lead acetate in cosmetics and toiletries has been restricted in the UK; under the 1978 Cosmetic Products Regulations[3] it is restricted to a maximum concentration of 3% in hair-care products.

Clinical manifestations of lead poisoning

Acute exposure

Acute lead poisoning occurs from the accidental ingestion of acid-soluble lead compounds.[4] The fatal dose of absorbed lead has been estimated as 500 mg. Symptoms are an intense thirst, a metallic taste, followed by nausea, vomiting, and a burning abdominal pain; there may be diarrhoea or constipation. The vomit may have a milky appearance, due to the formation of lead chloride, and the stools may become black, due to lead sulphide. Acute central nervous symptoms, which include paraesthesia, pain, and muscle weakness, develop. An acute haemolytic crisis is seen sometimes, resulting in anaemia and haemoglobinuria. Severe renal damage follows, with oliguria, shock, and coma; death may occur within 1–2 days.[4]

Chronic poisoning

Chronic poisoning is usually due to the accumulation of small quantities of lead in the body by inhalation, ingestion, or skin absorption. In general, the symptoms are mainly gastrointestinal with chronic exposure, mainly neuromuscular with subacute poisoning, and affect the central nervous system when there is more rapid, intense absorption. Detailed descriptions of the adverse effects are covered in the toxicology section.

General

Sources of exposure

Lead is found widely throughout the world in a number of ores, the most common being the sulphide, galena. The other minerals are carbonate,

cerussite, and the sulphate, anglesite. It is a non-essential element that occurs naturally in soils throughout the world and has, therefore, always been present in man's environment in food and beverages.[3] Man has been exposed to lead from the beginning of the metal era. During the time of the Roman Empire, water pipes and cisterns were made of lead, and lead vessels were in common use. Lead oxide has been the main white pigment of paint for over 2000 years.[5] More recently, lead has been a contaminant of food from the use of lead arsenate sprays and from contact with processing equipment and containers but these sources of contamination are decreasing. In the 19th and 20th centuries, however, industrial processes resulted in an increased exposure to lead, and inhalation of lead from air pollution has been increasing. Tobacco smoke may also contribute to the intake of lead.[5] Lead particles do not occur naturally in the atmosphere to any significant extent, but the addition of lead, almost exclusively as tetramethyl and tetraethyllead as 'antiknock' ingredients, to petrol over the past 50 years has added considerably to this airborne lead in the areas of dense traffic. The tiny particles of lead in the air eventually fall on soil, water, or vegetation, especially near highways or in localized areas near lead smelting works. This may raise the levels in plant and animal food and in the water in reservoirs.

Young children with pica have been exposed to lead that has been used in paints applied to buildings before the second World War, when white lead carbonate and red lead oxide were common constituents of both interior and exterior house paint.[4] In such paints lead may form 5–40% of dried solids. Children have become poisoned not only by nibbling lead-painted window sills and door frames but also from toys and furniture.

Food and beverages have on occasions resulted in fatal poisoning when acidic food and drinks like tomato juice, fruit juice, cola drinks, cider, or pickles, stored in improperly glazed containers have dissolved the lead in the containers.[4] Lead is also a contaminant of illicitly distilled whisky made in the USA, because the car radiators, which were frequently used as condensers, and other components of the improvised stills are connected by lead solder. Occasional cases of lead exposure have occurred from lead dust in shooting galleries, artists' paint pigments, fumes from burning painted wood, jewellers' waste, lead type, and soluble lead compounds in old lead pipes.[4] Occupational exposure of workers in lead smelting and in storage-battery factories has been greatly reduced by regulations ensuring appropriate preventive measures.[4]

Chemistry

Lead is a bluish or silvery-grey soft metal. The melting point is 327.5°C. Although lead has four electrons in its valence shell, only two ionize readily. The usual oxidation state of lead in inorganic compounds is therefore +2 rather than +4. The inorganic salts of lead (II), lead sulphide and the oxides of lead, are generally poorly soluble, with the exception of the nitrate, the chlorate and,

to a much lesser extent, the chloride.[6] Some of the salts formed with organic acids, for example, lead oxalate, are also insoluble.

Methods of detection and analysis

Special techniques for sampling and measurement are required, depending on the source; in air sampling, for example, liquid scrubbers containing iodine monochloride, and solid scrubbers with activated carbon, cristobalite, or iodine crystals have been used for sampling organic lead compounds in air. Extraction is followed by analysis by atomic absorption spectrophotometry. The method is applicable to lead concentrations ranging from 0.1 μg per m^3 up to 10 μg per m^3.[7,8]

For the study of lead in foods two methods have generally been employed, the duplicate diet or portions technique and the equivalent composite technique (theoretical diet). The duplicate portions method allows an average over a period of 4–8 weeks to be determined, but it is an expensive method.[6] When sampling body fluids and tissues for lead, special precautions are required to ensure that all blood-collecting and storage materials are as free from lead as possible. Various analytical techniques applying spectrography, polarography, or colorimetry have been employed in industry for the determination of lead in blood, urine, and other materials, but they are not suitable in clinical practice.[9]

A modification of a colorimetric technique involving the formation of a coloured complex of lead and dithizone has been used in clinical laboratories but, although sensitive, it lacked specificity.

Polarography, although fairly suitable in industrial screening programmes also lacks sensitivity for clinical use.[9]

Atomic absorption flame spectrometry is sensitive enough to detect lead levels less than 200 μg per litre (20 μg per cent, 0.2 ppm) in an aqueous solution. This method is rapid and requires only small amounts of blood or urine.[9]

Anode-stripping voltammetry has also been adopted as a suitable analytical method. Neutron-activation analysis has been investigated, but the cost, and need for access to a fast neutron source, limit the use of this method. Xray fluorescence has some disadvantages but has been used for measuring the concentration and amount of lead on the walls of houses.[6]

The paper-punch disk microtechnique was used in a population survey of blood lead content in Western Ireland with satisfactory results.[10] Atomic absorption spectrometry with electrothermal atomization has recently been reported to be an effective method of determination of lead in teeth.[11]

Pharmacology and pharmacokinetics

Absorption

The major routes of absorption of lead are from the gastrointestinal tract and the respiratory system. About 5–10 per cent of lead ingested in food is

absorbed.[12–15] mainly in the small intestine; some of the lead absorbed undergoes enterohepatic recycling.[2,14] The average daily dietary intake of lead in the US is 120–350 μg, of which about 25 μg is absorbed.[12–14] The average intake from food and water for an adult is about 200–250 μg daily in the UK.[16] Children absorb a substantially greater proportion, about 50 per cent, of dietary lead than do adults. The absorption of lead is affected by such factors as the presence or absence of food in the gut and the composition of the diet, although in this respect the influence of dietary milk on absorption remains unclear.[17] Low calcium, iron, and protein content of food increase gastrointestinal absorption. Inorganic lead is not absorbed through intact skin but organic lead compounds, such as lead naphthenate and tetraethyllead may be absorbed rapidly.[2] Fumes of organic lead compounds are highly toxic. Lead can be absorbed from all areas of the respiratory tract, including the nasal passages. It is absorbed by the lungs from dust particles; about 40 μg is inhaled daily, 15 μg of which is retained and absorbed.[4] Significant amounts can be absorbed from a bullet or shot wound, especially with lead shot because of its larger surface area. Lead poisoning has been reported within a month after a bullet wound.[3] Absorption of organic lead compounds is more rapid, and because of their higher lipid solubility, large amounts reach nerve tissue.

