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EMPIRE RHEUMATISM COUNCIL*

MULTI-CENTRE CONTROLLED TRIAL COMPARING CORTISONE ACETATE AND ACETYL SALICYLIC ACID IN THE LONG-TERM TREATMENT OF RHEUMATOID ARTHRITIS†

RESULTS OF THREE YEARS' TREATMENT

(RECEIVED FOR PUBLICATION JUNE 6, 1957)

(1) Introduction

In December, 1955, the Empire Rheumatism Council published an account of a therapeutic trial conducted in nine centres in Great Britain comparing the effects of cortisone acetate and acetyl salicylic acid given to patients with rheumatoid arthritis over a period of one year (Empire Rheumatism Council, 1955). The results coincided closely with those of the somewhat similar therapeutic trial of cortisone and aspirin in *early* cases of rheumatoid arthritis conducted by the Medical Research Council and Nuffield Foundation (1954, 1955); no significant differences were found between the two groups of patients over the course of the year, although clinical improvement and radiological deterioration had occurred to a similar extent in both groups. A report on the results of following-up these two groups of patients for the second year was prepared, but not published, and the present report, collating the results of all three years, carries the story to the end of the third and final year. Because of withdrawals at different stages of the trial, slightly fewer patients are available for the second year and fewer still for the third year, but sufficient remain for comparisons to be made between the groups at each point of time.

(2) Plan of the Trial

To recapitulate the more detailed account published earlier, 100 patients were selected with rheumatoid arthritis of any duration, after excluding any with gross irreversible changes in the joints and those under 17 and over 60 years of age, together with any known to have mental instability, gastric disease, or hypertension, those unlikely to co-operate, and those who were unable to walk or had major degrees of flexion deformity. The patients were allocated to one of the two treatment groups centrally and at random, stratifying by sex and treatment centre. The two groups were shown to be similar initially in all relevant respects, whether the 99 patients who were started on the trial or the 77 available at the end of the first year, or the 53 available at the end of the third year only were considered. This comparability was shown to exist in respect of age, sex, duration of symptoms, type of onset, number of joints affected, employment status, functional capacity—both objective and subjective rating—, erythrocyte sedimentation rate, haemoglobin level, and radiological appearance.

(3) Treatment Schedule

The treatment schedule consisted of a basic regime of general care, including the use of splints and physiotherapy plus cortisone acetate for one group and aspirin for the other. These two drugs were given at individual dosage levels during the year at the lowest level which kept each patient

* The Empire Rheumatism Council Sub-Committee conducting the trial was composed as follows:

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† A brief abstract of these results was given at the IX International Congress at Toronto in June, 1957, by Dr. F. Dudley Hart.

TABLE I
DOSAGE ANALYSIS

No. of Years Completed	Treatment	No. of Patients	Starting Dosage	Dosage at 12 mths	Dosage at 24 mths	Dosage at 36 mths
			Mean±S.E.	Mean±S.E.	Mean±S.E.	Mean±S.E.
1	Cortisone (mg./day)	38	75·0±1·1	68·7±2·6		
	Aspirin (gr./day)	39	58·7±1·4	58·6±3·3		
2	Cortisone (mg./day)	36	75·0±1·2	69·2±2·8	67·5±2·5 S	
	Aspirin (gr./day)	34	58·2±1·7	60·0±3·6	54·7±4·0	
3*	Cortisone (mg./day)	29	74·3±1·3	68·1±3·4	67·8±2·8 S	67·1±3·2 S
	Aspirin (gr./day)	24	58·1±2·1	60·6±4·6	53·7±4·4	52·5±4·9

* Excluding one patient who needed no cortisone during the third year. If he is included, the mean dosage at 36 months is 64·8±3·8 mg./day.
"S" indicates a statistically significant reduction compared with the starting dose.

largely symptom-free and restored maximal functional efficiency with minimal side-effects* (Table I).

The gradual change in the mean cortisone dosage from the 75 mg. per day stipulated at the start of therapy becomes significantly less (statistically) at the 24th month (67·5 mg. per day) and again (67·1 mg. per day) at the 36th month. Therapeutically this is a comparatively small fall. Only one patient on cortisone improved sufficiently to discontinue the drug entirely throughout the whole of the third year. No other patient was receiving less than 25 mg. or more than 100 mg. per day at the end of the third year. There was no significant change in the aspirin dosage over the three years.

Assessment of progress was as recorded previously and as detailed below.

(4) Withdrawals from the Trial

Patients were to be withdrawn from the trial for three reasons:

(*a*) Because they developed serious symptoms due to cortisone or aspirin which necessitated the discontinuance of that particular drug.

(*b*) Because they were deriving no benefit from, or were actually deteriorating on, a drug and in the opinion of the physician needed some other form of therapy. (In addition, patients on cortisone were to be withdrawn if they needed 100 mg./day for more than 1 month.)

(*c*) Because they did not attend hospital for treatment or assessment.

* If a patient needed 100 mg. or more per day as a permanent maintenance dose, he was to be withdrawn from the trial, as this was considered to be too high a level for continuous long-term safety.

In the earlier report it was stated that, of the fifty patients allocated initially to each group, one (on cortisone) never attended and was excluded; a further 22 were lost to the trial during the first year, leaving at the end of the first year 38 on cortisone and 39 on aspirin, and it was on the experience of these 77 that the first year's report was based. During the second year seven more were lost to the trial (two on cortisone, and five on aspirin). Losses in the third year were much heavier, amounting to seventeen in all (seven on cortisone and ten on aspirin), and it is with the three-year experience of the remaining 53 patients (29 on cortisone and 24 on aspirin) that the present report is particularly concerned. If one type of patient more than another is to derive benefit from cortisone, as has been alleged, this is the group that should show it.

