control animals" and stated that the firm's consulting pathologist "feels that the changes are inflammatory," and not caused by the drug.

By letter of March 28, 1960, FDA acknowledged six communications from the firm and commented that the application was incomplete in that it failed to report clinical studies in full detail. Our letter further stated:

"As brought out in our meeting of March 7, 1960, with representatives of the William S. Merrell Company, we are unable to resolve the apparent discrepancy in interpretation of the pharmacologic studies in dogs between your people and ours. Because of this dispute, because of the potential hazards of liver toxicity with this dog, and further because of the highly theoretical value of taking such a drug as MER/29 (to our minds), we are making the application incomplete until longer term clinical studies have been made utilizing periodic liver function studies to show that this blocker of intermediate cholesterol metabolism is not producing liver damage."

On March 31, 1960, FDA received personally from Dr. Murray, a tabulation of liver function tests. The firm continued to emphasize that an earlier toxicity study in monkeys, had likewise shown a total absence of toxicity from MER/29, and that monkeys being primates, were phylogenetically closer to man than either rats or dogs. Thus, he argued, the drug was safe under the conditions of use set forth in the New Drug Application. On April 19, 1960, FDA notified the William S. Merrell Company that the application was made conditionally effective and that the action allowing the application to become effective was based solely on the evidence of the safety of the drug. On May 12, 1960, FDA acknowledged receipt of the final printed labels and labeling and made NDA 12-066 fully effective, subject only to the terms set forth in the FDA letter of April 19, 1960.

My next involvement with this application was on November 7, 1961. I sent a memorandum to Dr. John Nestor, the medical officer then handling the application, in which additional data were reviewed. In light of reports of adverse reactions in humans, particularly the eye changes, the question had been raised as to whether or not the application should be suspended. While I agreed that the application should be suspended, I was not convinced that the new data submitted by the firm would be sufficient to support a revocation of the application. On November 13, 1961, various personnel within the Administration met to evaluate the situation and to decide on a course of action. The decision reached was that the drug should be removed from the market and the application suspended. In the absence of new clinical evidence that the drug was unsafe, however, this could not be done under the provisions of the Federal Food, Drug, and Cosmetic Act at that time. This question was reviewed with FDA scientists and the conclusion was reached that the available evidence would not support suspension action. On November 27, 1961, a drug warning letter was agreed upon by the William S. Merrell Company and FDA. This letter informed physicians of the incidence of cataracts and the necessity of early detection by slit lamp examination. It also advised that they be on the look out for hair changes, ichthyosis and other skin changes, depression of adrenocortical function, and other side effects associated with MER/29 therapy.

In March 1962, FDA was informed by a former employee of the firm that some parts of the chronic monkey data on MER/29 submitted to the Food and Drug Administration had been falsified. We were advised that one of the drug-treated monkeys had become ill and lost considerable weight during the latter part of the study and that a normal, untreated, healthy animal had been substituted. She stated that the report submitted to the FDA by the William S. Merrell Company, as part of the New Drug Application, had been modified to include data on this untreated monkey instead of the monkey receiving MER/29. There was also some question as to whether or not this sick monkey had been subject to autopsy.

It was decided that members of the Administration should visit the William S. Merrell Company to investigate this alleged falsification. On April 9, 1962, Dr. John Nestor of the Bureau of Medicine, Supervisory Inspector Thomas M. Rice, and I visited the firm's Cincinnati facilities and met with representatives of the firm. During the morning, a discussion was held regarding clinical experience with MER/29, particularly reports of the adverse effects. In the course of our discussion, we asked to see the raw data from the monkey studies. Pertinent laboratory records were made available to us. Our search for specific data was difficult because of the confusing manner in which these records had been kept. Upon reviewing some of their laboratory notebooks and weight charts, however, it became evident that the data were somewhat different from those submitted in the New Drug Application.