Distribution

Lead is distributed among three compartments: (1) in blood and some soft tissues, this is a rapidly exchangeable pool; (2) in soft tissue and loosely bound to bone, also rapidly exchangeable; and (3) tightly bound in the skeleton, forming 60–90 per cent of the total body burden.[15] In soft tissue it is found in higher concentrations in the tubular epithelium of the kidney and in the liver, and 95 per cent of lead in the blood is bound to erythrocytes. It is then redistributed to be deposited in calcified bone, hair, and teeth. Small quantities of inorganic lead accumulate in the brain, mainly in the grey matter and basal ganglia.[18] Non-polar organic lead compounds penetrate more rapidly into the brain as well as other membranes.[18]

Lead is deposited in bone as tertiary lead phosphate, which does not contribute to toxicity. Following recent exposure, the concentration of lead is often higher in the flat bones than in the long bones[13,14] although, in general, long bones contain more lead. Initially the concentration of lead is highest in the epiphyseal portions of long bones, especially in growing bones, in which it can be demonstrated radiographically as rings of increased density. Factors that affect calcium distribution similarly affect that of lead: a high phosphate intake, for example, favours storage in bone rather than in soft tissues, while a low-phosphate diet has the reverse effect. Vitamin D promotes bone deposition of lead; parathyroid hormone and dihydrotachysterol mobilize it from bone and raise its level in blood.[4] Acid–base disturbance or an upper respiratory tract infection may result in the mobilization of lead from bone, causing toxicity.[1]

Blood levels may only indicate the degree of lead absorption in acute cases, since blood is rapidly cleared of lead. In chronic cases blood lead levels are not remarkable. Blood levels of 0–21 μg per cent are considered to be within normal limits, 21–60 μg per cent as evidence of increased lead exposure, and above 60 μg per cent indicative of lead intoxication.[9] Blood levels alone are not sufficient to substantiate the diagnosis of lead intoxication; urine lead content as well as other investigations are needed to support it.

Lead crosses the placenta easily, and fetal blood has almost the same lead concentration as maternal blood.[19] A study involving the analysis of human fetal tissues[20] demonstrated that placental transfer of lead begins as early as the 12th week of gestation and that the content of lead in the fetus increases throughout the pregnancy. The highest concentrations were found in bone and liver, with significant amounts also in the blood, brain, heart, kidney, and placenta, totalling about 300 μg. This study showed that, in general, lead concentrations were lower in cord blood than in maternal venous blood. Human milk is reported to be low in lead.[16]

Excretion

In experimental animals, lead is excreted into bile, and much more lead is excreted into the faeces than into urine.[21] In man, urinary excretion is the main route,[13,14] accounting for 75–80 per cent, a lesser amount, about 15 per cent, appearing in gastrointestinal secretions. Other routes such as hair, nails, and sweat account for less than 8 per cent. Maternal milk contains small amounts of lead (a few μg per litre). The concentration of lead in urine is directly proportional to that in plasma,[22] but since most of the lead is in the erythrocytes, very little is filtered. The elimination of lead is slow. The half-life of lead in blood is variously stated to be about one month[4] to 70 days;[2] a steady state is achieved in about 5 months.

The adult excretes about 0.3 mg lead into the faeces and 0.03 mg in the urine daily. Urinary concentrations above 15 mg per litre in adults, and 0.08 mg (80 μg) per litre in children are considered to be toxic levels.[9]

Human toxicology

Gastrointestinal effects

The abdominal symptoms are initially vague—anorexia, epigastric pain, indigestion, nausea, malaise, headache, and constipation. These are important early signs.[4] Diarrhoea occurs occasionally. A persistent metallic taste appears early. With further exposure, anorexia and constipation become more marked. Intestinal spasm causing severe abdominal pain (lead colic) can be very distressing.[4] The attacks are paroxysmal and generally excruciating. The abdominal muscles become rigid and there is tenderness around the umbilical area.

Haematological effects

The haematological effects of lead can be attributed to the effects of inhibition of haemoglobin synthesis. Although punctate basophilic stippling, due to the formation of aggregates of ribonucleic acid in erythrocytes, is widely considered to be pathognomonic of lead poisoning, this is not the only cause. Reticulocytosis is prominent. Microcytic hypochromic anaemia is common and is invariably found in affected children. It may be the only clinical feature of chronic low-grade exposure to lead.[1] The anaemia is partly due to the destruction of erythrocytes. It appears that the type of haemoglobin HbA_3 found in red cells of anaemic children with raised levels of lead is characteristic of prematurely senescent red cells, but the life-span of the majority of the red cells is normal.[23] The anaemia is seldom severe. As a result of these effects, reticulocytosis and punctate basophilia occur. Disturbances in haem synthesis are demonstrated by the appearance of abnormal concentrations of haem precursors in blood and urine. Lead has been shown to inhibit haem synthesis at several sites, the enzymes concerned being haem synthetase,[24] δ-aminolaevulinic acid dehydratase (ALAD) and ferrochelatase,[4] δ-ALA synthetase,[25] uroporphyrinogen decarboxylase, and coproporphyrinogen oxidase.[4,16] Globin synthesis may be affected also,[26] as may incorporation of iron into protoporphyrin.[16] Many of these enzymes are sulphydryl-dependent for activity, and lead exerts its effect by blocking them.

Lead poisoning is characterized by accumulation of protoporphyrin IX and non-haem iron in red blood cells, by accumulation of δ-ALA in plasma, and by increased urinary excretion of ALA and coproporphyrin III.[4] Increased excretion of porphobilinogen and uroporphyrin has been seen in severe cases.[4]

Cardiovascular effects

A marked increase in cerebrovascular mortality was reported in lead workers in the first quarter of this century, when working conditions were poor;[27] no similar increase in mortality rate has been seen more recently.[6] The incidence of hypertension in industrially exposed men has been studied clinically,[28] and on the basis of urinary coproporphyrin levels, compared with non-exposed men but no statistical differences could be demonstrated.[29] A more recent study has confirmed this finding.[30] It is not clear whether the vascular effects are due to an effect on blood vessels directly, or are secondary to renal effects. An anecdotal report on lead-induced hypertension showed reduced β-adrenoceptor responses similar to those found in low-renin essential hypertension.[31] A recent experimental study in young dogs, however, has demonstrated hypertension associated with an increase in plasma renin activity.[32] Myocardial toxicity has also been associated with clinical lead poisoning in both adults and children. Heart failure due to subacute interstitial myocarditis was stated to be the cause in two of five fatal cases of lead poisoning.[33] In another report,[34] electrocardio-

graphic abnormalities found in 70 per cent of 30 children with lead poisoning disappeared with chelation therapy, whereas in other reports cardiac effects were aggravated by mobilizing lead by chelation.[6]

Endocrine effects

Impairment of thyroid[35] and of pituitary function[36] has been reported in case of lead poisoning.[6] Although there is some suggestive evidence of disturbed tryptophan metabolism, based on increased urinary 5-hydroxyindoleacetic acid excretion, this finding has not been confirmed consistently.[6]

Hepatic effects

Impairment of liver function has been reported in cases of severe lead poisoning,[6] but liver damage was not correlated with blood lead levels or disturbed porphyrin metabolism. In another study,[37] increased aspartate aminotransferase values could be linked with increased blood lead levels, about 10 per cent in those with blood lead levels below 70 μg per dl, 20 per cent in those with blood levels of 70 μg per dl, and 50 per cent in those with blood lead levels above 100 μg per dl. Definite conclusions about these changes could not be drawn, because dietary and other details of these exposed workers were not known.

