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A CONTROLLED TRIAL OF PHENYLBUTAZONE, OXYPHENBUTAZONE, AND A PLACEBO IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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In the past 10 years phenylbutazone (Butazolidin) has been recognized to be of value in the treatment of many painful musculo-skeletal disorders. Currie (1951, 1952) reported favourably, but after initial enthusiasm, it became evident that many side-effects could result. It is now generally accepted that its pain-relieving properties make it particularly useful in chronic disorders of bones and joints. The fact that up to 25 per cent. of patients given phenylbutazone react adversely to it, led to much research to find a similar substance which would be less toxic.

Several derivatives of phenylbutazone were detected in the urine of patients receiving the drug (Burns, Gutman, Yu, Paton, Perel, Steele, and Brodie, 1955a; Burns, Rose, Goodwin, Reichenthal, Horning, and Brodie, 1955b), and two of these have been synthesized. One of these, sulphinpyrazone (Anturan), a potent uricosuric agent, now has a definite place in the treatment of gout, and another, oxyphenbutazone (Tanderil),* which is also a naturally occurring metabolite of phenylbutazone, was the subject of this trial. Hart and Burley (1959), comparing oxyphenbutazone with phenylbutazone, found that the new substance was less liable to produce gastro-intestinal disturbance, but was somewhat less potent therapeutically. Other investigations, notably those of Mason and Cramer (1959), Cardoe (1959), and Graham (1960), reported substantially similar findings. Vaughn, Howell, and Kiem (1959) reported rather superior analgesic effects with oxyphenbutazone and noted only one important side-effect: initial salt and water retention.

* Chemical name: hydroxyphenylbutazone.
Official name (Pharmacopoeal Commission): oxyphenbutazone.
Trade name: Tanderil, sometimes known as G.27202.

The majority of side-effects of phenylbutazone occur in the first month and, not infrequently, in the first week. Sperling (1959) remarked that the incidence of side-effects was higher in rheumatoid arthritis than in other disorders. It was, therefore, decided that it would be useful to investigate oxyphenbutazone in rheumatoid arthritis over a short period. Previous experience of a double-blind trial (Ansell, Fearnley, Bywaters, and Meanock, 1953) suggested that this method of a short-term trial would be a satisfactory approach in a disorder where over longer periods the natural history is punctuated by fluctuations in severity.

General Design of the Trial

The trial was designed to compare the response of patients with rheumatoid arthritis to three substances—phenylbutazone, oxyphenbutazone, and a placebo—not by administering each of the substances to a different group of patients, but by giving to sixty patients all three substances successively. Each patient served as his own control, so that for each the trial lasted 9 weeks, made up of three 3-week periods, during each of which one of the three substances was given.

During the year July, 1959, to June, 1960, patients were selected from those attending the out-patient department of the Rheumatology Unit of the Royal Berkshire Hospital, Reading, the criteria for inclusion being that they had had bilateral involvement of the wrists and hands for at least one year, were not over 75 years of age, and had a positive sheep-cell agglutination test and a raised erythrocyte sedimentation rate. In the two weeks before the trial, no treatment was given except that the patients

were allowed to take aspirin as required. At the beginning and end of this fortnight, assessments were made to ensure that no major fluctuations were occurring.

Corresponding to the six possible orders of administration (BPT, BTP, PBT, PTB, TBP, TPB) there were six groups, each planned to comprise ten patients (total entrants to the trial = 60). Here and elsewhere, B = phenylbutazone; T = oxyphenbutazone; P = placebo.

Sixty bottles of each substance (each containing 168 tablets, sufficient for 3 weeks' treatment) were supplied to the chief pharmacist before the start of the trial. Although the three types of tablet were not identical, they were all coloured white and the bottles were labelled merely:

A TABLETS (*or* B tablets *or* C tablets)
Two tablets to be taken four times per day

The phenylbutazone and oxyphenbutazone tablets each contained 100 mg. active ingredient. The total daily dose of each of these substances was thus 800 mg.

A blank register of sixty treatment sequences (BPT, BTP, etc.) numbered 1 to 60, but randomized for sequence, was lodged with the pharmacist. Each of the six orders or sequences appeared ten times.

As each patient entered the trial he was given a number (serially) by the clinician and sent to the pharmacist, who entered the patient's name in the register opposite the appropriate numbered sequence. This automatically determined the sequence in which the substances were to be given and each substance was ticked off on the list as issued to the patient (one 3-week period at a time). Thus the register held by the pharmacist (and which had been independently prepared by the statistician) was the only key to the order of treatments. At no time during the trial did the clinician or the patient know which treatment was being, or had already been, received.

Assessments

Assessments were recorded for each patient on a standard form. They were made at the beginning of the trial and at the end of each 3-week period when the patient attended for a further supply of tablets.

Four indices were used to judge progress. Only one was objective and quantitative, namely, strength of grip. The others were the patients' own assessments of degree of pain and of freedom of movement, and the physician's estimate of functional capacity in five grades. In addition to these assessments of progress, toxic and other side-effects were inquired for and recorded, together with reasons for ceasing to take the tablets where this occurred, and at the end of the trial, patients stated their order of preference for the three types of tablet.

Further details of these indices are given in the sections allotted to each.

