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A COMPARISON OF PREDNISOLONE WITH ASPIRIN OR OTHER ANALGESICS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

REPORT BY THE JOINT COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND NUFFIELD FOUNDATION ON CLINICAL TRIALS OF CORTISONE, ACTH, AND OTHER THERAPEUTIC MEASURES IN CHRONIC RHEUMATIC DISEASES*

The results of previous trials conducted by the Joint Committee (1954, 1955, 1957a) showed that there was little to choose between cortisone and aspirin in the long-term management of patients with rheumatoid arthritis, and a similar result was obtained in a trial conducted by the Empire Rheumatism Council (1955, 1957). Since the time of these trials many analogues of cortisone have been introduced, and, of these, prednisone and prednisolone appeared to be particularly suitable for the treatment of rheumatic diseases. Further trials were therefore initiated by the Joint Committee in 1955. In the first of these prednisone was compared with cortisone in the long-term treatment of rheumatoid arthritis. The results of this trial, which have already been published (1957b), showed that for this purpose prednisone was better than cortisone. The present report concerns another trial in which prednisolone was compared with aspirin or other analgesics in the treatment of patients with rheumatoid arthritis.

Methods and Material

Diagnostic Criteria

The criteria for entry into the trial were similar to those used previously, and patients of either sex between the ages of 17 and 59 years were admitted if they had a rheumatoid type of arthritis of from 3 to 24 months' duration affecting more than three joints with bilateral involvement of hands or feet, ankles or wrists. A sheep cell agglutination test was done on all patients entering the trial, but the results of this test were not included in the criteria for entry.

Treatment

The general management of the patients in terms of rest, splintage, exercise, and physiotherapy was to be that used currently in each participating centre. Within each centre one group of patients received prednisolone in an initial dosage of 20 mg. daily, to be adjusted subsequently on an individual basis to give the maximum therapeutic response obtainable without serious side-effects. To a second group aspirin or other analgesics were given; most patients in this group received aspirin in an initial daily dose of 6·0 g. though seven of the 39 patients received phenylbutazone instead with an initial daily dose of 400 mg. For allocation to one or other group, randomized treatment orders, stratified for sex and for disease duration of under or over 9 months, were prepared for each of the eight participating centres separately.

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PARTICIPATING PHYSICIANS: Prof. E. G. L. Bywaters (Postgraduate Medical School of London), Dr. W. S. C. Copeman (West London Hospital Medical School), Dr. J. J. R. Duthie (Rheumatic Unit, Northern General Hospital, Edinburgh), Dr. A. G. S. Hill (Oxford Regional Rheumatic Diseases Research Centre), Prof. J. H. Kellgren (Rheumatism Research Centre, Manchester), Dr. G. D. Kersley (Royal National Hospital for Rheumatic Diseases, Bath), Dr. R. M. Mason (Dept. of Physical Medicine and Regional Rheumatism Centre, London Hospital); Dr. H. F. West (Sheffield Centre for the Investigation and Treatment of Rheumatic Diseases).

STATISTICAL ANALYSIS: Dr. W. J. Martin (Medical Research Council Statistical Research Unit, London School of Hygiene and Tropical Medicine).

Assessments

Clinical evaluation and simple laboratory tests such as the erythrocyte sedimentation rate, haemoglobin, and white cell counts were made on entry, and after 4, 8, 12 and 24 weeks and 1, 1½, and 2 years of therapy. Sheep cell agglutination tests were done on entry and after ½, 1, 1½, and 2 years of therapy. *X* rays of the hands and feet were taken on entry and after 1 and 2 years.

The clinical assessment, which was similar to that used in previous trials, included the physician's opinion about the following four characteristics:

(1) Degree of disease activity in four grades.
(2) Patient's general functional capacity in five grades varying from normality (1) to complete crippling (5).
(3) Joint pain and tenderness in four grades.
(4) Joint swelling in four grades.

The strength of grip with each hand was recorded in mm. Hg.

Body weight and blood pressure were recorded.

Certain defined side-effects of therapy, such as dyspepsia, moon face, hirsuties, tinnitus, deafness, changes of mood, etc., were recorded as absent or present, and details of other complications and intercurrent illnesses were also asked for.

Radiographs of the spine and a barium meal were included in the 2-year assessment.

Number of Patients

84 patients entered the trial. Their distribution by sex, disease duration, and treatment group is shown in Table I. One patient died early in the second year, four were lost to follow-up, and two have been excluded from the final analysis, so that the results of 2 years' therapy are compared in 77 patients, of whom 41 were originally allocated to prednisolone and 36 to analgesics.

Deaths and Withdrawals.—Two patients died during the trial. The first died at the time of the 2-year assessment and has therefore been included in the analysis of the clinical and laboratory data. She was a female aged 44 years with a disease duration of 4 months on entry. She was treated with 400 mg. phenylbutazone and 4 g. aspirin during the first year and by aspirin alone during the second year. During the second year she developed pneumonia for which she was admitted to another hospital where she later developed heart failure associated with mitral stenosis and bronchiectasis and she died from this at the end of the second year. The other death was that of a male aged 53 with a disease duration of 8 months on entry. He was treated with aspirin throughout, did badly, and died of heart failure at another hospital at the beginning of the second year. This patient has been excluded from the analysis.

Two female patients, one on prednisolone and one on aspirin, developed complete remission of the arthritis during the early weeks of the trial and could not be traced at follow-up. Neither showed any serological or radiological abnormalities and they may well have had some more benign form of polyarthritis.

Two further patients were lost to follow-up. One was a male of 59 years treated with prednisolone who developed recurrent pericolic abscesses from diverticulitis during the second year. Because of this he was transferred to another hospital where prednisolone was discontinued. The other was a male aged 39 who was treated with phenylbutazone and aspirin. He defaulted at the end of the first year and could not be traced.

The two patients who were followed for 2 years but have been excluded from the analysis were both females allotted to prednisolone, aged 53 and 19 respectively. The first developed an acute psychosis during the first week of therapy and was subsequently treated with aspirin for 2 years and did well. The second developed typical dermatomyositis a few weeks after entry. The sheep cell agglutination test remained negative throughout and the 2-year *x* rays

TABLE I

DISTRIBUTION OF PATIENTS BY SEX AND DURATION OF DISEASE AT ENTRY INTO THE TRIAL
(Figures in brackets represent patients not included in the analysis at 2 years)

Duration of Disease (mths)	Treatment Group	Sex			Total Entered
		Male	Female	Total	
3–8	Analgesics	5 (1)	10 (1)	15 (2)	17
	Prednisolone	8 (1)	7 (3)	15 (4)	19
9–24	Analgesics	10 (1)	11	21 (1)	22
	Prednisolone	9	17	26	26
Total	Analgesics	15 (2)	21 (1)	36 (3)	39
	Prednisolone	17 (1)	24 (3)	41 (4)	45

showed calcification in the soft tissues but no articular erosion. These findings suggest that the original diagnosis may have been incorrect.

Changes of Treatment and Dosage

The mean daily dosage of prednisolone given during the 2 years is shown in Table II. There is a steady fall from 17·4 mg. at Week 4 to 10·0 mg. at 2 years, and only 35 of the 41 patients seen at that time were still receiving prednisolone. Three were taking aspirin instead of prednisolone, one was on corticotrophin instead of prednisolone, and two were not taking any drugs. During the second year an increasing number of patients in this group also took aspirin in one form or another, so that by the end of the year seventeen patients were taking aspirin in addition to prednisolone.

Of the 36 patients who started on analgesics, five had changed to prednisolone and one to cortisone by the end of the second year. At this time twenty were still on aspirin only, seven on phenylbutazone mostly combined with aspirin, and three were taking no tablets of any kind. The dosage of analgesics was also gradually reduced during the 2 years of therapy, but since different preparations were used no mean dosages are shown.

