A Multicentre Trial of Voltaren in the Treatment of Rheumatoid Arthritis

O. L. MEYERS, O. P. QUANTOCK, P. G. JOUBERT, D. F. DU P. LOUW, D. F. MARAIS, W. A. McDONALD SCOTT, F. O. MÜLLER

SUMMARY

Voltaren, a compound with analgesic, anti-inflammatory and antipyretic properties, has been compared at two dose levels—25 mg *t.d.s.* and 50 mg *t.d.s.*—with indomethacin 25 mg *t.d.s.* and acetylsalicylic acid 1 500 mg *t.d.s.* Ninety-one patients with definite or classical rheumatoid arthritis took part in this study. The trial was a double-blind cross-over study, with each medication being given for one week. Patients were washed out for one week prior to the first active treatment. Each patient received only two of the four possible treatments. Voltaren in a dose of 25 mg *t.d.s.* was found to improve the symptoms of rheumatoid arthritis to a greater degree than indomethacin or acetylsalicylic acid.

Voltaren 50 mg *t.d.s.* evoked a greater response than acetylsalicylic acid and was at least as efficacious as indomethacin. Voltaren was better tolerated than either indomethacin or acetylsalicylic acid. The incidence of gastro-intestinal side-effects was similar with Voltaren and indomethacin, and half that produced by acetylsalicylic acid. Some evidence of possible drug interaction was found.

S. Afr. Med. J., **48**, 2013 (1974).

Arthritis Clinic, Groote Schuur Hospital, Cape Town
O. L. MEYERS, M.B. CH.B., F.C.P., *Head of the Arthritis Clinic*
O. P. QUANTOCK, M.B. B.CH., F.C.P. (S.A.), *Clinical Assistant*, (Present address: c/o Empangeni Hospital, Empangeni, Zululand)

Department of Orthopaedic Surgery, Karl Bremer Hospital, Tiervlei, CP
P. G. JOUBERT, M.B. CH.B., M.MED. (CHIR.), *Professor*

Department of Orthopaedic Surgery, National Hospital, Bloemfontein, OFS
D. F. DU P. LOUW, M.B. CH.B.

Pretoria
D. F. MARAIS, M.B. CH.B., M.MED. (CHIR.), *Orthopaedic Surgeon*

Department of Medicine, Addington Hospital, Durban
W. A. McDONALD SCOTT, M.B. CH.B., M.R.C.P.

Department of Pharmacology, University of the Orange Free State, Bloemfontein, OFS
F. O. MÜLLER, M.B. CH.B.

Date received: 10 May 1974.

Voltaren, sodium-(o-[(2,6-dichlorophenyl)-amino]-phenyl)-acetate, is a non-pyrazole, non-steroidal agent, which in pharmacological tests on animals has been shown to possess both analgesic and anti-inflammatory properties. Preliminary studies in human volunteers and in patients with rheumatoid arthritis showed that the drug was well tolerated and possessed few adverse properties.[1]

A multicentre trial of this drug was undertaken in six centres in South Africa to assess the efficacy and tolerability of two dose levels of Voltaren in comparison with acetylsalicylic acid and indomethacin in patients with rheumatoid arthritis.

PATIENTS AND METHODS

Consecutive patients with classical or definite rheumatoid arthritis[2] in whom there was disease of the proximal interphalangeal joints were selected. Juveniles, pregnant women and patients who gave a past history of peptic ulceration or a history of severe dyspepsia were excluded from this study. Liver or renal disease, diabetes mellitus and concomitant anticoagulant therapy were also regarded as contra-indications for inclusion in the trial. The recent use, within 6 weeks, of corticosteroids or chloroquine, or of gold salts within the preceding 6 months, were also regarded as reasons for excluding patients from this trial.

Trial Design

The trial was a double-blind, cross-over, within-patient study, randomised in balanced blocks of paired sequence. Packaging of the drugs was arranged so that the active principles were contained in identical capsules. These had similar dissolution characteristics when tested in artificial gastric juice. A dummy loading technique was adopted. The dosage in milligrams and capsules per day were as follows:

	Breakfast	*Lunch*	*Dinner*	*Total daily dose*
Voltaren	25 mg (PP)*	25 mg (PP)	25 mg (PP)	75 mg
Voltaren	25, 25 (P)	25, 25 (P)	25, 25, 25	150 mg
Aspirin	500, 500, 500	500, 500, 500	500, 500, 500	4 500 mg
Indomethacin	25 mg (PP)	25 mg (PP)	25 mg (PP)	75 mg

* P = 1 placebo capsule.

