June 4, 1964

Professor Martin I. Rubin, Ph.D.
Department of Chemistry, Graduate School
Georgetown University
Washington, D. C.

My dear Doctor Rubin:

I am writing to you, out of courtesy, although this may not appear, at first, to be the case, in connection with a reply of yours, printed in the Journal of the American Medical Association for May 4, 1964, to a question raised by Lewis M. Davis, M.D., of Greer, South Carolina, concerning "laboratory tests for lead poisoning," with specific reference to the determination of lead in the blood and urine.

My reason for writing to you directly, is that I have taken serious exception to your reply, in a letter to the editor of the Journal of the American Medical Association, and I wish you to know the bases of my critique.

First, let me say that the diagnosis of lead poisoning is a very difficult one for most physicians in private practice, in view of the prolonged, systematic confusion of the issues in this matter for many decades, and their lack of experience with the disease. The situation of the practitioner has been rendered much more difficult by the reliance that has been put lately on analytical determinations (lead, porphyrins, etc.) and other items of information from the clinical laboratory. This is the case because the interpretation of the latter findings continues to be based on empirical rules rather than physiological judgments, and on "authority" rather than evidence. Having spent much of my professional life in an intense and elaborate investigation of the physiological background involved in the metabolism of lead, and having contributed to the elucidation of these matters in clinical medicine, I feel strongly about the confusion that still exists, and also about the practical problems with which the practicing physician is confronted.

First let me say that the adjectives, acute, subacute and chronic as applied to lead poisoning, in our day, are almost utterly inept, for physiological reasons. Therefore, such references to ancient concepts, which came into being in the twilight zone of medical history in this relationship, maintains the confusion. The clinical picture of lead poisoning varies with the quantities of lead absorbed, and with the time over which absorption took place, but the patterns have only a modest range of variability.

Next I should like to emphasize the fact that the diagnosis of lead poisoning is made on the basis of the symptoms and signs that characterize the disease. Analytical findings with respect to lead, never make the diagnosis, since there is no concentration of lead in the tissues or body fluids which denotes the existence of illness. The analytical findings, however, do give evidence of the past occurrence of the absorption of lead, and present information enables us to differentiate between those levels of concentration which have not, as yet, been found to be associated with illness of any type, and those which, while not being indicative of illness, are associated, without

exception, with some incidence of typical lead intoxication within a group. That is to say that a group of men working side by side, may have roughly equivalent, and potentially dangerous quantities of lead in their bodies, but only a small proportion of them become ill at any one time. We do not know what precipitates intoxication under such circumstances, for this, at present is some, presumably biochemical, factor to which no important clue has been found. The condition of risk, therefore is recognizable, but the intoxication is identified by its clinical manifestations, and in no other way.

Third, the so-called "provocative" administration of a chelating agent such as calcium disodium "edetate" and the measurement of the response is an unscientific and highly unreliable means of determining the "body burden" of lead. The response to it is erratic, unpredictable and impossible of physiological interpretation except under the most carefully controlled conditions of lead intake. By far the best means of measuring the "body burden" of lead (most of which is in the skeleton, where it is virtually unaffected by the administration of any of the presently known chelating agents), is that of measuring the concentration of lead in the blood under the most nearly normal metabolic conditions that can be maintained. Under these conditions, the lead in the soft tissues of the body is in approximate equilibrium with the skeleton, in this respect, and the blood, being one of the soft tissues of the body which is in delicate equilibrium with the other soft tissues, is by all odds, the best available evidence of the lead content of the body as a whole quantitatively. The relatively slow metabolism of lead in the skeleton provides a special variable here which is linked to the factor of time, but even this can be given an approximate mathematical expression if an accurate history of exposure (with respect to time and approximate severity) can be obtained. One might suspect, therefore, that any method which distorts the normal metabolic pattern of the body will also distort the excretory process, and what happens under these circumstances requires much more careful investigation (for its interpretation) than do the normal processes of the metabolic pattern. In short, only the soft tissues of the body respond promptly to chelation therapy, and this response depends more upon what has happened within the body during the last day or two (with respect to the absorption of lead, mainly from the alimentary tract), than upon the body burden.

I have gone to some trouble to explain this matter, because it has come to be essential to consider this problem in physiological terms, rather than in terms of analytical chemistry.

From the practical point of view as the problem is presented to a practicing physician, it is necessary for him to understand that the analytical technique required to obtain reliable information is not generally or frequently available. Indeed it is rare that such services can be obtained in his immediate locale. He must be told that such data are useful only if the sampling and analyses are carried out by fully informed experts in the field, and that he will do well to rely upon purely clinical evidence as a basis for a diagnosis, unless he can establish the competence and utter reliability (based on current experience) of the laboratory to which he resorts for help. If this is true, as a rule, of the clinical diagnostic laboratories of the country, (and it is), it is even more difficult to obtain that degree of cooperation of doctor (hospital) and laboratory, that will enable the "provocative test" to be carried out with even an approximate degree of accuracy. On the other hand it is entirely possible to obtain containers and instructions for the collection of samples of blood (and urine) from any patient, almost anywhere,

these to be returned to a responsible laboratory for analysis and for interpretation by knowledgeable persons.

I hope you will not conclude from my letter, that I am critical of you for replying, as an expert chemist, to a question which was believed in AMA to be essentially chemical. In my view, you should not have had the question referred to you. You could hardly fail to answer when it was put to you. My purpose in writing is not, therefore, to quarrel with you, but to suggest to you, as I have to the responsible people in AMA headquarters, that the medical considerations here are paramount despite the intrinsic importance of the analytical precision. I do, however, wish to indicate to you, that from a physiological viewpoint, the provocative test is based on an unsound principle, and that it should not be employed as a diagnostic procedure. I recognize the fact that there is not complete agreement on this point, but I state the matter flatly, nevertheless, not on my authority, but on evidence.

Faithfully yours,

RAK:vr

Robert A. Kehoe, M.D.