obtained in 45 (in all of the spinal) and only a fair (indecisive) effect was obtained in 10. No benefit was noted in 6.

The duration of treatment was sufficiently long to permit good clinical observation, being between 12 and 18 months in at least 22 of the patients. As you know, placebos were used, both in single and double blind and 128 relapses were produced by substituting placebo.

As regards dosage, the spondylitics uniformly required less than the peripherals and the daily dose for them varied from as low as 50 mg. to 200 mg. with an average of about 125. In the peripheral arthritis, the average therapeutic dosage level was about 200 to 250 mg. daily. However, in many cases, the dose was taken up to 300 and higher and at least 6 patients received 400 mg. daily for at least one week. Few improvements were noted in the peripheral arthritis group at dosage levels of 150 mg. daily. Most of the peripheral arthritics are now being carried on a daily dose of 300 mg. daily but a significant number are benefitted to a striking degree on 200 mg. daily.

The greatest deterrent to increasing dosage to an effective level is the appearance of cerebral toxicity. This manifests itself clinically in excruciating severe headaches, dizziness, lightheadedness, disturbances of sensorium, a feeling that the head is floating away or even separating from the body and feelings of detachment from reality.

The higher the dose, the more severe the symptoms but there was some variation in individual susceptibility. A few individuals experienced considerable toxicity at levels of 100 mg. daily whereas, a goodly number could take 300 mg. a day without any adverse symptoms. However, the usual appearance of symptoms was at the range of about 200 to 225 mg. although cerebral toxicity occurred in over half of our patients, that is 31 out of 61. In 80% of these, the toxicity could be adequately ameliorated or abolished by reduction in dosage. We did not run a specific questionnaire regarding an antecedent history of migraine but a prominent history of headache was present in only about 8 to 10.

I trust the above will provide you with the information you desire. If however you desire additional information, please let me know.

Yours truly,

NORMAN O. ROTHERMICH, M.D.

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COLUMBUS MEDICAL CENTER RESEARCH FOUNDATION, INC.,
*Columbus, Ohio, July 3, 1963.*

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

DEAR NELSON: Enclosed is the Indomethacin questionnaire which you asked me to fill out from our work. As you know, we have interested ourselves almost exclusively in the benficial effect of Indomethacin on rheumatoid arthritis and have used it only sporadically and in a random way on other rheumatic disorders. We have chosen to exclude the latter groups since they have not been formally organized and analyzed.

From the nature of the questionnaire, you must understand that all of our patients have been treated for a greater or less period of time with 150 mg. or less and hence are included on the questionnaire but in a significant number of these, the dose was raised to a much higher level to achieve a satisfactory result. Consequently, the number listed under unimproved should not be looked upon as the total number of Indomethacin failures. Furthermore, the number experiencing headache is given as that number which occurred at the dosage range of 150 mg. or less. As you know, we had a considerably higher incidence of cerebral toxicity at higher dosage levels. These data are well explained in my previous report to you several weeks ago. The one case of bleeding was probably from a diverticulum and not ulcer and furthermore is not included among those who experienced gastrointestinal symptoms since his only symptom was that of weakness and faintness.

We are in the process of trying to develop satisfactory control techniques for determinations of Indomethacin blood levels. I don't see how you can possibly refute the finding of a zero blood level in every instance where blood was drawn 24 hours after the preceding dose. We hope to resolve this question.