CLOTRIMAZOLE AND RHEUMATOID ARTHRITIS

SIR,—The nitroimidazole drug BT 985 (Merck) is a derivative of naxogin (Erba) and metronidazole and is protozoocidal. It has been used successfully in the treatment of amœbiasis, giardiasis, and trichomonas infections.[1] Dramatic disappearance of evidence of active disease in nine of ten cases of rheumatoid arthritis treated by this drug has been reported.[2] Levamisole also contains an imidazole group and has antiprotozoal properties. It was at first thought to affect immune mechanisms,[3] but this has been denied.[4] Schuermans[3] has reported on six patients with active classical or definite long-standing rheumatoid arthritis who had responded poorly to anti-inflammatory or analgesic drugs; on levamisole the patients improved strikingly within a month, and rheumatoid factor became negative in three patients. Similar results have been recorded by others.[5] Clotrimazole is another imidazole-containing antiprotozoal drug.[6,7] The manufacturers say it has no anti-inflammatory effects.

Twelve successive patients whose active rheumatoid arthritis had not been controlled by antirheumatoid drugs, including steroids or tetracosactrin (Synacthen), were studied. They were admitted to hospital but were not confined to bed. Drugs were withdrawn, sometimes resulting in severe exacerbation of the symptoms, and oral clotrimazole was started orally. No other drugs were given. The daily dose was adjusted to between 25 and 100 mg/kg body-weight depending on tolerance. Gastrointestinal disturbance proved a problem in four patients, and a further two patients were withdrawn from the study due to intolerance. Treatment was continued for 6–12 weeks and the patients were followed up for 12–15 months.[8]

All ten patients tolerating treatment showed a rapid improvement, often beginning within 24 h, with reduction in joint pain, swelling, and stiffness, improvement in joint mobility, and cessation of pyrexia. Active disease disappeared in 3–28 days. After 6 weeks the blood-count and erythrocyte-sedimentation rate became normal. In 4–6 months the albumin/globulin ratio and the electrophoretic pattern returned to normal. At the end of the follow-up the rheumatoid factor and autoantibodies had disappeared from the blood. There was no return of disease activity during the period of observing during which no other treatment was necessary.

Subsequent experience with clotrimazole revealed that similar results could be obtained with daily doses of only 10–12 mg/kg. Occasionally treatment with clotrimazole, even though previous drugs were continued, resulted in a transient violent increase in joint pain, swelling, and hotness with pyrexia and blood eosinophilia, constituting a Herxheimer reaction and typical of many parasitic diseases treated by drugs which kill the causative organism.

The similar effects on the activity of rheumatoid arthritis of a number of antiprotozoal drugs containing imidazole groups, the rapid action of clotrimazole, the efficacy of clotrimazole when other drugs had failed, the non-recurrence of disease activity long after clotrimazole treatment was stopped, the disappearance of the rheumatoid factor and auto-antibodies from the serum, and the occasional Herxheimer reaction all point to a parasitic, probably protozoal, cause of the disease.

Dr Otterness and Dr Niblack (Jan. 17, p. 148) suggest that clotrimazole acts in rheumatoid arthritis through an anti-inflammatory effect and by stimulating adrenal secretion. Their findings, however, cannot explain the action of clotrimazole because some of my patients were already taking steroids or tetracosactrin before clotrimazole was successfully substituted. An anti-inflammatory and adrenal stimulating action cannot explain the Herxheimer reactions. Daily doses of clotrimazole of 10–12 mg/kg produce much lower tissue concentrations than do the doses used by Otterness and Niblack. At 33 mg/kg they found only a 2% inhibition of inflammatory response; 10–12 mg/kg would have even less effect. Similar arguments apply to any adrenal-stimulating effect of the drug. Disease activity did not recur when the drug was stopped as it would if its action had been anti-inflammatory and adrenal stimulating.

2 Hill Brow,
Richmond Hill,
Surrey

R. WYBURN-MASON

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5. McGill, P. E. *ibid.* 1976, i, 149.
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Dr.J.A.Wojtulewski
St.Mary's Hosptal,Eastbourne,England

CLOTRIMAZOLE IN RHEUMATOID ARTHRITIS

Legend:

Table 1

Effect of Clotrimazole on plasma cortisol which returns to normal after discontinuation of the drug.

