April 15, 1949

Dr. Henry W. Ryder,
19 Garfield Place,
Cincinnati 2, Ohio.

Dear Henry:

I have read your letter of April 5 with considerable care, and I should certainly not want to urge upon you the desirability of including in the paper the discussion which I added. I agree with you that the paper is too long and that it should be reduced rather than increased. If I felt that it might be helpful to deal very simply with certain of the physiological implications of the facts, it was because I felt that the conclusions would not already repay the reader who was interested in the significance of the observations rather than the statistical procedure. I also felt that it was necessary to amplify in some measure your statement in the summary or conclusions that lead occurs in a different form in the plasma than in the erythrocytes. I certainly felt that this was a matter for discussion rather than for factual statement, and unless you do discuss it I think you should delete any reference to this point. I think you took too seriously my use of the word "barrier" which was not meant to have any technical significance, any more than that which was involved in some degree of hindrance to simple and prompt diffusion.

I indicated certain other suggestions in the manuscript returned to you, which I think are important, and I have no doubt they will be taken care of appropriately. Nevertheless, I do mention the fact that the paper should not be set up without very careful and critical examination of any statements with reference to analytical procedures, by Cholak. Then again, there is another point which may not seem important to you, but which is very important, namely, that any reference to exposure to leaded gasoline should be stated with great care. This subject is so badly misunderstood by most doctors at present, that we in this Laboratory must not be guilty of contributing to the confusion. It is obvious that any paper on this subject which carries the name of members of our staff must be regarded as speaking for all of us, and therefore I shall wish to see the final draft of the paper before it is offered for publication. Otherwise, of course, it could not carry my name.

Sincerely yours,

Robert A. Kehoe, M. D.

RAK ef

N 6210

HENRY W. RYDER, M.D.
19 GARFIELD PLACE
CINCINNATI 2, OHIO
PARKWAY 7696

April 5, 1949

Dr. Robert A. Kehoe
Kettering Laboratory
Eden and Bethesda Avenues
Cincinnati 19, Ohio

Dear Bob:

I would like to refer to your extended discussion of the plasma lead paper.

If lead is ordinarily lost from the kidneys by a combination of glomerular filtration and tubular resorption, as is the diffusible substance urea, the concentration of diffusible lead in the plasma sufficient to account for the normal concentrations of lead in the urine would be $\frac{.025}{40.10} = .06$ γ%, which is about 1% of the amount found in the plasma of men without lead exposure. If lead appears in the urine following tubular excretion, like phenol red, the plasma-urine concentration ratio might be 10 or 20 times this 40:1 urea ratio, which means that the normal plasma diffusible lead would be .0015 γ%. The same mechanisms in cases of severe lead exposure would demand plasma diffusible lead concentrations of about 1 and .02 γ%.

After BAL administration the amount of lead excreted in a given time is more constant than the concentration. This suggests that the BAL-lead complex appears in the urine following tubular excretion. A urine concentration of 10mg., γL would demand a blood concentration of $\frac{10}{400.10} = 2.5$ γ%. Quite possibly the excretory mechanism would not be saturated by such concentrations of plasma diffusible lead so that the blood-urine concentration ratio could be considerably higher than it is for phenol red.

The observed concentrations of lead in the urine and blood can therefore be explained by known mechanisms if we make the same assumptions for the behavior of lead that are reasonable in the light of the behavior of other substances; that is, on the average from 99.0 to 99.95% of the plasma lead is bound to protein, that the remainder is diffusible and cleared rapidly from the blood either like urea (usually) or phenol red (when it is part of a poorly dissociated diffusible complex). While these mechanisms are admittedly complex, they are the same which handle all substances about which we have information.

From these considerations one would not speak of the plasma lead as a "barrier", but an inert fully saturated component that took no part in physiological or pathological mechanisms. An investigation of the plasma lead in patients with nephrosis, multiple myeloma, lymphogranulum venereum, renal failure and hyperparathyroidism might shed indirect confirmatory light on this formulation.

Further considerations are that the amount of lead in the erythrocytes is small compared to that in the rest of the body, and that certain, at least, of the body cells might act just as well or better than the erythrocytes in removing

diffusible lead from the plasma. Further, we have no clinical or experimental evidence to suggest that the erythrocytes act as an effective, active buffering mechanism, independent of other systems.

You may guess that I am not anxious to include the extension of the discussion in the present paper. The paper is admittedly too long even though it is devoted solely to a statistical analysis with direct conclusions therefrom. We would not have to resolve our differences in opinion as to the physiological significance of our findings if you would expand your comments into a more clinical paper and publish them where they would be more widely read.

I am enclosing a copy of your suggestions which I wish you would interpret in the light of these considerations and send them on to me to be incorporated in the paper.

Sincerely yours,

Henry W. Ryder, M. D.

HWR/fk
enc.

It seems apparent from the facts set forth that the lead which is carried in the plasma of the blood exists in an entirely different form from that in the erythrocytes. Furthermore there is no evidence of the existence of an equilibrium between the two, but rather it appears that they exist independently. The lead concentration in the whole blood is clearly dependent, among other factors, upon the extent of the current stream of lead absorption, whereas the concentration in the plasma is substantially constant, unless indeed, it varies within quite narrow limits which are below the limits of present analytical precision. Considering the rapid loss of lead from the blood following the administration of one dose of BAL, its prompt appearance in the urine in greatly increased concentration, and the present lack of any evidence of even fleetingly high concentrations of lead in the plasma, it seems apparent that there is only a minute but apparently constant barrier to the passage of lead from the plasma into the tissues and the urine. Likewise, within a few hours after the administration of BAL, the return of lead from the tissues into the blood occurs readily, but the overwhelming portion of that which enters the blood stream is taken up promptly by the erythrocytes and is removed from the plasma down to a virtually fixed concentration, by the erythrocytes. This behavior on the part of the erythrocyte must be a profoundly important factor, under the usual conditions associated with the absorption of lead, in the prompt removal of lead from easy or continuing access to the tissues of the body. It might be suspected that the onset of the symptomatology of lead intoxication might well be due to some loss of capacity on the part of the erythrocytes to retain lead, whereby the tissues come to be bathed, so to speak, by plasma having an higher than normal concentration of lead. If such is the case, there is no present evidence of it. Either it does not occur, or the shift from the erythrocyte into the tissues and excreta occurs so rapidly as to evade detection. Nevertheless, it is difficult to demolish the suspicion that somewhere in this complex mechanism may be found the explanation of the common observation that two men with substantially identical concentrations of lead in their tissues may be so

disparate in their physiological status that one may be perfectly well at a time when the other is acutely ill.