

### THIRD REPORT ON THE INVESTIGATION OF LEAD POISONING.

An investigation of lead poisoning which has been in progress for the last three years at the Harvard Medical School is now being terminated. The funds for the investigation were donated by the National Lead Institute. It is very gratifying that this organization has not at any time offered suggestions as to any policy or point of view, but has allowed the work to run its course and to demonstrate the truth without regard for a possible economic effect upon the lead industries.

The staff engaged in studying the various problems has been as follows:- Dr. Joseph C. Aub, Dr. Lawrence T. Fairhall, Dr. Anne S. Minot, Dr. Paul Reznikoff, Dr. J. Albert Key, aided by Dr. John Brady, Dr. Herman Blumgart, Miss Dorothea E. Smith, Miss Charlotte Shaw, Miss Mary Morrison, and Mrs. Marion Frankfurter. Much benefit has also been obtained by consultations with many members of the faculty of the Harvard Medical School.

During these three years the problem of lead poisoning has been studied neither as an industrial hazard nor in the light of preventive medicine, but with the desire to understand more fully the chemistry, physiology, and clinical aspects of the disease itself. This point of view was taken because the other types of investigation have been carried out frequently in recent years, and do not permit careful scientific work. Any measures for preventing the deleterious effects of lead must be fundamentally dependent upon an under-

standing of its action in the organism if they are to be effective. We have, therefore, undertaken an investigation of the problems of the absorption, retention, and excretion of lead by the body and we have been able in this way to obtain a far clearer conception of how and why lead produces the clinical signs characteristic of lead poisoning and also of the conditions which control its excretion.

The following is a brief statement of the conclusions drawn from this work:-

Lead is absorbed from the gastro-intestinal tract, the lungs, the mucous membrane of the nose and mouth, and the subcutaneous tissues. Absorption from the respiratory tract is the most dangerous because most rapid and because it permits direct entrance of lead into the general circulation. Absorption by the gastro-intestinal tract is made less dangerous by the primary passage of lead through the portal circulation to the liver -- which catches much of the lead and excretes it in the bile. The rate of absorption from the alimentary canal is also reduced because of excretion of <sup>unabsorbed</sup> lead compounds in the feces. in the blood serum

Lead is transported <sup>as</sup> a highly dispersed lead phosphate, and is deposited in the tissues largely by adsorption of colloidal particles. This lead phosphate is most insoluble at the normal hydrogen ion concentration of the body, -- pH 7.4. When a solution is more acid or alkaline than this, the lead is dissolved to a greater amount.

During active absorption lead is present in many of the tissues of the body, for the most part in the bones, liver, kidneys, and gastro-intestinal tract, but after absorption ceases it becomes localized until nearly all is stored in the bones as a harmless deposit of tri-lead<sup>phosphate</sup>. If lead would stay permanently in the bones it would probably exercise no toxic action except that which occurred during absorption. It is not perfectly stable in the bones, however, because for a long time after exposure has ceased it may appear in the excreta. Occasionally certain abnormal conditions develop which apparently cause a sudden liberation and flood the organism with soluble lead. This may cause an acute attack of lead poisoning. Such late acute attacks are usually associated with acute infections, heavy drinking or unusual activities. It is therefore important to know just what are the mechanisms which liberate lead, in order to establish a logical treatment and prevent development of the active manifestations of the disease.

In making chemical and physiological studies it became evident that if the reaction (pH) of the body becomes more acid or alkaline than normal, the triple phosphate of lead becomes more soluble. We have therefore studied the effect of changing the hydrogen ion concentration of the body by the administration of a diet low in calcium with acids or acid-forming substances such as phosphoric acid or ammonium chloride. This causes loss of calcium from the bones. When tried on animals it was found to increase the lead excretion.

Ingested soda bicarbonate also increased the lead excretion,--probably by making the body so alkaline that the triple phosphate of lead is rendered soluble. These experiments illustrate how a change in the general metabolism of the body may suddenly liberate lead from the bones and have thus suggested a new treatment of plumbism which has been used on patients with success. This may be briefly outlined as follows:-

When lead is causing acute symptoms, in other words, when too much is circulating in the body, large quantities of calcium are given in order to favor deposition and prevent release of lead from the bones. This may be done by giving adequate quantities of milk. For lead colic active catharsis and atropine should also be given. After the acute symptoms have subsided elimination of the more easily mobilized lead may be accomplished in several ways,--the most satisfactory of which is to give a diet containing little calcium plus acid-forming substances. The diet consists of meat, potatoes, rice, macaroni, apples, bananas, sugar, salt butter, and bread made without milk. Milk, green vegetables or other fruits may not be included. With this eight to ten grams of ammonium chloride is given daily in water. By this treatment lead excretion is increased more than three times. Other methods which are not so effective but which do increase elimination of lead involve administration of large doses of soda bicarbonate or potassium iodide. Thus, by varying the diet and the medication control of lead metabolism is now possible.

