We rejected this proposal, and while strengthening the warning was suggested, the decision was made to continue the warning as recommended by the scientific committee.

In December 1959, one of our physicians, who was also in private practice, was visited by Parke-Davis detail men who claimed that there was no more danger of blood dyscrasias with Chloromycetin than with any other antibiotic. The company was informed of this impropriety, and gave assurance that the statement was both unauthorized and contrary to company policy.

In April of 1960 the Council on Drugs of the American Medical Association made another report on blood dyscrasias associated with chloramphenicol. The report said that although the warning had been in use for a long time, physicians continued to use the drug indiscriminately for minor infections, including those associated with the common cold.

FDA asked the National Research Council in November 1960 to again consider the chloramphenicol problem in light of the new evidence accumulated since 1952. Specifically, FDA wished to obtain the Council's opinion as to whether chloramphenicol should be allowed to remain on the market; whether its use should be restricted to hospitals if it were to remain on the market and what label changes the Council would recommend if the drug was allowed to remain on the market.

The recommendations of the Council were received by FDA in January 1961. The Council concluded that, due to its therapeutic value, chloramphenicol should remain on the market; due to some of its proper indications for use, home treatment, as opposed to hospital treatment exclusively, was reasonable; due to its serious effects, further warnings and increased education of the medical profession were necessary.

In accordance with these recommendations the labeling of chloramphenicol was revised in February of 1961 to include a prominent "warning box" containing the following information:

"Warning—Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective. It must not be used in the treatment of trivial infections such as colds, influenza, or infections of the throat; or as a prophylactic agent to prevent bacterial infections. Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia."

Parke-Davis was required to mail the new prescribing information to all medical doctors and osteopaths in February 1961 with a statement that the prescribing information would accompany all oral and parenteral Chloromycetin products.

Between 1963, when our prescription drug advertising regulations were first adopted, and 1966, Parke-Davis advertised Chloromycetin by reminder ads, which carried no indications and no warnings. The regulations permitted this. In 1964, the Company decided to advertise the drug promotionally and met with our medical advertising group to consider how this should be done. Our physicians noted that the package insert had no "Indications" section, but instead described the broad range of antimicrobial activity of the drug. To correct this, an indications section was devised and other changes made to emphasize that the drug was only indicated for, and should be prescribed in accordance with, the important information in the "warning box." In 1966, the Company made the requested changes and discontinued the reminder ad campaign.

The labeling was reviewed again in 1966 by the Acting Deputy Director of the Bureau of Medicine and the "box warning" was changed to say that the drug must (instead of should) not be used in trivial infections or in any other conditions except as described in the box.

Despite these label revisions, editorials in the *Journal of the American Medical Association*, and warnings in other publications such as *The Medical Letter*, the use of chloramphenicol has increased and continues to increase. Most of this use,