

July 16, 1959

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Dear Doctor Gerlach:

I am sending you a reprint of the article of Bambach and Burkey, in which the "improved" procedure (a modification of Hubbard's method) of the dithizone method, essentially as we now use it, is described. Included with this is a further article by Cholak, Hubbard and Burkey, in which another significant improvement is described. There is also a typed out statement of the modifications, dated 3/18/58. With these at hand your analyst will be able to follow the procedure precisely, if he so desires.

The methods applicable to various materials were put together by Cholak and the procedures of sampling and the like were discussed by myself, in the booklet issued by the American Public Health Association in 1955. I send a copy of this, for such use as it may be to you.

Please accept my thanks for the analytical data which you forwarded to me. In going over these, I am impressed by the apparent fact that your results tend to run higher than ours. Since there is no direct comparison of results obtained on equivalent samples, the appearances may be deceptive, but it was just such a possible variable as this that caused me to insist upon having the analytical work done here. Our prior data on men in the occupations under investigation constitute the all-important base-line for these analytical findings, and I simply could not accept the intervention of a technical variable. No two laboratories obtain identical results for a variety of reasons, and this factor, which could be avoided so easily, might have made a great deal of difference.

In answer to your question concerning the concentration of lead in samples of urine of small volume, I think it wise to say that I have never approved of the use of a correction to reduce all results to the same specific gravity. This is a part of the same problem, and I can cover both aspects of the matter in the same answer.

There is no doubt, as we showed many years ago, that the volume

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of water put through the body in unit time - i.e., the rate of throughput - is an important factor in the concentration of lead (and many other substances) in the urine. It is not, however, the only variable, and there are times at which it is not the most important variable. These facts can be seen readily by the examination of the data on our experimental subjects who either ingested or inhaled known quantities of lead over long periods of time. Moreover, in following large numbers of men in a considerable number and variety of lead trades over the past twenty years, we have noted (1) that samples of urine of small volume are not representative of the individual general excretory performance; (2) that the smaller in volume they are, the less representative they are; and (3) that the two sets of samples that deviate most from the normal or average performance of the individual - namely, those that are very dilute and much too low in their lead content, and those that are very concentrated and are much too high in their lead content - are the least capable of being interpreted. It is actually foolhardy to draw any conclusion at all from them. The observations must simply be repeated under more favorable conditions. The application of a correction factor to them is not only foolish, physiologically but dangerous and irresponsible, clinically, for it is not quantitatively correct. In general, I prefer to disregard the results of the analysis of samples under 50 ml., and I do not trust the "normality" of a sample of urine that is provided at a single voiding unless it is of the order of 100 milliliters.

In dealing with inorganic lead, I rely mainly upon the lead concentration in the blood for clinical purposes. That is why I wanted these results on the blood of the men involved in the current tests. Unfortunately, the concentration of lead in the blood is not a sound indicator of the extent of the absorption of tetraethyl lead, and therefore one must rely upon the analysis of the urine in relation to exposure to, and absorption of, tetraethyl lead. In the present tests we are concerned with both types of lead compounds, and so I wanted both sets of results. I didn't need many results on the blood, for the reasons that the variability of the blood level, from any other cause than that of an increase or decrease in the lead in the body, is so slight that one determination of the blood lead is equivalent, in the statistical sense, to several determinations of the urinary lead. Moreover, there is a time lag in the change in the level of lead concentration as exposure to lead is incurred and as absorption (and accumulation) ensue, so that one confidently expects the change to occur in the urine before it occurs in the blood. In effect, the best means of detecting promptly a change in the current rate of lead absorption is that of determining the rate of lead excretion in the urine, while the best means of estimating the general increase in the total lead content of the body (skeleton and soft tissues too) is that of determining the lead content of the blood. So

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far as samples of urine are concerned, considering the physiological variability of the renal excretion of lead, one must do either one of two things, or both, if he is to establish a quantitative relationship between the rate of lead absorption and the rate of lead excretion; namely, he must either obtain a sample of urine of large volume by collecting it over a representative period of hours, or he must obtain quite a number of samples at intervals over a representative period of hours. In the first instance the vagaries of the urinary excretion will be averaged out in the one sample (for this reason we continue to collect samples of large volume from a representative group of men engaged in the manufacture of tetraethyl lead); in the second instance the average of several analytical results fulfills the same purpose. In the first instance, judgment must be exercised as to the length of time required, while in the other one's judgment is concerned with the number of samples required. In the latter instance, it is possible to discard certain samples, which, because of their very nature, are undesirable. Contaminated samples are misleading and distort the average; these can often be detected by their extraordinarily high content of lead. Samples of minute volume, also, are unsatisfactory, by their very nature, for the reason that they cover either too little time or are associated with abnormal stress.

I had not intended to write at such length, but the physiological principles involved in any such investigation as this, simple though it may be, need to be fully understood as a prelude to the interpretation or statistical manipulation of the data.

I trust that I have answered your question, even if I may appear to have taken a roundabout course.

Cordially yours,

Robert A. Kehoe, M. D.

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Enclosures

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