# TOXICITY OF INDUSTRIAL METALS

SECOND EDITION

ETHEL BROWNING, M.D.

*Formerly H.M. Medical Inspector of Factories;*
*Adviser on Toxicology to the Courtauld Organization*

1969

NEW YORK
APPLETON-CENTURY-CROFTS
Division of Meredith Corporation

LONDON
BUTTERWORTHS

CHAPTER 20

# LEAD

LEAD IS one of the oldest metals to have served mankind. Even before Roman times lead water pipes were used and in 1285 the first cistern of lead was constructed in the City of London. King Henry III " in the twenty-first year of his reign " granted permission to the citizens of London to convey water from the Town of Teybourne by pipes of lead into their city (Stow, 1945). Lead mining is of great antiquity, for the conditions in which it was worked have been described by many historians and archaeologists.

## OCCURRENCE

Lead ores are found in U.S.A., England, Germany, Mexico, Spain, New South Wales and South America. The most abundant lead-containing ore is galena, in which it occurs as the sulphide, PbS, and from which commercial lead is chiefly obtained. It is also found in cerussite (the carbonate), anglesite (the sulphate), crocoisite (the chromate), wulfenite (the molybdate), pyromorphite (the phosphate), matlockite (the chloride) and vanadinite (the vanadate).

It is present in plants and soils in very small amounts; fixation by the clay of normal soil converts added lead to insoluble inactive compounds, but very acid soils increase the solubility and soluble compounds are toxic to plants except in very low concentrations (Gilbert, 1957).

## PROPERTIES

Lead is a bluish-grey metal with a bright metallic lustre when cut. In moist air it becomes coated with a film, probably an oxide, ultimately converted into a basic carbonate. It is not tough enough to be hammered into foil or drawn into wire but can be pressed into pipes or rolled into thin sheets. It is fairly rapidly dissolved by nitric acid, and is soluble, to some extent, in organic acids such as acetic and food acids, and by water in pipes if the water holds nitrates, ammonium salts and carbon dioxide in solution. The presence of carbonates from limestone or chalk prevents this process by the formation of a film on the interior of the pipes which protects the lead from further action.

Atomic weight, 207; specific gravity, 11·25–11·4; melting point, 327°C.; boiling point, 1620°C. The maximum allowable concentrations are: metallic lead, 0·2 mg. per c.m.; lead arsenate, 0·15 mg. per c.m.

## INDUSTRIAL USES

### INORGANIC COMPOUNDS AND METALLIC LEAD

(1) In the manufacture of pipes, cisterns, roof coverings, etc. and in the metallizing of lead wires.

(2) In the chemical industry for containers for sulphuric acid, evaporation pans, etc.

(3) In the manufacture of lead shot, bullets, linotype metal, etc.
(4) In storage batteries, as accumulator plates.
(5) In various alloys, with antimony, tin, copper, etc.
(6) In paints, varnishes and pigments, as litharge, red lead, white lead, chromates, sulphate and titanate.
(7) In flint glass and vitreous enamelling as a lead or lead-potash silicate.
(8) In the pottery industry as a low-solubility lead glaze or frit. Cases of lead poisoning from these low-solubility glazes in the pottery industry are no longer reported, but in Italy, in a factory making glazed tiles for mosaic work, where the proportion of lead in the frit was as high as 10–40 per cent and the solubility relatively high, many workers were admitted to hospital with symptoms and signs of lead intoxication (D'Onofrio, 1949).
(9) In the manufacture of litharge rubber.
(10) In the manufacture of insecticides (lead arsenate).
(11) In certain plastics, as the borate.
(12) As Noise Barriers. It has recently been proposed (Fader, 1966) that lead in the form of sheet lead and/or lead-loaded flexible plastic should be used as barriers to industrial noise. Either could be hung above ceilings or on pipes, conduits, gas turbines and air ducts to prevent the noise from fluids and pressure of air and gases. This procedure has been found to reduce considerably the peak intensity of noise.

The severity of the inorganic lead hazard in the various processes has been estimated by Elkins (1959). From the results of investigations by himself or his associates he considers that the most severe hazard occurs in the spraying of molten lead and lead paint; in the grinding or power sanding of lead or solder and the pouring of leaded iron and steel; in certain operations in storage battery manufacture; the operation of wire patenting, the mixing and weighing of lead powders. Lead smelting and burning are also sources of harmful exposure, while soldering, lead casting, brush painting, linotyping, and steel tempering are regarded as relatively non-hazardous.

It may be of interest to note a statement given in answer to a question (Question Clinic, 1967) that lead silicate dust can be absorbed in sufficient amounts to produce lead intoxication.

## ORGANIC COMPOUNDS

Tetraethyl lead ($Pb(C_2H_5)_4$) is the chief organic compound used, as an "anti-knock" addition to motor fuels. It gives rise to a syndrome of intoxication quite different from that of inorganic lead (see p. 178) and is considered hazardous during the process of manufacture or mixing with motor fuel, but not in the handling of dilute solutions or in the exhaust gases of petrol engines.

## METABOLISM

The metabolism of lead follows closely that of calcium, particularly with regard to its deposition in and mobilization from bone. Many factors influence both of these in a similar manner. When bone marrow activity

is increased, as in leukaemia or severe anaemia, calcium mobilization may take place, causing hypercalcaemia and osteolysis. In these conditions lead may also be liberated and give rise to an increased lead content of the blood even when there has been no undue exposure to lead. Thus, when an excessive amount of lead has been deposited in bone, either from ingestion or from industrial exposure, and has remained immobilized for years, intercurrent factors causing mobilization may cause a sudden outbreak of clinical symptoms of lead poisoning.

Lead is not among the metals considered essential to the nutrition of animals or human beings; it is classified by Schroeder (1957) as "one of the trace metals with organic specificities". Certain foods contain significant and more than average amounts—bread, meats, tinned foods and vegetables (Kehoe *et al.*, 1933), and according to Schroeder, the daily intake from exposures to the "functions of civilization" (lead pipes, food containers, articles soldered with lead, insecticides) is about 0·4 mg.

Lead is present in practically all organs and tissues. According to Kehoe (1949) the average gross quantity of lead in the body of the normal human adult in the U.S.A. varies according to the body weight from 100 to 400 mg. In Japan, the average total body content of lead has been estimated as about 78 mg. in adolescence and 131 mg. in old age, the difference being probably accounted for by variations in constitution, mode of life and food (Horiuchi *et al.*, 1959). The bones contain the highest concentration, but the actual amounts vary considerably according to various investigators. Horiuchi and co-workers, expressing the values in terms of micrograms per 100 g., give tables of these differing results both for adult and also for foetal bones, attributing the variation to different methods of analysis. Their own estimations of adult bone, while showing much higher levels than in the soft tissues, show a wide variation in individual specimens, the amounts ranging from 215 to 1,240 μg. per 100 g. for ribs, from 242 to 890 μg. for vertebrae, and from 311 to 2,980 μg. for femurs. By comparison, Hansmann and Perry (1940) give an average value of 870 μg. for ribs, and Tompsett and Anderson (1935) 710 μg. for vertebrae. In the soft tissues a similar discrepancy appears in the various estimations, but all are agreed that the liver and kidneys contain the largest amounts. For the liver these range from an average of 173 μg. per 100 g. (Tompsett and Anderson) to 190 μg. (Horuichi and co-workers) and 79 μg. (Kehoe *et al.*, 1933).

In blood, Kehoe gives a range of 0·01–0·05 mg. per 100 g.; Bessman and Layne (1955) 0 to 0·3 mg.; Tompsett and Anderson an average of 0·05. This variability naturally depends to a great extent on the fact that a single blood sample gives only the concentration of lead at that time, while the lead discharged into the blood stream in unusual amounts is constantly being removed from the circulation, re-distributed and excreted. The most recent opinion, that of Egli *et al.* (1957), considers 0·05 mg. per 100 g. the "tolerance limit" for the appearance of lead poisoning.

Teisinger (1965) believes that when the level of lead in the urine is 3 mg. per 24 hours, symptoms of poisoning appear with some frequency and that excretion within the range of 0·8 to 1 mg. per l. per 24 hours should be regarded as the permissible maximum.

## ABSORPTION

Absorption from the gastro-intestinal tract is very small. Most of the lead ingested passes through and is excreted in the faeces. Kehoe (1960) states that only 10 per cent or less actually reaches the tissues, blood, body fluids and secretions. In workers exposed to lead processes where dust or fume is evolved, a certain amount is absorbed from the respiratory passages after it has been retained there, but some is either exhaled or trapped in the upper passages and subsequently swallowed.

Absorption of inorganic lead by the skin is not generally of great significance though according to Patty (1958) lead acetate and lead oleate can be absorbed in appreciable amounts. Lead tetraethyl, on the other hand, can enter through the skin both in liquid and vapour form (Marchenko and Beilikhis, 1946).

## EXCRETION

Lead is excreted both in the urine and also to a greater extent, in the faeces. In normal persons who show no evidence of lead accumulation the daily faecal lead intake is almost equivalent to the amount ingested from the food and other usual sources. In such persons an equilibrium is established in which excretion keeps pace with absorption and urinary excretion is small and relatively constant at levels varying from 0·01 to 0·08 mg. per l. (Tompsett and Andersen, 1935, give their results in amounts per diem (average 0·05 mg. for urine and 0·22 mg. for faeces) because, in the case of urine, the concentration of lead varies with the volume secreted.) When lead is ingested in amounts above that normally contained in food and beverages it produces a measurable increase in the rate of urinary excretion during the period of active absorption and for some time afterwards. A level of 0·15 mg. per l. is considered by Egli *et al.* (1957) as the " threshold " for lead intoxication. Excretion by the sweat was not considered a possibility by some of the earlier observers who regarded any lead found on the skin as a mere surface contamination. In 1954, however, Shiels, using sensitive methods of analysis, estimated the amount of lead deposited on pads of cotton wool attached to the skin of the chest of persons suffering from lead poisoning or having deliberately ingested lead acetate. Comparing the amount of lead deposited with that of controls, he found it significantly greater in those exposed to lead; in the case of ingested lead the amount during the period of ingestion increased from 0·012 mg. per l. to 0·024 and 0·05 mg. Retention by the lungs, in lead workers, ship breakers and controls was studied by Mehani in 1966. He found that 39–47 per cent by weight of the inspired lead was retained in the lungs of lead-exposed workers but varied with several factors, including severity of effort at work, and size of the particles, a considerable portion of those of 3$\mu$ and more being retained in the mouth and throat and either expectorated or swallowed and excreted in the faeces. The retention was not associated with the depth of breathing, and the final conclusion was that in present working conditions, with an average atmospheric concentration of

lead of 2 mg. per 10 c.m. the amount retained per shift would be less than half the amount which can be tolerated without producing evidence of ill-health.

## STORAGE

Before 1924, when Minot and Aub made a special investigation of the storage of lead in bone, its presence in bone was considered relatively unimportant compared with its widespread distribution in the soft tissues. It then became apparent that while in the softer tissues the deposited lead is loosely held and decreases in amount with time, the highest concentration remains in the bones (Fairhall and Miller, 1941). The trabeculae have been found especially rich in lead, and while the epiphyseal portion is particularly rich in the early stage of absorption, deposition occurs throughout the compact tissue on all surfaces over which blood passes, first, according to Fairhall (1943) in colloidal form, and finally as segregated crystalline masses localized in clumps around the Haversian canals in the compact and cancellous tissue. Thus the more recently absorbed lead is stored in a situation from which it can be readily mobilized (Brown, 1946).

## LEAD IN THE FOETUS

In mothers unexposed to lead the distribution of lead in foetal tissues and organs appears to follow that of the adult; in bones it tends to increase with their development. On the basis of their analyses of foetal tissues, placenta and umbilical blood (Horiuchi and co-workers, 1959), and by the observations of earlier workers (including Legge and Goadby (1912) that long-term over-exposure of the mother may be followed by toxic effects on the foetus), it is believed that lead passes from the mother through the placenta to the foetus, since the lead content of the bones increases with the development of the foetus at the expense of its blood lead; the bones, with their harmless deposition of lead at this time, may have a protective function in this respect.

