Six dogs were administered 25 mg/kg for 6 months. Three of the male dogs died early in the study. They indicated that one died of congestive heart failure secondary to heart worm infestation, and the cause of death of the other 2 was undetermined due to post mortem changes. Two of the three dogs surviving the study had distended gall bladders but the organs were normal upon histologic examination. In the one male dog surviving the study there was no indication of an effect on spermatogenesis.

Five dogs were administered MER–29 for 3 months at a dosage of 40 mg/kg/day. Three of these animals died within 6 weeks after the start of the experiment. With respect to the cause of death, they indicated that in the first dog the changes in the liver and massive interstitial hemorrhage are changes consistent with canine viral hepatitis. They indicated that the cause of death of the second animal could have been due to either the bronchial pneumonia, the acute hemorrhagic pneumonia, or hepatic failure secondary to the necrosis and inflammatory response of the liver. Gross examination of the third animal revealed the liver dark and mottled and the entire intestinal tract edematous and hemorrhagic. Histological examination of the liver showed a general ballooning of the parenchymal cells, some disruption of the hepatic cord, areas of coagulative necrosis, and extensive inflammatory response. They indicated that the most likely cause of death in this animal was hepatic failure secondary to chronic inflammatory response and cirrhotic changes in the liver.

In the two dogs surviving the study, no effect was seen in the hematological studies. Gross examination revealed the gall bladders distended and in one of the animals the liver was mottled and there was extensive mesenteric lymphadenopathy. The urinary bladder was very thick and purulent material was present in the urethra. Histological examination revealed some changes in the liver and a reduction in the number of mature spermatocytes in the seminiferous tubules, and a paucity of spermatozoa in the vas. The lymph nodes showed simple hyperplasia.

As you know the clinical dose of this drug is 250 mg daily or about 4–5 mg/kg. We would conclude on the basis of the animal toxicity studies conducted that there is little margin for safety with this drug. Certain changes seen in these animals appear to be due directly to the toxic action of the compound. The inhibition of the spermatogenesis in the dog, the effect on the cornea in the rat, the marked reduction in weight gain in the rats at relatively low dosages, all the liver changes, and the deaths of the animals lead us to conclude that this compound is producing toxic effects in the animals at relatively low dosages. We are not convinced that the changes observed in the dogs were due to distemper or hepatitis, particularly since the inclusion bodies characteristic of these diseases, particularly viral hepatitis, were not mentioned.

We are seriously concerned about the safety of the use of such a drug for reducing blood cholesterol. In the first place, we don't know if a reduction in blood cholesterol really helps the patient. To use a compound that is potentially toxic to produce such an effect is highly questionable. Besides the specific toxic potential of the drug itself, we are worried about the effects of a build-up of desmosterol in the blood. What are the long term effects of this material in the blood stream? It is certainly an abnormal condition. We do not know that perhaps desmosterol is itself atherogenic?

On the basis of the results of the studies conducted so far, we cannot see the necessity for any further animal studies. On the basis of the studies seen so far we would be opposed to this type of compound being marketed for reduction of serum cholesterol. Of course, the final evaluation of safety must be in the clinical studies. Before we release this drug for general distribution, it is our view that the company should submit results of well controlled extensive clinical studies in which the individuals have received the drug for periods of several years.

E. I. GOLDENTHAL.

THE WM. S. MERRELL CO.,
Cincinnati, Ohio, February 29, 1960.

Dr. EDWIN GOLDENTHAL,
New Drug Branch, Food and Drug Administration,
Washington, D.C.

DEAR DOCTOR GOLDENTHAL: This will confirm our recent telephone discussion on the corneal opacity reported in rats in our MER/29 NDA. As I indicated, these corneal changes have now been found in the control animals.