Details of the reasons for withdrawal in the first year of the trial have already been given. Table II summarizes the reasons for withdrawal in each of the two groups during the first, second, and third years.

TABLE II
CASES WITHDRAWN IN FIRST THREE YEARS OF TRIAL

Reasons for Withdrawal	First Year		Second Year		Third Year		Totals	
	Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin
"Toxicity"*	4	5	2	—	2	—	8	5
Deterioration and/or Change of Therapy	6	1	—	3	3	4	9	8
Non-attendance	2	5	—	—	—	5	2	10
Intercurrent Disease	—	—	—	1	1	1	1	2
Death	—	—	—	1	1	—	1	1
Totals	12	11	2	5	7	10	21	26

* This includes, for cortisone, two with hypertension and one each with indigestion, severe headaches, healed tuberculosis, psychosis, oedema of legs, and perforating peptic ulcer, and for aspirin, five with indigestion.

Cortisone Group.—Of the nine patients on cortisone who withdrew in the second and third years, one died from carcinoma of the bronchus, having been admitted to hospital in the 30th month of the trial; up to this time his arthritis had shown improvement. Another patient developed a perforated peptic ulcer in the 13th month and cortisone was stopped. Another developed pulmonary tuberculosis and was admitted to hospital in the 26th month of the trial when cortisone was discontinued (tabulated as intercurrent disease). Another developed oedema of the legs and was transferred to delta hydrocortisone during the latter part of the third year. Another developed such severe headaches that she was admitted to hospital in the 26th month; investigations revealed no organic lesion, but it was considered that cortisone was at least an aggravating factor and the drug was discontinued with subsequent improvement in symptoms. Another patient early in the second year began to develop various diffuse aches and pains in her limbs not related to tender joints, and although she showed no further joint involvement she became dispirited, miserable, and considerably depressed; cortisone was stopped and she was seen by a psychiatrist who considered the basis of her mental trouble to be a latent reactive depression which had probably been brought to the fore by cortisone. Since stopping cortisone more joints have become affected, but her general health and mental state have improved. The remaining three patients felt that the treatment was no longer of value to them and a change of therapy (to phenylbutazone or salicylates) was made.

Aspirin Group.—Of the fifteen withdrawals during the second and third years of the trial, one patient died from coronary thrombosis in the 14th month and one developed severe schizophrenia in the second year. Another entered hospital with haemoptysis due to pneumoconiosis (Caplan's syndrome), and therapy was discontinued in the third year. In seven there was a change of therapy: one was transferred from aspirin to cortisone because of severe pain at the end of the first year, three were transferred to cortisone because of deterioration on aspirin in the third year, two requested and were started on a course of gold treatment early in the second year, and one was transferred to phenylbutazone in the third year. The remaining five either refused further therapy or refused to attend for assessment.

The effect of these withdrawals on the composition of the two groups is dealt with in Section 6. After detailed study it was not possible to demonstrate that the loss of these 47 patients disturbed the relative composition of the two groups on entry to the trial to any significant extent.

(5) Complications and Side-Effects

During the first year eighteen patients on cortisone and seventeen patients on aspirin suffered from complications, most of these being of a minor nature. This is in addition to the complications which were severe enough to warrant withdrawal from the trial during the first year (four on cortisone and five on aspirin).

During the second and third years, in addition to the complications and intercurrent tuberculous infection detailed above in five patients on cortisone necessitating withdrawal from the trial, only minor complications were seen. These were of the same nature as in the first year:

Cortisone Group.—Oedema was noted in two patients. Flatulence, dysphagia, and pylorospasm was noted in seven; amenorrhoea and menorrhagia occasionally. Depression was recorded in two patients and intercurrent infections of a mild nature in four patients, including one with pyoderma. Hypertension occurred in four patients—in one up to a level of 150/110.

Asthma, sciatica, thrombosis, and dermatitis were also encountered, each in one patient. None of these were sufficient to warrant discontinuation of therapy, although the dosage was dropped temporarily by 12½ mg. in, for instance, the patient with severe hypertension.

Aspirin Group.—Nausea and tinnitus were noted in six patients, mostly from one centre where the mean dosage level appeared to be slightly higher than elsewhere. Heart failure was noted in one patient, indigestion in three, and mild intercurrent infections in four. One patient developed a pulp infection of the big toe and gangrene of the finger tips.

No patients in the aspirin group were withdrawn because of complications.

Many of these "complications" were of doubtful aetiology and it was difficult to ascribe such symptoms to the medication given. In general, however, considering the toxic reactions severe enough to need withdrawal together with these minor reactions, aspirin was responsible as expected for dyspepsia, nausea and tinnitus only; it served as a useful "control" for assessment of the "toxicity" encountered in the cortisone group. Thus corneal ulceration, schizophrenia, pulp space infection, or gangrene, if encountered in the cortisone group, might

possibly be ascribed partly to the drug, whereas it seems clinically unlikely that these reactions could have been due to aspirin.

In the cortisone group, the toxic effects were more serious and were similar to those now widely recognized as due to this substance. Most of them occurred in the first year (hypertension and indigestion), but during the second year a peptic ulcer perforated, and during the third year pulmonary tuberculosis developed in one patient and oedema of the legs was severe enough in another to offset any therapeutic advantage of cortisone over aspirin. The "side-effects" of effective cortisone dosage are undoubtedly more severe and more numerous than those of aspirin, as has been more easily learned over the last 7 years without the tribulations of a controlled trial.

