BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 29 1954

A COMPARISON OF CORTISONE AND ASPIRIN IN THE TREATMENT OF EARLY CASES OF RHEUMATOID ARTHRITIS

A 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

In 1951 the Medical Research Council and Nuffield Foundation Joint Committee on Clinical Trials of Cortisone, A.C.T.H., and Other Therapeutic Measures in Chronic Rheumatic Diseases decided that, for an effective assessment of the value of cortisone within its field of study, it was essential to carry out relatively small-scale but carefully controlled clinical trials. One of these trials, it was agreed, should deal with the important problem of the treatment of patients in the early stages of rheumatoid arthritis. The aim would be to measure the therapeutic effects of cortisone treatment upon the rheumatoid process while that process is still uncomplicated, either by severe anatomical changes in the joints or by metabolic or endocrine disturbances resulting from a prolonged and debilitating disease. In short, such a trial would have two objects: first, to compare the relative efficacy of cortisone and another drug usually regarded as efficacious in relieving symptoms and in improving the patient's functional capacity; and, secondly, to study the evolution of the rheumatoid process during prolonged therapy with these different agents. A scheme for this trial was drawn up by a subcommittee of the Joint Committee, and six centres in England and Scotland agreed to take part.*

Type of Patient

It was agreed that the patients to be included in the trial must (*a*) be within the ages of 2 to 59 years inclusive; (*b*) have a polyarthritis of rheumatoid type affecting at least four joints and bilateral involvement of either hands or feet, ankles, or wrists; and (*c*) have had the disease at their time of entry to the trial for not less than three months and not more than nine months. In deciding upon this duration it was required that the initial symptoms of the present illness, which had brought the patient to the centre, should be the first evidence of any rheumatoid disease in the patient—except that a previous episode of polyarthritis suggestive of rheumatoid disease would not exclude the patient from the trial provided that this episode had been of less than 12 months' duration, had left no residual signs, and had resolved completely at least one year before the onset of the present illness. A previous history of a painful incident of up to three weeks' duration would not be considered evidence of previous rheumatoid disease.

No other diagnostic criteria were considered necessary, but centres were asked to make every effort to exclude other diseases such as rheumatic fever, Reiter's disease, and neisserian infection. In addition the sheep-cell agglutination test first described by Rose *et al.* (1948) was performed in most of the patients, and usually on several occasions.

Allocation to Treatment

In a long-term trial of this nature it was obviously out of the question, on ethical grounds, to set up a control group on a dummy treatment. The contrast must lie between treatment by cortisone and another drug usually regarded as efficacious in the treatment of rheumatoid arthritis. The two modes of treatment adopted, and allocated at random, were therefore (1) cortisone and (2) aspirin, with both groups receiving the same basic regime of splints, physiotherapy, etc. No patient would, of course, be brought into the trial unless he or she could be regarded as a suitable case for treatment by *either* of these agents.

Because clinicians at the participating centres would have to select patients for admission to the trial it was necessary to ensure that they would not know whether each patient, in the event of being brought in, would be on cortisone or on aspirin. The procedure adopted was as follows. The clinician at the centre accepted a patient as suitable on the basis of the criteria laid down. Having done so he applied to a central office to know whether the treatment of that patient should be with cortisone or aspirin. At the central office a register had been constructed showing the order in which the

*The members of the Joint Committee are: Sir Henry Cohen (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, Dr. 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 Dr. F. T. G. Prunty.

The Subcommittee was assisted at these centres by the following workers, to whom it expresses its thanks: Dr. B. Ansell, Dr. C. K. Crawford, Dr. G. Fearnley, Dr. H. Lackner, Dr. I. Meanock, Dr. J. Redmill, Dr. O. A. Savage, Dr. J. Sharp, and Dr. M. Thompson.

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.

treatments were to be applied. It was held by one person. Such a random order of treatments was constructed separately for each of 48 small subgroups of patients—namely, according to whether they were (*a*) male or female, (*b*) aged 2–16 or 17–59 years, (*c*) had a duration of symptoms of three to five months or seven to nine months, and (*d*) were treated at one or other of the six centres. Within each of these small subgroups random sampling numbers were used to give approximately equal numbers of patients on cortisone and aspirin. In summation, therefore, the cortisone and aspirin groups would be very similar in these four characteristics—sex, age, duration of illness, and treatment centre.

