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CHLOROQUINE DIPHOSPHATE IN RHEUMATOID ARTHRITIS*

A CONTROLLED TRIAL

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Page (1951), reporting on the value of treatment with the synthetic antimalarial mepacrine in lupus erythematosus, mentioned that one patient who had a polyarthritis of rheumatoid type showed simultaneous improvement of both the skin lesions and the arthritis. Since this report, the use of synthetic antimalarial compounds in the treatment of inflammatory polyarthritis has steadily increased; at the present time chloroquine and hydroxychloroquine are the drugs most commonly used.

Freedman (1956) reported a controlled trial of chloroquine in 66 patients with rheumatoid arthritis; over a period of 16 weeks the treated group, who received 200 mg. chloroquine sulphate daily, showed significantly greater clinical improvement than controls who were given dummy tablets; there was no significant change in haemoglobin concentration or erythrocyte sedimentation rate.

Cohen and Calkins (1958) described a double-blind controlled trial in 22 patients with rheumatoid arthritis of more than 1½ years' duration; half the patients were treated first with chloroquine phosphate in doses of 250-500 mg. daily for 10 weeks and then with dummy tablets for 8 weeks, and in the other half of the patients the order of treatments was reversed. During treatment with chloroquine there was a significantly greater improvement in morning stiffness and pain than when dummy tablets were given, but grip strength and erythrocyte sedimentation rate showed little change.

These reports indicated that treatment with chloroquine might have a favourable effect upon at least some of the clinical manifestations of rheumatoid arthritis, but, as the authors pointed out, the period of observation was not long enough to assess the effectiveness of the treatment in relation to the natural history of the disease.

About twenty reports of the use of synthetic antimalarials in the treatment of rheumatoid arthritis have already been published. Few of these trials have been adequately controlled, and little would be gained by reviewing the reports in detail: in general terms, most authors have found that treatment with chloroquine or a related substance was of some value, while toxic effects were seldom serious, but were relatively frequent with doses in excess of 250 mg. daily of chloroquine diphosphate or its equivalent. Bagnall (1957) reported that 71 per cent. of a series of 108 patients with rheumatoid arthritis experienced remission or major improvement of symptoms during long-term treatment. Scherbel, Harrison, and Atdjian (1958) carried out a comparative trial of chloroquine and hydroxychloroquine in 106 patients, and concluded that there was little difference in the effectiveness of the two drugs; no control group was included, however, and the data do not establish the effectiveness of either treatment. Kersley and Palin (1959) reported 36 cases treated with alternating 3 months' courses of hydroxychloroquine sulphate, amodiaquine, and control tablets: as judged by clinical criteria, hydroxychloroquine produced worthwhile benefits in five of ten patients given doses of 800 mg. daily, but little effect in doses of 400 mg. daily.

The study reported here was undertaken with the aim of assessing the value of treatment with chloroquine in patients suffering from various types of inflammatory polyarthritis: it was thought desirable to determine whether the clinical improvement during short-term treatment, reported by others, would be apparent after continuous treatment for a year or longer and whether there would also be laboratory and radiological evidence of a beneficial effect. It was hoped, by the inclusion of adequate

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numbers of patients in the trial, that the results would indicate whether chloroquine treatment should be considered in the routine management of patients with inflammatory polyarthritis.

Material and Methods

The trial originally included patients suffering from polyarthritic syndromes other than rheumatoid arthritis, in separate controlled groups, but the numbers of patients in these other categories were too small for analysis. This report therefore deals only with the results of treatment with chloroquine in patients with an inflammatory polyarthritis of rheumatoid type.

Eligibility for Entry.—All patients with active rheumatoid arthritis admitted to the beds of the Rheumatism Unit in the Manchester Royal Infirmary or in the Devonshire Royal Hospital, Buxton, were eligible. The patients normally entered the trial during the second or third week after admission, when the results of the sheep cell agglutination test and other data were complete. A few patients who had by this time shown rapid improvement were not entered. The out-patients who were entered in the trial were those whose progress with conservative measures was not satisfactory; four had relapsed after in-patient treatment. The patients with rheumatoid arthritis who entered this trial were those for whom gold therapy would previously have been advised.

Diagnostic Criteria.—The criteria for entry into the trial were broadly similar to those used in the comparative trial of prednisolone with aspirin or other analgesics conducted by the Joint Committee of the Medical Research Council and Nuffield Foundation (Joint Committee Report, 1959), except that patients with disease of more than 24 months' duration were included as well as those with disease of 3 to 24 months' duration: patients of either sex with a rheumatoid type of arthritis affecting more than three joints, with bilateral involvement of hands or feet, ankles, or wrists were admitted. A positive result in the sheep cell agglutination test was not made a condition of entry but was used in the stratification of the patients into treatment groups.

Stratification and Allocation to Treatment.—All rheumatoid patients were stratified by sex and positive or negative result in the sheep cell agglutination test (SCAT). The patients showing a positive SCAT result were further stratified by duration of disease (3 to 24 months and over 24 months). As it was expected that there would be comparatively few patients with negative SCAT result eligible for the trial, these were not stratified by duration of disease.

The first patient in each of the six strata thus obtained was treated with tablets each containing 250 mg. chloroquine diphosphate: these tablets were referred to as Tablets "A".

The second patient in each stratum was treated with tablets each containing 2·5 mg. chloroquine diphosphate: these tablets were referred to as Tablets "B". The alternation of treatments was continued so that consecutive patients in each stratum received different treatment.

Dosage of Chloroquine.—The tablets, which were sugar-coated, were identical in size, shape, and appearance. All in-patients were given one tablet twice daily while they were in hospital, and were instructed to take one tablet each evening when they returned home. Out-patients were treated with one tablet daily throughout. The patients were told that they were being given special tablets for rheumatism; their general practitioners were informed that this was a special chloroquine preparation and were asked to discontinue it in the event of serious toxic effects.

Other Treatment.—Chloroquine was given as an adjunct to whatever other treatment the patient would normally have received, except that gold was not used. The management of the patients followed a conservative regime of rest, splintage, and gradual mobilization, with modifications to suit the needs of individual patients. Analgesics were given as necessary: aspirin was most frequently used, but occasional patients were given other analgesics, such as tab. codein co. or phenylbutazone, if these appeared more effective. Some patients were treated with corticosteroids; the decision to do so was made independently of the fact that chloroquine was also being used, and was based on the currently accepted indications for steroid treatment (Empire Rheumatism Council, 1960).

Assessments.—During the course of the trial five different observers were indiscriminately concerned in making the assessments; four of the observers did not know which dose of chloroquine the tablets contained; the fifth (A.J.P.), who was concerned in the arrangements for the supply of the tablets and who did approximately a quarter of the follow-up assessments, was aware of their identity.

Assessments were entered on a form kept with the patients' notes, and were made on entry, at 1 month, at 6 months, and between 1 and 2 years after entry.

The methods of assessment were broadly similar to those used in the therapeutic trials conducted by the Joint Committee of the Medical Research Council and Nuffield Foundation (Joint Committee Reports, 1954). They included the following features:

(1) At the initial assessment, the patient's score on the classification proposed by the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1958).
(2) At each assessment:
   (*a*) Clinical assessment of disease activity, in four grades.
   (*b*) General functional capacity, in five grades varying from normality (1) to complete crippling (5). (These grades are detailed under Table V.)
   (*c*) Details of any symptoms or signs which might represent complications or side-effects of the treatment.

(*d*) Haemoglobin concentration and erythrocyte sedimentation rate (Westergren).
(*e*) Sheep cell agglutination test (Ball, 1950; Kellgren and Ball, 1959).
(*f*) Strength of grip (mm. Hg). Average of three readings with each hand, with an initial bag pressure of 30 mm.

(3) On entry and at follow-up after 12 to 24 months, *x* rays of hands and feet.

Number of Patients.—The total number of patients entering the trial was 134. The distribution of these patients between the two treatment groups by duration of disease, sex, and SCAT result is shown in Table I. 126 patients were classified as suffering from "definite" rheumatoid arthritis, as defined by the criteria proposed by the American Rheumatism Association (Ropes and others, 1958). The remaining eight patients, of whom five were in the treated and three in the control group, were classified as having "probable" rheumatoid arthritis; all these were females and seven had arthritis of less than 24 months' duration and a negative sheep cell test.

Patients not Followed Up.—Twelve patients failed to complete the trial and are completely excluded from the analysis: these patients were not followed up and are shown in Table I as "Withdrawals with initial assessment only". The reasons for withdrawal are shown in Table IA and details are given in the Appendix.