Characteristics of the Entrants

In therapeutic trials, where one group of patients receives Drug A, another group Drug B, and so on, it is imperative to ensure that the groups are at the outset similar as regards relevant characteristics (age, sex, severity of disease, etc.). This is avoided in trials, as this one, where the patients serve as their own controls, but it is necessary nevertheless to describe the principal characteristics of the patients who took part.

Of the sixty entrants admitted to the trial (eleven males and 49 females), the ages ranged from 22 to 75 years (average 52·8; standard deviation 11·7). The duration of disease ranged from 1 to 17 years (average $5 \cdot 31 \pm 0 \cdot 54$). Judged by functional status (physician's estimate) the disease was of Grade 2* severity in 37, Grade 3 in 21, and Grade 4 in two. The mean Westergren erythrocyte sedimentation rate was 42·8 mm./hr, and the mean haemoglobin level 11·7 g. per cent. (see last column of Table I).

Similarity of Six "Order of Treatment" Groups

It was impracticable to secure at the outset that the six "order of treatment" groups would be similar in regard to these characteristics. In the event, however, the only significant difference found was in relation to the erythrocyte sedimentation rate. Here the ten patients who started on the placebo and finished on phenylbutazone had the lowest mean E.S.R. (32·7 mm./hr), whilst the group who started on phenylbutazone and finished on oxyphenbutazone had the highest (50·8 mm./hr). Between these two extremes appeared the only significant difference at the 0·05 level. In regard to all the other characteristics listed in Table I (opposite), the "order of treatment" groups were similar.

Numbers at Risk for Assessment of Side-Effects

For three patients, the only assessment was that made on completion of the first 3-week period. Two of these failed to attend subsequently (one because of pregnancy) so that in both patients side-effects

* For definitions of grades, see section on functional status.

TABLE I

SIMILARITY OF THE SIX "ORDER OF TREATMENT" GROUPS

Order of Treatment	TBP(*)	TPB	BTP	BPT	PTB	PBT	All Groups Combined
Total Entrants	10	10	10	10	10	10	60
Males	2	3	1	2	1	2	11
Mean Age (yrs)	51·8	51·8	53·9	48·7	52·8	57·9	52·8
Mean Duration of Disease (yrs)	5·1	4·4	5·0	4·3	7·4	5·6	5·3
Mean Strength of Grip: Right	126·0	140·5	141·5	118·5	124·5	149·5	133·4
Left	156·0	150·5	117·5	107·5	141·5	142·0	135·8
Mean Haemoglobin Concentration (g. per cent.)	11·4	11·8	11·7	11·5	12·1	11·5	11·7
Mean(†) E.S.R. (mm./hr Westergren)	46·1	39·1	48·4	50·8	32·7	39·4	42·8
Mean(‡) Functional Capacity (Physician's Assessment)	2·5	2·3	2·3	2·2	2·8	2·4	2·4

(*) B = phenylbutazone (Butazolidin); T = oxyphenbutazone (Tanderil); P = calcium phosphate, maize starch, etc. (placebo).
(†) Excludes one patient in group PBT (E.S.R. not stated).
(‡) Use of the term "Mean" here is unjustifiable statistically, but convenient as an index to summarize the distribution.

were not recorded on phenylbutazone or the placebo. The third was admitted to hospital after the first assessment (on placebo) for operation on an ankle joint and neither phenylbutazone nor oxyphenbutazone was given (see Table II).

Five patients were withdrawn because of toxic effects. In consequence, four were not assessed for side-effects on phenylbutazone, one was not assessed on oxyphenbutazone, and three were not assessed on placebo.

This left 53 at risk to side-effects on phenylbutazone, 58 on oxyphenbutazone, and 55 on placebo (Table II).

TABLE II

NUMBERS AT RISK FOR ASSESSMENT OF SIDE-EFFECTS

Drug		*B*	*T*	*P*
Total Entrants		60	60	60
Side-effects NOT recorded because of:	(1) Failure to attend for assessment	2	—	2
	(2) Admission for operation on ankle	1	1	—
	(3) Withdrawal on earlier treatments	4	1	3
Number at Risk for Side-effects		53	58	55

Results

TOXICITY

The incidence of side-effects can be measured in one of two ways:

(*i*) as the number of persons who experienced at least one side-effect—expressed as a percentage of the number at risk,

or

(*ii*) as the number of side-effects recorded per patient at risk on each drug.

(i) Persons experiencing at least One Side-Effect

Side-effects were reported by 28 per cent. of the patients on phenylbutazone (15 out of 53 at risk), by 31 per cent. on oxyphenbutazone (18 out of 58 at risk), and by 31 per cent. on placebo (17 out of 55 at risk).

These side-effects fall into three severity grades according as they necessitated (*a*) cessation of tablets (and in some instances no subsequent medicaments were taken); (*b*) reduction in dosage; (*c*) no action (Table III).

TABLE III

PATIENTS WITH SIDE-EFFECTS, BY GRADE OF SEVERITY

Drug		*B*	*T*	*P*
Side-effects involving:	(*a*) Cessation of tablets	3	4	4
	(*b*) Reduction of dosage	2	3	1
	(*c*) Neither (*a*) nor (*b*)	10	11	12
Patients with at least One Side-effect	No.	15	18	17
	Per cent.	(28)	(31)	(31)
No. of Patients without Side-effects		38(*)	40	38(†)
Total at Risk for Side-effects		53	58	55

(*) Includes one patient who became so much worse on phenylbutazone that he "gave up and went back to codeine".
(†) Includes one patient who found the placebo tablets (first period) useless and took solprin instead.

