ADVERSE EFFECTS

There were substantial adverse reactions in the study. Thirty-seven of the 97 patients (37 percent) found it necessary to discontinue the medication after a short period because of adverse effects (Table II). Thirteen patients experienced neither benefit nor side effects, despite a stepwise increase in dose to 400 mg. daily. Six patients did not return.

TABLE II.—SIGNIFICANT ADVERSE EFFECTS FROM INDOMETHACIN IN 97 TREATED PATIENTS

Disease	Number treated	Headache	Peptic ulcer	Other gastrointestinal symptoms	Lightheadedness and dizziness	Mixed symptoms	Other [1]	Total	Percent
Rheumatoid arthritis	71	5	6	6	8	4	3	32	45
Rheumatoid spondylitis	6	1						1	
Reiter's syndrome	4	1						1	
Osteoarthritis	4				1			1	
Scleroderma	2	1						1	
Adiposa dolorosa	1			1				1	
Total		8	6	7	9	4	3	37	

[1] 1 each: ankle edema, abnormality of glucose tolerance, and urticaria.

The major reasons for discontinuation of indomethacin were, in order of frequency, gastrointestinal symptoms, lightheadedness, giddiness, headache, and psychic changes (Table II). In almost all cases the adverse effects were evident within hours or a few days. Occasionally, gastrointestinal symptoms did not develop for a week.

Nine patients had to stop taking the drug because of lightheadedness, giddiness, loss of equilibrium, inability to concentrate, and dissociation of mind and body. No neurological signs were evident, although a majority of the patients had discontinued the drug before they were examined again. One subject had a syncopal attack and fell, sustaining minor injuries. Four patients who were still taking indomethacin had similar symptoms which, however, were mild and transient.

Seven patients had bothersome gastrointestinal complaints which necessitated discontinuation of the drug, and another 5 had transitory symptoms but were able to continue with the medication as the symptoms lessened. The symptoms included epigastric burning, nausea and vomiting, diarrhea, and melena. Peptic ulcer developed in 6 of the 97 patients (6 per cent). In each case the drug was stopped immediately. Three of these patients were also taking small doses of prednisone (5 to 10 mg. daily), but each had been on a corticosteroid preparation continuously for several months at least, often in the higher dosage range, without epigastric distress. In one patient, a 60-year-old woman with advanced active grade IV rheumatoid disease, who was on prednisone 7.5 mg. per day and indomethacin 250 mg. per day, a prepyloric ulcer perforated into the lesser omental sac 4 months after treatment with indomethacin, with only 4 or 5 days of mild epigastric symptoms.

Four of the 6 patients who developed ulcer did so very rapidly after receiving indomethacin. Epigastric distress usually began after the first two or three doses. In one patient, a prepyloric ulcer was demonstrated 48 hours after the start of treatment and 24 hours after the onset of symptoms. Only 1 of the 6 patients had a prior history of ulcer, which was known to have healed. Antacids were not given routinely since this was not part of our protocol in the early phases of study. Antacids, however, were used in most of the patients late in the study.

Headache developed in 13 patients, 8 severe enough to discontinue the drug. There was no apparent pattern as to location, although the bifrontal type was the most common. Both steady and throbbing headaches were encountered. Although most patients with headaches had an accentuation of symptoms shortly after each dose, 2 reported partial relief of their headaches after each dose of medication and an accentuation of headache proportional to the length of time between medication. Three subjects were given ergotamine tartrate with caffeine without relief of headache.

Urticaria developed in one patient on two separate occasions following ingestion of indomethacin. However, she had had urticaria once previously without known