# TOXICOLOGY

Although symptoms now known to be those of lead poisoning appeared very early in the history of its use—Hippocrates in 370 B.C. described a severe attack of colic in a man extracting metals, and the ancient Egyptians well understood the properties of lead as a homicidal agent—the recognition of an association between symptoms of poisoning and the use of lead in industry was long delayed. Industrial poisoning in lead miners must have occurred in the appalling conditions in which they are known to have worked, but the "Miners' sickness" described by Paracelsus in the sixteenth and Pansa in the seventeenth centuries was not specifically correlated with their exposure to lead. It was not until 1831 that Thackrah first definitely associated lead with the ill-health of miners. "Miners of lead," he stated, "suffer considerably from their employ," and went on to describe the high rate of mortality among them though without giving details of the symptoms which caused it. A more favourable opinion of the health of the lead miners of Derbyshire was given by William Webb (1857), but he noted that "a miner can generally be pointed out by his pallid face". In the same year Jackson, while stating

that the miners of Arkendale and Swaledale " are not liable either to paralysis, colica pictonum or lead poisoning ", asserted that miners absorb lead through their skin and lungs. Actually, lead mining itself has never produced the severest cases of lead poisoning, and recent investigations have revealed few acute symptoms. In the Moroccan lead mines, for example, Rodier (1948) reported that no acute lead poisoning had been observed, and that while 11 out of 50 examined showed " signs of intoxication ", the diagnosis was based only on the presence of punctate basophilia of 2,500 per million. Another survey by Belden and Garber (1949) of men handling galena also revealed no evidence of intoxication by lead.

The whole problem of lead poisoning, not only in the mines but also in the potteries, the painting industry and other fields of use of lead in industry in Great Britain, received its most serious attention up to that time when Legge and Goadby (1912) published their book " Lead Poisoning and Lead Absorption ". The preventive measures and statutory legislation which have so greatly reduced the incidence of severe lead poisoning in Britain have been based essentially on their work. In America, the most detailed historical account of lead poisoning is that of Carey P. McCord (1953 and 1954) in a series of articles in *Industrial Medicine and Surgery*, vols. 22, 23. They deal with lead poisoning as it relates to early cases of poisoning from food contamination, medicines, cosmetics, paints and ceramic glazes, mining, and many other aspects, and draw an interesting picture of the effects of exposure to lead in earlier times as compared with the present knowledge, gained by sometimes bitter experience.

The picture has indeed changed to a very great extent. Some of the severe manifestations, especially encephalopathy, are practically never encountered in industry, and the distinction between lead intoxication and lead absorption has been made much more factual by the development of laboratory techniques for the estimation of lead in air, blood and urine; these are not only aids to diagnosis but also to the control of the health of those exposed to lead. This aspect is well summarized by Bloomfield (cited by Johnstone, 1957) when he says " Lead intoxication rarely occurs at all and only in its mildest manifestations among regularly employed industrial workers if the mean urinary lead concentrations of representative groups of such workmen is kept below 0·01 mg. per l. and if the exposure is controlled so uniformly that individual results are generally below 0·15 mg. per l. and very rarely in excess of 0·2 mg. per l.". The fall in the incidence of cases notified as lead poisoning is as striking as the decrease of severity of its manifestations. In the *List of Diseases* prescribed under the *National Insurance (Industrial Injuries) Act*, 1946, the occupations in which lead poisoning is involved include " the use or handling of or exposure to the fumes, dust or vapour of lead or a compound of lead, or a substance containing lead " and there are 6 specified processes concerned with lead manufacture in which, under the *Factories Acts* (*Section 58*) women and young persons are prohibited from working.

Between 1900 and 1958 the number of cases listed in the *Annual Report of the Chief Inspector of Factories* had fallen from 1058, with 38 deaths in 1900 to 55, none fatal, in 1958. The highest incidence was in the painting of

buildings (15) and shipbuilding (11). In electric accumulator works, apart from the industrial poisoning occurring in workers in battery manufacture and repair, the hazard of this industry was emphasized by a non-industrial outbreak among children in Rotherham in 1954, as the result of using discarded battery casings as domestic fuel (Gillet, 1955). Lead poisoning was not suspected as the cause of death in 2 children until 2 further cases were diagnosed; a full investigation of 232 children exposed to risk then revealed 55 cases of lead poisoning or lead absorption.

The most hazardous compounds of lead in industrial use are those of high solubility. Lead chromate and sulphide are undoubtedly less toxic than the more soluble acetate, chloride and oxide, but Elkins (1959) states that chronic industrial lead poisoning is caused as readily by the dust of lead sulphate, carbonate or metallic lead as by these soluble compounds. The fact that many operations such as soldering and linotyping, involving molten lead, have not produced a high incidence of intoxication is because the temperature at which the vapour pressure of lead produces a high atmospheric concentration (500°C.) is not necessarily reached in such processes. The real risk arises not from the fume itself but from the dust of lead oxide which forms on the surface of the molten metal. This applies to the process of " wire patenting ", which is generally regarded as a " low toxicity " operation. This is so if adequate precautions are taken to keep the surface of molten lead (through which the wire passes) free from dust; to prevent the accumulation of dust in the workroom, and to avoid careless handling and unhygienic measures. Where these precautions are not observed, severe cases of poisoning have occurred.

## INORGANIC LEAD POISONING

The clinical picture of lead poisoning is so well recognized and the subject has been so widely investigated during the past fifty years that a complete account of all its aspects would necessitate a whole volume devoted to this one metal. Only those aspects relevant to the modern concept of lead poisoning and absorption will therefore be dealt with, together with the most important references needed to fill in the picture.

An excellent review of the symptoms and physical signs was given by Professor Lane (1949) in the Milroy Lectures delivered before the Royal College of Physicians in 1947.

It must again be emphasized that there is a clear distinction between lead poisoning and lead absorption, and that organic lead compounds give a different pathological picture from that of inorganic lead.

### SYMPTOMS OF INORGANIC LEAD POISONING

The chief early symptoms of intoxication are fatigue, disturbance of sleep, and constipation. More prolonged and severe exposure may be followed by colic, anaemia and neuritis. The most acute and severe effect of all, very rarely seen nowadays from industrial exposure in adults (but still occurring occasionally in children from ingestion), is encephalopathy.

Encephalopathy.—Encephalopathy from exposure to inorganic lead com-

pounds was reported with some frequency in Britain 50 to 60 years ago. Between 1900 and 1909, 262 cases were recorded; between 1939 and 1948 only five; in 1940 only two, and since then only one (Hay, 1950). This case may justify a somewhat detailed description, not only on account of its rarity, but because it emphasizes so clearly the fact that such a case is likely to occur only when all necessary precautions have been neglected. It also exemplifies some of the differences which exist between the cerebral syndrome of inorganic lead poisoning and that caused by tetraethyl lead; the inorganic lead prognosis is more favourable, its effects are less permanent and more subjective, and it is rarely accompanied by the objective signs of loss of vision, paresis and aphasia. The case recorded by Hay was that of a man employed as a cooper, carrying out the repair of barrels which had contained white lead. The conditions of exposure to lead were exceptionally bad, and owing to the fact that the firm had failed to notify the Factory Department that they were engaged in this process they had for some time escaped supervision and had not attempted to institute hygienic measures of any kind. Two of the four men exposed to this heavy risk developed lead poisoning but only in one were the symptoms those of encephalopathy. This man's chief complaints were headache, anorexia, weakness and loss of weight during the last 6 months. He showed a fine tremor of the lips and hands, slight bilateral papilloedema, loss of power in the right arm and unsteady gait. Later he developed diplopia, mental confusion and excitement, and hallucinations. Lead poisoning was only suspected when a blue line on the gums was observed. His blood picture was that of anaemia: red blood cells 3·5 millions per c.mm., haemoglobin 9·7 g., marked punctate basophilia (16,000 per million) and a reticulocyte count of 4·5 per cent. The cerebrospinal fluid was under high pressure, with a cell count of 10 per c.mm. The lead content of urine, blood and cerebrospinal fluid were all above normal, the urinary lead at its highest 0·48 mg. per l., the blood 0·33 per 100 g. After 6 months all physical and biological abnormalities had disappeared except for a slightly excessive blood lead level, but there was some evidence of residual intellectual deterioration. It may be of interest in this connection to note that the encephalopathy of children who have ingested lead compounds is more severe in its manifestations, and is frequently fatal; it is sometimes followed in those who survive by permanently retarded development (Williams *et al.*, 1952).

Colic.—This is sometimes so severe as to simulate an acute appendicitis, and in fact has been so diagnosed and surgically treated when the nature of the employment has been overlooked. That colic does not depend on the level of lead in the blood was shown by Vigliani and Zurlo (1951) who found that in cases with active colic it was 0·138 mg. per l. as compared with 0·116 in those who had had an attack some few days or weeks before. They consider that the colic is caused not by involvement of the intestinal tissue itself but by alterations in the autonomic system.

Anaemia.—Anaemia is not usually severe but is hypochromic. The total red cell count in cases of moderate severity is generally between 4 and 4½ millions per c.mm. with a haemoglobin level between 70 and 80 per cent and a colour index of about 0·8 per cent.

The most specific feature of the blood picture is a high level of *punctate*

*basophilia*; there is also polychromasia and usually an increase in the number of reticulocytes. The extent of the haemolytic breakdown of red cells has been shown in animals by the deposition of iron in the spleen (Goldblatt and Goldblatt, 1956).

This increased rate of red cell destruction has been regarded by some observers as the result of damage to the peripheral cell, its envelope having been rendered brittle by the action of lead in the circulating blood (Aub *et al.*, 1925). The actual mechanism of this action has been suggested to be that of contact of the plasma lead causing increased fragility of the corpuscles. *In vitro* experiments by Clarkson and Kench (1958), however, have led them to conclude that *in vivo* plasma lead will cause only minimal changes in the fragility of circulating red cells and that all the injurious effects (inhibition of haem synthesis, and morphological changes such as punctate basophilia) will have already been produced in precursor cells developing in the bone marrow. Other observers, including McFadzean and Davis (1949) and Baikie and Valtis (1954) suggest that the increase in cell destruction is associated with the elimination of the immature and presumably defective cells; Baikie and Valtis have shown, in animals poisoned with lead, that the oxygen consumption of stippled cells and reticulocytes is higher than that of the mature cell, and they discuss the hypothesis advanced by Rimington (1938) that lead interferes with the elaboration of haem by blocking an enzymic process in its synthesis.

The results of an investigation by Eriksen (1955), using the radioactive tracer technique, on the other hand, appear to indicate that lead interferes with protoporphyrin synthesis but has no effect on the iron incorporation. The actual mechanism of the action of lead as a haemolytic agent remains in the realm of conjecture at present.

Changes in the bone marrow.—There have been a number of reports on the condition of the bone marrow in lead poisoning, especially with reference to the morphological characteristics of the erythropoietic cells. Beritić and Vandekar (1956) found a marked tendency to an increased production of erythrocytes in the bone marrow in a group of persons suffering from lead poisoning. The most characteristic feature was the presence of a large number of stippled erythroblasts (values as high as 371 per 1,000) and of nuclear abnormalities, these findings being recently confirmed by David (1959). He noted morphological changes in the erythroblasts which included a typical formation of the nuclei (karyorrhexis, deformation, polypoidosis), the presence of paraerythroblasts, variation in cell size, and deficient haemoglobin content. Siderocytes, sideroblasts and reticuloendothelial cells, present in numbers considerably above the normal, contained an abnormally large amount of iron, suggesting a disturbance of the iron metabolism of these cells, and the plasma frequently showed discrete basophilic stippling.

As in the case of the mechanism of the action of lead in changes in the peripheral blood cells, there is still uncertainty as to the true cause of these changes in the bone marrow, but most recent observers believe that the initial effect of lead is a primary hyperstimulation, followed by a delay in maturation; the anaemia, of a haemolytic character, is a secondary feature.

**Peripheral neuritis (lead palsy).**—Actual paralysis of the muscles of the hands and feet—wrist-drop and foot-drop—is now a relatively rare occurrence among lead workers though some weakness of the muscles, evidenced by decrease of strength of the hand grip, can still occasionally be observed. When wrist drop does occur the paralysis usually begins in the extensor muscles of the fingers, at first in the right hand of right-handed persons, and may become bilateral. It is accompanied by wasting of the posterior muscles of the forearm and is not associated with sensory disturbance. Foot-drop, due to paralysis of the extensor muscles of the toes, is even less common.

**Tremor.**—A fine tremor, or fibrillary twitching, used to be a feature among lead workers but is rarely seen in modern industry.

**The lead line (Burtonian or "blue line").**—This sign is regarded as a manifestation of excessive absorption of lead though it is not always present in cases of true intoxication. It consists of a deposit of dark blue-grey particles in the substance of the gum, in a line about 1 mm. from the margin. It must be distinguished from the discoloration of pyorrhoea, carbon-carrying tartar from neglected teeth, and from the dark patches on the gums frequently present in coloured workers. It is believed to be caused by patches of lead sulphide, the lead having been brought by the blood stream to the gum, where it is converted to the sulphide by the sulphuretted hydrogen arising from the decomposition of protein foods, particularly in unhealthy or unclean mouths. In some cases the "line" is not fully developed, but consists of only a few granules around one or two teeth; these may clear in a few weeks if there is no further absorption, whereas the gross blue line may remain for months after cessation of exposure.

