Despite suppression of articular symptoms in all but two of the 28 patients, serial x-rays of axial and involved peripheral joints disclosed progressive changes in the majority of patients.

7. A total of 13 side effects, often transient and usually observed during latter months of indomethacin administration, occurred in 8 patients on maintenance dosages of 25 to 200 mg. daily (Table 1). Each of the 4 patients receiving the daily maximum of 200 mg. had adverse reactions.

Headache was noted in 4 of the 8 patients. Of the 4 patients with headache, one also had nausea, and another nausea and diarrhea. Two patients had dizziness, one of whom also had nausea. Two other patients had nausea, one of whom also had diarrhea.

All side effects disappeared spontaneously even though the drug was continued at the same dosage, except for 2 patients whose symptoms persisted until the daily maintenance of indomethacin (200 mg.) was temporarily reduced. Side effects did not reccur in these 2 patients when 200 mg. dosages of indomethacin were reinstituted at a later date.

Upper GI series, performed on the 5 patients with gastrointestinal side effects, revealed no abnormalities. Overt gastrointestinal bleeding did not occur, despite the intermittent presence of positive stool guaiac tests in 6 patients.

There was no evidence of any ocular, renal, hepatic or hematopoietic side effects. There appeared to be no increased susceptibility to infection.

Indomethacin was discontinued in three patients. It was withdrawn in one patient (patient no. 25) with regional enteritis and active foot and heel involvemnet because his response to indomethacin was poor, after having been tried on three different occasions over a six-month period. It was discontinued in another patient (patient no. 28) because of a poor response after 5 months on the drug. Both patients have been more adequately controlled with 300 mg. phenylbutazone daily.

Indomethacin was temporarily discontinued in a man with associated ulcerative colitis (patient no. 18) when the patient developed multiple recurrent ulcerations of the left foot and ankle after he had taken 200 mg. of the drug daily for 36 months. But indomethacin was resumed three months later after two biopsies of the lesion proved negative for vasculitis. The ulcer has now healed.

DISCUSSION

Our most striking observation about indomethacin is the clear-cut benefit it seems to provide in ankylosing spondylitis.

When indomethacin is used in other rheumatic disorders, such as rheumatoid arthritis, psoriatic arthritis, Reiter's syndrome or juvenile rheumatoid arthritis, one cannot predict if a patient will benefit from its use.[1,4,10-12]

But as demonstrated in this study, and as suggested by other reports,[1,3,4,6,9] indomethacin seems to be almost consistently effective in ankylosing spondylitis. Despite this enthusiasm about indomethacin, it must be kept in mind that this drug, like other antirheumatic agents, does not specifically alter the underlying disease process. Thus, while articular manifestations of ankylosing spondylitis are suppressed with indomethacin, systemic features appear not to be affected.

The disease activity of most rheumatic disorders is usually reflected in the erythrocyte sedimentation rate (ESR), but this relationship does not seem to be as precise in ankylosing spondylitis as in rheumatoid arthritis.[20] A possible correlation between disease activity and the ESR was suggested in this study, when more than half or 16 of the 28 patients either maintained or achieved a normal ESR value paralleling a favorable therapeutic response. This finding has not been reported previously.

In most cases, ankylosing spondylitis tends to be relatively stable for long periods, so that the symptomatic effects of a single drug can be evaluated by using the patient as his own control. Consequently, when indomethacin was temporarily withdrawn, articular manifestations usually recurred within 48 hours, and were then promptly alleviated when indomethacin was resumed. Therefore, we agree with Kass [11] that it is not necessary to utilize complicated therapeutic experiments in a disease such as ankylosing spondylitis. But, since we did not use a double-blind crossover approach, including a placebo and other antirheumatic agents, we cannot report any objective comparisons between indomethacin and other drugs useful in AS. Furthermore, we were convinced at the beginning of this study that the long-term administration of a placebo to patients with active disease and its attendant distress and discomfort cannot be justified ethi-