SESSION I

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OPENING ADDRESS

Review of recent advances of lead in clinical research

'They were the respectable ones. Well, what did they get by their respectability? I'll tell you. One of them worked in a white lead factory twelve hours a day for nine shillings a week until she died of lead poisoning. She only expected to get her hands a little paralysed; but she died. . . . That was worth being respectable for, wasn't it? . . .' (Mrs Warren's Profession, George Bernard Shaw, 1902).

This quotation from George Bernard Shaw's play at the beginning of the 20th century evokes, as only art can, a poignant record of what lead poisoning meant to the individual at that time. Lead is still one of the most important industrial poisons at the present time, but the incidence of industrial lead poisoning has dropped sharply during the present century, no doubt because of the application of vigorous measures of hygiene. In 1900, 1058 cases of lead poisoning, of which fifty-eight were fatal were notified. Whereas, in the annual report of Her Majesty's Chief Inspector of Factories in 1971 the number of notifications of industrial lead poisoning was 123, of which no case was fatal.

Constant vigilance is of course necessary to maintain and even improve this good industrial record, but the wider consideration is now the effect of environmental lead pollution on the whole community. This introduces the subject of subclinical lead poisoning which may be defined as the possible, yet unproved, effects on community health of an increased exposure to lead, insufficient to cause frank lead poisoning. In dealing with this much wider context, let us in turn look at several aspects of this problem: (1) the fate of lead in the body; (2) the sources of lead; (3) the effect of lead on various important organs and organ systems within the body; (4) the measures that may prevent excessive lead exposure.

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Fate of lead in the body

About 10% of ingested lead, whether by food or water, is absorbed in adult man, and after absorption most of it is transported in the blood, 95% bound to erythrocytes, to the soft tissues and the highest concentration is found in the liver and kidneys, but some undoubtedly goes to the brain, lungs and spleen. Deposition takes place in bone as the relatively insoluble lead triphosphate. The main excretion of lead takes place in the urine, but there is a small amount in sweat, and some is excreted into the bowel. Under certain conditions such as infection or a disturbance of the acid base metabolism of the body, there may be a mobilisation of lead from the bone to the soft tissues. The work of Kostial *et al.* (1971) has shown that the lead absorption from the intestine in newborn rats (55%) is very much higher than in adult rats (1%). Clayton (1974) has observed an increased lead absorption in children.

The fraction of atmospheric lead retained in the body will vary with the solubility and particle size of the various lead compounds. That fraction has been considered to be anything from a half to a third or even a tenth of the lead content of the atmosphere. As much as 40% of inhaled lead of large diameter, trapped in the upper respiratory tract may be swallowed.

Sources of lead

(a) Food

This is an area of controversy at the present moment. The average daily intake of lead from food-stuffs would appear to be 170 µg in the adult, equivalent to a weekly intake of approximately 1.2 mg which is below the provisional tolerable weekly intake of 3 mg proposed by the FAO/WHO Joint Committee on Food Additives. The intake of lead in food by children appears to be half that of the adult, giving the average figure of 100 µg/day (0.7 mg/week), although this varies with age.

Bryce-Smith and Waldron (1974) have recommended the introduction of low lead foods suitable for children, pregnant women and invalids. They believe that the average lead content for food for young children should not exceed 0.01 p.p.m. An important point for further work is the accepted level of lead in canned foods, particularly baby foods. There is some danger of contamination of fish and shell-fish caught in coastal waters of the United Kingdom because of the sewage and industrial wastes discharged into the sea.

(b) Water

It is now appreciated that lead contamination of domestic water supplies can be significant, particularly in soft water areas and where the plumbing systems are made of lead, especially lead storage tanks for drinking water. The critical point about the work of Beattie *et al.* (1972b) was that they found a direct correlation between the level of lead in the water and the level of blood lead, and an indirect correlation with the level of erythrocyte ALA dehydratase, in the inhabitants of the households in the Glasgow area. It must be emphasized that this urban survey did not define any clinical abnormality attributable to these elevated blood levels. However, in a corresponding rural study of long-standing exposure to drinking water with a high lead content there was frank lead poisoning in some cases (Beattie *et al.*, 1972a). The recent finding of Meredith, Moore and Goldberg (1975) that soft water in comparison to hardened water is associated with an increased absorption of lead in experimental animals, is another factor that must be taken into consideration.

