

cause. A patient with rheumatoid arthritis had ankle edema on two separate trials of indomethacin.

LABORATORY FINDINGS

Almost all patients had a large number of laboratory examinations before treatment was begun. There was the expected high percentage of moderate anemia and elevated erythrocyte sedimentation rates. Other pretreatment laboratory abnormalities included moderately increased Bromsulphalein retention in 5 patients with rheumatoid arthritis, elevated SGOT levels (3 patients), elevated serum alkaline phosphatase (1 patient), and elevated serum uric acid (4 patients). A not unexpectedly high percentage of patients with reversed albumin/globulin ratio was also found.

Complete blood count, urinalysis, and erythrocytic sedimentation rate were all performed routinely and repeatedly in follow-up. With two exceptions, no pattern of change was noted that could not be attributed to chance or spontaneous variation in disease activity. Other laboratory examinations performed randomly in the follow-up period, which showed no abnormalities, were: serum creatinine (19 determinations), serum uric acid (23 determinations), albumin/globulin ratio (21 determinations), serum bilirubin (17 determinations), cephalin flocculation (18 determinations), and thymol turbidity (22 determinations). Five of 51 patients had guaiac-positive stools. Of these, 2 had melena without radiologically demonstrable cause and 3 had peptic ulcer.

One subject with diabetes mellitus noted increased glycosuria after starting indomethacin. The patient was then studied on a constant dosage of aspirin, with and without indomethacin. While on indomethacin, the glucose tolerance curve appeared to be more abnormal; on 200 mg. of indomethacin daily, there was 0.5 per cent to 2.0 per cent glycosuria, whereas it was negative to 0.5 per cent before medication.

Other abnormalities were noted in 2 patients with rheumatoid arthritis while on treatment, but neither had control determinations for the specific abnormality. One had a serum SGOT of 106 and a serum pyruvic oxaloacetic transaminase (SGPT) of 123 after 2 weeks of treatment. Two weeks after discontinuation of the drug, the SGOT was 37 and SGPT was 46. Indomethacin was then administered for 5 days, after which the SGOT was 53 and the SGPT 56. The patient had no clinical signs that could be related to the changes and had symptomatic relief of the arthritis. The second patient was found to have a serum alkaline phosphatase of 25 King-Armstrong units (normal 2.9) 3 weeks after starting indomethacin. Bilirubin and transaminase were normal. The drug was discontinued and over the next 6 weeks the alkaline phosphatase slowly fell to normal.

DISCUSSION

The discovery of a new class of compounds with antirheumatic effects is a significant advance. Indomethacin is not related chemically to the salicylates, pyrazalones, or corticosteroids, and yet in many respects it seems to operate like them. The way in which indomethacin induces symptomatic relief is unclear. The compound possesses antipyretic, analgesic, and perhaps "anti-inflammatory" effects, although specific histologic evidence on the latter point is so far lacking in man. The dramatic effect of indomethacin in cases of acute gout^{2,7} suggests actions resembling those of the corticosteroids. In the rheumatic diseases indomethacin is, in some respects, nonspecific in its action, since symptomatic relief is obtained in a variety of conditions; rheumatoid arthritis, gout, Reiter's disease, ankylosing spondylitis, osteoarthritis of the hip, and other conditions.^{1,4,6,9,10}

So far, it has not been possible for us to select the patients who will respond to indomethacin. Our observations seem to indicate that indomethacin does not specifically alter the basic rheumatoid process or that of other diseases which have been treated. Synovial effusions have generally persisted, and the sedimentation rate and titer of rheumatoid factor have not decreased significantly. Where these have improved, in a few cases, the change probably was a result of the natural course of the underlying disease.

The incidence of adverse effects from indomethacin is unfortunately high. Annoying headache and gastrointestinal irritation come soon after the drug has been given. We have found no satisfactory way of overcoming them. The more serious problem of peptic ulcer aligns indomethacin with other established antirheumatic agents. Most of the ulcers in our series were noted in the latter