January 3, 1966

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Dear Doctor Williams:

I am pleased to answer (somewhat tardily) your letter of December 9, 1965. I have returned, only recently, from a mission of three months duration in Santiago, Chile, and my correspondence suffered appreciably during that time and since.

I should let you know, further, that I have retired, as of July 1st, from the direction of the Kettering Laboratory and the Department of the Medical College of which it is a part. My successor, Edward P. Radford, Jr., is now in charge, although, at this time, he is on leave fulfilling a commitment which he made before being appointed to this post. I shall continue here for a time with some experiments on the inhalation of lead compounds which have been carried on under my direct guidance for a number of years. I hope to find an understudy soon and to leave further experiments in good hands.

With respect to the threshold values, relating to the danger of intoxication with lead, whether of the urine or blood (the latter, for a number of physiological reasons is the more trustworthy of these two values), it should be said that these relate to the lowest level of concentration (in either fluid) at which lead poisoning has been found to occur within the somewhat selected populations of industry, that is, among male adults who are able to carry on their work. The question as to the precise numbers, excluding the margin of the analytical error, which is of the usual order of plus or minus 0.01 mg. (per liter of urine or per 100 grams of blood) for samples of the size usually obtained for analysis, is one of the sensitivity of the criterion to be satisfied. These which we have advocated depend upon the utter non-occurrence of any symptom or sign that may be identified by a physician of competence and experience as due to lead. (Thus when, for example, any interference with the synthesis of hemoglobin can be discerned, as an expression of the effects of the absorption of lead, we regard this as intoxication.) For preventive purposes it is inadvisable to wait for the classical clinical signs of plumbism. In short, in our experience, no industrial workmen has developed lead intoxication when his blood level (confirmed by multiple analyses) has remained <u>below</u> 0.08 mg. per 100 grams, while <u>at</u> this level an occasional case is found, and at levels progressively higher, the incidence of poisoning increases, as does also the severity of the poisoning.

This is not equivalent to saying that intoxication occurs, necessarily, above the threshold value, for there is <u>no level</u> of the concentration of lead in the

urine, blood, or tissues, individually or collectively, that signifies illness. The diagnosis of lead poisoning is made clinically, and not by analytical means. Just what it is that converts "inert" lead to toxic lead, in the body, is not known. (We have some working hypotheses, and some opinions, but no conclusions. I suspect that some biochemical factor releases intracellular lead from its chemical bonds and permits ionic lead to exert toxic effects, but there is no real evidence that such is the case.) Incidentally, Cantarow and Trumper, combined, knew very little about these matters. They reviewed the literature, and in my view misinterpreted (or underinterpreted) much of it, through unfamiliarity with either the clinical problems or their physiological background.

The application of the threshold value, as a principle, is made in industry, - and occasionally in general medical practice - as a means of recognizing danger and of avoiding it before it has taken effect. Its value as a diagnostic procedure is limited to the determination of whether, in the individual case, (at the right time, during or immediately after exposure) ~~is that of demonstration~~ [redacted] the patient has absorbed enough lead to be capable of inducing intoxication. This level was derived in a purely pragmatic manner, as being the lowest level of concentration that has been found in association with any form of (recognizable) lead intoxication. If we should come across some type of intoxication due to lead which has not, previously, been recognized as such by our best and most thorough clinicians, we might have to change the threshold downward.

I have spoken thus far of industrial exposure, but we have been able to extend this threshold to infants and young children. We have had a long and extensive experience in Cincinnati with lead poisoning in childhood. We have yet to see even one child with lead poisoning (at the onset of illness, i.e., in immediate temporal relationship to the actual exposure), whose blood has not contained at least 0.08 mg. of lead for 100 grams. Most of them have had much higher levels of concentration, and most of them have had a very severe (and relatively brief) exposure. (This is why I have taken exception - in a letter to the authors - to the statements in the article by Moncrieff and Clayton which appeared fairly recently in one of the British journals concerned with diseases of children - I shall not trouble to look it up and give the reference, since you have seen or heard of it no doubt. They have had neither the experience nor the analytical precision that would enable them to make some of their statements of fact without challenge.)

You ask for evidence in support of my statements, I am sending certain reprints that deal with this point, but I call your attention to the data cited on page 57 of the Harben lectures and the discussion on pages 58 and 59. The discussion is brief, indeed, but it is quite to the point. (I am planning now that I have been freed from my responsibilities for directing the affairs of the Kettering Laboratory, to spend the next few years in assembling, studying and publishing (in a monograph) the data of various types that have been collected during the past twelve or fifteen years.)

As to the relationship of the analytical data (concerning urine, blood and tissues) to the hematological findings, both histological and chemical, I must insist that

the extent of the alterations in the blood depends upon a variety of factors other than the absorption of lead. One cannot say that any analytical finding correlates with any abnormality, or with any degree of severity in the abnormality, in the blood. The question always arises - is this person, with unusual quantities of lead in his body, actually ill? If he has a reduction in his hemoglobin that can be attributed to the absorption of lead, he has lead poisoning. This is not a question of fact, but of degree. Moreover, if he has unusual quantities of porphyrins in his blood or urine, because of the presence of lead in his body, he has intoxication, since this, when due to lead, (not always easily determined, to be sure) is an interference with a physiological process. I am not splitting hairs; in my view, an interference with a physiological process is an expression of intoxication. For preventive purposes, I would not wait for colic, palsy or encephalopathy, but would get the endangered man out of exposure before he becomes ill. This is the meaning of the threshold point of danger. This is the means by which occupational plumbism is prevented. I stress the occupational situation, since here, ideally, we have the means of determining the status of the individual workman and the occupational group, whereas this is hardly ever possible in general medical practice.

Your other point, that the incidence of poisoning is low among workmen exposed to lead under fairly constant conditions, in contrast with that of persons subjected to brief periods of severe exposure, is well taken. There is a wealth of evidence that this is true, and indeed I have come to believe that the triggering mechanism of occupational lead poisoning is often, if not usually, a sudden significant increase in exposure. The evidence for this viewpoint is not as clearly defined as I would like, but there are bases in both physiology and clinical medicine for this opinion. However, I have made a practice of not advancing hypotheses in published articles, except in the most tentative manner. My reason for this is that the literature of lead poisoning is horribly cluttered with hypotheses which, because of their frequent repetition, have become cherished beliefs. When we began our investigations, in 1924, there was so much "authoritative opinion" and so little substance in the physiological approach to lead poisoning, that we began to look for facts, and to allow the explanations to come only when the facts were overwhelmingly weighted in their direction. I am still wedded, as an investigator, to this approach. When as a physician, I must accept responsibility for action, I put the facts together in the most favorable light in relation to human safety, or to put the matter in the opposite form, in the most unfavorable light with respect to human risk. I'd like, very much, to gain some better insight into the actual mechanism of the toxic effects of lead, but, for the present, I must be content with the description of an effect and the conditions under which it occurs. In this respect, the study of lead intoxication resembles, in its results, many other phenomena of nature, in that the more one knows, the more difficult becomes the ultimate interpretation of the facts.

I hope my lengthy letter will have acted toward the answer to some of your questions, rather than having added to your uncertainties. As you are aware, there is much to be done and learned, and perhaps the most useful posture is that of further open-minded observation.

Sincerely yours,

RAK:wp

Robert A. Kehoe, M.D.

P.S.: I should appreciate it if, in conveying the Season's greetings to yourself, I might count on your passing them along to my friends in the London School.

RAK