BALTIMORE CITY HOSPITALS

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DEPARTMENT OF PUBLIC WELFARE

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Robert A. Kehoe, M.D.
The Kettering Laboratory
College of Medicine
Eden Avenue
Cincinnati 19, Ohio

Dear Dr. Kehoe:

Thank you for your letter of July 16th. I appreciate your answers to the questions that I raised.

I am particularly glad to know that your data indicate definitely that the lead concentration in the brain is significantly elevated in acute lead encephalopathy. I certainly agree with you that the most important aspect of this problem is the preventive one. We hope to turn to this problem when the current studies on treatment are completed.

I am enclosing a copy of my paper before the American Pediatric Society, May 1963, on the combined use of EDTA and BAL. Perhaps even without slides it may give you some idea as to our findings. I am also enclosing a pencil drawing of the urine stream spliter that we have employed for some special studies in the past. This device will work if great care is taken to level it exactly and if the two capillary siphon arms are very carefully made by the glass blower. They should be identical in size and shape.

Concerning question #3 that I raised, in rereading your paper I cannot find the exact paragraph from which I gained the impression that lead absorption is accelerated in the lead intoxicated patient. However, your response has clarified this point.

Yours sincerely,

J. Julian Chisolm, Jr., M.D.
Associate Pediatrician-in-Chief

JJC/esp

THE USE OF EDATHAMIL CALCIUM DISODIUM (EDTA) AND 2,3-DIMERCAPTOPROPANOL (BAL) IN COMBINATION FOR THE TREATMENT OF ACUTE LEAD ENCEPHALOPATHY

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Introduced by Harold E. Harrison, M.D.

Mr. Chairman, members of the American Pediatric Society and guests - the present treatment of acute lead encephalopathy with edathamil calcium disodium is far from satisfactory. While no obvious clinical complications arise from the use of EDTA in children without encephalopathy, we have observed children with acute encephalopathy whose impaired renal and central nervous system functions deteriorate further during the first 48 - 72 hours of EDTA administration. While such deterioration may reflect the natural progression of fulminant disease, recent studies in animals suggest that EDTA may itself contribute to this deterioration.

This report is addressed to two questions:

1) Does EDTA enhance the toxic effects of lead in children with severe plumbism? and

2) If so, can such toxic metabolic effects be reversed by the simultaneous administration of a thiol reagent such as 2,3-dimercaptopropanol or BAL?

To investigate these questions 40 young children with acute plumbism, including 15 with encephalopathy, have been studied at the Baltimore City Hospitals and Harriet Lane Home. Biochemical parameters sensitive to the toxic effects of lead were measured serially during treatment. EDTA and BAL were given in a uniform manner as follows: Both were given intramuscularly at 4 hour intervals for 5 days: BAL in a dose of 4 mg/kg/dose and the calcium salt of EDTA in a dose of 12.5 mg/kg/dose.

One of the principal toxic actions of lead is inhibition of sulphydryl enzymes. Such an enzyme is d-aminolevulinic acid dehydrase. This enzyme is widely distributed throughout the tissues and many studies show that it is <u>exquisitely</u> sensitive to the toxic effects of lead. Thus, changes in the concentration of its substrate, d-aminolevulinic acid, in body fluids can provide an index of lead's toxic effect upon it. May I emphasize that d-aminolevulinic acid, a precursor of heme, is not

toxic and is not known to bear any direct relation to the symptoms of plumbism. This system is chosen only as a model for study.

SLIDE 1 PLEASE - The concentration of d-aminolevulinic acid in plasma was measured in all 40 patients prior to treatment. Measurements were also made in 10 healthy children. The results are shown here. Reading from right to left, the values tend to rise with increasing severity of plumbism. In patients with mild encephalopathy - second column from your left - plasma d-aminolevulinic acid ranges between 0.2 and 1.4 γ/ml. This is 4 - 25 times greater than the mean normal value found in healthy children - as shown in the column at the far right.

LIGHTS PLEASE.

The studies were carried out in 3 phases. First - EDTA alone was administered to 10 patients and the concentration of d-aminolevulinic acid in plasma was measured after the injection of each dose. During the initial 48 hours of EDTA therapy, plasma d-ALA concentration increased further if the pre-treatment concentration was greater than 0.25 γ/ml, but not if the pre-treatment concentration was less.

