enthusiasm and influence of advocates of this or that approach. A final solution will probably never be possible.

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At the meeting of the council of the Royal College of Nurses last month final approval was given to a new training scheme which would lead to State registration and the health visitor's certificate. It is being organized by the College with the help of King's College Hospital. A four-year course is envisaged (excluding six months' training for part I midwifery). An introductory term at the Royal College of Nursing would be followed by three years' training at King's College Hospital. Then would come seven months of more specialized training at the College as a health visitor, leading to the health visitor's examination. To ensure continuity and integration of study, one health-visitor tutor at the College would be responsible for the students throughout; during the hospital period she would remain in contact with them in co-operation with the hospital sister-tutors. She would undertake certain lectures at the preliminary training school of the hospital, and also join in the case-study discussions. The scheme is now to be submitted to the Royal Society of Health and the Ministry of Health, with a view to beginning the course in September, 1958.

LONG-TERM RESULTS IN EARLY CASES OF RHEUMATOID ARTHRITIS TREATED WITH EITHER CORTISONE OR ASPIRIN

A THIRD REPORT BY THE JOINT COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND NUFFIELD FOUNDATION ON CLINICAL TRIALS OF CORTISONE, A.C.T.H., AND OTHER THERAPEUTIC MEASURES IN CHRONIC RHEUMATIC DISEASES*

A comparative study of the value of cortisone and aspirin therapy in early cases of rheumatoid arthritis was started in 1951 by the Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone, A.C.T.H., and Other Therapeutic Measures in Chronic Rheumatic Diseases. The findings during the first and second years of therapy have already been published (Joint Committee, 1954, 1955). Although the therapeutic trial in its original form was not continued after the second year, most of the 61 patients originally taken into the trial have been followed by the physicians at the five participating centres, and a review of the condition of these patients at between three and four years from the start of therapy has provided some interesting information. The patients originally admitted to the trial form a well-defined and homogeneous group of early cases, since only patients with a disease duration of not less than three and not more than nine months were included. In addition the patients had to have a polyarthritis of rheumatoid type affecting at least four joints, with bilateral involvement of hands, feet, ankles, or wrists, and they had to be between 17 and 59 years of age at the time of entry into the trial. The sheep-cell agglutination test was carried out during the first year in 53 of the 61 patients studied and a positive result was recorded at least once in three-quarters of them.

Completeness of Follow-up

The number of patients available for assessment during the three to four years of study is shown in Table I. As previously reported, 3 of the 31 patients allocated to aspirin were lost during the first year of therapy. One woman aged 60 who did well emigrated to New Zealand. A woman aged 53 had a psychological breakdown after three months of therapy and declined to return. And a man aged 48 whose condition was deteriorating felt he was deriving no benefit from the tablets after six months. During the second year there were no losses, but during the third year five patients were lost sight of. In two women aged 45 the disease had been in complete remission throughout most of the second year, and they were untraceable at the

*The members of the Joint Committee are: Lord Cohen of Birkenhead (chairman), Dr. E. G. L. Bywaters, Dr. W. S. C. Copeman, Sir Charles Dodds, Dr. J. J. R. Duthie, Professor A. Bradford Hill, Mr. H. Osmond-Clarke, Professor F. T. G. Prunty, Dr. J. Reid, Dr. H. F. West; Professor J. H. Kellgren and Mr. W. A. Sanderson (joint secretaries).

The Subcommittee and participating centres were: Professor J. H. Kellgren (chairman), Rheumatism Research Centre, Manchester; Dr. E. G. L. Bywaters, Postgraduate Medical School of London and Canadian Red Cross Memorial Hospital, Taplow; Dr. W. S. C. Copeman, West London Hospital; Dr. J. J. R. Duthie, Northern General Hospital, Edinburgh; Dr. H. F. West, Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases; Professor A. Bradford Hill; and Professor F. T. G. Prunty.

