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Dear Doctor Chisolm:

I appreciate very much your letter of January 10, to which my reply has not been as prompt as I should wish, because of a profusion of matters that have had to be attended to on my return recently, from an assignment of three months in South America.

Your letter, plus the information in the report (which I had seen but was pleased to examine again), enable me to recognize the basis for your views with which I have no reason to disagree. The question which I raised had to do not with the clinical effects of infections in children only lately recovered from lead intoxication, nor with such biochemical effects as those associated with the porphyrin metabolism (even though these are linked, under ordinary circumstances with the over-all concentration of lead in the tissues, as revealed by the concentration in the blood). Rather, I was concerned to know whether you had found any evidence of a gross or even a considerable "mobilization" of lead from one tissue to another or from the skeleton into the soft tissues.

Primarily, my primary reason for this inquiry, was my concern about this possibility, which we have never been able to discover or demonstrate. Secondarily, I was somewhat piqued by the flat contradiction of a statement of mine at the recent symposium (or conference, or meeting or whatever you may call this somewhat abortive effort to cover this subject), by Harriet Hardy. I was quite sure that she had no evidence on which to base her remarks, but she cited you, in your absence, as authority on the matter. I had not so construed your remarks, and so I thought I should make sure of your meaning.

I have little doubt that infections may complicate the processes of convalescence from the quite serious effects of childhood plumbism. I have had little direct day by day experience at the bedside of sick children, but I've been privy to a great deal of clinical information that has been gathered by my associates in the Children's Hospital near at hand, for we have been following their cases analytically, and with exchanges of facts and opinions. One thing that happens, that is of considerable interest, is the following. After the initial clinical threat has subsided, and the initial high levels of lead concentration in the blood have subsided following chelation therapy, the concentration of lead in the blood of the child increases during a period of weeks or months (without further exposure to abnormal quantities of lead), and may return to a level not far below the original high level. This, almost certainly, I should say, is the result of the

removal of lead from the soft tissues to some considerable extent, under the influence of chelation (without any corresponding effect upon the lead in the skeleton). The lead in the skeleton, being then unduly high in proportion to that in the soft tissues, is redistributed to the latter to re-establish an equilibrium, therewith. At this time, the child is in grave danger of the recurrence of symptoms, although such recurrences are unlikely to be serious. (I do not say that serious illness has not occurred, for I have not had the means of being sure, but it has certainly not been frequent. The coproporphyrinuria has returned or increased, however. Now, if a child were to develop an acute infectious disease during such a period, I would certainly expect that his symptoms might well be mixed.

I should say, also that in my view, the combined mechanisms of an incomplete recovery from lead poisoning, and the additional toxic effect of other disease process, including infections are very likely to be much more subtle than that represented by gross changes in the distribution of lead in the body. I am increasingly concerned about the intra-cellular relationships. Let me give a crude representation of what I mean. I have examined groups of men who have been (and are being) subjected to exposure to, and absorption of, large quantities of lead (well above those regarded as safe) without finding anything indicative of toxic effect, despite the dangerously high levels of the concentration of lead in the urine and blood. Shortly thereafter, I have seen certain of these same men, without any apparent or significant change in these concentrations, in an agony of lead colic. I have also seen definite, localized, muscular involvement of the typical plumbic distribution in a stage merely of demonstrable weakness, without any evidence, otherwise, of illness. Suddenly, some of these men develop paralyses. These may not be related phenomena - that is, the man who is well one day and the victim of severe colic the next, on the one hand, and the man with weakness one day and palsy the next. But these represent, to me, the results of biochemical changes which convert bound (or at least, relatively inert) lead to ionic (or chemically active) lead. I am concerned to know how this occurs, and when anyone tries to tell me that this is due to changes in the gross distribution of lead in the body, I feel the need to remind him (or her) that there is no evidence that such gross changes occur. This is not because, I react very vigorously to differences of opinion or interpretation, but because such mistakes of fact or emphasis, tend to blind us and to prevent our search for the more subtle mechanisms of physiology.

In this connection I am not surprised to find that the relationship between the concentration of lead in the blood and that of the coproporphyrin in the urine (or blood) is disturbed somewhat during chelation therapy. The behavior of the porphyrins during this procedure is an interesting one. Since I do not understand the process in undisturbed (i.e., untreated) plumbism. I cannot interpret it during therapy, but I think it likely that the behavior under the latter circumstances may, with sufficient investigation, offer a clue to the former, and vice versa.

In any case, I am grateful for your letter and its information.

Cordially yours,

Robert A. Kehoe, M.D.

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