

February 13, 1959

Dr. Forrest E. Rieke
1313 N.W. 19th Avenue
Portland 9, Oregon

Dear Forrest:

I am sorry to have been so unresponsive to your correspondence, but I have been flooded with all kinds of correspondence for months, and in addition I've been trying to catch up with a great number of neglected duties while trying without success to keep my head above the daily current of entirely valid claims for my time. The result, so far as correspondence has been concerned, was inevitable, and you have noted it. I am in no better situation right now, but the uses of courtesy will not permit me to ignore your last note.

I went over your letter of December 8 when it arrived, but a suitable answer required a more or less detailed discussion, for which I couldn't take the time. No more can I do so now, so that I shall have to make statements which, without substantiation, may sound dogmatic.

With respect to mental deterioration in association with prolonged exposure to, and absorption of, abnormal quantities of lead. I have no such impression as you have. This has been referred to previously by other observers, but it does not fit in my experience. The only situation of which I am certain, in this regard, is that some small children who have suffered from well-defined lead encephalopathy (with greatly increased intracranial pressure and ~~care~~ escaped from fatal brain compression) have sustained permanent damage to the brain. I cannot say that your impression of your present patient or others, who have incurred grossly excessive exposure to lead, is incorrect, but I have not seen this phenomenon. It is true, of course, that I have not permitted such exposure to continue for longer than was required to bring it under control, when I had an opportunity to exert some influence, and so in recent years I have not had continuing situations of this type to study. On the other hand, I followed a group of heavily exposed persons years ago, and while the mentality of the group was low, I saw no evidence of advancing cerebral impairment. On theoretical grounds, I consider this outcome to be unlikely, but I cannot say that it does not occur.

Your second question cannot be answered from our data until I (or some

N 6264

0002320

February 13, 1959

other person in our group) find time to put the data together. It is my candid opinion that it is impossible to judge the level of lead absorption in the body of an individual on the basis of his response to EDTA. Certainly the best basis is that of studying the excretion and the concentration in the blood at a time when the individual, although ill (of lead intoxication or other disease) is being kept on a reasonably normal regimen and without any special therapy or any special effort to push fluids. The very principle of disturbing the metabolism of lead by means of a chelating agent, and then undertaking to interpret the response, in any but very broad terms, is at fault. It is simply bad physiology to expect to do this in view of what we know about the effects of the administration of EDTA.

I can tell you that the normal individual, with a normal lead metabolism and bodily content of lead, responds vigorously to the administration of EDTA, and that the individual with more than normal quantities of lead in his soft tissues responds even more vigorously. So much depends upon the precise situation in the body at the time of the administration of EDTA, however, that I would never count on any other than a very rough interpretation of the results obtained during therapy. I'm sorry, but the opinion of Harriet Hardy (of whom I think very highly as a person and as a clinician, but very disparagingly as a physiologist) on this matter of the significance of EDTA - induced lead excretion should not be taken seriously.

Your third question is answered largely, I believe, in certain of our publications. Unfortunately much of the mountain of evidence from industrial observations has gone unpublished. However, let me state the conditions which influence the rate of loss of lead from the body and the duration of high levels of excretion following the discontinuance of exposure. The best evidence here may be found in our experiments on the ingestion of lead by human subjects, but one of our earliest publications illustrates the prolonged maintenance of a high level of excretion. (Read the article on "Lead Absorption and Excretion in Relation to the Diagnosis of Lead Poisoning" in J I H, XV, 320-340 (see especially Figs. 3, 4, 5, 6, 7, 8 and 9). The article immediately preceding that cited above, in the same journal, will give you the kind of urinary results that can be obtained in industry under varying conditions of exposure, with respect to severity. We have reams of unpublished data of the same general type.

But to return to the statement of the principles:- The duration of the period of excessive (abnormal) loss of lead from the body after the cessation of exposure, varies (1) according to the quantities of lead retained in the body during the entire period of excessive (abnormal) exposure, and (2) according to the length of time during which this abnormal absorption occurred. In general, a rule of thumb can be stated to the effect that it will take twice as long (or more perhaps) to get the lead out of the body (most of it, of course, is in the skeleton) as was involved in getting it retained therein.

VF

0002221

Dr. Forrest E. Rieke - (3) - February 13, 1959

Incidentally, the skeletal lead is not reduced directly by the use of EDTA, but only by disturbing the equilibrium between the skeleton and the soft tissues, (when the lead in the soft tissues has been greatly diminished by EDTA, the flow of lead from the skeleton into the soft tissues is increased). Not infrequently the lead in the soft tissues (including the blood) returns very nearly to its previous levels following the discontinuance of the EDTA therapy. Consequently, we repeat courses of therapy intermittently (with an interval of at least three weeks before the second or third course is instituted) if the blood lead goes up into the dangerous range again, and we continue so until it remains down within the safe range.

Incidentally you mention the fact that you seem not to be able to obtain reliable analytical results on the blood. I must caution you that if this is true, you hardly dare trust the results on the urine. I would say that the analyst who cannot do both equally well is not competent to do either. In fact I could not fail to cast a dubious eye on the analytical results which you cited. Certainly it is that nothing short of substantially precise (i.e. absolutely precise) analytical results can be trusted at all. This has been such a tremendous difficulty in almost all parts of the country, and unfortunately there are only a few laboratories that can be trusted either for the suitability of the samples they obtain or for the accuracy of their analytical results.

I think I should make one other general comment. In the course of thirty years of experience and of careful investigation of cases of lead poisoning by myself and my associates, I have been compelled to conclude that the manifestations of lead poisoning in the adult, particularly, are comparatively few and relatively distinct in type and character. The bizarre cases of our time and of the earlier literature are generally those that have been unsubstantiated by adequate evidence and rendered doubly dubious by incomplete clinical and physiologic study. I am convinced that the one time accepted "protean manifestations of lead intoxication" are an expression of inadequate methods of differential diagnosis, and of an almost superstitious attitude toward this "insidious poison". I do not mean by this that there are not toxic mechanisms which we fail to understand fully. I do mean that we tend too much to attribute all manner of abnormalities which occur in association with lead absorption to the toxic effects of lead, forgetting that the worker in the lead trades is attacked by all the diseases to which flesh is heir.

I have done just what I feared I would do, and hadn't time to do, but I do not regret it. It is always a pleasure to talk to you, and if you had dropped in on me I would (as would you also) have stopped what I was doing to talk to you.

Best regards to yourself and your charming wife.

Sincerely,

Robert A. Kehoe, M.D.