The results of the trial were analysed by Dr. J. T. Boyd, of the Statistical Research Unit of the Medical Research Council, London School of Hygiene and Tropical Medicine, and the Subcommittee is greatly indebted to him for his work.

three- to four-year follow-up; one had been treated with cortisone, the other with aspirin. One man aged 58 who was receiving cortisone (75 mg. daily) developed haematemesis and melaena, for which gastrectomy was performed at another hospital. After this, cortisone was stopped and

TABLE I.—*Number of Patients Available for Assessment and Drugs Actually Taken at Different Stages of the Trial*

Drug Taken	Treatment Groups											
	Cortisone				Aspirin				Total			
	Start	1 Yr.	2 Yr.	3–4 Yr.	Start	1 Yr.	2 Yr.	3–4 Yr.	Start	1 Yr.	2 Yr.	3–4 Yr.
Cortisone ..	30	30	26	12	—	—	—	—	30	30	26	12
Aspirin ..	—	—	—	7	31	28	20	19	31	28	20	26
Other ..	—	—	1	2	—	—	4	4	—	—	5	6
None ..	—	—	3	6	—	—	4	3	—	—	7	9
Total ..	30	30	30	27	31	28	28	26	61	58	58	53
Not known	—	—	—	3	—	3	3	5	—	3	3	8

the patient was not seen again. A woman aged 60 was found to have a peptic ulcer during the third year of therapy, when on a cortisone dosage of 62.5 mg. daily; cortisone was gradually withdrawn under corticotrophin (A.C.T.H.) cover, but she had a severe flare-up of her arthritis, became seriously disabled, and was transferred to a long-stay hospital. Finally, a woman aged 58 who was receiving aspirin fractured her femur in a car accident, and was admitted to another hospital, where she was also receiving treatment for rheumatoid arthritis and anaemia at the time of the follow-up.

Thus of the eight patients not available for follow-up, two on aspirin and two on cortisone were lost because they did badly or developed serious complications. In one on cortisone and one on aspirin the disease had gone into complete remission during the second year. And two from the aspirin group were lost through unconnected events—namely, emigration and a motor-car accident.

Therapy

At the start of treatment all 61 patients were admitted to hospital for one month, but subsequently they were mainly treated as out-patients, though a small number were readmitted from time to time if the physician-in-charge considered this advisable. Other measures, such as splintage and physiotherapy, were prescribed throughout as indicated.

Details of the dosage of cortisone and aspirin employed in the trial were described in the previous reports. During the first year of therapy both substances were given in 12-week courses, but during the second year treatment was continuous at a dosage determined by the patient's physician, who was asked to employ the minimum dose that would produce maximum functional efficiency and relief of symptoms without producing serious side-effects.

During the third and fourth years treatment was left to the discretion of the physician, though the hope was expressed that, where possible, the patient should be encouraged to continue on the treatment originally allocated at the start of the trial.

The changes in treatment that took place during the period of observation are shown in Table I. At the end of the second year and at the three- to four-year follow-up there were three patients in the aspirin group and five in the cortisone group who were receiving no tablets because their disease was in full remission. One patient in the cortisone group was receiving no tablets of any kind in spite of continuing disease activity. By the end of the second year one patient in the cortisone group and four in the aspirin group were receiving other medicaments, such as tab. codein. co. or phenylbutazone, but by the last follow-up there were nine patients from the original cortisone group who were receiving other treatments, and seven of these were receiving aspirin, one was having phenylbutazone and one tab. codein. co., whereas from the original aspirin group 19 were still receiving aspirin, three phenylbutazone, and one gold.

Thus, of the 53 patients still available for follow-up at three to four years, 27 were originally started on cortisone and 26 on aspirin, but at the last follow-up only 12 were still taking cortisone, whereas 26 were taking aspirin, seven patients having been transferred from cortisone to aspirin, while none had been transferred from aspirin to cortisone. The mean daily dosage during the first and second years was 80 and 75 mg. for cortisone and 4.5 and 4.5 g. for aspirin.

At follow-up the mean daily dosage for those patients receiving the same tablets as at entry into the trial was 66 mg. for cortisone and 3.5 g. for aspirin.

Apart from two patients lost to follow-up through peptic ulceration, only four had their cortisone stopped because of undesirable side-effects. These were mainly not dangerous, consisting of dizziness, hypertension, headaches, dyspepsia, moon-face, etc.* The remaining six who had changed from cortisone to other tablets had done so because they were either deriving little benefit from cortisone or because they had discovered that other tablets were more effective, or for various reasons which were not clear. The small number of patients still on cortisone at the three- to four-year follow-up precludes a comparison between cortisone and aspirin therapy at this stage, but the status of patients originally allocated to the two treatment groups has been compared at three to four years after the start of therapy and the progress of all the patients admitted to the trial has been reviewed.