(*a*) *Cessation of Tablets* (*11 patients*)

PHENYLBUTAZONE (3 patients)

(1) Severe dermatitis after 12 days' treatment in the first 3-week period. Neither oxyphenbutazone nor the placebo was given subsequently.
(2) Nausea and abdominal pain after 10 days in the middle 3-week period.
(3) Experienced nausea and indigestion on placebo (first period), developed sore throat and ulcer of tongue on oxyphenbutazone (second period),

had recurrence of sore throat on phenylbutazone (third period). The side-effects in the first two periods are included under (*c*) in Table III.

OXYPHENBUTAZONE (4 patients)

(1) Patient paid a special visit after 10 days on the drug in the second period because of severe vomiting and diarrhoea, and the trial was stopped. Phenylbutazone was not given subsequently.
(2) Severe reaction reported at the end of the first period (oedema of face, generalized urticarial skin reaction). Neither phenylbutazone nor placebo was given. The rash was still present one month later.
(3) Severe mouth ulcers developed in the first period and the tablets were stopped. Although the patient went on to take placebo tablets in the second period, the ulcers recurred with cervical glandular enlargement. The patient was withdrawn from the rest of the trial and the side-effects were assumed to arise from the oxyphenbutazone.
(4) This patient had to stop after 10 days in the final period because of indigestion. However, in the first period on phenylbutazone she had experienced flatulence and dyspnoea, and had had to reduce the dosage.

PLACEBO (4 patients)

(1) Had developed mild indigestion after meals—lasting 2 to 3 hours, on oxyphenbutazone in the first period. In the second period on placebo the trial was stopped after 10 days. The general practitioner reported "fever, sore throat, oedema of legs, white blood count 8,400 per c.mm.".
(2) Tablets stopped after 2 weeks in the first period because of severe indigestion.
(3) Headache and severe nausea in the second period.
(4) Tablets stopped after 2 weeks in the second period because of headache and blurred vision.

(*b*) *Reduction of Dose* (*6 patients*)

PHENYLBUTAZONE (2 patients)

(1) First period—flatulence and dyspnoea—tablets reduced to four a day (see also Section (*a*)—Oxyphenbutazone (No. 4)).
(2) First period—diarrhoea—tablets reduced to six a day.

OXYPHENBUTAZONE (3 patients)

(1) Third period—headaches persisted until tablets reduced to six a day.
(2) Second period—nausea, vomiting—reduced to six for last week.
(3) First period—nausea, vomiting, diarrhoea—4 tablets a day after 4 days.

PLACEBO (1 patient)

First period—indigestion, dyspnoea, palpitation on effort—reduced dose.

(ii) Mean Number of Side-Effects per Patient

Some patients experienced more than one side-effect whilst on a specified treatment. The fifteen patients with side-effects whilst on phenylbutazone reported altogether eighteen such effects (three recorded two). The eighteen who had side-effects whilst on oxyphenbutazone recorded 22 such effects (two listed two, and one listed three). The seventeen who had side-effects whilst on the placebo tablets recorded 24 such effects (five listed two and one listed three).

Relating these to the total patients at risk on each drug (see foot of Table IV) the mean number of side-effects was 0·34 per person for phenylbutazone, 0·38 for oxyphenbutazone, and 0·44 for the placebo (no significant difference at the 0·05 level).

These side-effects are classified under general headings in Table IV (opposite). The numbers are too small for firm conclusions, but it appears that approximately one-third of the side-effects occurring on phenylbutazone and the placebo, and half of those occurring on oxyphenbutazone affected the gastro-intestinal system. Only one instance of buccal ulcers or sore throat was recorded on phenylbutazone, four on oxyphenbutazone, and two on the placebo. Oedema of the ankles was recorded more frequently on the placebo (five instances) than on phenylbutazone (four) or oxyphenbutazone (two).

Side-Effects while on Placebo.—Twenty patients received the placebo in the first 3-week period, and nine side-effects were reported by six of them.

Eighteen received the placebo in the second period, and twelve side-effects were reported by eight of them.

Seventeen received the placebo in the third period, but only three side-effects were recorded by three patients.

Thus, side-effects on the placebo were recorded by 30 per cent. of the patients who received it as the first, by 50 per cent. of those who received it as the second, and by only 18 per cent. of those who received it as the third drug. Also, of all the 24 side-effects observed whilst the patients were having placebo tablets, 37 per cent. occurred when it was the first drug given, 50 per cent. when it was the second, and 13 per cent. when it was the third.

