C (CORRESPONDENCE)

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Dear Doctor Chisolm:

There are certain statements in the article which you sent me with which I am not in agreement, certain others of which I am in doubt, and certain others about which I wish to raise questions. These are not of earthshaking importance, and I shall refer to them later. The principal matters come first and I should like to state my viewpoints on them and the reasons behind them.

First let me say that, in the course of preparing a monograph on lead, I have set myself the task of reviewing carefully the literature of this subject - the older and newer clinical reports, and the later interpretations that have come out of recent analytical and biochemical work. I have not had an opportunity, yet, to do so. I cannot comment on work I am not familiar with, and therefore I may be a bit behind in my awareness of the evidence. We are now in a period in which this is a bit hazardous, considering the work that is being done, and it is no time to be dogmatic. However, I shall state my views and to the extent that they are erroneous or incomplete, I shall be prepared to retract or expand them on suitable evidence.

Of first importance to me is the attempt to find means of visualizing the distribution of lead in the intact (living) person, whether he is ill or apparently well. In my experience, the best of all ways to set the stage for doing this is to make sure that the distribution of lead in the body is disturbed as little as possible, during a period in which the intake and absorption of lead are kept under control, preferably at the usual (otherwise spoken of as normal, in the sense of arising out of the general prevalent environment); that is, the patient has been removed, entirely, from his abnormal source of exposure, is not treated in any way until samples of blood and urine have been obtained. This, of course, does not mean that therapy need be or should be delayed, if it seems urgently required, but certainly blood can be obtained for analysis, and a spot specimen of urine can usually be obtained. (I shall say something about this vis-a-vis the 24-hour specimen later, but what one wishes to determine is whether the urinary concentration of lead is in general keeping with the concentration in the blood, in evidence of the functional integrity of the excretory apparatus.

I do not consider the "provocative test" with a chelating agent to be appropriate, for the simple reason that it distorts the distribution of lead in the body, and renders it impossible to determine its pattern. I do not believe that anyone can interpret the meaning of such a test, for despite the fact that the response is usually related to the dosage of the chelating agent, it has no

meaning as to the source of the lead that is chelated. With the exception of the period that follows shortly after the removal of much of the lead from the soft tissues, something like 15 to 20 percent of the lead in the body may be in the soft tissues. This amounts in the average "normal" adult to [illegible] milligrams. One is not likely to get this entire amount out of the body in any one course of chelation therapy. The quantity will be several times this amount in the person with even a moderately elevated body burden, and, in the quantitative sense, the body burden will be revealed more definitively by the concentration of lead in the blood than by the amount removed from the body in the urine. The latter, in our experience is much too variable to be interpreted with a reasonable degree of precision. I think we are being deceived here by an empirical "rule of thumb" that has no physiological meaning. Now it is possible that there is something in the mechanisms of chelation that I understand much less completely than some of my colleagues, but I have been totally unable to find any rationale in this procedure, and I have no faith in it whatever.

The idea behind your use of B.A.L. (or some other agent that releases the lead from the erythrocytes), in concert with disodium-calcium edathamil, is an entirely reasonable one. So far as I know, B.A.L. is the only agent that does this effectively, (how about penacillamine?) and it is entirely possible that the brevity of its action (about 8 hours following a single injection of B.A.L.) can be combatted in some manner that will maintain the effect for a longer period. I have not thought much of the usefulness of B.A.L., alone, for this purpose, because of the slender quantitative effect. The removal of a few milligrams of lead from the body, when there are several hundred milligrams to be removed, does not strike me as being very significant - unless, of course, one can remove it from some vital site. Is there any evidence that such can be done? Incidentally, I had hoped that a thiol of lesser toxicity than B.A.L., might be made available to us, so that a more prolonged effect could be achieved through repetitive dosage. If one could release the lead in the blood, remove it from the body, allow the blood to pick up more lead from the tissues and remove it again and again, we might accomplish the "deleading" much more rapidly and effectively.

Returning to the consideration of the blood as a soft tissue that reveals the general order of magnitude of the lead content of the body, because it partakes in the distribution of lead according to a pattern which appears to be very characteristic (unless it is disturbed by chelation), I believe we shall be able, through the careful study of our metabolic data, to write a formula in which the time factor, (the length of the abnormal exposure, and the actual time of its beginning and ending in relation to the time of analysing the blood), is given its proper weight, and the body burden can then be calculated. I believe this, because, in our experience, the metabolism of lead in the body is remarkably stable in its pattern. In this connection you have considered the relative abundance of the erythrocytes, as indicated by the hematocrit, to be an important factor in the concentration of lead in the blood. I cannot say flatly that this is not the case, but I'd like very much to see the evidence for it. I doubt the truth of the statement, for the reason that the erythrocytes have a very large capacity for binding lead. There must, of course, be some kind of equilibrium between the erythrocytes and the plasma, but the avidity of the erythrocytic binding of lead is so great that the concentration of lead in the plasma is always very low, so low, in fact, that it is difficult to find differences in the

concentration of lead in the plasma between samples of blood that are very high in lead and those that are very low. That is, the total range of the quantities of lead in the plasma are within the range of the analytical deviation. (Some more recent methods of analysis may overcome this hurdle. At least, I hope they will.)