(6) Comparison of Cortisone and Aspirin Groups at the Beginning of the Trial

Tables III and IV (Section A)* show that the two groups were similar in all analysed factors at the start of the trial. To summarize the distributions of patients by employment status and function—whether measured objectively or subjectively—"means" have been calculated (although strictly such means are not statistically valid). These "means" are identical or nearly so; χ^2 tests show that the probability of finding such differences as do exist, other than by chance, is very remote.

All differences referred to throughout the report are considered to be statistically significant when they reach the 0·05 probability level unless some other specific statement is made.

Effect of Withdrawals on the Composition of the Groups.—As detailed in Table II, during the 3 years of the trial, 47 patients (21 on cortisone and 26 on aspirin) were lost to the trial (including one female who failed to attend from the start); 23 (twelve on cortisone and eleven on aspirin) were lost during the first year; seven (two on cortisone and five on aspirin) dropped out in the second year; seventeen (seven on cortisone and ten on aspirin) were lost in the third year.

Thus, in the first year's report, results could be compared for 38 on cortisone and 39 on aspirin, but over the whole of the 3-year period covered by the present report, data were available for only 29 on cortisone and 24 on aspirin.

Very fortunately, after a series of comprehensive statistical tests, it was not possible to deduce that the loss of these 47 patients prejudiced the comparison of the two treatment groups. The report on the first year showed that the similarity of these groups at the beginning of the trial when it was based on the original 99 patients still held good when tested on the 77 who completed the first year (Tables III and IV (Section B). Detailed analysis of the second and third year results has shown that this similarity between the two treatment groups at the beginning

* Reproduced from Empire Rheumatism Council (1955). Report on the First Year of the Trial.

TABLE III

SIMILARITY OF TWO TREATMENT GROUPS AT BEGINNING OF TRIAL

Point of Comparison		(A) All Entrants		(B) Excluding Cases withdrawn during First Year		(C) Excluding Cases withdrawn during First and Second Years		(D) Excluding Cases withdrawn during First, Second, and Third Years	
		Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin
Number of Patients		49 (20 males)	50 (20 males)	38 (15 males)	39 (14 males)	36 (15 males)	34 (11 males)	29 (13 males)	24 (8 males)
Mean Age (yrs)		46·0±1·34	47·0±1·92	44·7±1·67	47·4±1·51	44·7 ±1·76	47·0 ±1·55	43·5±1·88	47·9±1·80
Mean Duration of Symptoms (yrs)		7·1±0·78	6·8±0·75	6·9±0·91	7·6±0·90	6·7 ±0·92	7·9 ±0·97	5·7±0·94	8·2±1·28
Type of Onset	Acute	9	8	6	6	5	3	5	3
	Non-acute	40	42	32	33	31	31	24	21
Mean Number of Affected Joints		20·5±2·0	18·0±1·8	19·8±2·28	17·0±1·85	19·2 ±2·40	17·1 ±2·30	15·7±1·71	19·2±2·9
Mean Erythrocyte Sedimentation Rate (mm./hr Westergren)		40·2±3·8	35·8±3·5	37·2±4·2	36·4±4·1	38·3 ±4·44	36·2 ±4·46	37·4±5·29	34·2±4·33
Mean Hb (g. per cent.)		12·6±0·22	12·8±0·19	12·5±0·22	12·5±0·27	12·4 ±0·27	12·5±0·30	12·4±0·29	12·4±0·34

TABLE IV

SIMILARITY OF TWO TREATMENT GROUPS AT BEGINNING OF TRIAL

INITIAL GRADING BY EMPLOYMENT AND FUNCTION

Patients Compared	Employment Status			Functional Capacity					
				Physician's Estimate			Patient's Own Estimate		
	Grade	Cortisone	Aspirin	Grade	Cortisone	Aspirin	Grade (% well)	Cortisone	Aspirin
(A) All Entrants	I (Fit)	5	8	1 (Best)	2	4	100	1	1
	II	24	21	2	31	33	75	10	18
	III	14	15	3	14	10	50	25	23
	IV (Unfit)	6	6	4 (Worst)	2	3	25	12	6
							1	1	2
	Total ..	49	50	Total ..	49	50	Total ..	49	50
	Mean Grade*	2·4	2·4		2·3	2·3		(49 per cent.)	(60 per cent.)
(B) Excluding Cases withdrawn during the First Year	I (Fit)	5	6	1 (Best)	2	2	100	1	1
	II	18	17	2	25	27	75	9	14
	III	10	12	3	9	8	50	18	18
	IV (Unfit)	5	4	4 (Worst)	2	2	25	9	5
							1	1	1
	Total ..	38	39	Total ..	38	39	Total ..	38	39
	Mean Grade*	2·4	2·4		2·3	2·3		(50 per cent.)	(56 per cent.)
(C) Excluding Cases withdrawn during the First Two Years	I (Fit)	4	5	1 (Best)	2	1	100	1	—
	II	18	15	2	23	24	75	8	13
	III	9	10	3	9	7	50	17	15
	IV (Unfit)	5	4	4 (Worst)	2	2	25	9	5
							1	1	1
	Total ..	36	34	Total ..	36	34	Total ..	36	34
	Mean Grade*	2·4	2·4		2·3	2·3		(49 per cent.)	(54 per cent.)
(D) Excluding Cases withdrawn during the First Three Years	I (Fit)	4	5	1 (Best)	2	1	100	1	—
	II	16	9	2	19	16	75	7	10
	III	6	6	3	7	5	50	14	10
	IV (Unfit)	3	4	4 (Worst)	1	2	25	7	3
							1	—	1
	Total ..	29	24	Total ..	29	24	Total ..	29	24
	Mean Grade*	2·3	2·4		2·2	2·3		(52 per cent.)	(55 per cent.)