Renal effects

Two general types of effects have been reported due to lead exposure. The first is fairly clearly defined as being due to renal tubular damage characterized by aminoaciduria, hypophosphataemia, and glycosuria (the Fanconi syndrome); hyperphosphaturia may follow.[38] This is due to decreased reabsorption of glucose and α-amino acids reflecting proximal tubular damage. Children who have had intense short-term exposure may develop the Fanconi syndrome.[39] A similar renal tubular syndrome has been reported to occur in industrially exposed adults,[40] but lead blood levels were not reported. In the second type of renal syndrome aminoaciduria was not found. Inulin clearance and renal blood flow were also normal during investigation; the blood lead levels ranged from 70–100 μg per dl. The ALA urinary excretion was markedly raised, however. Renal biopsy studies showed diffuse interstitial and peritubular fibrosis, which is termed chronic lead nephropathy. This type of lesion is characterized by slow development of contracted kidneys with arteriosclerotic changes, interstitial fibrosis, glomerular atrophy, and hyaline degeneration of the vessels. This may progress to renal failure, and has been shown to occur in industrially exposed workers, in long-term drinkers of lead-contaminated whisky, and among middle-aged people who had lead poisoning much earlier.[41–46] It does appear, that lead exposure levels and the duration of exposure was higher, with blood lead levels of 80–200 μg per dl being found.[44,45] It seems likely, from available

J-9042

evidence, that prolonged high-level exposure is necessary, even in childhood, to cause progressive chronic nephropathy.[6] A follow-up of subjects with well-documented exposure to lead in childhood, in the USA, was not able to confirm similar development of chronic renal disease[47] as found in Australian subjects.[41–43]

Hyperuricaemia, with or without manifest gout, has been associated with chronic renal insufficiency.[43,48] In a study of 13 cases of renal insufficiency, due to lead nephropathy, no alteration in uric acid secretion was shown;[49] the authors suggested increased tubular reabsorption to account for the decreased clearance of uric acid. Later studies have tried to clarify the association between gout and lead exposure. Joint pains have been recognized as a symptom of lead poisoning. In one study, they occurred in 20 per cent of patients with chronic lead poisoning.[50] A further study reported that, while a history of clinical lead poisoning is uncommon in patients presenting with gout in the UK, the effects of chronic exposure to lead from drinking water showed hyperuricaemia to be significantly associated with raised blood lead concentrations in a symptom-free population.[51] In a more recent controlled study, raised blood lead concentrations were found in patients with gout who gave no history of overt lead exposure, suggesting that gout may be another manifestation of subclinical lead poisoning.[52] Following this, another study[53] investigated the amount of lead that could be mobilized, with a 3-day $CaNa_2EDTA$ (EDTA) test, in patients with gout and found that those who had renal impairment excreted significantly greater amounts of lead; it is suggested that it could be a useful test when the cause of the nephropathy is unclear.

Neuromuscular effects

Muscle weakness and easy fatigue occur early and may be the only symptoms. The lead palsy of advanced subacute poisoning is rarely seen now. The weakness or palsy may only become noticeable after prolonged muscle activity. The muscle groups usually involved are the most active ones, like the extensors of the forearm, wrist, and fingers, and the extraocular muscles. The dominant side is often the only side affected. Wrist-drop and to a lesser extent foot-drop are typical of exposure to lead, without any sensory involvement. Occasionally, greatly increased muscle tone, and spontaneous pain and tenderness in muscles and joints occurs after prolonged severe exposure to lead in association with hard physical effort.[54] Degeneration of the myelin sheaths and their axons has been demonstrated.[55] Segmental demyelination and proliferation, as well as Wallerian degeneration of the posterior roots of the sciatic and tibial nerves, have been seen. Based upon electron microscopic observations, others[56] have suggested that axonal degeneration of the nerves is more prominent in human poisoning. Slight functional impairment can be detected only by sensitive electrophysiological techniques.[9] Several investigators[56–60] have shown slowing of peripheral nerve conduction velocity. Schwartz and colleagues[59] confirmed

that slowing of nerve conduction in a group of asymptomatic children was caused at blood levels of over 30 μg per dl. A presynaptic block may be a contributory mechanism to the abnormal findings, since reduction of the end-plate potential has been described.[39]

Central nervous system effects

The most severe manifestation of inorganic lead poisoning is encephalopathy. It is common in children but uncommon in adults, and only as a result of rapid and intense absorption. The initial signs are dullness, clumsiness, muscular tremor, ataxia, unsteadiness, headache, insomnia, restlessness, and irritability. This may progress to excitement and confusion, hallucinations, and loss of memory, and inability to concentrate, followed by delirium, mania, and grand mal fits, or paralysis and coma.[6,61,62] These clinical effects were seen in lead workers in the early 1900s but are rarely seen now. Visual disturbances and optic atrophy have also been reported in chronic poisoning, as well as auditory defects and vertigo. In fatal cases, cerebral oedema with obliteration of the convolutions of the cerebral hemispheres has occurred. Also, changes in cerebral blood vessels are seen as swelling of capillary endothelial cells. Perivascular haemorrhages occur with patchy neuronal loss, serous exudate, glial proliferation, and occasional areas of demyelination.[62,63] Children are at greater risk from neurological damage than adults, and encephalopathy is often an early manifestation.[64] The risk appears to be inversely related to age.[65] Children between 12 and 48 months of age are most severely affected, with the highest incidence of encephalopathy and death occurring during the hot summer months.[66] Twenty-five per cent of the survivors of acute encephalopathy are said to have permanent neurological sequelae.[67] Although the fits and behaviour abnormalities tend to improve during adolescence, mental incompetence is permanent. A further finding is that if children who have had lead encephalopathy are re-exposed and suffer another episode then they almost certainly develop severe brain damage.[66,68] The prognosis has improved substantially since the introduction of therapy, provided this is commenced before the onset of encephalopathy.[69–71] The most severe sequelae are cortical atrophy, hydrocephalus, convulsions, and severe mental subnormality. More commonly the effects are more subtle: learning ability may be impaired due to motor incoordination, lack of sensory perception, or inability to concentrate. These changes are also stated to occur in children with high lead exposure without a history of encephalopathy.

Effects on mental development

Moncrieff and colleagues,[72] in 1964, drew attention to the frequent finding of raised blood lead concentrations in children with mental handicap, severe behaviour disorder, or pica, most of whom showed no clinical signs of exposure. Since then many studies have been undertaken, some but not all supporting this

finding. Bicknell and co-workers,[73] in a study of a population of hospitalized mentally handicapped children, showed that there are three groups of children: those with pica; physically handicapped children without pica; and mobile children without pica. Excessive lead ingestion by about 70 per cent of the children in the first group was shown by blood lead concentrations and urinary lead excretion. There was no evidence that moderately raised blood lead concentrations had any relation to the original cause of the mental retardation.[15]

Lansdown and others,[74] who studied all children under 14 years living around a lead-producing factory in London, found no relation between blood lead concentrations and either IQ or behaviour disturbance. Similarly, in a study in Birmingham,[75] the mental capability score of children living since birth in a lead-polluted area was not lower than that of children living in two similar unpolluted areas. The results were not significantly affected by adjustment for social class, birth rank, and maternal age distribution. A study in the USA,[76] of two carefully matched groups of children living near a lead smelter in El Paso, Texas, found no significant differences between those with higher blood lead concentrations and their controls with respect to intelligence, school performance, or hyperactivity. Landrigan and co-workers,[77] in another study of children living in the same area, reported that performance IQ was lower and finger-wrist tapping slower in those with raised lead concentrations though full-scale IQ, verbal IQ, behaviour, and hyperactivity scores were similar. The findings have been difficult to interpret, however, because of the methodological problems of this study.[78]

Clinical lead poisoning from water-borne lead in areas with soft acidic water has been reported in adults;[79,80] and another study,[81] in Glasgow, showed higher amounts of lead in the water in homes occupied during fetal life and infancy by 77 mentally handicapped children compared with matched controls from the same area. This study was also criticized in respect of matching controls. Also, the severity of the mental handicap seemed to be out of proportion to the measured blood lead levels.[78]

Pueschel and colleagues,[82] in 1972, demonstrated minor neurological dysfunction, and motor impairment in about 25 per cent of children with an increased lead burden. Psychological assessment revealed mental abilities to be lower than average but after 1.5 years' treatment these were noted to have significantly improved. About that time concern was expressed in the UK[83] about airborne lead pollution from the use of tetraethyllead in petrol. Although raised blood lead concentrations had been shown in adults exposed to exhaust fumes, there appeared to be little evidence of overexposure in children.[84] Workers in the USA [85] measured blood lead levels in the deciduous teeth of urban and suburban children and considered these could be used as an indication of lead exposure. Using this method, Needleman and colleagues[86] provided evidence suggesting lead-related neuropsychological deficits in children in the general population.

