

July 12, 1935

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My dear Edgar:

I have your letter of July 10th and I can understand your uncertainty about the present situation of normal urinary lead. I do not think the situation is as bad or as unexplainable as it seems to you, however, and therefore I want to point out to you a few points that must be taken into account.

(1) During the period of years in which we have been studying this question we have learned many things about the collection of samples. We now send out detailed instructions with every container, and the evidence is quite adequate to show that we receive better samples. There are fewer gross contaminations and the mean results are therefore lower.

(2) Our analytical procedures have been modified from time to time to give greater precision, and with the development and standardization of our spectrographic method we are obtaining analytical results which are without doubt more accurate than those obtained in previous years. No small part of the improvement occurred with the removal from our former laboratory to the present one. This change meant better and cleaner space, better storage facilities for samples, better distilled water, and better general chemical technique.

(3) We have also learned much as to the variation in the lead excretion of individuals for purely physiological reasons. Thus the following factors measurably influence the rate of excretion in the urine.

(a) The quantity of food eaten influences the quantity of lead ingestion and also the extent of absorption, upon which urinary excretion depends.

(b) The water metabolism influences the quantity and concentration of lead in the urine. Thus the quantity of lead output in the urine in the winter is greater than in the summer, but in winter the concentration is lower.

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(c) Physical activity increases the urinary lead output. Men working hard, and in hot weather, will show a considerably higher urinary lead concentration. There is even a difference between the lead content of the urine in the daytime, as compared to the night, the latter giving a lower lead concentration.

Now all of these factors have played their part in the picture which we now have. The medical students referred to in the J.A.M.A. were relatively sedentary, and all the samples were obtained in cold weather. We obtained very large samples and it is possible that some of these were obtained after drinking excessive amounts of water, although this was discouraged in the instructions. These factors favored a low urinary concentration. Other normal subjects studied during the same general period as these medical students (i.e. within that year), gave slightly higher mean results. Thus one of our subjects showed a mean of 0.055 for a series of samples obtained during hot weather. You see therefore that physiological variation is not without significance.

(11) Now for just one other point. The discrepancy between our earlier figures, and the more recent ones is not as great as it seems from your statement that the "average of 0.012 by the chemical method" is only about "one-fifth of the former results". In the same article in which the figure of 0.012 for medical students is given normal mean values on other subjects are recorded as high as 0.029 ± 0.002 by the chemical method. This is almost half the former mean of 0.07.

I must take exception, too, to your use of the word "average" as applied to "mean". It seems a small point but actually it is quite important for the simple reason that occasional high results make little difference in an "average" but they are much more heavily weighted in the calculation of a mean. Thus when you recognize that the difference between our former mean of 0.07 and our present one, which would certainly come to 0.025, is only 0.045, it is not very great either chemically or statistically. For example, the average of the means obtained on the ten subjects studied by the continuous laboratory method (p.3 of the reprint from the J.A.M.A.) is 0.021 ± 0.002 . Comparing this with the mean value for medical students given on p.283 of the article "On the Normal Absorption and Excretion of Lead, II Lead Absorption and Lead Excretion in Modern American Life", the difference is 0.046 ± 0.0054 . This difference is significant statistically, of course, but it is actually only 8 times its own probable error. It must be at least 4 times its own probable error to be regarded as beyond the range of purely chance biological variation. Thus, you may see that we are still dealing with figures of the same order of magnitude both chemically and biologically.

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Graham Edgar

There is no real question as to the accuracy of our present results. The only question relates to the upper range of normal values. It will take time to settle this point, in view of the possibilities for variation which I have mentioned. There may well be certain others with which we are not familiar. I, personally, am convinced that the final figures on the basis of present environmental conditions will be nearer 0.07 (our original figure) than it is to 0.012 (the medical students figure). Therefore, I do not consider it wise to go to great lengths to explain the differences in various groups, or the difference between individuals as studied over a long period of time.

As to the reduction in the use of lead sprays, let me point out that the mean fecal lead, which in normal persons is largely an expression of ingestion has not changed appreciably since our initial observations. This fact also demonstrates that the sampling errors and the analytical errors in dealing with urine are concerned only with a few hundredths of a milligram of lead.

So much for the present. I am off tonight for a fishing trip and a much needed rest.

With kindest regards,

Very truly yours,

RAK:is

Robert A. Kehoe, M.D.

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