July 5, 1955

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Dear Tom:

Thanks for your letter of the 24th and for the further information on the type of renal damage that is associated with the administration of suitable quantities of EDTA over sufficient periods of time. The cellular changes described would seem to me to be quite capable of induction by the removal of minute amounts of mineral substances from the cells, and I assume that some such thing does occur to some degree. Whatever the process may be, the observation is an interesting one.

In the matter of the retention of lead under a variety of conditions, and the total quantities which are associated with signs and symptoms of intoxication, we know a fair amount from both direct and indirect evidence. Some of this is in the literature and some (much in fact) is not. We have quite a number of fairly comprehensive data on necropsy material, especially on the tissues of children fatally poisoned by inorganic lead compounds; we have all that would be desired in fatal cases of tetraethyl lead poisoning in adults, and some (but only a scattering) on cases of inorganic lead poisoning in adults. The indirect information obtained in metabolic experiments is extensive. From these combined sources, estimates could be made that are fairly realistic. There are, however, two jokers in the situation, and one of these cannot be solved by the use of radioactive tracers. The one lies in the initial or normal or, if you wish, incidental, lead content of the tissues (principally the skeleton) of the child or the adult at the time one begins to make observations. The error of the estimation here is of the same order of magnitude (proportionally) as that of estimating the content of the individual who has been subjected to unusual exposure and is ill. The other joker is the factor of time. The amount retained without symptoms or danger of symptoms varies with the rate at which the absorption and retention occurs. One can introduce a relatively small quantity quickly and induce illness, but much larger quantities can be introduced slowly, and relatively large quantities retained, without illness. The explanations for these differences lie in at least two major phenomena, whatever may be their mechanisms:

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(1) Lead is removed from the plasma of the blood almost quantitatively by the erythrocyte, thereby lowering the concentration (presumably the effective concentration) in other soft tissues, at least temporarily; (2) Lead is removed from the soft tissues of the body generally by the skeleton, this being a sort of second-stage and slower operation than that of the erythrocytes. The lead taken into the skeleton moves slowly in some manner from a part of the skeleton from which it is readily lost to a part from which its escape is retarded (never stopped), or perhaps this is a matter of its being changed slowly into a less labile form of compound or structure. In any case, the matter of potential toxicity is a matter of the type of distribution in the body (including the skeleton) or of composition within the body (including the skeleton), as well as of quantity or, as you speak of it, of body burden. The skeleton is so large, and so relatively inactive (in the metabolic sense) that the total quantity of lead held in it in relatively inactive form may be quite variable from individual to individual, within certain limits. This is not true to anything like the extent that it was believed to be by Aub and his associates, since there is no such thing as really inert stored lead. There is always a rate of excretion which is determined in the final sense by the body burden, but the time factor involved in the storage necessitates the introduction of a moving variable into the equation by which one would calculate the burden from the rate of excretion. I feel sure that a careful study of the available data would provide us with a suitable equation, but this has not been done as yet. I hope to have a chance to do it, with the help of a mathematician, in the not too distant future. To give you some idea of the extent of the variability I might mention a few figures from memory. A child exposed to lead from only normal sources will have the concentration of about 1 milligram per 100 grams of fresh bone. A healthy child may have a concentration of from 1 to 3 or 4 milligrams of lead per 100 grams of fresh bone, this being from 75 to 80 per cent of the lead in the body. A fatally poisoned child may have from 10 to 40 milligrams per 100 grams of fresh bone, this again constituting 75 per cent or more of the lead in the body; or a child fatally poisoned by the ingestion of lead over the period of a few days only may have 3 or 4 milligrams of lead per 100 grams of fresh bone, and 50 per cent or less of the lead in the body in the skeleton. All of this concerns itself with inorganic lead. Despite these variables, however, given a fairly constant set of conditions in an industrial environment, a definite period of exposure, the data on the blood and urine of the individual from time to time over the period or an appreciable part of it, and the weight and height of the individual, the quantity of lead in the body can be estimated with reasonable accuracy, on the background of our industrial and metabolic (experimental) experience. It is quite certain that the metabolism of lead in the human organism is characterized by a remarkable degree

of stability. The mechanisms, therefore, are subject to but little interruption and variation, and if and when we have a bit more information on these mechanisms, the problem of determining the burden will be very simple. The entire range of actual quantities of which I've been speaking above (in the entire human body of the adult) extends from 130 milligrams or so, in the normal person, to 300 milligrams in the entirely healthy person who has taken in somewhat more than the usual (unavoidable) quantity of lead in his food and drink, up to 2500 or perhaps as much as 3000 milligrams in some of the more "heavily leaded" persons. Fatal poisoning may result when there are quantities of 1000 milligrams or less in the body, but considerably greater quantities (two or three times) may be found when the build-up is sufficiently gradual. I doubt if it ever goes much above the outside figure of 3000 milligrams, but one might devise conditions, perhaps, in which it would. I'll have to look over the data to see if I am correct in this, but I am not far off.

So much for this business, which I didn't intend to pursue when I started this.

Sincerely yours,

Robert A. Kehoe, M. D.

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C.C.: Mr. Manfred Bowditch