South African Multicentre Trial with Voltaren in Osteo-arthritis of the Knee

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SUMMARY

Patients suffering from osteo-arthritis of the knee were admitted to a multicentre, double-blind trial comparing the efficacy and tolerability of two dose levels of Voltaren (diclophenac sodium), 25 mg *t.d.s.* and 50 mg *t.d.s.*, and acetylsalicylic acid 1 000 mg *t.d.s.* Eighty-three patients from 4 centres were evaluated. Three racial groups were studied: White, Asian, and Coloured. Both preparations were effective in alleviating the symptoms of osteo-arthritis. The two dose levels of diclophenac sodium had slightly superior effects over acetylsalicylic acid. Preference statements by both investigators and patients favoured diclophenac sodium. In this short-term study both dose regimens of diclophenac sodium were better tolerated. The incidence of gastro-intestinal side-effects was lower with diclophenac sodium. No major adverse reactions were recorded. Results of the blood morphology and uric acid study carried out in one centre showed that none of the treatments produced any abnormalities.

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Voltaren (diclophenac sodium), a non-steroidal, non-pyrazole compound, was developed in the laboratories of Ciba-Geigy. It was found to possess good antirheumatic activity in the treatment of degenerative inflammatory and extra-articular forms of rheumatic disorders.[1] Chemically this compound is an aminophenylacetic acid derivative, named sodium-(o-[(2,6-dichlorophenyl)-aminol]-phenyl)-acetate; $C_{14}H_{10}Cl_2NO_2Na$.

Pharmacologically diclophenac sodium was found to display potent anti-inflammatory, analgesic, and antipyretic activity. Its anti-inflammatory effect is present in the adrenalectomised animal and was demonstrated at low doses in a number of systems. Diclophenac sodium was found to stabilise platelets *in vitro* and to counteract the contraction of the guinea-pig ileum induced by arachidonic acid peroxide in very low concentrations. This latter action is particularly characteristic of agents exhibiting analgesic activity.[1] The object of the present study was to establish by quantitative methods, in a controlled, multicentre, double-blind within-patient trial, the anti-inflammatory and analgesic effect of two dose levels of diclophenac sodium and to compare its efficacy and tolerability with those of acetylsalicylic acid.

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PATIENTS AND METHODS

Eighty-five patients with osteo-arthritis of the knee, as determined by the radiological criteria of Kellgren and Lawrence,[2] and with definite clinical disability, took part in the trial. Both medial, lateral and anterior compartment osteo-arthritis were included, and in bilateral cases only the worst knee was assessed.

Patients were distributed between 4 centres: Bellville, Bloemfontein, Durban and Johannesburg. White, Asian and Coloured populations were studied. The 3 treatment regimens (Table I) were made up in identical capsules. These had similar dissolution characteristics when tested in artificial gastric juice. A dummy loading technique was utilised in order to maintain double-blindness. Patients were allocated at random to treatment for one week on 1 of the 3 trial medications, and then crossed over to 1 of the 2 alternative treatments for the second week. The 2 treatment periods were preceded by a 1-week wash-out, when all antirheumatic and anti-inflammatory

TABLE I. DAILY TREATMENT REGIMENS

Drug	Breakfast	Lunch	Dinner	Total (mg)
Diclophenac sodium (25 mg)	**25**	**25**	**25**	**75**
Diclophenac sodium (50 mg)	**50**	**50**	**50**	**150**
Acetylsalicylic acid (mg)	**1 000**	**1 000**	**1 000**	**3 000**

therapy was discontinued. None of the patients had received either systemic steroid or corticosteroid therapy for the preceding 6 weeks, or intra-articular steroid therapy during the previous 6 months. Other exclusions were patients under 16 years of age, pregnancy, a history of peptic ulceration, current physiotherapy, concomitant anticoagulant therapy, severe hepatic and/or renal impairment and diabetes mellitus.

ASSESSMENTS

Observations were made on day 0 (commencement of wash-out period), and subsequently on days 7, 14 and 21. The following parameters were assessed by the observers: knee score for pain, stiffness, and tenderness,[3] and they were scored as follows: 0 = absent, 1 = mild, 2 = moderate and 3 = severe.