Here also - that is, as to analytical precision - something needs to be said. You seem to have been impressed by the significance of the findings referred to by Moncrieff and his associates. I have no doubt as to the clinical abilities of this group, but I think they went far beyond their competence in interpreting their analytical results. Their ideas are naive and their analytical procedures leave something to be desired. I have corresponded with them, but without any meeting of the minds. There is no depth of understanding, and no appreciation of quantitative relationships in their approach. Or so it seems to me. It is necessary to bring a severe analytical critique to bear on results within the range of values with which they dealt. I do not take, too seriously, from that source, the suggestion that clinical lead poisoning occurs or recurs in association with levels of lead concentration in the blood of 0.05 mg. (50 micrograms) per 100 grams of blood. It is true that evidences of lead poisoning continue to be found in persons whose blood lead concentration has subsided, but I have never seen the onset of symptoms at a level under 80 micrograms, and I have never seen symptoms recur after they and the hematological signs have disappeared completely, when the blood has fallen to and remains at such low level as 50, 60 or 70 micrograms (checked for accuracy) per 100 grams of blood. I shall, of course, be convinced if and when we obtain such findings, or if there are such results from experienced and reliable analysts (who know the limitations of the methods which they use). Most of our clinical colleagues do not know that the error of the dithizone method at best is of the order of ±10 micrograms in the normal range of findings.

I now return to the question which I raised with you in my earlier letter. You have stated in this article that significant amounts of lead are (or may be) mobilized from the skeleton by, or as you have put it, in association with, acute infections in children. I have never seen this phenomenon in the adult, even under the influence of serious infections and intoxication, and while this need not apply to the child, I'd like to see the evidence that it does not. Is it possible that you are assuming that this is the case because of clinical rather than analytical findings? Please do not think that I am denying, by implication, the truth of your statement. My question is, rather, a straight forward one. In line with this question, you have also said that the rate of turnover of bone in children differs from that in the adult. This seems probable, and if so it may result in differences in the "mobilization" of lead - I should say in the metabolism of bone, generally, and in most of its constituents - but here again, I'd like to be better informed as to the evidence, and as to the extent of the difference.

With respect to the means of determining the average or general rate of the urinary excretion of lead. I should like to take exception to the idea that the collection and analysis of a 24-hour specimen is the answer to this problem. I don't think Byers is any authority on this matter. The variability of the process is considerable and several days of observation are necessary for this purpose, if one wishes to be precise. Some compromise or approximation is necessary, and I should prefer, for very practical reasons,

to have several spot samples, collected directly into a satisfactory container under direct observation, to ensure that no contamination occurs. The latter is the chief obstacle to precision, especially in the case of the child, for the use of catheters, or other special equipment, is fraught with the very great likelihood of contamination. The problem is not insurmountable but extremely difficult, and only a few people are aware of the difficulties. This is the principal reason for turning to the blood for trustworthy results.

As to the renal damage associated with acute intoxication by lead in the child, we have observed the phenomenon, not infrequently, of a very sick child with a high concentration of lead in the blood, and a very low concentration and output of lead in the urine; if and when such a child survives and begins to recover, we have seen the urinary excretion of lead increase and eventually reach a level compatible with the concentration in the blood. This fits the tubular injury that has been described at times. What disturbs me is that this type of functional effect is the only type I have seen. I distrust the alleged evidence of fibrotic and vascular renal damage that has been attributed to lead, even in the Queensland children. This has been in controversy for a long time, and the evidence is not convincing to me or to many others, including some of the excellent clinicians there. The controversy occupied a lot of space in the Australian Medical Journal, and was not resolved satisfactorily. Here again, I am being a bit stubborn perhaps, but, while I respect the views of my colleagues, I am unconvinced.

There is one point in your article, a minor one in most minds, but a significant one to me since we are now concerned about the total incidental exposure to lead of the general population. The dietary intake of lead of the "normal" person in our population is not 0.5 to 1.0 mg. per day, but is considerably less, the mean value, for a large number of individuals, being of the order of 0.30 mg. per day. (It may be as low as 0.12 mg. per day in a person who eats sparingly.) The difference is important, since somewhere near 0.5 is just about the maximum that would be safe, under present conditions with respect to airborne lead, while an intake of 1 mg. per day is potentially dangerous, if our interpretation of our balance experiments is correct. At this level of daily intake, the body burden would probably reach a dangerous level in from 8 to 10 years (for under these conditions, accumulation occurs in the body at a steady rate, indefinitely).

You may believe that I am finding a great deal to criticize in your paper. But this is not the case. It is an excellent and thought-provoking paper. What I am doing is deliberately picking out all or almost all points that can be questioned, as I would if we were to sit down together and exchange ideas with complete frankness. The written word always sounds more severe in its implications, because there is not the opportunity for exchange. I hope you will reply both to my criticisms and my questions in the same spirit.

With best regards,

Sincerely,

Robert A. Kehoe, M.D.

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Dictated but not read