**Premature loss of teeth.**—The fact that many lead workers lose apparently healthy teeth at an early age has led some observers to regard this as a manifestation of lead poisoning. Confirmatory evidence of the association of lead with changes in the jawbone that can lead to loosening of the teeth has been put forward by Koelsch (1959) in a series of animal experiments. He found that the jawbones of rabbits poisoned with lead carbonate showed decalcification, erosion and progressive osteoclasis. The mechanism of this action is attributed to a demineralization caused by chemical displacement of the bone calcium by lead carried in the blood as colloidal secondary lead phosphate and deposited as tertiary phosphate.

## POSSIBLE LATE SEQUELAE OF LEAD POISONING

Chronic kidney disease and arteriosclerosis in lead workers of many years' standing was believed by the early observers (who saw many more cases of heavy exposure to lead than is possible to-day) to be a direct though delayed consequence of their occupational exposure. In America this view is not generally held. Animal experiments have certainly shown that lead is a renal and vascular poison (Calvery, 1938; Fishberg, 1939; Fairhall and Miller, 1941; and others). These observers have recorded degenerative changes in the renal tubules and vascular lesions, in the form of multiple minute haemorrhages and thickening of the walls of the blood vessels of the type usually terminating in nephrosclerosis. From this evidence lead would be regarded as a vascular poison with an effect on the renal circulation which in human

beings would eventually develop into the condition known as "chronic Bright's disease". This was the view of Legge and Goadby (1912) and of Oliver (1914), who said that interstitial nephritis had come to be regarded as the typical renal lesion of lead poisoning.

With this view Lane (1949) was in agreement. He stated that during the last 15 years he had seen 9 deaths from hypertension with renal failure in lead workers who had formerly had severe exposure and whose death had occurred at the relatively early average age of 48–52. Histological examination of the kidneys showed a picture varying from that of benign hypertension with progressive renal damage to one similar to the malignant phase of arteriolar necrosis.

Albuminuria is not a frequent finding in lead workers, though in the investigation of Dreessen *et al.* (1941) a statistically significant higher incidence was present in lead workers, especially in those exposed to higher concentrations. Lane found only a trace of albumin in 3 out of 56 storage battery workers, this being present also in two controls.

No actual rise in blood pressure of workers in the accumulator industry (still one of those carrying a major lead hazard), has been demonstrated by Belknap (1936), Dreessen *et al.* (1941) or by Lane, who believe that this absence of significant change shows that their exposure has not reached a dangerous level and that the disappearance of chronic Bright's disease in lead workers is due to the improvement of conditions in modern lead industries and in 1963, in an investigation, together with Dingwall Fordyce, of a large group of pensioners and present employees of storage battery workers, they reported a highly significant excess of deaths from cerebrovascular disorders; these men had been heavily exposed for many years. This view appears to be supported by the studies of Henderson and Inglis (1957) in Australia, which showed that though 63 per cent of the cases could not be allotted to any known cause of renal disease, they had a history of childhood plumbism and excessive amounts of lead in the bones. The controversy on this subject is however not yet ended; it was stated in 1965 by Prerovska and Roth after biochemical examination of 50 lead workers that they found no proof of a hazard of premature arteriosclerosis, and they confirmed their opinion by the results of experiments on rabbits, where they found no evidence of atherosclerotic changes in vessels or organs.

## LEAD ABSORPTION

The danger of continual absorption of lead in amounts which do not of themselves cause clinical symptoms and signs of poisoning is that a point may be reached when the "threshold level" for potential poisoning can be exceeded, and then an intercurrent factor may produce a metabolic disturbance which has the appearance of toxic manifestations.

## DIAGNOSIS OF EXCESSIVE LEAD ABSORPTION

Estimation of the level at which lead absorption has become potentially dangerous usually depends upon examination of the blood for anaemia, punctate basophilia and reticulocytosis, of the urine and faeces for a raised lead content, and of the urine for its coproporphyrin level.

**Blood examinations.**—Anaemia, if unassociated with clinical symptoms, is usually mild, with a total red cell count of not less than 4,000,000 per c.mm. and a haemoglobin level of 75–80 per cent. Even when mild, however, it is sometimes accompanied by a noticeable and characteristic pallor; this differs from the pallor of severe anaemia not due to lead and from that sometimes seen in workers in hot, airless conditions, in that it has a peculiar greyish " leaden " tinge and is often associated with a pinched appearance round the nose and temples. Lane suggests that it is due to spasm of the capillaries of the skin of the face.

PUNCTATE BASOPHILIA.—The nature and significance of stippled cells in lead absorption has been the subject of a voluminous literature. It occurs both in experimental animals (McFadzean and Davis, 1949) and also in human beings ingesting or inhaling lead compounds. The fact that it occurs also in haemolytic anaemias unrelated to lead intoxication has to a certain extent detracted from its specificity for lead, but its presence in much greater numbers in lead poisoning, and in practically all workers exposed to lead, even though they exhibit no clinical symptoms and no severe anaemia, has made it a useful diagnostic aid in lead absorption. The relation between the actual numbers of basophil cells and the degree of lead absorption has also been subject to much variation of opinion. Undoubtedly some of these differences have arisen from the fact that examination of blood smears by dark-ground illumination, a much less fatiguing procedure than by transmitted light, gives a considerably higher punctate count—approximately twice as great and Jensen (1965) has stated that he has failed to find basophilic cells when some variations are used in preparing the blood smear. When thick smears were made and dried slowly, a greater number of basophils were present than in thin rapidly dried smears. The actual level at which punctate basophilia gives warning of impending lead intoxication differs in individual subjects, but most observers now consider anything above 10,000 per million (dark-ground method) a danger signal and an indication for suspension from work even if unaccompanied by symptoms or physical signs.

Lane (1931) made a distinction between fine and coarse granules in the punctate cells, the fine granules indicating a less severe effect and the coarse an excessive and rapid absorption. He has also noted that polychromasia often appears before punctate basophilia. (By transmitted light, very finely granulated basophil cells may easily be counted in error as polychromatic cells, which may partly account for the lower count by this method than by dark-ground illumination). Lane has also suggested that a raised average level in a group of exposed workers is a significant finding and of greater value in the control of absorption and the diagnosis of plumbism than individual counts. With this statement some observers would make the reservation that individuals with high basophil counts and with no clinical symptoms other than moderate anaemia sometimes unexpectedly develop signs of acute intoxication within a short time of their examination.

BASOPHILIC AGGREGATION TEST.—This test, described by McCord *et al.* (1924) and McCord *et al.* (1935) depends on the enumeration of all red cells containing basophilic material, including reticulocytes and polychromatic cells. The red cells are haemolysed and the " clumped " basophilic material stained

with Romanovsky stain; the percentage relationship between the aggregations on the unfixed portion and the total number of red cells in the fixed portion is calculated. In healthy individuals this percentage is on the average 0·85 per cent; findings above 2 per cent are said to suggest the possibility of approaching lead poisoning or its early presence. It is not always positive in chronic lead poisoning.

RETICULOCYTE COUNTS.—Some observers regard a mild reticulocytosis as a measure of lead absorption on the grounds that it is a feature of haemolytic anaemia (Fleckel and Tschernow, 1930). It is even less specific to lead than punctate basophilia and should not be regarded as a method of diagnosis in individual cases, though it is a useful aid in the group control proposed by Lane. Dreessen *et al.* (1941) point out that if a patient has a high stippled count there is a strong probability that he will also have high reticulocyte and polychromatophilic levels. They found that in men with a low lead exposure (up to 0·74 mg. per c.m. of lead) the reticulocyte count averaged 1·7 per cent; it rose with increasing exposure and length of employment to 3·9 per cent in men employed for 15 years in an atmospheric concentration of over 3 mg. per c.m.

SIDEROCYTE COUNT.—Siderocytes are erythrocytes containing fragments of non-haematin iron which can be stained by $\alpha\alpha'$dipyridine and potassium thiocyanate. According to Case (1945) these are "ageing" cells and should be found in increased numbers in haemolytic conditions where there is a high rate of erythrocyte destruction. He estimates the percentage in normal blood as 0·5 to 0·8, and found it increased from 10 to 30 per cent in 4 cases of lead poisoning.

BLOOD LEAD LEVEL.—The level of lead in blood does not increase as much in lead absorption as does that of urine, but it fluctuates less widely (Elkins, 1959). The actual level indicative of absorption considered dangerous has been given varying values by different observers, as does the range of normal values (see p. 174). According to Patty (1949) 0·07–0·08 mg. per 100 g. are indicative of non-harmful absorption, and between 0·08 and 0·15 mg. per 100 g. of dangerous absorption. A lower value (0·05 mg. per 100 g.) is given by Egli *et al.* (1957) as the "tolerance limit" for intoxication.

**Lead content of urine and faeces.**—As already observed (p. 175) faecal excretion of lead is greater than urinary excretion; it represents mainly lead swallowed with secretions from the upper respiratory passages and from contamination of the hands. Thus the faecal lead output, while giving a rough picture of the lead exposure, is not a direct measure of the absorption. It has been estimated, however, that lead exposure is safe if it does not give an average daily faecal lead excretion of more than 0·6 mg. and that the threshold for potential poisoning may be exceeded if it is not in excess of 1·4 mg. (Kehoe *et al.* (1933).

Urinary lead increases rapidly with even moderate absorption. According to Elkins (1959) there may be an increase from the normal average of about 0·03 mg. per l., to 0·10–0·15 within a few weeks. He considers levels between 0·15 and 0·2 mg. per l. as "borderline" and above 0·2 mg. as indicative of harmful exposure, while others, including Egli *et al.* (1957) and Lynch (1949) agree that 0·15 mg. per l. represents the "bottom level for exposure";

Lynch regards 0·3 mg. per l. as the "top level indicating absorption". Elkins states that "lead levels in excess of 0·4 mg. per l. are usually associated, sooner or later, with some degree of lead intoxication". He also states that with regard to the correlation between urinary and blood lead levels, the average level in the blood corresponding to 0·2 mg. per l. of urine is 0·07 mg. per 100 g. of blood and a blood lead level of 0·9 mg. per 100 g. is comparable to 0·3 mg. per l. of urine.

Coproporphyrinuria.—There is a normal range of daily excretion of coproporphyrin, depending on constitution, diet and activity—0–120 $\gamma$ in the urine and 150–400 $\gamma$ in the faeces, (Dobriner *et al*,, 1937). Cantarow and Trumper (1955) give the normal daily level in the urine as 160 $\gamma$ and in the faeces 300–400 $\gamma$. In animals and human beings lead absorption results in an increased excretion of protoporphyrin in the urine, and this is considered an earlier indication of lead absorption than punctate basophilia (De Langen and ten Berg, 1948). Such an increased excretion is not specific to lead poisoning; it occurs also in poisoning by mercury, organic arsenicals, some organic solvents and aromatic amines, and in some diseases such as Weil's disease, cirrhosis of the liver and obstructive jaundice (Watson, 1952). It is not definitely known whether the porphyrinuria of lead poisoning differs from that of the disease porphyria (Singer, 1953), but in lead poisoning there is an increase, of coproporphyrin III, in which it differs from true haemolytic anaemia (Holaček and Pěničkovà, 1957) and to a smaller extent of uroporphyrin, which is found in large amounts in conditions where there is stress on the bone marrow (Kench *et al.*, 1952).

