We felt we had demonstrated a reasonably high margin of safety, and after careful reevaluation of the data we still feel we have demonstrated a low level of toxicity with a wide margin of safety.

The dosage we are recommending for M. E. R.–29 is 250 mg. once daily. On a weight basis, this would constitute a dose range of 3.6 to 4.16 mg./Kg. The acute toxicity studies we reported showed the LD_{50} dose to be 1600 mg./Kg. intraperitoneally and 2000 mg./Kg. orally. We consider this to be extremely low acute toxicity.

Data submitted showed no untoward hematopoietic response at dose levels used in rats or monkeys. The dose range used in rats went as high as twenty times our proposed clinical dose, and monkey dosage was ten times the proposed clinical dose. Body weight gains were not affected in rats or monkeys at doses far in excess of the proposed clinical dosage. Relative organ weight changes in rats were due to total body weight changes, and in each case histopathologic examination failed to suggest other causes for such change.

Three male and three female dogs with appropriate controls have been on M. E. R.–29 for better than 3 months at 25 mg./Kg. We have evaluated hematopoietic response, body weight and food consumption, and liver studies (serum bilirubin, alkaline phosphatase, serum transaminase, and BSP retention determinations). At 3 months all were within normal limits. We plan to autopsy these animals after 6 months to complete our records. We are agreeable to making the autopsy data available to you at that time. However, we strongly feel that the 16-month study in monkeys has more than adequately demonstrated the safety of M. E. R.–29. We would, of course, be willing to withdraw the product from the market if real toxicity problems were uncovered in our autopsy work.

As I indicated, we have very carefully and objectively re-evaluated our safety data and we feel that the margin of safety demonstrated is exceptionally good for a metabolic drug. I hope this will enable you to complete your consideration of our New Drug Application for M. E. R.–29. I should greatly appreciate a telephone call if there are any further problems needing discussion.

Sincerely yours,

F. Jos. Murray.

October 6, 1959.

Memorandum of Interview

Present:

Dr. Wm. King and Dr. F. Jos. Murray, The Wm. F. Merrell Company, Cincinnati, Ohio.

Dr. E. L. Goldenthal, Dr. R. Megirian, and Dr. B. J. Vos, Division of Pharmacology, Food and Drug Administration.

The visitors called to discuss their NDA 12-066, M.E.R.–29, Triparanol capsules, intended for lowering blood cholesterol. They have a 6-month dog study which has been in progress 5 months at dose levels of 10 and 25 mg./kg. No adverse effects have been noted. A rat study at 3 and 10 mg. per kg. has also been completed in 5 months. These tests were not included in the original NDA because no results had been obtained. We said the top dose in both the dog and the rat tests should be higher. We advised starting a minimum of one group of dogs for a minimum of three months at the highest dose they could tolerate in the hope of producing some evidence of toxicity. Also, we advised starting 3 additional dosage groups of rats as the dosage employed was far too low. The rat study will go for one year. We stated the earliest that we could pass on safety was after these rats had completed 6 months.

B. J. Vos, M.D.

The Wm. S. Merrell Co.,
Scientific Division,
Cincinnati, Ohio, October 13, 1959.

Dr. Jerome H. Epstein,
New Drug Branch, Food and Drug Administration,
Washington, D.C.

Dear Doctor Epstein: This will confirm our plans for meeting in your office at 10:00 a.m. on Friday, October 16, to discuss our M. E. R.–29 New Drug Application.

We have once again reviewed our animal studies in the light of your Pharmacology Division's opinion that we have not satisfactorily demonstrated safety