In the UK, study of associations between behaviour, intelligence and other psychological skills showed no significant link between IQ and tooth lead levels after controlling for confounding factors.[87–91] A recent study[92] from Edinburgh, however, appears to contradict the above study and a significant association between blood lead and IQ in children aged 6–9 years was reported. Exposure to low levels of lead had a small deleterious effect on ability and attainment tests.

Investigators in this field have now been able to demonstrate effects on slow cortical potential in young children.[93,94] The Port Pirie Cohort Study,[95] in Australia, has shown that postnatal blood lead concentrations below 30 μg per dl is inversely related to cognitive development in young children. Another investigation[96] has demonstrated consistent association between disruption of visual–motor integration and reaction performance and blood lead levels below 30 μg per dl in children.[95] To find out whether these findings where age-dependent and reversible, Wistar rats were exposed to lead acetate in their diet prenatally and postnatally; their offspring were found to show similar cognitive deficits that were persistent with exposure during the early stages of brain development.

Other workers[97] have also found significant differences in neuropsychological performance between control subjects and workers exposed to lead levels traditionally accepted as safe, that is, levels below which overt tissue damage or obvious clinical features are produced. In a further controlled study,[98] it was confirmed that occupationally exposed workers with blood levels between 16–80 μg per dl (mean 49 μg per dl) show neuropsychological effects, the most distinctive impairment being their long latency in reaction time; deterioration in perceptual-motor speed and visual scanning was noted to a lesser extent.

Mutagenicity

Lead compounds have not been reported to have produced mutagenic effects in bacterial systems.[99] Nuclear polyploidy and mitotic abnormalities in bone marrow cells have been reported,[100] as well as an increased number of gap-break type of aberrations in leucocyte cultures from mice fed 1% lead acetate in their diet.[101] In other studies, lead acetate has induced dose-related transformations in hamster embryo cells;[102] lead oxide has enhanced transformation by Simian adenovirus;[103] and lead chloride has been shown to decrease the fidelity of DNA synthesis.[104]

One study reported that the rate of abnormal metaphases in leucocyte cultures increased concurrently with urinary lead and coproporphyrin levels.[105] Other groups of workers[106–8] have also reported chromosomal aberrations in humans exposed to lead, with blood levels in the 40–70 μg per dl range, yet others[109–11] have not been able to confirm such findings, even with blood levels ranging from 40 to over 120 μg per dl. A controlled study on human peripheral lymphocytes *in vitro* and *in vivo* did not show any evidence of lead-induced

chromosome aberrations.[112] Another study, of sister chromatid exchange in cultured peripheral lymphocytes from people exposed to lead, was negative.[113] In two investigations,[108,114] chromosome aberrations were significantly increased but, as the workers were exposed to cadmium and zinc as well, these results are difficult to interpret. Also, the authors' suggestion that exposure to several metals could have a synergistic effect remains to be investigated further. In 1982, the International Agency for Research on Cancer (IARC) working group[115] noted the conflicting reports of chromosomal aberrations and sister chromatid exchanges in cultured mammalian cell systems and in *in vivo* studies, both in animals and in humans, following exposure to lead.

Carcinogenicity

In 1972, the initial IARC report[116] stated there was no evidence that exposure to lead salts caused cancer in man, because only one epidemiological study[101] was available and it did not show evidence of increased malignancy. Later, a cohort study,[117,118] in which over 7000 smelter and battery workers exposed for a minimum period of one year and followed up for 23 years, showed a significant excess mortality from lung and digestive tract cancer in smelter workers but not in battery plant workers. In a 5-year follow-up[119] of over 5000 workers from the same cohort, the initial mortality pattern was not maintained, as a non-significant excess of lung cancer was seen in battery plant workers. In a further report,[120] elevated standardized mortality ratios for lung and stomach cancer were found in both types of workers. Smoking histories were not obtained, however; an excess of smokers could have accounted for the small increased mortality in lung cancer.[99] As a result, the IARC, in its 1980 report,[121] considered that the carcinogenicity of metallic lead and organic lead compounds could not be evaluated, because of the inadequacy of experimental and epidemiological data. But, on the basis of animal experiments, and in the absence of human data, the IARC concluded that it was reasonable, for practical purposes, to regard lead acetate, lead subacetate, and lead phosphate as presenting a carcinogenic risk to humans. A case of a smelter worker with renal carcinoma similar in appearance to lead-induced tumours in animals has been reported;[122] three cases had also been noted in the cohort study.[118] It is suggested that as the kidney is the only organ clearly implicated in experimental cancer caused by lead compounds, studies are needed to assess lead exposure in cases of renal cancer.[99] Nine cases of glioma were found in the cohort study,[118] as had been reported by another group of investigators, who fed rats lead subacetate.[123]

Reproductive effects

It has long been known that lead compounds are abortifacients, and that women working with lead have a high miscarriage rate.[124,125] It is probable that

these reports led to the legislation forbidding the employment of women in the lead trades in many countries.[6] There is no epidemiological evidence, however, of an effect of lead on the fertility of women. The reproductive capability of occupationally exposed men has also been studied, and this indicates that both greatly and moderately increased lead absorption decreases fertility. An increased frequency of hypospermia and abnormal sperms was found; this was considered to be due to a direct effect on reproductive function, as no endocrine abnormality was found.[126] Barlow and Sullivan[127] refer to two reports concerning sexual function and spermatogenesis in men poisoned by petrol containing tetraethyllead. Apart from general and neurological effects, they also complained of impotence with related symptoms. Hypospermia and abnormal sperms were confirmed. Although potency improved following treatment, persistence of low sperm counts and low motility up to 5 months after exposure suggested that spermatogenesis may be particularly sensitive to organic lead poisoning.[127] Other workers have, more recently, reported endocrine and reproductive dysfunction, especially of the hypothalamo–pituitary–testicular axis, in men associated with occupational inorganic lead exposure.[128–130] A decrease in serum testosterone levels, an increase in steroid binding globulin levels, and a decrease in the free testosterone index was shown.[131] It is suggested that prolonged exposure causes direct testicular toxicity followed by a hypothalamic or pituitary effect depending on the length of exposure to lead.[131]

Teratogenicity

Lead has been shown to be teratogenic in some species; fetal hamsters have developed abnormalities of the tail and sacrum following maternal exposure to lead,[132] and chick embryos have demonstrated cardiac anomalies, including aortic stenosis and valvular defects.[133] The severity of other similarly produced abnormalities was dose-related.[134] In man, there appears to be only one report, of neuromuscular abnormalities and failure to grow in an infant who was exposed to lead *in utero* as a result of the mother having consumed illicit whisky.[135] No other information could be found suggesting lead is teratogenic in man.

Effects on the fetus and newborn

The mechanism of lead transport across the placenta is unknown. Studies in rats have demonstrated that lead crosses the placenta.[136] Later it was shown in the human that lead transfer begins about the 12th–14th week of gestation.[20] This transfer continues throughout fetal life,[137] with the greatest concentration of lead being found in bone. The relatively large absolute amounts of lead in the brain and blood reflect their total mass. At delivery there is a significant correlation between the maternal blood lead concentration and that in the infant's cord blood.[20,138]

Fetal lead intoxication has been reported following maternal exposure to lead during the 8th month of pregnancy, confirmed by biochemical blood estimations, raised amniotic fluid lead, and erythrocyte protoporphyrin levels.[139] The infant had a blood level of 50 μg per dl at birth, and no neurological abnormalities were detected then. The severity of the sequelae due to lead is related to the maturity of the central nervous system at the time of exposure. At 13 months of age, the child demonstrated delayed cognitive skills associated with object permanence, spatiality, causality, and imitation tasks as had been previously described.[140] In another case, in which the mother had been ingesting paint chips during the latter months of pregnancy,[141] and was given intravenous EDTA therapy for 3 days following diagnosis, the infant showed no abnormal physical or neurological signs at birth, although the cord blood lead level was 60 μg per dl with a free-erythrocyte protoporphyrin of 330 μg per dl. At 2 weeks of age, the blood level was still raised and intramuscular chelation therapy with EDTA (50 mg per kg per day) was given for 5 days, bringing the level down to 40 μg per dl. At 5 months, a second course brought the level down to 21 μg per dl. At 18 months of age, developmental evaluation was within the normal range. Although encouraging, the effects of prolonged exposure to lead *in utero* on optimal brain development and function can only be ascertained by long-term follow-up.