Table 2 and table 3

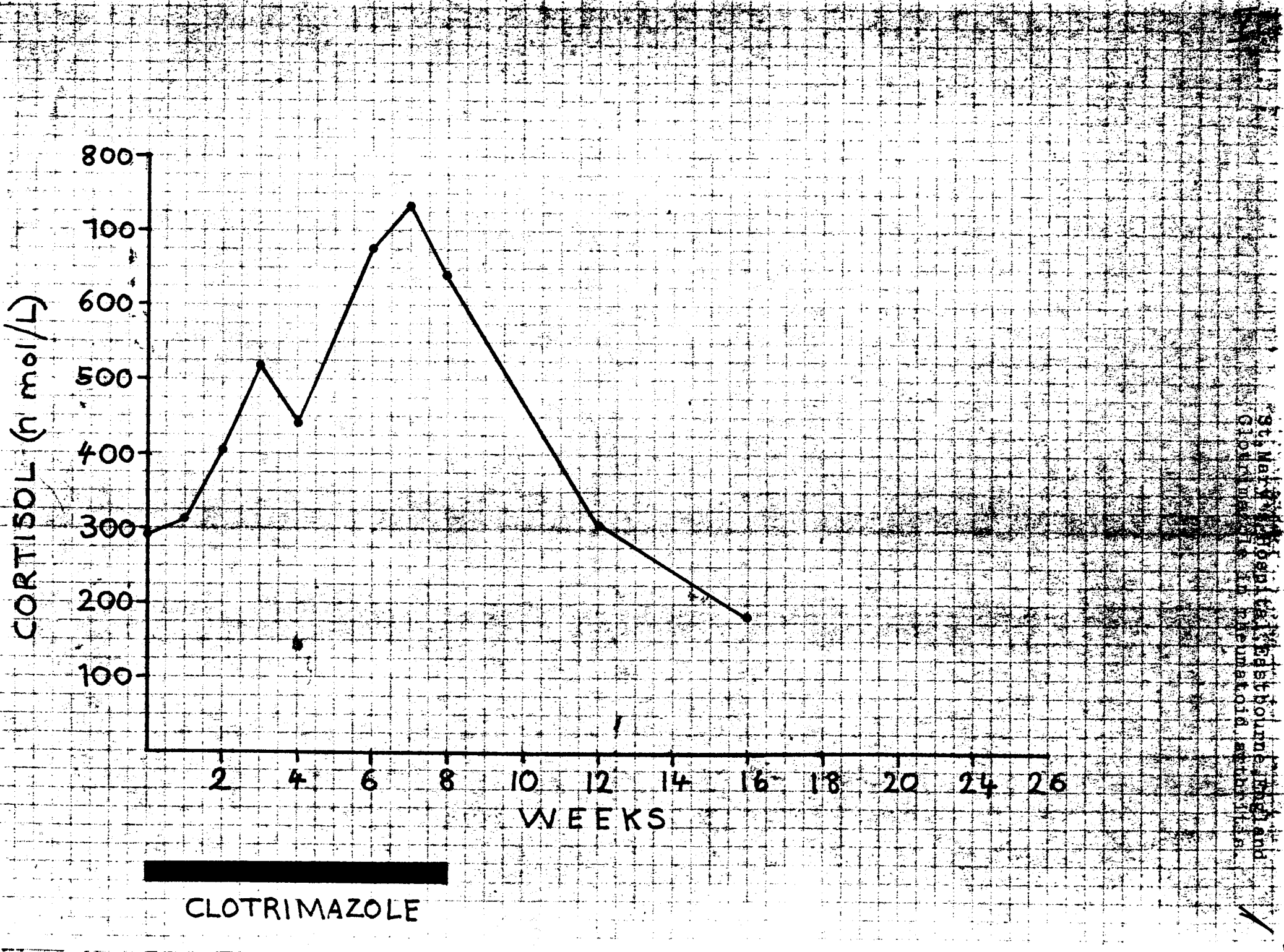
Cross-over study to compare the effect of Ketoprofen and Clotrimazole on plasma cortisol with one week "wash-out" period.