Assessments

Of the detailed assessments used in the first two years of the trial, some, including tenderness and range of movement in certain specified joints, were not universally recorded thereafter. Comparisons at three to four years have therefore been based upon a clinical statement of progress in general terms, such as functional capacity, disease activity, and remission rate, and also on radiological changes in the hands and feet, and laboratory findings such as sedimentation rate and haemoglobin level.

Results

The general functional capacity of the patients originally allocated to cortisone and aspirin therapy is shown in Table II. The two groups were very similar at the start.

TABLE II.—*Number of Patients With Given Functional Capacity at Different Stages of the Trial*

Grade	Treatment Groups											
	Cortisone				Aspirin				Total			
	Start	1 Yr.	2 Yr.	3–4 Yr.	Start	1 Yr.	2 Yr.	3–4 Yr.	Start	1 Yr.	2 Yr.	3–4 Yr.
1 Normal and 2 only light work ..	4	23	21	19	5	23	23	20	9	46	44	39
3—Unemployable but ambulant ..	18	5	7	6	18	5	5	6	36	10	12	12
4 Wheel-chair, etc., and 5 bed-ridden	8	2	2	2	6	0	0	0	14	2	2	2
Total ..	30	30	30	27	29*	28	28	26	59*	58	58	53

* No record was made at the start of treatment for two patients on aspirin; subsequently these two patients appear in Grades 1 and 2.

Both improved considerably by the end of the first year and the position was virtually unchanged during subsequent follow-up. If we consider the eight patients lost sight of, it seems probable that at least two of them would have been in grade 1 or 2—that is, with virtually normal function—and at least two would have been in grade 4 or 5—that is,

*One man aged 43 whose rheumatoid arthritis went into complete remission during the second year of cortisone therapy developed nephritis (Ellis type II) shortly after stopping cortisone. Lupus erythematosus cells were looked for on several occasions with negative results, and after being invalided by his nephritis for most of the third year he eventually recovered.

seriously disabled—while the remaining four might have been in any grade. Thus the results on the whole may not be quite as good as the three- to four-year follow-up suggests. Whether the patients were treated with cortisone or aspirin initially appears to have been immaterial.

The number of patients in whom the disease was recorded as being in complete remission is shown in Table III. It will be seen that the numbers in remission increase

TABLE III.—*Numbers of Patients (a) Reported by Physicians as Being in Remission and (b) With Given Clinical Assessment of Activity, at Different Stages of the Trial*

Characteristic and Grade	Treatment Groups								
	Cortisone			Aspirin			Total		
	1 Yr.	2 Yr.	3–4 Yr.	1 Yr.	2 Yr.	3–4 Yr.	1 Yr.	2 Yr.	3–4 Yr.
In remission ..	2	4	6	3	4	6	5	8	12
Activity:									
Inactive	2	4	6	2	4	5	4	8	11
Slightly active ..	21	20	12	19	19	16	40	39	28
Very active ..	7	6	9	7	5	5	14	11	14
Total ..	30	30	27	28	28	26	58	58	53

steadily each year, and if we were to add the two patients lost to follow-up who had been recorded as in remission during the second year the final remission rate would be 14 of the original 61, or 23%. At three to four years the remissions are distributed equally between the cortisone and aspirin groups, and there is clearly nothing to choose between the two treatments in this respect. The total number of patients showing a period of complete remission at some stage was actually 18, but four of them were known to have relapsed by the last follow-up.

A clinical assessment of disease activity based largely upon examination of the joints was also recorded by the physician in charge of the patient; the results are shown in the lower half of Table III. This shows a slight inconsistency in that only 11 patients were stated to have inactive disease at follow-up, but the general picture is the same and there is little to choose between the cortisone and aspirin groups.

The mean haemoglobin levels and sedimentation rates in the two treatment groups at the various assessment times are shown in Table IV. The advantage shown by the cortisone group at the end of the first year's treatment was subsequently lost, and at follow-up the mean haemoglobin in the cortisone group was only 0.5 g.% higher than that of the aspirin group, while the mean sedimentation rate was 8 mm. higher in the cortisone group. The distribution of sedimentation rates at follow-up in the two groups is shown in Table V.

X-ray films of the hands and feet were taken at the end of the second year of therapy in most patients and further films were taken at the three to four year follow-up. To eliminate variations of grading due to the changes in interpretation which occur with the passage of time (Kellgren, 1956), both of these sets of films were read at one time by the clinician who had read the two-year films previously (Joint Committee, 1955). Both porosis and erosion were read separately, and the changes were graded as follows: 0=None, 1=Doubtful, 2=Slight, 3=Moderate, 4=Severe. The grading of the films is shown in Table VI. Most of the films showed either no change or further progression of both porosis and erosion during the follow-up period, but a few films showed improvement, mainly of porosis. The mean grading for erosion in the aspirin group is rather higher than that of the cortisone group, but the difference is not great and the radiological follow-up in the aspirin group is less complete.