Methods Used for Evaluation

The total duration of the trial was three weeks, and both the patient and the investigator made independent assessments of the disease on each occasion. These assessments were carried out at the commencement of the trial, after one week during which no anti-inflammatory drugs were taken, and at the end of each week on the double-blind trial. Provision was made for a rescue analgesic: paracetamol 500 mg was used when necessary.

Patients' assessments: A 100-mm visual analogue scale[3] was used to record the patient's assessment of the degree of morning stiffness, severity of pain, ability to walk and global feeling of well-being. Each patient placed a mark on the scale which he regarded as reflecting the status of each of these four parameters, as in the example:

I have no stiffness ———— I have severe stiffness

Each assessment was carried out without reference to that of the previous week. At the end of the trial the patient was asked to express a preference for either of the two active treatment weeks.

Investigators' assessments: The investigator used three parameters of disease activity: the articular index of Ritchie,[4] grip strength,[5] and the proximal interphalangeal joint circumference.[6]

For the purpose of the trial, the temporomandibular, cervical spine, sternoclavicular and acromioclavicular joints were regarded as four single joints. In each hand, all the proximal interphalangeal joints and the metacarpophalangeal joints were each regarded as single units.

Grip strength was measured with a 7,5-cm diameter sphygmomanometer cuff inflated to 30 mmHg. The patient rested the elbow on the table while the inflated cuff was squeezed. The best of three readings was recorded. The proximal interphalangeal joints were measured with a plastic strain gauge (Geigy) and the total for each hand recorded.

At the end of the trial the investigator recorded a preference for either one of the two weeks of active treatment.

RESULTS

Ninety-one patients with definite or classical rheumatoid arthritis completed the trial. Most of these subjects were females whose ages ranged between 20 and 75 years. Unless it is specifically mentioned otherwise, the groups of patients assigned to the two different treatment sequences of each comparison were not significantly different with regard to age, race or sex, or the pretreatment values of each of the patients' and investigators' assessments.

Voltaren 75 mg/day Compared with Acetylsalicylic Acid 4,5 g/day (Table I)

Seventeen patients entered this trial group. One patient dropped out because she did not take the full medication as prescribed.

Patients' assessments: Both drugs were equally effective in reducing morning stiffness, relieving pain and improving the patients' ability to walk. The global feeling of well-being was better in the periods when the patients were receiving Voltaren, and this occurred irrespective of treatment sequence.

Investigators' assessments: Both drugs reduced the articular index, although Voltaren appeared slightly

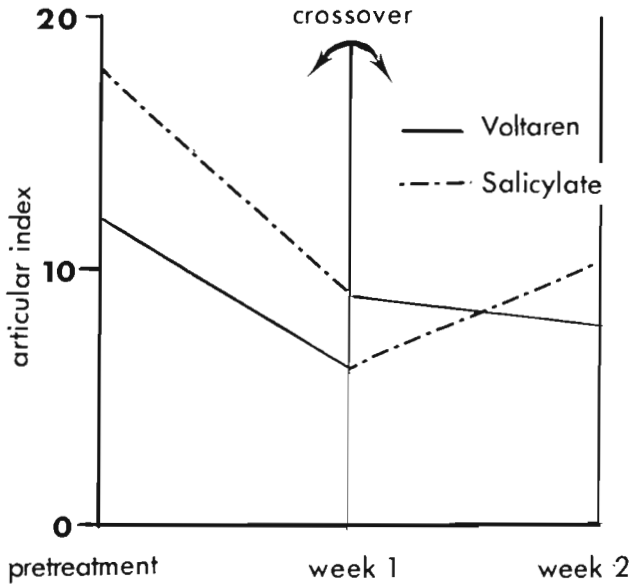

Fig. 1. The effect of Voltaren 25 mg *t.d.s.* and acetylsalicylic acid 1 500 mg *t.d.s.* on articular index.