* The use of the term "Mean" here is unjustifiable but convenient as an index to summarize the distribution.

of the trial also holds good even when tested on the still smaller groups of seventy and 53 who completed 2 years and 3 years respectively in the trial.

Tables III and IV (Sections C and D) summarize this evidence. Just as Section A showed how similar were the two treatment groups as they were originally constituted, and Section B showed their similarity when those who withdrew in the first year were excluded, so Section D shows the similarity of the two groups when all 47 who withdrew in the 3 years are excluded.

Not only do Tables III and IV (Section D) show that, after excluding the 47 withdrawals, the two groups were still alike at the start of this third-year survey, but also a comparison with Sections A and B shows that the differences between the values of the indices arising from the removal of those 47 patients were very slight.

(7) Results: Comparison of Progress in the Two Treatment Groups

Employment Status (Table V, overleaf).—In this the two groups remained remarkably similar throughout the trial. Although Table V shows the distributions only at the end of each year of the trial—based on the number still left in the trial in each year—equal similarity was apparent at 6 and 18 months. (Records at the middle of the third year—at 30 months—were not consistently made.) There is no significant difference between the distributions of the two groups at any point of time, between either group from one assessment to the next, or between the first and final assessment. This is, however, a rather coarse grading. The results of a similar analysis restricted to those patients who completed 3 years in the trial were the same.

TABLE V

DISTRIBUTION BY EMPLOYMENT STATUS

(BASED ON NUMBER OF PATIENTS LEFT IN TRIAL IN EACH YEAR)

Employment Status (Grade)	Beginning of Trial		End of First Year		End of Second Year		End of Third Year*	
	Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin
I (Fit)	5	8	7	10	7	11	5	7
II	24	21	20	17	18	8	16	9
III	14	15	9	10	10	13	5	6
IV (Unfit)	6	6	2	2	1	2	3	2
Total	49	50	38	39	36	34	29	24
"Mean Grade"	2·4	2·4	2·2	2·1	2·1	2·2	2·2	2·1

* When patients who completed 3 years were considered alone, a comparable tabulation showed no difference between the two treatment groups at any point of time.

Functional Capacity (Table VI).—Functional capacity, as estimated objectively by the physician on the basis of examination and interrogation, showed a tendency to improvement in each treatment group during the first year, but the improvement was without statistical significance. No similar tendency was apparent in the second year, and little further change was apparent in either group at the end of the third year. So again there was no significant difference between the distribution of the treatment groups at any point of time, nor between either group from one assessment to the next, nor between the initial and any subsequent assessment for either group.

The middle section of Table VI shows that more patients were up-graded than down-graded in both treatment groups in the first year—the majority (61 per cent. of those who completed the first year in each group) showing no change.

During the second year, the functional status of a high proportion of those who completed 2 years—72 per cent. on cortisone and 85 per cent. on aspirin—remained as it was at the end of the first year. During the third year the functional status of 75 per cent. of each treatment group remained as it had been at the end of the second year. Over the whole of the 3-year period, eight on cortisone and seven on aspirin were up-graded; four on cortisone and three on aspirin were down-graded, and seventeen on cortisone and fourteen on aspirin remained in the same grade as at the start of the trial. It may be of interest to add that, of the eleven on cortisone

TABLE VI

DISTRIBUTION ACCORDING TO FUNCTIONAL CAPACITY (PHYSICIAN'S ESTIMATE) AT BEGINNING, END OF FIRST YEAR, END OF SECOND YEAR, AND END OF THIRD YEAR (NUMBER UP-GRADED AND DOWN-GRADED IN EACH PERIOD)

(BASED ON NUMBER OF PATIENTS LEFT IN TRIAL IN EACH YEAR)

Functional Capacity	Beginning of Trial		End of First Year		End of Second Year		End of Third Year*	
	Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin
1 (Best)	2	4	6	5	6	5	4	3
2	31	33	23	26	22	19	17	15
3	14	10	9	8	7	9	8	5
4 (Worst)	2	3	—	—	1	1	—	1
Total	49	50	38	39	36	34	29	24
"Mean Grade"	2·3	2·3	2·1	2·1	2·1	2·2	2·1	2·2
Re-grading	**First Year**		**Second Year**		**Third Year**		**Complete 3-Year Period**	
Up-grading	11	10	5	1	2	3	8	7
Down-grading	4	5	5	4	5	3	4	3
No Change	23	24	26	29	22	18	17	14
Losses	11	11	2	5	7	10	20	26
"Actual" as Percentage of "Possible" Scores	**First Year**		**Second Year**		**Third Year**		**Complete 3-Year Period**	
Up-grading	24	24	13	3	7	11	22	22
Down-grading	6	7	7	7	9	7	10	8

* When patients who completed 3 years were considered alone, a comparable tabulation showed no difference between the two treatment groups at any point of time.

and ten on aspirin who were up-graded in the first year, six and four respectively were still on their new grade or had improved still further (by the functional status index) at the end of the trial.

The lowest section of Table VI takes into account the amount of up-grading and down-grading which was *possible* for each group of patients. This was done by expressing the amount of change which actually occurred as a percentage of that which was possible. To illustrate the method, consider the initial grading of the 38 patients on cortisone who completed the first year (not shown in the Table). Two were Grade I and could not therefore be up-graded at all. Twenty-five were Grade II and could each have moved up one grade (25), nine were Grade III and could each have moved up two grades (18), two were Grade IV and could each have moved up three grades (6). Thus the total possible score for up-grading in the first year of the trial for the cortisone group was 25+18+6 =49. As it happened, the possible score in the aspirin group was also 49. Both groups actually improved twelve grades each, *i.e.* 24 per cent. of their possible scores.