Since most of these changes in therapy only occurred towards the end of the second year they have been disregarded in the Tables of results which show the patients in the treatment groups to which they were originally allocated.

The reason for changing from analgesics to prednisolone was usually inadequate symptomatic control, whereas the abandonment of prednisolone therapy or its partial substitution by aspirin was usually due to complications and side-effects; these will be described in detail later.

TABLE II
DAILY DOSAGE OF PREDNISOLONE

Time of Assessment	Mean Dosage (mg.)	Standard Deviation	Number of Patients
Week 4	17·4	3·74	41
Week 8	16·1	3·92	38
Week 12	15·0	4·04	39
Week 24	13·6	5·03	39
Week 52	12·0	3·48	38
Year 1½	11·2	3·38	36
Year 2	10·0	3·54	35

Results

The general condition of the patients in the two treatment groups as judged by the physician's opinion about disease activity, functional capacity, joint pain or tenderness, and joint swelling are set out in Tables III to VI, in which the results at the various assessment times up to 2 years of treatment are shown. It will be seen that in all these characteristics the two treatment groups were reasonably comparable at the start, though the prednisolone group contained a few more of the severely ill patients. The patients in this group showed, however, a greater early improvement on the average than those in the analgesics group, and this advantage to prednisolone persisted and was still

TABLE III
NUMBER OF PATIENTS WITH GIVEN GRADES* OF DISEASE ACTIVITY

Time of Assessment	Treatment Group	Grade				Died	Total
		0	1	2	3		
Week 0	Analgesics	—	13	21	2	—	36
	Prednisolone	—	9	27	5	—	41
Week 4	Analgesics	1	22	11	2	—	36
	Prednisolone	9	29	3	—	—	41
Week 8	Analgesics	2	17	15	1	—	35
	Prednisolone	14	24	3	—	—	41
Week 12	Analgesics	3	19	10	2	—	34
	Prednisolone	16	21	4	—	—	41
Week 24	Analgesics	4	22	8	1	—	35
	Prednisolone	10	22	8	1	—	41
Week 52	Analgesics	4	18	11	1	—	34
	Prednisolone	10	25	5	—	—	40
Year 1½	Analgesics	3	18	12	1	—	34
	Prednisolone	6	27	8	—	—	41
Year 2	Analgesics	4	22	9	—	1	36
	Prednisolone	5	30	6	—	—	41

* *Grade:* 0 = None 1 = Slight 2 = Moderate 3 = Severe

TABLE IV

NUMBER OF PATIENTS WITH GIVEN GRADES* OF FUNCTIONAL CAPACITY

Time of Assessment	Treatment Group	Grade					Died	Total
		1	2	3	4	5		
Week 0	Analgesics	—	8	24	3	1	—	36
	Prednisolone	—	11	16	9	5	—	41
Week 4	Analgesics	1	21	13	—	1	—	36
	Prednisolone	8	22	8	2	1	—	41
Week 8	Analgesics	3	17	14	—	1	—	35
	Prednisolone	16	20	3	1	1	—	41
Week 12	Analgesics	4	18	11	1	—	—	34
	Prednisolone	20	16	3	1	1	—	41
Week 24	Analgesics	5	23	5	2	—	—	35
	Prednisolone	19	16	3	1	2	—	41
Week 52	Analgesics	10	18	6	—	—	—	34
	Prednisolone	22	14	3	—	1	—	40
Year 1½	Analgesics	6	21	6	1	—	—	34
	Prednisolone	17	22	2	—	—	—	41
Year 2	Analgesics	9	18	7	—	1	1	36
	Prednisolone	19	18	3	1	—	—	41

* *Grade:* 1 = Fully employed or employable in normal work and able to undertake normal physical recreation.
2 = Fully employed in special work after vocational training, or doing light or part-time work in normal occupation. Limitation in amount of physical recreation. Housewives, all except the heaviest housework. In-patients, in hospital for investigation only.
3 = Not employed or employable. Very limited physical activity and little or no capacity for physical recreation. Housewives, light housework and/or limited shopping only. In-patients in hospital for treatment but up and about in ward.
4 = Confined to hospital, house, or wheelchair, but able to look after themselves in the essentials of life. In-patients in hospital for treatment sitting up but not getting about.
5 = Confined to bed and unable to look after themselves. In-patients on complete rest in bed.

TABLE V

NUMBER OF PATIENTS WITH GIVEN GRADES* OF JOINT PAIN OR TENDERNESS

Time of Assessment	Treatment Group	Grade				Died	Total
		0	1	2	3		
Week 0	Analgesics	—	11	21	4	—	36
	Prednisolone	—	13	19	9	—	41
Week 4	Analgesics	3	17	15	1	—	36
	Prednisolone	19	18	3	1	—	41
Week 8	Analgesics	4	16	13	2	—	35
	Prednisolone	20	17	4	—	—	41
Week 12	Analgesics	5	19	7	3	—	34
	Prednisolone	20	18	3	—	—	41
Week 24	Analgesics	3	23	7	2	—	35
	Prednisolone	12	21	7	1	—	41
Week 52	Analgesics	4	22	5	3	—	34
	Prednisolone	12	21	7	—	—	40
Year 1½	Analgesics	2	19	12	1	—	34
	Prednisolone	12	19	9	—	—	40
Year 2	Analgesics	3	23	8	1	1	36
	Prednisolone	9	22	10	—	—	41

* *Grade:* 0 = None 1 = Slight 2 = Moderate 3 = Severe

present though less marked by the end of the second year.

The changes in strength of grip and in the results of laboratory tests such as the erythrocyte sedimentation rate, haemoglobin, and white cell count are set out in Table VII (opposite), which also includes body weight. The mean value for each characteristoc at each assessment time is given.

The patients receiving prednisolone showed a large improvement in strength of grip at Week 4

TABLE VI

NUMBER OF PATIENTS WITH GIVEN GRADES* OF JOINT SWELLING

Time of Assessment	Treatment Group	Grade				Died	Total
		0	1	2	3		
Week 0	Analgesics	1	14	20	1	—	36
	Prednisolone	1	20	18	2	—	41
Week 4	Analgesics	2	25	8	1	—	36
	Prednisolone	19	19	3	—	—	41
Week 8	Analgesics	5	18	11	1	—	35
	Prednisolone	19	20	2	—	—	41
Week 12	Analgesics	6	19	9	—	—	34
	Prednisolone	17	22	2	—	—	41
Week 24	Analgesics	6	21	8	—	—	35
	Prednisolone	11	23	6	1	—	41
Week 52	Analgesics	5	19	10	—	—	34
	Prednisolone	12	20	8	—	—	40
Year 1½	Analgesics	2	23	9	—	—	34
	Prednisolone	12	20	8	—	—	40
Year	Analgesics	5	18	12	—	1	36
	Prednisolone	16	18	7	—	—	41

* *Grade:* 0 = None 1 = Slight 2 = Moderate 3 = Severe

TABLE VII

AVERAGE MEASUREMENTS OF VARIOUS CHARACTERISTICS

Time of Assessment	Treatment Group	Strength of Grip (mm. Hg)		Erythrocyte Sedimentation Rate (mm./hr)	Hb (g. per cent.)	White Cell Count	Weight (lb.)
		Left	Right				
Week 0	Analgesics	133	131	36	13·1	8,900	136
	Prednisolone	119	110	41	12·7	8,300	141
Week 4	Analgesics	152	155	32	12·9	8,100	137
	Prednisolone	209	217	14	14·1	11,200	142
Week 8	Analgesics	152	163	34	13·1	8,000	138
	Prednisolone	222	222	14	14·6	10,600	146
Week 12	Analgesics	151	160	27	13·2	8,100	138
	Prednisolone	225	226	18	14·4	10,600	149
Week 24	Analgesics	159	175	23	13·8	7,200	136
	Prednisolone	206	210	21	14·3	9,800	150
Week 52	Analgesics	154	166	31	13·1	8,000	137
	Prednisolone	203	210	22	13·8	11,000	150
Year 1½	Analgesics	144	157	32	12·8	7,500	136
	Prednisolone	206	206	22	13·6	9,000	149
Year 2	Analgesics	152	163	29	13·2	8,500	138
	Prednisolone	195	199	25	13·7	9,500	146

and a further small improvement at Week 8; by 6 months a slight decrease commenced and the values at the end of the second year, though much above the starting point, were slightly below those of Week 4. In the analgesics group there was only a slight improvement throughout the 2 years. At 2 years the improvement in the prednisolone group was still significant ($p < 0{\cdot}001$), but that in the analgesics group was not.