In a Zambian community, mothers exposed to high atmospheric as well as high ground lead concentrations in the vicinity of a lead mine and smelter works, had mean blood levels of 41 μg per dl and their infants 37 μg per dl. This was stated not to have affected birth-weight or red cell values of the newborn.[142]

In the USA, however, the results of a recently reported study did not agree with these findings: Bellinger and colleagues[143] undertook a longitudinal study allowing the dose, timing, and duration of lead exposure and children's behaviour to be measured periodically. Depending on the umbilical cord level, 249 children were placed into one of three groups: low (<3 μg per dl), medium (6–7 μg per dl), or high (≥ 10 μg per dl). At all periods up to 2 years the high prenatal exposure group (10–25 μg per dl) scored lower than infants in the other two groups. It is suggested that, although 25 μg per dl is considered to be the highest acceptable level for young children, it may affect the fetus adversely. Human milk is low in lead;[15,144] maternal exposure to lead is, however, associated with an increased concentration in breast milk.[145]

Adverse reactions

Medicinal products

The adverse effects of medicinal products containing lead have been almost exclusively due to the use of traditional or herbal remedies. Lead is a constituent of many herbal products used world-wide, and has caused major adverse effects.[146] Chan and colleagues[147] reported on a 4-month-old child in Hong

Kong who developed acute lead poisoning involving his renal, haemopoietic, and central nervous systems after being given certain Chinese herbal medicines since birth for minor ailments. Analysis of 11 related brands showed a mean lead content of up to 7.5 mg per unit dose. Another case of lead poisoning was seen in South Korea when a herbal medicine with a high lead content was taken to cure epilepsy.[148] The use of oriental herbal remedies is not restricted to the Far East. Chinese herbal medicines were also implicated in severe lead intoxication suffered by a 59-year-old woman in California for whom two types of herbal pills were prescribed by a herbalist–acupuncturist for some 4 months, for post-traumatic arthralgia. Her 24-hour urinary lead concentration was 1044 μg and blood lead level 90 μg per dl.[149] The pills were found each to contain 0.5 mg lead; the patient had therefore been ingesting up to 15 mg lead daily. In another report, imported Chinese medicines were considered to be responsible for 24 cases of lead poisoning in Laotian refugees in the United States.[150] The children were given a Hmong folk remedy known as 'pay-loo-ah' for fever and rashes. Analysis of one sample showed 8% lead, and samples from some remedies revealed 1–90% lead, while others contained 70–80% arsenic.[151] Lead poisoning from ingestion of folk medicines has been reported from other immigrant groups, mostly in children. In Mexicans it resulted from the use of 'azarcon', containing 86–95% lead tetroxide, and 'greta' (lead oxide), usually administered to infants and children for gastrointestinal illness.[152–4]

Several reports on the use of lead-containing Asian medicines have also appeared in the UK. Ali and colleagues,[155] and Aslam and others[156] found significant concentrations of heavy metals including lead in a number of Asian medicines used by immigrants. Preparations called 'kushtay', used especially as tonics and aphrodisiacs, contain oxidized heavy metals such as arsenic, mercury, tin, zinc, and lead; a typical kushtay may contain 10–12% of each of several of these metals.[146] 'Bal jivan chamcho' is an Indian medicine recommended for several conditions in children such as bronchitis, greenish diarrhoea, rickets, croup, and convulsions. Made into a paste, the material is spread on a spatula-shaped spoon. The dried preparation is allowed to soak in milk or water and the liquid is drunk. Investigations showed that not only did the preparation contain lead but that lead was also leached from the spoon.[157] Because of the toxic hazard of this preparation, particularly to children, its import, sale, and supply were prohibited in the UK in 1977. 'Bala guti' pills, prescribed as a children's tonic, were found on analysis to contain 58 ppm of lead and 750 ppm of antimony, as well as 2 ppm of arsenic.[157] Lead poisoning from an Asian folk remedy for diabetes was reported in Canada in 1985. This traditional remedy, acquired in India, also contained large amounts of lead.[158]

Dietary supplements

The risk of exposure still continues because, even more recently, tonics taken by Bengali Asian women, especially during pregnancy, were found to contain

J-9c42

18 mg lead per kg. Eaten as mineral supplements, they are dried clays that are sold in small chocolate-like blocks. Samples from different areas of the UK have shown them to contain up to 70 mg lead per kg as well as smaller amounts of arsenic and cadmium. Environmental health officers are continuing to take steps to stop their use and health warnings have been issued.[159,160] In the USA, a dietary supplement prepared from powdered animal bone, prescribed for dysmenorrhoea, resulted in severe lead poisoning.[161]

Cosmetic products

The possibility of lead poisoning from the use of 'surma' was first raised by Warley and colleagues[162] in the UK, in 1968. Their report of an Asian child with lead encephalopathy resulted in a warning notice from the Home Office.[163] Surma, a fine powder applied to the conjunctival surface of the eyelids, has been used for medicinal and cosmetic purposes by Asians over many centuries. It has been regarded as a good remedy for eye strain and soreness, and a good hygienic measure, though it is mainly used as a cosmetic. Surma includes salts of antimony, zinc, and lead, mainly as lead sulphide.[155,156,163] In London, some varieties were found to contain up to 85% lead and to be associated with blood lead levels of over 36 μg per dl in 12 children, 3 of whom needed urgent treatment.[164] Other investigators also demonstrated that the use of surma was associated with high blood lead levels and that the source of lead poisoning in Asian children was usually surma.[155,165] An appreciable absorption of lead, it seems, occurs from drainage down the tear duct or from rubbing the eyes and then licking the fingers. Other investigators[166] measured the blood lead levels of 217 Asian children aged 4 months to 18 years in Glasgow, but no essential difference was found in the 8 per cent who had used surmas regularly compared with the 82 per cent who had never used them. No association was found between the use of surma and blood lead concentrations, although the samples of surma analysed were found to contain 5–30% lead. It was concluded that this was because surma was not widely used among the Asian population, probably as a result of government health warnings and the voluntary ban imposed on the importation of surma by the Home Office in 1968. The possible health hazards of an increased lead burden and its implications for mental health remain, however, as long as the use of surma continues.[156,167] Barltrop and Meek[168] reported a five-fold increase in the absorption of lead in the gut when the particle size was reduced from 197 μ to 6 μ. Aslam and colleagues[156] showed that most particles of the lead in surmas fell at the lower end of this range, where absorption was greatest. This would account for the cumulative lead burden in children whose sole exposure to lead was from this source.

The marketing of surma and other lead-containing cosmetics was prohibited by an EEC directive in 1976, and by the UK Cosmetic Products Regulations of 1978, which came into force in January 1979. A further EEC Directive indicated that action to trace the source should be taken when the blood lead level

exceeded 35 μg per dl in more than 2 per cent of a population. Sixteen per cent of the surma-using children in the Nottingham Study had higher levels than this, and it remains doubtful whether these regulations will prove effective, because Ali and colleagues[155] found that most of the Asians in their study obtained supplies of surma from friends or relatives from abroad.