Similarly, the possible down-grading score in the first year was 65 for the cortisone group and 68 for the aspirin group. In the event the cortisone group deteriorated four grades and the aspirin group five grades, 6 per cent. and 7 per cent. of their respective possible scores.

Calculations on a similar basis for the second and third years and over the whole of the 3-year period showed only non-significant differences between the two groups.

The results in this section were unchanged when the analysis of functional status was repeated on only those patients who completed the 3 years.

Subjective Well-being (Table VII).—As judged subjectively by the patient, well-being shows a similar but more marked tendency to improvement in the first year of the survey. This improved state was reached by the end of the first 6 months, as shown in the previous report, and was maintained to the end of the year. In the cortisone group this degree of improvement was maintained to the end of the third year, but in the aspirin group there was some slight deterioration. In other words, both groups show a change in distribution (statistically significant) indicating that many felt better at the end of the first year. Only in the cortisone group are the distributions at the end of the second and third years significantly different from the distribution at the start. This can also be seen from the middle section of Table VII which shows that, whereas 25 of the cortisone group and eighteen of the aspirin

TABLE VII

DISTRIBUTION ACCORDING TO FUNCTIONAL CAPACITY (PATIENT'S OWN ESTIMATE) AT BEGINNING, END OF FIRST YEAR, END OF SECOND YEAR, AND END OF THIRD YEAR
(NUMBER UP-GRADED AND DOWN-GRADED IN EACH PERIOD)
(BASED ON NUMBER OF PATIENTS LEFT IN TRIAL IN EACH YEAR)

Functional Capacity (per cent. well)	Beginning of Trial		End of First Year		End of Second Year		End of Third Year*	
	Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin	Cortisone	Aspirin
100	1	1	5	4	8	5	7	3
75	10	18	20	23	12	13	12	9
50	25	23	12	10	12	14	4	8
25	12	6	1	2	4	2	4	2
1	1	2	—	—	—	—	—	—
Not Known	—	—	—	—	—	—	2	2
Total	49	50	38	39	36	34	29	24
"Mean" Grade (per cent.)	49	60	69 S	69 S	67 S	65	70 S	65
Re-grading	**First Year**		**Second Year**		**Third Year**		**Complete 3-Year Period**	
Up-grading	25	18	6	4	4	2	18	10
Down-grading	3	4	8	10	7	3	4	3
No Change	10	17	22	20	16	17	5	9
Not Stated	—	—	—	—	2	2	2	2
Losses	11	11	2	5	7	10	20	26
"Actual" as Percentage of "Possible" Scores	**First Year**		**Second Year**		**Third Year**		**Complete 3-Year Period**	
Up-grading	42	35	13	10	12	6	45	26
Down-grading	4	5	9	11	10	5	8	6

* When patients who completed 3 years were considered alone, a comparable tabulation showed no difference between the two treatment groups at any point of time.
"S" indicates a statistically significant difference as compared with the initial distribution.

TABLE VIII

MEAN NUMBER OF JOINTS AFFECTED PER PERSON AT BEGINNING, END OF FIRST YEAR, END OF SECOND YEAR, AND END OF THIRD YEAR

(BASED ON NUMBER OF PATIENTS LEFT IN TRIAL IN EACH YEAR)

Time of Examination	Cortisone		Aspirin	
	No. of Patients	Mean±S.E.	No. of Patients	Mean±S.E.
Beginning of Trial	49	20·5±2·0	50	18·0±1·8
End of First Year	38	11·2±1·9 (S)	39	9·3±2·3 (S)
End of Second Year	36	13·1±1·9 (S)	34	10·0±1·7 (S)
End of Third Year*	29	10·2±1·5 (S)	24	10·2±1·6 (S)

* A comparable tabulation, based on only those who completed 3 years, gave very similar results.
"S" indicates a statistically significant reduction in the mean number of joints affected compared with the initial figure.

group were up-graded by the end of the first year, only small numbers (six on cortisone and four on aspirin) were up-graded in the second year, and still fewer (four on cortisone and two on aspirin) were up-graded in the third year. Of the 29 on cortisone and 24 on aspirin who completed the trial, eighteen of the former and only ten of the latter said that they felt better at the end of the third year than they had felt at the start. It may be added that, of the 25 on cortisone and eighteen on aspirin who were up-graded in the first year, thirteen (52 per cent. of the former and only eight (32 per cent.)of the latter were still in their new grade or a higher one at the end of the third year.

Thus, both treatment groups behaved very similarly, and, apart from the fact that the aspirin group failed to maintain the subjective improvement noted in the first year, there is little difference between them either in distribution or in change of grade, whether considered absolutely or (bottom section of Table VII) as a percentage of possible change.

Precisely similar results were again reached when this analysis of the patients' estimate of improvement was restricted to those who had completed 3 years in the trial.

Number of Joints Affected (Table VIII).—The mean number of joints affected per patient in each treatment group at the beginning of the survey, is compared with the mean number affected per patient at the end of each subsequent year—assessed clinically not radiologically—out of the 68 joints listed individually. A small but similar amount of improvement occurred in both groups in the first year of treatment, which reached significance level. The earlier report showed that most of this improvement occurred in the first 6 months of treatment. During the second and third years no significant change could be demonstrated in the mean number of joints affected per patient, so that for each group the mean value at the end of every year is lower than the mean value at the start.