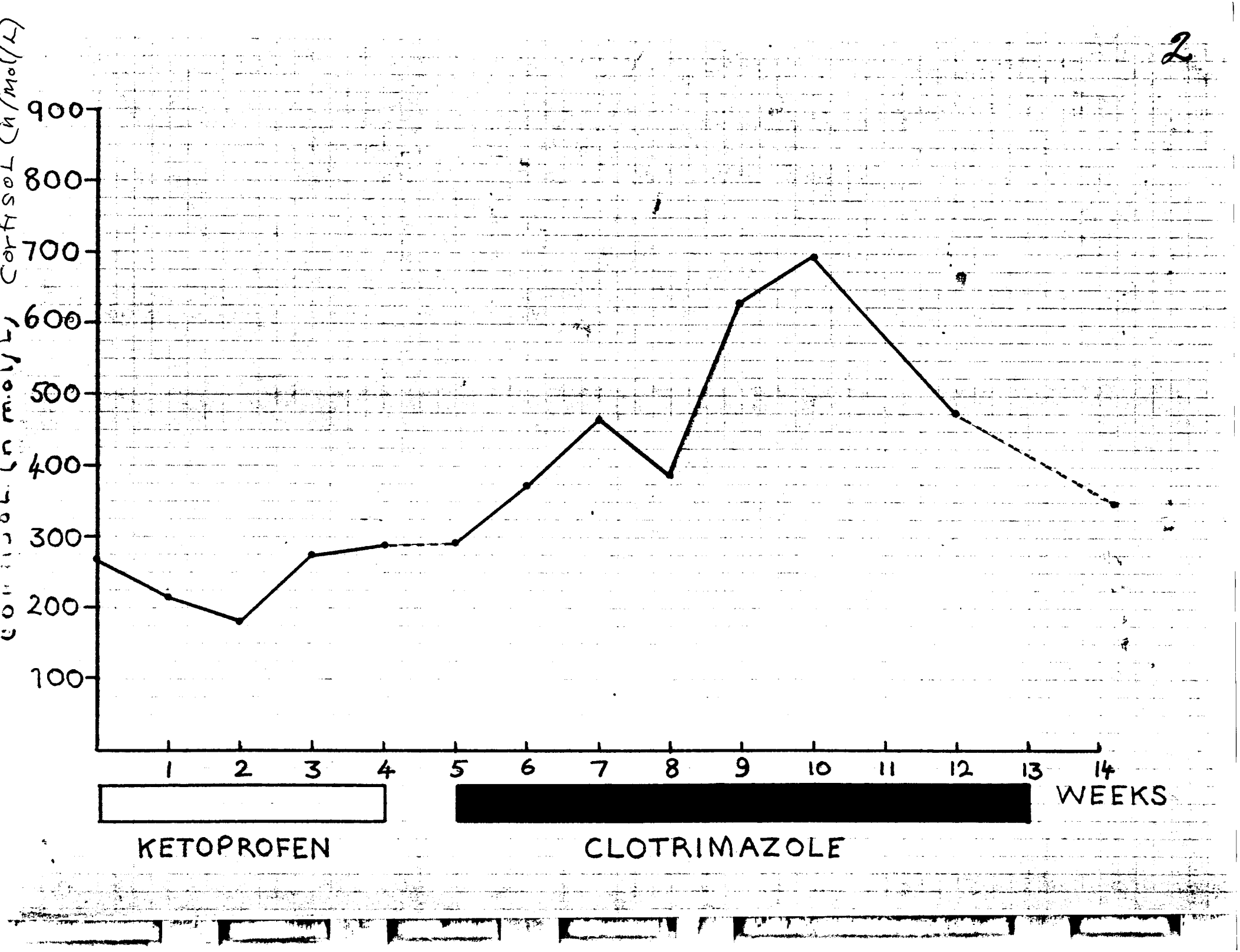
Table 4

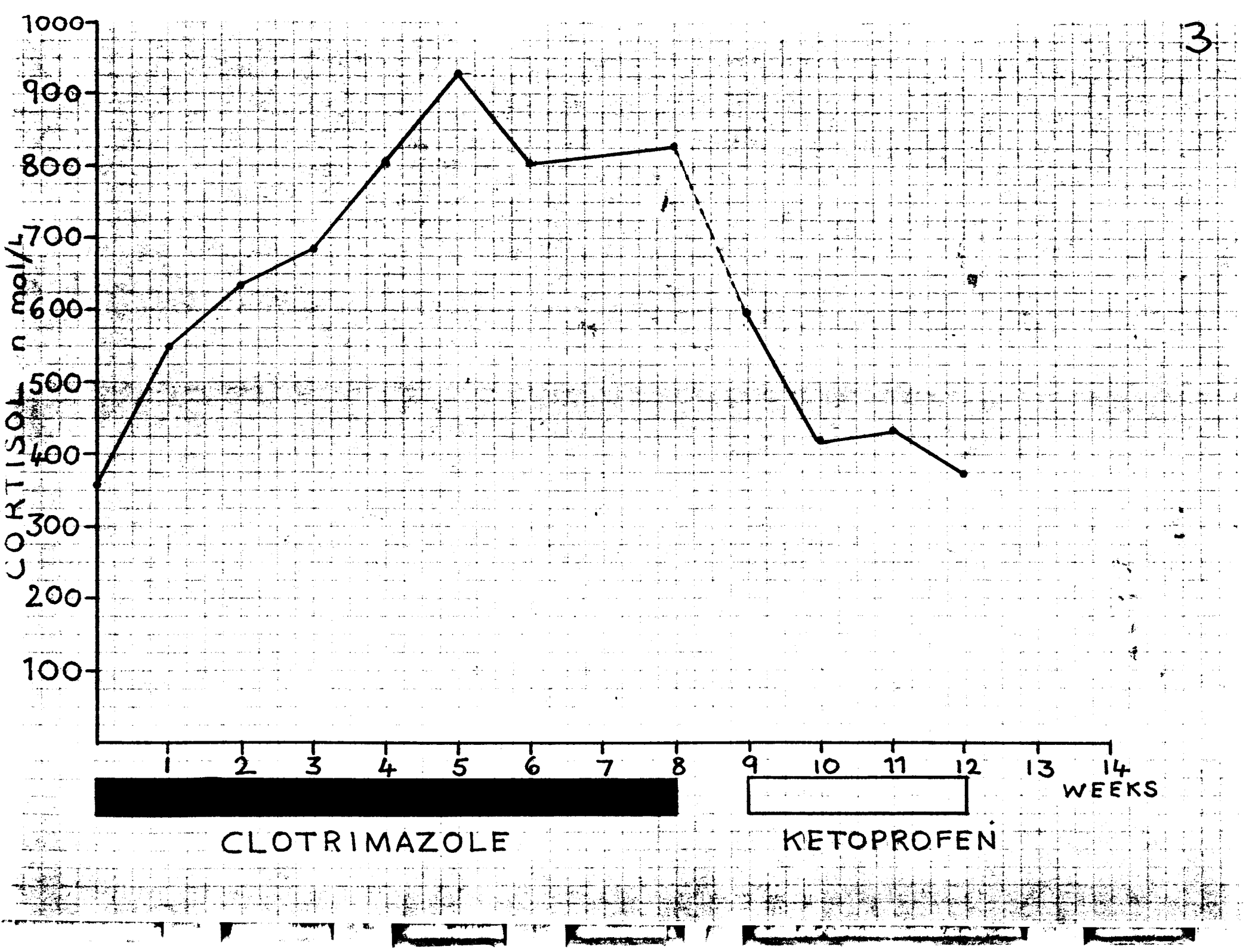
Cross-over study to compare the effect of Ketoprofen and Clotrimazole in P.I.P.joint swelling(both hands) with one week "wash-out" period.