Patients Followed Up but Excluded from Detailed Analysis.—In twenty of the 122 patients followed up, treatment with corticosteroids was given for more than 3 months, or, in the treated group, chloroquine was withdrawn because of toxicity (Table IB). These twenty patients are shown in brackets in Table I; they are described in more detail below and are also included in the analysis of all patients followed up (Table VIII).

In six patients the period of follow-up was less than 1 year, but since the 6-months assessments were available and further observations had been made towards the

TABLE I

DISTRIBUTION OF PATIENTS AT ENTRY INTO TRIAL, BY SEX, DURATION, AND RESULT OF SHEEP CELL AGGLUTINATION TEST

Duration of Disease	Daily Dosage of Chloroquine Diphosphate (mg.)	Sheep Cell Agglutination Test Result					Total Followed Up	Withdrawals with Initial Assessment Only*	Total Entered
		Positive			Negative Females Only	Total in Trial			
		Males	Females	Total					
3 mths to 2 yrs ..	250–500	9 (1)	9 (3)	18 [2] (4)	8 (1)	26 [1] (5)	31	1	32
	2·5–5·0	6 (2)	9 (1)	15 [2] (3)	6 (1)	21 [1] (4)	25	3	28
Over 2 yrs	250–500	3 (2)	14 (4)	17 [3] (6)	6 (1)	23 (7)	30	6	36
	2·5–5·0	5 (0)	19 (4)	24 [3] (4)	8 (0)	32 (4)	36	2	38
Total	250–500	12 (3)	23 (7)	35 (10)	14 (2)	49 (12)	61 [4]	7	68
	2·5–5·0	11 (2)	28 (5)	39 (7)	14 (1)	53 (8)	61 [4]	5	66

* Table IA.

[1] Patients described in Tables III–V and IX–X.
[2] Patients described in Table VI.
[3] Patients described in Table VII.
[4] Patients described in Table VIII.

Figures in brackets represent twenty patients followed up though receiving steroids and also those in whom chloroquine treatment was stopped owing to toxicity (Table IB).

TABLE IA

PATIENTS EXCLUDED FROM ANALYSIS

Reason for Exclusion	Treated	Control
Death early in trial	1	1
Refusal to attend	1	2
Patient untraceable	1	0
Chloroquine toxicity*	1	0
Wrong treatment	0	2
Changed diagnosis	1	0
Psychosis	1	0
Transfer for surgery	1	0
Total	7	5

* All other patients with symptoms possibly related to chloroquine treatment were followed up.

TABLE IB

PATIENTS FOLLOWED UP THOUGH RECEIVING STEROIDS, AND THOSE IN WHOM TREATMENT WAS STOPPED

Treatment			Treated	Control
Treated with Steroids	Continued chloroquine		3	6
	Stopped chloroquine	Without having experienced toxicity ..	3	1
		Because of toxicity ..	2	1
Chloroquine toxicity, but not receiving steroids			4*	0
Total			12	8

* These four patients all had disease of more than 2 years' duration.

end of the first year these patients are included in the detailed analysis. One of these who died is described below.

Duration of Treatment.—Of the 102 patients used in the detailed analysis, who completed the trial according to plan and who were not treated with steroids, 93 (46 treated, 47 controls) received the prescribed treatment throughout the trial. In nine patients treatment was interrupted, but this was thought unlikely to have influenced the results of the trial; these patients are detailed below.

One control patient discontinued treatment after 8 months because of a rash, and one after 6 months because of dyspepsia.

Contrary to instructions, two control patients ceased taking the tablets when they were discharged from hospital since they were doubtful whether they were obtaining any benefit from them.

Three treated and two control patients temporarily discontinued treatment because of symptoms ascribed to toxicity, but resumed treatment when these symptoms had subsided.

Of the twenty patients shown in brackets in Table I and also in Table IB, who were excluded from the detailed analysis, but were included in the final analysis of all 122 patients followed up (Table VIII), nine who had steroids (three treated, six controls) received the prescribed treatment throughout the trial. In eleven the tablets under trial were discontinued (in each case after less than 3 months) and in most instances the chloroquine was replaced by steroids.

Corticosteroid Treatment.—Of the 122 patients in the trial, eighteen received corticosteroid treatment, usually with prednisolone, at some period. Of these, two (one treated, one control) who had corticosteroid therapy for a few weeks only and were not receiving it at the times of assessment were included in the detailed analysis.

The remaining sixteen who received corticosteroids for more than 3 months were assessed at the usual times, but were excluded from the detailed analysis: these patients are among those shown in brackets in Table I; by chance, eight were in the treated and eight in the control group. Six of the sixteen were receiving steroids on entry and continued to receive them throughout the trial: six started steroid treatment within 2 months of entry: four had steroids for variable periods or started later in the trial. Seven of them (five treated, two controls) ceased taking chloroquine within a few weeks of entry, but the remainder continued to take both steroids and chloroquine. The dose of prednisolone ranged from 5 to 15 mg. daily; for those in the treated group the mean daily dose was 10·0 mg., and for the controls 8·8 mg.

The reason for embarking on steroid treatment was invariably that the patients were suffering from severe disease and had shown little or no improvement with conservative treatment. These patients formed too small a group for separate analysis but were included in the analysis of all patients followed up (Table VIII), and it was found that inclusion or exclusion of corticosteroid-treated patients did not affect the conclusions.

Deaths.—Three patients died during the course of the trial. Two who died early in the trial are excluded altogether from the analysis, and are described in the Appendix. The third, who died after the 6-months assessment, is included in the analysis of clinical and laboratory data shown in Tables VII and VIII. This patient, a male aged 59 in the treated group, had severe nodular SCAT positive rheumatoid arthritis of 22 years' duration. He was treated as an in-patient for 3 weeks initially, but 3 months after discharge he stopped taking the tablets for 2 months, because he thought they made his legs swell; he had resumed treatment at the time of the 6 months' assessment. After attending for an interim interview 10 months after entry he developed a chest infection and died at home 3 weeks later: no autopsy was performed.

Toxicity.—Table II shows the number of times various symptoms were reported at different doses of chloroquine; 23 patients (thirteen treated, ten controls) reported symptoms which might have been due to chloroquine.

TABLE II

TOXICITY

Symptoms	Dose of Chloroquine Diphosphate (mg.)			
	500	250	5·0	2·5
Gastro-intestinal	4	3	1	4
Rashes	0	2	0	2
Dizziness	2	0	0	0
Visual disturbance	1	1	0	1
Headache	1	0	0	0
Insomnia	1	1	0	0
Other	0	1	1	1
Number of patients with symptoms at given dose levels	7	8	2	8
Chloroquine permanently withdrawn	5	2	0	3
Number treated	64	63	64	62
Total number of patients with symptoms	13		10	

Gastro-intestinal Symptoms.—These were reported by seven patients in the treated group, in five of whom chloroquine treatment was permanently discontinued on this account. These symptoms, which consisted of anorexia, nausea, vomiting, heartburn, epigastric pain, glossitis and dysphagia, and diarrhoea, were generally noticed after less than 2 weeks' treatment and subsided within a few days when it was withdrawn.

Five patients in the control group had gastro-intestinal symptoms, and in one of them treatment was permanently discontinued. These symptoms arose after more than 6 months' treatment and were generally slow to subside; they consisted of ulcer-type dyspepsia and various non-specific symptoms.

Visual Disturbances.—These were experienced by two patients in the treated group. One developed micropsia and dizziness after 2 weeks' treatment with 500 mg. daily. The other complained of gradually failing vision after 6 months' treatment with 250 mg. daily: he was found to have bilateral cataract, but slit-lamp examination showed the cornea to be clear; on entry to the trial he had had active scleritis which responded well to treatment with cortisone locally and prednisolone by mouth.

A woman in the control group complained of failing vision after a year's treatment with one tablet daily: she too was found to have incipient cataract when examined at another hospital, and no corneal abnormality was reported.

Rashes.—Two patients in the treated group had rashes. One developed a maculo-papular rash on the trunk after 2 weeks' treatment with 250 mg. daily; the rash disappeared a few weeks after chloroquine was stopped. The other developed an itching rash on the breast and trunk after 2 months' treatment with 250 mg. daily: the rash, which had the features of a neuro-dermatitis, did not improve when chloroquine was stopped for a few weeks, while the joint symptoms became worse; treatment was resumed and later the rash slowly cleared.

Two patients in the control group had rashes. One developed a rash almost certainly due to phenobarbitone sensitivity on the hands and forearms. The other developed a rash on the face after 7 months' treatment with one tablet daily: the rash disappeared when chloroquine was stopped but recurred when it was resumed.

Miscellaneous Symptoms.—Headache attributed to chloroquine was complained of by one patient in the treated group while taking 500 mg. daily.

