

June 24, 1963

Professor Harry V. Warren
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Dear Professor Warren:

Your letters of May 13 and May 24, to Dr. Sidney Lerner were referred to me because of certain questions which you raised, which are in my bailiwick. Whether or not I can answer them satisfactorily, is another matter. I shall do my best, however, to deal with them.

It is fair to say, I believe, that the form^(in nature) in which lead is presented to the animal organism, whether in combination with inorganic or organic acid radicals is a matter of little consequence, so long as the compound has an appreciable solubility. That is to say that lead chloride and lead acetate, for example, within the limits of their solubility, are one and the same, for all practical purposes. When, however, lead is linked to the alkyl radicals, thus producing a liquid compound with distinct fat solubility and very slight water solubility, a very different situation exists. I shall not go into this, for many (by no means all) of the facts that arise out of this difference are too well known to justify further discussion.

Very little is known of the nature of the lead compounds which occur in water, food and biological materials. One can make reasonable inferences, but I shall spare you from them, and point out that there is not too much difference in the result when these are taken into the alimentary tract, without much regard for their form, unless, as I have suggested, previously, they are quite insoluble in the gastro-enteric contents. The absorption of lead from the alimentary tract is poor at best unless one introduces an highly soluble compound into a virtually empty tract, since the anions that are present in the alimentary tract are capable of converting most of the lead to relatively insoluble compounds.

Most of our knowledge of the pertinent facts has come from experiments in which animals or men have been given specific compounds of lead in or with their food. As you are fully aware, the analysis for lead in biological material has always been carried out after the destruction of the organic compounds, and, therefore, the nature of the original combinations remain unknown for the most part.

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With reference to the varied effects of different compounds of mercury (I have only slight familiarity with the information on zinc) there is a considerable amount of information. I suspect that the simple compounds of mercury with organic acid radicals behave very much like those of the inorganic acids, but the pyridyl compounds behave quite differently (in their distribution and excretion), and others of the more complex type, so far as they have been investigated are similarly variable in their respects and also, inevitably, in their detailed effects. The same is true, of course, of the complex arsenicals.

Your comments in your letter of May 24 as to the lead content of the soil, are quite pertinent. Dr. deTreville worked hard and long to gather together the information presented in the paper to which you refer. Not being a chemist, primarily, and having the point of view of a physician (who tends to accept the chemical information in the literature at its face value), the refinements of which you speak are not clearly elucidated. Moreover, there is no good way, as a rule, by which the available data can be presented in a strictly comparable form, even if one undertakes to do so.

The same of course, is true, of the manner in which the analytical data relative to animal tissues are expressed. The investigator has had his own idea of what he wants to know and has adapted his method of analysis - or perhaps of recording the results - to suit his purposes. We, for example, have been interested, almost solely, in the distribution of lead within the tissues and organs, in as nearly the living state as it is possible to determine. From the physiological point of view which I have held, this is the important matter. I freely admit that there are variables here that are difficult to gauge, but I doubt that there is a better means of expression that is not based on some assumption of physiological knowledge which is by no means certain. Let us suppose that the lead is expressed in relation to the dry weight or the weight of the ash. Is there any better basis for comparison than the weight of the organ? I doubt that there is, since the latter two qualities of a tissue are subject to considerable variation without definitive physiological basis of interpretation. For myself, I have not advised Mr. Cholak (who is the analytical expert) to deviate from conventional analytical practice, except when there was a relationship to be explored which was important from the physiological or pathological aspect of the situation. We have attempted to devise experiments (including the analytical data and their expression) in such manner that they would reveal physiological relationships, whether of mechanism, or of space (distribution) or of time, merely describing the manner of making the observation so that it could be duplicated by any other investigator. It is unfortunate that many investigators do not regard the detailed description of method to be crucial, and some of course, lack critique with respect to method. You are not alone, therefore, in your concern about these matters.

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With respect to the "natural lead content" of various materials, the critique which I would apply rigidly to this point is not generally followed, and I regret to say that this was not followed with sufficient care and precision by Dr. deTreville in assembling his data. In editing his paper I could not (without going back to the original data) apply my own criteria to the assembled data, and it would have been difficult in some cases, even if I had taken the time (as well as the responsibility) for so doing. What is meant by the term "natural." If one considers natural phenomena to be those which have not incurred any change through the intervention of man, that is one thing; but if one considers man to be a part of nature, and his acts, therefore, as springing from the nature of man, it is something else again. You may believe that I am being either facetious or precious, but such is not the case, for these are views which are not only held but acted upon. What, for example, in our time (or any other) is a normal population? Let me say that my view of this is very simple, and when I have spoken of the natural lead content of soil, vegetation and animal tissue, I have referred, so far as knowledge permitted, to that which resulted from a state of nature uninfluenced by the intervention of man. Thus in the tabulated data which have been obtained in this Laboratory, this point has been made as clear as the facts would permit.

I think you have overlooked something in your comments in the last paragraph on the first page of your letter of May 24. I confess that I have no idea what you mean when you say that we have not taken into account the lead that is in vegetables and other organic media. We have followed experimental subjects for months at a time when they were deriving their alimentary lead from their ordinary food and water. The physiological relationships here have been explored as fully as the sources of food of the subjects has permitted. Only after many of such observations has lead been administered in addition to that in the diet. If there are important differences in the physiological mechanisms during the two different periods of the experiments, they have not come to light. On the contrary, one may say from these observations that the metabolism of lead in the human body is one of the most, if not the most, stable and predictable of physiological processes. I am not being unduly critical of your inference that there is probably a significant difference between the inorganic and organic compounds of lead as they occur in nature, but I have no idea of what you are talking about or thinking. Most of the "organic" compounds of the minerals, as taken into the animal organism, do not remain organic, for very long, but with the destruction of the organic radical (acetate, citrate, etc.) they cease to be organic in their original form but as ions they unite with the organic (and inorganic) components of the tissues of the organism into which they enter. I find myself unable to develop much concern about the form in which lead enters the body, unless, as in the case of the alkyls, it persists as the original compound long enough to reach some unusual site in the body in unusual concentration. If the lead in an absorbed compound is tightly bound (as when chelated) and if the chelate is stable within the internal environment of the organism, it can be

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expected to be essentially inert. Under these conditions it will exert little effect and will be lost from the body rapidly, through much the same mechanism that permitted its absorption. Thus far, in nature, I have encountered very little reason for concern, beyond the matter of aqueous solubility, as to whether a compound of lead was organic or inorganic. I would be greatly interested, of course, in any observation that would lead to a contrary view of this matter.

Sincerely yours,

Robert A. Kehoe, M. D.

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cc: Sidney Lerner, M.D.

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