

February 15, 1945

Copy by Air Mail

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Dear Mr. Meston:

I want to thank you for your very great courtesy in sending us the copy of your article "The Lead Content of 'Normal' Urine," and in taking the trouble to write me on the subject. Your courtesy indeed calls for corresponding consideration on my part, and therefore I am taking this occasion to call your attention to a number of matters that seem to me of considerable consequence, in connection with both your articles and the certificate issued by your laboratory to medical practitioners. In so doing I am actually taking exception to some of your statements, but I wish to assure you that I do so not in any unkindly or carpingly critical sense. Rather it seems quite important to me that certain facts which are now available, should be taken into careful consideration in relation to this problem.

With this idea in mind, I am sending you under separate cover a number of reprints. Some of the later ones cover in a very brief manner, work in which we have been engaged for a period of some five or six years. The details of these experiments have not been written up as yet, partly because one or two of the experiments are still in progress, but largely because the urgency of the war has made it impossible for me to devote the time required for the careful study of the data and the preparation of a rather elaborate publication. -Therefore, I want to make certain additional comments on the available information and its significance in relation to the problem of normal lead, and lead accumulation in relation to varying levels of lead exposure.

First, let me say that the conditions with respect to the level of daily lead intake on the part of general populations, are variable in various parts of the world. The review by Dr. Monier-Williams has not made very much point of this fact, although the author, I feel sure, was thinking primarily in terms of the British Isles, or specifically England, Scotland, and Wales. The situation there is not like it is in the United States, if Monier-Williams' estimate of the lead intake in water in his country is correct. We have investigated that situation in this country with much greater care, I believe, than it has been done elsewhere, and we are quite certain that

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the lead intake in drinking water here is something less than 0.1 mgs. of lead per day. Our drinking waters in general, with a few well recognized exceptions, do not contain in excess of 0.02 or 0.03 mgs. per liter. In the main the lead concentration is even less than this. Therefore, 0.1 mgs. per day from this source is a very generous figure. Our lead intake in food is only rarely of the order of magnitude of 0.5 mgs. per day. In a rather large series of individuals on whom random observations have been made, and in a smaller group on whom daily observations have been made for weeks or months or years, we have established the fact beyond any doubt that the lead content of the food while variable from day to day, has a mean value slightly under 0.3 mgs. per 24 hours. In round numbers one is justified in saying, therefore, that $1/3$ of a milligram of lead per day is our average daily intake.

It is not fair to conclude that this is the result of contamination of the food in the various steps of its preparation for eating. No doubt some portion of this is the result of contamination, and we have had occasion to discuss the sources in considerable detail. On the other hand, the evidence is very good that something like $1/2$ of this comes from the natural lead content of food materials. Most of the rest of it is wholly inevitable, and quite unavoidable in the organized community, and it is, therefore, to be regarded as the natural consequence of organized community life. Generally speaking, the use of aprays on fruits and vegetables is not a very important factor, even though it may give rise to nearly half of the total intake in many instances. The fact is that the use of these obviously contaminated foods is not universal by any means, and moreover the methods of handling the food and preparing it for the table serve to dispose of a very large proportion of this potentially hazardous source. In any case, I feel quite sure from rather widespread and long-continued observation, that the lead content of the present dietary in this country is actually somewhat lower than it was in many sections of the country in an earlier period when there was less care taken in the handling and preparation of food material. A rather sizable number of earlier sources for the contamination of food have been eliminated. New sources arise from time to time, but in the main these are recognized rather promptly, and in general they are likely to be eliminated. In any case, during the period of nearly twenty years in which we have been making observations in the United States, we have found no evidence of any significant increase and some suggestive evidence of a decrease.

For the reasons I have given above, I think it is not sound to use the word normal in quotation marks in this relationship. What we are dealing with here substantially is a normal biological phenomenon, that has always been with us. It suffers some variation,

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but so does every other biological phenomenon by virtue of changes in the natural conditions of life.