TABLE I. MEAN INITIAL AND POST-TREATMENT VALUES* (AND STANDARD ERROR) FOR MORNING STIFFNESS, PAIN, ABILITY TO WALK, FEELING OF WELL-BEING, AND PIP JOINT CIRCUMFERENCE, IN THE SERIES VOLTAREN 75 mg/day AND SALICYLATE 4,5 g/day

	Sequence			Sequence		
		Post-treatment			Post-treatment	
Parameters	Pretreatment	Voltaren	Salicylate	Pretreatment	Salicylate	Voltaren
Early morning stiffness (mm) ...	80,3 ± 4,9	56,0 ± 8,5	56,7 ± 9,9	67,7 ± 9,5	50,6 ± 7,0	27,7 ± 7,9
Pain (mm)	56,3 ± 12,4	29,0 ± 9,9	34,4 ± 8,9	58,6 ± 10,4	45,1 ± 7,9	23,6 ± 7,5
Ability to walk (mm)	42,7 ± 12,3	31,6 ± 11,0	31,4 ± 12,1	53,8 ± 11,5	47,7 ± 10,1	33,0 ± 11,6
Feeling of well-being (mm)	22,4 ± 9,7	17,3 ± 8,5	11,4 ± 6,6	29,4 ± 8,7	25,9 ± 6,7	10,3 ± 3,9
PIP joint circumference (mm) ...	608,1 ± 31,2	600,1 ± 29,3	606,9 ± 32,8	575,1 ± 14,5	566,2 ± 12,7	564,0 ± 11,5

* The lower the post-treatment value the better the response.

superior to salicylate in this respect (Fig. 1). The grip strength of both hands improved to a similar, but not significantly different extent, although the pretreatment value for finger joint circumference was significantly greater for the group receiving Voltaren first ($P<0,05$). The combined finger joint circumference was decreased by both drugs to the same extent.

Voltaren was preferred by both patients and investigators (81,25% : 18,75%). These differences were significant ($P<0,01$). By coincidence, the patients' and investigators' totals were identical.

Voltaren 150 mg/day Compared with Acetylsalicylic Acid 4,5 g/day (Table II)

Fifteen patients entered this trial group and there were no drop-outs.

Patients' assessments: The pretreatment mean value for early morning stiffness was not homogeneous, since the patients in the sequence salicylate/Voltaren complained of significantly more early morning stiffness ($P<0,01$). The capacity of both drugs to decrease early morning stiffness was, however, similar. No significant after-treatment differences were seen in the three parameters, pain, ability to walk, and general feeling of well-being; both treatments were equally effective. The global feeling of well-being was slightly lowered while patients were receiving salicylate, and this appears to be due to worsening of their symptoms during the sequence when salicylate was administered after Voltaren.

Investigators' assessments: Both drugs, in whichever sequence they were used, reduced the articular index to a similar extent. There were no differences in grip strength and combined finger joint circumference measurements.

The patients' and investigators' preference statements both favoured Voltaren.

Voltaren 75 mg/day Compared with Indomethacin 75 mg/day (Table III)

Sixteen patients entered this trial group, with 1 drop-out because the patient proved unreliable.

Patients' assessments: Both drugs reduced early morning stiffness and pain, and improved the patients' ability to walk and their feeling of well-being to a similar extent.

Investigators' assessments: As can be seen from Fig. 2, both drugs reduced the articular index, with a trend favouring Voltaren which failed to reach significance. Grip strength and finger circumference improved with both drugs, but slightly more so with Voltaren.

There was a trend for both the investigators and the patients to prefer Voltaren, in whichever sequence it was administered.

Voltaren 150 mg/day Compared with Indomethacin 75 mg/day (Table IV)

Seventeen patients entered this trial group and there were 4 drop-outs, none of whom were drug-related.

Patients' assessments: Both drugs effectively reduced morning stiffness and pain, although indomethacin appear-

TABLE II. MEAN INITIAL AND POST-TREATMENT VALUES* (AND STANDARD ERROR) FOR MORNING STIFFNESS, PAIN, ABILITY TO WALK, FEELING OF WELL-BEING AND PIP JOINT CIRCUMFERENCE, IN THE SERIES VOLTAREN 150 mg/day AND SALICYLATE 4,5 g/day