Neither initially nor at any subsequent assessment was there any significant difference between the treatment groups as regards the mean number of joints affected per patient.

Where the analysis was repeated on only those patients who had completed 3 years, the results were very similar.

Erythrocyte Sedimentation Rate (mm./hr Westergren) (Table IX).—There was no significant difference between the two treatment groups as regards

TABLE IX

ERYTHROCYTE SEDIMENTATION RATE LEVELS AT BEGINNING, END OF FIRST YEAR, END OF SECOND YEAR, AND END OF THIRD YEAR

(BASED ON NUMBER OF PATIENTS LEFT IN TRIAL IN EACH YEAR)

Time of Examination	Cortisone		Aspirin	
	No. of Patients	Mean±S.E.	No. of Patients	Mean±S.E.
Beginning of Trial	49	40·2±3·8	50	35·8±3·5
End of First Year	38	23·4±2·9 (S)	39	24·3±3·2 (S)
End of Second Year	36	23·9±3·0 (S)	34	29·4±3·1
End of Third Year*	29	30·9±5·1	24	30·0±3·5

* A comparable tabulation, based on only those who completed 3 years, gave very similar results.
"S" indicates a statistically significant reduction in the mean E.S.R. compared with the initial value.

the mean erythrocyte sedimentation rate at the start and at the end of each subsequent year. Both groups showed improvement in the course of the first year, but no real additional improvement could be demonstrated in the second year. Indeed, in the aspirin group in the second year and in the cortisone group in the third year, some slight retrogression is suggested by the figures, not sufficient to make the differences between the two groups statistically significant, but sufficient to reduce the difference between the initial mean value and the third year mean value in both groups to below significance level. These results were unaltered when restricted to those who completed 3 years.

The earlier report included a diagram presenting the average erythrocyte sedimentation rates at successive monthly intervals from the start of treatment, and noted that in patients on cortisone the level declined markedly in the first 2 months and gradually rose again. (This is in accordance with the observations made by other workers.) No such fall in the first and second months was apparent for the aspirin group which in the aggregate presented a more gradual decline over the first year.

No monthly variation similar to that noted above could be demonstrated in regard to other indices, *viz.* functional activity and haemoglobin levels, and absence of data precluded a similar interval analysis in the second and third years.

Haemoglobin Level (Table X).—Both treatment groups had similar low average levels initially (12·4 and 12·5 g. per cent. respectively). By the end of the first year these had been increased to 13·3 g. per cent. in the cortisone group—a statistically significant increase—and to 13·1 g. per cent. in the aspirin group—not significant. During the second year the levels in both groups fell again. At the end of the third year the average for the cortisone group was still low (12·6 g. per cent.), but the aspirin group again showed a significant increase from the initial value (to 13·5 g. per cent.). Similar values were obtained by repeating the tabulation for only those patients who completed the 3 years.

***X*-Ray Findings (Tables XI and XII,** overleaf).—Insufficient *x*-rays were available for comparison of the changes over the 3-year period (26 of the cortisone group and 12 of the aspirin group). The analysis is therefore confined to the changes seen over the first 2 years.

The assessment of radiological change was again confined to the hands and wrists for reasons given in the first report, and the same division of 44 radiographic joints was used. Of seventy patients who completed the 2 years in the trial, *x*-ray films of the hands were available initially and at approximately 24 months after treatment for 48 (26 on cortisone and 22 on aspirin).

These 48 patients showed no significant difference at the start of the trial in respect of any of the factors listed in Tables III and IV, neither could any significant difference (in respect of these same factors) be established between these residual groups and either the original group of 99 or the group of seventy patients who completed 2 years in the trial. Thus, there is no evidence that the absence of *x*-ray films in respect of certain patients invalidates radiological comparison of the two treatment groups over the 2-year period.

Change was measured over the whole 2-year period and the films at the start and at the 2-year mark were compared in the same way as before, using the measurement of defined change in a few radiological signs (joint narrowing, surface erosions, pocketed and enclosed erosions, periosteal reactions, and subluxation) as the basis of the scoring system. A subdivision of slight change and marked change was made for the two types of erosion. The radiologist was unaware of the individual's treatment group at the time of reading the films.

TABLE X

AVERAGE HAEMOGLOBIN LEVELS AT BEGINNING, END OF FIRST YEAR, END OF SECOND YEAR, AND END OF THIRD YEAR

(BASED ON NUMBER OF PATIENTS LEFT IN TRIAL IN EACH YEAR)

Time of Examination	Cortisone		Aspirin	
	No. of Patients	Mean ± S.E.	No. of Patients	Mean ± S.E.
Beginning of Trial	49	12·6 ± 0·22	50	12·8 ± 0·19
End of First Year	38	13·3 ± 0·15 (S)	39	13·1 ± 0·20
End of Second Year	36	12·8 ± 0·30	34	12·4 ± 0·34
End of Third Year*	29	12·6 ± 0·32	24	13·5 ± 0·32 (S)

* A comparable tabulation, based on only those who completed 3 years, gave very similar results.
"S" indicates a statistically significant reduction in the mean haemoglobin levels compared with the initial value.

Qualitative Differences in Radiological Progression.—The number of joints assessable for each radiographic sign varied from patient to patient. Except as regards joint narrowing (see below), there were in the cortisone group 26 patients with 1,144 radiographic joints, of which 28 were considered unassessable, leaving a total of 1,116; in the aspirin group there were 22 patients with 968 joints, of which 50 were unassessable, leaving a total of 918.

