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IN REPLY REFER TO:

March 29, 1966

Dr. Robert A. Kehoe
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Dear Dr. Kehoe:

Many thanks for your thought-provoking letter of February 23rd. I shall try to answer it point by point where I can. My experience with urine lead determinations is limited to very young children in whom we have found the results so variable that they are impossible to correlate with other parameters of the disease measured at the same time.

With regard to the EDTA Mobilization Test, I am in general agreement with you in the sense that I believe much more evidence is needed before we can assess its real value. Since the calcium disodium salt of EDTA presumably does not directly remove lead from brain, red blood cells or bone it seems likely that the mobilization test measures lead from soft tissues only. Even so, I know of no data which excludes the possibility that the lead measured in the urine by this test is mainly that removed from the kidney. I had hoped that the provactive test might be helpful when the blood lead lines are between 40 and 80µg because in this area δ-aminolevulinic acid studies and urinary coproporphyrin values have tended to be quite variable in young children. This is a point on which we are trying to accumulate some evidence, but have not sufficient data as yet.

I am enclosing some photocopies of slides that I used in my presentation on the combined use of BAL and EDTA in acute lead encephalopathy. This data is, as yet, not published. I hope to prepare the manuscript within the next few months. As you can see the combined therapy seems to change the urinary excretion pattern of lead, in that the first day's excretion represents 35 to 40% of the 5-day total. Also, studies of kidney function, including endogenous creatinine, phosphate and amino acid clearances in these patients indicate that there is no temporary increase in renal disfunction during combined BAL-EDTA administration. In addition, I am enclosing a photocopy of some slides showing our recent experience with long-term oral use of penicillamine. This appears to be feasible and we plan to undertake formal

studies to determine whether penicillamine used in this fashion accelerates the "deleading" of the body more rapidly than normal processes might. To date we have used it in 7 patients for 6 months or longer and there appears to be no significant toxicity.

If you are able to develop a formula for assessing total body burden of lead from serial blood determinations, I should be most interested.

I think that the hematocrit is important in assessing blood lead concentration, particularly in sickle cell patients. I say this because we have given two patients with hematocrits of 10 to 12% blood transfusions sufficient to double their hematocrit; coincident with this we have doubled the blood lead concentration. However, the blood leads were low in these patients (approximately 25µg% before transfusion and 50µg% afterwards); so that one might question the significance of the analytical data.

I have also noted, following treatment, a rise in blood lead concentration which parallels the rise in hematocrit when these children are treated with iron for their coincident iron deficiency anemia. In children recovering from acute lead poisoning and protected from exposure the parallel rise in blood lead concentration and hematocrit continues for about 3 months. Thereafter, hematocrit may continue to rise and blood lead begins slowly to fall. This we see only in very young children and it is presumably the result of the associated iron deficiency anemia which is often quite severe, with hemoglobins of 6gms or less, and hematocrits of 20 to 25. I have also studied at least one child with severe cyanotic congenital heart disease and grossly elevated hematocrit who had a blood lead of 89µg/100 gm whole blood but no symptoms, no lead line, no evidence of kidney injury and no increase in urine coproporphyrin output. These are my reasons for thinking that extreme deviations of hematocrit must be taken into account in assessing blood lead concentrations. I am assuming that in the relatively steady state there is an equilibrium between bone, blood and other soft tissues.

With regard to Moncrieff's report, I am impressed only on a clinical basis. He has drawn attention to the fact that lead intoxication may appear when mental retardation and behavior disturbance are the only clinical manifestations. I believe the pediatricians' attention needs to be drawn to these presentations in view of the fact that so much emphasis is placed upon acute lead encephalopathy. As to his statement that blood leads above 40µg/100 gms of blood are abnormal, I cannot agree with this and do not think he has any evidence to support such a statement. With regard to the occurrence of symptoms with blood lead concentrations less than 80µg I may say this: I have seen symptoms in children with sickle cell disease. We recently had such a child who had severe lead neuritis with very painful tender muscles. The pain and tenderness responded dramatically within 12 to 24 hours following the administration of chelating agents. I have also seen children with positive spinal fluid findings, recurrent convulsions and evidence of pre-existing brain damage in whom the symptoms appeared at a time when blood lead concentration was between 70 and 80µg. Again this is a clinical observation and one cannot, of course, rule out an oassociated viral infection.

With regard to the mobilization of lead from the skeleton by infections, here again you are correct in the sense that I have no direct data on this point. I will say that we

have serial porphyrin and levulinic acid determinations in urine which show rises in the presence of infection. This, of course, could be due to increased toxic effect of lead already in the soft tissues as a result of the increased metabolic rate caused by the infection, nevertheless it is not unreasonable to assume that lead may be mobilized from the skeleton because the occurrence of growth arrest lines in association with prolonged infections has long been recognized in the bones of young growing children. Studies in rachetic infants show that new bone is not deposited until infection is brought under control. My assumption is that bone disillusion continues with the release of lead. In the well child this would be immediately redeposited with new bone, but in the ill child this does not occur. Unfortunately, I doubt if we are likely to get any clinical evidence on this point because we treat infections in leaded children so vigorously. I can only say from the clinical point of view that the only symptomatic cases of lead intoxication we see during the winter months are those occurring in association with chronic infection.

With regard to renal injury in lead intoxication in the child, the only thing I have seen is the transitory occurrence of the Fanconi Syndrome. We are at present calling back a group of children 10 to 15 years after their initial attack of lead poisoning and hope at the completion of this study to be in a much better position to comment upon chronic renal injury resulting from early childhood lead intoxication. I believe we can only speculate about the Queensland children although I find the experimental production of vascular lesions in rats most provocative. I am most grateful to you for your comment on the dietary intake of lead. My apologies if I have misquoted you. Thank you for pointing out the assumptions that I have made. I hope in a long-term study of childhood lead intoxication to be able to obtain data which can clarify some of the points raised in our recent correspondence. I do hope you will write again if there are further points that you wish to raise.

Sincerely yours,

J. Julian Chisolm, Jr., M. D.

JJC:jb

Enclosure