Dizziness was experienced after 5 and 14 days' treatment respectively, by two patients in the treated group on 500 mg. daily; it subsided within a few days when treatment was withdrawn.

Insomnia was complained of by two patients in the treated group. In one who also developed glossitis and dysphagia chloroquine was withdrawn. The other noticed the symptom after 3 weeks' treatment with 250 mg. daily: mild sedation was effective and she was able to continue treatment.

Oedema was complained of by one treated and one control patient, but its relation to the treatment was very doubtful.

One patient in the control group complained of menorrhagia after 3 weeks' treatment with one tablet daily.

In seven patients in the treated group the use of chloroquine was abandoned because of toxicity: six of these had chloroquine for less than 2 weeks and the seventh for less than 6 weeks; no patient in this group developed severe toxic symptoms at a later date. Of the remaining six in the treated group who had symptoms which might have been due to chloroquine, three stopped the treatment temporarily and three continued it without interruption. Only one patient in the control group developed symptoms of any severity early in the trial: this was the woman who had menorrhagia, and it seems most unlikely that this was related in any way to her treatment; the remaining nine patients in the control group all developed symptoms after more than 6 months' treatment.

Symptoms which might have been related to the treatment were therefore observed in thirteen of the 68 patients originally entered in the treated group, a total incidence of 19·1 per cent.: ten out of 66 patients entered in the control group complained of symptoms attributed by themselves at least partly to the treatment, a total incidence of 15·2 per cent. On the other hand the real incidence of toxic effects may well be lower than these figures would suggest: three patients in the treated group and nine in the control group had symptoms which were doubtfully related to chloroquine treatment, and if these patients are excluded the incidence falls to 14·7 per cent. in the treated and 1·5 per cent. in the control group.

Comparability of Treatment Groups

Tables III to X show that the treatment groups were reasonably comparable on entry, and although there were minor differences in the various characteristics these did not approach conventional levels of significance. A difference between the groups in respect of one characteristic was to some extent balanced by a difference of opposite direction in another characteristic, and in general the differences tended to favour the control group.

Of the sixty patients with disease of 3 to 24 months' duration, only eighteen (30 per cent.) had symptoms of less than 1 year's duration, and of these early cases ten were in the treated and eight in the control group.

The mean ages of the patients in each treatment group varied between 45 and 49 years for those with a positive sheep cell agglutination test, both for those with recent and for those with long-standing disease. Of the patients with a negative sheep cell test, those with recent disease were slightly older (mean 52 years) and those with long-standing disease slightly younger (mean 43 years): the age distributions of the treated and control patients were similar.

Results

Table I shows that the trial included many patients with disease of more than 2 years' duration; a number of these had such severe joint destruction on entry that their capacity for improvement in function was limited and it was difficult to assess progression or improvement in the radiological changes. In order that the results of this trial might be compared with those of the prednisolone/analgesics trial conducted by the Joint Committee, a detailed analysis of patients with disease of less than 2 years' duration, irrespective of the results of the initial SCAT, will be considered first (Table III and Fig. 1, opposite; Tables IV and V, IX and X, overleaf).

TABLE III

AVERAGE GRADINGS AND MEASUREMENTS OF VARIOUS CHARACTERISTICS IN ALL PATIENTS WITH DISEASE OF 3 TO 24 MONTHS' DURATION

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Disease Activity Grading	Functional Capacity Grading	Strength of Grip		Erythrocyte Sedimentation Rate (mm./hr)	Hb (g. per cent.)	S.C.A.T. (tubes above or below min. pos.)	X-ray Grading $\frac{\text{hands+feet}}{2}$
				mm. Hg	Per cent. of Higher Reading				
(*a*) Entry	250–500	1·81	2·85	170		42	12·4	+0·92	1·40
	2·5–5·0	1·90	2·80	164		34	12·7	+0·42	1·31
b) After 1 yr ..	250–500	0·83	1·83	228		23	12·7	−0·96	1·65
	2·5–5·0	1·54	2·26	186		46	12·8	+0·24	1·64
(*b*)–(*a*)	250–500	−0·98	−1·02	+58	+25·5	−19	+0·3	−1·88	+0·25
	2·5–5·0	−0·36	−0·54	+22	+ 5·8	+12	+0·1	−0·18	+0·33

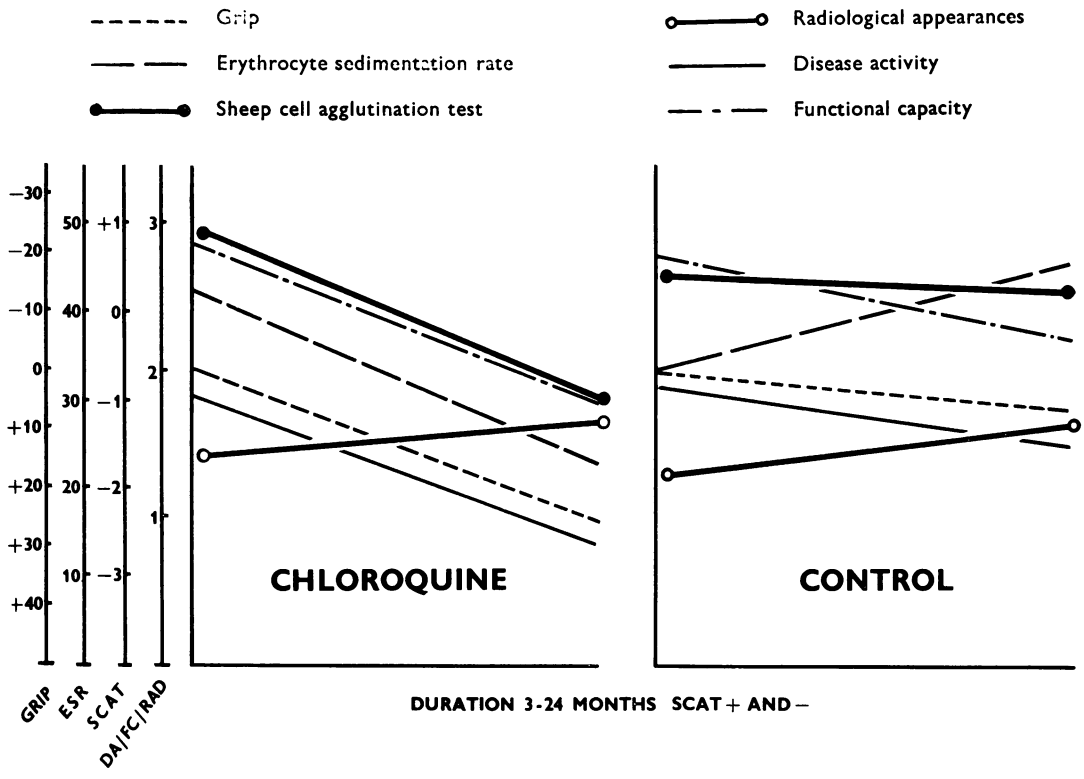

Fig. 1.—Diagrammatic representation of the data in Table III.

Tables IV and V show the numbers of patients in the two treatment groups with given grades of disease activity and functional capacity at entry and at follow-up. The two groups were reasonably well balanced in terms of these characteristics at entry; on follow-up both groups showed improvement, but the group treated with the higher dose showed greater improvement in both characteristics the difference in disease activity being significant ($p < 0{\cdot}02$); the difference in functional capacity

TABLE IV

NUMBER OF PATIENTS WITH DISEASE OF 3 TO 24 MONTHS' DURATION WITH GIVEN GRADES OF DISEASE ACTIVITY

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Grade of Disease Activity				Total	Change in Grade (*b*)–(*a*)				
		0 to ½	1 to 1½	2 to 2½	3 to 3½		+1½ to +2	+½ to +1	±0 to −½	−1 to −1½	−2 to −2½
(*a*) Entry	250 to 500	5	5	9	7	26					
	2·5 to 5·0	1	6	11	3	21					
(*b*) After 1 yr ..	250 to 500	11	13	2	—	26	—	2	8	9	7
	2·5 to 5·0	4	8	6	3	21	1	1	13	5	1

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

TABLE V

NUMBER OF PATIENTS WITH DISEASE OF 3 TO 24 MONTHS' DURATION WITH GIVEN GRADES OF FUNCTIONAL CAPACITY

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Grade of Functional Capacity					Total	Change in Grade (*b*)–(*a*)							
		1	2	3	4	5		+4	+3	+2	+1	±0	−1	−2	−3
(*a*) Entry	250–500	2	7	11	5	1	26								
	2·5–5·0	3	2	12	4	—	21								
(*b*) After 1 yr ..	250–500	6	18	2	—	—	26	—	—	—	—	10	7	8	1
	2·5–5·0	4	10	6	—	1	21	1	—	—	1	8	7	2	2

Grade: 1 = Fully employed or employable in their normal work and able to undertake normal physical recreations for their type.
2 = Fully employed in their special work after vocational training, or doing light or part-time work in normal occupations. Limitation in the amount of physical recreation that can be taken. Housewives, all except the heaviest housework. In-patients, in hospital for investigation only.
3 = Patients 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 the 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 bed rest.

is not formally significant. The changes in grip strength, erythrocyte sedimentation rate, and haemoglobin concentration are shown in Table III. The treated patients showed a significantly greater improvement in grip strength* ($p < 0{\cdot}02$) and in erythrocyte sedimentation rate ($p < 0{\cdot}001$); in the control group there was a slight improvement in grip strength, but the mean erythrocyte sedimentation rate was higher at follow-up. The changes in haemoglobin concentration are not significant, both groups showing a marginal improvement which was slightly greater in the treated group. The changes in the SCAT and the radiological changes are considered below.