A correlation between the concentration of coproporphyrin in the urine and that of the lead in blood and urine of industrial lead workers (and in children suffering from acute lead poisoning) has been recorded by several observers (Maloof, 1950; Shiels *et al.*, 1953; Bashour, 1954; Chisholm and Harrison, 1956) and it is generally agreed that estimation of the coproporphyrin content of the urine is a valuable supplement to urine or blood lead estimations. Meek *et al.* (1948), although their results of examining workers exposed to lead fumes did not show complete correlation between the excretion of lead and that of coproporphyrin in the urine, considered the coproporphyrin test as a "potential laboratory tool". An attempt by Wyllie (1955) to correlate the urinary coproporphyrin values with the punctate basophil count showed that with mild exposure the coproporphyrinuria increased from an average value of 3 $\gamma$ to 120 $\gamma$ per 100 ml., with a punctate count of 1,000 or less per million red cells, to 1,300 $\gamma$ per 100 ml. when the punctate count rose to 9,800. The uroporphyrin values, estimated by the spectrophotometric method of Rimington and Svensson (1950) also increased, as did the ratio between coproporphyrin and uroporphyrin; with punctate counts of 1,000 per million this ratio is seldom greater than 2/1, but as the stippled cells increased to 9,800 the ratio rose as high as 6/1. In Bashour's (1954) investigation, both urinary and blood porphyrins were increased, though only 5 of the 44 exposed individuals showed clinical symptoms of lead poisoning. The daily urinary coproporphyrin averaged nearly ten times the normal while the blood values were only slightly above. The blood lead concentration was above the normal level in 39 individuals. Elkins states that a high coproporphyrin level (above

1 mg. per l. of urine) together with a urinary or blood lead value indicative of harmful exposure, is a warning which should not be ignored. The " tolerance limit " recommended by Egli *et al.* (1957) based on a study of workers in accumulator and lead colour factories, where about two-thirds of these workers had a urinary coproporphyrin level greater than 6 $\gamma$ per 100 ml., is 6–8 $\gamma$ per 100 ml., though none showed the complete picture of lead intoxication.

The factors involved in the porphyrinuria of lead poisoning are still not completely understood. Some investigators (e.g. Kench *et al.*, 1952) have attributed it to a breakdown of the iron-porphyrin (protoporphyrin) in the haemoglobin molecule, with increased red cell destruction and bone marrow hyperactivity—in other words to a haemolytic action of lead; others, such as Vanotti (1954) consider it an inhibition of the utilization of iron in the synthesis of haemoglobin, with formation of porphyrin type III, a non-iron-containing blood pigment. The most recent and, according to Goldblatt and Goldblatt (1956), most reliable view is that " the porphyrins excreted in poisoning, in disease, and in the normal organism derive not from the breakdown of haemoglobin but from the processes of synthesis of haemoglobin ".

A diagnostic criterion in the form of the presence in the urine of aminolaevulic acid has been suggested by Kramer and Selander (1965) on the grounds that it may be correlated with the amount of metabolically active lead, and therefore of lead intoxication.

Versenate ($Ca_2EDTA$), has in recent years been suggested by several authorities as a reliable test for excessive absorption of lead, both in lead workers and in non-industrially exposed persons. (Leckie and Thompsett (1958), Albahary, Truhaut and Boudéne (1958), Teisinger and Srbova (1959), Williams, Leigh and Matthews (1966). Some of these have found that intravenous injections have produced the highest excretion of lead, while others have given an oral dose of 1 g. of versenate at 10 p.m. and estimated the total lead in the urine in two early morning tests. Leckie and Thompsett found that one group of laboratory workers with no known exposure to lead showed, on the basis of haemoglobin level, stipple cell count, coproporphyrinuria and lead in urine, no changes sufficient to indicate more than small absorption, while all workers with lead, who were considered on these findings to show excessive absorption, showed after versenate administration urinary lead levels of over 760 $\mu$ per l. and Teisinger (1965) has stated that persons exposed to lead whose blood picture shows punctate basophilia of more than 1,000 per million, porphyrinuria of more than 0·150 mg. per l. and a lead blood level of more than 0·70 mg. per cent show an excretion rate of lead of more than 1·7 mg. per l. after EDTA, while those suffering from anaemia excrete an average of 5·05 mg. per 24 hours. He summarizes the value of the versenate test by stating that when at least two of the more widely used tests are positive, the mobilization test would not be useful, but that it is suitable for dubious cases, and also in order to decide whether the patient, after an episode of lead poisoning, should resume work with lead.

The various tests for lead absorption have also been exhaustively discussed by Rainsford (1968), who states that there is sometimes a very incomplete correlation between them, but that this is more apparent than real, since the

pathological findings suggest that a worker exposed to a lead hazard can pass through several stages before developing overt plumbism, namely an initial rise in the blood-lead level followed by a rise in urinary excretion of coproporphyrin and aminolaevulin and these may be followed by a hypochromic anaemia combined with a rise in the reticulocyte and punctate counts. He points out that the coproporphyrinuria test is only reliable when the urine has a specific gravity of more than 1,008, and that this test and that for A.L.A. are time-consuming procedures needing highly qualified technicians.

He has also shown that the relationship between haemoglobin and blood-levels is that all specimens with haemoglobin levels of less than 13·0 g. per cent have blood-lead levels exceeding 50 $\mu$g. per 100 g. while those with less than 12·0 g. of haemoglobin per cent have blood-lead levels of more than 75 $\mu$g. per 100 g., though in his investigation some workers with haemoglobin levels exceeding 14·9 per cent had blood-lead levels of more than 100 $\mu$g. per 100 g.

Estimation of lead in blood and urine by Atomic Absorption Spectrophotometry has been described by Slavin and Sprague (1964) and recommended as being less time-consuming than other methods, especially when combined with a chelating agent, but they issue a warning that in the case of blood estimation there may be a potential error; for example, the chelating agent may not recover all the organically bound lead, or that in the blood samples lead may be lost in the precipitate unless the blood had been dissolved in $HNO_3$.

**Methods of estimation.**—There are many methods in present use for the estimation of lead in air, blood and urine, and for coproporphyrinuria. The most complete and exhaustive account of these is given by Marmet (1958) in his survey of three accumulator and two colour factories in Switzerland. He discusses the advantages of the methods used by himself, and correlates the results of the various tests with each other and with the extent of the existing potential hazard. Similar conclusions have been reached by Reinhold and Holzapfel (1967) as the results of their investigation of two groups of workers, one in a ceramic works and the other in a factory producing lead colours. Both groups were given 1 g. of $CaNa_2EDTA$ twice daily over a period of one year. Estimation of the lead in air in the colour factory gave values of 6·750 to 12·50 mg. per c.m., indicating a high lead risk. A preliminary investigation had revealed a blue line on the gums of one female worker in the ceramic group and anaemia in one of the colour grinders. At the end of the investigation two other grinders showed signs interpreted as early symptoms of lead poisoning, and the lead line of the girl in the ceramic group had not improved and her blood picture had deteriorated. Only in two cases was there a statistically acceptable improvement. It was concluded that while EDTA administration is valuable when clear symptoms of early lead intoxication are present, the only true prophylaxis of lead poisoning is a lead-free working atmosphere.

## PROPHYLAXIS AND PREVENTION OF LEAD POISONING

This preventive measure of control of lead exposure is emphasized by Berg and Zenz (1967) in a non-ferrous foundry, based on environmental, hygienic and clinical measures. These consisted of atmospheric analyses, engineering adjustments in the melting and pouring areas in the form of mechanically exhausted hoods, prohibition of eating and drinking in the work places, urine analyses and coproporphyrin tests. Berg and Zenz state that no cases of outright lead intoxication occurred during these preventive procedures.

## TREATMENT OF LEAD POISONING

Practically all the former suggested remedies for lead poisoning (administration of citrates, calcium and BAL) have now been superseded by the method of chelation. This was introduced by Bessman *et al.* (1952) to the Conference on Lead Poisoning at the Massachusetts General Hospital that year, following the preliminary report of a case treated by this method. The case, a 3 year old child, having eaten paint from window sills for the past 8 months, had suddenly developed convulsions. On the 9th day after admission to hospital, he was given 50 mg. of calcium EDTA intravenously in 50 ml. of 5 per cent glucose solution. In view of developing oliguria and high blood pressure, and since little was then known about the effects of versenate, the treatment was discontinued for the next 2 days, when for the first time punctate basophilia appeared, with a 4 per cent reticulocytosis. With improvement of the renal symptoms, but resumption of the encephalitic signs, treatment was re-started with gradually increasing doses. After a total dose of 6·5 gm. during 12 days the improvement was so marked that it was finally discontinued, with no further appearance of symptoms. Since that time the efficacy of versenate treatment both in children and adults has been established and supported by a large number of investigations in Europe and America. The first report in Great Britain was published by Giles *et al.* (1955), the mode of action and chemical characteristics having been investigated by Karpinski *et al.* (1953).

EDTA, tetracetic acid, or versenate, is a synthetic polyaminoacid, only slightly soluble in water and most organic solvents, but soluble in dilute mineral acids. It forms salts with alkali metal bases and the solubility of these salts in water increases as the acidic groups of EDTA are neutralized one after another. The importance of this substance from the point of view of therapy of metallic poisoning, especially lead, is its ability to form inner complexes with many metals, called chelates, which are stable and water-soluble; it has therefore a " sequestering " action on metals. In the case of lead stored in the body the calcium complex of EDTA, calcium disodium versenate, is used in order to prevent the removal of calcium to an extent which might cause hypocalcaemia. Its formula is as follows:

## ) PREVENTION OF LEAD ISONING

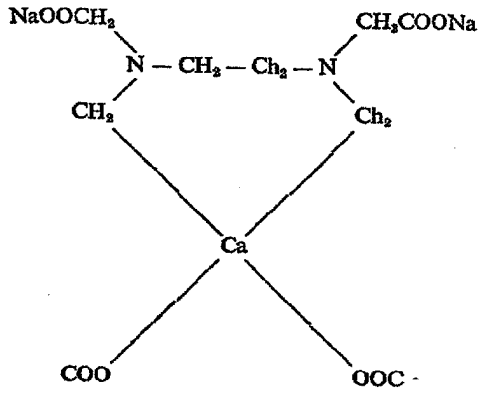
ol of lead exposure is emphasized by Berg foundry, based on environmental, hygienic sisted of atmospheric analyses, engineering ɔouring areas in the form of mechanically ating and drinking in the work places, urine ts. Berg and Zenz state that no cases of ɔd during these preventive procedures.

## ?OISONING

ested remedies for lead poisoning (admini- 1 BAL) have now been superseded by the introduced by Bessman *et al.* (1952) to the it the Massachusetts General Hospital that report of a case treated by this method. ving eaten paint from window sills for the veloped convulsions. On the 9th day after ven 50 mg. of calcium EDTA intravenously olution. In view of developing oliguria and little was then known about the effects of continued for the next 2 days, when for the ppeared, with a 4 per cent reticulocytosis. ymptoms, but resumption of the encephalitic with gradually increasing doses. After a days the improvement was so marked that it ıo further appearance of symptoms. Since te treatment both in children and adults has ɔy a large number of investigations in Europe n Great Britain was published by Giles *et al.* chemical characteristics having been investi-

ɪrsenate, is a synthetic polyaminoacid, only nost organic solvents, but soluble in dilute th alkali metal bases and the solubility of these acidic groups of EDTA are neutralized one : of this substance from the point of view of , especially lead, is its ability to form inner called chelates, which are stable and water- questering " action on metals. In the case of ılcium complex of EDTA, calcium disodium prevent the removal of calcium to an extent mia. Its formula is as follows:






This stable and soluble lead-versenate complex is excreted in the urine without significant toxic effects and with great relief of symptoms and signs of blood disturbance. It is believed that most of the lead is excreted from the soft tissues and that lead deposited in the bones is less readily accessible.

**Effects of Versenate Therapy.**—All observers are agreed upon three results of treatment of lead poisoning by calcium disodium versenate—alleviation of symptoms, rapid increase in urinary lead excretion and decrease in punctate basophilia. A decrease in coproporphyrinuria has also been recorded, and an increase in the level of lead in the blood, though there is some difference of opinion on the latter point.

ALLEVIATION OF SYMPTOMS.—The most strikingly favourable results of versenate treatment have been observed in those cases where encephalitic symptoms have been prominent, as in children who have ingested lead, but colic is also rapidly relieved, in some cases within 2 days. Anaemia, according to Saita and Moreo (1957) does not respond with the same certainty as the other phenomena of intoxication, though the punctate basophilia does.

URINARY LEAD EXCRETION.—The increase in excretion of urinary lead is rapid and very marked. Elkins (1959) states that CaEDTA when given intravenously will cause a ten to thirty-fold increase in the lead content of the urine, and comparable results have been obtained by many other observers. Karpinski *et al.* (1953) recorded an increase in a 24-hour specimen from 2 mg. on the second day of treatment to 4 mg. on the seventh, and Leckie and Tompsett (1958) an excretion of over 1·5 mg. in 24 hours as compared with 0·32 mg. and 0·65 mg. in controls. Even higher levels of excretion have been reported by Saita and Moreo (1957); they state that a daily dosage of 2 g. produced a lead elimination in the urine as high as 20 mg. daily, and up to 70 mg. in 9 days of treatment.

