

November 30, 1948

Dr. E. C. Dodds,  
25, Porchester Gate,  
W.2., London, England.

Dear Dodds:

I must apologize in sack cloth and ashes for my unduly prolonged delay in commenting on the data and statistical work left in my hands. Actually, however, my slowness can be attributed in large part to my uncertainty as to what I should say. Not being an expert statistician, I have to struggle with the underlying philosophy of the procedure as well as with the figures, before I can see my way to any answer even in a fairly simple situation. When, as in this instance, the situation is far from being simple, I am somewhat at a loss. Nevertheless I shall do my best.

The problem which you and Smith are trying to solve is one that has given us a considerable amount of trouble for some time. You will remember that we observed a positive relationship between urinary volume and gross lead output years ago. This situation can be stated simply in the following terms:- the greater the volume of the urine voided by a given individual the greater will be his lead output per unit of time. The through-put of water being a factor in the gross output of lead from the body, it then becomes apparent, that a leaching-out, or a solubility effect of some type, occurs. The equation for this, at different levels of apparent lead content of the body, has not been determined, but this effect must be accepted as a fact. Now, there is also an effect, which we demonstrated several years ago by depriving an individual of water for some time, after allowing it freely for a time (a dilution, concentration test of the more or less orthodox type), - that of concentrating lead in the urine when the latter is excreted in relatively small volume per unit of time. We have also called attention to the seasonal variation which occurs in this climate and which we described as being based on these phenomena. Obviously these two effects - leaching out, so to speak, and concentrating - operate in opposed directions and depend upon different mechanisms and the one combats the other. It is not to be supposed, therefore, that there will be a simple linear relationship between water output and lead output. Moreover, I doubt if any simple mathematical expression would obtain at the extremes of the urinary volume or of its representation in the terms of specific gravity. One variable that is certain to influence the outcome is the disturbed equilibrium which is associated with current lead exposure and absorption. If the latter is highly variable, as it may well be from day to day or even (in a TEL plant) from hour to hour (the absorption in association with exposure to inorganic lead compounds in the main is too gradual to create much of a problem from one hour to the next, but TEL vapor is a big variable),

KE 0010382

Dr. E. C. Dodds - (2) - November 30, 1948

the whole relationship of urinary volume to lead concentration is likely to be correspondingly disturbed. Other physiological factors can only be dealt with speculatively, but certainly the equilibrium in the blood between lead in the erythrocytes - there is probably a complicated intracellular equilibrium also - and lead in the plasma, and between the non-diffusible and diffusible lead in the plasma itself, has to be considered. (The influence of BAL on the blood and urinary lead concentrations demonstrates that such factors have to be given serious consideration.)

Because of the foregoing considerations I am skeptical of the physiological validity of the mathematical expression proposed by Levine and Fahy. I am quite prepared to accept their procedure, however, if it will work pragmatically, i.e. if it has statistical validity despite the complexity and uncertainty of the physiological factors involved. Our own observations have not satisfied me on that score, nor have those of Levine and Fahy, and while yours looks much more convincing, your questions about your data and calculations are sufficient for me. I feel that it will be necessary to carry out further observations, and that it is especially important to do so under conditions which will control the factor of variable exposure during the observations. I think we should be able to answer the questions quite satisfactorily if we had determined regularly the specific gravity of the urine specimens voided by the subjects of our long-term experiments when the lead intake per day was being kept substantially constant over months and years.

Unfortunately this was not done, but we plan to make suitable observations when we resume our work on subjects exposed to constant concentration of lead in the air. I know of no other way to obtain a really satisfactory answer to the problem presented by the variability of the lead metabolism and excretion from hour to hour and from day to day. I have great hope of establishing the facts clearly as to the relationships between urinary volume and urinary lead output and concentration, by the careful study of our data on the subjects referred to above. Unfortunately I have been so involved in other things that this has not been done.

It is my belief that the most important factor in the lead output of exposed workmen from day to day is the extent of their lead absorption from day to day. Therefore, I am dubious of the wisdom, from the aspect of safety, of using a factor based on water output, by which to scale down high results. (In practice, one is more likely to scale the high results down than to increase them, because of the conditions that prevail with respect to the collection of samples of urine from workmen.) I prefer to take the high results as a warning, to check them by means of repeated analyses on individuals suspected of having been unduly exposed, and by multiple analyses to arrive at a safe and conservative conclusion. It is for that reason that I have never been willing to apply the procedure of Levine and Fahy. In practice we look either at repeated results on the same individual, or we use the lead concentration in the blood as a means of stabilizing and checking the conclusions drawn from the analysis of the urine. When one is dealing with groups of persons, in sufficient number in relation to specific

3.10.19

I shall send you some information on the beryllium problem when I can get together a satisfactory resume of its present status. It is a long story in some respects, and I had better deal with it separately.

See letter 10/2/64 to Dr.  
Tebrock filed under  
Schlosser

Robert A. Kehoe, M. D.

P. S. We succeeded in finding a very good man to take our job on the petroleum problem, and we expect to have him at work very soon.

Copy by Air Mail.  
Original by Steamer.

KE 0010384