In Kuwait, 'al kohl', a traditional medical preparation and eye cosmetic containing 80% per cent lead, is used by women and their children, and applied not only to the eyes but as a pack on the raw umbilical stump as an astringent. In another practice, known as 'bokkoor', patients are exposed to the fumes from heated lead or lead sulphide; this has resulted in lead poisoning in children.[169]

Unconventional use of lead and opium pills, by addicts who injected themselves with ground-up pills, has resulted in lead poisoning.[170] Abuse of such preparations should no longer be a risk in the UK, because the manufacture of lead and opium pills was discontinued in the mid-1980s. Several cases of lead poisoning have been reported to have occurred in heroin addicts in Malta, as a result of adulteration of heroin by lead salts, available as a white powder, to increase the selling weight. The 22 addicts had gastrointestinal symptoms, weakness, pallor, anaemia, and raised blood lead levels.[171] Lead poisoning has been reported in the UK from taking aphrodisiacs originating from the Indian subcontinent, where they are available to improve both general health and sexual performance.[172]

Other sources of poisoning are food and drink stored in improperly glazed food containers. Because there are now control measures in most Western countries, this risk seldom arises any more although recently Italian-made ceramic fruit bowls, pitchers, and jars sold in the USA were recalled by the FDA because they contained dangerous amounts of lead.[173] In the Middle East, this health hazard could still occur frequently, because lead-glazed pottery is produced by obsolete methods, and a wide variety of local foods are sufficiently acidic to leach out the metal from such utensils.[174]

Recently the Ministry of Agriculture, Fisheries, and Food in the UK issued a warning to wine drinkers that the lead foil on wine bottles can be a hazard:[175] if wine seeps past an ill-fitting cork it can corrode the tin-coated lead closure, and lead salts may be deposited around the lip of a wine bottle. To reduce exposure to lead it is advised that the tops of wine bottles be wiped before pouring.[175] The wine trade is discussing the possibility of alternatives to tin-coated lead seals.[176] Leaching of lead from lead-crystal decanters occurs into wine stored in them for some weeks.[177]

Diagnosis and treatment of lead poisoning

The clinical diagnosis of lead poisoning can easily be missed, especially in the absence of an obvious history of exposure, as the signs and symptoms are not specific to it. The concentration of lead in blood is the best indication of recent absorption of the metal.[4,178] In adults the normal range is 10–40 μg per dl blood;[4]

levels of 40–60 μg per dl are not associated with any symptoms but a decrease in δ-ALAD activity and a slight increase in urinary excretion of δ-ALA.[4] Those with a blood lead concentration of 68–80 μg per dl have a decrease in δ-ALAD activity in erythrocytes, an increased urinary excretion of δ-ALA and coproporphyrin, and mild symptoms of lead poisoning.[4] Obvious symptoms of lead poisoning are associated with lead concentrations of 80 μg per dl blood;[13,14] and with levels higher than 120 μg per dl lead encephalopathy is almost invariably present. It is stated that in the presence of anaemia the significance of blood lead concentrations can be improved by correcting for deviation of the subject's haematocrit from normal.[4] The urinary excretion of lead is normally less than 65 μg per litre; with a mean of 35 μg;[179] in cases of poisoning levels in the urine rise to 150–300 μg per litre. It is useful to be aware that, in persons with chronic lead nephropathy or in renal insufficiency, urinary excretion of lead may be within the normal range and not raised.[179] The body burden of lead in persons environmentally exposed can be estimated by the use of the EDTA mobilization test, which employs an intravenous infusion, over an hour, of 1 g of EDTA in 250 ml of a 5% solution of dextrose. All urine is collected for 4 days; the upper limit of excretion of lead in normal adults is 600 μg.

Organic lead exposure is rare because of health measures and restrictions on industrial use. The major symptoms of tetraethyllead exposure are those affecting the central nervous system: insomnia, nightmares, headache, muscular weakness, emotional instability, and anorexia, nausea, vomiting, and diarrhoea. Subjective symptoms like irritability, restlessness, and anxiety become apparent. Bradycardia, hypotension, and hypothermia develop. If exposure continues, or in the event of acute exposure, delusions, ataxia, and exaggerated muscular movements develop, and finally a maniacal state occurs. Although the urinary excretion of lead increases markedly, the blood level remains almost normal. The metabolism of porphyrins is not affected, and basophilic stippling of red cells is uncommon. If exposure is severe, death may occur within a few hours or it may be delayed for several weeks. If death does not occur, recovery is usually complete; occasionally, however, residual central nervous system damage has been reported.[4,61]

Treatment of chronic lead poisoning is by the use of chelating agents to mobilize lead from tissues and promote its excretion. The usual regimen in adults is 1 g of EDTA given by an intravenous glucose drip over a 6-hour period;[61] This is repeated twice daily for 3–5 days.[4] To allow redistribution of the lead, so that the amount of metal available for chelation is increased, no treatment is then given for 2 days; further courses are given if necessary. The therapy relieves symptoms rapidly; colic may improve within 2 hours; muscular weakness and tremors improve in 4–5 days. Corproporphyrinuria, red blood cell stippling, and gingival lead lines improve in 4–9 days. Urinary excretion of lead is highest in the first 24 hours after the infusion and then decreases progressively throughout the course as tissue lead becomes less readily available.[61]

In acute exposure, initial supportive measures are required, followed by administration of chelating agents. Adequate urine output must be ensured. In patients with acute lead encephalopathy, excitement, mania, or convulsions are best controlled by lorazepam or diazepam; later phenytoin can be used.[4]

Lead poisoning in small children has more far-reaching effects, in that severe encephalopathy has a mortality of up to 65 per cent if untreated, and survivors are left with brain damage exhibited as ataxia and impaired mental ability; in severe cases hemiplegia, blindness, and severe mental disability follow.[4]

Treatment consists of five measures:[72] removal of the child from the source and careful supportive management for the first 48–72 hours; removal of lead from the gastrointestinal tract by mild purgation or enemata; removal of lead from blood and tissues by chelating agents; a thorough search for lead in the child's home or other environment; and psychiatric advice and guidance if an underlying emotional disturbance accounts for evidence of pica.[180]

Three chelating agents are available: EDTA, 2,3-dimercaptopropanol (BAL); and D-penicillamine. It is recommended that all severely affected children with whole blood lead levels of over 80 μg per dl,[70] be treated with both intramuscular EDTA and BAL for 5 days to minimize toxic effects and accelerate urinary excretion of lead.[181] A course of EDTA and BAL or EDTA alone is often followed by penicillamine.[181] Even though the latter does not mobilize lead as well as EDTA, it is effective by mouth whereas the other two chelating agents are not.[4] Not only has oral EDTA therapy been shown to be less effective than intravenous or intramuscular administration, it may also promote absorption of any lead present in the gastrointestinal tract and precipitate encephalopathy with fatal results.[66] Long-term follow-up of children after chelation therapy for lead poisoning[182] has shown that the fall in blood lead concentration after treatment is independent of the maximum level before treatment, but because there is a correlation between age and blood lead levels one can predict the response to therapy at specific ages. There is also a slow natural decline in blood lead level; once it has fallen to about 50–70 μg per dl further chelation results in only a minimal response.

In a recent report,[183] following experience with the lead mobilization test over an 11-year period, it is recommended that this initial test be reserved for children whose blood levels range from 40–60 μg rather than 25–55 μg per dl to determine the need for chelation therapy. It is suggested that children with higher levels require chelation without prior studies. Chelation with EDTA has been widely used as a treatment for lead poisoning after it was shown to alleviate clinical signs of poisoning and reverse some of the haematological signs. Decreases in blood lead levels and marked rises in urinary lead follow such therapy in both paediatric and occupationally exposed groups. As a result it was accepted that EDTA reduced lead concentrations in all tissues. Other evidence suggests that this may not be so, and that the amount excreted is proportional to either the body burden or the amount in soft tissue. Studies in rats[184] receiving 5-day treatment with EDTA following chronic exposure to

J-9042

lead, however, showed no decline in the brain lead levels, but others were not able to confirm this.[185] Further recent investigations have demonstrated that the current 5-day therapeutic regimen for EDTA has little effect on the brain and liver, and that the 24-hour diagnostic chelation test may even increase the concentration of lead in these tissues.[186] Tissue analyses indicated that lead was mobilized from bone and kidney and redistributed initially to both brain and liver. Levels in both brain and liver decreased with further injections but there was no net loss in spite of a lowering in blood levels and marked increase in urinary lead excretion.[186] These findings are of some concern especially in relation to the safety of the mobilization test, and suggest that the role of EDTA should be investigated further.