PUNCTATE BASOPHILIA.—A sharp drop in punctate basophilia is another marked feature of versenate treatment. Markus and Spencer (1955) recorded a rapid fall in the punctate count of three vitreous enamellers, one of whom

showed 11,200 per million before treatment, and Belknap (1952) and many others have reported similar results.

COPROPORPHYRINURIA.—A reduction in coproporphyrin excretion was noted by Ruotolo and Elkins (1954) and by Saita and Moreo (1957); the latter did not find a corresponding reduction in the protoporphyrin of the blood.

LEAD IN BLOOD.—There is some disagreement as to whether versenate treatment increases the level of lead in the blood. According to Manville and Moser (1955) the blood lead is not appreciably affected by EDTA, but Karpinski *et al.* (1953) observed a prompt rise following versenate therapy. They considered this to indicate the mobilization of lead from extravascular tissues; as treatment progressed the blood lead level at first declined and then rose again, suggesting that there were storage places for lead in the body not easily reached by versenate.

**Mode of administration and dosage of versenate.**—There appears to be no doubt that the intravenous method of administration is more rapid and more efficacious than the oral, but, if the efficacy is based on the production of increased elimination of lead there is some evidence that oral therapy can produce this effect. Naturally the effect of oral therapy is less striking since, according to Elkins (1959) possibly less than 1 per cent of the ingested EDTA is absorbed. Other authorities have estimated the absorption at much higher levels, Teisinger and Srbova (1956) at 2·6 per cent; Foreman *et al.* (1953) at 18 per cent.

INTRAVENOUS DOSAGE.—There still exists some difference of opinion as to the optimum dosage. Leckie and Tompsett (1958) investigated 8 men employed in the process known in Great Britain as "wire patenting". Only one man had acute symptoms of lead poisoning; in the remainder excessive lead absorption was diagnosed principally on an increased urinary coproporphyrin, varying from 4 to 100 $\gamma$ per 100 ml. It was found that the most satisfactory urinary excretion of lead was obtained by giving 0·5 g. over 3 hours twice daily in four-day courses. As the second course, separated by 3 days from the first, produced less than half the excretion of the first, it was assumed that the available lead was being rapidly eliminated. In order to discover whether there was a further quantity which would become gradually available, an identical course was given 7 weeks later. This produced 7 mg. of lead as compared with 8·4 mg. from the second course.

The unfortunate result of a case reported by Bessman *et al.* (1954) when a patient after an initial improvement following her first dose of EDTA relapsed and died from cerebral oedema suggested that this one dose did not lower the concentration of intracellular lead sufficiently to prevent the redistribution on withdrawal of the chelating agent. Leckie and Tompsett advise therefore that in severe cases the therapy should be given continuously for at least 48 hours before resuming the intermittent dosage. By the intermittent method the optimum daily dose is 2 g., and this should be given in an intravenous infusion of saline over 6 hours daily, in 5-day courses separated by 3 or 4 days.

ORAL ADMINISTRATION.—In animals poisoned with lead it has been stated by Rieders (1954) that while feeding with EDTA calcium disodium does not cause a significant increase in the combin
lead, it does cause a marked shift from fa

A comparison of oral with intravenous
Sidbury *et al.* (1953) showing that oral adr
lead excretion, and this has been confirm
Bell *et al.* (1956) and others. The shift fr
also been confirmed, but this is not ap
administration. Bell and co-workers f
intravenous administration, in men suffe
The actual elimination of lead by urine a
administration of 3 g. over a period of
to lead, caused a 2½ to 3-fold total incre
thirds of that produced by intravenous t

ORAL THERAPY AS A PROPHYLACTIC ME
CaEDTA given by mouth might be a usef
exposed to lead (Savicević *et al.*, 1959).
view. He points out that the end resul
favour of the urinary would probably be
of lead from the body and that even if t
the rate, the quantities involved in the co
probably be too small to be of practical
would be required to maintain the effect

Savicević *et al.* base their strong recom
laxis on actual cases of lead poisoning
(2 g. daily) of a CaEDTA preparation.

**Toxic effects of EDTA.**—Possible tox
kidneys, the bone marrow, the cardiac
have been suggested. On the kidneys,
Cottier (1957) was the result of an error
per kg. body weight was followed by a

On the bone marrow, Belknap (1952
the blood-forming elements in one of 3
with marked success. Signs of regene
days after cessation of treatment. Suc
and Moreo (1957). They state that th
treated for lead poisoning by calcium ve
treatment; only in patients with colic v
hyperplasia and this was regarded as
episode. No change in the erythrocyt
Savicević and co-workers in their cases

In the heart, Bradley and Powell (195
cardiogram in 4 out of 5 child patie
between the second and fourth day of tr
75 mg. per kg. body weight per day in

The question of interference with th
the assumption that copper and iron
(Teisinger and Ficerova-Bergerova, 195
of about 70 g. by mouth no fall in hae

ore treatment, and Belknap (1952) and many
sults.
eduction in coproporphyrin excretion was
(1954) and by Saita and Moreo (1957); the
ding reduction in the protoporphyrin of the

some disagreement as to whether versenate
lead in the blood. According to Manville and
is not appreciably affected by EDTA, but
d a prompt rise following versenate therapy.
e the mobilization of lead from extravascular
the blood lead level at first declined and then
e were storage places for lead in the body not

losage of versenate.—There appears to be no
hod of administration is more rapid and more
if the efficacy is based on the production of
here is some evidence that oral therapy can
the effect of oral therapy is less striking since,
ibly less than 1 per cent of the ingested EDTA
have estimated the absorption at much higher
956) at 2·6 per cent; Foreman *et al.* (1953) at

e still exists some difference of opinion as to
nd Tompsett (1958) investigated 8 men em-
Great Britain as "wire patenting". Only one
d poisoning; in the remainder excessive lead
ipally on an increased urinary coproporphy-
per 100 ml. It was found that the most
f lead was obtained by giving 0·5 g. over 3
ourses. As the second course, separated by
less than half the excretion of the first, it was
was being rapidly eliminated. In order to
rther quantity which would become gradually
as given 7 weeks later. This produced 7 mg.
g. from the second course.
ase reported by Bessman *et al.* (1954) when a
vement following her first dose of EDTA
l oedema suggested that this one dose did
intracellular lead sufficiently to prevent the
the chelating agent. Leckie and Tompsett
ises the therapy should be given continuously
ming the intermittent dosage. By the inter-
ily dose is 2 g., and this should be given in
over 6 hours daily, in 5-day courses separated

imals poisoned with lead it has been stated
ding with EDTA calcium disodium does not



cause a significant increase in the combined faecal and urinary excretion of lead, it does cause a marked shift from faecal to urinary lead.

A comparison of oral with intravenous therapy in children was made by Sidbury *et al.* (1953) showing that oral administration did cause an increase in lead excretion, and this has been confirmed by Bradley and Powell (1954), Bell *et al.* (1956) and others. The shift from faecal to urinary excretion has also been confirmed, but this is not apparently an effect specific to oral administration. Bell and co-workers found that it occurred also with intravenous administration, in men suffering from chronic lead poisoning. The actual elimination of lead by urine and faeces combined, following oral administration of 3 g. over a period of 10 days while away from exposure to lead, caused a 2½ to 3-fold total increase in excretion, amounting to two-thirds of that produced by intravenous therapy.

ORAL THERAPY AS A PROPHYLACTIC MEASURE.—It has been suggested that CaEDTA given by mouth might be a useful prophylactic measure for workers exposed to lead (Savicević *et al.*, 1959). Kehoe (1955) is not in favour of this view. He points out that the end result of a decreased faecal excretion in favour of the urinary would probably be a lowering of the rate of elimination of lead from the body and that even if there should be an overall increase in the rate, the quantities involved in the conditions of potential exposure would probably be too small to be of practical significance; also continuous dosage would be required to maintain the effect.

Savicević *et al.* base their strong recommendation of this method of prophylaxis on actual cases of lead poisoning treated by oral medication of tablets (2 g. daily) of a CaEDTA preparation.

**Toxic effects of EDTA.**—Possible toxic effects of versenate therapy on the kidneys, the bone marrow, the cardiac muscle and the electrolyte balance have been suggested. On the kidneys, the toxic effect reported by Vogt and Cottier (1957) was the result of an error in dosage. A daily dose of 600 mg. per kg. body weight was followed by a necrotizing nephrosis.

On the bone marrow, Belknap (1952) recorded a transient depression of the blood-forming elements in one of 3 cases which he had treated by EDTA with marked success. Signs of regenerative hyperplasia were observed 19 days after cessation of treatment. Such an effect has been denied by Saita and Moreo (1957). They state that the bone marrow function of patients treated for lead poisoning by calcium versenate was satisfactory at the end of treatment; only in patients with colic was there a decrease of erythroblastic hyperplasia and this was regarded as normal towards the end of an acute episode. No change in the erythrocyte or haemoglobin level was noted by Savicević and co-workers in their cases treated by oral CaEDTA.

In the heart, Bradley and Powell (1954) noted slight changes in the electrocardiogram in 4 out of 5 child patients, but they became normal again between the second and fourth day of treatment. These children had received 75 mg. per kg. body weight per day in divided doses at six-hour intervals.

The question of interference with the electrolyte balance has arisen from the assumption that copper and iron are excreted together with the lead (Teisinger and Ficerova-Bergerova, 1958). The fact that with a total dosage of about 70 g. by mouth no fall in haemoglobin was observed led Savicević

to consider that such a disturbance of iron and copper metabolism was improbable.

## ORGANIC LEAD POISONING—TETRAETHYL LEAD

The organic lead compound of chief industrial importance is tetraethyl lead, which is used as an " anti-knock " addition to motor fuels, not in its pure form but as " ethyl fluid ", a mixture of 49–63 per cent of TEL with ethylene bromide, dibromide or dichloroethane. According to Marchenko and Beilikhis (1946) ethyl fluid is added to motor fuel in amounts of 2–6 c.c. to 1 kg., corresponding to 1·5–8 parts by weight of TEL, to 1,000 parts by weight of fuel.

### PROPERTIES

Pure TEL ($Pb(C_2H_5)4$) is a clear oily liquid with a sweetish odour. It is practically insoluble in water but readily soluble in many organic solvents, and in fats and lipids. It is strongly decomposed, with liberation of heat, by halogens and their solutions, and by concentrated nitric and sulphuric acid, not by weak mineral acids and alkalis. It has a very high volatility—at 18°C. air saturated with its vapour contains about 5 mg. per l.

Specific gravity, 1·64; boiling point, about 200°C.; at 135°C. it begins to decompose slowly.

### METABOLISM

**Absorption.**—Owing to the high volatility of TEL, absorption is most commonly by inhalation but the liquid is readily absorbed from the gastro-intestinal tract and also from the skin. Animal experiments have shown that the greater part of the lead absorption from a single application to the skin takes place during the first hour.

**Distribution and excretion.**—The distribution of TEL in the tissues after absorption differs, at least in the initial stages, from that of inorganic lead, as does its final site of deposition. Kehoe and Thamann (1931) found that in rabbits, following skin absorption, the absorbed TEL became decomposed in the tissues and after a period of 3 to 14 days both its distribution and excretion followed quantitatively that of water-soluble lead compounds.

The site of greatest concentration, however, unlike that of inorganic lead, is the brain. It is known from animal experiments that there is very little deposition of inorganic lead in the brain, even when given intravenously (Ginsberg and Weatherall, 1948), and Goldblatt and Goldblatt (1956) found no cumulation in the brain of animals inhaling lead compounds even when there was extensive damage to the kidneys. In animals and human beings poisoned with TEL, lead in both volatile and also non-volatile form has been found particularly in the brain. Thus, Norris and Gettler (1925), examining the tissues of 4 fatal cases of poisoning occurring during the manufacture of TEL, found a volatile lead compound (estimated by a colorimetric micro method) in the brains of 2 of these and values for both volatile and non-volatile lead up to 12–21 $\mu$g. per g. It is believed that the volatile organic lead compounds have a special predilection for lipoid and nerve tissue and on the basis of animal

LE

experiments Goldblatt and Goldblatt which overt signs of encephalopathy n

In the liver of animals subjected to TEL vapour, lead has been demonst 1956); they used a special technique, and measured the infra-red absorptior by vacuum distillation.

### TOXICOLOGY

The majority of fatal cases of tetr been non-occupational in origin; fro excessive inhalation of the compound of contaminated food or drink. Mai drinking of contaminated beverages higher rate than in cases due to inhal skin.

