serum protein electrophoresis the alpha-2 globulin was found elevated at some time during the study in 26 (86%) of the 30 patients; in the majority of patients the elevation was slight. The level of the alpha-2 globulin returned to normal values in eight patients (26%) while receiving indomethacin and in three patients (10%) while receiving placebo ($p > 0.05$) (Table IV). Eight (26%) of the patients demonstrated a slight elevation of the serum gamma globulin on paper electrophoresis and none of these showed a significant change in this value during the period of observation. No significant difference at the 0.05 level ($p > 0.05$) was noted with respect to the few patients who developed on abnormal elevation of the level of the serum alkaline phosphatase and glutamic oxaloacetic transaminase (Table III).

DISCUSSION

The relative value of any medication must be assessed with respect to potentially harmful side effects and the degree of both subjective and objective therapeutic benefits derived from it. The present study was undertaken to assess these factors as they applied to indomethacin in the treatment of ankylosing spondylitis.

In the majority of instances the rate of occurrence of side effects in the present group of patients with spondylitis was not shown to be significant by statistical analysis. It is probable that the many "placebo reactors" in this group resulted because the patients were specifically cautioned regarding these side effects at the onset of the study and because, during the course of the study, considerable attention was directed both to their occurence and to their possible dose relationship. Accordingly, we do not feel that sufficiently unbiased data were obtained from this portion of the study to warrant extensive extrapolation.

Although the data were not shown to be statistically significant, note should be taken of the three patients who developed pulmonary infections while receiving indomethacin. In one patient, resolution occurred only after three weeks of antibiotic administration and withdrawal of indomethacin. In two of these patients a brisk leukocyte response was noted in the blood while in the third, the individual with the prolonged course who did not respond to antibiotics, no leukocytosis was detected. Since some experimental studies with indomethacin [12] do indicate an enhanced susceptibility to infection in animals the recent report by Phelps and McCarty [13] of decreased leukocyte mobility in the presence of indomethacin should prompt close re-evaluation of the incidence of infection in patients receiving this drug.

Abnormal urinalyses were noted intermittently in 14 patients (47%) during this study. Although apparent interference with normal renal function has been reported with indomethacin administration,[14] there was no statistical evidence in the present group of patients that the abnormal urinalyses were related to indomethacin therapy. Similar abnormalities have been previously reported by us [8] and are a recognized accompaniment of ankylosing spondylitis.[15]

The observations relating to the subjective and objective therapeutic responses to indomethacin provided more definitive data than those relating to the side effects. From the point of view of subjective evaluation, only the relief from chronic spinal pain and from peripheral arthralgia were found to be statistically significant responses. The failure of indomethacin to relieve morning stiffness in the spine and, in particular, to decrease the frequency and severity of acute exacerbations of spondylitis in this group of patients is in distinct contrast with the results reported in previous studies which did not employ a controlled, cross-over technique.[6,7] From the point of view of subjective response, therefore, indomethacin provided only minor benefit in the management of this group of spondylitis patients.

In none of the objective parameters of assessment was there a significant improvement with the administration of indomethacin. It should also be noted that the subjective improvement reported in peripheral arthralgia was not substantiated by objective assessment of the involved peripheral joints. These data clearly demonstrate the failure of indomethacin to produce objective improvement in the ranges of movement of the spinal and peripheral joints in this group of patients with ankylosing spondylitis.

It was considered possible that the very poor objective responses which were noted did not accurately reflect the anti-inflammatory potential of idomethacin, since, as has been previously indicated, the mean duration of illness in this group of patients was 20.1 years. In other words, it was possible that extensive immobilization of the vertebral column by ligamentous ossification and apophyseal joint fusion would prevent an objective display of improvement in the various ranges of movement. Accordingly, an attempt was made to reassess the data with