The erythrocyte sedimentation rate showed similar changes, the prednisolone group recording a marked fall at Week 4 followed by a gradual rise and the improvement at 2 years being still significant ($p < 0{\cdot}01$). The analgesics group showed no significant improvement.

The haemoglobin values showed a similar early rise and later slight decline in the prednisolone group with a significant remaining improvement at 2 years ($p < 0{\cdot}01$), but no such improvement occurred in the analgesics group.

The total white cell count rose at Week 4 in the patients receiving prednisolone and then declined,

but the 2-year figure was not significantly higher than that recorded initially in either group.

Thus, in the prednisolone group, all these characteristics showed marked early improvement which later became less but, with the exception of the white cell count, this improvement was still significant at 2 years, whereas there was no significant improvement in the analgesics group.

Body weight rose steadily in the prednisolone group during the first 6 months of therapy and during the second 6 months the patients in the prednisolone group were on average 13-14 lb. heavier than the patients in the analgesics group who had shown no change in body weight. During the second year the patients in the prednisolone group lost weight, so that after 2 years' treatment their average weight was only 8 lb. greater than that of the patients in the analgesics group.

X-Ray Changes

The *x* rays of the hands and feet were all read at one time by a single observer (J. H. Kellgren) who was unaware of the treatment given, and the overall gradings for rheumatoid change, which include articular erosion, subluxations, and osteoporosis, are shown in Table VIII which gives the rheumatoid gradings of the initial, one-year, and two-year films. Initially the two groups were similar, but the patients treated by analgesics showed a steady increase in the more marked changes. Thus the number of films in this group showing only doubtful changes or none declined from eighteen to five for the hands and from sixteen to seven for the feet, whereas the number of films showing moderate or severe changes increased from six to seventeen for the hands and from nine to eighteen for the feet. In the prednisolone group the increase in severity was much less; the number of films showing only doubtful changes or none declined from 23 to seventeen for the hands and from seventeen to fifteen for the feet, and the number showing moderate or severe changes increased from five to eight for the hands and from ten to twelve for the feet. The significance values in the analgesics group for the differences between the rheumatoid gradings of the initial and the 2-year films of the hands and feet are $p < 0{\cdot}001$ and $p < 0{\cdot}02$ respectively, whereas in the prednisolone group the differences, though in the same direction, are not formally significant. In addition to these gradings of severity the degree of improvement or deterioration was also recorded, since minor degrees of improvement or deterioration, though definite enough to record with confidence, may not always be sufficient to alter the overall grading for severity, and useful minor differences may thus be missed. The numbers of films showing improvement, deterioration, or no change in the two treatment groups are shown in Table IX (opposite). The differences in distribution between the two treatment groups at 2 years has a significance of $p < 0{\cdot}03$ for the hand films and $p < 0{\cdot}0001$ for the foot films.

Improvement in the radiological appearances, such as healing of erosions and increase of bone density, was observed in a few films in both treatment groups. Thus, at the end of 2 years, three of 35 hand films and four of 34 foot films from the analgesics group, and four of 41 hand films and seven of 41 foot films from the prednisolone group showed improvement when compared with the films taken on entry into the trial, but the main difference

TABLE VIII

GRADINGS BY OBSERVER I OF RADIOLOGICAL CHANGES OF RHEUMATOID ARTHRITIS IN FILMS OF HANDS AND FEET

Films	Time of Assessment	Treatment Group	Grade					
			0	1	2	3	4	Total
Hands	Initial	Analgesics	13	5	11	5	1	35*
		Prednisolone	15	8	13	4	1	41
	Year 1	Analgesics	7	3	15	7	3	35
		Prednisolone	13	6	16	4	2	41
	Year 2	Analgesics	4	1	13	11	6	35
		Prednisolone	9	8	16	4	4	41
Feet	Initial	Analgesics	10	6	9	8	1	34
		Prednisolone	10	7	14	9	1	41
	Year 1	Analgesics	7	4	13	9	2	35
		Prednisolone	10	6	12	13	0	41
	Year 2	Analgesics	5	2	10	14	4	35
		Prednisolone	11	4	14	9	3	41

Grade: 0 = None 1 = Doubtful 2 = Slight 3 = Moderate 4 = Severe

* The patient who died at the end of the second year is not included in this Table or in Tables IX, X, and XV.