Separate analyses were made of the two SCAT-positive sections of the sample—those with disease duration of 3 to 24 months and of more than 2 years —and of all cases followed up irrespective of duration of disease and SCAT result and including those treated with corticosteroids and those in whom chloroquine was withdrawn. The results are shown in Table VI and Fig. 2 (opposite), and in Tables VII and VIII, and Figs 3 and 4 (overleaf).

In practically every instance the changes recorded at follow-up were in the same direction as those observed in the complete group of patients with disease of short duration (Fig. 1). The differences between the changes in the two treatment groups in patients with disease of short duration and positive SCAT are even greater than when patients with negative SCAT are included, and they show, in spite

* Improvement measured in per cent. of final, deterioration in per cent. of initial average reading.

TABLE VI

AVERAGE GRADINGS AND MEASUREMENTS OF VARIOUS CHARACTERISTICS IN PATIENTS WITH DISEASE OF 3 TO 24 MONTHS' DURATION AND POSITIVE REACTION TO THE SHEEP CELL AGGLUTINATION TEST

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Disease Activity Grading	Functional Capacity Grading	Strength of Grip		Erythrocyte Sedimentation Rate (mm./hr)	Hb (g. per cent.)	S.C.A.T. (tubes above or below min. pos.)	X-ray Grading $\frac{\text{hands+feet}}{2}$
				mm. Hg	Per cent. of Higher Reading				
(*a*) Entry ..	250–500	1·89	2·78	172		45	12·6	+2·61	1·41
	2·5–5·0	1·93	2·93	157		38	12·8	+2·00	1·58
(*b*) After 1 yr ..	250–500	0·89	1·78	236		21	12·6	+0·21	1·74
	2·5–5·0	1·67	2·37	173		50	13·0	+1·93	1·88
(*b*)−(*a*) ..	250–500	−1·00	−1·00	+64	+28·4	−24	±0·0	−2·39	+0·33
	2·5–5·0	−0·26	−0·56	+16	+ 4·1	+12	+0·2	−0·07	+0·30

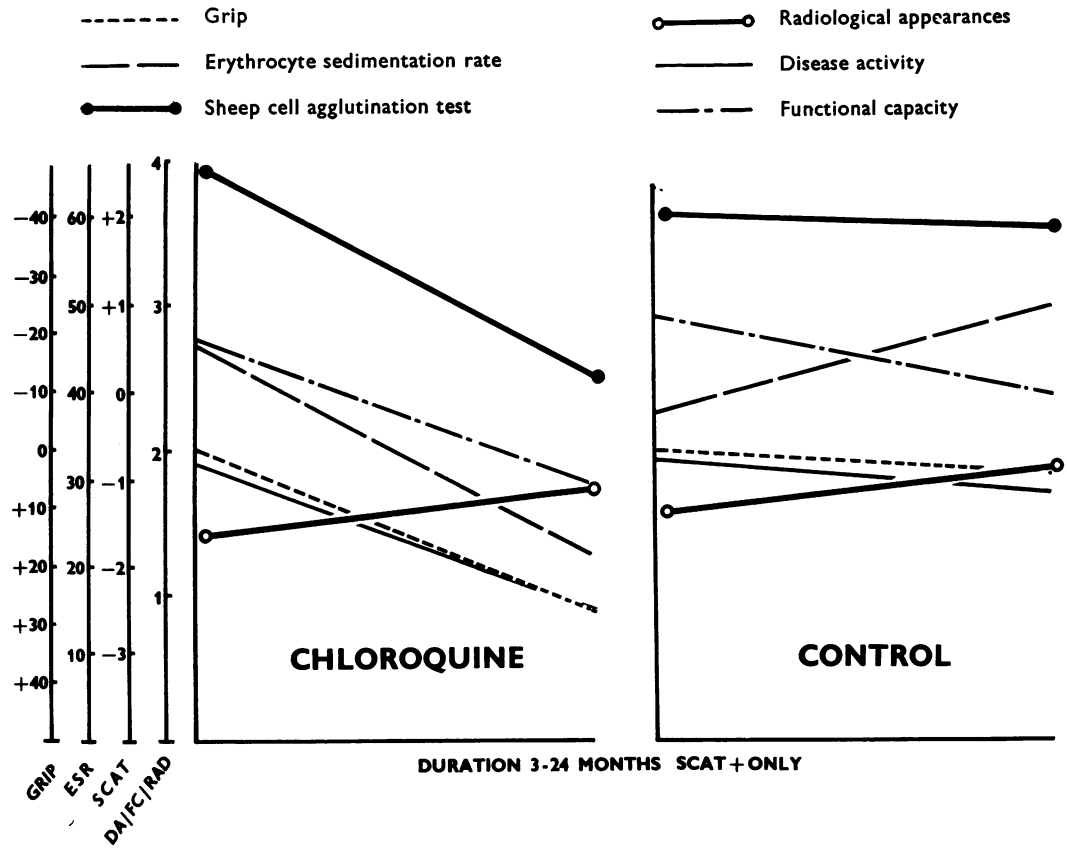

Fig. 2.—Diagrammatic representation of the data in Table VI.

of the small number of patients in this section, a significant advantage to the treated group in disease activity ($p < 0{\cdot}05$), percentage increase in grip strength ($p < 0{\cdot}02$), and erythrocyte sedimentation rate ($p < 0{\cdot}001$). As might be expected, the changes among the SCAT-positive patients with disease of long duration are less striking, and the differences between the changes in the two treatment groups reach formal significance only in functional capacity ($p < 0{\cdot}01$).

TABLE VII

AVERAGE GRADINGS AND MEASUREMENTS OF VARIOUS CHARACTERISTICS IN PATIENTS WITH DISEASE OF MORE THAN 2 YEARS DURATION AND POSITIVE REACTION TO THE SHEEP CELL AGGLUTINATION TEST

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Disease Activity Grading	Functional Capacity Grading	Strength of Grip		Erythrocyte Sedimentation Rate (mm./hr)	Hb (g. per cent.)	S.C.A.T. (tubes above or below min. pos.)	X-ray Grading $\frac{\text{hands+feet}}{2}$
				mm. Hg	Per cent. of Higher Reading				
(*a*) Entry ..	250–500 2·5–5·0	1·62 1·98	3·21 2·90	130 106		41 41	12·2 12·0	+2·41 +2·21	2·79 2·73
(*b*) After 1 yr ..	250–500 2·5–5·0	1·06 1·77	2·24 2·85	165 124		28 38	13·1 13·1	+1·12 +1·33	2·79 2·89
(*b*)−(*a*) ..	250–500 2·5–5·0	−0·56 −0·21	−0·97 −0·05	+35 +18	+22·3 +13·3	−13 − 3	+ 0·9 +1·1	−1·29 −0·88	±0 +0·16

