

the time 'Indocin' was started. Of this group, we have had a good response in 9 patients; a fair response in 2; and 1 patient had side effects that required cessation of the drug before any effect could be noted. Of this group, 5 patients have required stopping 'Indocin' because of side effects, even though the response had been fair or good.

In our work with 'Indocin', we have found that headache, while not an infrequent side effect, has not been particularly difficult to control, responding either to antihistamines or to reduction in dosage of 'Indocin'. The dizziness, nausea and vomiting, however, have been refractory to most efforts at control with the exception of stopping 'Indocin'. Using antacids, anti-emetics, etc. has had no effect in stopping this complication. We have found in a few patients that stopping the drug for a period of time, and then re-starting it, has been successful. We have made frequent checks of blood chemistry and hematological studies, and have found no disturbance with hematopoiesis or hepatic or renal toxicity. We have had several patients on 'Indocin' develop peptic ulcer disease, and have had two episodes of massive upper G.I. bleeding. However, in the 2 patients with upper G.I. bleeding, 'Indocin' has been continued after their acute episode and these patients are now 9 months and 4 months post-hemorrhage with no symptoms, or only minimal symptoms remaining. All of the patients who have developed ulcers have also been on corticosteroids.

The possibility of obtaining fewer side effects with as good or better results from the use of the capsule form of 'Indocin' has been of interest to us. As we discussed with you, we would be anxious to try the capsules also in a double blind crossover fashion, similar to our study with the tablet form. To run such a study with the number of patients we would have available would require 90 bottles of 25 mg. 'Indocin' capsules, and 90 bottles of placebo capsules. Anticipating the number of patients who will respond favorably to this, and in whom we would like to continue the capsules past the double blind study, we would need approximately 400 bottles of 25 mg. capsules to carry these patients for a total of six months. We feel that there would be certain other studies that should be pursued in the use of 'Indocin'. These would include correlation of blood level with therapeutic effect and with side effects or toxicity. Because of the peculiar mental reactions we have had, we would feel that an attempt to correlate electroencephalographic findings with blood level and with effect should be done. We would like to receive some of the bulk 'Indocin' so that its effect in experimental models of arthritis could be pursued shortly. Ultimately, the determination of 'Indocin's' place in the therapeutic armamentarium of the rheumatologist should be done. Several of these things will require more detailed planning before they can be accomplished. However, the capsule double blind study and use of the bulk drug in experimental models of arthritis could be accomplished as soon as we can receive the necessary drug.

From our experience with your drug 'Indocin', we feel that you have developed an agent that has a definite place in the treatment of rheumatoid arthritis, even though we have had considerable disappointment in the amount of side effects. We would feel that with further work, maybe the difficulties might reasonably be expected to be overcome. Although it is still too early to tell, we have noticed in 4 or 5 patients, a tendency for the development of remission of their disease activity. Whether they are truly going into remission remains to be seen, but the evidence suggesting that they are is there.

We can discuss the necessary financial support for a double blind study using capsules when the decision is reached to initiate the study.

Very truly yours,

JOHN R. WARD, M.D.

STANFORD UNIVERSITY SCHOOL OF MEDICINE,
STANFORD MEDICAL CENTER,
DEPARTMENT OF MEDICINE,
Palo Alto, Calif., August 22, 1963.

NELSEN H. REAVEY CANTWELL, M.D.,
Merck Sharp & Dohme Research Laboratories, West Point, Pa.

DEAR DR. CANTWELL: I am sorry I haven't answered your previous request for information about Indomethacin. For various reasons I have not put our results together yet but will do so in the not too distant future. This was our first effort at drug evaluation, and I am afraid we have been somewhat inefficient in maintaining precise up-to-date evaluations of the patients. Though all the necessary information is in their charts, we have not extracted it all as yet.