As you know, we are also keenly interested in whatever effects, if any, Indomethacin may have on tryptophane and serotonin metabolism and how this may relate to the disease of rheumatoid arthritis.

Best wishes always.

Sincerely yours,

NORMAN O. ROTHERMICH, M.D.

INDOMETHACIN QUESTIONNAIRE, JUNE 19, 1963

Name of Investigator: Norman O. Rothermich, M.D.

1. How many patients have been treated with 150 mg. or less?	60
a. Number who experienced relief of pain?	40
b. Number who experienced relief of swelling & inflammation?	40
c. Number who had definite over-all improvement?	40
d. Number unimproved?	20
2. How many of the above patients experienced headache?	15
3. Of those who had headaches	
a. how many had to discontinue the drug because of it?	8
b. how many became tolerant of the headache and continued on the drug?	3
c. how many had relief of their headache at a lower dosage?	4
4. How many of the patients experienced gastrointestinal symptoms (abdominal distress, nausea, vomiting, etc.)?	3
a. How many had to discontinue the drug because of these symptoms?	0
b. How many developed a definite ulcer or bleeding?	1
5. How many of your treated patients have	
a. chronic rheumatoid arthritis?	48
spondylitis?	12
b. Arthritis or inflammatory disorders other than chronic rheumatoid arthritis?	---
6. Does acute inflammatory disease respond better than chronic disease?	No

NORMAN O. ROTHERMICH, M.D.

COLUMBUS MEDICAL CENTER RESEARCH FOUNDATION, INC.,
Columbus, Ohio, October 9, 1962.

NELSON H. REAVEY CANTWELL, M.D., Ph. D.,
Merck Sharp & Dohme Research Laboratories,
Division of Merck & Co., Inc., West Point, Pa.

DEAR NELSON: A special report to you is in order regarding the appearance of an adverse effect of the new drug, MK-615, now under investigation. This effect is an entirely symptomatic one and as yet not measurable by any objective methods. The patient complains of a distressing lightheadedness, a feeling of "the head being in outer space", a feeling of the head being foggy and a feeling of difficulty in concentration or in cerebration. There may or may not be an associated violent headache and in a few cases, the headache was so violent that it was predominant or alone. In a few instances, these symptoms have been so severe as to be totally incapacitating and even prostrating.

The physical findings at this time are not remarkable. The ocular fundi are negative and there is no papilledema. The neurologic examination is likwise negative in all other respects. In a few instances, the electroencephalogram has shown no decisive or characteristic changes. Other laboratory studies are not changed significantly during these episodes. The spinal fluid has not been studied.

In general, this adverse effect appears to be a dosage related phenomenon and in most cases, does not appear until 250 mg. daily has been reached. However, there is a considerable variation in individual susceptibility to this effect. Some patients have been on 300 mg. or more daily for some time without any adverse effects. Some patients have felt this effect at dosages as low as 150 mg. daily. It is definitely reproducible in the same patient at approximately the same dosage levels. There appear to be no residuals from this adverse effect. Symptoms disappear usually within 24 to 48 hours after discontinuing the drug. The antirheumatic effects of the drug are not reduced by this effect. As a matter of fact, the antirheumatic effect may be very striking at these higher dosage levels. In some severe arthritics, it has been impossible to control the arthritis without producing these adverse effects. As of this date, 16 patients have had toxic effects out of a total of 49 patients receiving the drug. No other ill-effects of the drug have been noted.

Yours truly,

NORMAN O. ROTHERMICH, M.D.