

September 4, 1964

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Dear Doctor Clayton:

I am pleased to have your letter of August 25, and I hasten to deal with the point of special concern as to the "levels of lead" (in the blood and tissues, associated with) "clinical evidence of toxicity." This is a matter that has continued to give rise to misunderstanding of the specific significance of the analytical findings in the urine, blood, spinal fluid, or other body fluids or tissues, including those obtained at necropsy. The fact, quite clearly, is that the concentration of lead in tissues or body fluids is not indicative of the existence of intoxication, but rather of the general level of the absorption of lead. These findings measure hazard but not illness, in as much as illness never (as so far observed) occurs unless the concentration of lead in the body has reached a certain level, but it does not necessarily occur when the potentially dangerous range has been reached. For one example, we have never seen a case of lead poisoning, at the onset of the illness, in a person whose blood contained less than 80 micrograms of lead per 100 grams (whole blood). On the other hand, we have seen persons without symptoms whose blood contained ten times this concentration. It is evident, from these facts, that there is some mechanism, presently unknown and not capable of being even postulated, whereby lead in the tissues (in the gross sense) in an essentially inert form is activated. I think of this as being chemically bound (un-ionized) and then coming into an ionized state, but there is no evidence that such is the case, and the matter may be quite complex. The phenomena of chelation fail, so far as I am concerned, to shed any very clear light on the problem.

From the point of view of diagnosis, therefore, the analytical results contribute only the conclusion that the lead content of the blood (or indirectly, the soft tissues) is either compatible or incompatible with the diagnosis of plumbism. In practice, it can be said, under appropriate conditions, that this is definitely not lead poisoning, or that it is compatible with the diagnosis of lead poisoning. The tendency of modern physicians and, of course, the non-physicians who are involved in diagnostic problems, is to employ the laboratory to furnish "scientific" proof of the nature of disease. This is at least one example of the fallacy of this type of thinking, for the diagnosis of lead poisoning is made on clinical grounds within the limits of the situation defined by the analytical findings. This is hard for many modern physicians to accept, but in your country, in which clinical medicine has been practiced for so long and so

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skillfully by so many keen observers, this should not pose too much of a problem.

You will note of course, that there is no difference between your definition of the "normal range" of the findings in the blood, urine or tissues. It is likely, however, that this range, as so defined, differs quantitatively in England and the U.S.A. We know fairly well the contribution made by various environmental factors in the U.S.A., and we have some, but not nearly enough, information about your environment, with respect to food, water and air. It is my tentative opinion that your environment differs significantly from ours, but there may not be enough difference to be of any practical consequence. So long, however, as it does not approach the level of danger, it makes very little difference clinically. I do not suppose, for a moment, that the physiological differences in the human population, will cut much of a figure in the outcome. (I am, of course, unable to appraise the nutritional situation within your juvenile population, and I am by no means certain of the facts within the varied economic levels of this population in the U.S.A. I would consider it likely, however, that this factor may play some part in the incidence of lead poisoning among children.)

One other feature of your letter seems to call for some emphasis in my reply. You may not have meant to do so, but your reference to the "possibility of lead poisoning..... in industry" seems to minimize, somewhat, the significance of this matter. It appears (on somewhat unsatisfactory statistical evidence) that lead poisoning is the most frequent type of intoxication that occurs in American industry. In any case, my experience of nearly forty years in relation to a broad spectrum of the lead trades in the U.S.A., enables me to have a fair idea of the situation. The most significant advance in preventive medicine in this series of industries during the past several decades has been the establishment of the threshold of the danger of lead intoxication in terms of the lead content of the blood and (somewhat less effectively) the urine. It is at this point which I had wished to emphasize in my letter to Sir Alan, since there is no question as to the fact that there is a sharp threshold. This is the precise reason that I objected to the statement, in the article, that the significance of the level of lead concentration in the blood is uncertain. There is, of course, the mathematical uncertainty, as between 80 micrograms of lead per 100 grams of whole blood and the analytical error of the analytical method which may be as little as $\pm$ 0.01 microgram, or as much as 0.05 microgram, dependent upon the specific method (among the good methods) employed by a competent analyst. However, there is no doubt as to the physiological fact that there is a well-defined threshold. (There may be, of course, highly unusual persons who do not fit the common pattern, but our thousands of observations over many years, under highly varied conditions, have established, as fact, the essential stability of the metabolism of lead in the human organism.)

I must get on with the mountain of work which has accumulated on my desk during a vacation which has ended just now. This brings me to terminate this discussion. My interest in your efforts, which will be evident to you,

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derive, in considerable part, from my hope that you and your associates will extend your work on this dread disease of childhood, so as to visualize clearly the environmental factors which affect it in Great Britain, and the means by which these factors can be brought under adequate control.

Sincerely yours,

RAK:vr

Robert A. Kehoe, M.D.

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