If the placebo complications were residual effects from earlier treatments in the trial, one would expect them to be non-existent when the placebo was issued first. Yet 30 per cent. of the patients

TABLE IV

CLASSIFICATION OF SIDE-EFFECTS RECORDED BY PATIENTS ON THE THREE TREATMENT SCHEDULES

Side-Effects Recorded			Treatment B	Treatment T	Treatment P
Gastro-intestinal Reactions	Loss of appetite		—	—	1
	Nausea		1	2	2
	Epigastric distress		3	5	4
	Vomiting		—	3	—
	Diarrhoea		2	2	—
Skin Reactions	Mild dermatitis		1	—	1
	Severe dermatitis		1	1	1
Oedema	Ankles		4	2	5
	Swelling of eyelids		1	—	—
Ocular Reactions	Blurred vision		1	—	1
	Glaucoma		—	1	—
Miscellaneous Reactions	Objective	Buccal ulcers	—	3	—
		Sore throat	1	1	2
	Subjective	Headache	—	2	2
		Giddiness	2	—	3
		Dyspnoea	1	—	—
		Fever	—	—	1
		Palpitation	—	—	1
Total Side-effects			18	22	24
No. of Patients recording these Side-effects (see Table III)			15	18	17
No. of Patients at Risk			53	58	55
Side-effects per Patient at Risk			0·34	0·38	0·44

who had it in the first period experienced 37 per cent. of all the "placebo side-effects". Add to this the fact that, in the final period when residual effect, if any, might be expected to be most pronounced, 18 per cent. of patients accounted for only 13 per cent. of placebo side-effects (the lowest incidence for the three periods). There seems to be little evidence that the side-effects on the placebo tablets were residual manifestations of reactions which started during phenylbutazone or oxyphenbutazone treatment.

It is certainly curious that five instances of oedema should have occurred whilst the patient was having placebo tablets. Two of these occurred in the initial period, the previous treatment having been chloroquine and aspirin for one, and aspirin only for the other. The remaining three occurred in the middle period. In two of these, the placebo followed phenylbutazone, which had been taken without side-effects; unfortunately no record was made of how long after the end of the first period the onset of oedema occurred. In the third patient, it is known that the onset of oedema occurred within 10 days of the end of the first period on oxyphenbutazone. But, except for this last instance, and certainly not as regards the two instances in the initial period, oedema of the ankles cannot be ascribed to any drug. In most drug trials, oedema has been regarded as a side-effect of the drug. Present findings remind us that it is often a feature of the disease.

Gastro-intestinal Reactions.—Mason and Cramer (1959) found that, of thirteen patients unable to tolerate phenylbutazone because of gastro-intestinal reactions (dyspepsia, nausea, and diarrhoea), nine were able to tolerate oxyphenbutazone. The data were in agreement with this finding. In the present survey, we were able to confirm this finding. 29 patients received phenylbutazone before oxyphenbutazone (orders BPT, BTP, and PBT); six recorded gastro-intestinal side-effects on phenylbutazone, and only one of the six was unable to tolerate oxyphenbutazone for the same reason.

On the other hand, 23 patients received oxyphenbutazone before phenylbutazone (orders PTB, TBP, and TPB); only two recorded gastro-intestinal effects on the former, and both of them subsequently tolerated phenylbutazone.

STRENGTH OF GRIP

One important aspect to be considered in trials in which different treatments are given in succession to the same patients is the hangover or residual effect of the previous treatments. The only objective and quantitative index lending itself to numerical manipulation was strength of grip and the assessment of residual effects was mainly derived from analysis of these data.

The strength of grip of each hand was measured (in mm. Hg) at each assessment on a sphygmomanometer, with an initial bag pressure of 30 mm. Hg maintained for 3 seconds, the hand being held away

from the body. The grip at the end of each 3-week period, expressed as a percentage of the initial (pre-trial) value, gave an index of improvement (or deterioration) in grip in each treatment as compared with the pre-trial level.

Since estimation of the residual effects of previous treatments on these results involved the use of somewhat sophisticated statistical procedures, only the results are reported here, details and discussion of the method being relegated to the Appendix.

From this detailed statistical analysis of variance the following conclusions were relevant:

(*i*) There was great variation between patients in the amount of improvement on each drug. Such individual variation was, of course, to be expected.

(*ii*) The order in which the three treatments were given did not affect the results, *e.g.* the mean improvement on phenylbutazone did not vary significantly whether it was the first, second, or third treatment.

(*iii*) There was no evidence of any secular trend in the results. Irrespective of type of treatment, the average improvement in the right grip was 17·6 per cent. for the first period, 15·8 per cent. for the second, and 21·1 per cent. for the third. Comparable figures for the left grip were 15·8 per cent., 13·9 per cent., and 21·5 per cent.

(*iv*) It could be definitely stated that the residual effects of previous treatments (within the trial) were negligible. The amount of variation due to residual effects was not greater than would be expected merely from chance, and this was true of both left and right grip. In consequence, the adjustments required to allow for residual effects when comparing the *direct* results of the three treatments were also negligible, as is shown in Table V.

TABLE V

MEAN IMPROVEMENT IN GRIP STRENGTH (per cent.)

Treatment	Right		Left	
	Unadjusted Means	Adjusted for Residual Effects	Unadjusted Means	Adjusted for Residual Effects
Phenylbutazone ..	27·9	28·0	22·4	22·1
Oxyphenbutazone ..	23·4	24·4	20·3	20·8
Placebo	8·4	7·4	7·9	7·8
Standard Error of Differences (see Appendix) ..	4·53	5·06	5·49	6·13

The right grip improved to a greater extent than the left on both drugs, but not on the placebo. Possibly this is related to the greater use of the right hand generally, and suggests that activity plus drug treatment gives better results than drug treatment alone.