	Sequence			Sequence		
		Post-treatment			Post-treatment	
Parameters	Pretreatment	Voltaren	Salicylate	Pretreatment	Salicylate	Voltaren
Early morning stiffness (mm) ...	36,4 ± 7,8	24,3 ± 4,4	34,5 ± 9,6	76,3 ± 9,7	47,6 ± 11,4	34,3 ± 11,0
Pain (mm)	60,5 ± 10,6	28,4 ± 7,4	41,9 ± 10,1	72,7 ± 9,2	36,1 ± 11,9	25,4 ± 11,4
Ability to walk (mm)	38,6 ± 8,8	34,5 ± 9,5	41,6 ± 12,4	49,1 ± 13,9	35,7 ± 12,1	28,3 ± 10,2
Feeling of well-being (mm)	29,1 ± 9,0	14,0 ± 3,9	29,3 ± 10,2	47,6 ± 14,8	29,6 ± 6,6	22,4 ± 9,7
PIP joint circumference (mm) ...	579,0 ± 20,3	574,3 ± 20,0	577,3 ± 22,3	590,7 ± 12,7	582,9 ± 10,9	587,0 ± 11,2

* The lower the post-treatment value the better the response.

TABLE III. MEAN INITIAL AND POST-TREATMENT VALUES* (AND STANDARD ERROR) FOR MORNING STIFFNESS, PAIN, ABILITY TO WALK, FEELING OF WELL-BEING AND PIP JOINT CIRCUMFERENCE IN THE SERIES VOLTAREN 75 mg/day AND INDOMETHACIN 75 mg/day

	Sequence			Sequence		
		Post-treatment			Post-treatment	
Parameters	Pretreatment	Voltaren	Indomethacin	Pretreatment	Indomethacin	Voltaren
Early morning stiffness (mm) ...	47,1 ± 9,0	23,6 ± 5,4	18,4 ± 5,0	70,4 ± 7,3	28,1 ± 9,8	24,0 ± 12,0
Pain (mm)	53,0 ± 7,4	25,1 ± 10,2	29,8 ± 10,8	73,0 ± 6,6	32,9 ± 13,4	29,4 ± 12,2
Ability to walk (mm)	59,8 ± 10,5	33,9 ± 12,1	41,8 ± 11,9	70,4 ± 10,1	36,9 ± 15,4	28,1 ± 13,1
Feeling of well-being (mm)	37,4 ± 11,0	21,0 ± 9,9	20,6 ± 8,2	46,1 ± 15,8	40,6 ± 17,4	23,0 ± 13,7
PIP joint circumference (mm) ...	565,1 ± 5,5	562,1 ± 6,7	567,4 ± 6,6	576,7 ± 21,3	578,1 ± 19,3	572,3 ± 19,3

* The lower the post-treatment value the better the response.

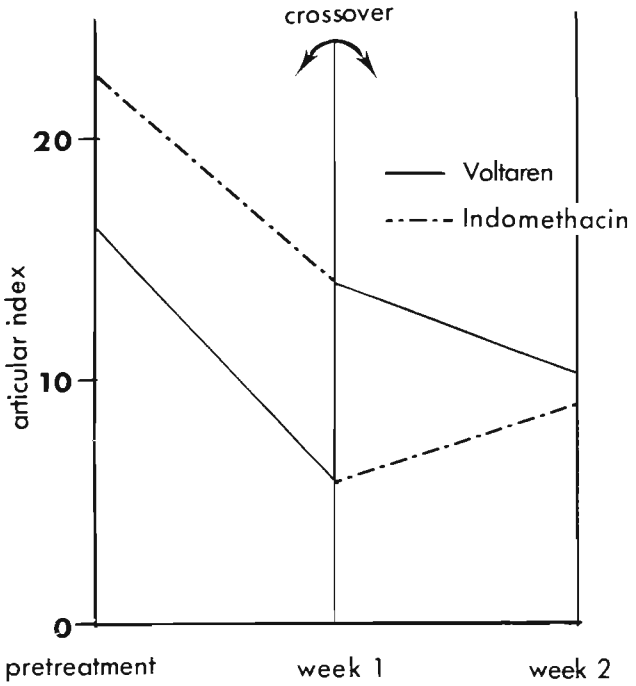

Fig. 2. The effect of Voltaren 25 mg *t.d.s.* and indomethacin 25 mg *t.d.s.* on articular index.

ed slightly more effective (the differences were not significant). The patients' ability to walk and their global feeling of well-being was similarly improved by both drugs. The second week of treatment tended to be better than the first, irrespective of which drug was used.

Investigators' assessments: Both drugs reduced articular index and increased grip strength to a similar extent. Reduction in finger joint circumference was slightly better with Voltaren.

Both the investigators' and patients' preference statements favoured indomethacin, but the difference was not significant.

