January 12, 1943.

Dr. Karl Bambach,
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Dear Dr. Bambach:

I have read with interest your paper with Kehoe and Logan in the latest Journal of Pharmacology and Experimental Therapeutics and should be grateful for a reprint.

It is unfortunate that you were led to state that your data cast doubt upon my conclusions, when as a matter of fact the data you reported are rather irrelevant to those conclusions. Since I may have failed to some extent in making myself perfectly clear in my paper on the lead citrate complex, perhaps I may take this opportunity of clarifying the issue.

By studying potentiometrically certain solutions of sodium citrate and lead nitrate I was able to arrive at a formula and a dissociation constant (at the ionic strength and pH of plasma) for a lead citrate complex which I had previously shown to exist. From the value for this constant and the normal citrate concentration in human blood it was possible to arrive at a value of about 20 for the ratio: (lead citrate complex)/(lead ion). To state it simply these data indicate that 20 times as much lead existed as a soluble lead citrate ion than as simple lead ion. Since without knowledge of the presence of soluble complexes of lead in the blood all the soluble lead must be in the form of the simple lead ion, I was able to state that "the normal blood citrate is capable of keeping in solution an amount of lead 20 times as great as that which the solubility of the insoluble lead compounds of the body would otherwise permit. I do not see how your findings of less than 10% of the blood lead in the serum (a fact which I had always assumed as so on purely theoretical grounds) in any way casts doubt on or is even pertinent to my conclusion. Note that I did not say that citrate of normal blood keeps 20 times as much lead in solution as in insoluble form. Note also that you have no reason for assuming that blood in plasma is in solution, as a matter of fact there is good reason to feel that most of the plasma lead is non-diffusible. Even with 1% of the lead of the blood present in the plasma there could still be 20 times as much lead present as the citrate complex than as simple lead ion.

In only one case do your results approach pertinence to my conclusions.

This is your experiment with citrate as an anti-coagulant. From purely theoretical considerations I should expect citrate to cause an increase in plasma lead at the expense of erythrocyte lead, but even here a failure to observe such a redistribution would not reflect upon the validity of my conclusions since citrate could cause an increase in diffusible over non-diffusible lead entirely within the plasma lead fraction without causing a change in total lead in the plasma. In your experiment, however, the citrate was in contact with the whole blood only momentarily before centrifugation - hardly a fair length of time in which to detect changes in so complex a system of equilibria. Nevertheless, tho you find no significant change in plasma lead after the addition of citrate, I find on examining your own figures a significant increase in plasma lead where citrate was used over that with no anticoagulant. (If one ignores the "less than" sign in the experiment on animal 7 one finds a mean increase in plasma lead with citrate of 45% with a standard error of 15.4, a t value of 2.92 and a p value of 0.05 or less which is certainly significant. If one leans over backwards and calls the increase in animal 7 nil, one finds a mean increase of 40% with a standard error of 17.1, a t of 2.34 and a p value slightly greater than 0.05, which certainly approaches statistical significance.) Thus we find that far from casting doubt on my conclusions, the one pertinent experiment in your paper actually confirms my theoretical predictions.

As a matter of fact for the past six months I have been working in association with Dr. Aubin in an effort, among other things, to test my theoretical conclusions as they apply to the lead partition in blood in vitro and in vivo. It requires more than an understanding of the partition of lead between plasma and cells to confirm or reject the significance of the lead citrate complex in the state of lead in the blood. A direct approach would be by a study of lead ion concentration in blood, but since that is manifestly impossible with present techniques, an approach can be made by studying the diffusible fraction of plasma lead and the effect of citrate thereon.

Perhaps I, in turn have misunderstood your criticism of my conclusions. If so the above explanation may have been unnecessary. Aside from that one regrettable misconstruction I feel that your paper was most interesting and has answered a problem of fundamental importance in the physiology of lead poisoning.

Respectfully,

Seymour S. Kety

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