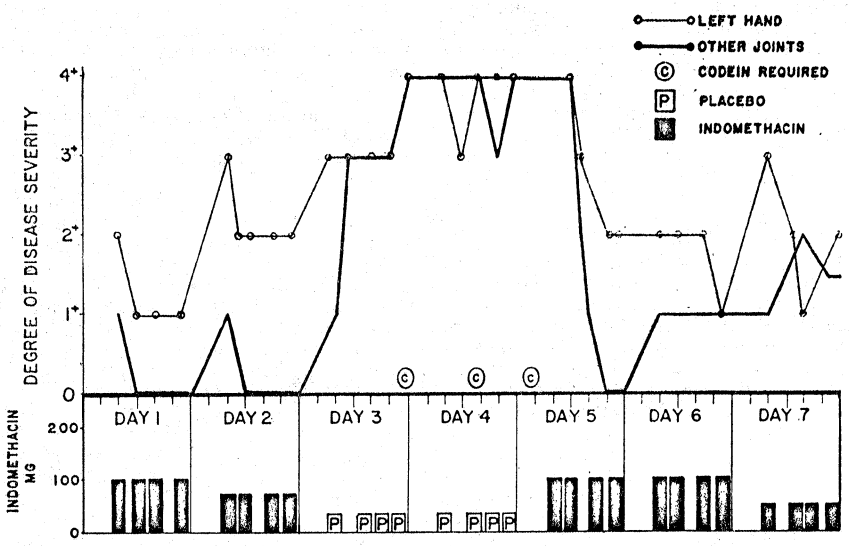
In "fresh" cases of rheumatoid arthritis where corticosteroid therpay had not been previously used, a patient was rated as having good or excellent response to indomethacin if evidences of active synovitis, the jelling phenomenon, and painful disability, as indicated by the patient's symptoms and the physician's observations, receded under active drug therapy and promptly exacerbated when placebo was substituted. In some patients, the placebo trials were made several or more times in order to establish with certainty the relapsing character of the disease under placebo influence. In cases other than rheumatoid arthritis, such as spondylitis, psoriatic arthritis, and chronic gouty polyarthritis, therapeutic evaluation was based on control of disease activity on indomethacin alone, with relapses precipitated by placebo substitution. Occasionally, patients would suspect placebo substitution by a change in side effects. For this reason from the statistician's viewpoint, the placebo trials in this report (and probably in most clinical drug reports) cannot be considered as true "blind" studies. Usually there was enough delay in this awareness to permit the therapeutic assessment. Furthermore, the appearance of side effects is often capricious and inconsistent, thus further limiting the patient's ability to detect placebo. In some of these cases, adequate control had previously been achieved by the use of phenylbutazone, and effectiveness of indomethacin could be measured by its ability to replace such therapy.

Placebo substitutions were made in 86 of the patients. In 70 of these, there was decisive clinical relapse on placebo; this was verified on repeated trials in 55 patients. In most instances, placebo was introduced whenever a patient seemed to be established and well-controlled on indomethacin therapy. In addition, at times when an adverse reaction appeared, a placebo was substituted to determine if the adverse reaction was actually due to indomethacin or some other cause. Occasionally, in a patient whose therapeutic response to indomethacin could not be determined with any reasonable accuracy or whose disease continued to progress even though he was on other antirheumatic medications as well, a placebo was administered to observe if actual worsening of disease occurred while administration of other medications was continued in exactly the same dosage. In 21 instances, neither the patient nor the physician was informed of the placebo substitution, and in one such case a striking effect was observed and charted (Fig 1).

FIGURE 1



1. Placebo trial on a 40-year-old woman with severe psoriatic arthritis. Note profound relapse on receiving placebo and partial loss of disease control on day 7 with reduction in dosage.