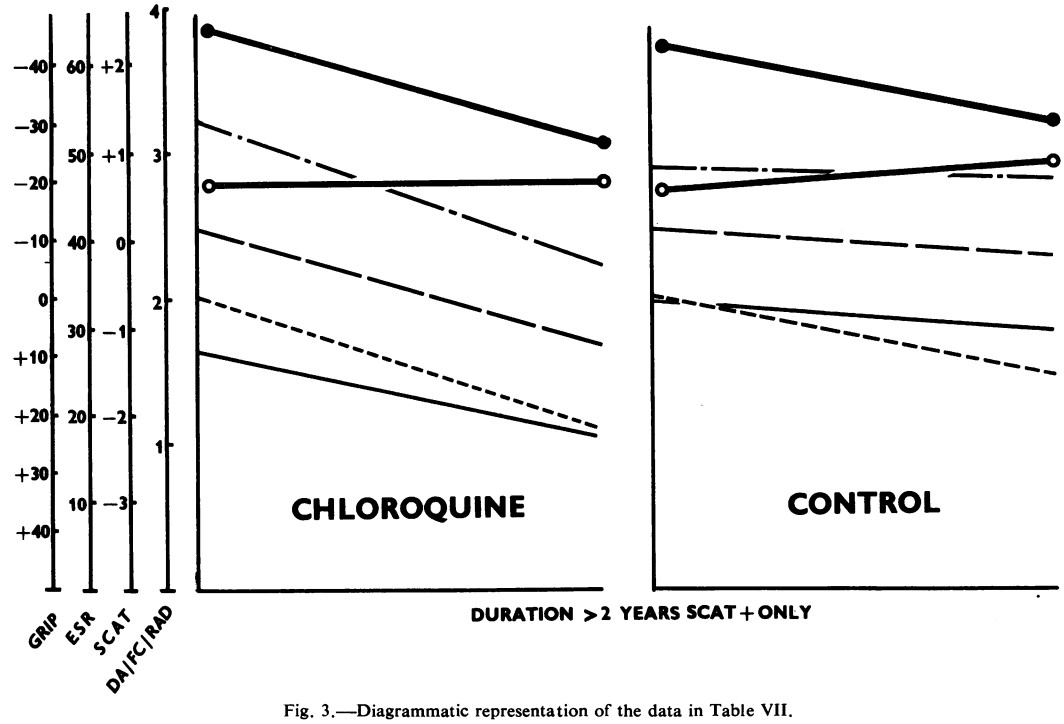

Fig. 3.—Diagrammatic representation of the data in Table VII.

When all the cases followed up are taken together (Fig. 4), the size of the changes lies between those for the short and long duration groups. In this large sample the differences in changes between treatment groups are all formally significant (disease activity $p < 0{\cdot}01$; functional capacity $p < 0{\cdot}05$; per cent. change in grip $p < 0{\cdot}02$; erythrocyte sedimentation rate $p < 0{\cdot}01$). Two reservations have to be made, however. The greater proportion of long-duration cases in the control group introduces a bias in favour of the treated group, as also previously found by Duthie, Thompson, Weir, and Fletcher (1955); on the other hand, the inclusion in both treatment groups of patients who had corticosteroids and those in whom chloroquine was withdrawn acts in the opposite direction: it is probable that the effects of these opposing factors balance each other to some extent.

TABLE VIII

AVERAGE GRADINGS AND MEASUREMENTS OF VARIOUS CHARACTERISTICS IN ALL PATIENTS FOLLOWED UP

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Disease Activity Grading	Functional Capacity Grading	Strength of Grip		Erythrocyte Sedimentation Rate (mm./hr)	Hb (g. per cent.)	S.C.A.T. (tubes above or below min. pos.)	X-ray Grading $\frac{\text{hands + feet}}{2}$
				mm. Hg	Per cent. of Higher Reading				
(*a*) Entry ..	250–500	1·76	3·04	145		41	12·2	+1·11	2·06
	2·5–5·0	2·02	2·93	132		40	12·3	+0·87	2·07
(*b*) After 1 yr ..	250–500	1·02	2·13	187		30	12·9	−0·22	2·22
	2·5–5·0	1·70	2·52	150		41	12·8	+0·39	2·31
(*b*)−(*a*) ..	250–500	−0·74	−0·91	+42	+22·5	−11	+0·7	−1·33	+0·16
	2·5–5·0	−0·32	−0·41	+18	+8·8	+ 1	+0·5	−0·48	+0·24

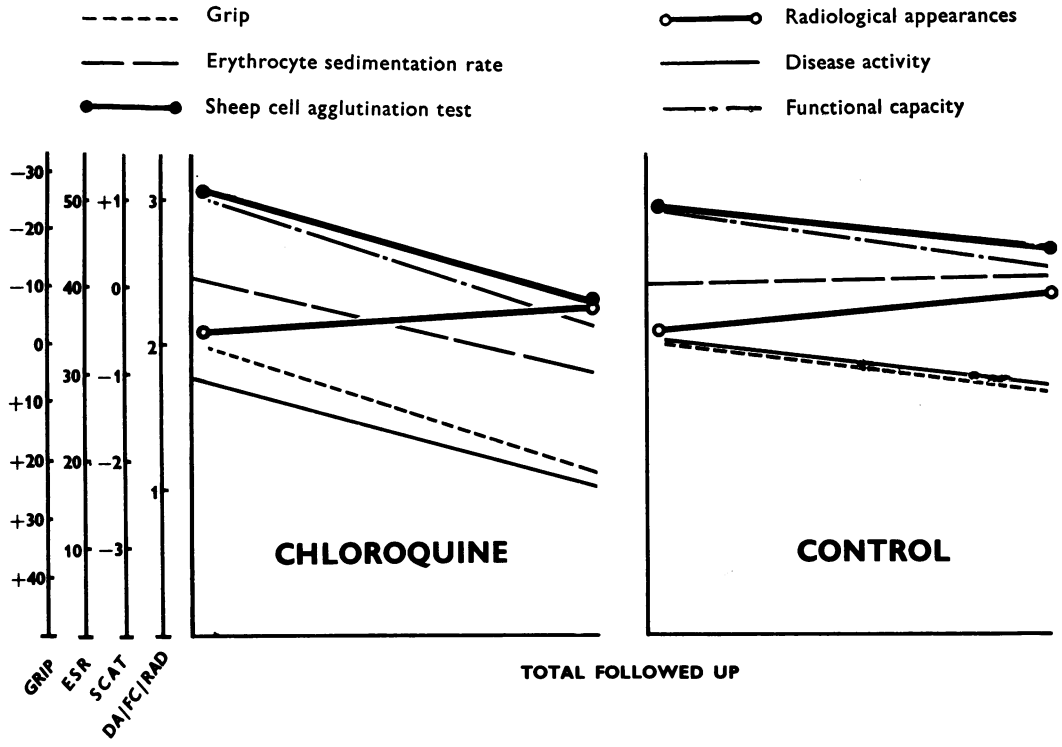

Fig. 4.—Diagrammatic representation of the data in Table VIII.

Radiological Changes.—The *x*-ray changes in the hands and feet taken at entry and at follow-up were all read in consecutive sessions by one observer (A.J.P.) who was unaware at the time of the treatment each patient had received. The films were assessed for osteoporosis, erosion of bone, narrowing of joint space, and subluxations, and an overall grading was made for the severity of rheumatoid changes. A detailed analysis of the results in all patients with disease of 3 to 24 months' duration is shown in Table IX (overleaf). The results in the SCAT-positive patients and in the total sample followed up were also analysed; these are not shown in detail, but the mean gradings for rheumatoid appearances at entry and at follow-up, and their changes over this period, are shown in Tables VI, VII, and VIII, and illustrated in Figs 2 to 4. In many cases the degree of change, although definite, was insufficient

TABLE IX

NUMBER OF PATIENTS WITH DISEASE OF 3 TO 24 MONTHS' DURATION WITH GIVEN GRADES OF RADIOLOGICAL CHANGES IN FILMS OF HANDS AND FEET

Site	Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Grade					Total X-rayed	Not X-rayed	Change in Grade				Deterioration or Improvement (b)−(a)		
			0	1	2	3	4			+2	+1	±0	−1	Deteriorated	No Change	Improved
Hands	(a) Entry ..	250–500	3	7	10	4	—	24	2							
		2·5–5·0	5	3	9	1	—	18	3							
	(b) After 1 yr ..	250–500	3	4	11	5	1	24	2	1	4	19	—	14	8	2
		2·5–5·0	4	1	10	3	—	18	3	2	3	12	1	12	4	2
Feet	(a) Entry ..	250–500	7	9	6	1	1	24	2							
		2·5–5·0	4	7	6	—	1	18	3							
	(b) After 1 yr ..	250–500	6	5	10	3	—	24	2	2	4	16	2	13	9	2
		2·5–5·0	3	5	7	2	1	18	3	—	6	12	—	11	7	—

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

to alter the absolute grading for severity of rheumatoid appearances; a statement regarding improvement or deterioration could, however, be made, and Table IX also contains the results of this analysis.

At follow-up there had been a slight but definite progression of radiological change in both the treated and the control groups, but there was no significant difference in the rate of progression of radiological changes in the two groups. The numbers of patients whose films showed given grades of abnormality were remarkably similar in the two groups both at entry and at follow-up; the numbers of patients whose films showed given grades of improvement or deterioration were also similar. Improvement in the radiological appearances was seen in only four patients, of whom two were in the treated and two in the control group; in no case was there any definite evidence that treatment with chloroquine had influenced the rate of progression of the radiological joint changes.

