Because that labeling did not accurately represent the present status of opinion concerning the possible danger of side effects, the warning statement was changed to read: "A cause and effect relationship has been *neither established nor disproved.*" [Italic supplied.] The FDA regards the advertisements as potentially misleading because they omitted this important change which emphasizes the possibility of these serious hazards.

Further, the advertisements failed to include the following side effects which, although causation has not been established, have been reported in users of oral contraceptives: an ovulation post treatment, premenstrual-like syndrome, changes in libido, changes in appetite, cystitis-like syndrome, backache, nervousness, dizziness, fatigue, headache, hirsutism.

We have modified our current advertising to reflect these changes.

Sincerely,

HERBERT HELLING,
Food and Drug Administration Affairs.

ARDSLEY, N.Y., *February 15, 1968.*

DEAR DOCTOR: In our promotion of Persantine® (brand of dipyridamole) for long-term therapy in anginal patients, we sent a letter to physicians stating that "Several studies document the effectiveness of Persantine in extending walking distance and general increasing exercise tolerance." Enclosed with the letter was a reprint of a study in the *Journal of Chronic Diseases* of March 1967 to support the claims for effectiveness.

The Food and Drug Administration has asked us to inform you that the claims for effectiveness of Persantine, and many other drugs marketed prior to 1962, have been neither approved nor disapproved by the Agency. The FDA is proceeding on the basis that the Drug Amendments of 1962 require the Agency to evaluate the effectiveness of such drugs, and this is currently being done with the assistance of the drug efficacy panels of the National Academy of Sciences/National Research Council.

The FDA regards the promotional letter as potentially misleading because it presented only favorable information regarding the drug's effectiveness when there is a substantial body of opinion that does not suport the claimed effectiveness of the product. For example, the AMA Council on Drugs (in *New Drugs* 1967) has stated that double-blind studies comparing dipyridamole with a placebo have shown equivocal results and that the drug has not been convincingly shown to be effective in the long-term treatment of angina pectoris.

Recently, in the *JAMA* issue of September 11, 1967, a paper by Sbar and Schlant disclosed results of a six-month double-blind study. The authors concluded that "The study failed to detect a statistically significant difference between the improvement in patients receiving dipyridamole and the improvement in patients receiving a placebo."

Our future promotion will express the range of expert medical opinion on the effectiveness of Persantine when any segment of that opinion is referenced.

GEIGY PHARMACEUTICALS.

Dr. MCCLEERY. Also along the way of developing public awareness of the type of expectations which the FDA considered the law to require, the Commissioner of Food and Drugs had appeared before the Fountain Subcommittee of the House Committee on Government Operations, and had reviewed for them our programs in this important area of our public responsibilities.

In short, and in many ways, we felt that the industry's attention had been brought emphatically to promotion excesses in specific and in many ways.

As far as our experience with the problem represented by the drug under discussion today is concerned, we felt that there were three approaches to the promotion of this new product by Merck & Co., all of which had elements with which we disagreed—one of which was mentioned yesterday by Dr. Jennings, in his testimony, in the use of a "Dear Doctor" letter sent by the company, accompanying with it the