March 24, 1944

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Dr. Seymour S. Kety,
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Dear Dr. Kety:

I am afraid I have been guilty of a considerable tardiness in replying to your letter of September 20, 1943. Unhappily it arrived just a few days after I left for what turned out to be an extended trip outside the United States. Since my return some weeks ago I have had no opportunity to do anything that was not most urgently forced upon me, and therefore my correspondence has had to lie dormant. I cannot pretend that I have had the time to study carefully everything you have said in relation to my former letter to you. The purpose of this letter, therefore, is to convey my appreciation of the spirit of your reply and to make some additional comments.

May I say first that I consider your criticism of the reference to your work contained in the article by Bambach, Kehoe and Logan as well taken. I think it is fair to say that there was no intention in that article to take exception to the work itself. Our feeling was that its practical importance was not too great in view of the character of partition of lead between cells and plasma. However, I agree that this is not the proper way to look at the significance of your work.

With respect to the matter of lead in the food, I am afraid I cannot agree so readily. It really does not matter why any set of data fail to prove a point. The only important thing is whether they do or do not. We have been studying the total lead intake and output of a number of experimental subjects over a period of years, not for fanciful reasons but rather because we found some time ago that it was absolutely necessary to do so in order to control certain variables that could not otherwise be controlled or even anticipated. I believe we have established on an incontrovertible basis that this must be done in order to determine the facts with respect to the alimentary lead excretion. There are a number of problems in the general field of the mineral metabolism that cannot be handled on any other basis than that of a balanced study. That of lead excretion is one such problem. In view of the huge mass of evidence obtained by methods of precision on this aspect of the problem, I cannot agree that this factor can be ignored by any investigator. It

has simply become one of the necessities of the experimental method in this field. There is no point in thinking about alimentary lead excretion without knowing the magnitude of the current alimentary lead intake. For example, if the cook buys a new skillet or otherwise changes the cooking utensils, the experimental results are likely to change very significantly. The number of factors that influence the lead content of the food is legion, and therefore it is absurd to attempt any metabolic experiment that does not control this set of factors.

As to the actual magnitude of the alimentary lead excretion, if you will refer to my letter, you will see that I did not say that it is negligible. Rather I said, "There is very good experimental evidence to indicate that it is usually slight. It may even be negligible." The latter reference to the possibility of its being negligible was based on experimental observation and not on conjecture. The alimentary excretion of lead may be quite high for periods of time that vary with the dosage of lead and with the length of time over which a high lead intake extended. Alimentary lead excretion may be negligible if the lead content of the body has been increased slowly over a considerable period of time. The mere presence of radioactive lead in the bile or in the contents of the alimentary tract is not in itself proof of the importance of the alimentary excretion of lead. Considerable quantities of lead occur in the alimentary tract of all persons at practically all times. Undoubtedly some of this is absorbed in the upper portion of the alimentary tract, some of it is re-excreted by way of the liver and the bile, and some of this, as well as some of that unabsorbed in the upper alimentary tract, is absorbed further down. The composite result is that the quantity evacuated usually bears a close quantitative relationship to that which was swallowed in the corresponding period of time. You are right as to the uses of statistics, but the value of statistics and of statistical calculations must always be determined mathematically in relation to the variability of the universe under consideration. Any small number of samples of feces may show a low variability, either by chance, or because of carefully controlled experimental conditions. However, if the conditions are not so controlled one must take into account the variability of the entire universe so far as it has been explored. This variability unfortunately, is quite large, and it therefore tends to vitiate any small differences between experimental and control conditions.

I should also like to say that I am not convinced by the fact that the taking of aliquots of feces for analysis "is the accepted technique for such balance studies." I agree that it can often be done, but we have found that the difficulties are considerable,

and in some instances unsurmountable. Certainly what is true in the handling of a number of other elements is not necessarily true in the case of lead. In fact, it not infrequently happens that lead compounds are introduced into the food in discrete form, and in such a manner that it does not lend itself at all to distribution through the entire mass of a suspension of the feces in some medium. Therefore, the only evidence that I would consider as proving your point would be a series of analyses on the aliquot and on the residue as well. If such a series of parallel analyses yielded good results with uniformity and with a very small error, I would accept the conclusion that aliquots can be used. Otherwise I am afraid I would not be satisfied to accept the data on aliquots.

You may think I am being very sticky about this, but I have had the responsibility over a number of years of having to know as many facts as I could obtain in order to bear the responsibility for the safety of people who are working in quite hazardous jobs. This responsibility has made me rather chary of accepting anything other than proof. Most of the serious blunders I have made have been the result of accepting something that was generally believed, only to find by the hard way that the facts were somewhat at variance with the current belief.

I should hesitate to express myself so frankly if I had any fear that I would discourage you or offend you. I have no fear on either score in view of your response to my first letter. I am interested in your work and your ideas and expect to follow them up with some observations on patients, when opportunity permits.

I trust we may have an opportunity in the not too distant future to meet and talk.

Cordially yours,

Robert A. Kehoe, M. D.

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