Penicillamine is given daily for 3–6 months in those children who manifest encephalopathy, a blood lead level above 60 μg per dl, and evidence of deposition of lead in bone. It was previously suggested that children with 50–80 μg lead per dl blood might also require brief chelation to reduce soft-tissue levels if they also showed disturbance in haem synthesis, because the precise level associated with subtle neurological impairment was not clearly evident.[70] Estimation of erythrocyte protoporphyrin has been stated to be a good predictor of response to chelation therapy.

With increasing information and further clinical experience, criteria for defining lead poisoning have been revised downwards: severe poisoning as indicated by lead blood levels $\geq$70 μg per dl; moderate poisoning as indicated by levels of 41–69 μg per dl of blood lead; and low level exposure as 25–40 μg per dl. It has been shown that, without intervention, the process of lead redistribution and excretion continues over months to years during which irreversible toxic changes can occur, especially in the central nervous system.[187] When treatment for low-level exposure is undertaken as outpatient therapy, EDTA must be given parenterally and be limited to 5 days followed by a 2–5-day interval to avoid nephrotoxic effects and to allow zinc levels to normalize. Intramuscular EDTA is also painful and, even more importantly, its efficacy is confined to children with blood levels above 35 μg per dl.[188] Penicillamine has, therefore, advantages because it is effective in low-level lead poisoning. As it can be given orally it is easier for outpatient treatment and its relative lack of adverse renal effects allows uninterrupted long-term therapy. There is also evidence that it is effective in mobilizing lead from bone, as well as blood.[189] Several studies[190–2] in children with blood levels of 40–65 μg per dl have demonstrated 30–40 per cent reduction. A further report,[193] has also shown that oral penicillamine was effective in treating 84 children who had levels between 25–40 μg per dl. This retrospective cohort study was able to obtain a 33 per cent reduction in mean blood levels ($p<0.001$) and a 35 per cent reduction, compared with a control group, in the mean erythrocyte protoporphyrin levels ($p<0.001$) in 75 children treated for a mean period of 11 weeks. Adverse reactions known to be associated with penicillamine therapy occurred in 28 patients (33 per cent); in 10, treatment was discontinued and all adverse effects

resolved. Like previous studies, progress during treatment suggested that courses of 6–8 weeks could be sufficient to reduce blood levels to an acceptable range.

Another oral chelating agent, dimercaptosuccinic acid, has been used to treat heavy metal poisoning,[194,195] and has been reported to be very effective in treating children with blood levels of 30–50 μg per dl.[196] At high doses it was more effective than EDTA, which evoked a greater urinary lead output and was associated with significant rises in urinary zinc, copper, iron, and calcium. This effect was not noted during dimercaptosuccinic acid treatment, indicating that it is more specific for heavy metals.

There appear to be few reports on the progress of children with an increased lead burden, and these are conflicting. Byers and Lord[67] reported unsatisfactory school progress, behaviour difficulties, and limited sensory-motor abilities. Smith and colleagues[197] stated that increased lead exposure only caused significant sequelae if associated with encephalopathy, and others[82] have demonstrated a significant increase in certain areas of intellectual performance 18 months after treatment.

Tetraethyllead is absorbed through the skin and the respiratory and alimentary mucosae; it is distributed in the non-ionic form and, being lipid-soluble, is concentrated in the brain, body fat, and liver.[198] Inhalation of tetraethyllead vapour for even a brief period may be fatal. Mild intoxication causes headache, irritability, restlessness, anxiety, fatigue, nightmares, sexual impotence, impairment of memory, and minor gastrointestinal symptoms, including anorexia, vomiting, and diarrhoea. There is sometimes a persistent metallic taste. In more severe cases these symptoms last about a week and are followed by a toxic psychosis. Hallucinations, delusions, and intense fear are usual, and suicidal attempts not uncommon. Coma and convulsions occur in the more severe cases. The most important physical signs are tremor, increased tendon reflexes, hypothermia, bradycardia, hypotension, and loss of weight. The classical signs of inorganic lead poisoning are not seen; relapse is common, but no chronic effects or permanent sequelae have been reported. The diagnosis is confirmed by urinary lead excretion, as blood lead levels are seldom much increased.[198] Treatment is mainly symptomatic, as the lead is present in the non-ionic form and therefore inaccessible to EDTA, although some increase in urinary excretion of lead does follow parenteral EDTA therapy.[199]

Measures to reduce exposure to lead

The incidence of lead poisoning in industry has fallen dramatically since the beginning of this century. This reduction has been due to increased awareness, improved ventilation and hygiene facilities, improved surveillance of workers exposed to lead, and also technical changes that have allowed other substances to replace lead.[50] The use of lead in the cable industry has declined because of the introduction of plastic sheathing/insulation.[6] Many lead pigments are still produced but they are increasingly being replaced by other less toxic pigments.[6]

The longer life of batteries has led to a reduction in lead consumption by the battery industry, and therefore also in less need to recover lead from exhausted batteries.[9] Statutory control measures have been passed[199–204] for those defined industries in which lead exposure occurs, to ensure that the standards for lead in air are not exceeded: that for lead (except for tetraethyllead) is 0.15 mg per m^3 of air, and that for tetraethyllead is 0.10 mg per m^3 of air.[201]

The *Control of Lead at Work Regulations* restrict the employment of women of reproductive capacity on work in which exposure to lead is significant. Should their blood lead concentrations exceed 40 μg per dl they are suspended from work.

The use of lead as a fuel additive has declined since the mid-1970s because the US Environmental Protection Agency's programme aimed reducing lead in petrol to 0.13 g per litre by 1979. The maximum permissible level in the Federal Republic of Germany has been 0.15 g of lead per litre since 1976, and in Japan it has been 0.31 g of lead per litre since 1971. Some European countries, for example Austria, Norway, Sweden, and Switzerland, introduced limits of 0.4 g per litre, but other governments deferred their decision because of the economic implications of lowering the permissible lead content.[9]

In North Wales, in old lead mining areas, random blood lead estimations in residents indicated that there had been a fall of about 5 per cent per year compared with previous recordings in 1976 and 1981;[205] these changes were ascribed to changes in the exposure of subjects to lead in sources other than air. The falls were similar to those reported in the USA and New Zealand. In 1981, following the publication of the Lawther Report[206] the British Government announced that the maximum permissible lead content of petrol would be reduced from 0.4 to 0.15 g per litre from 1986.

In April 1983, in response to the Royal Commission on Environmental Pollution's 9th Report,[207] the Government recommended that the remaining lead in petrol should be phased out as soon as possible throughout the EEC. Following these recommendations, the UK blood lead monitoring programme demonstrated that, in 1984, over 98 per cent of adults had levels below 35 μg per dl, and over 99 per cent of children below 25 μg per dl.[208] In 1985, these levels were on average under 1 μg per dl lower,[209] and in 1986 the level in children fell a further 1.5 μg per dl, confirming that steady progress is being made in reducing environmental lead, as recommended by the Medical Research Council's advisory group on lead and neuropsychological effects in children.[210]

The trends mentioned above represent a continuing fall in lead exposure; nevertheless, lead in water still needs action. Replacement of lead pipes results in a dramatic fall in both water and blood lead concentrations.[211,212] It is suggested that hardening the water supply with calcium salts lowers blood lead concentrations more than would be expected from the fall in water lead.[213] An earlier report has indicated that mental retardation of unknown aetiology in children could be linked to high water lead concentrations.[213] The results of the Edinburgh studies also suggest that the control of lead in drinking water needs

to be tightened up.[214] Blood lead concentrations were found to be specifically related to both dust and water lead concentrations.[214] That dust and soil can be important sources of lead in young children, not only in areas of industrial pollution but also in highly urban areas, has been confirmed by other studies.[212,215–21]

The Royal Commission on Environmental Pollution[207] pointed out that some of the highest blood lead concentrations can be traced to leaded paint ingested by young children. There is modern equipment for detecting lead in paintwork *in situ*: its use needs to be ensured, as does the dissemination of sufficient publicity about the dangers of old paintwork. Removing such paint is not without hazard, however, and such techniques as scraping, sanding, and burning, used to remove the paint may further expose children with raised blood levels.[222] Adults involved in removing lead-based paintwork have developed elevated blood lead levels as a result of the lead released into the air and dust.[223] Guidance on the safe removal of lead paint was therefore issued. Complete removal of all chipping and peeling paint must be followed by proper cleaning of the dust by vacuuming and thorough wet mopping, preferably with high-phosphate detergents. Pregnant women, infants and children should be removed from the house until the de-leading and cleaning is completed.