In detail, the technique was that on admitting a patient a treatment centre would send particulars of the sex, age, and duration of illness to the holder of the register. The prepared list for a person of that sex, age, and duration would be consulted, the patient's name entered on the next available line, and the nature of the treatment already inscribed on that line would, with supplies of hormone or aspirin, be sent to the treatment centre.

Treatment

Each patient was admitted to hospital for a minimum period of four weeks, but subsequently could be treated and observed as an out-patient. It proved impossible to make up cortisone and aspirin suspensions to look alike. The aspirin was therefore given in brown tablets with a bitter flavour so that they would be unrecognizable by the patient as "merely aspirin." They were labelled "Tabs. Rheumatic C."* Cortisone acetate was given orally either in tablet form or as a suspension made up in syrup. It was labelled "Tabs. (or Mist.) Rheumatic A." Patients were asked not to take additional drugs or tablets. For the first year of treatment it was laid down that therapy would be given in twelve-weeks courses separated by one week off treatment. Each course would start with a standard dosage, after which the physician was free to adjust the dose to suit the requirements of individual patients. The specified courses for adult patients, given in divided doses not fewer than three times a day, were as follows :

		Cortisone	*Aspirin*
First week:	Day 1	300 mg. ..	6 g.
„ „	„ 2	200 „ ..	6 „
„ „	„ 3 to day 7 ..	100 „ daily	6 „ daily
Second week:	„ 8 „ „ 14 ..	50 „ „	2 „ „
Third to twelfth week:	„ 15 „ „ 84 ..	Individualized at 25 to 200 mg. daily with graded withdrawal in week 12	Individualized at 1 to 8 g. daily with graded withdrawal in week 12

In the "free" period—that is, the third to twelfth week—the physician was asked to employ the minimum dosage that would restore maximal functional efficiency without producing serious side-effects. In the thirteenth week no treatment by cortisone or aspirin was given, observations and measurements being made (in this week analgesics other than aspirin could, if necessary, be given). If symptoms recurred the twelve-weeks course was repeated, except that the selected dose for the individual patient replaced the standard dose of the second week.

Assessment of Patient

Clinical assessment of each patient (including measurement of the haemoglobin level and blood sedimentation rate) was required one week before and also immediately before the start of treatment. After therapy had begun, an assessment of some or all characteristics was called for at the end of the first, second, fourth, eighth, twelfth, and thirteenth weeks of the first course, and at the end of the first, eighth, and thirteenth weeks of the second and subsequent courses.

The clinical assessment included (*a*) a defined judgment of the patient's general functional capacity (for the five grades laid down, see Table VII); (*b*) a judgment of the activity of the disease as inactive, slightly active, or very active; and (*c*) a statement whether the patient appeared to be in remission. In addition to these subjective assessments the clinician was required to measure the strength of grip for each hand. (The patient had to squeeze an oblong rubber bag 5 by 3 in. (12.5 by 7.5 cm.) inflated at a pressure of 10 mm. Hg, and the figure recorded was the average of three grips.) Two tests of dexterity were applied—namely, in patients with affected hands the time taken to tie six double knots with 12-in. (30-cm.) pieces of household string, and in patients with affected legs the time taken to go up and down ten steps. Estimates were also made of joint tenderness and of range of movement, and the number and site of any new joints involved were recorded as well as of previously affected joints which had recovered. Complications and side-effects were noted. The only obligatory laboratory tests were the blood sedimentation rate and the haemoglobin level.