The mean differences between the three treatments as regards improvement in grip are shown in Table VI.

TABLE VI

MEAN DIFFERENCES BETWEEN THE TREATMENTS AS REGARDS PERCENTAGE IMPROVEMENT IN GRIP STRENGTH

Treatment	Right	Left
Phenylbutazone and Oxyphenbutazone (B-T)	3·6	1·3
Phenylbutazone and Placebo (B-P)	20·6s	14·3s
Oxyphenbutazone and Placebo (T-P) ..	17·0s	13·0s

s = Significant difference.

The right grip improved 21 per cent. more on phenylbutazone and 17 per cent. more on oxyphenbutazone, than on the placebo. Comparable figures for the left grip were 14 and 13 per cent. (all significant at the 5 per cent. level).

But there was only a slightly (non-significant) greater improvement on phenylbutazone than on oxyphenbutazone—the difference being 4 per cent. for the right grip and 1 per cent. for the left.

ASSESSMENT OF PAIN

At the end of each 3-week period, the patients recorded a subjective impression whether the degree of pain was greater, less, or the same as at the beginning of each period.

52 patients completed all three treatments, providing 104 direct comparisons between two consecutive treatments.

Phenylbutazone *v.* Placebo (35 patients).—Nineteen (54 per cent.) experienced *less* pain on phenylbutazone, six (17 per cent.) *more* pain, and ten (29 per cent.) the *same* degree of pain.

Oxyphenbutazone *v.* Placebo (34 patients).—21 (62 per cent.) experienced *less* pain on oxyphenbutazone, five (15 per cent.) *more* pain, and eight (23 per cent.) the *same* degree of pain.

Oxyphenbutazone *v.* Phenylbutazone (35 patients). Fifteen (43 per cent.) experienced *less* pain on oxyphenbutazone, thirteen (37 per cent.) *more* pain, and eight (20 per cent.) the *same* degree of pain.

To facilitate comparison, these results are assembled in Table VII. In brief, between 55 and 65 per cent. of patients had less pain on both drugs than on the placebo, but there was little difference between the percentage who felt less pain on oxyphenbutazone than on phenylbutazone (43 per cent.), and the percentage who felt the opposite (37 per cent.).

TABLE VII

DIFFERENCES (per cent.) BETWEEN EACH PAIR OF TREATMENTS AS REGARDS PATIENT'S ASSESSMENT OF "AMOUNT OF PAIN"

Difference Between		Less Pain on 1 than on 2 %	More Pain on 1 than on 2 %	No Difference %	No. of Patients
1	2				
B	P	54	17	29	35
T	P	62	15	23	34
T	B	43	37	20	35
B	Pre-trial period	78	11	11	19
T	Pre-trial period	73	7	20	15
P	Pre-trial period	33	44	22	18

78 per cent. of the nineteen who started on phenylbutazone and 73 per cent. of the fifteen who started on oxyphenbutazone, but only 33 per cent. of the eighteen who started on the placebo tablets felt less pain in this first period than before starting the course (Table VII).

ASSESSMENT OF FREEDOM OF MOVEMENT

As with pain, this also was a subjective estimate by the patient whether there was more, less, or the same freedom of movement on each type of tablet compared with the previous type (or for first tablets, compared with the pre-trial period). The results are tabulated in Table VIII.

TABLE VIII

DIFFERENCES (per cent.) BETWEEN EACH PAIR OF TREATMENTS AS REGARDS PATIENT'S ASSESSMENT OF FREEDOM OF MOVEMENT

Difference Between		More Movement on 1 than on 2 %	Less Movement on 1 than on 2 %	No Difference %	No. of Patients
1	2				
B	P	51	31	17	35
T	P	56	15	29	34
T	B	43	34	23	35
B	Pre-trial period	84	16	nil	19
T	Pre-trial period	67	7	26	15
P	Pre-trial period	28	56	17	18

Phenylbutazone *v.* **Placebo** (35 patients).—Of those who received phenylbutazone immediately before or after the placebo tablets, eighteen (51 per cent.) felt they had *more* freedom of movement on phenylbutazone than on the placebo, eleven (31 per cent.) *less*, and six (17 per cent.) the *same*.

Oxyphenbutazone *v.* **Placebo** (34 patients).—Nineteen (56 per cent.) had *more* freedom of movement on oxyphenbutazone as on the placebo, five (15 per cent.) *less*, and ten (29 per cent.) the *same*.

Oxyphenbutazone *v.* **Phenylbutazone** (35 patients). Fifteen (43 per cent.) had *more* freedom of movement on oxyphenbutazone than on phenylbutazone; twelve (34 per cent.) *less*, and eight (23 per cent.) the *same*.

Thus, between 50 and 60 per cent. thought that both drugs gave more freedom of movement than the placebo, but there was little difference between the percentage who considered oxyphenbutazone gave more movement than phenylbutazone (43 per cent.) and the percentage who thought the opposite (34 per cent.).