(Since two joints in each wrist were by definition not suitable for measurement of joint narrowing, the maximum possible number for this sign was only forty per patient.) Some patients had narrowed joints in the initial film and these by definition could not progress (this does not apply to the other radiographic signs). Hence, in many patients, the joints assessable and the joints capable of narrowing were very different. In only 827 joints in the cortisone group, and in only 641 in the aspirin group, would narrowing have been possible.

Because of these differences, the number of joints showing any specific radiographic sign was expressed for each patient as a percentage of the possible joints in which that specific sign could appear. The means of these series of indices are shown in Table XI.

It will be seen that, in the cortisone group, the average per patient was 5·5 per cent. of joints capable of narrowing. In the aspirin group this average was higher (9·5 per cent.), but on these numbers (because of the great variability in the percentages around the means) the difference is not significant.

Similarly, with regard to the other signs, the index in each case was higher in the aspirin group, but no real difference could be demonstrated statistically.

The high ratio of marked change to slight change in both types of erosion implies that the standards laid down originally have not proved adequate to make this distinction over a 2-year period. If any change occurs, few surface erosions increase less than 2 mm. and few pocketed erosions less than 1 mm. in a 2-year interval.

Subluxation was recorded in only three patients (one on cortisone and two on aspirin).

TABLE XI

X-RAY RESULTS

Radiographic Sign		Change over 2 Years (per cent.) Frequency of Specified Sign as a Percentage of Possible Joints in which that Sign could Appear				
		26 Patients on Cortisone		22 Patients on Aspirin		Difference ± S.E.
		Mean per Patient	S.D.	Mean per Patient	S.D.	
Joint Narrowing		5·5±1·5	7·4	9·5±2·7	12·5	4·0±3·0
Surface Erosions	Slight Change	1·0±0·3	1·7	2·0±0·5	2·3	1·0±0·6
	Marked Change	8·1±2·0	10·4	11·1±2·5	11·8	3·0±3·2
Pocketed and Enclosed Erosions	Slight Change	0·8±0·3	1·4	1·0±0·4	1·7	0·2±0·5
	Marked Change	4·2±1·4	6·9	3·8±1·3	5·9	0·4±1·9

TABLE XII

SCORE OF *X*-RAY PROGRESSION IN HANDS DURING FIRST TWO YEARS OF TREATMENT IN 26 PATIENTS ON CORTISONE AND 22 ON ASPIRIN

Score		Cortisone Mean ± S.E.	Aspirin Mean ± S.E.	Difference ± S.E.
Possible		115±2·8	112±3·2	3±4·2
Actual		15±2·6	21±3·8	6±4·6
Actual as Percentage of Possible		13%±2·4	18%±3·1	5%±3·9
New Joints Radiologically Involved	Joints not Initially Affected	29±1·8	28±2·1	1±2·7
	Number of Such Joints which Later became Involved	3±0·7	6±1·2	3±1·4
	Percentage of Possible Joints becoming Affected	10·2*±2·2%	17·7*±4·6%	7·5±4·3%

* Mean of individual values for each patient.

Quantitative Differences in Radiological Progression.—The arbitrary method of scoring progression was used, giving equal weight to each joint as detailed in the previous report. Any deterioration of the 44 joints considered in any individual could score two points—a possible score of 88 per patient. A joint scored one point if only slight changes had occurred, but if one or more marked changes were recorded for it, two points were given. Joints not affected initially scored an additional point if they became affected, so that the total *possible* score varied according to the number of joints initially affected, the maximum possible score (no joints initially affected) being 132. Allowance was made for joints which were initially so damaged that further progression was impossible (this reduced the possible score), but it was not possible to discriminate joints which were originally so damaged that they could only "deteriorate" and not "markedly deteriorate".

The method of scoring took no account of radiological improvement and little direct attention was paid to this possibility when the radiographs were inspected. However, in two patients, both in the cortisone group, improvement was striking.

Table XII shows that the cortisone group could make an average possible score of three points more than the aspirin group. Thus the two groups were similar as regards severity of the disease—judged by *x* rays of joints of the hands. The mean score for radiological deterioration was 15 in the cortisone group and 21 in the aspirin group—scores equivalent to 13 per cent. and 18 per cent. of the possible scores, not a significant difference. Table XII also shows that on the average 29 new joints in the two hands of the average patient on cortisone could have become affected, and a very similar number (28) in the average patient on aspirin, *i.e.* it was possible for the disease to spread to an equal number of new joints in each group. In the event, it spread to an average of three per patient on cortisone and six per patient on aspirin, a difference which is significant at the 5 per cent. level. Expressing the actual joints newly affected as a percentage of the possible number (for each patient individually) and calculating means, in the cortisone group the disease spread to 10 per cent. of the possible joints and in the aspirin group to 18 per cent., the difference not quite reaching the 5 per cent. level of significance.

(8) Discussion

The continuance of this trial for a further 2 years has therefore shown no marked differences between the two groups. Slightly more were withdrawn from the cortisone group for reasons of toxicity or deterioration than from the aspirin group. Rather more were withdrawn from the aspirin group than from the cortisone group because they failed to attend. In those remaining in the trial there was no difference between the two groups over this period of 3 years in employment status, or in functional status as judged by the physician on an objective basis. The subjective judgment of well-being, which had improved in both groups during the first year, was maintained in the cortisone group to the end of the third year, but some slight deterioration occurred in the aspirin group over the latter period. There was, however, little difference in distribution or in change of grade. There was a similar decrease in the number of joints affected in both groups over the 3-year period. Apart from the temporary initial fall in erythrocyte sedimentation rate, which was noticed previously in the first 2 months on cortisone but was absent at the end of the first year, there was no difference between the two groups in this respect in the second or third years. The haemoglobin level was slightly increased in the cortisone group at the end of the first year, but this was not maintained; the level rose slightly in the aspirin group by the end of the third year, but not in the cortisone group.