Voltaren 75 mg/day Compared with Voltaren 150 mg/day (Table V)

Sixteen patients entered this trial group and there were no drop-outs. No significant differences were found between these two dose levels, but the higher dose appeared to afford more relief from pain. The higher dose was preferred by both patients and investigators.

Salicylate 4,5 g/day Compared with Indomethacin 75 mg/day

Seventeen patients entered this trial group and there was 1 drop-out. The subjective and objective parameters were almost the same with both drugs. The patients preferred indomethacin while the investigators tended to prefer salicylate. These differences were not significant.

Consumption of Rescue Analgesic

The requirements for extra analgesic therapy during the trial weeks was approximately the same during the periods on Voltaren, salicylate and indomethacin. All three drugs produced equally marked reduction in the paracetamol requirements when compared with the wash-out period.

Side-Effects (Table VI)

Salicylate produced the greatest number of side-effects in whichever sequence it was used. The effects were the usual symptoms referable to the gastro-intestinal tract and the ears. In marked contrast were the fewer side-effects produced by Voltaren and indomethacin. Voltaren did produce some upper gastro-intestinal symptoms of nausea and dyspepsia, but these were mild and did not necessitate discontinuation of the drug.

DISCUSSION

The data presented here show that when Voltaren was used for a week in doses of either 75 mg/day or 150 mg/day, it improved morning stiffness, pain, ability to walk and the patients' feeling of well-being. In these doses, the drug also reduced the articular index and finger joint circumference and improved grip strength. The drug was well tolerated and produced significantly fewer side-effects than salicylate ($P<0,001$). The side-effects which were encountered were generally mild.

TABLE IV. MEAN INITIAL AND POST-TREATMENT VALUES* (AND STANDARD ERROR) FOR MORNING STIFFNESS, PAIN, ABILITY TO WALK, FEELING OF WELL-BEING AND PIP JOINT CIRCUMFERENCE, IN THE SERIES VOLTAREN 150 mg/day AND INDOMETHACIN 75 mg/day

	Sequence			Sequence		
		Post-treatment			Post-treatment	
Parameters	Pretreatment	Voltaren	Indomethacin	Pretreatment	Indomethacin	Voltaren
Early morning stiffness (mm) ...	66,6 ± 8,3	40,4 ± 10,8	55,0 ± 10,9	61,4 ± 12,1	38,0 ± 13,0	28,8 ± 10,4
Pain (mm)	69,6 ± 5,4	40,1 ± 12,1	25,4 ± 12,8	68,0 ± 11,8	31,5 ± 7,8	34,0 ± 13,2
Ability to walk (mm)	60,9 ± 7,5	35,6 ± 10,7	21,4 ± 7,6	44,9 ± 12,1	32,2 ± 13,2	26,8 ± 14,7
Feeling of well-being (mm)	30,0 ± 10,3	16,9 ± 9,7	18,6 ± 13,1	39,3 ± 9,9	15,4 ± 5,8	11,2 ± 67,4
PIP joint circumference (mm) ...	584,4 ± 25,6	577,9 ± 24,0	578,9 ± 25,5	570,1 ± 16,6	572,7 ± 18,6	561,0 ± 21,0

* The lower the post-treatment value the better the response.

TABLE V. MEAN INITIAL AND POST-TREATMENT VALUES* (AND STANDARD ERROR) FOR MORNING STIFFNESS, PAIN, ABILITY TO WALK, FEELING OF WELL-BEING AND PIP JOINT CIRCUMFERENCE, IN THE SERIES VOLTAREN 75 mg/day AND VOLTAREN 150 mg/day

	Sequence			Sequence		
		Post-treatment			Post-treatment	
Parameters	Pretreatment	Voltaren 25 mg	Voltaren 50 mg	Pretreatment	Voltaren 50 mg	Voltaren 25 mg
Early morning stiffness (mm) ...	55,7 ± 8,6	37,2 ± 8,7	37,7 ± 10,9	65,6 ± 10,1	33,7 ± 8,6	35,9 ± 9,4
Pain (mm)	74,0 ± 7,6	51,0 ± 7,8	35,3 ± 9,1	52,3 ± 10,0	50,1 ± 12,8	56,3 ± 10,8
Ability to walk (mm)	65,2 ± 7,5	29,1 ± 6,4	23,2 ± 8,4	47,4 ± 15,1	33,4 ± 11,1	29,7 ± 10,1
Feeling of well-being (mm)	39,6 ± 10,5	18,3 ± 4,8	13,8 ± 4,8	20,6 ± 7,4	16,9 ± 6,1	12,6 ± 4,3
PIP joint circumference (mm) ...	578,7 ± 7,5	578,8 ± 12,4	581,0 ± 10,9	569,9 ± 19,9	565,9 ± 16,6	566,1 ± 15,4

* The lower the post-treatment value the better the response.