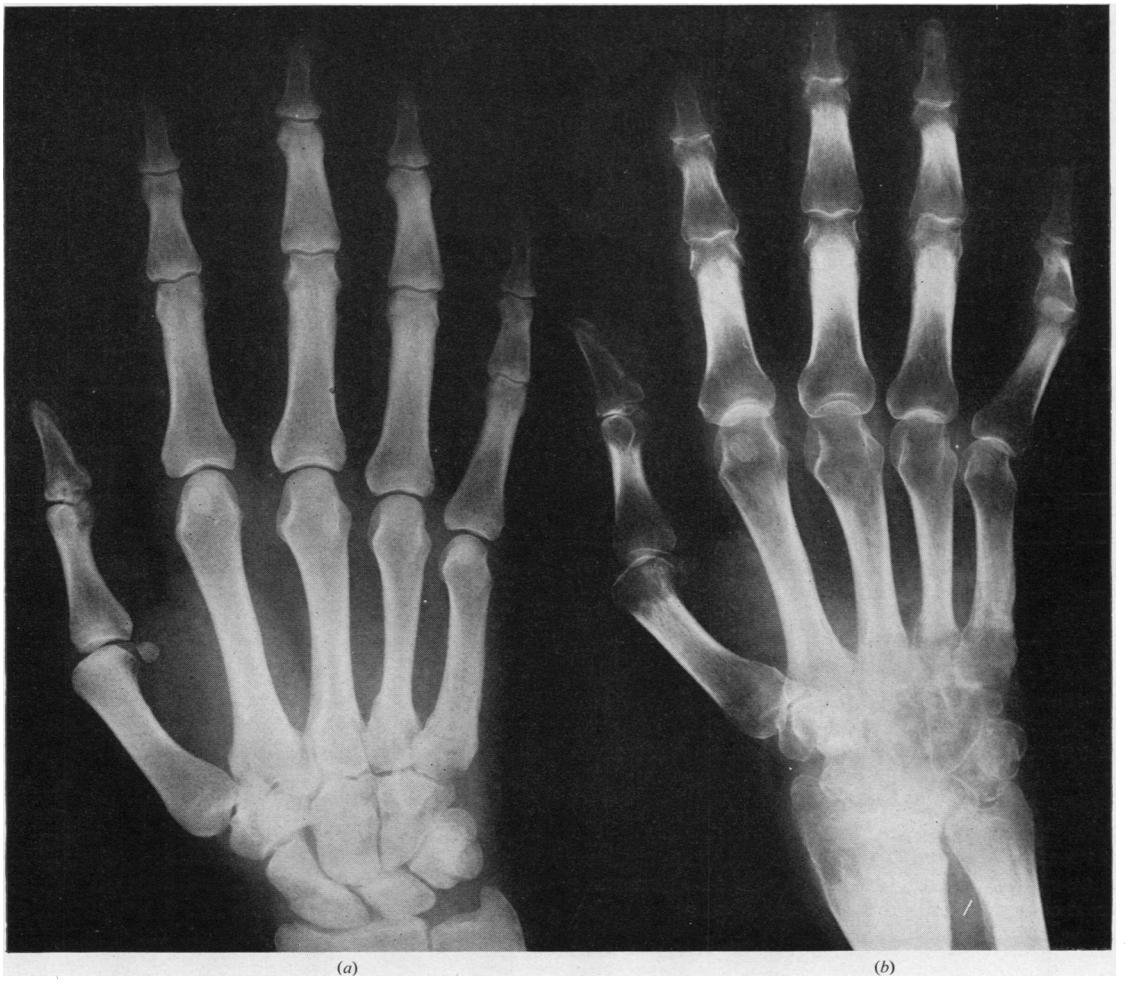
TABLE IX

CHANGES OF *X*-RAY APPEARANCES IN COMPARISON WITH INITIAL FILMS RECORDED BY OBSERVER I

Films	Time of Assessment	Treatment Group	Changes in *X*-ray Appearances			
			Deterioration	No Change	Improvement	Total
Hands	Year 1	Analgesics	17	17	1	35
		Prednisolone	7	30	4	41
	Year 2	Analgesics	26	6	3	35
		Prednisolone	17	20	4	41
Feet	Year 1	Analgesics	15	15	4	34
		Prednisolone	5	26	10	41
	Year 2	Analgesics	24	6	4	34
		Prednisolone	4	30	7	41

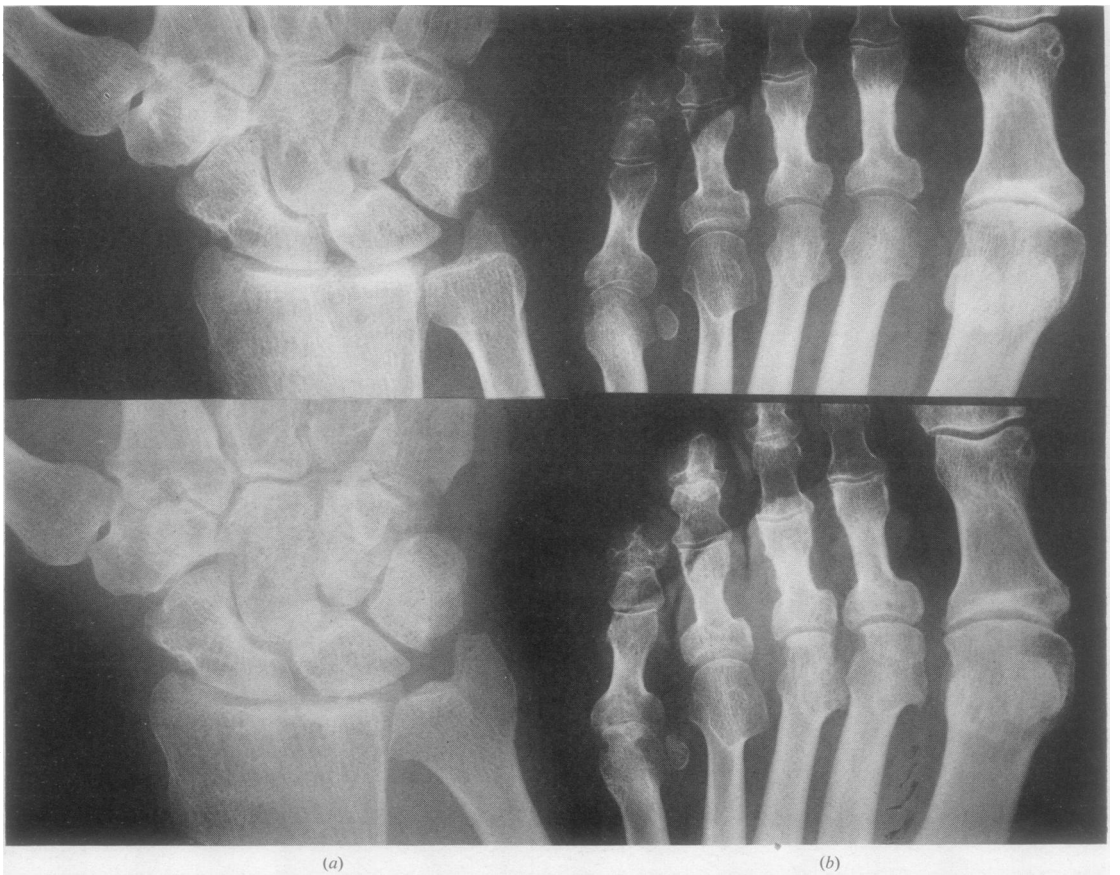
is the lack of radiological deterioration in the prednisolone group, especially in the feet.

Examples of the type of improvement or deterioration noted are shown in Figs 1 to 3; deterioration



(*a*) (*b*)

Fig. 1.—*X* ray of right hand (*a*) at the start and (*b*) after 2 years of treatment, illustrating the greatest degree of deterioration observed in the trial (Grade 0 to 4). This patient was treated with prednisolone initially, and with corticotrophin during the second year.



(a) (b)

Fig. 2.—The greatest degree of improvement observed in the trial (*a*) in the wrists (Grade 2 to 1) and (*b*) in the feet (Grade 3 to 2).The initial film is above, the 2-year film below. The hands and feet are from two separate patients, both of whom were treated with prednisolone throughout the 2 years.

was sometimes pronounced, whereas improvement with actual healing of erosions and recovery of osteoporosis was less striking.

The initial and first year films were also read in a similar way by three other observers (J. J. R. Duthie, H. F. West, and R. M. Mason). Though the criteria for grading varied widely between one observer and another, all noted the same order of difference between the patients treated with analgesics and those receiving prednisolone.

The radiological findings thus reveal a definite advantage to prednisolone, in that during the 2 years of the trial patients receiving prednisolone showed significantly less increase in destructive joint changes than did those treated with analgesics.

Results of Sheep Cell Agglutination Tests

In making the sheep cell agglutination tests somewhat different techniques were used by the participating centres. Details of the methods used are given in the Appendix. Because of these differences in technique, direct comparison of agglutinating titres between one centre and another cannot be made. However, the minimal positive titre used by each centre has been taken as zero and dilutions above and below this have been scored as +1, +2, etc., and −1, −2, etc. The results so obtained are set out in Table X (opposite), to permit some comparison of the two treatment groups. This method of comparing the treatment groups seems justified, since approximately equal numbers of patients in each group were tested by each of the different methods, and it is the changes in agglutinating titre during the course of the trial that are the main interest. At the start of the trial the two treatment groups were similar, although there were somewhat fewer patients with high agglutinating titres in the prednisolone group. The distribution