Quadriceps power was tested with a calibrated spring gauge under standardised and controlled conditions, and knee circumference was measured in cm. The patients assessed early-morning stiffness, pain, ability to walk and over-all feeling of well-being by means of 100-mm visual analogue scales.[4] On completion of the trial, patients' and investigators' opinions of the trial medications were assessed independently by means of preference statements. All side-effects were noted, as well as their nature, severity and incidence. In one centre the effect of the trial drugs on blood morphology and uric acid was examined.

RESULTS

Diclophenac Sodium 25 mg t.d.s. Compared with Acetylsalicylic Acid 1 000 mg t.d.s.

The 28 patients in this series consisted of 17 Whites, 8 Asians and 3 Coloureds. There were no significant differences with respect to the distribution of age, sex and race within the two treatment sequences, i.e. diclophenac sodium as first drug, acetylsalicylic acid as second drug and *vice versa*.

Diclophenac sodium improved the parameters of joint circumference, early-morning stiffness, pain, ability to walk and over-all feeling of well-being to a greater degree than did acetylsalicylic acid. These differences did not reach statistical significance. Quadriceps power was increased by both treatments to an equal degree (Fig. 1).

Preference statements by both the observers and patients clearly favoured diclophenac sodium, but again this did not quite reach statistical significance, *P* values of 0,12, and 0,07 respectively being obtained (Tables II and III).

Tolerability. Of the 28 patients who entered the trial, 27 completed treatment and 1 dropped out for non-drug-related reasons. Six patients developed side-effects while on diclophenac sodium, and 13 patients while being treated with acetylsalicylic acid. None of the side-effects was serious. Gastro-intestinal side-effects occurred in 3 patients during the diclophenac sodium period and in 6 patients during the acetylsalicylic acid period (Tables IV and V).