It is not generally considered that tl of cars using ethyl fluid, to the passers- the concentration of TEL is not in ( author, however (Fatzer, 1953), has pu complaints of muscular pain, headа diarrhoea and constipation, sleep distu dystonia ", that inhalation of exhaust petrol can be responsible for these distu tion has usually arisen from the clean tained leaded petrol. The sludge in t centrations of 1 per cent or over. Acc possible for men exposed to the air i lethal dose of TEL in half an hour, whi of exposure in one day or successive illness.

### SYMPTOMS OF POISONING

The symptoms and time of onset va of exposure. With a heavy single exp hours and the symptoms rapidly pr exposure there may be a latent period the symptoms may differ from those of

In fatal cases acute mental disturb tions, convulsions and coma usually p a few days. Less severe cases also s excitement, agitation and disorientati nausea and vomiting. Between the a may be periods of depression and ap good once the critical period, within a and restoration may be complete with uncommon. In mild cases the com dreams, restlessness, loss of appetite a

ınce of iron and copper metabolism was

## ONING—TETRAETHYL LEAD

ief industrial importance is tetraethyl lead, " addition to motor fuels, not in its pure ure of 49–63 per cent of TEL with ethyl ne ethane. According to Marchenko and ed to motor fuel in amounts of 2–6 c.c. to by weight of TEL, to 1,000 parts by weight

ır oily liquid with a sweetish odour. It is readily soluble in many organic solvents, gly decomposed, with liberation of heat, by by concentrated nitric and sulphuric acid, alkalis. It has a very high volatility—at ır contains about 5 mg. per l. oint, about 200°C.; at 135°C. it begins to

## ABOLISM

h volatility of TEL, absorption is most iquid is readily absorbed from the gastro- kin. Animal experiments have shown that otion from a single application to the skin

e distribution of TEL in the tissues after initial stages, from that of inorganic lead, Kehoe and Thamann (1931) found that in ı, the absorbed TEL became decomposed of 3 to 14 days both its distribution and hat of water-soluble lead compounds. n, however, unlike that of inorganic lead, is l experiments that there is very little deposi- even when given intravenously (Ginsberg att and Goldblatt (1956) found no cumula- ling lead compounds even when there was n animals and human beings poisoned with non-volatile form has been found particu- nd Gettler (1925), examining the tissues of g during the manufacture of TEL, found a l by a colorimetric micro method) in the both volatile and non-volatile lead up to t the volatile organic lead compounds have ıd nerve tissue and on the basis of animal experiments Goldblatt and Goldblatt (1956) suggest that the critical level at which overt signs of encephalopathy may appear is 2–3 μg. per g. in the brain.

In the liver of animals subjected to inhalation of air nearly saturated with TEL vapour, lead has been demonstrated in small amounts (Stevens *et al.*, 1956); they used a special technique, with pentane as the extraction solvent, and measured the infra-red absorption spectrum of the solution concentrated by vacuum distillation.

## TOXICOLOGY

The majority of fatal cases of tetraethyl lead intoxication reported have been non-occupational in origin; from misuse, accidental spillage causing excessive inhalation of the compound in its undiluted state, or from ingestion of contaminated food or drink. Marchenko and Beilikhis (1946) state that drinking of contaminated beverages caused 72·2 per cent of fatalities, a higher rate than in cases due to inhalation. It can also be absorbed by the skin.

It is not generally considered that there is any risk of poisoning to drivers of cars using ethyl fluid, to the passers-by, or even to garage attendants where the concentration of TEL is not in excess of 0·1 per cent. One German author, however (Fatzer, 1953), has put forward arguments, based on vague complaints of muscular pain, headache, nasal inflammation, alternating diarrhoea and constipation, sleep disturbance and other signs of " vegetative dystonia ", that inhalation of exhaust gases from automobiles using leaded petrol can be responsible for these disturbances. In industrial cases intoxication has usually arisen from the cleaning of storage tanks which have contained leaded petrol. The sludge in these tanks may contain TEL in concentrations of 1 per cent or over. According to Kitzmiller *et al.* (1954), it is possible for men exposed to the air in such tanks to inhale and absorb a lethal dose of TEL in half an hour, while in less severe conditions a few hours of exposure in one day or successive days may cause serious or even fatal illness.

## SYMPTOMS OF POISONING

The symptoms and time of onset vary with the time, degree and duration of exposure. With a heavy single exposure the onset may be within several hours and the symptoms rapidly progressive; with repeated intermittent exposure there may be a latent period of 2 to 3 weeks; with slight exposure the symptoms may differ from those of an anxiety state.

In fatal cases acute mental disturbance, with delirium, mania, hallucinations, convulsions and coma usually precede death, which may occur within a few days. Less severe cases also show mental confusion, sleeplessness, excitement, agitation and disorientation, sometimes also abdominal pain, nausea and vomiting. Between the attacks of mania and delirium there may be periods of depression and apathy. The prognosis for recovery is good once the critical period, within a week or two of the onset, has passed, and restoration may be complete within 4–10 weeks, but relapses are not uncommon. In mild cases the complaints include insomnia, with bad dreams, restlessness, loss of appetite and gastro-intestinal disturbance; they

usually disappear within a few weeks. Symptoms of this kind were described by Müller (1954) in 4 men employed in the recovery of lead scrap used for the production of TEL.

## TISSUE LEAD IN TEL POISONING

The presence of lead, in both volatile and also non-volatile form, has been demonstrated in the tissues, particularly the brain, of animals and human beings poisoned with TEL. In the experiments of Kehoe and Thamann (1931), it was found that the greater part of the lead absorption from a single application of TEL to the skin of rabbits took place during the first hour and was distributed in the tissues, initially differently from that of water-soluble lead compounds, but later became decomposed in the tissues, and after a period of 3 to 14 days both distribution and excretion followed quantitatively that of water-soluble lead compounds.

In human beings, Norris and Gettler (1925), examining the tissues of 4 fatal cases occurring during the manufacture of TEL, found in the brains of 2 of these, volatile and non-volatile lead in amounts up to 12–21 $\mu$g. per g. It is known from animal experiments that when inorganic lead is given even intravenously there is very little deposition in the brain (Ginsberg and Weatherall, 1948); Goldblatt and Goldblatt (1956) also found no accumulation in the brains of animals given lead by inhalation, even when there was extensive damage to the kidneys. It appears that the volatile organic lead compounds have a special predilection for lipoid and nerve tissue. Goldblatt and Goldblatt suggest that the critical level in the brain, at which encephalopathy may appear, is 2–3 $\mu$g. per g.

In the liver of rats subjected to inhalation of air nearly saturated with TEL the presence of lead in small amounts has been demonstrated by Stevens *et al.* (1956).

## LEAD CONTENT OF BLOOD AND URINE IN TEL POISONING

The blood level is not consistently altered in TEL poisoning. In the series of cases described by Kitzmiller *et al.* (1954), even in those of great severity, the blood lead levels were only slightly above the normal (0·06–0·07 mg. per 100 g.) and in those of Müller the values were normal in subjects with varying degrees of intoxication. The urinary lead excretion is more definitely affected; in both the above series the level was above normal. Elkins (1959) suggests levels of "maximum allowable concentration" and of "harmful exposure" as 0·08 mg. per l. and 0·15 mg. per l. respectively.

The urinary coproporphyrin is apparently not a reliable index of early TEL poisoning.

## TREATMENT OF TEL WITH CaEDTA

While there is no definite evidence of the therapeutic efficiency of chelate treatment in organic lead poisoning, Kitzmiller *et al.* found that when given intravenously in doses of 1 g. per 30 pounds of body weight CaEDTA did cause a varying increase in the excretion of urinary lead, but not in the level of lead in the blood. In one severe case the urinary lead rose from 0·3–2·2 mg. per l. at one period 2 days later, falling again to 0·26 mg. per l. at the end of a



week and to lower values when treatment was well tolerated.

## BIBLIOGRAPHY AND RE


Albahary, C., Truhaut, R., and Boudène, C. (1958) le Test de la Plomburie provoquee par le Ve *Archs. Mal. prof. Méd. trav.*, 19, 121.

Aub, J. C., Fairhall, L. T., Minot, A. S., and Reznik *Medicine (Baltimore)*, 4, 1.

Baikie, A. G., and Valtis, D. J. (1954). "The C Experimental Lead Poisoning." *Brit. J. expe*

Bashour, F. A. (1954). "Urinary Uroporphyrin, phyrin Excretion in Lead Exposed Workers."

Belden, E. A., and Garber, L. F. (1949). "Health *J. industr. Hyg.*, 31, 347.

Belknap, E. L. (1936). "Clinical Studies on L Blood Pressure Observations." *Ibid.*, 18, 380.

— (1952). "EDTA in the Treatment of Lead 21, 305.

Bell, P. F., Gilliland, J. C., Boland, J. R., and Su Oral EDTA CaDisodium on Urinary and *indust. Hlth.*, 13, 366.

Berg, B. A., and Zenz, C. (1967). "Environment Exposure in a Non-ferrous Foundry." *Amer.*

Beritić, T., and Vandekar, M. (1956). "Erythro Poisoning." *Blood*, 11, 114.

Bessman, S. P., and Layne, E. C. (1955). "Dete Urine." *J. Lab. clin. Med.*, 45, 159.

— Ried, H., and Rubin, M. (1952). "Treatme CaDisodium Versenate." *Med. Ann. D. C.*, 2

— Rubin, M., and Leikin, S. (1954). "Treat *Pediatrics*, 14, 201.

Bradley, J. E., and Powell, A. M. (1954). "Oral Children." *J. Pediat.*, 45, 297.

Brown, A. (1946). "The Lead Content of Bloo Processes in Bone." *Quart. J. Med.*, 15, 77.

Calvery, H. O. (1938). "Chronic Effects of Ingest *med. Ass.*, 111, 1722.

Cantarow, A., and Trumper, M. (1955). *Clinical Bi* W. B. Saunders Co.

Case, R. A. M. (1945). "Siderocytes in Haemolyt 271.

Chisholm, J. J., and Harrison, H. E. (1956). porphyrin Excretion and its Relation to EDTA Acute Lead Intoxication." *J. clin. Invest.*, 35,

Clarkson, T. W., and Kench, J. E. (1958). "Sedi Human Erythrocytes *in vitro* after Exposure *Industr. Med.*, 15, 115.

David, A. (1959). "Das Knochenmark bei Gewer *Arch. Gewerbepath. Gewerbrhyg.*, 17, 329.

De Langen, and ten Berg, J. A. G. (1948). "Porp of Lead Poisoning." *Acta. med. scand.*, 130, 3

Dingwall-Fordyce, I., and Lane, R. E. (1963). Workers." *Brit. J. industr. Med.*, 20, 311.

D'Onofrio, V. (1949). "Il Saturnismo nell'Indu *industr.*, 18, 155.

Dobriner, K., Strain, W. H., and Localio, S. A. (193 of Coproporphyrin and Total Coproporphyrin *Soc. exp. Biol.* (N.Y.)., 36, 752.

Symptoms of this kind were described in the recovery of lead scrap used for

## ONING

ile and also non-volatile form, has been arly the brain, of animals and human experiments of Kehoe and Thamann art of the lead absorption from a single oits took place during the first hour and r differently from that of water-soluble lecomposed in the tissues, and after a n and excretion followed quantitatively

tler (1925), examining the tissues of 4 facture of TEL, found in the brains of id in amounts up to 12–21 $\mu$g. per g. It hat when inorganic lead is given even position in the brain (Ginsberg and ldblatt (1956) also found no accumula- lead by inhalation, even when there

It appears that the volatile organic dilection for lipoid and nerve tissue. the critical level in the brain, at which g. per g.

lation of air nearly saturated with TEL ts has been demonstrated by Stevens

## ND URINE IN TEL POISONING

y altered in TEL poisoning. In the r *et al.* (1954), even in those of great nly slightly above the normal (0·06– iller the values were normal in subjects

The urinary lead excretion is more e series the level was above normal. imum allowable concentration " and r l. and 0·15 mg. per l. respectively. arently not a reliable index of early

## CaEDTA

of the therapeutic efficiency of chelate itzmiller *et al.* found that when given pounds of body weight CaEDTA did n of urinary lead, but not in the level the urinary lead rose from 0·3–2·2 mg. again to 0·26 mg. per l. at the end of a



week and to lower values when treatment was discontinued. The drug was well tolerated.

## BIBLIOGRAPHY AND REFERENCES


Albahary, C., Truhaut, R., and Boudéne, C. (1958). " Depistage de Saturnisme par le Test de la Plomburie provoquee par le Versenate de Calcium Disodique." *Archs. Mal. prof. Méd. trav.*, 19, 121.