The Analysis of the Data

In total, 62 adult patients (aged 17 to 59) and 14 children were admitted to the trial. The latter are too few to be informative, and the present report is confined to the adult group. One of these patients, allotted to the aspirin group, refused to co-operate, so that the numbers available are 30 on cortisone and 31 on aspirin. In 53 cases the results of a sheep-cell agglutination test are available. They are lacking for three patients on aspirin who were lost to the trial at an early stage (see below) and for five other patients who were followed up for the first year but never tested (three on aspirin and two on cortisone). 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 1:4 or higher when read at one hour, or 1:32 or higher when read at 18 hours : a positive result was obtained on at least one occasion in 29 out of 40 patients (73%). The cases admitted at Hammersmith and West London were tested by the original method of Rose, in which the test is considered positive if the two titres recorded show a ratio of 1:16 or higher : in 9 out of 13 cases a positive result was obtained on at least one occasion (69%). In view of the close similarity of the results given by the two methods the data from the different centres may be added in comparing the two treatment groups. It is then found that 18 of the 28 patients on cortisone who were tested were positive at one time or another (64%), and 20 of the 25 patients on aspirin who were tested (80%). In other words, each treatment group had a high proportion of positive tests and there is no statistically significant difference between them.

Ball, whose method was principally used in this trial, has reported 50% of positive results in a large unselected series of out-patients diagnosed as suffering from rheumatoid arthritis; and in a carefully selected series of typical cases of varying duration admitted to the Manchester Royal Infirmary for special study 41 out of 61 (67%) gave a positive test (Ball, 1952). Scott (1952), using the Rose method, has reported positive results (a ratio of 1:16 or more) in 60% of an unselected series of 124 confirmed rheumatoid arthritis patients. The 38 positive results in 53 patients in the present trial (72%) compare very favourably with these various figures. They are good evidence of the accuracy of the diagnosis of rheumatoid arthritis in the patients admitted to the trial.

Details of the patients by centre, sex, age, and duration of symptoms are given in Table I. The data show how effective the method of allocation has been in equalizing the two treatment groups in these respects. Their initial equalities or inequalities in other characteristics will be seen

*The Committee is indebted to Mr. J. B. Lloyd, chief pharmacist at the Manchester Royal Infirmary, for the preparation of the tablets.

TABLE I.—*Comparison of the Patients on Cortisone and Aspirin at Start of Treatment*

Treatment Centre	No. of Patients on			Male		Female	
				No. of Patients on		No. of Patients on	
	Cortisone	Aspirin		Cortisone	Aspirin	Cortisone	Aspirin
1	2	5	Age: 17–39 years	5	5	4	6
2	5	4	40–59 ,,	8	6	13	14
3	1	—	Total	13	11	17	20
4	8	8					
5	6	6	Duration of symptoms: 3–5 months	5	4	6	8
6	8	8	7–9 ,,	8	7	11	12
Total	30	31	Total	13	11	17	20

in each of the tables that follow, where these initial assessments are set alongside the subsequent observations.

It must be noted that during the first year of treatment and observation three patients, all on aspirin, were lost to sight. The reasons were as follows :

(1) Male aged 48, West London Centre. After some preliminary improvement his condition deteriorated and he did not, after six months, feel that he was gaining any benefit from the tablets.

(2) Female aged 53, Sheffield Centre. Relapsed on leaving hospital, had a psychological breakdown and declined to return (at week 12).

(3) Female aged 60, Edinburgh Centre. Left the country for New Zealand (at week 30).

The first two must clearly be counted as failures of treatment and must be remembered in considering the results. The third patient was responding satisfactorily up to week 30, and subsequent information has confirmed that she continues to do well on aspirin. For the remaining 58 patients assessments were available towards the end of the first year. The centres, however, were not able invariably to fulfil the agreed schedule, and it was found that the number of patients off treatment in week 52, as required by it, was not sufficient to allow an effective analysis at that point (only about half had the off-treatment week at the end of the year). On the other hand, assessments were available for all 58 patients at some point close to the end of the year while they were still on their personal dosage. The week chosen for analysis, therefore, was, for each patient, that week of personal dosage which provided assessments and was nearest to week 52—with the proviso that it must lie at least four weeks before an off-treatment week—that is, before any " tapering off " of dosage would have begun. There were six patients (four on cortisone and two on aspirin) who at the end of the year had been off treatment for periods varying from 9 to 26 weeks. In these cases the personal dosage was taken to be nil and the week nearest to the end of the year was chosen for inclusion. The actual points taken lay between the 46th and 54th week in all but three cases (which were at the 42nd, 44th, and 45th week).