A study of the mechanism underlying wrist drop is not completed, but the experiments so far all suggest that wrist drop is

produced by muscular fatigue and that the action of the lead is on muscle and not nerve.

We have also ~~ascertained the distribution of~~ lead in the bones of individuals who had, so far as they knew, not been exposed to lead in industry. It was present in only three of twenty-two cases. This indicates that the average individual does not retain lead under present conditions of life. The knowledge of distribution is important from the medico-legal point of view in regard to deaths ascribed to lead poisoning. If lead has been an important factor in causing death it should be distributed in many organs. If, however, it is present only in the bones, it signifies only that absorption has taken place, but that lead has not recently produced active intoxication or death.

Studies of the mechanism by which lead affects the body cells were made with red blood corpuscles and muscle. Its action on blood cells was carefully investigated, and the results partly checked by its action on muscle cells. The effect on red cells is to make them hard, brittle, and inelastic. They break up more rapidly than normal cells. This is the explanation of the high peripheral blood destruction in lead poisoning -- with the resulting anaemia. This is due to a reaction of the lead with the inorganic phosphate of the cell surface, which produces a change in permeability and elasticity with a resultant definite strain. In isolated muscles, this is demonstrated by an increased permeability.

to inorganic phosphates and by more rapid fatigue.

The following detailed reports of these investigations have been published, and they give a complete outline of the work done:-

Fairhall, L. T.: Lead Studies, I, The Estimation of Minute Amounts of Lead in Biological Material, J. Indust. Hyg. 4: 9-20 (May) 1922.

Minot, A. S.: Lead Studies, II, A Critical Note on the Electrolytic Determination of Lead in Biological Material, J. Biol. Chem. 55: 1-8 (Jan.) 1923.

Aub, J. C.; Reznikoff, Paul; and Smith, D. E.: Lead Studies, III, The Effects of Lead on Red Blood Cells, J. Exper. Med. 55: 151-208, 1924.

Key, J. A.: Lead Studies, IV, Blood Changes in Acute Lead Poisoning in Rabbits, Am. J. Physiol., to be published.

Minot, A. S.: Lead Studies, V, The Distribution of Lead in the organism in Acute and Chronic Lead Poisoning, J. Indust. Hyg. 6: 125-126, 137-143, 149-158 (Aug) 1924.

Blumgart, H. L.: Lead Studies, VI, The Absorption of Lead from the Nasopharynx, J. Indust. Hyg. 5: 153-158 (Sept.) 1923.

Fairhall, L. T.: Lead Studies, VII, The Phosphates of Lead Equilibrium in the System Lead Oxide-Phosphoric Anhydride-Water at 25 deg., J. Am. Chem. Soc. 46: 1593-1598 (July) 1924.

Fairhall, L. T.: Lead Studies, VIII, The Microchemical Detection of Lead, J. Biol. Chem. 57: 455-461 (Sept.) 1923.

Fairhall, L. T.: Lead Studies, IX, The Solubility of Various Lead Salts in Blood Serum, J. Biol. Chem. 60: 481-484 (July) 1924.

Fairhall, L. T., and Shaw, Charlotte: Lead Studies, X, The Deposition of Lead Salts in Bone Tissue, J. Indust. Hyg. 6: 159-168 (Aug) 1924.

Fairhall, L. T.: Lead Studies, XI, A Rapid Method of Analyzing Urine for Lead, J. Biol. Chem. 60: 485-488 (July) 1924.

Minot, A. S., and Aub, J. C.: Lead Studies, XII, The Mechanisms for Storage and Excretion of Lead, to be published.

Aub, J. C., and Minot, A. S.: Lead Studies, XIII, The Treatment of Lead Poisoning, to be published.

Reznikoff, Paul; and Aub, J. C.: Lead Studies, XIV, Experimental Studies in Lead Palsy, to be published.

Aub, J. C.; Minot, A. S.; L. Fairhall, L. T.; and Reznikoff, Paul: Lead Studies, XV, Recent Investigations of Absorption and Excretion of Lead in the Organism, J. of the A. M. A., 83, 588-591, (Aug. 23) 1924.

In addition to these there is still one report to be published, a monograph, which is now nearing completion. It is to appear in the medical journal entitled "Medicine" in the near future, and also as a monograph published by Williams and Wilkins of Baltimore. This study has

This study has thrown light on several new aspects of the action of lead on the body which should be of importance not only in understanding the action of lead itself but also that of other toxic substances.

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