Aub, J. C., Fairhall, L. T., Minot, A. S., and Reznikoff, I. (1925). " Lead Poisoning." *Medicine (Baltimore)*, 4, 1.

Baikie, A. G., and Valtis, D. J. (1954). " The $0_2$ Consumption of the Blood in Experimental Lead Poisoning." *Brit. J. exper. Path.*, 35, 434.

Bashour, F. A. (1954). " Urinary Uroporphyrin, Porphobilinogen and Coproporphyrin Excretion in Lead Exposed Workers." *J. Lab. clin. Med.*, 44, 764.

Belden, E. A., and Garber, L. F. (1949). " Health of Workers Exposed to Galena." *J. industr. Hyg.*, 31, 347.

Belknap, E. L. (1936). " Clinical Studies on Lead Absorption in the Human; Blood Pressure Observations." *Ibid.*, 18, 380.

— (1952). " EDTA in the Treatment of Lead Poisoning." *Industr. Med. Surg.*, 21, 305.

Bell, P. F., Gilliland, J. C., Boland, J. R., and Sullivan, B. R. (1956). " Effect of Oral EDTA CaDisodium on Urinary and Faecal Lead Excretion." *Arch. indust. Hlth.*, 13, 366.

Berg, B. A., and Zenz, C. (1967). " Environmental and clinical Control of Lead Exposure in a Non-ferrous Foundry." *Amer. ind. Hyg. Ass. J.*, 28, 175.

Beritić, T., and Vandekar, M. (1956). " Erythropoietic Cell Morphology in Lead Poisoning." *Blood*, 11, 114.

Bessman, S. P., and Layne, E. C. (1955). " Determination of Lead in Blood and Urine." *J. Lab. clin. Med.*, 45, 159.

— Ried, H., and Rubin, M. (1952). " Treatment of Lead Encephalopathy with CaDisodium Versenate." *Med. Ann. D. C.*, 21, 312.

— Rubin, M., and Leikin, S. (1954). " Treatment of Lead Encephalopathy." *Pediatrics*, 14, 201.

Bradley, J. E., and Powell, A. M. (1954). " Oral EDTA in Lead Intoxication in Children." *J. Pediat.*, 45, 297.

Brown, A. (1946). " The Lead Content of Blood and its Relation to Rarefying Processes in Bone." *Quart. J. Med.*, 15, 77.

Calvery, H. O. (1938). " Chronic Effects of Ingested Lead and Arsenic." *J. Amer. med. Ass.*, 111, 1722.

Cantarow, A., and Trumper, M. (1955). *Clinical Biochemistry*. p. 534. Philadelphia; W. B. Saunders Co.

Case, R. A. M. (1945). " Siderocytes in Haemolytic Diseases." *J. Path. Bact.*, 57, 271.

Chisholm, J. J., and Harrison, H. E. (1956). " Quantitative Urinary Coproporphyrin Excretion and its Relation to EDTA Administration in Children with Acute Lead Intoxication." *J. clin. Invest.*, 35, 1131.

Clarkson, T. W., and Kench, J. E. (1958). " Sedimentation Rate and Fragility of Human Erythrocytes *in vitro* after Exposure to Lead Chloride." *Brit. J. Industr. Med.*, 15, 115.

David, A. (1959). " Das Knochenmark bei Gewerblicher Bleivergiftung." C. D. *Arch. Gewerbepath. Gewerbrhyg.*, 17, 329.

De Langen, and ten Berg, J. A. G. (1948). " Porphyrin in Urine as First Symptom of Lead Poisoning." *Acta. med. scand.*, 130, 37.

Dingwall-Fordyce, I., and Lane, R. E. (1963). " A Follow-up Study of Lead Workers." *Brit. J. industr. Med.*, 20, 311.

D'Onofrio, V. (1949). " Il Saturnismo nell'Industria Ceramica." *Rass. Med. industr.*, 18, 155.

Dobriner, K., Strain, W. H., and Localio, S. A. (1937). " Quantitative Measurement of Coproporphyrin and Total Coproporphyrin I Excretion in Animals." *Proc. Soc. exp. Biol.* (N.Y.), 36, 752.

Dreessen, W. C., Edwards, T. I., and Reinhardt, W. H. (1941). "The Control of the Lead Hazard in the Storage Battery Industry." *U.S. Treas. publ. Hlth. Bull.* No. 262.
Egli, R., Grandjean, E., Marmet, J., and Kapp, H. (1957). "Der Verbreitung der Chronischen Bleivergiftung in Akkumulatoren und Bleifarben Fabriken." *Schweiz med. Wschr.*, 87, 1171.
Elkins, H. B. (1959). *The Chemistry of Industrial Toxicology.* New York; John Wiley and Sons.
Eriksen, L. (1955). "Effect of Lead on the *in vitro* Biosynthesis of Heme and Free Erythrocyte Porphyrins." *Scand. J. clin. Lab. Invest.*, 7, 80.
Fader, B. (1966). "Practical Designs for Noise Barriers based on Lead." *Amer. Ind. Hyg. Ass. J.*, 27, 520.
Fairhall, L. T. (1943). "The Identification and Localisation of Lead in Bone Tissue." *U.S. Treas. Pub. Hlth. Rep., No.* 58, 209.
— and Miller, J. W., (1941). "The Deposition and Removal of Lead in the Soft Tissues." *Ibid.* 56, 1641.
Fatzer, R. (1953). "Anzeichen von Bleivergiftung?" *Schweiz. Med. Wschr.*, 83, 631.
Fishberg, A. M. (1939). *Hypertension and Nephritis.* London; Baillière, Tindall and Cox.
Fleckel, L. M. and Tschernow, I. G. (1930). "Zur Frühdiagnosis der Bleivergiftung." *Z. Gew-Hyg.*, 17, 65.
Foreman, H., Vier, M., and Magell, M. (1953). "Metabolism of $Ca^{45}$-labelled EDTA in the Rat." *J. biol. Chem.*, 203, 1045.
Gilbert, F. A. (1957). *Mineral Nutrition and the Balance of Life.* Univ. Oklahoma Press.
Giles, H. McC., Moore, C. J., and Still, B. M. (1955). "Treatment of Lead Poisoning with CaDisodium Versenate." *Lancet*, 1, 183.
Gillet, J. A. (1955). "An Outbreak of Lead Poisoning in Rotherham." *Ibid.*, 1, 1118.
Ginsberg, M., and Weatherall, M. (1948). "Acute Distribution of Intravenously Administered Lead Acetate in Normal and BAL-treated Rabbits." *Brit. J. Pharmacol.*, 3, 223.
Goldblatt, M. W., and Goldblatt, J. (1956). "Industrial Carcinogenesis and Toxicology" in *Industrial Medicine and Hygiene.* Ed. E. R. A. Merewether. London; Butterworth.
Hansmann, G. H., and Perry, M.C. (1940). "Lead Absorption and Intoxication in Man." *Arch. Path. (Chicago)*, 30, 226.
Hay, W. (1950). "Lead Encephalopathy in a Cooperage." *Brit. J. industr. Med.*, 7, 177.
Henderson, D. A., and Inglis, J. A. (1957). "The Lead Content of Bone in chronic Bright's Disease." *Australas. Ann. Med.*, 6, 145.
Holaček, V., and Pěničkovà, M. (1957). "Excretion of Urinary Coproporphyrin in Lead Poisoning." *Brit. J. industr. Med.*, 14, 198.
Horiuchi, K., Horiguchi, S., and Suekane, M. (1959). "Studies on the Industrial Lead Poisoning." *Osaka C. med. J.*, 5, 41.
Jackson, T. H. (1857). "Diseases of Miners of Arkendale and Swaledale." *Brit. med. J.*, p. 619.
Jensen, (1965), cited in Editorial. "Basophilic Stippling in Lead Poisoning." *J. occup. Med.*, 8, 343.
Johnstone, R. T. (1957). "A Re-examination of the Picture of Plumbism." *Industr. Med. Surg.*, 26, 323.
Karpinski, F. E., Rieders, F., and Girsh, L. S. (1953). "CaDisodium Versenate in the Therapy of Lead Encephalopathy." *J. Pediat.*, 42, 687.
Kehoe, R. A. (1949). *Industrial Lead Poisoning in Industrial Hygiene and Toxicology*, Vol. II Patty, F. A., New York; Interscience Publishers Inc.
— (1955). "Misuse of EDTA CaDisodium for Prophylaxis of Lead Poisoning." *J. Amer. med. Ass.*, 157, 341.
Kehoe, R. A. (1960). "The Metabolism of Lead in Health and Disease." *Harben Lecture.* pp. 30 and 39.
— and Thamann, F. (1931). "Behaviour o —TEL." *Amer. J. Hyg.*, 13, 478.
— — and Cholak, J. 1933. "On Normal A *J. industr. Hyg.*, 15, 257.
Kench, J. E., Lane, R. E., and Varley, H. (1952 Lead Poisoning." *Brit. J. industr. Med.*, 9,
Kitzmiller, K. V., Cholak, J., and Kehoe, R. A Lead (TEL) Intoxication with CaEDTA."
Koelsch, F. (1959). "Bleivergiftung und Zahnau
Kramer, K., and Selander, S. (1965). "Studies between different Laboratory Tests." *Brit. J*
Lane, R. E. (1931). "Punctate Basophilia in C *Hyg.*, 13, 276.
— (1936). "The Prevention of Industrial Pl
— (1949). "The Care of the Lead Worker."
— (1965). "The clinical Aspects of Poisonir *Ann. occup. Med.*, 8, 31.
Leckie, W. J. H., and Tompsett, S. L. (1958). " EDTA (Versene) in Excessive Inorganic Lead
Legge, T. M., and Goadby, K. W. (1912). *Le* London and New York; Longmans, Green
Lynch, J. G. B. (1949). "The Problem of Lead 60, 495.
McCord, C. P. (1953). "Lead and Lead Poisc *Med. Surg.*, 22, 573.
— (1954). *Ibid.*, 23, 27.
— Holden, F. R., and Johnston, J. (1935). the Lead Poisoning Epidemic of 1934–35."
— Munster, D. K., and Rehm, M. (1924). in Lead Poisoning." *J. Amer. med. Ass.*, 8
McFadzean, H. J. S., and Davis, L. J. (1949). Poisoning." *Quart. J. Med.*, 18, 57.
Maloof, C. C. (1950). "Role of Porphyrins *industr. Hyg.*, 1, 296.
Manville, L. D., and Moser, R. (1955). "R Workers exposed to Lead." *Arch. industr.*
Marchenko, E. N., and Beilikhis, G. A. (1946). Tetraethyl Lead." *Gig. i Sanit.*, 11, 17.
Markus, A. C., and Spencer, A. G. (1955). "T with CaDisodium Versenate." *Brit. med.*
Marmet, J. (1958). *Industrietoxicologische* (Thesis), Zurich; Eidgenossischen Technisc
Meek, S. F., Mooney, T., and Harrold, G. C Lead Poisoning." *Industr. Med. Surg.*, 17
Mehani, S. (1966). "Lead Retention by the *Ann. occup. Hyg.*, 9, 165.
Minot, A. S., and Aub, J. C. (1924). "The Organism." *J. industr. Hyg.*, 6, 149.
Müller, K. (1953). "Zur Kasuistik der Bleiletr
Norris, C., and Gettler, A. O. (1925). "Poiso *med. Ass.*, 85, 818.
Oliver, T. (1914). *Lead Poisoning.* London; I
Patty, F. A. (1949). "The Significance of Lead *Surg.*, 18, 368.
— (1958). *Industrial Hygiene and Toxico* York; Interscience Publishers Inc.
Prerovska, I., and Roth, Z. (1965). "Einfluss rungen in der Ader-Wand und Serum in I *Gewerbepath; Gewerbehyg*, 21, 256.

d Reinhardt, W. H. (1941). "The Control of the Battery Industry." *U.S. Treas. publ. Hlth. Bull.*

., and Kapp, H. (1957). "Der Verbreitung der n Akkumulatoren und Bleifarben Fabriken."

*istry of Industrial Toxicology*. New York; John

id on the *in vitro* Biosynthesis of Heme and Free *and. J. clin. Lab. Invest.*, 7, 80.
igns for Noise Barriers based on Lead." *Amer.*

lentification and Localisation of Lead in Bone *'th. Rep., No. 58*, 209.
"The Deposition and Removal of Lead in the

i Bleivergiftung?" *Schweiz. Med. Wschr.*, 83, 631.
*rsion and Nephritis*. London; Baillière, Tindall

G. (1930). "Zur Frühdiagnosis der Bleivergif-

l, M. (1953). "Metabolism of $CI_4$-labelled EDTA 203, 1045.
*utrition and the Balance of Life*. Univ. Oklahoma

l Still, B. M. (1955). "Treatment of Lead Poisonate." *Lancet*, 1, 183.
eak of Lead Poisoning in Rotherham." *Ibid.*, 1,

d. (1948). "Acute Distribution of Intravenously in Normal and BAL-treated Rabbits." *Brit. J.*

att, J. (1956). "Industrial Carcinogenesis and *Medicine and Hygiene*. Ed. E. R. A. Merewether.