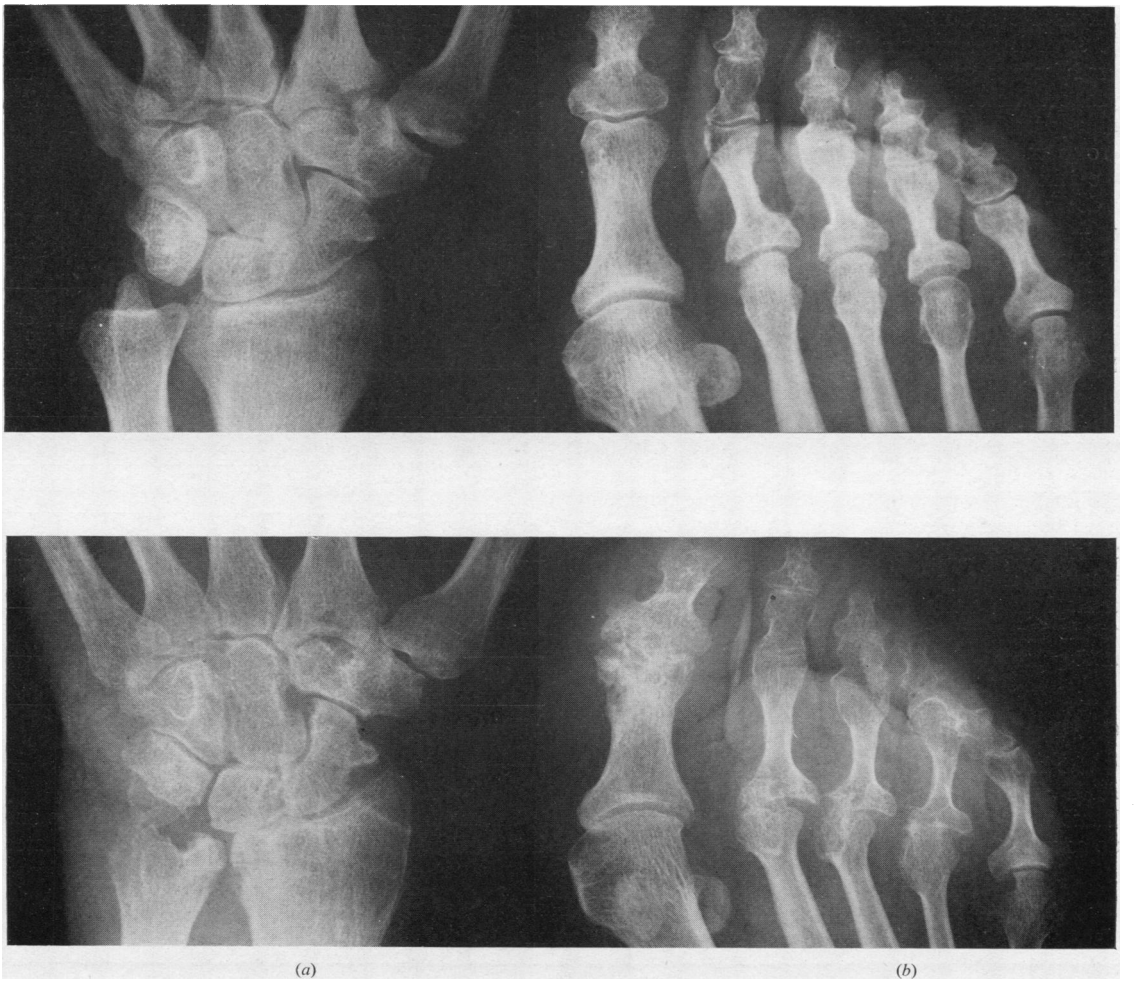


Fig. 3.—Typical examples of moderate deterioration (*a*) in the hands (Grade 1 to 3) and (*b*) in the feet (Grade 3 to 4). The initial film is above, the 2-year film below. Both hands and feet are from the same patient, who was treated with aspirin throughout.

TABLE X

RESULTS OF SHEEP-CELL AGGLUTINATION TESTS*

Time of Assessment	Treatment Group	Results of Sheep Cell Agglutination Tests							Total Negative and Positive
		Negative			Positive				
		−5 to −3	−2 to −1	Total	0 to +1	+2 to +3	+4 to +7	Total	
Initial	Analgesics	6	6	12	8	10	5	23	35
	Prednisolone	5	8	13	14	11	3	28	41
Year 1	Analgesics	11	4	15	7	8	5	20	35
	Prednisolone	9	7	16	6	12	7	25	41
Year 2	Analgesics	5	9	14	9	7	5	21	35
	Prednisolone	6	6	12	5	12	12	29	41

* Based on minimal positive titre = 0, with deviations above and below in numbers of tubes showing agglutination.

of positive and negative tests was almost identical: 23 to 12 in the analgesics group and 28 to 13 in the prednisolone group. After 2 years of therapy the proportions of positive and negative tests had only changed slightly, being 21 to 14 in the analgesics group and 29 to 12 in the prednisolone group. On the other hand, in the prednisolone group, there was a decline in the number of patients giving borderline positive tests from fourteen to five and an increase in those with high agglutinating titres from three to twelve. This change in the distribution of titres within the group of patients with positive tests treated with prednisolone is significant ($p < 0{\cdot}003$). No such systematic change occurred in the sera of patients in the analgesics group in which the distribution of titres amongst those giving positive tests at the end of 2 years was similar to that recorded initially ($p \sim 0{\cdot}4$).

Thus, in the present trial, the agglutinating titres have behaved differently from all the other characteristics recorded: The patients treated with prednisolone show greater improvement in both the clinical and radiological signs of arthritis while at the same time showing a general rise in agglutinating titres amongst those with positive tests.

Complications and Side-Effects

The incidence of the defined side-effects of therapy listed on the record form is shown in Table XI. These were mainly of a minor character and require no comment.

The changes in blood pressure are shown in Table XII. There was a greater tendency for the blood pressure to rise in the prednisolone group, but hypertension did not become a therapeutic problem in any patient during the period of the trial.

TABLE XII

BLOOD PRESSURE

Time of Assessment	Treatment Group	Number of Patients with	
		Systolic Recordings of 160 mm. and over	Diastolic Recordings of 90 mm. and over
Week 0 ..	Analgesics	6	6
	Prednisolone	7	12
Week 4 ..	Analgesics	4	8
	Prednisolone	5	14
Week 8 ..	Analgesics	4	6
	Prednisolone	6	16
Week 12 ..	Analgesics	4	8
	Prednisolone	8	17
Week 24 ..	Analgesics	5	6
	Prednisolone	8	17
Week 52 ..	Analgesics	4	8
	Prednisolone	9	19
Year 1½ ..	Analgesics	5	10
	Prednisolone	12	19
Year 2 ..	Analgesics	6	14
	Prednisolone	12	23

There were a number of major complications and intercurrent illnesses which may have been related

TABLE XI

NUMBER OF PATIENTS WITH GIVEN SIDE-EFFECTS

Time of Assessment	Treatment Group	Side-Effects							
		Tinnitus or Deafness	Dyspepsia	Moonface	Acne	Hirsuties	Oedema	Euphoria	Depression
Week 0	Analgesics	1	2	—	—	1	1	—	5
	Prednisolone	2	3	—	—	—	2	1	4
Week 4	Analgesics	11	12	—	1	2	1	—	5
	Prednisolone	2	4	7	1	—	—	2	—
Week 8	Analgesics	7	9	—	1	—	2	—	3
	Prednisolone	1	2	20	2	—	2	1	1
Week 12	Analgesics	8	5	—	2	—	1	1	2
	Prednisolone	1	10	20	2	1	1	1	—
Week 24	Analgesics	9	7	—	1	1	1	—	—
	Prednisolone	1	9	27	4	2	—	1	1
Week 52	Analgesics	8	7	—	—	1	3	—	—
	Prednisolone	2	6	24	2	4	1	1	—
Year 1½	Analgesics	4	6	1*	—	—	5	—	1
	Prednisolone	—	9	22	1	3	4	2	3
Year 2	Analgesics	1	7	4*	—	1	2	—	—
	Prednisolone	2	8	14	3	2	2	3	2

* These patients changed to cortisone or prednisolone during the trial.

to therapy. The major complications summarized in Table XIII will now be considered in detail.

