both the side effects and the ability of indomethacin to suppress the various laboratory indices of inflammation. The following tests were performed routinely by conventional methods: complete urinalysis, complete hemogram including erythrocyte sedimentation rate (ESR-Wintrobe), blood urea nitrogen (BUN), serum creatinine, serum alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), serum protein paper electrophoresis, latex test for rheumatoid factor,[10] and antinuclear factor (ANF-LE-Test, Hyland). When indicated, chest film, barium meal, electrocardiogram, urine culture and antibiotic sensitivity (if any), and serum protein immunoelectrophoresis were also done. Statistical evaluation of the results was carried out by the chi-square test according to the method of McNemar, using one degree of freedom.[11]

TABLE III.—30 PATIENTS ON INDOMETHACIN AND PLACEBO: FREQUENCY OF SIDE EFFECTS

| Type of side effect | Indomethacin | | Placebo | |
|---|---|---|---|---|
| | Number | Percent | Number | Percent |
| CNS: | | | | |
| Headache | 15 | [1] 50 | 7 | 23 |
| Dizziness | 12 | [1] 40 | 3 | 10 |
| Depression | 2 | 6 | 1 | 3 |
| "Feeling inebriated" | 5 | 16 | 2 | 6 |
| Miscellaneous | 3 | [2] 10 | 2 | 6 |
| Gastrointestinal: | | | | |
| Anorexia and nausea | 7 | 23 | 7 | 23 |
| Symptoms of peptic ulcer | 11 | 36 | 9 | 30 |
| Skin eruption | 3 | 10 | 0 | 0 |
| Anemia | 6 | 20 | 2 | 6 |
| Elevated alkaline phosphatase | 3 | 10 | 1 | 3 |
| Elevated SGOT | 1 | 3 | 1 | 3 |

[1] Significant at the 0.05 level.
[2] Decreased hearing, blurred vision and drowsiness—1 each.

## RESULTS

Twenty-seven patients completed six-week courses of both indomethacin and placebo, while one patient completed three-week courses of each. Two patients whose initial six-week course consisted of indomethacin and who experienced a severe clinical relapse during the first three weeks of placebo administration were subsequently restarted on indomethacin without the knowledge of the assessing physician. These 30 patients represent those who were assessed by the previously described clinical and laboratory parameters. Three additional patients who were lost to the study had received indomethacin only (Table I).

### *Dose tolerated*

The maximum daily dose of indomethacin tolerated without incapacitating side effects by 15 (50%) of the 30 patients was six capsules (150 mg.) per day, and by five others (16%) was four capsules (100 mg. per day). Thus, only 10 patients (34%) tolerated eight capsules (200 mg.) per day; in comparison to the placebo this was a highly significant difference ($p=0.0015$).

### *Side effects*

Three patients who had received only indomethacin were forced to withdraw from the study (Table I). All of these patients experienced severe central nervous system reactions, principally headache and dizziness. One of these also developed extensive right middle and lower lobe pneumonitis which required hospitalization. The occurrence of a pulmonary infection was also noted in two other patients while they were receiving indomethacin.

Of the 30 patients who completed the study, 24 (80%) developed some form of side effect, as demonstrated either clinically or in the laboratory. Thus only six patients (20%) experienced no side effects while receiving indomethacin. On the other hand, 18 patients (60%) experienced some form of side effect while receiving placebo and 16 (53%) of the entire group experienced one or another of the side effects on both indomethacin and placebo. Viewed in this respect, there was no significant difference in the total number of side effects experienced on indomethacin or placebo ($p > 0.05$).

The types and frequency of the various side effects are listed in Table III. It will be noted that reactions involving the central nervous system occurred with the greatest frequency, particularly those manifesting as headache and dizziness.