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Dear Harriet:

Quite a period of time has elapsed since our exchange of correspondence in which I promised to write to you at some length and in greater clarity (I hope), concerning various aspects of the metabolism of lead and the therapy of lead poisoning.

First, with respect to the latter problem, let me say that the use of chelating agents of the type of sodium calcium EDTA in the therapy of lead poisoning (as opposed to its prophylactic use) is the best means we have of combatting the active disease. There is evidence, I believe, that it is beneficial, and if used properly, it is not harmful. I am not as enthusiastic about it as I might be, because it is not as good a remedy as we need. I have been particularly distressed by the fact that the severe cases of lead poisoning in childhood - those that threaten life at the time they come to us, are but little benefited. The duration of the illnesses of those that recover is shortened, and it appears that the incidence of serious sequelae is reduced, but the mortality appears to be little affected by anything short of drastic surgery. It is likely, it seems to me, that the fatal cases (encephalopathy) in children are the result of intracranial dynamics which are secondary, rather than primary, effects of toxemia induced by lead, but even so, these infants die, and if we had an agent that would combat the toxemia effectively, (and if we got at these children soon enough) they would survive, and be restored to normal health, i.e. without the serious sequelae that now occur with considerable frequency.

It is not that I am disinterested in combatting the distress of the persons poisoned in industry, but the fact is that those people, as a rule, when removed from exposure recover without theraphy, or do quite satisfactorily when treated to relieve their immediate symptoms. I am impressed (and intrigued as an investigator) by the reversal of their hematological

abnormalities. This is something important. I am also satisfied that we can remove the large portion of the lead in their blood and other soft tissues by appropriate therapy. However, the quantity of lead so removed, in cases of occupational plumbism, amounts to not more than 10 to 25 per cent of the body burden even after the most intense treatment. As such therapy is being administered generally (1 or 2 courses of intravenous therapy), it removes only a very small proportion of the body burden, and when the poor victims of this misunderstanding of the situation return to their work under the same conditions, they are right back where they were when they became ill, within a few weeks of further work. Consider, for example, the cases which you reported in JAMA in 1954. After 6 days of therapy (with 2 intervening days without therapy), your patient designated as Case I had eliminated 33.77 milligrams of lead in his urine. At this time, I would estimate that 10 to 25 per cent of the lead in his body was in the soft tissues, and that his body burden was not less than 1500 or more than 3500 milligrams. (I have only the concentration of lead in the urine, in the "control" period, to go on, rather than that in the blood, and therefore my estimate is fairly crude.) Assuming that there were 150 to 375 mg. of lead in the soft tissues, the concentration of lead therein was not greatly reduced by this much therapy. Regardless, therefore, of the symptomatic improvement that resulted from the therapy (from whatever beneficent mechanism) this was not much of a "deleading". Time can do much better, if it can be had.

This, of course, was my quarrel with the other alleged methods of deleading. Putting water through the body at an increased rate (as we have shown) will achieve quite as much increase in the excretion of lead as will the administration of ammonium chloride, or better, that of sodium citrate, while the administration or deprivation of either or both calcium and phosphorus has no demonstrable effect upon either the retention or the excretion of lead. Incidentally, there is simply no important relationship between the calcium and lead metabolism. They can and do go in opposite directions, dependent upon the rate of the absorption of lead (i.e. the exposure). It seems virtually certain that they compete with each other at the point of chemical reaction, rather than to go along together.

Moreover, as to the alimentary excretion of lead, there are no means of assessing its relative importance unless one carries out complete balance observations, i.e. unless one knows what enters the alimentary tract, he cannot, possibly, estimate the source of that evacuated in the feces. The amount ingested varies, under ordinary conditions from day to day, from something less than 0.1 mg. to more than 2.0 mg. per day, and one never knows, during short periods of time, whether it is on the high side or the low, unless he measures it.