TABLE XIII

MAJOR COMPLICATIONS AND INTERCURRENT ILLNESSES

Disease	Treatment Group	
	Analgesics	Prednisolone
Psychosis	0	2
Clinical Presentation of Peptic Ulcer during Trial	0	3
Major Intercurrent Infections	3	4
Ecchymosis	1	3
Miscarriage	0	1
Amenorrhoea	0	1
Glycosuria	0	1
Cardiac Infarct	0	1
Insomnia	0	1
Thrombophlebitis	1	1
Herpes Zoster	1	1
Leg Ulcer	1	0
Arteropathy	1	0
Severe Diarrhoea	1	0

Two patients developed a psychosis while on prednisolone therapy. One was a female aged 53 years, who was given 20 mg. prednisolone daily. She developed an acute psychosis on the fourth day of therapy, but recovered rapidly when the treatment was changed to aspirin. This patient was followed for 2 years and did well, but was not included in the analysis. The other was a male aged 59 years who was given 20 mg. prednisolone for 3 months and then developed attacks of panic. The dosage was reduced to 5-10 mg., but he became more disturbed, and by the time of the 2-year assessment he was in a mental hospital as a voluntary patient. No patient receiving analgesics developed psychosis.

Two patients on prednisolone developed bleeding peptic ulcers. One male, aged 39, given 20 mg. prednisolone for over 6 months, developed dyspepsia for the first time and after a few weeks had a severe uncontrollable melaena for which emergency gastrectomy was done at another hospital, where the prednisolone was stopped. Following this, he became extremely ill with febrile rheumatoid disease which could only be controlled by corticotrophin therapy in high dosage. He had a second continuing melaena from a stomal erosion which had to be undersewn. He also had staphylococcal septicaemia and multiple pyarthrosis, but finally recovered enough to leave hospital. The other patient with melaena was a male aged 55 who was given 20-25 mg. prednisolone daily for 6 months when he developed an ulcer type dyspepsia for the first time. A barium meal at that time was normal and the prednisolone dose was reduced to 17·6 mg. supplemented by 4 g. aspirin, but 2 months later he had a melaena and a barium meal showed duodenal ulcer. Prednisolone was gradually withdrawn and aspirin therapy continued, but dyspepsia persisted and the ulcer did not heal during the following 6 months, and after a second melaena a gastrectomy was performed. He was subsequently treated successfully with enteric-coated salicylate. No patient in the analgesics group had an overt gastro-intestinal haemorrhage, though it must be noted that one of the episodes of melaena reported above occurred at a time when the patient was on aspirin only. Another male patient, who received prednisolone in a dosage of 20 mg. daily during the first year, developed ulcer type dyspepsia for the first time during the second year of therapy while receiving 15 mg. prednisolone daily. A barium meal revealed a large gastric ulcer.

Major episodes of infection were reported in seven patients, four in the prednisolone group and three in the analgesics group. Those on prednisolone included the case of staphylococcal septicaemia and the case of peritonitis and pericolic abscesses already described plus one case of cholecystitis and one episode of pleurisy. The infections in the analgesics group included the patient with pneumonia who later died of heart failure and bronchiectasis who has already been described, plus one case of pleural effusion followed by spontaneous pneumothorax and empyema, and an episode of pneumonia in a patient with chronic bronchitis. Thus severe infection appears to have occurred with similar frequency in both treatment groups.

The following were reported once only in patients receiving prednisolone: miscarriage, amenorrhoea, cardiac infarct, glycosuria, thrombophlebitis, herpes zoster, and insomnia. Three patients were reported to have ecchymosis. Amongst the patients receiving analgesics there were also single reports of thrombophlebitis with arteropathy, varicose ulceration, severe diarrhoea, herpes zoster, and ecchymosis.

The main difference as regards complications appeared to be the cases of psychosis and gastro-intestinal bleeding occurring in the prednisolone group, but the numbers are far too small for statistical significance.

Since peptic ulceration and osteoporosis have been regarded as major side-effects of prednisolone therapy, a routine barium meal and spinal x rays were included in the 2-year assessment. The results are summarized in Tables XIV and XV (overleaf).

The withdrawals are the two patients excluded from the trial because of early changes of treatment and incorrect diagnosis who both had barium meals at the 2-year assessment. The patient who had prednisolone for 3 days and aspirin for 2 years was reported as having appearances suggestive of

TABLE XIV

EVIDENCE OF PEPTIC ULCERATION AT 2-YEAR ASSESSMENT

Treatment Group	Barium Meals	Evidence of Ulceration				Other	Normal
		Gastrectomy	Duodenal	Gastric	Total		
Analgesics	34	1*	0	0	1	1	32
Prednisolone	40	2	2	2	6	2	32
Withdrawals	2	0	1	0	1	0	1
Total	76	3	3	2	8	3	65

* This gastrectomy was done before entry into the trial.

TABLE XV

SPINAL *X*-RAY CHANGES AFTER 2 YEARS' TREATMENT

Characteristic	Treatment Group	Grade				
		0	1	2	3	Total
Osteoporosis	Analgesics	16	10	1	1	28
	Prednisolone	13	6	13	—	32
Expansion of Disks	Analgesics	23	4	1	—	28
	Prednisolone	25	6	1	—	32
Collapsed or Crushed Vertebrae ..	Analgesics	21	6	—	1	28
	Prednisolone	26	4	2	—	32

Grade: 0 = None 1 = Doubtful 2 = Slight 3 = Moderate

One centre did not take lateral films.

duodenal ulceration, and the patient who had been treated with prednisolone throughout was reported as showing no abnormality in the barium meal.

The radiologists' reports given in the Appendix show that only two of the ulcers were regarded as definite active ulcers at the time of the examination, two duodenal ulcers were reported as healed, and one gastric ulcer was doubtful. Only one of the five patients with radiologically demonstrated ulcer was reported to have dyspepsia, though all the patients who had had gastrectomies had suffered from dyspepsia before their operations and one still had dyspepsia at the 2-year assessment. In contrast to this, there were fourteen additional patients reported to have dyspepsia at the 2-year follow-up in whom no radiological evidence of ulcer was reported.

The most striking feature of Table XIV is the absence of active peptic ulceration amongst the 34 patients in the analgesics group. This is not surprising since patients known to have peptic ulceration would not have been entered for the trial. The barium meal also revealed no abnormality in 32 of the forty patients in the prednisolone group, but some evidence of peptic ulceration was noted in six (15 per cent.). This may be compared with reported ulcer rates ranging from 31 per cent. (Kammerer, Freiberger, and Rivelis, 1958) to 5·3 per cent. (Henderson, 1955) in patients with rheumatic disease treated with corticosteroids.

Of the total 76 patients investigated at the end of 2 years' therapy, eight showed some evidence of past or present peptic ulceration. This figure corresponds closely to the 10 per cent. prevalence in the general population quoted by Kirsner, Kassriel, and Palmer (1956). Even if we bear in mind the facts that all the patients in the trial were under 60 years of age on entry and that only 32 of these were males, the prevalence of peptic ulceration still resembles that reported by Avery Jones (1957) for autopsy findings in coroners' cases.

On the other hand, serious clinical manifestations of peptic ulcer developed for the first time during the 2 years of the trial in three of the seventeen men in the prednisolone group, whereas Avery Jones reports an estimated incidence of 3·2 per 1,000 man years. Furthermore, the three men who developed ulcers during treatment had all received prednisolone in a daily dose of 20 mg. or more for over 3 months, a dosage substantially higher than that given to most patients in the trial. Indeed, this order of dosage was given to only eight patients and of these four had evidence of ulcer and a fifth developed psychosis so that the question of dosage may be crucial.

The films of the lumbar spine were read by Obser-

ver 1. The results are shown in Table XV. Lateral views of the spine were not taken at one centre so that only sixty films were available for study. All that can be said is that these films did not reveal any significant incidence of disk expansion or vertebral collapse in either treatment group. Although more films from the prednisolone group were recorded as showing slight degrees of osteoporosis, the difficulties of estimating osteoporosis in spinal films are great.

