

July 19, 1943

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Dr. Seymour S. Kety,
Massachusetts General Hospital,
Boston, Massachusetts.

My dear Doctor Kety:

It seems the better part of courtesy to direct to you certain critical comments concerning your articles on the therapy of lead poisoning (Am. J. Med. Sci. 205 and J. Pharm. and Exp. Therap. 77), rather than to have them come to you at second hand. Moreover, if in this way ~~as~~ I suggest that there is need of modification in your experimental technique, I trust I shall not embarrass you. In any case, I shall speak freely and pointedly.

First, with respect to the diminution in the lead concentration in the blood following citrate therapy, I should like to be convinced, but I am not. It may be that the results obtained in the control period were indicative of the facts as they exist without therapy, but I beg leave to doubt it. From a wealth of observations on patients with varied types and degrees of exposure, it can be stated as a generalization that the speed of decrease of the lead concentration in the blood of untreated patients varies considerably with the rate at which lead absorption has occurred during exposure, and with the duration of the exposure. There is a very well defined tendency for the occurrence of some decrease as soon as exposure and excessive absorption come to an end. In some cases it is precipitate, in others gradual. For this reason your data on patients before treatment are unconvincing. There were not enough control observations for purposes of adequate comparison. Moreover, the control periods of observation were brief, - too brief in my opinion, to promote any valid prediction as to what would occur subsequently. There should have been at least a few cases carried without treatment so as to establish the base line for comparison. We have such information, and on the whole, it is not unlike that obtained in your observations following therapy. I hope, and rather suspect, that the decrease in your cases was more rapid in relation to the over-all quantities of lead available for excretion from the tissues, but that remains to be proved.

Second, I am both surprised and sorry that you considered it

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unnecessary to determine the lead intake in the food and drink of these patients as a means of balancing intake and output in the feces. You must be familiar with our work on this phase of the problem. If anything at all is clear on this subject, it is the fact that the lead intake from day to day is highly variable as an expression of daily variation in both quantity and quality of food. The magnitude and the variability of this factor in your observations cannot be guessed within even approximate limits. Elsewhere you stated that the patients improved under the therapy. If so, they probably ate more in quantity and more variably, and if they did, their lead intake increased considerably during the period of therapy. The lack of control here is a gross and fundamental experimental fault. Without such control you are not at liberty to arrive at any conclusion whatever, with regard to the fecal lead excretion. There is very good experimental evidence to indicate that it is usually slight. It may have been negligible. The data on the feces, in short, are wholly worthless in connection with the question you were seeking to answer, and to deal with them statistically is to treat them with a respect they do not deserve. There are just two factors that greatly influence the fecal lead content, - (1) the magnitude of the lead swallowed with the food and otherwise during the corresponding physiologically speaking) period of alimantation, and (2) the rate of the alimetary emptying time - if it is short, there is only a very slight discrepancy between that swallowed and that evacuated. The actual excretion of lead into the intestive byway of the bile or otherwise, is too small, as a general thing in short-term observations, to be detected in the presence of the factor of lead ingestion. If you doubt this, examine our data in the two last articles on lead ingestion. (J.I.H. 22: and 25)

In connection with the fecal lead, I pass over the dubious technical procedure of analysing feces by taking aliquots. Presumably you have proved that this can be done by carrying out parallel observations on the aliquots and the remainder. In view of the difficulties you should have presented the evidence. In any case, I doubt the wisdom of such a procedure in dealing with a material so lacking in homogeneity, and by methods that involve danger of contaminating the sample.

The exclusion of the data on the feces, which in my opinion must be done, allows your case to rest upon the urinary data. Here, by your own admission it is weak. But it is even weaker than you have indicated, since no data are given on the urinary volume for the respective periods. It has been demonstrated that an

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increase in the urinary volume brought about by any means, results generally in an increase in the gross urinary lead output. I think I need not cite the evidence. If there were appreciable variations in the urinary volume during these periods, they must be taken into account. My guess is, that when they are so considered the differences between the two periods will be negligible. I hope I am wrong, but the guess is based on rather broad experience with a number of other unsuccessful therapeutic attempts to influence the rate of urinary lead excretion. There is, in fact, no evidence of the usefulness of any specific therapeutic procedure in this direction. Therefore, it behooves any experimentalist who works in this field to use critically considered technique for the study of this problem if he is to escape the errors of the past and the severe criticism of his colleagues.

It may be, of course, that you have data with which to rebut my criticisms, and that you have abbreviated your articles to satisfy editors. If this is the case, I should be glad to be corrected. Unfortunately, however, I have had to rely upon the published material, and in this somewhat confused field it is not possible to accept anything on faith.

With best wishes, and with sincere regret at the necessity of being critical of your work, I am

Cordially yours,

Robert A. Kehoe, M. D.

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