(c) Air

There seems no doubt that the introduction of tetraethyl lead in 1923 as an anti-knock substance in petrol has made a major contribution to the lead content of the atmosphere. Atmospheric lead concentration within cities is a function of traffic density. With increasing traffic congestion, the ambient lead levels rise. Whether this is a significant source of lead contamination in man is at present a controversial point; but there seems unanimity on the fact that such contamination should be at least restrained. Beattie *et al.* (1972c) described four cases of poisoning by tetraethyl lead in subjects simultaneously exposed during the process of scaling a tank which contained leaded petrol. Exposure was followed after a short period by an illness in which mental symptoms were prominent, and blood lead levels were elevated, and there was a pronounced reduction in the blood activity of the enzyme ALA dehydratase.

(d) Lead from industry

The effect of contamination from industrial sources to the community at large is certainly much less than during the early years of the industrial revolution. But the recent experience at Avonmouth shows that this source from lead smelters must be vigilantly controlled. The experience of Lansdown and colleagues failed to show any correlation between such contamination and the intelligence of children (Lansdown *et al.*, 1974).

(e) Lead in opium pills

Another source of lead contamination has been that obtained from lead medication. The continued use of the antiquated preparation, lead and opium pills, originally suggested by Paracelsus in the 16th century, did provide cases of lead poisoning (Dagg, Goldberg and Lochhead, 1965). More recently Beattie and his colleagues recorded the horrifying tale of young delinquents who stole lead and opium pills from a chemist's shop and injected a solution of these into their own veins with some fatal results (Beattie *et al.*, 1975).

Effect of lead on organs

(a) The brain and C.N.S.

At the end of the 19th century excessive lead exposure to children was found to have a profound effect on the nervous system and indeed to produce convulsions. The gross effects of acute involvement of the nervous system were well described by McKahn in 1932 but it was Byers and Lord in 1943 who drew attention to the serious impairment of mental development which could occur in children who had been exposed in infancy to lead poisoning. Of twenty children with mild lead poisoning acquired in infancy, they found that only one had progressed satisfactorily at school. In the recent conference on low level lead toxicity in Raleigh, North Carolina, October 1973, many of the reports from humans and from animals dealt with the effects of frank lead poisoning on the nervous system. Albert *et al.* (1974) and Sachs (1974) noted definite signs of neurological damage in children with blood lead levels of just over 60 $\mu\text{g}/100\text{ ml}$. There were in addition a number of reports which suggested that levels of blood lead considered to be raised but not toxic (25–55 $\mu\text{g}/100\text{ ml}$) could be associated with behavioural and intellectual abnormalities in children. On the other hand, Alexander (1974) found no relationship, in children, between elevated blood lead levels and any measure of mental function.

In addition, a number of animal studies related low levels of lead to behavioural changes which supported the concept of abnormality at these levels, and this was particularly interesting in work done by Carson *et al.* (1974) on lambs. These lambs

were exposed to maternal blood lead levels of 34 $\mu\text{g}/100\text{ ml}$ during gestation and this demonstrated slowed learning of two choice visual discrimination problems. Of particular interest was the observation of David on the relationship which existed between hyperactivity in children and concomitant increased body lead stores. More than 50% of the hyperactive children had blood lead levels in the range of 25–55 $\mu\text{g}/100\text{ ml}$ and 60% of them had post-penicillamine urine levels which were in the toxic range. The work that he described in North Carolina was an elaboration in greater detail of his previous publication. (David *et al.*, 1972) Sauerhoff and Michaelson (1973) have also shown hyperactivity in newborn rats from suckling mothers fed on excessive lead for four weeks. There was also a 20% decrease in brain dopamine in these animals.