TABLE IV.—*Average Levels of (a) Haemoglobin and (b) Erythrocyte Sedimentation Rate*

Characteristic Measured	Treatment Group	Average Measurements			
		Start	1 Year	2 Years	3–4 Years
Haemoglobin (g.%)	Cortisone	12·2	13·1*	13·0	12·9
	Aspirin	12·1	11·3	12·3	12·4
E.S.R. (mm./hr.)	Cortisone	42	27	29	35
	Aspirin	42	35	28	27

* The averages shown by the cortisone and aspirin groups differ significantly.

TABLE V.—*Frequency Distribution of Erythrocyte Sedimentation Rates at 3–4 Years*

E.S.R. (mm./hr.)	Treatment Groups		
	Cortisone	Aspirin	Total
Under 10	2	5	7
10–	7	5	12
20–	11	7	18
40–	2	6	8
60–	2	2	4
80+	2	0	2
Not known ..	1	1	2
Total	27	26	53

Discussion

The progress of this group of patients with early rheumatoid arthritis has probably not been better than that of other series of patients, on a variety of treatments, with a disease duration of less than one year. Thus Short and Bauer (1948) reported a remission rate of 37% in a follow-up of 81 patients over five years, while Duthie *et al.* (1955)

TABLE VI.—*X-ray Films of the Hands and Feet. Number of Patients with Given Gradings Amongst Those Who Were X-rayed at Two Years and at Three to Four Years*

Grade	Porosis						Erosion					
	Cortisone		Aspirin		Total		Cortisone		Aspirin		Total	
	2 Yr.	3–4 Yr.	2 Yr.	3–4 Yr.	2 Yr.	3–4 Yr.	2 Yr.	3–4 Yr.	2 Yr.	3–4 Yr.	2 Yr.	3–4 Yr.
Hands												
0=Nil	9	7	7	5	16	12	7	6	2	1	9	7
1=Doubtful	7	5	5	4	12	9	4	2	5	4	9	6
2=Slight	4	7	8	9	12	16	11	9	8	6	19	15
3=Moderate	4	3	2	2	6	5	3	5	7	6	10	11
4=Severe	2	4	1	3	3	7	1	4	1	6	2	10
Total	26	26	23	23	49	49	26	26	23	23	49	49
Average grade ..	1·35	1·69	1·35	1·74	1·35	1·71	1·50	1·96	2·00	2·52	1·74	2·22
,, change ..		+0·34		+0·39		+0·36		+0·46		+0·52		+0·48
Feet												
0=Nil	12	6	6	5	18	11	9	5	5	3	14	8
1=Doubtful	1	2	6	4	7	6	2	3	1	2	3	5
2=Slight	3	8	6	6	9	14	10	9	10	11	20	20
3=Moderate	4	2	1	3	5	5	1	4	3	2	4	6
4=Severe	2	4	0	1	2	5	0	1	0	1	0	2
Total	22	22	19	19	41	41	22	22	19	19	41	41
Average grade ..	1·23	1·82	1·12	1·53	1·17	1·68	1·14	1·68	1·58	1·79	1·34	1·73
,, change ..		+0·59		+0·41		+0·51		+0·54		+0·21		+0·39

give a rate of 40% for inactive disease in 84 patients at a mean follow-up period of two and a half years. In this series of 53 patients the proportion of patients in remission at three and a half years was 23%. Detailed comparisons are, however, of doubtful value, since the dividing line between inactive and slightly active disease is difficult to define and the difference between "complete remission" as used in this series and "partial remission" is far from clear and almost certainly not uniformly applied in different centres. In general terms, however, it may be said that in a quarter of the patients in this series the disease went into remission, in a similar proportion of patients the disease remained very active, while in the remaining half the disease remained slightly active. Only a quarter of the patients became seriously disabled. This approximates to the expected results that could be derived from previous follow-up studies (Short and Bauer, 1948; Ragan, 1949; Duthie *et al.*, 1955).