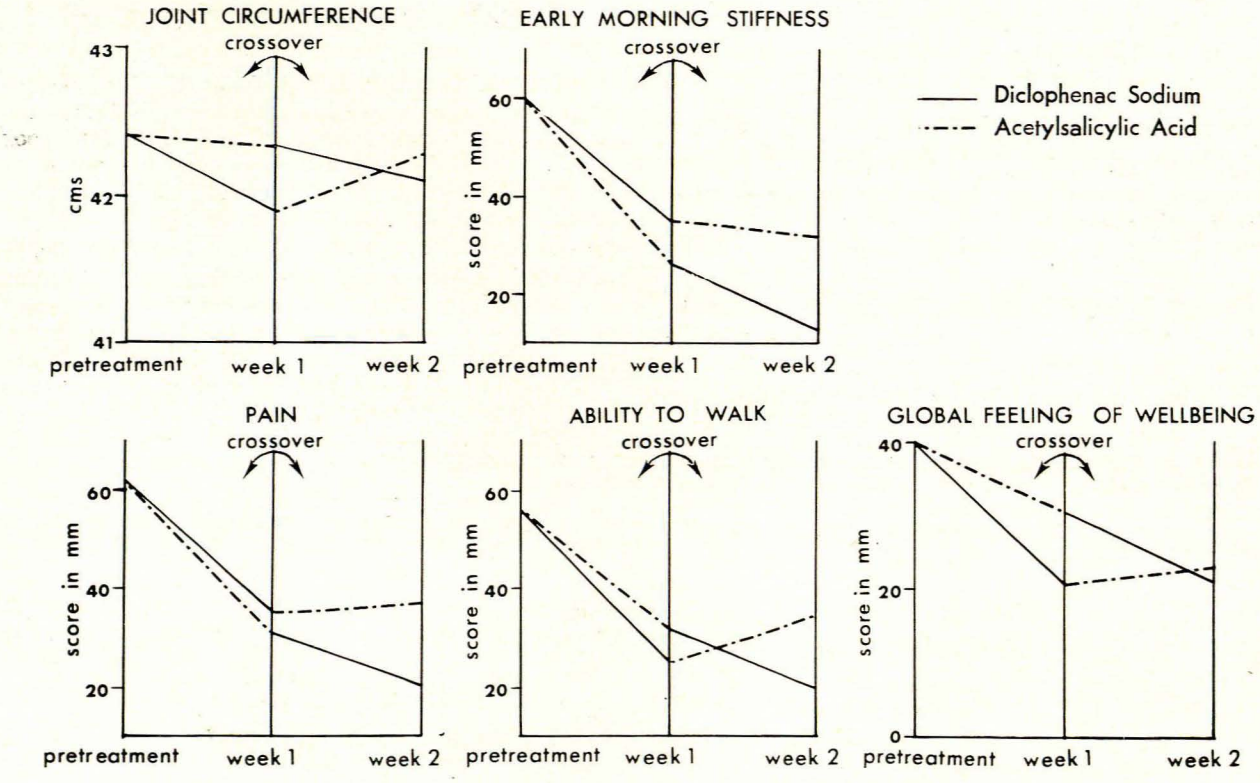

Fig. 1. Effect of diclophenac sodium (Voltaren) 25 mg *t.d.s.* and acetylsalicylic acid 1 000 mg *t.d.s.*

TABLE II. INVESTIGATORS' PREFERENCE STATEMENTS COMPARING THE TWO TREATMENT SEQUENCES

	Sequence: Diclophenac sodium—Acetylsalicylic acid		Sequence: Acetylsalicylic acid—Diclophenac sodium		Total	
Preference for	f	%	f	%	f	%
Diclophenac sodium	8	66,6	5	35,7	13	50,0
Acetylsalicylic acid	2	16,6	6	42,9	8	30,8
No difference	2	16,6	3	21,4	5	19,2
Total	12	99,8	14	100,0	26*	100,0

* The results of the effect of treatment were not reported for 2 patients.

TABLE III. PATIENTS' PREFERENCE STATEMENTS COMPARING THE TWO TREATMENT SEQUENCES

	Sequence: Diclophenac sodium—Acetylsalicylic acid		Sequence: Acetylsalicylic acid—Diclophenac sodium		Total	
Preference for	f	%	f	%	f	%
Diclophenac sodium	8	80,0	6	46,2	14	60,9
Acetylsalicylic acid	2	20,0	6	46,2	8	34,7
No difference	—	0,0	1	7,6	1	4,4
Total	10	100,0	13	100,0	23*	100,0

* 5 patients did not complete the section dealing with preference statements.