Results

(a) Joint Tenderness

The changes in joint tenderness are shown in Table II. In reaching the figures there set out an overall " tenderness " index was first computed separately for each patient by taking the average of his recorded joints. The mean of these averages gave, at each point of time, an index for the treatment group as a whole. It will be seen that the average position at the start of treatment is almost identical in the two groups—1.91 cortisone and 1.89 aspirin. In both there is a significant and considerable reduction in pain in the first week of treatment, when the averages fall by 0.80 and 0.72 respectively. This fall continues, though more slowly, up to week 8, and very slightly thereafter, between week 8 and the end of the year. As a result the final averages are still almost identical, though at a much lower level (0.74 cortisone and 0.76 aspirin); the percentage reduction over the year has been some 60% in each group.

TABLE II.—*The Average Changes Observed in the Joint Tenderness Index**

Joints Measured	Treatment Group	Average Joint Tenderness in Week 0	Average Changes in Joint Tenderness			Joint Tenderness at 1 Year	
			Week 0 to Week 1	Week 1 to Week 8	Week 8 to 1 Year	Average	As % of Average at Week 0
All relevant joints (including wrist and hand, given below)	Cortisone	1·91	*−0·80*†	*−0·29*	−0·09	*0·74*	39
	Aspirin	1·89	*−0·72*	−0·21	−0·15	*0·76*	40
Wrist-joints	Cortisone	1·80	*−0·83*	−0·10	+0·13	*1·00*	56
	Aspirin	1·93	*−0·79*	−0·21	+0·08	*0·96*	50
Small joints of hand	Cortisone	2·25	*−0·93*	*−0·50*	−0·25	*0·58*	26
	Aspirin	2·05	*−0·82*	−0·24	−0·34	*0·53*	26

* Tenderness was graded on the scale 0 for no pain, 1 for slight pain, 2 for wincing, and 3 for wincing and withdrawal. The records have been used as an ordinary numerical scale.

† In this and subsequent tables, values in italics are statistically significant changes between specified times, and in the penultimate column between the beginning and end of the year ($P < 0.05$).

In the second and third rows of Table II similar figures are given separately for the wrist-joints and the small joints of the hand. Though the changes are not statistically significant, it appears that with each of the treatments the average levels of pain tended to continue to decrease up to the end of the year in respect of the small joints of the hand, but to show some increases after week 8 in the wrist-joints. In both instances, however, the initial and final averages are closely similar for the cortisone- and aspirin-treated groups.

(b) Range of Movement and Strength of Grip

Table III gives the figures for range of movement in the wrists and strength of grip. In these respects the cortisone group reveals, by chance, some advantage before treatment was started—the average range of movement and average strength of grip were greater. (The difference in the average range of movement is statistically significant.) It is not possible, however, to detect any material difference between the two groups in their responses to treatment. There is, in each characteristic, a substantial improvement in the first week of treatment; week 1 to week 8 and

TABLE III.—*The Average Changes in (a) Range of Wrist Movement and (b) Strength of Grip*

Characteristic Measured	Treatment Group	Average Measurement in Week 0	Average Changes in Measurement			Measurement at 1 Year	
			Week 0 to Week 1	Week 1 to Week 8	Week 8 to 1 Year	Average	As % of Average at Week 0
Range of wrist movement (in degrees)	Cortisone	99*	*+13·9*	+4·6	+1·1	*120**	121
	Aspirin	78	*+23·2*	−1·8	+2·3	*103*	132
Strength of grip (in mm. Hg) left hand	Cortisone	138	*+33·3*	+17·8	+12·2	*202**	146
	Aspirin	111	*+35·3*	+8·5	+0·4	*164*	148
Strength of grip (in mm. Hg) right hand	Cortisone	134	*+46·7*	+2·5	+3·7	*187*	140
	Aspirin	116	*+34·5*	+15·1	−7·1	*166*	143