It is just these things that we have undertaken to learn by long, elaborate and costly experiments on human subjects under a variety of controlled conditions. There is not the slightest reason, therefore, for doubt about some of the points I have made in my previous letter concerning the rates of absorption and excretion in the human subject, and concerning the relatively high variability of the output and concentration of lead in the urine in contrast with the stability of the concentration of lead in the blood. The blood is one of the soft tissues of the body, which binds lead, according to its own chemical composition, in a manner that relates it, at once, to the levels of concentration in the other parenchymatous organs and soft tissues of the body. The relationship of the soft tissues to the skeleton in this regard is somewhat of a problem, simply because the skeleton differs grossly in its various parts, with respect to its vascularity and the overall rate of its metabolism (with respect to its general metabolism and that, specifically, of lead, therein.* Whereas other organs and tissues are somewhat inhomogeneous in the metabolic sense, the vascular and avascular parts of the skeleton differ so much, that there is a large factor of time in the rate of loss of lead from various parts, as, for example, the dense, white shafts of the long bones, and the spongy, red bone at the ends. There is an overall big difference between the absorption and release of lead from the long bones of the skeleton as compared with the flat. Thus in the "normal" skeleton the concentration of lead is high (relatively) in the shafts of the long bones, and low (relatively) in the spongy, flat bones. The reverse is true following any period of relatively rapid absorption (occupational or other "abnormal" exposure). Because the pattern of the distribution of lead in the human body, under varying conditions, is now known to be fairly stable (variable only within modest limits under fairly well defined conditions), ** it is now possible to visualize the approximate limits of variability within the several organs and tissues, including the skeleton, from the concentration of lead in the blood of the (untreated) patient, if one takes into account the relative severity of the exposure and the time over which such exposure occurred. At present, it is possible to estimate the body burden only roughly. I anticipate that when we have had an opportunity to study our accumulated data from industr and non-occupational situations that we have investigated, we shall be able to write an equation in which all of the main variables can be introduced, through the clinical investigation of a patient, and through a somewhat more precise investigation of his history than that which is n w being made.

I am sending you, herewith, some largely unpublished information, which has been extracted for a specific purpose, from our data on children. This will illustrate some of what I

*And also because of its gross capacity for absorbing lead, and because of its great mass.

**See our data and those of Tipton, et al.

have said above. Other information, not as full as I would wish, is in the Harben Lectures, and in the publications of our experiments on the ingestion of lead, and the inhalation of lead, by human subjects. You will be struck, I believe, by the uniformity of the metabolic pattern from one subject to another. Since we have investigated, systematically, some twenty subjects (of variable physiological patterns, and of widely varying age and physical habitus), by this time, these observations can no longer be regarded as isolated bits of evidence. We have not, of course, investigated varieties of physical and physiological impairments. I expect to spend the next several years of my retirement from the Directorship of this Department, in studying the results of these experiments, on the background of our industrial experience.

I have not covered all of the points in your letter or my earlier one, but I cannot write a book on this subject at this time, and if I were to do so I would be imposing upon both your free time and mine. I will desist, therefore, with the promise to try, as soon as possible, to answer such questions as you may wish to raise. Do not get the idea that I have all the answers, or that I think they will be attainable. There are many mysteries in the mineral metabolism to uncover, not the least of which is the mechanism of action of lead in the internal milieu. I cannot, for the life of me, imagine what happens to lead in the body, when it is present in sufficient concentration to be harmful, to convert it from something inocuous to something decidedly harmful. When I see a man who appears to be entirely well today, and then see him some days later when he is acutely ill, and realize that he had almost exactly as much lead in the same organs and tissues on the two occasions, I realize that this comes about not from the "mobilization" of lead, or its shifting from one point to another, but from some intricate reaction within specific cells of the body, I am properly humble as to the skill of our penetration into the facts of life.

This reminds me, that Dr. C.C. Patterson, a geochemist, oceanographer (or whatever he is), who appears to be very knowledgeable and skillful in his own field, has suddenly become a biologist and physiologist, by act of his will. I remark because I saw a manuscript of his in which he reviewed all of the literature with which you supplied him, with blood in his eye toward lead, and, it seems, toward me and my associates and all of our works. I wonder what manner of man he may be. I'd like to meet and talk with him, but this seems not to be his way of going about those things. I am not suggesting that you contributed to my downfall in giving him every possible assistance, but sometime, when the dust blows over, I'd be interested in your view of the

man, that is, not the scientist, but the personality.

Sincerely yours,

Robert A. Kehoe, M.D.
Director

RAK:meh

Enclosures