FUNCTIONAL CAPACITY

This was estimated by the physician in five grades:

(1) Fully employed or employable in normal work and able to undertake normal physical recreations.
(2) Fully employed in special work after vocational training, or doing light or part-time work in normal occupation. Limitation in the amount of physical recreation that could be taken. Housewives able to do all but the heaviest housework.
(3) Not employed or unemployable. Very limited physical activity and little or no capacity for physical recreation. Housewives able to do light housework and/or limited shopping only. In-patients in hospital for treatment, but up and about in the ward.
(4) Confined to hospital, house, or wheel-chair, but able to look after themselves in the essentials of life. In-patients in hospital for treatment sitting up, but not getting about.
(5) Confined to bed and unable to look after themselves. In-patients on complete rest in bed.

The distributions in these grades at the start of the trial of all entrants and of those who completed all three treatments (*i.e.* omitting the eight withdrawals) were:

Grade	All 60 Entrants	52 who Completed the Trial
2	37	33
3	21	18
4	2	1
Total ..	60	52

For two patients the gradings at subsequent assessments were incomplete (both were initially Grade 2) leaving fifty for comparison.

No changes of more than one grade occurred during any specified treatment. Of the fifty patients, the numbers who changed one grade up or down were:

Treatment	Improvement	Deterioration
Phenylbutazone ..	9	2
Oxyphenbutazone ..	5	2
Placebo	1	3

Of the nine who improved on phenylbutazone, two deteriorated on the placebo. One of these, initially Grade 4 (above), deteriorated to Grade 5 on placebo in the first period, improved to Grade 4 again on oxyphenbutazone in the second period, and improved still further to Grade 3 on phenylbutazone in the final period.

One patient deteriorated on phenylbutazone in the second period, but improved again on oxyphenbutazone in the third period; another patient, however, did the opposite.

Patient's Preference

At the conclusion of the trial, the patients were asked their order of preference in regard to the three types of tablets. This could not be indicated by the eight who did not complete the course, and was not recorded by two other patients. The views of the remaining fifty patients are tabulated in Table IX, where the six possible orders of preference are labelled *a* to *f*.

Table IX

PATIENT'S PREFERENCES FOR THE THREE TYPES OF TABLET

Group	Order of Preference			No. of Patients
	1	2	3	
a	B	T	P	20½*
b	B	P	T	4½*
c	T	B	P	12*
d	T	P	B	7
e	P	B	T	4
f	P	T	B	1
No preference (B = T = P)				1
Total				50
Withdrawals				8
Not Stated				2
Total No. of Patients				60

* The preference B, T = P given by one patient was allocated as ½ to (a) and ½ to (b).
The preference B = T, P given by two patients was allocated as ½ to (a) and ½ to (c).

Table IX shows that phenylbutazone was placed first by 25, oxyphenbutazone by nineteen, and the placebo by five; one patient considered all three types to be equal. This arrangement is in accordance with the results obtained from the analysis of improvement in grip.

Of the 25 who placed phenylbutazone first, twenty placed oxyphenbutazone second, and four the placebo; the remaining one considered there was no difference between oxyphenbutazone and the placebo.

Of the nineteen who placed oxyphenbutazone first, twelve placed phenylbutazone second, and seven the placebo.

Of the five who placed the placebo first, four placed phenylbutazone second.

Ignoring the placebo, 29 patients preferred phenylbutazone to oxyphenbutazone, twenty preferred oxyphenbutazone, and one considered them equal.

Discussion

This trial—in which two active drugs and a placebo were given in succession to each patient—was designed so that each treatment preceded the other treatments in an equal number of patients; and each treatment occurred with equal frequency as the first, second, and third in order.

This facilitated the application of statistical procedures whereby the residual effect of the drugs could be estimated. It is remarkable that, despite the slow excretion of the two active drugs (Burns and others, 1955a, b, reported this as "a biologic half-life of 2-3 days"), only a negligible residual effect could be demonstrated in relation either to progress or to side-effects when the treatments were changed at 3-week intervals. Because the residual effect was negligible it was permissible to compare the direct effects of the three types of tablet and this confirmed the findings of other workers that both drugs have a significant therapeutic effect. This is judged by the relative improvement in strength of grip, relief of pain, freedom of movement, and functional capacity on these drugs as compared with the placebo.

On an equivalent dosage (800 mg. per day) no statistically significant differences could be shown between phenylbutazone or oxyphenbutazone as regards any of the five assessments made. The small differences found (which could well have been chance ones) favoured oxyphenbutazone as regards

pain and freedom of movement, but as regards grip, functional capacity, and patient's preference, they tended, if anything, to favour phenylbutazone. Three of the five assessments therefore favoured the parent substance, and two favoured the derivative, which again is what one would expect if these were purely chance differences. We conclude therefore that in regard to both pain relieving properties and therapeutic potency there is little to choose between phenylbutazone and oxyphenbutazone. Thus, we were unable to confirm the impressions of Hart and Burley (1959), Mason and Cramer (1959), and others.

Furthermore, in this short-term trial, side-effects were no more frequent on phenylbutazone than on oxyphenbutazone, or indeed than on the placebo. They were reported by 28 per cent. of the patients whilst on phenylbutazone, by 31 per cent., whilst on oxyphenbutazone, and by 31 per cent. whilst on the placebo. Also the mean number of side-effects per patient on phenylbutazone was 0·34, compared with 0·38 per patient on oxyphenbutazone and 0·44 per patient on placebo. Nearly twice the number of gastro-intestinal reactions were reported on oxyphenbutazone as on phenylbutazone, and the three instances of buccal ulcer all occurred during the oxyphenbutazone period.