TABLE VI. NATURE AND NUMBER OF SIDE-EFFECTS REPORTED WHILE ON VOLTAREN, SALICYLATE AND INDOMETHACIN

Symptom	Voltaren	Salicylate	Indomethacin
CNS symptoms			
Tinnitus	0	13	0
Deafness	0	6	0
Vertigo	1	3	3
Dermatological			
Pruritis/stiff skin ...	0	2	0
Respiratory			
Upper respiratory infection	0	1	0
Gastro-intestinal			
Nausea/vomiting ...	4	5	4
Dyspepsia/heartburn	5	7	3
Constipation	1	0	0
Total	11	37	10
Total patient exposure to 3 drugs	75	47	44
Total side-effects (%)	14,7%	78,7%	22,7%
CNS side-effects (%)	1,3%	46,8%	6,8%
Dermatological side-effects (%)	0 %	4,3%	0 %
Respiratory side-effects (%)	0 %	2,1%	0 %
Gastro-intestinal side-effects (%)	13,3%	25,5%	15,9%

The effects of Voltaren 150 mg daily were generally comparable to those achieved with salicylate and indomethacin. The response to Voltaren appeared marginally better than that to salicylate. The differences between these two drugs were, however, not significant. The responses to Voltaren and indomethacin were almost identical, indomethacin being favoured slightly, but not to a significant degree.

When Voltaren was administered in a dose of 75 mg/day, there was an impressive and consistent preference for Voltaren compared with salicylate by both patients and investigators ($P<0,01$). In the other parameters tested, Voltaren was favoured, but not significantly so. The responses from Voltaren and indomethacin were almost identical, except for improvement in articular index where a trend in favour of Voltaren was observed. Both the investigators and the patients preferred Voltaren. These results did not reach statistical significance.

When a difference in efficacy occurred, Voltaren proved superior in most instances, irrespective of treatment sequence.

With the parameter articular index (Figs 1 and 2), Voltaren 75 mg daily proved superior to both acetylsalicylic acid and indomethacin, these findings being particularly noticeable in the second week of therapy after crossover; clear drug superiority or altered disease situation may explain these findings. Reduced plasma binding of salicylate may be invoked to explain this phenomenon, in the same way as lower indomethacin and indomethacin and fenoprofen levels have been demonstrated during concomitant salicylate administration.[7] The reduced levels of indomethacin and fenoprofen which have been described have not yet been correlated with reduced clinical activity, and this could be important. The phenomenon of reduced salicylate activity may represent another example of pharmacodynamic interaction.

Voltaren produced fewer side-effects than were encountered during either salicylate or indomethacin administration. The most common symptoms were gastro-intestinal, but they were mild and did not require cessation of the drug.

The fewer side-effects, its tolerability and its consistent favouring over salicylate, suggests that Voltaren will prove a worthwhile addition to the therapeutic agents used in the treatment of rheumatoid arthritis.

More extended trials are now clearly indicated and its general use in arthritic patients is indicated to assess its usefulness and to determine its place in the management of rheumatoid arthritis.

REFERENCES

1. Ciba-Geigy (1971): Orientation GP 45'840, pp. 1 - 20. Basle: Ciba-Geigy.
2. Ropes, M. W., Bennett, G. A., Cobb, S., Jacox, R. and Jessar, R. A. (1959): Arth. Rheum., **12**, 16.
3. Joyce, C. R. B. ed. (1968): *Psychopharmacology 1968: Dimension and Prospectus*. London: Tavistock.
4. Ritchie, D. M., Boyle, J. A., McInnes, J. M., Jasani, M. K., Dalakos, T. G., Grierson, P. and Buchanan, W. W. (1968): Amer. J. Med., **37**, 1.
5. Wright, V. (1959): Clin. Sci., **18**, 17.
6. Boardman, P. L. and Hart, F. D. (1967): Brit. Med. J., **2**, 264.
7. Rubin, A., Rodda, B. E., Warrick, P. and Gruber, C. M. jun. (1973): Arth. Rheum., **16**, 635.