

March 17, 1952

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Dear Doctor Richards:

I realize the dilemma in which you are placed by my statements in the matter of "de-leading," and I should have made my position a little more clear. Unfortunately, that cannot be done without considerable discussion, and it cannot be substantiated without the proof that I have not had the time to put together. It is part and parcel of the confusion of this situation which has been created by casual observers and investigators who have not recognized the problem presented by physiological variability as it relates to the lead metabolism at normal and abnormal levels of absorption. What I have said is based on the fact that the variation described in response to specific therapy, with the exception of BAL, has been within the range of physiological variability, and could have been observed without any therapy at all.

The original data of Aub and his associates on this subject related to the alimentary excretion of lead, and not to blood levels or urinary excretion of lead. These data must be discarded as essentially irrelevant, since the lead in the feces is predominantly ingested lead. The latter must be carefully controlled to validate any conclusion drawn with reference to lead excretion, and since this was not done, the conclusions are invalid. This is being brief and flat, but since we have published adequate evidence on this point, I would not argue the point.

The articles by others have also been reviewed by us, and the experiments, with but few exceptions, can be dismissed as unsatisfactory. Those not as easily dismissed fail to adduce conclusive evidence, since the authors were willing to accept minor changes in the rate of urinary excretion or in blood levels as evidence of the effect sought. The following criticisms cover these observations, and invalidate the conclusions:

1. The experiments were not adequately controlled. Either the observer failed to observe the facts under conditions unassociated with therapy, either before or after therapy, or in parallel observations on untreated patients. For example, Seymour Kety failed to observe the normal rates of diminution in the blood levels of patients with variable exposure, and interpreted the decrease in their blood levels (incorrectly) as being an expression of "de-leading" under the influence of citrate. Actually his rates of decrease

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correspond to those which are commonly associated with discontinuance of exposure. Such rates vary considerably with the severity and especially the duration of the lead exposure.

2. The observations were not made long enough or carefully enough to portray the spontaneous variability of the urinary lead excretion from hour to hour or from day to day or week to week. Our long term and numerous observations have revealed the pattern and scope of such variability and demonstrate that what has been described is to be expected without therapy. If, therefore, one ignores the instances in which apparent decrease in excretion have followed therapy, he will conclude, incorrectly, that the increases resulted from the therapy.

3. The analytical methods have not been carried out with such rigidity of control and interpretation as to be reliable. Generally investigators do not appreciate the very great difficulties here, and few of them have provided evidence of the actual size of their analytical error, or whether it is irregular or systematic in one of the other direction.

4. Urinary results have been accepted as evidence of specific deleading when they were the result of diuresis alone. The effect can often (not always) be seen to be proportional to the degree of diuresis. This is practically always true in response to the first course of ammonium chloride administered. Thus one always has to relate the lead output to the water output, since we showed, years ago, that increase in water intake (and output) almost always increases the output of lead in unit time. Such effects are small, generally, but investigators have been well satisfied with small responses. Incidentally, the more lead there is in the body, the greater is the variability in the excretory results from day to day.

This is by no means the entire story, but it will give you enough of it to realize that the investigation of this matter under any other than the most carefully established conditions is fraught with great difficulties and the certainty of error. Most of the investigators have been willing to publish a few observations and to draw hasty conclusions, because they have not had enough experience to know better. We have learned to be very cautious. We have studied large numbers of patients and experimental subjects, have carried out thousands of analyses, (something like 8 to 10 thousand per year for 15 years), have been most meticulous in the checking of analytical data by means of parallel methods and repeated analyses, and have published only what we were certain we would not have to retract. I must acknowledge that we have been unduly slow in our publications.

I trust this will convey my viewpoint.

Sincerely yours,

Robert A. Kehoe, M. D.