November 19, 1941.

Mr. Gordon C. Harrold, Ph. D.,
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341 Massachusetts Avenue,
Detroit, Michigan.

Dear Harrold:

In accordance with my promise I am writing to you concerning the subject of our sketchy talk in Pittsburgh last week. I am presenting my views in some detail, because it seems advisable to clarify certain points on which we were in apparent disagreement. I trust the disagreement is not as significant as it may have appeared to be.

First, let me indicate the genesis of the various sets of data on normal lead that came out of this laboratory. Our first figures, obtained in 1925, by an early modification of Fairhall's Chromate method, were published in J.A.M.A. 87:2081, 1926. Some of these were too high as judged by present experience, and these can be explained almost entirely as contaminated in process of collection. The analytic method, generally, yielded low results, but in the absence of a sulphate step between the sulphide precipitation and the chromate step, certain other metals could have been included under suitable conditions. This method was improved and was subsequently described in J.I.H. 15, 261, (1933). The latter was a very sound method, which, unfortunately, could not be used with small samples for the reason that a loss of lead occurred in the process, to the extent of approximately 0.07 mg. per sample. We, therefore, used quite large samples in order to keep the error from this source of small magnitude.

Our second set of results appeared likewise in J.A.M.A. 92: 1418, (1929), and the calculated mean values were 0.08 ± 0.008 for medical students. These results, likewise were high as judged today, and for two reasons; - (1) occasional contaminations in collection, and (2) slight and irregular contaminations in analysis, because of certain inadequacies in our laboratory facilities. The method as indicated above, while not so good as present methods was fairly satisfactory, but yielded low results.

The third, and this time, an extensive series of results were published in the articles in J.I.H. 15: 257-340, (1933), these all having been obtained by the chromate-dipheryl carbazide method as applied to large samples of urine, feces, foods, and

tissues. The results obtained in our new laboratory, where proper provision had been made for the avoidance of contamination (from 1931 on), gave us a new base line level for normal persons, but we did not confine our data to those so obtained, for we did not quite appreciate the necessity for so doing at that time. It will be noted that we gave the detailed results of our carefully controlled metabolic studies on human subjects under laboratory conditions (J.I.H. 15:277, (1933), these having mean values slightly under those now obtained by more sensitive methods), and compared these with the results obtained on persons outside the laboratory. Some of the latter results had been obtained in our previous laboratory, and by methods of sampling which we now know to be somewhat inadequate. The data showed higher variation than we would find at present, and the mean values were approximately 0.07 mg. per liter. It is quite clear to me now that a certain proportion of these samples was contaminated both in collection and in process of analysis in a laboratory that was not adequately equipped with dust collection apparatus, etcetera. There was no way by which we could have known this with any confidence at that time. My comments on the difference between these results and those on persons under laboratory conditions, given on page 283-4 are of some interest in this connection.

The next step in this story was accomplished by our publication of a new series of results on medical students and on a larger group of individual subjects studied over prolonged periods, in J.A.M.A. 104:90, (1935). We showed here that the medical students yielded a mean normal result of approximately 0.04 mg. Pb per liter of urine by spectrographic analysis, and that the results of the carbazide method checked this value, if due allowance was made for the loss of 0.07 mg. Pb per sample in the numerous separatory steps of that method. These were the first spectrographic results we published, and despite the fact that the method then used was less accurate than the present one, it yielded highly satisfactory results. It may be that you were thinking of the discrepancy between these spectrographic results and those of the carbazide method wherein you stated that the spectrographic results were too high. This, however, was not the case, as reference to the data will show.

In this same article we gave results on human blood, giving a mean value of 0.058 ± 0.002 for normal. This unfortunately was in error, and was subsequently acknowledged so to be, J. Nutrition 20:92-93, (1940). The error here was not in analytical method, but rather in the method of collecting samples, in that contamination occurred from needles, soft glass syringes, and soft glass bottles, cleaned without benefit of lead free distilled water, as we would now define such water. (This, by the way, is the type of error that is still being made by many people who think they know how to deal with blood samples.)