Analysis of changes in *x*-ray appearances of the hand and wrist show that both groups were similar initially, that both showed comparable worsening, and that a comparable number of new joints became affected during the first year. By the end of the second year further deterioration had occurred in both groups, slightly more in the aspirin than in the cortisone group, but reaching significant levels in only one out of several different methods of scoring. At the third year there were not sufficient films available for valid comparison, but there was no difference between the groups in those still available for study.

These results show that the tendencies deduced for the first year of treatment have been continued during the second and third years. This was also shown in a study of the somewhat similar controlled trial of early cases conducted by the Medical Research Council and Nuffield Foundation (1955).

(9) Summary

A multicentre controlled therapeutic trial comparing cortisone and aspirin in the long-term treatment of rheumatoid arthritis over a period of 3 years has been completed. The results obtained by comparison of the two treated groups at the end of one

year (Empire Rheumatism Council, 1955) showed little difference between the two treatments, and this same conclusion is reached from a comparison of the two groups at the end of the second and third years from the start of treatment. Although fewer patients remained for comparison (due to death, withdrawal because of toxicity, non-attendance, or change to some other form of treatment), these withdrawals affected both groups equally and did not appear to bias the results.

It is concluded that the effect of this dosage of cortisone acetate in the treatment of rheumatoid arthritis is similar in almost all respects to that of aspirin; little advantage is shown by either drug at the end of the first, second, or third year in regard to any of the functional tests. Subjective well-being was slightly better maintained in the cortisone group than in the aspirin group. Haemoglobin levels showed transient improvement at the end of the first year in the cortisone group and at the end of the third year in the aspirin group. Both groups showed radiological deterioration; this was more marked at the end of the second year in the aspirin group, but the difference did not reach significance levels. In all other respects, both groups showed improvement at the 3-yearly assessment compared with the condition at the start of the trial.

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Essai comparé et contrôlé, dans plusieurs Centres, de l'acétate de cortisone et de l'acide acétyl-salicylique, dans le traitement à long terme de l'arthrite rhumatismale. Résultats de trois ans de traitement

RÉSUMÉ

On vient de terminer un essai thérapeutique contrôlé, dans plusieurs Centres, comparant la cortisone et l'aspirine dans le traitement à long terme de l'arthrite rhumatismale; la période de traitement fut de 3 ans. Les résultats de traitement des deux groupes comparés au bout d'un an (publiés déjà dans ce journal, 1955, 14, 353) ont montré qu'il y avait peu de différence entre les deux traitements, et on arrive à la même conclusion en comparant les deux groupes au bout de deux et de trois ans. Bien que le nombre de malades pour comparer devint plus petit (en raison de mort, abandon à cause de toxicité ou absences, ou bien change de traitement), ces abandons affectent les deux groupes de la même manière et ne semblent pas influencer les résultats.

On conclut que l'effet de l'acétate de cortisone en doses indiquées ci-dessus dans le traitement de l'arthrite rhumatismale est similaire de presque tous les points de vue à celui de l'aspirine; qu'aucune des deux substances ne s'est montrée supérieure à l'autre au bout de la première, deuxième ou troisième année en aucun des tests de la fonction. Le bien-être subjectif se maintenait un peu mieux dans le groupe à la cortisone. Il y avait une amélioration passagère des taux d'hémoglobine au bout d'un an dans le groupe à la cortisone et au bout de trois ans dans le groupe à l'aspirine. On nota une détérioration radiologique dans les deux groupes, plus marquée au bout de la deuxième année dans le groupe à l'aspirine, mais cette différence n'a jamais atteint un niveau significatif. De tous les autres points de vue, il y avait une amélioration dans les deux groupes à l'évaluation triennale en comparaison avec l'état des malades au début de l'essai.

Investigación controlada en varios Centros del acetato de cortisona y del ácido acetil-salicílico comparados en el tratamiento de termino largo de la artritis reumatoide. Resultados de tres años de tratamiento.

SUMARIO

Se llevó a cabo una investigación terapéutica controlada, de tres años de duración, en varios Centros, comparando la cortisona y la aspirina en el tratamiento de termino largo de la artritis reumatoide. Los resultados de tratamiento de ambos grupos comparados al cabo de

un año (publicados en este periódico, 1955, 14, 353) revelaron poca diferencia entre los dos tratamientos; ahora se llega a la misma conclusión al comparar estos grupos al cabo de dos y de tres años. Aunque menos enfermos quedaron para comparar (debido a muertes, abandonos por razones de toxicidad, ausencias o cambios de tratamiento), estos abandonos afectan ambos grupos de manera igual y no parecen prejuiciar los resultados.

Se concluye que el efecto del acetato de cortisona en dosis indicadas en el tratamiento de la artritis reumatoide es similar, desde casi todos los puntos de vista, al de la aspirina; que ninguna de las dos substancias se mostró superior a la otra al cabo del primer, segundo o tercer año en ninguno de los *tests* de función. El bienestar sujetivo mantúvose algo mejor en el grupo de cortisona. Hubo una mejoría transitoria en las cifras de hemoglobina al cabo de un año en el grupo de cortisona y al cabo de tres años en el grupo de aspirina. Deterioro radiológico fué notado en ambos grupos, más pronunciado al cabo del segundo año en el grupo de aspirina, pero esta diferencia no alcanzó un grado significativo. Por lo demás, en la valoración trienal, se encontró una majoría en ambos grupos en comparación con la condición al empiezo de la investigación.