About three-quarters of the *x*-ray films were read independently by a second observer (K.A.E.M.); although there were slight differences in the scores recorded for each feature by the two observers, there was no important disparity between them, and in every case changes in grade were recorded in the same direction.

Results of Sheep Cell Agglutination Test (SCAT).— The tests were done by Ball's method (Ball, 1950; Kellgren and Ball, 1959). In order to facilitate comparison, the results are expressed in the same manner as in the report of the prednisolone/analgesics trial: the minimal positive titre of 1 in 32 is taken as zero, and dilutions above and below this are scored as +1, +2, etc., and −1, −2, etc. The results for all patients with disease of 3 to 24 months' duration are shown in detail in Table X.

TABLE X

RESULTS OF SHEEP CELL AGGLUTINATION TESTS* IN PATIENTS WITH DISEASE OF 3 TO 24 MONTHS' DURATION

Time of Assessment	Daily Dosage of Chloroquine Diphosphate (mg.)	Results of Tests							Total	Changes in Results of Tests (b)−(a)				
		Negative			Positive									
		−4 to −3	−2 to −1	Total	0 to +1	+2 to +3	+4 to +5	Total		+4 to +3	+2 to +1	±0 to −1	−2 to −3	−4 to −5
(a) Entry	250–500	5	3	8	6	5	7	18	26					
	2·5–5·0	5	1	6	4	10	1	15	21					
(b) After 1 yr	250–500	9	5	14	6	5	1	12	26	—	1	9	14	2
	2·5–5·0	7	—	7	5	5	4	14	21	—	6	12	3	—

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

The mean SCAT titre at entry into the trial was higher in the treated than in the control group. On follow-up, however, there was a striking change: the number of patients showing positive tests had fallen from eighteen to twelve in the treated group, but only from fifteen to fourteen in the controls. In the treated patients the titre had fallen in sixteen and had increased in only one, whereas in the control group the titre had fallen in only three and had increased in six: the greater fall in the mean titre in the treated group is highly significant ($p < 0{\cdot}001$).

Separate analysis of the SCAT-positive patients (Tables VI and VII) and of all patients followed up (Table VIII) reveals a similar trend: the mean SCAT titres were higher in the treated group at entry but showed a greater fall at follow-up than the control group: the greater fall in the treated group was highly significant in the SCAT-positive patients with disease of short duration ($p < 0{\cdot}001$) and in all patients followed up ($p < 0{\cdot}01$), though not in the SCAT-positive patients with disease of long duration.

The SCAT results are therefore in accord with the changes in the clinical status and the erythrocyte sedimentation rate, the treated patients showing greater improvement.

Correlation of Changes in SCAT Titre with Changes in Other Characteristics.—Fig. 5 shows the percentage changes in grip strength plotted against changes in SCAT titre for all patients who were SCAT-positive at entry. In both the treated and the control patients decrease in SCAT titre is associated with increase in grip strength and *vice versa*; the correlation coefficient ($r = 0{\cdot}40$), while not showing very close functional relation of the two characteristics, is significant ($p < 0{\cdot}001$). Treated and control patients do not overlap closely, the treated patients spreading more to the upper right, the control patients more to the lower left in the figure; this, however, is due not solely to the differences in treatment but also to the fact that there was a greater proportion of patients with disease of short duration in the treated group; it is evident from the data given earlier that such patients in either treatment group did better than those with disease

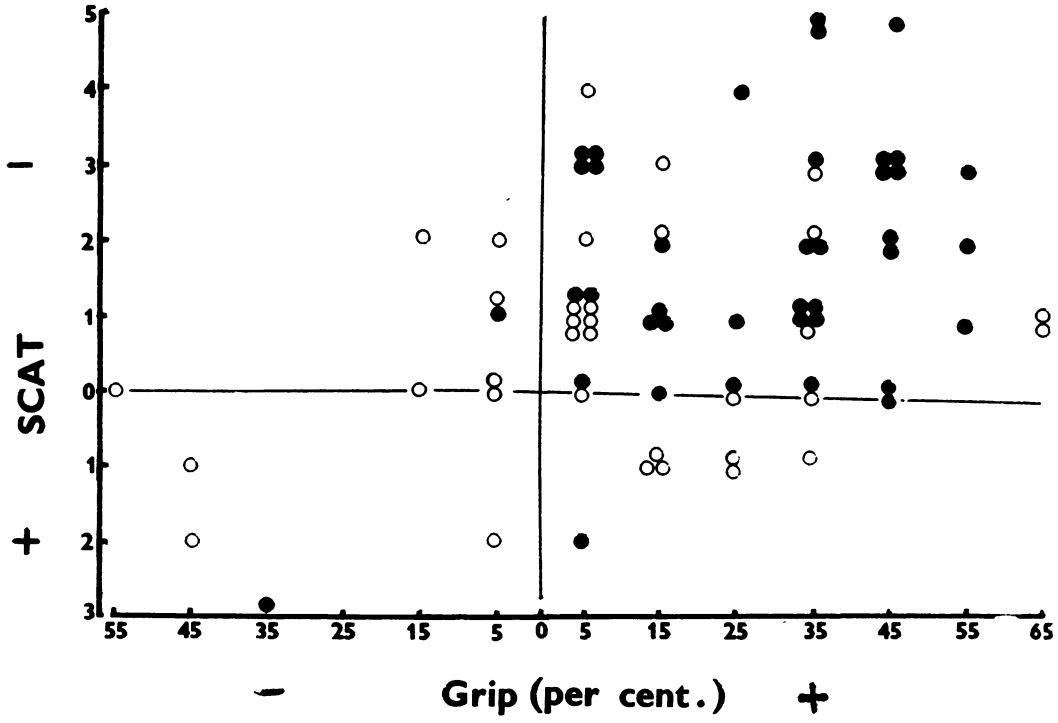

Fig. 5.—Correlation between SCAT results and grip in SCAT-positive patients with disease of any duration.
Black circles = Chloroquine-treated patients.
Hollow circles = Control patients.

of long duration. For the same reason it is not surprising that the correlation coefficient for the control group separately ($r = 0{\cdot}23$) does not differ significantly from zero in this small sample, whereas for the treated group the correlation is still significant ($r = 0{\cdot}40$).

An attempt was made to express by a single figure (composite score) the "change in clinical state" of the patient. The value chosen was the sum of the changes in functional capacity, disease activity, sedimentation rate, and grip strength, the values for each of these being scaled to give approximately equal weight to each characteristic.*

In Fig. 6 the "change in clinical state" of those patients who were SCAT-positive at the start of the trial is plotted against the change in SCAT-titre. The picture is very similar to that in Fig. 5, improvement in clinical state being generally associated with a fall in SCAT titre and deterioration with a rise.

In treated and control patients combined, the correlation coefficient was 0·35, which was significant ($p < 0{\cdot}01$). In the treated group by itself the correlation coefficient was 0·58 ($p < 0{\cdot}001$) and in the control group it was only 0·16, but the inequality of the proportions of patients with disease of long and short duration again probably accounts for some part of the difference between the two groups; the overall picture leaves little doubt that in the treated group clinical improvement tended to be accompanied by a decrease in the SCAT titre.

The possibility that chloroquine in the serum might influence the SCAT and so produce spuriously low titres was investigated. The highest serum concentration observed with doses of 500 mg. is between 150 and 250 μg. per litre (Alving, Eichelberger, Craige, Jones, Whorton, and Pullman, 1948); it was found that the addition *in vitro* of chloroquine diphosphate to give a concentration of either 1,000 or 10,000 μg. per litre in the serum did not alter the SCAT titre (Ball, 1960).

* Changes in grades of disease activity and functional capacity, and 1/10 each of changes in grip (per cent. of higher reading) and erythrocyte sedimentation rate (mm./hr), added together and divided by 4.