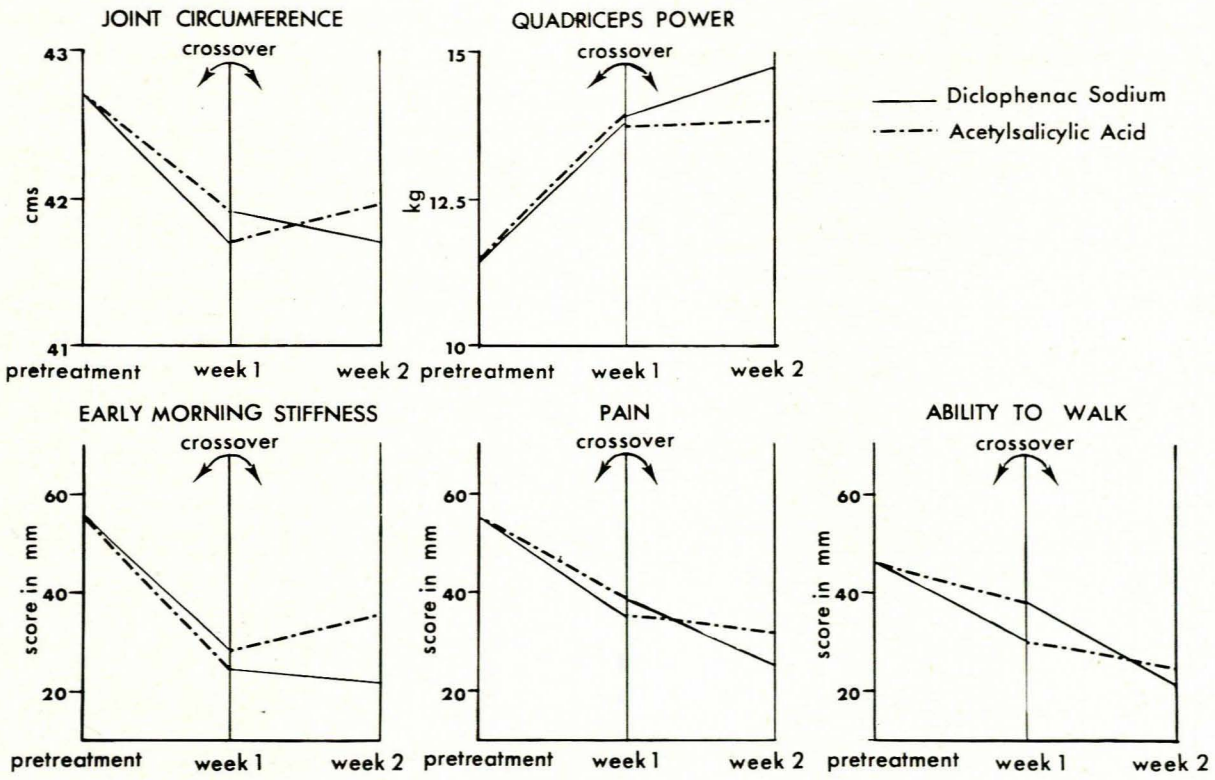

Fig. 2. Effect of diclophenac sodium (Voltaren) 50 mg *t.d.s.* and acetylsalicylic acid 1 000 mg *t.d.s.*

TABLE IV. INCIDENCE OF SIDE-EFFECTS

Total cases	Diclophenac sodium	Acetylsalicylic acid
27	6 (22%)	13 (48%)

TABLE V. INCIDENCE OF GASTRO-INTESTINAL SIDE-EFFECTS

Total cases	Diclophenac sodium	Acetylsalicylic acid
27	3 (11%)	6 (22%)

Diclophenac Sodium 50 mg t.d.s. Compared with Acetylsalicylic Acid 1 000 mg t.d.s.

Of the 29 patients who entered this series 18 were White, 9 Asian and 1 Coloured. The race of 1 patient was not reported. The 2 treatment sequences were homogeneous with respect to age, sex and race. Results of the analysis of the post-treatment scores revealed that both treatments were effective. The effects on joint circumference, quadriceps power, early-morning stiffness, pain and ability to walk, favoured diclophenac sodium, although the results did not reach statistical significance (Fig. 2).

Investigator and patient preference statements are shown in Tables VI and VII respectively. Diclophenac sodium was significantly preferred ($P<0,05$) by the patients. Investigator assessments showed that diclophenac sodium was again preferred, although this just failed to reach statistical significance (Tables VI and VII).

Tolerability. Diclophenac sodium was the better-tolerated medication (Tables VIII and IX).

TABLE VIII. INCIDENCE OF SIDE-EFFECTS

Total cases	Diclophenac sodium	Acetylsalicylic acid
29	10 (34%)	13 (45%)

TABLE IX. INCIDENCE OF GASTRO-INTESTINAL SIDE-EFFECTS

Total cases	Diclophenac sodium	Acetylsalicylic acid
29	8 (27%)	11 (38%)

Diclophenac Sodium 25 mg t.d.s. Compared with Diclophenac Sodium 50 mg t.d.s.

Tests for homogeneity on the 27 patients who completed this section of the trial, showed that the 2 treatment sequences were similar with respect to age, sex, and race. One patient dropped out for non-drug-related reasons, and was replaced. The population studied consisted of 17 Whites, 8 Asians and 2 Coloureds. Both treatments improved all the parameters assessed, although no statistically significant differences between the 2 treatments were found (Fig. 3).

TABLE VI. INVESTIGATORS' PREFERENCE STATEMENTS COMPARING THE TWO TREATMENT PERIODS

	Sequence: Diclophenac sodium—Acetylsalicylic acid		Sequence: Acetylsalicylic acid—Diclophenac sodium		Total	
Preference for	f	%	f	%	f	%
Diclophenac sodium	8	53,3	7	50,0	15	51,7
Acetylsalicylic acid	5	33,3	5	35,7	10	34,5
No difference	2	13,3	2	14,3	4	13,8
Total	15	99,9	14	100,0	29	100,0

TABLE VII. PATIENTS' PREFERENCE STATEMENTS COMPARING THE TWO TREATMENT PERIODS

	Sequence: Diclophenac sodium—Acetylsalicylic acid		Sequence: Acetylsalicylic acid—Diclophenac sodium		Total	
Preference for	f	%	f	%	f	%
Diclophenac sodium	9	64,3	6	46,2	15	55,6
Acetylsalicylic acid	2	14,3	5	38,5	7	25,9
No difference	3	21,4	2	15,3	5	18,5
Total	14*	100,0	13*	100,0	27	100,0

* One patient did not record a preference statement.

