the patients experienced some degree of clinical relapse. Some statisticians would consider this to be evidence of activity, but the committee chose not to accept these factors as criteria of effectiveness.

The study has yet to be designed which all would agree is the ideal format for a controlled study of such agents. Some double-blind studies were included in our original indomethacin submission to the FDA, and you have heard testimony in criticism of their structure. Dr. Mainland has stated that his study is part of a continuing, long-range effort to eliminate the unreliable factors and variables. More recently, we have been involved with the further development and design of double-blind studies. Many of these are being carried out. But here, too, it is impossible to say whether the principles underlying these studies will be generally accepted as satisfactory.

During the coming years, I am convinced, controlled clinical methodology will be developed so that truly objective data will result. As physicians in medical research at Merck, this is our job and our effort is dedicated to this end. However, it should be recognized that the clinical sciences have not yet reached the scientifically controlled state that has been attained in the laboratory. The patient is not and can never be the exact counterpart of a highly inbred, genetically and environmentally controlled laboratory animal.

If we had to do our clinical research over again with indomethacin, we would do it the same way, by first going to the expert. We would subsequently supplement our basic clinical evaluation with the best double-blind control studies we could devise. This, in fact, is what we are doing today as we take a new anti-inflammatory drug to the clinic. But so long as we do not yet know of a wholly satisfactory double-blind method of proving effectiveness for drugs used to treat rheumatoid arthritis, we do not believe there is any medical basis for postponing the introduction of a drug experts believe to be valuable.

The question of the safety of indomethacin has also been raised. It is important to distinguish between safety for use as contrasted with side effects experienced during use of the drug. The issue of safety deals with the potential threat of serious, life-threatening consequences. The issue of side effects deals with sometimes bothersome, sometimes annoying effects which are not in themselves of serious potential.

These issues have been grouped together in the discussion of indomethacin. In the resulting confusion, the major point—that most of the side effects of indomethacin are of a minor or manageable nature—has been lost. Many disappear in a short time with continuation of the medication or an adjustment of dose. Only 10 to 15 percent of all patients receiving the drug have to discontinue it because of side effects or reactions. In rheumatoid patients the incidence of patient intolerance appears to be greater than in patients with other forms of arthritis. But this is not surprising. It is well known that patients with rheumatoid arthritis have a greater sensitivity or a lower threshold to the adverse effects of many drugs, for reasons which are not known. It should be pointed out also that most of such patients are on multiple drug therapy. This, together with the vagaries of the disease itself, often sets the stage for higher incidence of adverse drug effects.

Sufficient clinical experience was accumulated with indomethacin over the years of investigation before its approval by FDA to assure