In the general population of the UK, it is reported[224] that the major source of lead intake is from food. The mean weekly intake is about 0.7 mg from food and beverages; there is no evidence that the intake has increased over recent years. The *Lead in Food Regulations 1979*[225] control the levels in foodstuffs, the highest levels being found in concentrated food and canned products. The FAO/WHO provisional tolerable weekly intake for dietary lead is 3 mg.[226] Although the present levels of dietary lead present no hazard, the margin between the combined exposure levels which may occur from all sources is relatively narrow; efforts to ensure a wider margin of safety should therefore continue.

The risk of lead exposure from conventional medicinal products such as lead subacetate and lead monoxide should no longer arise in the UK, as their manufacture has ceased. Homoeopathic preparations containing lead as a single ingredient or combined with other metals such as arsenic, continue to be marketed, however, in many EEC countries. As there is little formal evidence of efficacy and a continued risk of increasing the body burden of lead, their use appears to be quite unjustified. The use of lead-containing traditional and herbal medicines has resulted in adverse effects, as has that of dietary supplements and cosmetic preparations. Attempts to reduce the risk of lead from such uses by regulatory measures, publicity, and health education continue.

Update and summary

The sources of lead exposure are multiple and there is now much evidence that body lead burdens below that associated with clinical symptoms can affect

biochemical functions and neuropsychological performance.

The increased vulnerability of young children to lead is well accepted. Increased absorption from the child's gastrointestinal tract has been demonstrated,[227] and is supported by studies in the newborn rat.[228] At the same dose of lead, as measured by blood lead concentration, children have shown to have greater impairment of haem synthesis, as measured by free erythrocyte protoporphyrin, than adults. Additional studies have shown that lead affects other haem enzymes, notably cytochrome P-450 in the liver. Red cell δ-ALAD, an enzyme important in the synthesis of haem, is inhibited at blood lead levels below 10 μg per dl.[229] Ferrochelatase, the enzyme that converts protoporphyrin to haem, is inhibited in children at a blood lead level of about 15 μg per dl, so erythrocyte protoporphyrin becomes raised at this level.[187] Depression of circulating levels of 1,25-dihydroxyvitamin D starts at blood lead levels well below 25 μg per dl.[230] Brain levels of δ-ALAD in the rat parallel peripheral blood levels, suggesting that oxidative metabolism in the brain may be affected at blood levels as low as 20 μg per dl.[231] Lead inhibits adenyl cyclase in brain preparations, as well as pancreatic adenyl cyclase.[232] Interference with globin synthesis[26] and with collagen synthesis has also been demonstrated at a low concentration of lead.[232] Lead acts on the red cell mitochondrion, eventually resulting in raised free erythrocyte proptoporphyrin; this effect begins at a blood level of 15 μg per dl.[232]

Neuropsychological dysfunction characterized by reduction in intelligence and alteration in behaviour has been shown conclusively to occur in asymptomatic children with blood lead concentrations below 50 μg per dl,[86,87,233] and may be produced at levels under 35 μg per dl.[234] Others have shown that the dysfunction persists at follow-up.[235] Slower reaction time has been demonstrated. Slowing of motor and sensory nerve conduction has also been found in asymptomatic children with blood lead levels of 20–30 μg per dl.[59] Short stature, decreased weight, and diminished chest circumference have also been found in children exposed to lead.[236] Lead has been associated with reproductive damage in women and men exposed occupationally. It crosses the placenta and has been found in the cord blood of newborn infants.[20,137,138,237] Placental lead levels have been reported to be higher in malformed and stillborn than in normal infants.[238]

Lead has been shown to be teratogenic in the laboratory animal, and positively related to the incidence of minor anomalies in infants.[239]

Several factors are known to increase susceptibility to lead toxicity, which is greater among immature animals and very young children because of their higher levels of lead ingestion, greater absorption from the gastrointestinal tract, higher proportion of tissue retention, and the greater reaction lead has on their organs, especially the central nervous system. Nutritional and dietary factors that also increase absorption are deficiency of calcium, phosphorus, iron, and zinc[240] as well as total calories, fat, ascorbic acid, vitamin D, and protein.[214] Age-related oral behaviour, including pica, as well as metabolic

disease and sickle-cell disease, influence absorption. The form and particle size of lead have also been shown to be contributory factors.[168,187]

Apart from the more recently demonstrated subtle effects on the nervous system and reproductive function, evidence is also accumulating that chronic low level environmental exposure to lead may have subtle effects on renal function.[242] Intranuclear inclusion bodies in the renal cortical epithelium, as well as in hepatic parenchymal cells. were described as early as 1936.[242-5] Since then it has been shown that these bodies are composed of a lead–protein complex, and are formed rapidly after lead exposure.[245] It is suggested that they have a protective effect in sequestering circulating lead and thereby maintaining a relatively low cytoplasmic concentration of lead. In this way the toxic effects of lead on sensitive cellular functions such as mitochondria and cytoplasm could be reduced.[246] Animal studies have shown that renal mitochondria are very sensitive to lead, which may interfere with mitochondrial respiration and damage the organelles. Mitochondrial membrane permeability with subsequent swelling has been demonstrated experimentally,[247] as has preferential affinity for lead by mitochondrial inner membrane.[248] Proximal renal tubular epithelial cell proliferation and an increase in RNA and proteins has been detected; it is thought that lead may affect the cellular control of gene expression by stimulating RNA synthesis.[249]

Most standard tests of renal function do not appear to detect early effects of lead exposure. Multiple enzyme analyses have shown that *N*-acetyl-β-D-glucosamide, a lysosomal enzyme, and γ-glutamyl transpeptidase, found in the brush borders of proximal tubular cells, are raised in the urine at early stages of renal damage.[250,251] It is also suggested that detection in the urine of low-molecular-weight proteins, β_2-microglobulin, and retinol-binding protein, could be a sensitive index of altered proximal tubular function. The effects of lead on the kidney appear to occur only at exposure levels above those affecting haemoglobin formation. They involve both the renal tubules and glomerular–vascular apparatus; at present the dose–response relationship has not been clearly defined but tubular effects are stated to be more readily reversible than glomerular effects.

Much progress has been made in the last two decades in the understanding of how lead affects the body. Much progress has also been made to reduce and control exposure from lead in the environment from air, dust, paint, petrol, and food, but further measures are needed to decrease lead from drinking water. Blood lead levels of 30 μg per dl in children, previously considered safe, are known to affect neurological and intellectual function even in the absence of clinical symptoms. Because this effect is largely irreversible and cannot be fully restored by medical treatment, efforts must continue to reduce exposure of children further and to detect increased absorption early. Levels of increased exposure are now generally defined as whole blood lead concentrations of 25 μg per dl, together with an erythrocyte protoporphyrin level of 35 μg per dl. Recent studies[92,95,252-5] have shown, however, that blood lead levels even as low

as 3–25 μg per dl are associated with a decrease in the general cognitive index; it does appear, therefore, that there is no safe level at which environmental lead may not have adverse effects on mental development in early childhood.

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Note

The views expressed in this article are personal and not necessarily those of the Medicines Control Agency.

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J-9042

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J-9042

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J-9042

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