observing the patient's clinical response to the unknown substitution of placebo and to the unknown resumption of the active drug. Where emphasis is needed or where any doubt exists, the placebo trial can be repeated on a number of occasions in the same patient. The use of a placebo can also help the clinician to decide if the appearance of adverse effects or side reactions is drug-related. Oftentimes it is found that an adverse effect, thought to be drug-induced, was in truth the result of the patient's apprehension at taking part in an experiment.

In theory, the "double-blind" technique is the most desirable form of evaluation, but the non-clinician and the statistician fail to appreciate the numerous, often insurmountable difficulties in applying a "double-blind" study to a group of human patients. It is understandable that those who have done most of their work with testing in laboratory animals would want to carry-over this same methodology to the human, but it is becoming increasingly apparent from the reports of such statistician- and laboratory-oriented sources that the pitfalls of the "double-blind" study are manyfold and seem to increase exponentially with the increasing application of further controls and safeguards. Nevertheless, it may be advantageous for an experienced clinician to institute a "double-blind" study during the course of a therapeutic trial of a new drug, and derive important data from it.

In my many years of clinical experience with Indocin, I have used a number of "double-blind" trials, but I have not regarded them as having as much value to me as the hundreds of "single-blind" placebo trials which I carried out. The results of both, however, served further to convince me of the therapeutic efficacy of Indocin in the majority of patients with rheumatoid arthritis.

The Merck Company is to be congratulated for having labored so diligently to produce yet another effective drug for the treatment of this dread disease. I appreciate the opportunity to have developed the earliest clinical experiences with Indocin. However, the most important thing which I personally think makes your company especially deserving of commendation is the wholesome, objective, scientific atmosphere which all of the representatives of your company created and maintained throughout all my studies on Indocin. At no time were any pressures exerted on me in any manner or in any direction which could possibly have influenced my objective approach or created any prejudice or bias in my work or even in my thinking. At all times I felt completely free to report favorably or unfavorably and to state that in my opinion Indocin was good, bad or indifferent. In fact, at several stages I was hyper-critical of the drug and even now emphasize that it is not the last word in rheumatoid arthritis therapy, that improvements can probably be made with derivatives of the drug, that cerebral side-effects are a definite limitation, both in dosage ceiling and in more universal application of the drug. In this atmosphere I have developed the conviction that Indocin is a valuable drug and should not be denied to those patients with rheumatoid arthritis in whom it can and will produce decisive benefits.

Yours truly,

NORMAN O. ROTHERMICH, M.D.

BRONX, N.Y., *April 22, 1968.*

Dr. MAX TISHLER,
*Merck Research Laboratories,*
*Merck & Co., Inc.,*
*Rahway, N.J.*

DEAR DOCTOR TISHLER: I am aware that there has been a discussion in the Congress through their appointed Committees to evaluate the evidence with regard to the therapeutic efficacy and the place in our pharmalogic armamentarium of Indomethacin.

The studies that we have performed and our current studies indicate that Indomethacin has an anti-inflammatory action, and through this anti-inflammatory action, a potent analgesic effect in the treatment of inflammatory connective tissue disease, particularly the inflammation associated with traumatic osteoarthritis. It appears to be of use in some patients with acute and chronic rheumatoid arthritis. Of course its effect in acute gout is well known.

The problem with Indomethacin has been the variable response to the drug. This is extraordinarily unusual, but offers a challenge as to the difference between this anti-inflammatory compound and the other which are available. Certainly, further research with Indomethacin and its analogues is warranted, and we are currently actively engaged in this research.

The question of the design of the studies for Indomethacin efficacy has been a challenge to us. A double blind study of Indomethacin against a sugar placebo