.C. (1940). "Lead Absorption and Intoxication in o), 30, 226.
alopathy in a Cooperage." *Brit. J. industr. Med.*,

A. (1957). "The Lead Content of Bone in chronic s. *Ann. Med.*, 6, 145.
(1957). "Excretion of Urinary Coproporphyrin in *ndustr. Med.*, 14, 198.
Suekane, M. (1959). "Studies on the Industrial *med. J.*, 5, 41.
of Miners of Arkendale and Swaledale." *Brit.*

rial. "Basophilic Stippling in Lead Poisoning."

-examination of the Picture of Plumbism." *Industr.*

d Girsh, L. S. (1953). "CaDisodium Versenate in halopathy." *J. Pediat.*, 42, 687.
*Lead Poisoning in Industrial Hygiene and Toxicology*, York; Interscience Publishers Inc.
A CaDisodium for Prophylaxis of Lead Poisoning."
1.
etabolism of Lead in Health and Disease." *Harben*

— and Thamann, F. (1931). "Behaviour of Lead in the Animal Organism. —TEL." *Amer. J. Hyg.*, 13, 478.
— — and Cholak, J. 1933. "On Normal Absorption and Excretion of Lead." *J. industr. Hyg.*, 15, 257.
Kench, J. E., Lane, R. E., and Varley, H. (1952). "Urinary Coproporphyrins in Lead Poisoning." *Brit. J. industr. Med.*, 9, 133.
Kitzmiller, K. V., Cholak, J., and Kehoe, R. A. (1954). "Treatment of Organic Lead (TEL) Intoxication with CaEDTA." *Arch. industr. Hyg.*, 10, 312.
Koelsch, F. (1959). "Bleivergiftung und Zahnausfall." *Zbl. Arbeitsmed.*, 9, 114.
Kramer, K., and Selander, S. (1965). "Studies in Lead Poisoning. Comparison between different Laboratory Tests." *Brit. J. industr. Med.*, 22, 311.
Lane, R. E. (1931). "Punctate Basophilia in Control of Plumbism." *J. industr. Hyg.*, 13, 276.
— (1936). "The Prevention of Industrial Plumbism." *Lancet*, 2, 206.
— (1949). "The Care of the Lead Worker." *Brit. J. industr. Med.*, 6, 125.
— (1965). "The clinical Aspects of Poisoning by Inorganic Lead Compounds." *Ann. occup. Med.*, 8, 31.
Leckie, W. J. H., and Tompsett, S. L. (1958). "Diagnostic and Therapeutic Use of EDTA (Versene) in Excessive Inorganic Lead Absorption." *Quart. J. Med.*, 27, 65.
Legge, T. M., and Goadby, K. W. (1912). *Lead Poisoning and Lead Absorption*. London and New York; Longmans, Green and Co.
Lynch, J. G. B. (1949). "The Problem of Lead Poisoning." *Canad. med. Ass. J.*, 60, 495.
McCord, C. P. (1953). "Lead and Lead Poisoning in Early America." *Industr. Med. Surg.*, 22, 573.
— (1954). *Ibid.*, 23, 27.
— Holden, F. R., and Johnston, J. (1935). "Basophilic Aggregation Test in the Lead Poisoning Epidemic of 1934–35." *Amer. J. publ. Hlth.*, 25, 1089.
— Munster, D. K., and Rehm, M. (1924). "The Basophilic Aggregation Test in Lead Poisoning." *J. Amer. med. Ass.*, 82, 1759.
McFadzean, H. J. S., and Davis, L. J. (1949). "Significance of Stippling in Lead Poisoning." *Quart. J. Med.*, 18, 57.
Maloof, C. C. (1950). "Role of Porphyrins in Occupational Diseases." *Arch. industr. Hyg.*, 1, 296.
Manville, L. D., and Moser, R. (1955). "Recent Developments in the Care of Workers exposed to Lead." *Arch. industr. Hlth.*, 12, 528.
Marchenko, E. N., and Beilikhis, G. A. (1946). "Non-occupational Poisoning by Tetraethyl Lead." *Gig. i Sanit.*, 11, 17.
Markus, A. C., and Spencer, A. G. (1955). "Treatment of Chronic Lead Poisoning with CaDisodium Versenate." *Brit. med. J.*, 2, 883.
Marmet, J. (1958). *Industrietoxicologische Untersuchungen bei Bleiarbeitern*. (Thesis), Zurich; Eidgenossischen Technischen Hochschule.
Meek, S. F., Mooney, T., and Harrold, G. C. (1948). "Urinary Porphyrins in Lead Poisoning." *Industr. Med. Surg.*, 17, 469.
Mehani, S. (1966). "Lead Retention by the Lungs of Lead exposed Workers." *Ann. occup. Hyg.*, 9, 165.
Minot, A. S., and Aub, J. C. (1924). "The Distribution of Lead in the Human Organism." *J. industr. Hyg.*, 6, 149.
Müller, K. (1953). "Zur Kasuistik der Bleitetrāthyl Vergiftung." *Zbl. Arbeit.*, 3, 8.
Norris, C., and Gettler, A. O. (1925). "Poisoning by Tetraethyl Lead." *J. Amer. med. Ass.*, 85, 818.
Oliver, T. (1914). *Lead Poisoning*. London; H. K. Lewis.
Patty, F. A. (1949). "The Significance of Lead in Biological Fluids." *Industr. Med. Surg.*, 18, 368.
— (1958). *Industrial Hygiene and Toxicology*, 2nd Ed., Vol. 1, p. 162. New York; Interscience Publishers Inc.
Prerovska, I., and Roth, Z. (1965). "Einfluss von Blei auf biochemische Veranderungen in der Ader-Wand und Serum in Hinblick auf Atherosklerosis." *Arch. Gewerbepath; Gewerbehyg*, 21, 256.

Question Clinic (1967). *J. Occup. Med.*, 9, 141.
Rainsford, S. G. (1968). "The Problem of Medical Supervision of Lead Workers. 1968." *Royal nav. med. Service J.*
Reinhold, R., and Holzapfel, G. (1967). "Investigation into the Long-term Prophylaxis by $CaNa_2EDTA$ in Workers exposed to Lead." *Arch. Gewerbepath. Gewerbehyg.*, 23, 155.
Rieders, F. (1954). "Effect of Oral Disodium Calcium EDTA on Urinary and Faecal Excretion of Lead in Rabbits." *Fed. Proc.*, 13, 397.
Rimington, C. (1938). (Cited by Baikie and Valtis, 1954.) *C. R. Lab. Carlsberg, ser. chim.*, 22, 454.
— and Svensson, S. L. (1950). "Spectrophotometric Determination of Uroporphyrin." *Scand. J. clin. Lab. Invest.*, 2, 209.
Rodier, J. (1948). "Étude du Saturnisme dans les Mines de Plomb Maritimes." *Arch. Mal. prof.*, 9, 539.
Ruotolo, B. P. W., and Elkins, H. B. (1954). "Lead and Coproporphyrin Excretion of Patients treated with EDTA." *Arch. industr. Hyg.*, 9, 205.
Saita, G., and Moreo, L. (1957). "Mielogramma, Ricambio Porforinico, Sideremia, nei Saturnismo sotto Trattamento con Versenati di Calcio." *Med. d. Lavoro.*, 48, 130.
Savicević, M., Petrović, I., Slanković, M., and Djordjenić, S. (1959). "Unsere Erfahringen mit Ca $Da_3$ EDTA (Mosatel-Bagget) bei chronischer Blei Exposition." *Zbl. Arbeitsmed.*, 9, 6.
Schroeder, H. A. (1956). "Trace Metals and Chronic Diseases." *Advanc. Intern. Med.*, 8, 259.
Shiels, D. O. (1954). "Elimination of Lead in Sweat." *Aust. Ann. Med.*, 3, 225.
— Palmer, G. R., Cornish, P. E., and Kearley, E. J. (1953). "Porphyrinuria in Persons exposed to Lead Hazards." *Med. J. Aust.*, 2, 171.
Sidbury, J. B., Bynum, J. C., and Fetz, L. L. (1953). "Effect of Chelating Agent on Urinary Lead Excretion." *Proc. Soc. exp. Biol. (N.Y.).*, 82, 226.
Singer, K. (1953). "Intermittent Porphyria." *Metabolism*, 2, 280.
Slavin, W., and Sprague, S. (1964). "The Determination of Trace Metals in Blood and Urine by Atomic Absorption Spectrophotometry." *Atomic Absorption Newsletter*, Perkin-Elmer Corporation. Norwalk, Connecticut.
Stevens, C. D., Feldhake, C. J., and Kehoe, R. A. (1956). "Isolation from Liver of TEL after Inhalation." *J. Pharmacol. exp. Ther.*, 117, 420.
Stow, J. (1945). *The Survey of London.* London; J. M. Dent and Sons Ltd.
Teisinger, J. (1965). "Practical Significance of Diagnostic Mobilisation of Lead." *Scientific Reports on Industrial Hygiene and Occupational Diseases in Czechoslovakia*, 10, 71.
— and Ficerova-Bergerova, V. (1958). "Ueber den Einfluss des zur Therapie der Bleivergiftung Angewendetes Ca-dinatrium Salzes der EDTA auf den Eisen und Kupferspiegel." *Arch. Gewerbepath Gewerbehyg*, 16, 478.
— and Srbova, J. (1956). Zur Frage der Therapie der chronischen Bleivergiftung mit CaEDTA. *Ibid.*, 14, 579.
— and Srbova, J. (1959). "The Value of Mobilisation of Lead by CaEDTA in the Diagnosis of Lead Poisoning." *Brit. J. industr. Med.*, 16, 148.
Thackrah, C. T. (1831). *The Effects of Arts, Trades, Professions and of Civic States and Habits of Living on Health and Longevity.* London; Longmans, Green.
Tompsett, S. L., and Anderson, A. B. (1935). "The Lead Content of Human Tissues and Excreta." *Biochem. J.*, 29, 1851.
Vanotti, A. (1954). *Porphyrins. Their Biological and Chemical Importance.* London; Hilger and Watts.
Vigliani, E. C., and Zurlo, N. (1951). "Effects of BAL on Metabolism of Lead and Symptomatology in Lead Intoxication." *Brit. J. industr. Med.*, 8, 218.
Vogt, W., and Cottier, H. (1957). "Nekrotisierende Nephrose nach Behandlung einer Subakut-chronischen Bleivergiftung mit Versenat in Hohen Dosen." *Schweiz. med. Wsch.*, 87, 665.
Watson, C. J. (1952). "Porphyrin Metabolism." In *Diseases of Metabolism.* Ed. by G. G. Duncan. Philadelphia; W. B. Saunders Co.



— and Larson, E. A. (1947). "The Urinary
Disease." *Physiol. Rev.*, 27, 3.
Webb, W. (1857). "The Lead Miners of Derby
*med. J.*, p. 687.
Williams, H., Kaplan, E., Couchman, C. E., an
Poisoning in Young Children." *U.S. Treas. I*
Williams, J. D., Leigh, D. A., and Matthews, G.
sive Lead Absorption by Use of Oral CaNa
9, 1.
Wyllie, J. (1955). "Urinary Porphyrins in Lead A
12, 396.

— and Larson, E. A. (1947). "The Urinary Coproporphyrins in Health and Disease." *Physiol. Rev.*, **27**, 3.

Webb, W. (1857). "The Lead Miners of Derbyshire and their Diseases." *Brit. med. J.*, p. 687.

Williams, H., Kaplan, E., Couchman, C. E., and Sayers, R. R. (1952). "Lead Poisoning in Young Children." *U.S. Treas. Publ. hlth. Rep.*, **76**, 230.

Williams, J. D., Leigh, D. A., and Matthews, G. H. (1966). "Diagnosis of Excessive Lead Absorption by Use of Oral $CaNa_2$ Versenate." *Ann. occup. Hyg.*, **9**, 1.

Wyllie, J. (1955). "Urinary Porphyrins in Lead Absorption." *Arch. industr. Hlth.*, **12**, 396.


DUP050313210