(3) Rats will be run for 12 months at several dose levels, one group being a pan-fed control group to determine the actual toxicity of the drug.

Results of the above studies will either be submitted at the end of three or six months for our review.

JEROME H. EPSTEIN, M.D.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C., November 6, 1959.

THE WILLIAM S. MERRELL CO.,
Lockland Station, Cincinnati, Ohio.
(Attention of Dr. F. Jos. Murray.)

GENTLEMEN: Reference is made to your new drug application dated July 21, 1959, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation "M. E. R.–29."

We also acknowledged receipt of your additional communications dated September 24, 1959 and October 13, 1959.

As agreed upon by you and your colleague, Dr. R. McMaster, you will perform additional toxicity studies to further demonstrate the safety of this drug in chronic administration. We shall be happy to review this data when you feel that the evidence in the animal work is conclusive.

We shall withhold any comment on the revised labeling until the aforementioned toxicity studies are complete.

The application remains incomplete as stated in our letter of September 14, 1959.

Sincerely yours,

JEROME H. EPSTEIN, M.D.,
Medical Officer, New Drug Branch, Bureau of Medicine.

Office Memorandum, U.S. Government.

FEBRUARY 23, 1960.

To: New Drug Branch: Attn: Dr. Talbot.
From: Division of Pharmacology.
Subject: Triparanol Capsules, MER–29 (Wm. S. Merrell Co.) NDA 12–066.

The additional toxicity data submitted by Merrell have been reviewed. The original toxicity data submitted for rats included a 3 week study at 40 mg/kg/day, a 3 month study at 25 and 50 mg/kg/day and a 6 week study at 75 mg/kg/day. The consistent finding in these studies was a marked decrease in weight gain.

The new data include a 9 month study in rats administered 3 and 10 mg/kg/day in the diet. No significant effects attributable to drug administration were observed with respect to weight gain, food consumption, hematology and pathology. In addition, rats were administered 20 and 40 mg/kg in the diet for 3 months. Reductions in weight gain of 15–20% in the 20 mg/kg dosage group and 32–40% in the 40 mg/kg dosage group were observed. The food consumption paralleled the body weight response (15% less at 20 mg/kg and 36% less at 40 mg/kg). If the concentration of the drug in the diet was not increased to compensate for the reduced food intake, the actual dosage given to the animals would have been considerably less than stated. The relative weights of the liver, heart and adrenals were significantly increased over control values at both 20 and 40 mg/kg in both the male and female rats. In the rats receiving 40 mg/kg, 8 out of 20 animals had grossly visible opacity of the cornea at the end of the 3 month study. There was also an associated conjunctivitis. Several drugs (e.g. more potent narcotics, certain insecticides) have caused this effect in either mice or rats acutely and has been reversible. However, we would consider this observation in a chronic study of a more serious nature and something to be concerned about. Histologic examination of the cornea revealed inflammatory changes.

The company states that an evaluation of the dog studies is difficult because of concomitant, spontaneously occurring diseases in their dog colony with four cases of distemper being diagnosed. Whether the effects described below were due to poor animals, distemper or drug administration would be hard to evaluate. However it is our opinion that the drug is producing some of the observed effects. Three dogs were administered 10 mg/kg of MER–29 for 4 months. No effect on the peripheral blood counts were observed and in general the weights of the animals remained constant. However, both of the male dogs in the study showed some inhibition of spermatogenesis upon histological examination.