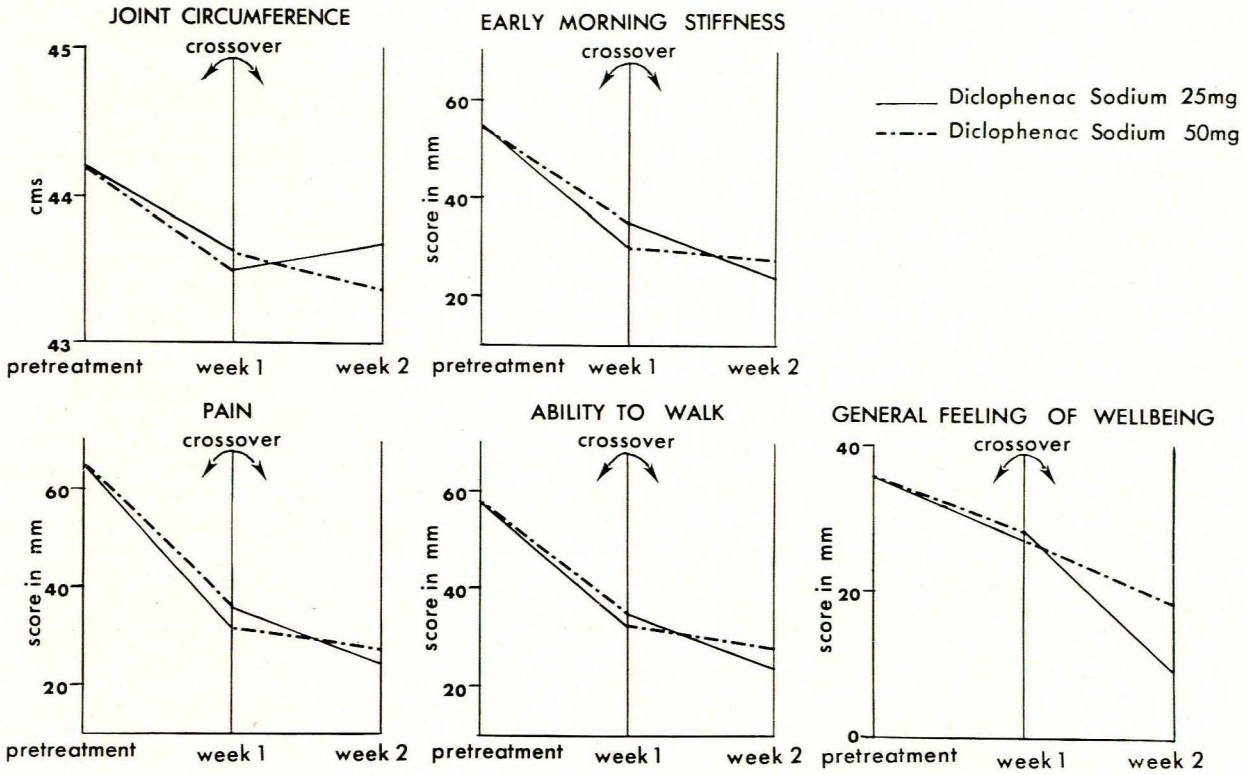

Fig. 3. Effect of diclophenac sodium 25 mg *t.d.s.* and diclophenac sodium 50 mg *t.d.s.*

TABLE X. INVESTIGATORS' PREFERENCE STATEMENTS COMPARING THE TWO TREATMENTS

	Sequence: Diclophenac sodium 25 mg *t.d.s.* — 50 mg *t.d.s.*		Sequence: Diclophenac sodium 50 mg *t.d.s.* — 25 mg *t.d.s.*		Total	
Preference for	f	%	f	%	f	%
Diclophenac sodium 25 mg	**4**	**28,57**	**6**	**46,16**	**10**	**37,04**
Diclophenac sodium 50 mg	**8**	**57,15**	**4**	**30,76**	**12**	**44,44**
Neither	**2**	**14,28**	**3**	**23,08**	**5**	**18,52**
Total	**14**	**100,00**	**13**	**100,00**	**27**	**100,00**

TABLE XI. PATIENTS' PREFERENCE STATEMENTS COMPARING THE TWO TREATMENTS

	Sequence: Diclophenac sodium 25 mg *t.d.s.* — 50 mg *t.d.s.*		Sequence: Diclophenac sodium 50 mg *t.d.s.* — 25 mg *t.d.s.*		Total	
Preference for	f	%	f	%	f	%
Diclophenac sodium 25 mg	**4**	**33,34**	**7**	**58,34**	**11**	**45,83**
Diclophenac sodium 50 mg	**6**	**50,00**	**3**	**25,00**	**9**	**37,50**
Neither	**2**	**16,66**	**2**	**16,66**	**4**	**16,67**
Total	**12***	**100,00**	**12†**	**100,00**	**24**	**100,00**

* Two patients did not record their preference statement.
† One patient did not record his preference statement.