The possible effect of lead-contaminated water on the incidence of mental retardation in Glasgow has been studied by Beattie and colleagues working with the Health Department of the Glasgow Corporation. Lead passes to the fetus through the placenta and 90% of infants are fed on powdered milk requiring an average of 1 litre of tap water per day. For these reasons water lead levels were measured in the homes occupied during the first year of life by seventy-five mentally retarded children aged 2–6 years and seventy-five normal matched controls, and in the homes occupied by their mothers during pregnancy. The water lead content was found to be significantly higher in the retarded group and the probability of mental retardation was significantly increased when water lead exceeded 800 $\mu\text{g}/\text{l}$. Blood lead levels were also significantly higher in the retarded group. It was concluded that lead contamination of water may be one factor in the multifactorial aetiology of mental retardation and that every effort should be made to reduce the lead content of drinking water (Beattie *et al.*, 1975).

(b) *The heart*

The effect of subclinical lead intoxication on heart muscle is of very great interest because of the reports of increased mortality rate from ischaemic heart disease in soft water areas. This is a subject which will be dealt with in detail later in this symposium.

(c) *The kidney*

As early as 1881, the name 'nephropathia saturnina' was in wide usage. There is now ample evidence accumulated which firmly establishes that lead can cause renal damage. The main structural changes are seen in acute lead poisoning in the proximal convoluted tubules and the characteristic finding is the presence of intranuclear inclusion bodies in the

cells of the proximal tubules. Cramer and his colleagues in 1974, in a renal study of exposed workers, have shown that typical intranuclear inclusion bodies were found only in those with short exposure. Mitochondrial changes were found in all of their subjects studied. Renal function in all cases was not reduced, which was also our own experience in an industrial study (Gibson, McKenzie and Goldberg, 1968). In contrast, several of the patients we studied in rural Scotland who had been exposed to high levels of lead in drinking water for long periods of time, say 15 or 30 years, had evidence of renal failure, hyperuricaemia and gout (Beattie *et al.*, 1972a).

(d) *The blood*

The anaemia of lead poisoning, of course, is well known and it is not appropriate here to dwell on the disorders of haem biosynthesis which are illustrated in the blood—the depression of the erythrocyte enzyme, ALA dehydratase, and the elevation of erythrocyte protoporphyrin—and which are typical of lead poisoning. In addition, it is known that there is a statistically significant reduction of the sodium/potassium activated adenosine triphosphatase (Na/K-ATPase) activity of erythrocyte membranes in lead poisoned workers (Secchi, Alessio and Cambiaghi, 1973). Another interesting effect of sub-clinical lead poisoning has been the ability of lead in experimental animals to increase the susceptibility to infection. In both rats and chicks lead has been shown to diminish resistance to bacterial endotoxins and in rats and primates it may even cause a massive sensitization to these agents. Koller and Kovacic (1974) have shown a decreased antibody formation in mice exposed to lead. These latter facts will undoubtedly provoke further investigation.

Prevention of environmental lead pollution

The air

The concentration of lead in the atmosphere which constitutes a long-term threat to health is yet to be established, but I would agree with Waldron and Stöfen (1974) that there is no justification in assuming that individuals are in fact in a state of lead balance since we have unequivocal evidence that the total body burden of lead rises with age, owing mainly to increasing skeletal deposition. Any further dissemination of lead into the environment from the inevitable increase of petrol fumes is bound to add to the body burden by exposure through the air and the diet. The evidence we already have about the metabolic effects in various organs of the body, particularly in the brain and in the young, is sufficient to allow us to say at this juncture that the lead exposure should be reduced to a minimum.

As regards the effects in water supplies, this of course is something which is already being dealt with in Glasgow at this juncture—removal of offending lead tanks containing drinking water; where this is not possible, the scaling of these and the coating with non-toxic materials; the abandonment of lead plumbing systems for drinking water. In Glasgow, too, the Corporation has also attempted to increase the hardness of water. Meredith, Moore and Goldberg (1974) have recently shown that calcium added to water will diminish the absorption of lead in experimental animals. In addition, there seems no doubt that it is imperative to decrease the risks of leaded paint to children. The whole subject of prevention of subclinical lead poisoning has become controversial and indeed obfuscated by frenetic overkill at both ends of the spectrum of controversy—on the one hand an exaggerated and overstated case of the dangers and on the other, a reactionary blindness to the possible dangers which are present. The truth might unfold somewhere between these two extremes.

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