Next, BAL and EDTA were given alternately to 4 patients whose initial plasma d-ALA was 0.25 γ/ml or higher in order to determine - whether - BAL might reverse the rise in plasma d-ALA observed following EDTA. SLIDE 2, PLEASE - This shows the result in two representative subjects of this group. BAL was injected first - as designated by the arrow at point B. During the ensuing 4 hours - as indicated by the solid portions of each line - the elevated plasma d-ALA decreased toward normal, but when EDTA was injected at point E the plasma d-ALA increased - as shown by the dotted portion of each line. When BAL was again given the rise following EDTA was reversed. These findings indicate that EDTA can enhance, at least one of the toxic metabolic effects of lead, and that this effect can be reversed by BAL.

The third phase of the study was carried out during the summer of 1962 and includes 11 patients with acute lead intoxication. Four patients, 2 of whom had mild encephalopathy, were randomly allotted to treatment with EDTA alone. Five patients were randomly allotted to combined BAL and EDTA therapy. In addition 2 comatose patients were arbitrarily placed in the combined therapy group, so that this group includes 7 children in all, 2 with severe encephalopathy, 2 with mild encephalopathy

and 3 symptomatic patients without encephalopathy. In this group BAL alone was given as the initial dose; beginning 4 hours later both BAL and EDTA were given simultaneously for the next five days. SLIDE 3, PLEASE - The most striking difference between the two groups was the much more rapid decrease in blood lead concentration in the combined therapy patients as shown in this graph. In each patient blood lead content was measured at 8, 24, 48, and 72 hours after the start of therapy. The values found at each time are plotted logarithmically on the ordinate as a percentage of the pre-treatment value. The dark circles show the data for the EDTA patients; the open circles the data for the BAL-EDTA group. By 72 hours blood lead is reduced to 25% or less of the initial value in the combined therapy group, but, at this time, it is still approximately 50% of the initial concentration in the EDTA group. The difference between the two groups is statistically significant at the 1% level at 8, 24, and 48 hours and at the 0.1% level at 72 hours. NEXT SLIDE, PLEASE. This shows some of the actual data from which the results on the previous slide were calculated. It is quite clear that blood lead concentration decreases far more rapidly during the first 72 hours in the combined therapy group - as indicated by the solid lines -

than it does in the EDTA group - as indicated by the dotted lines.

In these patients serial determinations were also made of d-Aminolevulinic acid in plasma and urine and of lead and amino acids in urine. NEXT SLIDE, PLEASE - This shows data from 6 representative patients. The urine d-aminolevulinic acid output is plotted on the ordinate as the d-ALA/creatinine excretion ratio against time on the abscissa. One can see that d-ALA excretion initially increases in the EDTA patients - as indicated by the dotted lines - but that it decreases steadily from the start of therapy in the BAL-EDTA group. The excretion of d-ALA shown here, mirrors well the changes in plasma d-ALA found in each of these patients. Simultaneously, urine amino acid excretion increased in 2 of the 4 EDTA treated patients; but no such increases were detected in the BAL-EDTA group. LIGHTS PLEASE.

Urine lead measurements indicate that the more rapid decrease in blood lead concentration in patients treated with both BAL and EDTA is largely due to the higher initial urinary excretion of lead in this group. SLIDE PLEASE - In this graph the daily urine lead outputs of 4 patients with <u>severe</u> encephalopathy are compared. The height of each bar indicates the amount of lead excreted on each of the 5 days

of therapy. Two combined therapy patients are compared with 2 cases of severe encephalopathy treated in prior years with EDTA alone. The left-hand member of each pair of bars is from the BAL-EDTA patients, the right-hand bars are from the EDTA patients. Patients R.N. and M.G. who received BAL and EDTA excreted 18.6 mg and 15.3 mg of lead during the first 24 hours. This is 37% and 39% respectively of their 5 day total lead outputs. Patients A.W. and C.R. who received EDTA only excreted 25% and 16% respectively of their 5 day totals during the first 24 hours.

LIGHTS PLEASE.

GIVE METHODS IF BELL HAS NOT RUNG.

