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Dear Doctor Currier:

I have examined your paper with interest, despite my impression that the probable worth of such investigations is destined, usually to be slight, because of certain intrinsic weaknesses of the methods of investigation which are available to us. For example, the histories of exposure obtained from the patients are indeed very faulty, both as to quantitative significance and occurrence in time. In the case of lead this is especially true, but it would probably be equally true in the cases of both mercury and arsenic, if we knew as much about them as we do about lead.

Certain comments seem to me to be justified. First, were I to look for evidence of the presence of unusual quantities of lead in the bodies of individuals in relation to disease, I would prefer, for many reasons, to analyse the blood. At one stroke, one eliminates wide physiological variability as a factor in the interpretation, as well as the likelihood of the occurrence of contamination in the process of the collection of the specimen. This is not the case in relation to mercury and arsenic for a number of reasons, but chiefly because neither of these elements enters importantly into chemical or physical combination with the formal elements of the blood, and so both of them vary, in much the same manner, physiologically speaking, in the blood as in the urine.

Speaking again of lead, which has been linked more frequently with ALS than have the other two, you have noted the variability in the expression of the upper normal limit of its concentration in the urine. There are several good reasons for this situation. Some of the analysts have no concept of the physiological aspects of this matter; others have not had sufficient experience to appraise the evidence; still others are noting without recognizing the differences due to analytical sensitivity and precision; while some have not bothered to define the range of the normal findings, but have confused the upper limit with the threshold value in relation to intoxication. The facts here are simple and significant: Individuals with no indication of abnormal exposure, have concentrations of lead ranging up to 80 micrograms per liter, and having a mean value of approximately 30 micrograms per liter, if one obtains, by proper methods, specimens of urine of large volume (of 2 or more liters; there is nothing sacred about a 24-hour specimen). If, however, one examines a large number of specimens of small volume, from one or a number of persons, in order, by numbers, to obtain physiologically representative specimens, the range will be larger at both ends of the spectrum and the mean value tends to be a bit higher. (These values depend upon the proper use of a method of analysis which has the same sensitivity and reproducibility as that used in this Laboratory.)

There is a range above the level described above which signifies abnormal exposure within the limits of safety. This range, in the case of specimens of urine of the same two types as those above, extends up to 120 micrograms per liter or 150 micrograms per liter (dependent upon the volume of the specimens).

Above these values we are dealing with a potentially dangerous range of values, the severity of which increases as one moves upward.

In the case of the blood, these ranges are identified more precisely, the normal ranging up to 50 micrograms per 100 grams of whole blood, with a mean value of about 26 micrograms. The abnormal range extends upward to about 70 micrograms (one cannot go above this with any degree of assurance because of the analytical error of about ±10 micrograms in this range, this meaning that 70 micrograms may in fact be as low as 60 or as high as 80 micrograms). With similar consideration for analytical error, one accepts 80 micrograms as the threshold value above which the danger of the development of intoxication is ever present. This value does not indicate the presence of intoxication. It is, rather, the level at which, under appropriate circumstances, the onset of intoxication may occur.

The figures given you above relate to an array of values obtained by our method of analysis, which have been tested by time and large numbers of analyses on large numbers of persons. I have no doubt that they will stand up under any amount of investigation; they may be made slightly more precise, where a method of analysis has been developed with deviations less than ±10 percent.

From what I have pointed out above, you will perceive that the upper limit of "normal" values, is in no sense synonymous with the lower limit of toxicity. Rather there is a significant gap between the two.

One other comment seems to me to be justified. On the assumption that the analytical results for lead are reasonably precise, it is evident (on the background of my remarks concerning normal values), that two members of your group were distinctly abnormal. This should not be taken too seriously in relation to your hypothetical objective. It is not possible, in our society, by means of histories of the usual type, to identify the time of occurrence or the severity of an exposure to lead which may have occurred. That two such instances popped up in your series is in no sense remarkable. One simply cannot appraise the significance of this, except to say that the exposure to lead had occurred fairly recently, since no such level of urinary excretion could be sustained for any prolonged period of time after the cessation of exposure. Such exposure may have been due to the ingestion of unusual amounts of lead in contaminated food or beverages, or to some similar but unknown source.

I do not believe that any further comments of mine, in this connection, will be of appreciable benefit to you. I repeat, however, that the work which you and your associates have carried out is of considerable interest to me, and will be to others. I believe it should be published.

Sincerely yours,

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Robert A. Kehoe, M.D.
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