cally. Wallace and Ragan[21] had similar convictions about the use of placebo in patients with active rheumatoid arthritis.

Despite the fact that the world literature now abounds with warnings of the potential side effects of even small doses of indomethacin, none of our 28 patients were forced to discontinue the drug because of side effects. Indomethacin was stopped in 3 patients, in 2 because of a poor therapeutic response, and in the other only temporarily, when he developed infected foot and ankle ulcerations which proved later not to be due to the drug.

Nevertheless, our findings support the view that side effects are most frequent among patients receiving larger amounts of the drug,[1-4] while they are also in agreement with the concept, stressed by Rothermich,[17] that cerebral side effects may occur on low dosages in susceptible individuals. All 4 patients on the highest daily indomethacin maintenance dosage of 200 mg. experienced adverse reactions to the drug, while 4 other patients receiving small daily dosages of 25 to 100 mg. developed headache and dizziness. Most drug reactions disappeared spontaneously, except in 2 patients whose side effects persisted until the dosage of indomethacin was reduced.

The rather *late* occurrence of most side effects, though briefly mentioned elsewhere,[3, 17] has not been stressed prior to this investigation. Annoying headache or gastrointestinal upset were *not* seen soon after patients were started on indomethacin. In fact, the 13 side effects observed in 8 of our 28 patients usually occurred only after months and even a year or more of indomethacin administration. In any case, close attention to minimal individualized dosages needed for disease suppression appears to reduce the occurrence of potential side effects. This has also been the experience of Boardman and Hart.[22]

In conclusion, despite the fact that indomethacin has been found of considerable therapeutic usefulness, we do not mean to give the impression that we are treating patients merely with drugs. On the contrary, we cannot emphasize sufficiently the overriding importance of treating the entire disease, particularly with physical, recreational and rehabilitative measures. All of these are intrinsic parts of the overall management of the patient w ith ankylosing spondylitis.[18]

ACKNOWLEDGMENTS

We are indebted to Dr. Rustom E. Mody, former Fellow in Rheumatology, for his early assistance in this study to Dr. Bertram W. Charap of the Mt. Sinai Hospital in New York City for ophthalmologic studies and to Mr. John Wykert of Science & Medicine Publishing Co., Inc., New York, for his assistance in the preparation of this manuscript.

The indomethacin used in this study was supplied by Dr. Nelson H. Reavey Cantwell of Merck Sharp and Dohme, Research Laboratory, West Point, Pennsylvania.

SUMMARY

Indomethacin was found to be highly effective in the management of 28 patients with ankylosing spondylitis in a clinical trial that is now in its fifth year. As judged by selected criteria, including joint pain, duration of morning stiffness, onset of fatigue and joint mobility, the response to the drug was good in 21 patients, fair in 5 and poor in 2. After receiving indomethacin for n average period of 33 months, 21 of the 28 patients were classified in ARA functional class I. Only one patient had been so classified prior to the drug trial. Joint symptons followed temporary withdrawal of the drug, but were promptly relieved when indomethacin was again taken by the patients. However, while articular manifestations of ankylosing spondylitis were suppressed by indomethacin, systemic features were not.

Therapeutic maintenance doses of indomethacin were carefully individualized. While the average daily dosage proved to be 100 mg., four patients with marked peripheral and axial joint involvement required 200 mg. daily.

A battery of laboratory tests accompanied the entire period of the drug trial. These tests revealed no ocular, renal, hepatic or hematopoietic changes due to the use of indomethacin.

Cerebral and gastrointestinal side effects, generally mild and usually transient, occurred most often after prolonged administration of the drug. Of the eight patients who experienced 13 side effects, 4 were taking 200 mg. of indomethacin daily. Side effects persisted in 2 of these 4 patients until their maintenance dosage was reduced. Otherwise all side effects disappeared spontaneously while the drug continued to be taken.