d-ALA - Mauzerall and Granick

Pb - Bessman and Layne

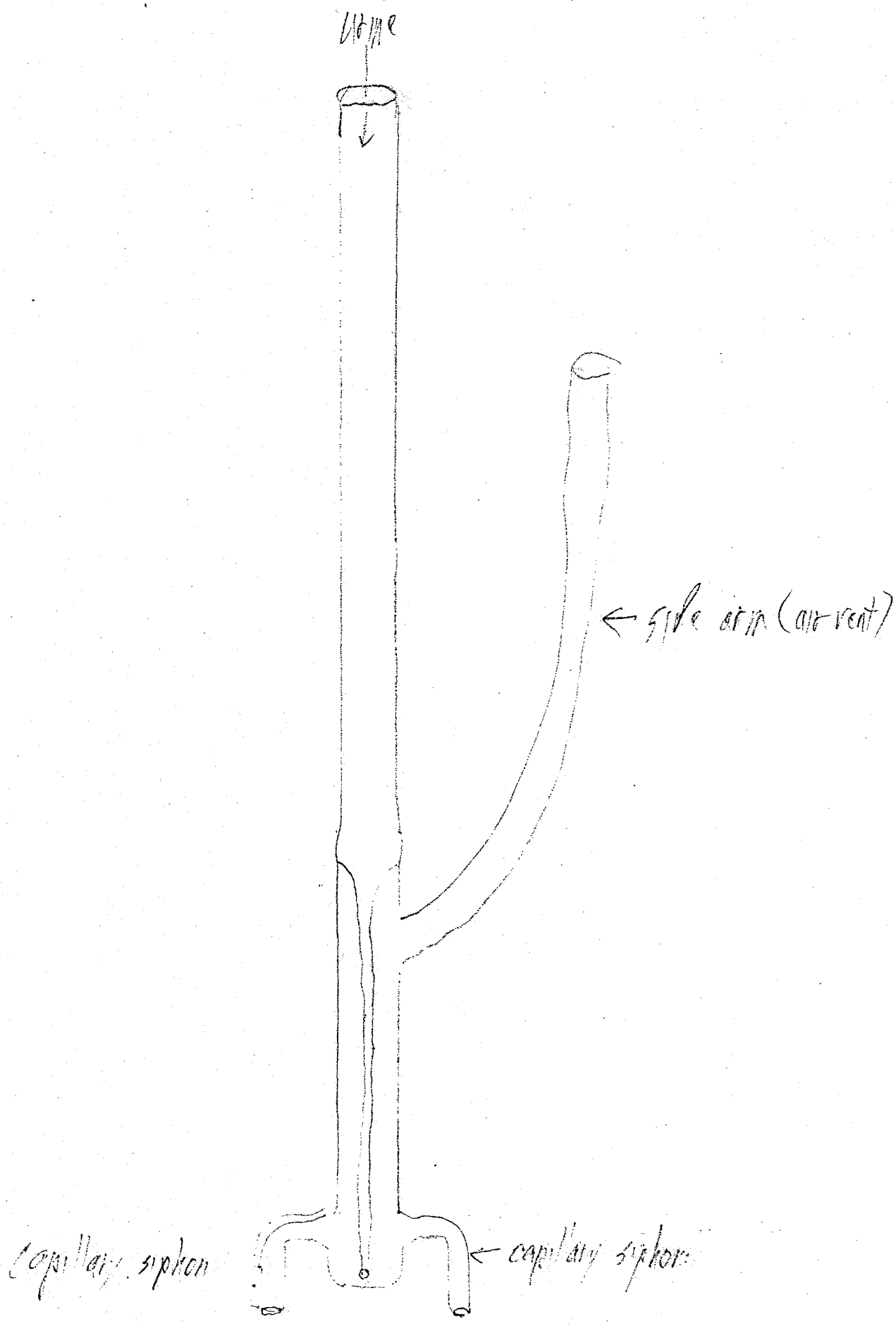
AA - paper chromatography

Although the number of patients studied is small the various parameters measured are consistent within each group so that the following conclusions seemed justified. Blood lead decreases much more rapidly when BAL and EDTA are given simultaneously than it does when EDTA is given alone. This difference is statistically significant at a P value of less than 1% and is probably due in large

part to the higher initial rate of urine lead excretion. In addition, BAL may ameliorate some of the toxic metabolic effects of lead in the tissues, whereas, EDTA, if given alone, initially enhances some of these toxic effects. The data on amino acid excretion and d-aminolevulinic acid levels in plasma and urine are in accord with this hypothesis. With respect to clinical comparisons - I can only say that deterioration of central nervous system function and renal function did not occur in the three sickest patients who received BAL and EDTA simultaneously. On the basis of previous experience such deterioration might have been anticipated had these children received EDTA alone. These data suggest that the combination of BAL and EDTA is superior to EDTA alone, especially in children with encephalopathy. For such patients supportive measures include: administration of parenteral fluids in amounts sufficient to meet basal needs, to replace deficits and to provide for adequate urine flow; withholding of oral fluids; maintenance of body temperature at normal but not hypothermic levels; control of convulsions with paraldehyde; and prevention of hypoxia. Finally, may I speculate that the combined use of metal binding agents such as EDTA and BAL - which have differing metabolic effects,

differing toxicities and differing distributions in the tissues may be efficacious in other heavy metal poisonings. At least the data in lead poisoning suggest that this idea merits exploration.

Thank you.



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