

December 13, 1938

Dr. Ann S. Minot
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Dear Doctor Minot:-

I am sorry if my recent criticisms of your review of "The Physiological Effects of Small Amounts of Lead" conveyed the impression that I did not believe it to be useful. On the contrary I thought well of it in many respects or I should not have taken the trouble to criticize it at all. I only believed it somewhat less useful and less revealing of the actual status of the problem than it reasonably could be expected to be. I did not complain that it was inaccurate except in so far as it was less complete than it should have been. I agree entirely with you in your feeling that any detailed discussion of methods of analysis would have been redundant in such a review, but, on the other hand, since the use of new and highly sensitive methods has done so much to alter previously accepted facts in many spots of this physiological field, one cannot ignore their practical importance. The available data must be evaluated on the basis of the sensitivity and accuracy of the methods employed in obtaining them or the whole literature of the subject becomes a maze. This, I admit, is difficult, but it is not impossible. It is not fair to say, moreover, that the advocates of various recent methods of analysis are in any very great disagreement among themselves as to the essential accuracy of their results. Doubtless Dr. Fairhall, with whom I discussed this question some time ago, is interested, as I am, in the utmost precision in the application of some modification of the "dithizone" method, and doubtless in his official capacity and with his present responsibilities he can afford no more than I, to sponsor any method for use without the most rigid and direct examination of its merits. And yet I do not believe that he would have the slightest reservation in agreeing that in dealing with the minute quantities of lead encountered in biological material several of the published modifications of that method are far superior both in sensitivity and in final accuracy to any one of the more typically analytical procedures used by any of us some years ago. He is quite properly cautious

sensitivity of those methods, but I do not think he regards these as insurmountable in view of his knowledge of their use by Willoughby et al, by Clifford and Wichmann and by ourselves. The men in his laboratory are now familiar with these methods, and his associates are also quite familiar with spectrographic methods very similar to ours. It must be recognized, however, that a much wider and longer experience with these methods has been had by other workers. I was surprised, therefore, that you had not had some recourse to the opinions of persons who like Willoughby, Wichmann, Calvery and certain of my associates, have had the benefit of that longer experience, especially so since Cholak and Hubbard in this laboratory had already carried out the comparison of certain methods which Fairhall is now making.

As to the question of your casting doubt on the accuracy of certain published data, I would be the last person to argue against this duty of a reviewer to do this just to the degree of his own doubt. However, I believe that data of sufficient accuracy were available to dispel your doubt - data obtained by several reliable workers which are in such essential agreement as to leave little room for doubt concerning their validity. (I may say, here, that I do not regard the incredibly bad papers of Myers et al as sufficient basis for incredulity as to the results of others.)

None of these matters would be of great importance as grounds for criticism except for their relation to what I regard as one of the most fundamental phases of the problem you were discussing, namely, the physiological aspects of lead metabolism. If I speak in a perfectly frank manner about the importance of a process which was first recognized in this laboratory, I trust I shall not be thought lacking in modesty. As a matter of fact, no great modesty is required on my part in respect to this matter since it came out of no brilliantly creative mental effort, but rather from the overwhelming evidence of a large mass of data. It appeared from our studies as outlined in 1933 (J. I. Hyg.) that normal lead metabolism was an equilibrated physiological process, in which a substantially constant level of lead concentration in the tissues was maintained over long periods of time through balanced intake and output. It also appeared that increased lead intake, up to a certain incompletely defined point, resulted in an increase in the lead content of the tissues and a corresponding increase in the lead excretion. The magnitude of the increase in the lead content of the tissues and in the excretory rate was roughly proportional to the magnitude of the increased intake within certain limits. There was evidence, therefore, of the maintenance of a balanced equilibrium at levels above that normally encountered. Granting the correctness of these facts, it is scarcely to be expected that any deleterious effects would occur within the limits of a physiological lead intake - i.e. that unavoidably associated with the natural lead content of food and drink. Further, within a certain range of quantities long tested by human experience,

such as the amounts of lead found in the diets of random Americans, as well as that of our experimental subjects over periods of many months, no untoward effects would reasonably be anticipated. It should be added, that with respect to still higher levels of exposure, industrial experience had provided considerable evidence for a definite differentiation of harmless and injurious exposure which indicated that somewhat larger quantities could be absorbed over indefinite periods of time without toxic effects. One could scoff at such evidence as based on inaccurate observation, unsound judgment, and indifference to the risks of occupation, until accurate clinical studies combined with precise air analyses and careful excretory data on exposed workmen provided quantitative criteria for the definition of safe occupational conditions. In terms of our observations, and of the concept derived therefrom, all of these situations could be described and classified under the category of normal i.e. physiological, lead metabolism, as a balanced process associated with non-injurious concentrations of lead in the tissues. The level of human lead intake at which the metabolic pattern changes or at which the concentration of lead as a metabolite becomes harmful to tissues, has not been defined with the required accuracy, but that there is such a level and that it is amenable to precise definition seems well assured. Nothing has contributed to this encouraging prospect so much as the development of comparatively simple and highly precise analytical methods. By means of such methods, the pattern of the process mentioned above, which originated from data obtained laboriously on very large samples of tissues and excreta, has been elucidated with much greater precision through their application to materials that could not be analysed accurately by older methods, and has been confirmed at certain essential points by the observations of a number of workers who have not been concerned with the entire problem. It was on account of such considerations that I regretted so much your failure properly to evaluate the new methods and the data obtained by their use. You may not be convinced of the validity of the general concept stated above. In that case I do not wish to argue, but merely to observe that my critical comments were based on my belief that you would have been fully convinced if you had given adequate consideration to some of the recent contributions which I cited.

I should not wish you to take what I have said as deliberately ungenerous criticism, nor as the expression of an interest in polemics. Rather have I attempted to make as constructive comments as I can, in relation to this important and interesting problem. With this idea uppermost, I am sending herewith some reprints of articles which may prove to be of some interest to you. You will not be greatly interested, perhaps, in the practical details of the study made on the hazards of leaded gasoline, but I think the rather complete studies on normal lead metabolism described therein will be

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worth your careful examination. Certain factors which influence the rate of urinary lead excretion are rather well demonstrated. I send you also typed copies of two papers which have been given at scientific meetings but which have been withheld from publication in order to save the duplication that would result from the fact that certain observations were incomplete. These, of course, have no relation to your review but they are, I think, of interest. Please return them to me when they have served your purpose.

Cordially yours,

RAK:ls

Robert A. Kehoe, M.D.

P.S. In relation to the problem of lead metabolism there is one point which I find no direct mention of in the foregoing paragraphs and which I should not have omitted. There is no doubt, from our observations (J.I.H.1933) that the word "stored" as applied to lead in the skeleton is a complete misnomer. Lead is deposited in the bones in equilibrium with other tissues and the lead stream. It is lost from the bones whenever the lead intake is reduced. Various factors may influence the rate of deposition and loss to greater or lesser degree but the final result is essentially independent of these factors, it being determined largely by the environmental lead exposure and absorption. There may, of course, be pathologic disturbances in the case of lead metabolism, but these have not been adequately or even tentatively investigated. All present evidences indicate a high degree of predictability and stability in the process under ordinary conditions.