* The mean of the cortisone group was significantly greater than the mean of the aspirin group.

week 8 to 1 year reveal, on the whole, some further increases, but the changes are much smaller and very variable At the end of the year the average for the cortisone group, compared with the aspirin group, is significantly greater for the range of movement in the wrists but by no more than it was initially. In respect of strength of grip the averages for the cortisone group at the end of the year are also above those for the aspirin group, but once again by no more than they were initially. In other words, the mean percentage changes have been remarkably similar—an increase of 20–30% in range of wrist movement and of 40–50% in strength of grip.

(c) Tests of Dexterity

Table IV gives the results of the timing tests. The average starting-points of the two groups are reasonably alike, and the progression under treatment and the end-results are again very similar. Each treatment group shows an average improvement of some 20–25%.

TABLE IV.—*The Average Changes in Time Taken to (a) Tie Six Knots and (b) Go Up and Down Ten Steps, by Patients With Affected Hands and Legs Respectively*

Characteristic Measured	Treatment Group	Average Measurement in Week 0	Average Changes in Measurement			Measurement at 1 Year	
			Week 0 to Week 1	Week 1 to Week 8	Week 8 to 1 Year	Average	As % of Average at Week 0
Time (in seconds) to tie 6 knots	Cortisone	38	*−4·2*	−0·2	*−4·2*	29	76
	Aspirin	41	*−3·0*	−3·9	−0·8	34	83
Time (in seconds) to go up and down 10 steps	Cortisone	14	−1·3	−2·6	+0·6	11	79
	Aspirin	18	−4·5	+0·8	−0·2	13	72

(d) Haemoglobin Level and Blood Sedimentation Rate

The changes in the level of haemoglobin and in the blood sedimentation rate are shown in Table V. In both these respects there is apparent some difference between the cortisone- and aspirin-treated groups. In haemoglobin level they start alike with mean values of 12.2 and 12.1 g.%. Under treatment the patients on cortisone show, on the average, an improvement, and at the end of the year the mean has reached 13.1 g.%. The corresponding changes under aspirin are erratic and statistically insignificant, with the final average of 11.3 g.%, rather below the initial level and significantly below the average for the cortisone group.

TABLE V.—*The Average Changes in (a) Haemoglobin and (b) Blood Sedimentation Rate*

Characteristic Measured	Treatment Group	Average Measurement in Week 0	Average Changes in Measurement			Measurement at 1 Year	
			Week 0 to Week 1	Week 1 to Week 8	Week 8 to 1 Year	Average	As % of Average at Week 0
Haemoglobin (in g.%)	Cortisone	12·2	+0·2*	*+0·6*	+0·1*	*13·1**	107
	Aspirin	12·1	−0·4	+0·4	+0·8	11·3	93
E.S.R. (mm./hr.)	Cortisone	42	−18·1*	−4·4	+5·5	27	64
	Aspirin	42	−1·4	+0·4	−6·1	35	83

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

The mean blood sedimentation rate at the start of treatment was identical—42 mm./hour in each group. In the first week of treatment there was a pronounced fall in the cortisone group and an insignificant fall in the aspirin group. Subsequent mean changes were slight, and at the end of the year of observation the final averages of 27 mm./hour for patients on cortisone and 35 mm./hour for patients on aspirin do not differ appreciably, though still slightly favouring the former group. On the other hand, in each treatment group five patients had a value of 10 mm./hour or below at the end of the year.

(e) Clinical Assessments

At the end of the year two patients on cortisone and three on aspirin were reported to be in remission (though two of those on aspirin were still on maintenance doses of 4 g. and 1.7 g. respectively). There were a further two patients on cortisone and a further one on aspirin who had not been on treatment for 10, 40, and 20 weeks respectively. Thus four patients in each group were regarded as either in remission or as not requiring treatment at that time. The overall assessments of condition and progress at the end of the first year are shown in Table VI, and reveal little difference between the two groups. If the two aspirin patients who progressed unfavourably and were lost to view are included as "very active" the picture would not be materially altered.