Our results were, however, in accordance with the findings of Mason and Cramer (1959), Graham (1960), and others, that a high proportion of patients intolerant to phenylbutazone are tolerant to oxyphenbutazone.

The incidence of side-effects on the placebo was high—31 per cent.—the same as on oxyphenbutazone. Most of these occurred when the placebo was the first treatment given, and it is remarkable that oedema of ankles occurred at least as frequently on the placebo as on the active drugs, even when it was the first treatment.

Summary

Phenylbutazone, its derivative oxyphenbutazone, and a placebo were administered in succession to sixty patients (11 males, 49 females) with rheumatoid arthritis. Their mean age was 53 years and the average duration of the disease 5 years. Each patient received each treatment for 3 weeks, and assessments were recorded of grip, degree of pain, freedom of movement, functional capacity, and side-effects. The order of administration was randomized and only the chief pharmacist knew which drug was being given at any time.

A method of analysis, designed to assess the hangover effects of the treatments, showed these to be negligible.

Results were in keeping with the findings of other workers, that phenylbutazone (Butazolidin) and oxyphenbutazone (Tanderil) are both potentially effective in the symptomatic treatment of rheumatoid arthritis, both drugs giving significantly better results than the placebo. But no significant differences could be demonstrated between phenylbutazone and oxyphenbutazone by any of the assessments made. Nor were the small differences obtained consistent. Three assessments slightly favoured phenylbutazone, and two oxyphenbutazone.

There was no significant difference between the percentage of side-effects recorded from phenylbutazone, oxyphenbutazone and the placebo; and whilst five out of six patients intolerant to phenylbutazone were tolerant to oxyphenbutazone, in two instances the converse was true.

We would express our great indebtedness to Dr. W. S. Stoddart for his assistance, not only in the preparatory stages of the trial, but at subsequent stages also, including discussions on the results.

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APPENDIX

A method described by Williams (1949) was used to estimate the *residual* effect of the preceding treatment, and to allow for that effect (if any) in comparing the *direct* effects of the three treatments—phenylbutazone, oxyphenbutazone, and placebo. The only other published trial we know of in which measurement of residual effect was attempted is that of Raymond, Lucas, Beesley, O'Connell, and Roberts (1957), who adopted the same method in a trial of six tranquillizing drugs.

The conditions essential for application of the method are that:

(1) Each treatment shall be preceded by each other treatment equally frequently;
(2) Each treatment shall occur equally frequently in each position.

As initially planned, both conditions were satisfied. There were ten patients in each of the six "order of treatment groups"—BTP, BPT, TBP, TPB, PBT, PTB (where B = phenylbutazone, T = oxyphenbutazone, and P = placebo). Oxyphenbutazone, for example, would have been preceded by phenylbutazone for twenty patients, and by the placebo for twenty patients. Also it would have been given to twenty patients in the first 3-week period, twenty in the second, and twenty in the third. The same was true of the other two treatments, and each order of treatment group would have comprised ten patients.

But because, for various reasons, eight patients did not receive all three types of tablets (see Section 6) some of the sets of ten were incomplete. The conditions (above) were then satisfied by forming seven complete sets of the six orders of treatment, taking the first seven who completed order BTP, the first seven who completed order BPT, and so on. This involved only 42 out of the 52 patients available, but as will appear later, the omission of the ten who formed incomplete sets did not prejudice the results.

Four sources of variation were taken into account:

(1) between patients
(2) between 3-week periods
(3) between the direct results of treatment
(4) between the residual effects of preceding treatment.

Following the technique set out by Williams

TABLE A

ANALYSIS OF VARIANCE PERCENTAGE IMPROVEMENT IN GRIP
Seven patients in each of six order (of treatment) groups

Percentage Improvement in Grip		Degrees of Freedom	Sum of Squares: Direct Results Adjusted	Sum of Squares: Residual Effects Adjusted	Mean Square Adjusted	Variance Ratio (F)	P
Right	Patients	41	104,879		2,558	5·94	<0·01
	Between Orders of Treatment	5		7,411	1,482	0·55*	>0·05
	Between Patients on the Same Order of Treatment	36		97,468	2,707		
	3-week Periods	2	775		387	0·90	>0·05
	Treatments:						
	Direct Results	2	5,930	6,229	2,965	6·88	<0·01
	Residual Effects	2	627	328	164	0·38	>0·05
	Error	78	33,608		431		
	Total	125	145,819				
Left	Patients	41	73,407		1,790	2·67	<0·01
	Between Orders of Treatment	5		7,394	1,479	0·81*	>0·05
	Between Patients on the Same Order of Treatment	36		66,013	1,834		
	3-week Periods	2	1,300		650	0·97	>0·05
	Treatments:						
	Direct Results	2	3,933	4,950	1,967	3·11	=0·05
	Residual Effects	2	1,089	72	36	0·06	>0·05
	Error	78	49,305		632		
	Total	125	129,054				

* Divisor = mean square for between patients in the same order of treatment.

(1949), suitable sums of squares were computed and the resulting analysis of variance for percentage improvement in right and left grip is shown in Table A.

For each grip the variation in improvement due to differences between patients was, as would be expected, significant at the 0·01 level. When this was subdivided into two parts, the mean square for the differences between the six orders of treatment was less than that between patients on the same order of treatment (within orders of treatment). Thus the amount of improvement was independent of the order in which the treatments were given.