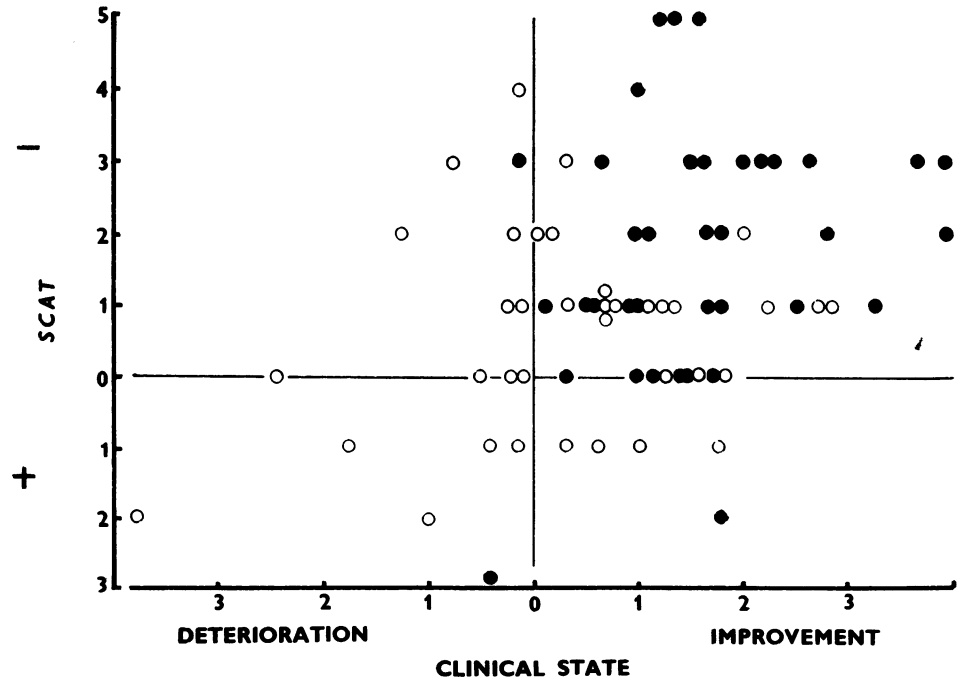

Fig. 6.—Correlation between SCAT results and clinical state in SCAT-positive patients with disease of any duration.
Black circles = Chloroquine-treated patients.
Hollow circles = Control patients.

Discussion

The results of this trial, which are in accord with the recent report by Freedman and Steinberg (1960), suggest that treatment with chloroquine diphosphate in doses of 250 to 500 mg. daily is beneficial in rheumatoid arthritis, particularly if the duration of the disease is less than 2 years, although it does not influence the progression of radiological changes in the first year of observation.

These findings are particularly interesting when compared with the results of the prednisolone/analgesics trial conducted by the Joint Committee of the Medical Research Council and Nuffield Foundation (1959, 1960), in which treatment with prednisolone was associated with significantly less increase of radiological changes in the joints and greater improvement in all clinical and laboratory characteristics studied except the sheep cell agglutination titre, which more often increased in the prednisolone-treated patients, especially during the first 2 years of the trial.

In the present trial, treatment with chloroquine was associated with a significant improvement in terms of the clinical and laboratory characteristics and also with a significant decrease in SCAT titres: progression of radiological changes, however, appears not to have been influenced. It has been suggested, on the basis of the results in the prednisolone/analgesics trial, that the processes responsible for joint erosion and for production of the rheumatoid serum factor might not be identical, since prednisolone appeared to suppress the former while enhancing the latter; the findings in the present trial are compatible with this interpretation, since chloroquine appears to favour regression of the serological changes while having no influence on joint erosion in a one-year period.

The observations of de Forest, Mucci, and Boisvert (1958) provided evidence that the titre of the agglutinating factor might be of prognostic significance, since the trend of the titres over a 2-year period was found to reflect the clinical course of the disease; remission was generally associated with reversion of the test from positive to negative, and continued positivity, usually in moderately high titres, with progressive disease. The results in our patients support this evidence, since clinical improvement was correlated with a decrease in SCAT titre; it therefore seems reasonable to infer that a decrease in SCAT titre is to the advantage of the patient.

Toxicity was not a great problem: although the total incidence of symptoms which might have been due to the treatment appears high (19·1 per cent.) no serious toxic effects were encountered. The incidence of toxic effects is similar to that reported by Merkel (1959) who used the same order of dosage and observed a similar spectrum of symptoms: in ninety of the patients treated with doses of 250 to 500 mg. diphosphate daily the total incidence of toxic symptoms was 22 per cent. Cohen and Calkins (1958) found a higher incidence: twelve of 21 patients given 250 to 500 mg. daily had symptoms attributed to the toxic effect of the drug, and in seven the treatment had to be withdrawn: one patient developed a bizarre psychosis, with delusions and euphoria, but recovered when chloroquine was withheld. Cohen and Calkins point out that their patients were specifically questioned concerning the known toxic manifestations of the drug and suggest that this may have contributed to the high incidence of minor symptoms; the present trial differed from that of Cohen and Calkins in this respect, since no systematic enquiry at regular short intervals was made. Some toxic effects reported previously were not observed in this series; in particular, bleaching of the hair (Sharvill, 1955), urticaria, alopecia, and exfoliative dermatitis (Scherbel and others, 1958), conjunctivitis and precordial pain (Stuart and Aukland, 1958) were not observed: most of these effects, and in addition visual disturbance due to difficulty with accommodation and diplopia, and slight loss of weight, had previously been described by Alving and others (1948). Leucopenia (Cohen and Calkins, 1958) was not observed in our patients, but white blood counts were not done routinely.

Perhaps the most important toxic effects, from the practical standpoint, are those recently reported to affect the eye. Hobbs and Calnan (1958) drew attention in patients treated with chloroquine to the development of deposits in the corneal epithelium; these were similar to those described by Mann (1947) in workers engaged in the manufacture of mepacrine, but their nature was undetermined. Out of a selected group of 28 patients to whom chloroquine was being administered for various indications, 22 had corneal changes, but there was no obvious relationship between dosage or duration of treatment and the development of keratopathy; in some patients the changes were noted to have disappeared after chloroquine treatment had been discontinued. A pathognomonic symptom of these corneal changes is the spontaneous perception of coloured haloes around bright lights, but this was noticed only by three of the patients in Hobbs and Calnan's series and by none in the present study. Zeller and Deering (1958) reported ten similar cases in which regression of the changes followed cessation of treatment. These

corneal deposits are visible only on slit-lamp examination, and this was not carried out routinely in our patients, so that we cannot state whether asymptomatic corneal changes occurred. Kersley and Palin (1959) reported an incidence of keratopathy of 47 per cent. in 36 patients treated with hydroxychloroquine in doses of 400 mg. daily or more, but in all cases the changes had disappeared within 6 months of stopping treatment. A different type of corneal reaction to antimalarial compounds has also been reported; Reese (1946) described an acute congestive reaction resulting in oedema, associated with transient blurring of vision, in airmen receiving mepacrine in suppressive doses, and a comparable experience was reported by Bleil (1958) as part of a severe toxic reaction to amodiaquine: this type of reaction has not been reported in patients treated with chloroquine. A third type of visual disturbance is mentioned by Hobbs and Calnan in which the patients, usually hypermetropes, complained of transient blurring of vision and difficulty with focusing; these symptoms arose either when treatment was started or when the dose was increased, and were attributed to temporary impairment of ciliary function as part of a general disturbance caused by incomplete tolerance of the drug, an effect which is seen also with other drugs such as the sulphonamides. Two treated patients in the present trial had symptoms of dizziness and visual disturbance of this latter type, after less than 2 weeks' treatment with two tablets daily: their symptoms ceased within a few days of stopping treatment. Cataract has not been reported as a complication of chloroquine treatment, and in the absence of further data it must be assumed that its occurrence in one treated and one control patient in this trial was coincidental. It is possible, however, that more serious effects on the eye may attend prolonged treatment; Hobbs, Sorsby, and Freedman (1959) described three cases in which retinopathy with macular degeneration and persisting impairment of vision followed treatment with chloroquine in doses ranging from 100 to 600 mg. daily: this is the most serious toxic effect which has yet been reported and clearly requires further study, although vision has improved in two of the three cases since chloroquine was withdrawn (Freedman, 1960).

Conclusion

The results of this trial suggest that treatment with chloroquine may be of some value in rheumatoid arthritis. Few serious and no irreversible toxic effects were observed, and in this respect chloroquine compares favourably with corticosteroids and gold; the risks of complications such as retinal damage require further investigation, but from the experience of this trial it seems unlikely that such toxic effects will occur frequently if the dose of chloroquine does not exceed 250 mg. of the diphosphate (150 mg. of the base) daily.

It is disappointing that the treatment did not influence the progression of joint damage shown radiologically, but the greater improvement in other respects in the patients given chloroquine appears to warrant its use as a supplement to conservative measures. It would also appear that a decrease in the sheep cell agglutinating titre may be correlated with clinical improvement. If it is confirmed that corticosteroid treatment results in a tendency for the SCAT titre to rise, or to fall less than in controls, and if it is accepted that this represents a disadvantage, it would not be unreasonable to give chloroquine concurrently when corticosteroids have to be used; the effects of corticosteroids on the agglutinating titre might then be counteracted. It also seems possible that adequate suppression of symptoms might be maintained with smaller doses of corticosteroids if chloroquine were given at the same time; it has not yet been shown that the two types of compound would act in synergism, but there seems no reason to suppose that they would not do so or that they would act antagonistically.