Discussion

In the treatment of rheumatoid arthritis short-term improvement can be obtained by giving corticosteroids in high dosage, but the toxic side-effects of steroid therapy increase with the duration of treatment so that when this is prolonged over years the acceptable dosage ceiling becomes severely restricted and the benefits of treatment are proportionately reduced. This emerged clearly from long-term trials in which cortisone did not prove to be superior to aspirin in the treatment of rheumatoid arthritis.

The introduction of more potent analogues with less effect on body electrolytes gave greater promise of success and in the controlled trials conducted by the Joint Committee prednisone has been shown to be superior to cortisone, and prednisolone superior to aspirin or other analgesics in the treatment of rheumatoid arthritis over a 2-year period.

The findings in the present trial are of special interest. The one- and two-year radiographs of the hands and feet more often revealed a distinct increase of erosive joint damage in the patients treated with analgesics than in the patients treated with prednisolone in whom there was much less progression of the joint disease. On the other hand, in the group treated with prednisolone there was in a number of patients a rise in the sheep cell agglutination titres during the two years of therapy, whereas in the patients treated with analgesics there was more often a fall in titre. This is an unexpected finding since, in a previous study (Kellgren, 1957), there was a positive correlation between high titres in the sheep cell agglutination test and the development of articular erosions. This association was much less apparent in the prednisolone-treated patients in this trial and this raises the interesting possibility that the process responsible for joint erosion may not be identical with that producing the rheumatoid serum factor and that prednisolone therapy may suppress the former while enhancing the latter.

In the treatment of rheumatoid arthritis with prednisolone as with all corticosteroids the question of dosage is crucial. After 2 years of therapy the mean dosage in this trial was 10 mg. daily, which is still above the maximum of 9 mg. for men and 5 mg. for menopausal women recommended by Slocumb, Polley, and Ward (1957). Of the eight patients in the trial who received 20 mg. prednisolone daily over 3 months, four had evidence of peptic ulceration and a fifth developed psychosis—a proportion of serious complications which is clearly unacceptable, and this high incidence of complications with high dosage accords with the experience of others (Howell and Ragan, 1956; Black, Yielding, and Bunim, 1957).

Conclusions

From the results of this trial it may be concluded that the administration of prednisolone instead of, or in addition to, analgesics, such as aspirin, to certain patients with rheumatoid arthritis for a period of 2 years will, on average, improve their functional capacity and general well-being and reduce the incidence of erosive joint damage; but more patients are likely to show a rise in sheep cell agglutinating titre, and the significance, if any, for the patients' future is not yet known.

If the daily dose of prednisolone approaches 20 mg., undesirable side-effects are likely to occur and the highest acceptable daily dose for long-term therapy is probably in the region of 10 mg.

Summary

(1) In a controlled therapeutic trial prednisolone has been compared with aspirin or other analgesics in the treatment of rheumatoid arthritis.

(2) Eight centres participated and 84 patients entered the trial. A few patients defaulted, died, or were withdrawn from the trial, so that the results after 2 years' treatment are based on the analysis of 77 patients, of whom 41 were originally allocated to prednisolone and 36 to analgesics.

(3) The patients treated with prednisolone showed an early significant improvement in both clinical and laboratory indices of inflammatory polyarthritis and this improvement, though less, was still present to a significant extent at the end of 2 years.

(4) In the group of patients treated with analgesics the frequency of radiological signs of erosive joint disease in the hands and feet increased significantly over the 2 years, whereas there was no significant change in the group treated with prednisolone.

(5) In many patients treated with prednisolone the agglutinating titre in the sheep cell test rose

during the 2 years of treatment, whereas such a rise occurred in only a few patients treated with analgesics.

(6) Two patients treated with analgesics died of heart failure. Five patients treated with prednisolone developed major complications (two cases of psychosis and three of peptic ulceration). These major complications all occurred in patients receiving a daily dose of 20 mg. or more of prednisolone. Patients receiving prednisolone also gained weight, and showed some rise in blood pressure and a tendency to mooning of the face. During the trial the mean daily dose of prednisolone was gradually reduced from 17·4 to 10·0 mg. and more than half the patients on prednisolone were also receiving aspirin or other analgesics. It is concluded that the optimal daily dose for long-term therapy in the average case of rheumatoid arthritis is not more than 10 mg.

The Committee are indebted to Boots Pure Drug Company and to Upjohn of England for the generous provision of initial supplies of prednisolone for this trial.

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APPENDIX

Serological Methods used for Estimating the Rheumatoid Serum Factor

The following centres used some form of sheep cell agglutination test:

London Hospital: Original Rose-Waaler method (Rose, Ragan, Pearce, and Lipman, 1948) during Year 1, and Ball's method (Ball, 1950) using 18-hour readings during Year 2.

Manchester Royal Infirmary and Edgar Allen Treatment Centre, Sheffield: Ball's method using 18-hour readings (Ball, 1950; Kellgren and Ball, 1959).

Northern General Hospital, Edinburgh: Modification of Ball's method using 18-hour readings in which haemagglutination plates are substituted for tubes (Duthie, Brown, Knox, and Thompson, 1957).

Postgraduate Medical School, London: Modification of original Rose-Waaler method as described by Scott (1952).

Stoke Mandeville Hospital, Aylesbury, Bucks.: Greenbury's method (Greenbury, 1957).

One centre used a human cell agglutination system:

Royal National Hospital for Rheumatic Diseases, Bath: Method described by Gibson and Ling (1956).

Radiologists' Reports on Barium Meals recording Abnormalities other than Gastrectomy

Patients on Analgesics

Male, aged 29 on Entry	"Generalized thickening of the gastric rugae with gastritis but no evidence of gastric or duodenal ulcer or neoplasm."

Patients on Prednisolone

Male, aged 51 on Entry	"No lesion found in the oesophagus. There is a very coarse gastric rugal pattern with a large gastric ulcer on the posterior wall towards the lesser curve. Whilst this may well be a simple ulcer a neoplasm cannot be excluded. No duodenal ulcer detected." *5 weeks later:* "Gastroscopy showed a shallow healing benign ulcer measuring ½ cm. in diameter on the posterior wall towards the lesser curve about 1½ in. from the pars angularis. There was no evidence of neoplasm, haemorrhage or abnormal mucus."
Female, aged 41 on Entry	"No abnormality seen in the oesophagus or stomach. Duodenum—the cap is deformed and there is an ulcer crater present. This was not tender."
Male, aged 52 on Entry	"Barium flowed normally down the oesophagus. No abnormality detected in his stomach. The duodenal cap was deformed. However, as the mucosa of the duodenal cap appears normal and there is no excess resting secretion, the probabilities are that these deformities are due to old and healed ulceration."

FEMALE, AGED 25 ON ENTRY	"There is a slight irregularity on the posterior wall between the fundus and body of the stomach. I cannot exclude a shallow ulcer there, but it is doubtful."
FEMALE, AGED 51 ON ENTRY	"The oesophagus is normal except that there is a tendency to dilation of the ampulla phrenica. No hiatal herniation. The stomach is of normal 'J' type and shows good tone and regular peristalsis. In the erect position there is a small projection on the lesser curve at about the site of insertion of the ligament of Treitz. I do not think this is an ulcer. The pylorus and duodenum appear normal."
MALE, AGED 44 ON ENTRY	"Negative apart from small short oesophagus-type hiatus hernia."

Withdrawals

FEMALE, AGED 52 ON ENTRY	"Oesophagus and stomach outlined normally. A small incisura was seen just above the left fornix of the duodenal cap which, though a duodenal ulcer was not seen, is suggestive of duodenal ulceration."

DISCUSSION

DR. M. THOMPSON (*Newcastle*) asked if there was a moral obligation to put all patients with active rheumatoid arthritis on a dose of about 10 mg. prednisolone daily, and why this trial had shown such a different result from that of the original Cortisone/Aspirin trial.