TABLE VI.—*Clinical Assessments of Activity at One Year*

Grade	Cortisone No.	Aspirin No.
Inactive	2	2
Slightly active	21	19
Very „	7	7
Total	30	28

The assessments of functional capacity are given in Table VII, and once again the two treatment groups are more remarkable for their similarity than for their dissimilarity. At the start of treatment the majority of patients were placed in grade 3—not employed and unemployable, no physical recreations. By the eighth week many had been moved to the higher grades—full or light work, etc. In the week off treatment, the thirteenth, a number returned to the lower grades, but by the close of the year about four-fifths of the patients were capable of either full (grade 1) or light work (grade 2). Division of these patients into grades 1 and 2 separately gives 13 and 10 patients on cortisone and 11 and 10 on aspirin, or approximately 40%, with full functional capacity in each treatment group. Only two patients, both on cortisone, were bedridden at the end of the year. The two missing aspirin cases may be set against these—that is, putting the most unfavourable complexion upon them.

TABLE VII.—*Number of Patients with Given Functional Capacity at Different Points of Treatment**

Treatment Group	Time of Assessment	Functional Capacity			Total
		1 or 2	3	4 or 5	
Cortisone	Week 0	4	18	8	30
Aspirin		5	18	6	29†
Cortisone	„ 8	18	11	1	30
Aspirin		15	11	3	29
Cortisone	„ 13	10	16	4	30
Aspirin		10	13	5	28
Cortisone	1 year	23	5	2	30
Aspirin		21	5	0	26

* Functional capacity grades were:
Grade 1: Fully employed or employable in usual work and able to undertake normal physical recreation.
„ 2: Doing light or part-time work and only limited physical recreation. For housewives, all except the heaviest housework.
„ 3: Not employed and unemployable. No physical recreations. Housewives, only light housework and limited shopping.
„ 4: Confined to house or wheel-chair, but able to look after themselves in essentials of life. Hospital patients confined to bed.
„ 5: Completely bedridden.

† No record was made in this respect for two patients, and, as stated previously, three were subsequently lost to view.

(f) Side-effects

Side-effects were recorded for 19 patients in the cortisone group and 21 patients in the aspirin group. Most of these patients had more than one complication, the most frequent in the cortisone group being moon-face or rubicundity (11 patients), depression (5 patients), and euphoria (4 patients), and in the aspirin group tinnitus (11 patients), deafness (10 patients), nausea, dyspepsia, or anorexia (13 patients). There were no severe complications in the cortisone group necessitating discontinuance of treatment despite a final personal dosage at the end of the year of between 100 and 125 mg. a day in 11 of the 26 patients.

The numbers of patients showing side-effects in each consecutive three months of this first year's treatment were 14, 15, 11, and 12 in patients on cortisone, and 16, 10, 6, and 6 in patients on aspirin. In other words, the numbers with these minor complications were equal in the early months of treatment, but became less in the aspirin group as time passed.

Discussion

This trial, as emphasized in the early paragraphs of the report, was designed to answer a specific but very important question—namely, in early and uncomplicated cases of rheumatoid arthritis is it possible to maintain the patient's well-being more efficiently by treatment with cortisone than by treatment with aspirin? Simultaneously, if the trial can be continued into a second or third year, as is envisaged, light may be thrown upon the evolution of the rheumatoid process during prolonged therapy with these different agents. While scientifically it would obviously be of much value to be able to compare the changes in both these treated groups with those taking place in a group receiving neither cortisone nor aspirin, ethically such a course is impossible. One or other agent, it was held, must be administered—together with any other basic treatment that might be required (splints, physiotherapy, etc.).

It was, however, decided that treatment should be tapered off at the end of each three-months period and then withheld for one week to allow of assessment of the patient's condition. Analysis of the data thus provided at the end of the first course—that is, at the thirteenth week—revealed a distinct "relapse" in some of the patients, though an equal degree of "relapse" occurred on the two forms of treatment. For example, the average joint tenderness at the start of treatment was 1.91 in the cortisone group and 1.89 in the aspirin group (see Table II). By week 8 the average had declined by 1.09 in the cortisone group and by 0.93 in the aspirin group. In the week off treatment it increased again by 0.49 and 0.31 respectively, giving average levels in the thirteenth week of 1.32 on cortisone and 1.29 on aspirin.

