and I have not encountered any unusual new reactions with its continued use. Side effects on the gastro-intestinal tract, headaches, dizzyness, or a feeling of confusion continue to be the common complaints in my experience.

Sincerely yours,

BERNARD M. NORCROSS, M.D.

MINNEAPOLIS, MINN., *April 23, 1968.*

MAX TISHLER, Ph. D.,
Merck Research Laboratories,
Merck & Co., Inc.,
Rahway, N.J.

DEAR DR. TISHLER: I am writing this letter to place on record my opinion that Indomethacin is an effective anti-rheumatic agent. Although, my own clinical research published in 1964, plus a fairly extensive experience with Indomethacin since then does not indicate a major anti-inflammatory effect in rheumatoid arthritis, the drug is useful in many such patients. But without doubt Indomethacin is of great benefit in patients with ankylosing spondylitis. Reiter's disease, psoriatic arthritis, and acute gout. It's benefit in these later patients is so unequivocal that a double-blind trial is, I believe, unnecessary and likely redundant. The few negative reports should not out weight the preponderant positive evidence of the usefulness of this drug.

Sincerely,

PAUL J. BILKA, M.D.

LOUISVILLE, KY., *April 23, 1968.*

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

DEAR DR. TISHLER: I have been asked to comment on the evaluation of drugs in rheumatoid arthritis, and the question of effectiveness of indomethacin.

I am enclosing a reprint of one of my papers published in the J.A.M.A. Although my remarks related to the difficulty in assessing the effects of drugs in rheumatoid arthritis were written with special regard to corticosteroids, I think they remain pertinent to the present question. (See bottom of page 1254 under heading "Rationale of Procedure" and top of page 1254 as marked.)

Concerning indomethacin, my feeling is that this compound is effective in acute gouty arthritis and ankylosing spondylitis. Response in rheumatoid arthritis is not predictable without clinical trial but certain rheumatoid patients seem to derive benefit.

I hope this information will be useful.

Sincerely,

DAVID H. NEUSTADT, M.D.,
Associate Clinical Professor of Medicine, Chief, Section on Rheumatic Diseases, University of Louisville School of Medicine.

[From J.A.M.A., July 11, 1959, p. 1254]

RATIONALE OF PROCEDURE

There is no completely reliable plan or method of evaluating a new agent in rheumatoid arthritis that is not associated with certain shortcomings. To control all variables that come into play in a chronic disease of unknown origin subject to spontaneous fluctuations is a problem which has recently received well-deserved attention.

Short-term observations may be misleading. However, if one omits patients from a study who received a drug for short periods, one may be accused of influencing the final statistical results. Also there may have been some important reason for withdrawing the drug early in the study.

Double-blind and random selection studies are considered by some to disclose results of greater scientific precision than the older and more conventional type of evaluation study. However a double-blind technique also carries with it certain disadvantages that may compromise its value. In conducting studies with a relatively inactive drug (slowly acting agent), such as an antimalarial agent or a gold salt, a double-blind study can be carried out. When employing a corticosteroid which has powerful suppressive capacity, abrupt withdrawal and