PROF. KELLGREN replied that the different result was due to the fact that a different steroid had been used. In a previous trial conducted by the Joint Committee prednisolone had been shown to be significantly better than cortisone in rheumatoid arthritis, and it was not therefore surprising that a different result had been obtained in comparing prednisolone with aspirin or other analgesics.

He did not know the answer to the other question. The rising D.A.T. titre worried him. He felt, with the others, that the rheumatoid serum factor was a nasty thing to have in one's blood, but a longer follow-up was needed.

PROF. S. J. HARTFALL (*Leeds*) asked if one treated the titre or the patient.

PROF. KELLGREN replied by citing syphilis and the Wassermann reaction. One did not really know the significance of the Wassermann reaction, but if it became more strongly positive in a patient under treatment for syphilis it would be worrying, although the patient might be feeling fine.

PROF. HARTFALL did not consider the analogy a good one, since the significance of the rheumatoid factor in this mysterious disease was not known.

PROF. KELLGREN felt that there was increasing evidence that a high agglutinating titre in arthritis indicated a poor prognosis and a negative test a good one.

PROF. BYWATERS (*Taplow*) remarked that remission or progression could occur in individual patients irrespective of the D.A.T. All one could do was to observe the patient and the D.A.T. It was not yet possible to foresee prognosis from changes in the D.A.T. in serial measurements.

DR. F. DUDLEY HART (*London*) asked whether complete remission had been seen in either group of patients.

PROF. KELLGREN replied that one patient on prednisolone and one on aspirin had gone into complete remission before the end of the first year; they had had negative tests and *x* rays before entry. Both had defaulted from the trial. In reply to a question whether the D.A.T. had fluctuated, he said that the D.A.T. had been done at 3- and 6-monthly intervals, and that a few negative had become positive and *vice versa*.

DR. M. THOMPSON (*Newcastle*) said that the single adverse finding, in the prednisolone-treated patients, of significantly more positive D.A.T. results at the end of treatment, could be very important. The significance of the D.A.T. titre in the series investigated by Dr. Duthie and himself had been emphasized, and he felt it necessary that in these trials a standard uniform test should be carried out in each centre.

DR. J. GLYN (*London*) asked whether anything could be learned from the failures, *i.e.* from the patients who had been changed from one drug to another.

PROF. KELLGREN replied that, broadly speaking, the patients who had changed over had not done so well.

DR. H. F. WEST (*Sheffield*) thought that Dr. Thompson's first question on the moral obligation to give prednisolone should be answered more fully. They had been heavily involved in these therapeutic trials, but their present view was no different from that held at the beginning—namely that steroid therapy should be used for the severely affected, ill patients (*i.e.* about one in twenty).

DR. J. J. R. DUTHIE (*Edinburgh*) thought that, if the progress of erosions could be arrested, it was surely better to use prednisolone in early mild cases rather than in late severe ones.

DR. J. NORRIE SWANSON (*Toronto*) said that treatment should be suited to individual needs. A good regime was to try aspirin, and (if that failed) phenylbutazone, and (if that failed) G 27202, and (if that failed) steroids. A large-scale therapeutic trial could not dictate the best treatment for each individual patient.

PROF. KELLGREN replied that all the hazards of long-term steroid treatment including pharmacological adrenalectomy had not come out in the trial, but would become apparent in a few year's time. The complete answer was not yet available, but would require a trial and follow-up lasting 10 years. The results of the present trial did, however, give some general guidance to help decide the treatment of choice for individual patients.

Comparaison de la prednisolone à l'aspirine ou aux autres analgésiques dans le traitement de l'arthrite rhumatismale

RÉSUMÉ

(1) Dans un essai thérapeutique contrôlé, la prednisolone fut comparée à l'aspirine et aux autres analgésiques dans le traitement de l'arthrite rhumatismale.

(2) Huit centres participèrent à cet essai et 84 malades s'y soumirent au début. Quelques malades se désistèrent, moururent ou furent retirés, de façon qu'au bout de deux ans de traitement les résultats à dépouiller ne se basent que sur 77 cas; 41 d'entre eux allotés à la prednisolone et 36 aux autres analgésiques.

(3) Les malades traités par la prednisolone accusèrent une amélioration précoce et appréciable, confirmée par des indices cliniques et de laboratoire de la polyarthrite inflammatoire. Cette amélioration, bien que moins prononcée, fut encore significative au bout de deux ans.

(4) Dans le groupe des malades traités par des analgésiques, la fréquence des signes radiologiques de maladie articulaire érosive des mains et des pieds augmenta appréciablement au bout de deux ans, tandis qu'il n'y eut pas d'altérations appréciables dans le groupe traité par la prednisolone.

(5) Chez beaucoup de malades traités par la prednisolone, le titre d'agglutination des globules de mouton augmenta au cours des 2 ans de traitement, tandis qu'une telle augmentation ne se produisit que chez quelques malades traités par des analgésiques.

(6) Deux malades traités par des analgésiques moururent d'insuffisance cardiaque. Cinq malades traités par la prednisolone accusèrent des complications majeures (deux cas de psychose et trois d'ulcération peptique). Toutes ces complications majeures survinrent chez des malades recevant 20 mg. ou plus de prednisolone par jour. Chez des malades à la prednisolone il y eut aussi une augmentation du poids du corps, une élévation légère de la tension artérielle et une tendance au boursouflement (*mooning*) du visage. Pendant l'essai, la dose moyenne par jour de prednisolone fut progressivement réduite de 17,4 à 10 mg. et plus de la moitié des malades à la prednisolone reçut aussi de l'aspirine et d'autres analgésiques. On en conclut, que la dose optimum par jour pour un traitement à longue échéance dans un cas moyen d'arthrite rhumatismale ne doit pas dépasser 10 mg. de prednisolone.

Comparación de la prednisolona a la aspirina o a otros analgésicos en el tratamiento de la artritis reumatoide

SUMARIO

(1) En una investigación terapéutica controlada se comparó la prednisolona a la aspirina y a otros analgésicos en el tratamiento de la artritis reumatoide.

(2) Ocho centros participaron en esta investigación, empezando con un total de 84 enfermos. Algunos de estos desistieron, murieron o fueron retirados, de manera que al cabo de dos años quedaron 77 casos para analizar; 41 de ellos tratados con prednisolona y 36 con otros analgésicos.

(3) Los enfermos tratados con prednisolona acusaron precozmente una mejoría apreciable, confirmada por los índices clínicos y de laboratorio, empleados en la poliartritis inflamatoria. Esta mejoría, aunque menos pronunciada, aún fué significativa al cabo de dos años.

(4) En el grupo de enfermos tratados con analgésicos, la frecuencia de signos radiológicos de enfermedad articular erosiva de las manos y de los pies aumentó significativamente al cabo de dos años, mientras que no se vieron alteraciones apreciables en el grupo tratado con la prednisolona.

(5) En muchos enfermos tratados con prednisolona, el título de aglutinación de globulos de oveja aumentó durante los dos años de tratamiento, mientras que tal aumentación se produjo sólo en algunos enfermos tratados con analgésicos.

(6) Dos enfermos tratados con analgésicos murieron de insuficiencia cardiaca. Cino enfermos tratados con prednisolona acusaron complicaciones mayores (dos casos de sicopatía y tres de ulceración péptica). Todas estas complicaciones mayores ocurrieron en enfermos recibiendo 20 mg. o más de prednisolona diaria. Los enfermos tratados con prednisolona presentaron también un aumento del peso corporal, un ascenso ligero de la tensión arterial y una tendecia a la "cara de luna". Durante la investigación, la dosis diaria media de prednisolona fué progresivamente reducida de 17,4 mg. a 10 mg. y más de la mitad de los enfermos tratados con prednisolona recibían además aspirina y otros analgésicos. Se concluye que la dosis diaria óptima en el tratamiento de plazo largo en un caso ordinario de artritis reumatoide no debe rebasar 10 mg. de prednisolona.