On purely statistical grounds it was impossible to perform an analysis of covariance on the results of the quadriceps power, and consequently a drug profile could not be obtained. However, analysis of variance confirmed that although not significantly different, both treatments did improve this parameter.

The results of the investigator and patient preference statements are shown in Tables X and XI. The second week's medication was preferred, irrespective of treatment.

Tolerability. Both treatments were equally well tolerated (Tables XII and XIII).

TABLE XII. INCIDENCE OF SIDE-EFFECTS

Total cases	Diclophenac sodium 25 mg *t.d.s.*	Diclophenac sodium 50 mg *t.d.s.*
27	7 (26%)	8 (30%)

TABLE XIII. INCIDENCE OF GASTRO-INTESTINAL SIDE-EFFECTS

Total cases	Diclophenac sodium 50 mg *t.d.s.*	Diclophenac sodium 25 mg *t.d.s.*
27	5 (19%)	6 (22%)

Blood Morphology and Uric Acid Examinations

In the Durban centre where 24 Asians completed the trial, blood studies were performed. Tests consisted of uric acid, white cell count, haemoglobin, mean corpuscular haemoglobin concentration, packed cell volume and erythrocyte sedimentation rate determinations. These tests were carried out before active drug treatment and after 2 weeks. Results indicated that the treatments did not change the values of the various tests to either a statistically or a clinically significant extent.

DISCUSSION

Although no definite statistical differences in response between the 3 treatments were found, all were effective. The 25 mg and 50 mg *t.d.s.* doses of diclophenac sodium were slightly superior to acetylsalicylic acid, irrespective of treatment sequence. The observation that most parameters tended to deteriorate after cross-over from diclophenac sodium to acetylsalicylic acid may point to an interaction of the two compounds *in vivo* at a pharmacokinetic level. This possibility is being investigated by one of the authors. Comparing the two dose levels of diclophenac sodium, both were found to be equally efficacious, the second week's medication being more active, irrespective of sequence (Table X). This result possibly indicates a clinical potentiating effect. Investigators and patients preferred both dose levels of diclophenac sodium to acetylsalicylic acid. A statistically significant preference for 50 mg *t.d.s.* compared with acetylsalicylic acid was recorded by the patients. A good correlation was found between the investigators' and patients' independent assessments of preference. This confirms the validity and usefulness of the observation, particularly as it reflects the outcome of the often diverse features of drugs, viz. effects *v.* side-effects.

Toleration of the two dose levels of diclophenac sodium was better than that of acetylsalicylic acid. The incidence of side-effects with acetylsalicylic acid was twice that found with 25 mg diclophenac sodium, and one and a half times that shown with 50 mg diclophenac sodium. Gastro-intestinal intolerance with acetylsalicylic acid was observed to be twice that of 25 mg diclophenac sodium and 1,2 times that of 50 mg diclophenac sodium.

The incidence of side-effects was particularly predominant in the Durban centre; 18 (75%) of the 24 Asians completing the trial complained of side-effects. This observation could indicate differences in psychological, ethnic or dietary factors in this group, compared with the two other racial groups studied. Results of the tests on blood morphology and uric acid indicated that none of the treatments produced any abnormalities.

REFERENCES

1. Ciba-Geigy (1971): Orientation GP 45'840, pp. 1 - 20. Basle: Ciba-Geigy.
2. Kellgren, J. H. and Lawrence, J. S. (1957): Ann. Rheum. Dis., **16**, 494.
3. Carson-Dick, W., Grayson, M. F., Woodburn, A., Nuki, G. and Watson-Buchanan, W. (1970): *Ibid.*, **29**, 643.
4. Joyce, C. R. B., ed. (1968): *Psychopharmacology: Dimension and Perspectives.* London: Tavistock Publications.