The variation due to differences between the three 3-week periods was not significant for either grip, *i.e.* there was no secular trend such as might have arisen from natural remission of the disease.

Two sums of squares are available for differences between the direct results of the three treatments. The lesser of the two is the result when allowance has been made for the residual effect of the preceding treatment.

Similarly, two sums of squares are available for these residual effects, the lesser taking into account the direct effects. The important point is the smallness of the adjusted mean square for residual effects—not significant at the 5 per cent. or even at the 20 per cent. level—so that it can be concluded that the improvement on any of the three treatments was independent of any residual effect from preceding treatment.

The mean square for direct effects when adjusted for residual effects (such adjustment being negligible in this case) was significant at the 0·01 level for the right grip, but was just on the borderline of significance at 0·05 level for the left grip.

This analysis shows therefore that the residual effects of the preceding tablets were negligible, and that it was valid therefore to compare the direct results of the three treatments. In doing this it was no longer necessary to restrict the comparison to the 42 patients comprising seven complete sets of the six orders. All 52 patients could be included. Comparisons of the mean improvement based alternatively on 42 and 52 patients gave the following results:

Treatment	Percentage Improvement of Right and Left Grip			
	Right		Left	
	N = 42	N = 52	N = 42	N = 52
Phenylbutazone ..	24·9	27·9	23·7	22·4
Oxyphenbutazone ..	20·5	23·4	18·9	20·3
Placebo	8·3	8·4	8·7	7·9

Essai controlé de la phénylbutazone, de la oxyphenbutazone et d'un *placebo* (substance inerte) dans le traitement de l'arthrite rhumatismale

RÉSUMÉ

On a administré successivement de la phénylbutazone, son dérivé oxyphenbutazone et un *placebo* (substance-témoin inerte) à soixante malades (11 hommes, 49 femmes) atteints d'arthrite rhumatismale. L'âge moyen des malades était 53 ans et la durée moyenne de la maladie 5 ans. Chacune de ces substances était administrée à chaque malade pendant 3 semaines et on enregistrait la force de la poigne, l'intensité de la douleur, l'amplitude des mouvements, la capacité fonctionnelle et les effets secondaires. L'ordre d'administration était déterminé par le hasard; seulement le pharmacien principal connaissait l'identité de la substance employée au moment donné.

Une méthode d'analyse conçue pour évaluer les effets secondaires des traitements a montré qu'ils étaient négligeables.

Les résultats s'accordaient avec ceux obtenus par d'autres auteurs, montrant que la phénylbutazone (Butazolidin) et l'oxyphenbutazone sont potentiellement efficaces dans le traitement symptomatique de l'arthrite rheumatismale et que les deux médicaments produisent des résultats appréciablement supérieurs à ceux du *placebo*. Toutefois, aucune des méthodes d'évaluation employées n'a décélé une différence significative entre la phénylbutazone et l'oxyphenbutazone. Les faibles différences observées étaient inconséquentes. Trois évaluations favorisaient légèrement la phénylbutazone et deux autres l'oxyphenbutazone.

On n'a pas noté de différence appréciable dans la proportion des effets secondaires provoquée par la phénylbutazone, l'oxyphenbutazone et le *placebo*; tandis que cinq malades sur six qui ne toleraient pas la phénylbutazone ont accepté l'oxyphenbutazone, chez deux autres malades c'était le contraire.

Prueba controlada de la fenilbutazona, oxifenbutazona y de un *placebo* (substancia inerta) en el tratamiento de la artritis reumatoide

SUMARIO

Se administraron en sucesión fenilbutazona, su derivado oxifenbutazona y un *placebo* (substancia inerta de control) a sesenta enfermos (11 hombres, 49 mujeres) con artritis reumatoide. La edad media de los enfermos era 53 años y el término medio de duración de la enfermedad 5 años. Cada una de las diferentes substancias fué administrada a cada enfermo durante 3 semanas, y se anotaron los resultados de las investigaciones de la fuerza al asir, intensidad del dolor, libertad de movimiento, capacidad funcional y efectos secundarios. El orden de administración fué seleccionado al azar y sólo el jefe de farmacia conocía la substancia administrada en cada momento.

Un método de análisis planeado para determinar los

post-efectos de los tratamientos demostró que dichos post-efectos eran negligibles.

Los resultados fueron similares a los de otros investigadores, demonstrando que la fenilbutazona (Butazolidin) y oxifenbutazona (Tanderil) son ambas potencialmente efectivas en el tratamineto sintomático de la artritis reumatoide, produciendo ambos productos resultados significativamente superiores a los obtenidos con el *placebo*. No se apreciaron diferencias significativas entre la acción de la fenilbutazona y la de la oxifenilbutazona en ninguna de las valoraciones efectuadas. Las pequeñas diferencias halladas no fueron consistentes. Tres valoraciones favorecieron ligeramente a la fenilbutazona y dos a la oxifenbutazona.

No se apreció diferencia significativa entre el percentaje de efectos secundarios producidos por la fenilbutazona, oxifenbutazona y el *placebo*; y mientras que cinco de los seis enfermos que no toleraron la fenilbutazona, aceptaron oxifenbutazona, en dos casos lo sucedió lo contrario.