I need not take this further, since little or no change in normal results has been brought about through the later work of ourselves or others. Some slight refinements have been contributed by our further data, J. Nutrition 19: 579, (1940), and these are in essential agreement with the observations of a number of other workers who have used methods of comparable precision.

I have restated the above facts to show that at no time did the use of a spectrographic method give rise to any of the errors we have made. It was this point which I wished specifically to correct in your statement of last Wednesday. We have not made an error on the high side, as our expression of the limitations of the spectrographic method. Indeed, we have clearly demonstrated that the spectrographic method developed and used by Cholak will give results that regularly check those of themore sensitive and accurate modifications of the dithizone method. Various persons have attempted to discredit the spectrographic method, and various workers have employed defective spectrographic methods. It is true that the method has certain limitations, but those limitations are of little practical disadvantage. However, if any trained person will establish the proper environmental conditions and will follow the methods used by Cholak, (or methods of equal precision), he will be able to duplicate our results. We have been running blood and urine in parallel by spectrographic and dithizone methods for over four years. We have thousands of results by the two methods on the same samples. The differences between them are so slight as to be utterly negligible. The one method is quite as good as the other. If you still doubt this, you will be well advised to examine Cholak's article in the Journal of the Optical Society, which is now in press.

The method published by Cholak, in 1935, had an acknowledged error of ± 25%. This error has been diminished by one technical improvement after another until now the error in dealing with the quantities actually ignited in the arc is practically constant at 0.02 micrograms. If one speaks of this error in relation to the solutions as they are usually prepared for testing, it is equivalent to approximately 0.01 mg. Pb over the concentration range from 0.01 mg. almost to 0.20 mg. Pb per 100 c.c. of solution.

It is true, of course, that at the lower concentrations, the error is considerable, but no more so than in the case of chemical methods. There is also a ceiling which is determined by the maximal blackening of the individual line used. However, it is possible to work within the zone of high accuracy of the method by paying proper attention to the preparation of the sample. If the sample to be introduced into the crater of the electrode is too dilute, with respect to lead, it can be further concentrated, and vice versa, so as to keep the quantities on the electrode within

the proper range. The quantity on the electrodes is usually considerably less than 1 microgram, and quantities as low as 0.02 micrograms can be dealt with. The error in so doing is approximately ± 0.02 micrograms, and this same absolute error, i.e. 0.02 micrograms, continues as a constant technical error up to 20 times that amount. Above these quantities, the error is from 5 to 10%. It is apparent, therefore, that this is the only method available f for use when the actual quantities of lead within a sample are considerably less than 1 microgram. It was for this reason that I demurred emphatically when you said that the spectrographic method was unsuitable for use in dealing with 1 microgram or less.

I am sending you several papers, which you may have seen, but which I believe are worthy of examination in relation to what I have said above.

Quite apart from the above discussion, I wish to refer to the presentation of a paper by you in the Symposium on Wednesday, April 15. I have planned this symposium in detail to present a unified and coordinated picture of the problems. It will not be a series of unrelated papers, but a sequence of parts to make a unit. I do not want to assemble in it other papers on lead which may be submitted for presentation unless they fit into the picture. Yours may do so, but if it does not, I should like it to be presented at one of the other sessions. I think, therefore, before deciding this point, I should know just what you are presenting. If that meets with your approval, we can consider it as soon as you are ready, but in any case you should ask for a place on some other part of the program by submitting your material to Drinker in the usual way. I should point out also that fifteen minutes will be the maximum available time, and perhaps, only ten can be had. There will be no time for discussion of the symposium on the floor, and therefore, I must be very careful what goes into it. If controversial material were to be used, we should be in a bad position on account of the lack of discussion, and I do not want to be found in any such positio. This may be an unorthodox way to put on a sumposium, but I believe it is justified in this instance, and I think it is worthy of a trial. I shall appreciate hearing from you on this score.

Cordially yours,

Robert A. Kehoe, M. D.

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