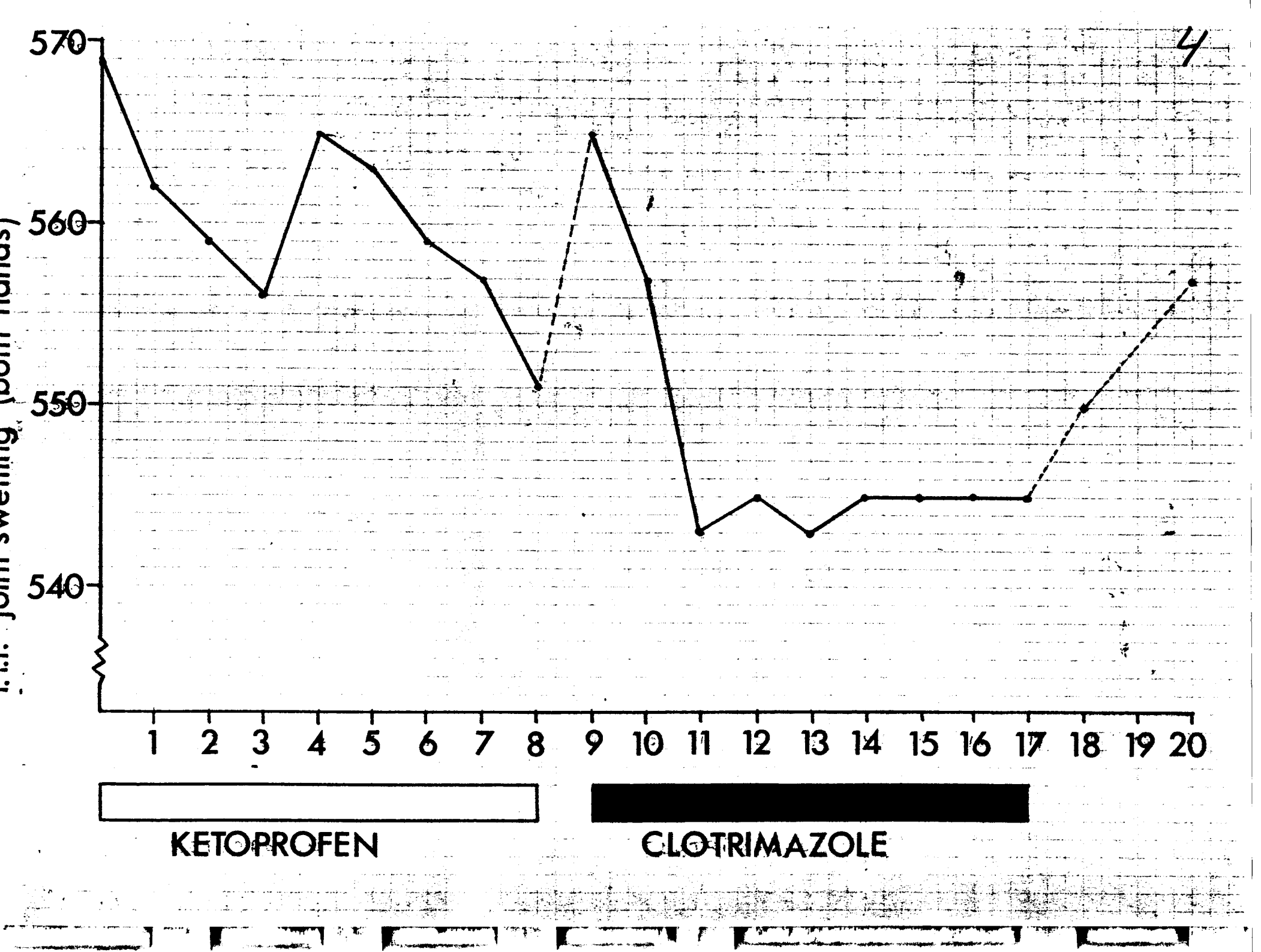
Table 5

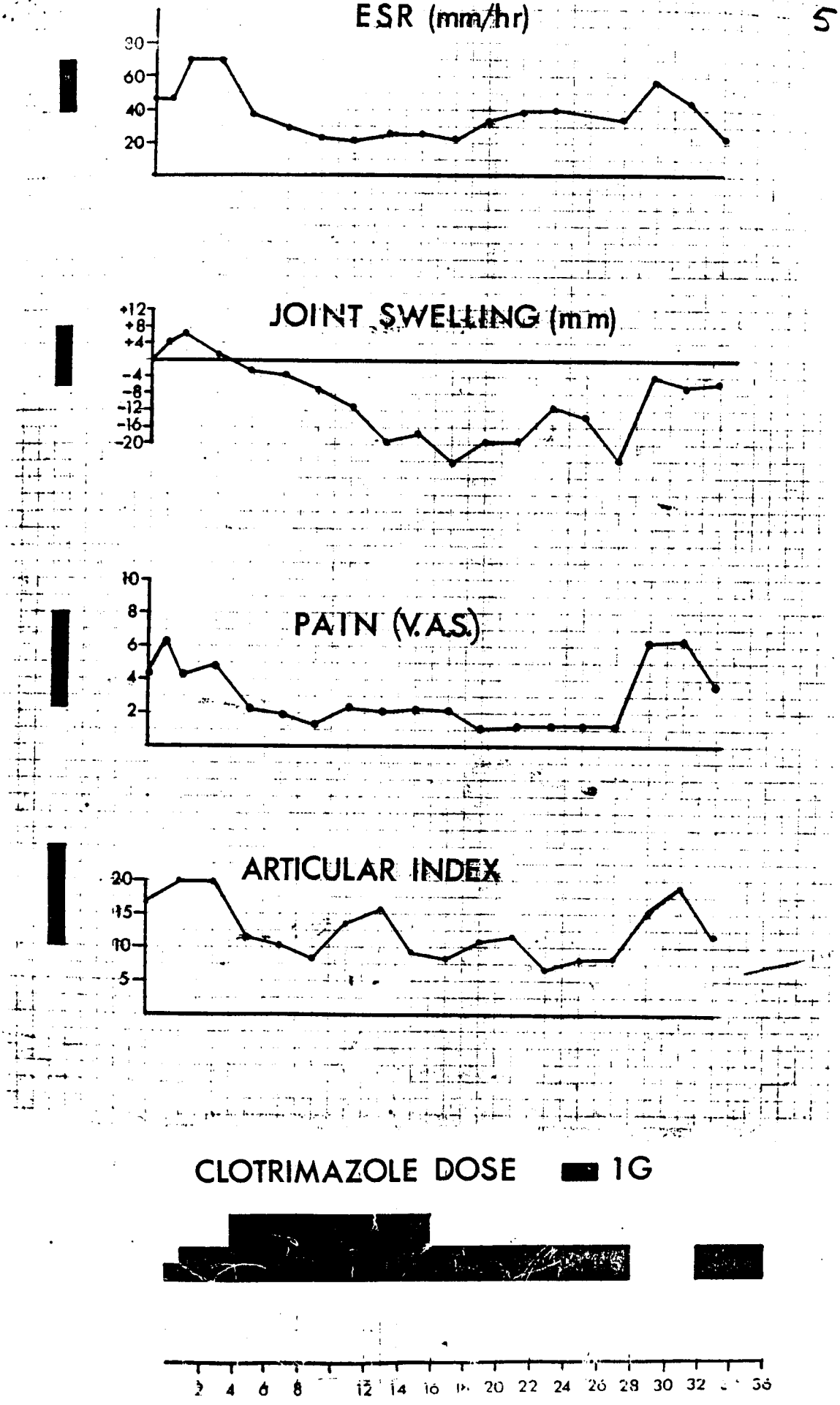
Effect of Clotrimazole in various dosages on ESR,JOINT SWELLING,PAIN and ARTICULAR INDEX.


800
700
600
500
400
300
200
100
CORTISOL (n mol/L)
2
4
6
8
10
12
14
16
18
20
24
26
WEEKS
CLOTRIMAZOLE


Cortisol (n/mol/L)
900
800
700
600
500
400
300
200
100
1
2
3
4
5
6
7
8
9
10
11
12
13
14
WEEKS
KETOPROFEN
CLOTRIMAZOLE


1000
900
800
700
600
500
400
300
200
100
CORTISOL n mol/L
1 2 3 4 5 6 7 8 9 10 11 12 13 14
WEEKS
CLOTRIMAZOLE
KETOPROFEN


4
570
560
550
540
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
KETOPROFEN
CLOTRIMAZOLE


ESR (mm/hr)
30
60
40
20
JOINT SWELLING (mm)
+12
+8
+4
-4
-8
-12
-16
-20
PAIN (V.A.S.)
10
8
6
4
2
ARTICULAR INDEX
20
15
10
5
CLOTRIMAZOLE DOSE
1G
2
4
6
8
12
14
16
20
22
24
26
28
30
32
36