Whether the patients were originally given aspirin or cortisone therapy appears to have been immaterial to the outcome. With the passage of time seven patients were transferred from cortisone to aspirin therapy whereas none were transferred from aspirin to cortisone. Serious complications of therapy were infrequent in this series, but were encountered only in patients on cortisone therapy. Though there is no significant difference between the two treatment groups at follow-up, the changes in therapy do suggest that with the passage of time both patients and physicians have in some cases come to prefer aspirin to cortisone therapy.

Conclusions

Certain conclusions can, we think, justifiably be drawn from this study. Firstly, the introduction of cortisone has not materially affected the prognosis of patients developing rheumatoid arthritis for the first time. Secondly, in early cases there appears to be little difference between the therapeutic effect of aspirin and cortisone, but in the long-term management of the disease, at least during the first four years, medication with aspirin is more often likely to prove satisfactory than medication with cortisone, though there are certainly some patients who feel they derive more relief from cortisone than from aspirin.

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NOTE ON THE SHEEP-CELL AGGLUTINATION TEST

BY

J. H. KELLGREN, M.B., F.R.C.P., F.R.C.S.

Professor of Rheumatology and Director of Rheumatism Research Centre, University of Manchester

Results of the differential sheep-cell agglutination test were finally obtained from all patients except the three lost to the trial in the first six months. The cases admitted at Edinburgh, Sheffield, and Manchester were tested by the method of Ball (1950), the test being regarded as positive if agglutination occurred in a titre of 1:32 or higher when read at 18 hours. The cases admitted at Hammersmith and West London were tested by the original method of Rose *et al.* (1948), in which the test is regarded as positive if the two titres recorded show a ratio of 1:16 or higher. Only single tests were done in six patients, and, of these, four were positive. The remaining 52 patients were tested on several occasions throughout the period of observation. Of the 58 patients tested the results were positive on all occasions in 26, sometimes positive and sometimes negative in 20, and negative only in 12. The distribution of test results in the patients originally allocated to cortisone and aspirin therapy is similar, as shown in Table I. The tests were not

TABLE I.—*Results of Differential Agglutination Test in Patients Originally Allocated to Cortisone and Aspirin Therapy*

Results of Test	Treatment Groups		
	Cortisone	Aspirin	Total
Positive { Multiple tests	11	11	22
Positive { Single "	2	2	4
Positive and negative "	9	11	20
Negative { Multiple tests	8	2	10
Negative { Single "	—	2	2
Total	30	28	58

done systematically at set time intervals in all patients, so that no precise statement can be made about the behaviour of the test during the period of observation in the group as a whole, but such information as is available does not suggest that the titre values tend to rise with the passage of time. Indeed, 17 patients showed a steady fall in titre values, whereas only four showed a persistent rise, while in the remaining 31 with repeated tests titres remained unchanged or fluctuated up and down.

The 12 patients in whom only negative tests were recorded are of special interest, since in this small group there were seven remissions and no relapses, so that they account for half of the total remissions at follow-up. There is also some relationship between the sheep-cell test and the development of *x*-ray changes in the last available films of the hands and feet as shown in Table II, in which the gradings

TABLE II.—*Correlation Between X-ray Gradings of Last Available Films and Differential Agglutination Test Results**

X-ray Gradings Porosis + Erosion	Results of Test			
2	Negative Only	Positive and Negative	Positive Only	Total
0	3	0	0	3
½	3	0	1	4
1	0	1	2	3
1½	1	5	3	9
2	4	4	4	12
2½	1	3	6	10
3	0	4	2	6
3½	0	2	3	5
4	0	1	5	6
Total	12	20	26	58

* All patients tested and *x*-rayed have been included.

for porosis and erosion found in either hands or feet, whichever was the higher, have been added and then divided by 2. It will be seen that six of the seven patients with *x*-ray gradings of less than 1 had only negative tests, and no patients with only negative tests had an *x*-ray grading of over 2½, whereas 16 of the 27 patients with *x*-ray gradings of 2½ and more had persistently positive tests.

In the small series studied in this trial the prognosis of patients giving only negative results in the test was much better than in those giving only positive results, but there appeared to be no difference between those giving only positive results and those giving both positive and negative results in the test. Among the patients in whom the test was always negative there were several with severe widespread polyarthritis and high E.S.R. on entry into the trial, so that the negative tests and good prognosis cannot be entirely explained in terms of trivial disease. Whatever the explanation may be, it is clear that in therapeutic trials in rheumatoid arthritis the sheep-cell test should be performed on several occasions in all patients, and those giving only negative results in this test should be studied separately.

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