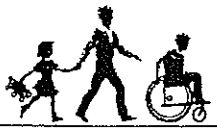
Exhibit 28



Kennedy Krieger Institute

A comprehensive resource for children with disabilities

January 25, 1993

Thomas R. Hendrix, M.D.
Chairman
Joint Committee on Clinical Investigation
Administration 129
Johns Hopkins University School of Medicine
720 Rutland Avenue
Baltimore MD 21205-2196

RE: RPN 92-11-19-01, entitled "Toxicity of Lead in Children - Clinical Center" and your letter of December 9, 1992

Dear Dr. Hendrix:

I am glad to respond to the questions set forth in you letter of December 9, 1992 and to provide some background for this multi-center study. Our application was submitted in response to an RFA issued by the National Institute for Environmental Health Sciences (NIEHS), in which they proposed a randomized, double-blind, placebo-controlled evaluation of a course of oral DMSA. They specify in the RFA that the outcome variable will be the child's neurodevelopmental status at four to five years of age. They invited proposals designed along the general outlines provided by them, with the understanding that the three proposals which they considered best would be funded and that the principal investigators for these three proposals would get together and agree to a single, common protocol. Therefore, the protocol which I submitted to you is not likely to be the final protocol. So much for the background. Now for the questions.

1. The current standard therapy for children with elevated blood lead levels is to give chelation therapy when the blood lead concentration exceeds 40-45 μg Pb/dL whole blood. When meso-2,3-dimercaptosuccinic acid (DMSA) is used at lower blood lead levels, it is considered investigational. In the NIEHS proposal, children with blood lead levels between 20 and 40 or 45 μg Pb/dL whole blood will be randomized to DMSA or a placebo. The proposal suggests that they receive a single course of oral DMSA. NIEHS would obtain the necessary IND from the FDA. Since NIEHS requires that this be an outpatient protocol, we have in our proposal specified safe housing for administration of the drug on an outpatient basis. Both DMSA-treated and placebo-treated subjects will have repeated housecleaning to suppress dust lead levels in the home. I know of no one who presently recommends treatment with chelation therapy at blood lead levels lower than 25 μg Pb/dL whole blood.

2. All subjects will be enrolled at either 12-30 months, or 18-36 months of age, and they will have repeated professional housecleaning until they are four or five years of

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age to suppress dust. We would not treat any children living in grossly substandard housing. Data from the prosepctive studies now in progress (Boston, Cincinnati, Port Pirie) indicate that cognitive outcome is best related to time-weighted lifetime average blood lead concentration. Thus, in the study proposed here, ability to lower this average will probably determine outcome. Those who receive DMSA will be compared with those who receive the placebo. In my view, the outcome of this study will not be determined by a single course of DMSA, but, rather, by the ability to suppress lead-bearing dust in the home over the long run and the degree and persistence of hand-to-mouth activity in the children. In short, the study involves children for whom chelation therapy with DMSA is not as yet approved by the FDA.

3. With regard to the question of side effects, I have now treated 60 children in a total of about 100 28-day courses of oral DMSA. In these children, I have not seen any significant elevations in the transaminases. We did have one child with an atopic history who developed giant urticaria when a second course was instituted. The only significant side effect that I have seen has been significant elevation in serum alkaline phosphatase. Measurement of isoenzymes indicates that the increase is due to alkaline phosphatase presumably derived from bone. There has been no evidence of liver dysfunction. This reaction has been reversible and has occurred in two patients on the study protocol. I am aware of its occurrence in two other children in the city of Baltimore not on my study protocol. The only significant reaction that I am aware of in adults occurred in a Danish worker who developed a fixed-drug eruption. I have observed neutropenia, but this has always been readily explained by a concurrent viral infection. I have treated two patients with sickle cell disease and six with G-6-PD deficiency, none of whom showed any untoward reaction. It would appear that the drug is remarkably free of serious side effects. The great increase in alkaline phosphatase activity (and I am talking about increases to 1500-4000 iu) is not readily explained.

I hope these responses will be adequate. Please let me know if there is any further information that you require. I await your reply before doing anything about the consent form.

Yours sincerely,

J. Julian Chisolm, Jr., M.D.
Director
Kennedy Krieger Institute Lead Program

JJC:crz

cc: G. Goldstein

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