U.S. DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE,
Washington, D.C., October 23, 1961.

The WM. S. MERRELL CO.
Division of Richardson-Merrell Inc., Lockland Station,
Cincinnati, Ohio.
(Attention of Dr. Robert McMaster.)

DEAR DOCTOR MCMASTER: This is in reference to our forthcoming meeting at 10:00 A.M. on Thursday October 26, 1961 to discuss the problem adverse reactions attendant on the use of MER/29.

As discussed at our recent conversations while we were both attending the American Heart Association Annual Meeting, it is our considered opinion that the meeting on Thursday must include a detailed discussion of all that is known from both experimental and clinical studies concerning the toxicity of MER/29.

Since your labeling and promotional literature has repeatedly stressed the freedom from major side-effects and lack of danger connected with the use of this drug, we feel it is now necessary for you to give us the complete background information to date.

Of necessity, this would include all the information concerning eye changes in humans and animals with reference to both the corneal and lenticular (cataracts) changes. It would include information concerning the role of MER/29 in the interference with steroid hormone metabolism and endocrine balance with resulting effects on ovulation, potency, reproduction, and response to stress. Of particular importance would be information that this drug has been shown to produce a reticulocytosis in animals which implies that it produces a compensated hemolytic anemia. Of lesser importance, but still necessary, are the skin and hair changes (icthyosis, thinning, color changes, and baldness).

We feel that it is particularly important that you correct the information previously provided concerning the degree of cholesterol lowering activity exerted by MER/29. Detailed analysis of your data indicates: (1) that the degree of cholesterol lowering effect is markedly less than you have previously indicated, (2) that the distribution of cholesterol levels on patients with heart disease in the MER/29 studies is significantly higher than that expected in the typical coronary population.

These factors are important since your data indicate to us that there exists a relationship between pre-treatment cholesterol levels and the cholesterol lowering effect of MER/29. The implications are that a significant proportion of patients with coronary artery disease do not experience the degree of hypocholesteremic effect stated.

In conclusion we re-emphasize the point made in the phone conversation with Dr. F. Joseph Murray on October 19th to the effect that the William S. Merrell Co. must furnish us all data concerning adverse and toxic reactions resulting from MER/29 therapy in both animals and humans.

Sincerely yours,

JOHN O. NESTOR, M.D.,
Medical Officer, Division of New Drugs,
Bureau of Medicine.

U.S. Government memorandum.

NOVEMBER 7, 1961.

To: Division of New Drugs; attention: Dr. Nestor.
From: Division of Pharmacology.
Subject: MER-29, TRIPARANOL; The Wm. S. Merrell Co., NDA 12-066 (AF 1-542).

We have reviewed the new data submitted. We are in agreement that this application should be suspended, but are not sure of how much help we can be on the basis of this recently submitted data. We were of the opinion that this application should never have been made effective because we were not sure of its safety (See our original comments 2/23/60). On the contrary, the compound appeared to be unsafe on the basis of the chronic animal toxicity studies. However, the data submitted by the firm might not be sufficient to support a revocation of the application.

We are particularly concerned with the ability of the adrenal of patients treated with the drug to respond to stress. In animals large doses of the drug