Very similar reversals were seen in all the other characteristics measured or observed. In Table VII they have already been shown for the functional capacity. It is, however, apparent that the two treatment groups have, on the whole, kept remarkably in step. They closely parallel one another in their immediate and favourable reaction to the first week of treatment; in the continuation of that reaction, but at a much slower rate, up to the observations made at week 8; in their unfavourable response to the cessation of treatment in week 13; and, finally, in their position at the end of the first year of the trial.

The haemoglobin levels and blood sedimentation rates have responded rather more favourably to cortisone than to aspirin. In all other respects there has been little to choose between the two agents. On each form of treatment joint tenderness is substantially reduced, on each form the disease is judged at the end of one year to be inactive, or only slightly active, in three-quarters of the patients, on each form two-fifths of the patients were regarded at the end of one year as capable of normal work and activity. As usual with cortisone treatment, certain more intangible differences have been observed. Some patients appear to experience a sense of well-being, and sometimes an almost excessive and inappropriate cheerfulness during therapy, followed by a swing to a mood of depression during the periods off treatment. On the other hand, the patients receiving aspirin tend to have changes in mood which are more in keeping with the increase and decrease in their symptoms. For practical purposes, however, there seems to have been surprisingly little to choose between cortisone and aspirin as adjuvants in the management of these 61 early cases of rheumatoid arthritis. The maintenance doses that were being employed at the end of the first year to produce these results are shown in Table VIII.

TABLE VIII.—*Daily Maintenance Doses being Administered at the End of the First Year (Before any Tapering-off)*

Cortisone (mg./day)	No. of Patients on Given Dose	Aspirin (g./day)	No. of Patients on Given Dose
125	2	6	8
100*	9	5	2
75†	7	4	13
62½	2	3	1
50	4	2	1
37½	1	1·7	1
25	1		
Total	26	Total	26
Nil (off treatment)	4	Nil (off treatment)	2
Mean value for those on treatment	80 mg.	Mean value for those on treatment	4·5 g.

* Including 1 at 105 mg. † Including 1 at 80 mg.

In the second year of the trial it is intended that treatment shall be continuous—unless the patient is in remission or is held to require no maintenance dose.

Summary

Sixty-one patients in the early stages of rheumatoid arthritis, and regarded as suitable for treatment with either cortisone or aspirin, have been allocated at random to treatment with one or other agent (cortisone 30 cases, aspirin 31 cases). Two comparable groups of these early cases were thus constructed and have now been treated and observed for one year. For most of the year treatment was "individualized" by the physician in charge of the patient at a level sufficient to restore maximal functional efficiency without producing serious side-effects.

Observations made one week, eight weeks, thirteen weeks, and approximately one year after the start of treatment reveal that the two groups have run a closely parallel course in nearly all the recorded characteristics —namely, joint tenderness, range of movement in the wrist, strength of grip, tests of dexterity of hand and foot, and clinical judgments of the activity of the disease and of the patient's functional capacity. The haemoglobin level and blood sedimentation rate were slightly more favourably influenced by cortisone, but in no other respect do the two groups differ materially.

On each form of treatment the disease was judged at the end of one year to be inactive, or only slightly active, in about three-quarters of the patients, and on each treatment some two-fifths of the patients were regarded as capable of normal work and activity. For practical purposes, therefore, there appears to have been surprisingly little to choose between cortisone and aspirin in the management of these 61 patients in the early stages of rheumatoid arthritis.

REFERENCES

Ball, J. (1950). *Lancet*, **2**, 520.
—— (1952). *Ann. rheum. Dis.*, **11**, 97.
Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O. (1948). *Proc. Soc. exp. Biol., N.Y.*, **68**, 1.
Scott, F. E. T. (1952). *Lancet*, **1**, 392.