It is under such conditions as these that we find lead normally in human tissues as well as the tissues of all animals, both wild and domestic. (Obviously we have not had the opportunity of examining all animal forms, but we have never found exceptions to the statement made above, despite a rather extensive search. Even the coral skeleton in the sea contains lead in concentrations of the order of magnitude found in other forms of animal life.) Lead is found in the circulating blood and in the excreta of men and animals. This is not an indication of toxicity or the danger of intoxication, but is rather a normal phenomenon of the mineral metabolism. What is true of lead is true of most of the other trace metals that are widely distributed on the surface of the earth. Moreover, the appearance of lead in the blood and urine, contrary to what you have believed and said, is not an evidence of continuing lead accumulation in the tissues of animals and men. You have said in your article that "It may be correctly assumed that, whatever the amount of lead that is being excreted in the urine, much more is being stored in the tissues." Our observations have demonstrated, beyond any reasonable doubt, I believe, that within the limits of normal or inevitable lead intake, lead accumulation in the tissues does not occur as a progressive phenomenon, in the sense of steadily increasing lead concentrations in the tissues. We have shown otherwise in analytical data on the tissues of people varying widely in age. More certainly, however, we have clarified the pattern of the lead metabolism and have shown that appreciable accumulation occurs only when there is a significant elevation above normal levels of the rate of lead intake.

The conclusions here are inescapable. Lead absorption is potentially dangerous only within certain quantitative limits. These limits can be established in terms of intake itself or in terms of observed lead concentration in the blood or urine or both. Generally speaking, the urinary lead concentration under suitable physiological conditions is the best measure of the current rate of lead absorption. It will be misleading only in the very rare case in which through some abnormality of the kidney, a urinary lead concentration is maintained at an unduly low level. We have seen only one such case among several thousand persons included in our observations.

The level of normal lead excretion is somewhat variable from country to country and from climate to climate, dependent upon the prevailing conditions with respect to the food, and the conditions with reference to urinary volume. In cold or temperate countries the lead concentration tends to be a little low. The reverse is true under comparable conditions when the temperature is high. On the whole, however, the variations in the lead output

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in the urine of normal persons with no extraneous exposure to lead in this part of the earth, range from about 0.01 to 0.08 mgs. per liter, as you have said in the copy of one of your reports. It is important to recognize that these variations are physiological in character. That is to say, the same individual observed from day to day will vary over this range with practically the same frequency that characterizes a sizable group of observations on individuals. This, then is the normal range, and from the statistical viewpoint, any result obtained on any individual that is within these limits must be regarded as normal. Obviously, if you were to make a series of observations on a single individual, and if you were to find that the average or mean result of such a series was much in excess of 0.03, you would be dealing with evidence of unusual lead absorption. However, unless the situation is different in Queensland than it is in United States, you are in error when you say that, "Any amount in excess of 0.05 milligram should be considered with the general clinical picture." Actually you are not at liberty to conclude that a single result of 0.08 is even suggestively abnormal.

For various reasons which I trust will be apparent in our published articles, we regard it as desirable to analyze both blood and urine in the individual case. Having these two values we are enabled to interpret the result with considerable security. Obviously we never draw any conclusion from an analytical result, except as to the significance of the exposure. That is to say, we never conclude or even imply that there is any illness or any likelihood of illness, except on the basis of purely clinical information. Moreover, we are very cautious about interpreting the significance of the exposure without having detailed information when it is available, on the nature, the duration, and the date of discontinuance of the lead exposure. This, of course, is usually impossible in the case of children and persons in the general population. Therefore, in these cases we often find it necessary to make repeated observations, and also to investigate the environmental conditions.

You have not solicited my remarks or advice on these matters, but I trust you will appreciate the spirit in which they have been extended to you. I feel sure you will realize it is only our mutual interest in this interesting and important field of work, that justifies the directness with which I have spoken.

Cordially yours,

Robert A. Kehoe, M. D.