of the product. We, of course, continue to have confidence in the safety of M. E. R.–29, as evidenced by our intention to market in Canada where we have an effective New Drug Submission. As you well realize, we can ill afford to be wrong in our judgment on the introduction of any new product, and we do not feel that M. E. R.–29 is going to spoil our record.

We feel that the significance of the studies carried out in monkeys has been entirely overlooked. We submitted data on three monkeys dosed continuously for sixteen months. If a new drug fails to show untoward effects in three animals, such effects would probably show up only in unreasonably large groups of twenty-five or more. Such groups are impractical and not used generally.

As discussed with representatives of your Pharmacology Division, we have drug diet experiments in progress in rats at 3 mg./Kg. and 10 mg./Kg. This was set up to be a lifetime study for our own information, and because of this objective we used a dose which we were sure would not interfere with eating.

A second rat experiment was carried out with oral tubing for six weeks at 75 mg./Kg. and 37.5 mg./Kg. Some adrenal and liver (fatty infiltration) changes were recorded at the higher dose. If we had continued at this dose, we assume this would have led to more serious damage. However, it is obvious that this damage could have been nutritional instead of drug-induced, since food consumption decreased.

A third rat study was carried out with tubing for three months at 25 mg./Kg. and 50 mg./Kg. At the higher dose level there was a 36 per cent reduction in body weight gain in males starting in six weeks. Again, it is our feeling that when the animals stop eating and lose weight there is no point in going on with the experiment, since nutrition enters into the picture and findings on the tissues would be meaningless.

Your Pharmacology Division has insisted that it is essential to show toxicity (even though we feel it is more important to show lack of toxicity at therapeutic dosage and at reasonable excesses of therapeutic dosage), and we would like to point out that lack of eating has been a consistent sign of toxicity in the rats. On this basis, one might assume that the first clinical evidence of toxicity would be loss of appetite. This is borne out by our clinical experience. You will note that the Hollander and Chobanian paper reports four cases of nausea, epigastric distress or heartburn on a daily dosage of 750 mg. The symptoms disappeared on a dosage of 250 mg. The paper by Oaks and Lisan reports 13 per cent (5) subjects with nausea and vomiting at 1000 mg. per day. It was not necessary to discontinue the drug in these patients. No side effects were encountered at 250 mg. We again stress that the decrease in food consumption in animals on moderately high doses suggests we will not be able to obtain tissue damage in animals (other than fatty infiltration of the liver) without complicating the picture with inadequate nutrition.

I appreciate your taking the time to meet with me, and I hope we may be able to reach some satisfactory solution on this problem.

Sincerely yours,

F. Jos. Murray.

Memorandum of a Conference

October 16, 1959.

Present: Dr. F. Jos. Murray, Dr. R. McMaster, The Wm. S. Merrell Company, Cincinnati, Ohio; Dr. Robert Megirian, Dr. Edwin Goldenthal, Division of Pharmacology, Food and Drug Administration; and Dr. Irwin Siegel (part time), Dr. J. H. Epstein, New Drug Branch, Bureau of Medicine.

Subject: Toxicity data for M.E.R.–29, FDA 12–066.

The representatives of the Wm. S. Merrell Company came in to discuss the existing differences concerning the toxicity data submitted in support of their new drug application for "M.E.R.–29."

Since there is a wide difference of opinion concerning what they feel is sufficient data and what we feel is sufficient, it was agreed that the company would submit additional animal work in support of their application.

The following types of studies shall continue or be instituted:

(1) Present animal work will be continued to completion.

(2) A six-month study in dogs will be run at these level(s) calculated to produce toxicity.