Finally, chloroquine has the advantage over gold of being easily administered, while supervision of the treatment need cause the general practitioner little anxiety.

Summary

The results are reported of a long-term, controlled, double-blind therapeutic trial of chloroquine in 134 patients with rheumatoid arthritis.

Alternate patients were treated with one tablet daily (two tablets while in hospital) each containing either 250 or 2·5 mg. chloroquine diphosphate, as an adjunct to a conservative regime; gold was not given, but 21 patients also received corticosteroids.

The results of clinical, laboratory, and radiological assessments at entry are compared with those at follow-up after 1 to 2 years' treatment.

Patients treated with 250 mg. tablets showed significantly greater improvement, in terms of clinical and laboratory criteria, than controls; a similar degree of progression of disease was seen radiologically in both groups.

There was a significant correlation between decrease in the sheep cell agglutinating titre and clinical improvement.

Thirteen treated patients and ten controls had symptoms ascribed to chloroquine toxicity; seven treated patients and one control discontinued

chloroquine treatment after less than 6 weeks for this reason.

It is concluded that chloroquine may be of some value as an adjunct to the conservative treatment of rheumatoid arthritis.

We are greatly indebted to Prof. J. H. Kellgren for advice on the planning and management of this trial, which was carried out on patients under his care, and to Dr. J. Ball for the sheep cell agglutination tests. We also record our thanks to Dr. L. J. Atkinson and Dr. K. D. Coorey, who carried out a number of the assessments, to the Nursing Staff of the Manchester Royal Infirmary and Devonshire Royal Hospital, Buxton, and the secretarial staff of the Rheumatism Research Centre. We are also grateful to Dr. J. M. Mungavin, of the Imperial Chemical Industries Pharmaceutical Division, for arranging the supply of specially prepared chloroquine tablets.

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APPENDIX

Details of the Twelve Patients not Followed-up

Died.—Two patients died early in the trial.

One was a female aged 72 in the control group, who had SCAT-positive rheumatoid arthritis of one year's duration superimposed on long-standing generalized osteo-arthritis. Conservative treatment in hospital was ineffective, and prednisolone was therefore added in a dose of 10 mg. daily. Following an initial improvement, she developed intestinal obstruction, pyelonephritis, and pneumonia, and died 5½ months after entry into the trial.

The second death was that of a female aged 34 in the treated group, who had SCAT-positive rheumatoid arthritis of 10 years' duration and also otosclerosis; she had been subject to attacks of depression for several years. After some initial improvement she had a recurrence of her depression and committed suicide 6 months after entry into the trial.

Not Traced or Refused to Attend.—Four such patients were lost to follow-up.

One was a female aged 51 in the treated group, with SCAT-positive arthritis of 9 years' duration; she received treatment as an in-patient for 5 weeks and seemed to be making satisfactory progress on discharge, but did not attend for follow-up and could not be traced.

The second was a female aged 61 in the treated group, with SCAT-positive arthritis of 1 year's duration, who had shown some improvement after 4 weeks' treatment as an in-patient; she did not attend for follow-up, but in answer to a postal inquiry replied that there had been no change in her condition and that she was not taking any special tablets.

The third was a man aged 59 in the control group, with advanced SCAT-positive arthritis of 11 years' duration, who started treatment after undergoing arthroplasty of the left hip and arthrodesis of the left knee. His disability was chiefly due to destructive changes in the joints, and only limited rehabilitation was achieved: he did not attend for follow-up and wrote to say he had ceased taking the tablets soon after he had returned home.

The fourth was a female aged 66 in the control group, with SCAT-positive rheumatoid arthritis of 18 months' duration superimposed on generalized osteo-arthritis, who received 7 weeks' treatment as an in-patient. Little progress was achieved with conservative treatment and prednisolone was added to the regime with improvement, though she remained much disabled. She did not attend for follow-up, and postal inquiry elicited no reply.

Exclusion for Other Reasons.—Six patients who were withdrawn from the trial after the initial assessment were not subjected to formal follow-up.

A female in the treated group, aged 32, with SCAT-positive arthritis of 2½ years' duration, started treatment as an in-patient; after 5 days she complained of severe dizziness on sudden movements of the eyes and head, but there were no objective neurological signs and the symptoms subsided within 2 days of ceasing treatment. In spite of prolonged conservative treatment, with the addition of prednisolone in low dosage, her symptoms have remained severe; when seen a year after entry to the trial there was evidence of widespread active arthritis and she was considerably disabled.

In two patients there was confusion over the treatment. A man aged 61, with very mild SCAT-positive arthritis of 1 year's duration, started treatment with control tablets as an in-patient, but was shortly afterwards transferred to the care of another physician; treatment with chloroquine was continued, but it is not certain whether the specially-prepared control tablets or the ordinary commercial preparation was used. This man's disability was due largely to a severe compensation neurosis and at entry his arthritis showed little activity; when he was seen a year after entry there was no objective sign of active arthritis. A female aged 56, with SCAT-negative arthritis of 10 months' duration, received control tablets as an in-patient, and after 3 months of conservative treatment her arthritis had passed into complete remission; 8 months after entry she was still almost free of symptoms, but it emerged that she had for some months been taking chloroquine prescribed by her general practitioner instead of the control tablets. A year after entry her condition remained generally satisfactory though there had recently been a mild recurrence of symptoms in the knees and feet.

A female, aged 45 in the treated group, was originally diagnosed as having advanced nodular rheumatoid arthritis but later her illness developed the features of systemic lupus erythematosus; corticotropin was given together with chloroquine from the beginning, and for a year she did well but then relapsed; prednisolone was later substituted for corticotropin with great symptomatic benefit.

A female aged 68 in the treated group, with SCAT-positive arthritis of 20 years' duration, started treatment as an in-patient, but it soon became apparent that she was suffering from a mild psychosis which had in fact been present before treatment was started. Since she showed paranoid features it was thought wiser, after 10 days, to withdraw her from the trial. Her mental state was apparently unaffected by the treatment; no follow-up was attempted.

A female aged 42 in the treated group, with nodular rheumatoid arthritis of 17 years' duration, started treatment as an in-patient. She was severely disabled by destruction of the hip joints, her disease generally appearing quiescent: chloroquine was discontinued a few weeks after her transfer to the care of an orthopaedic surgeon. During the succeeding 2 years there has been a slight increase in her various deformities.

Discussion.—DR. B. ANSELL (*Taplow*) commented on three corneal opacities seen in the first ten patients treated with chloroquine and two incidents of hair bleaching, and asked for information on the incidence of these in the trials.

She then reported the results of a small trial conducted by Dr. E. B. D. Hamilton at Taplow and Dr. J. T. Scott at Hammersmith. 32 patients had completed a 6-month trial, during which they received 600 mg. Plaquenil daily for 3 months and 1 mg. Plaquenil daily for 3 months. In addition there had been three withdrawals, two cases of dyspepsia (one being on placebos at the time), and one of deterioration requiring steroids. Only one instance of visual disturbance (zigzagging of light) had been seen in this trial.

Both subjectively and objectively improvement was slightly greater during the treatment period.

DR. POPERT replied that he had not seen bleaching or loss of hair as a complication, but the patients in the Manchester series had received a lower dosage of chloroquine.

DR. R. M. MASON (*London*) asked how long it took to obtain improvement, and Dr. Popert replied that their impression was that 3 to 6 months' treatment was needed.

DR. G. D. KERSLEY (*Bath*) reported that amodiaquine (camoquin) appeared more toxic than hydroxychloroquine (plaquenil). Improvement was seen after one month, and relapse after stopping therapy in about the same time. Corneal opacities had been noted in 35 per cent. of the patients, but these had cleared in 1 to 4 months after withdrawal of the drug. 10 per cent. of the patients had complained of mistiness of vision but no retinal changes had been observed. One fatal case of agranulocytosis with camoquin had been seen.

PROF. S. J. HARTFALL (*Leeds*) asked for some information concerning the different preparations of antimalarial drugs, and also expressed concern about the unknown influence of placebo reactors in clinical trials.

DR. A. J. POPERT replied that chloroquine diphosphate 250 mg., chloroquine sulphate 200 mg., and hydroxychloroquine sulphate 200 mg. were equivalent in terms of chloroquine base content. There was no evidence that they differed in antimalarial potency or that one salt was more effective than another.

DR. A. FREEDMAN (*London*) said that he was pleased to learn from the Manchester clinical trial that 250 mg. chloroquine diphosphate had proved effective; he thought that this lower dosage, compared with the 400 mg. chloroquine sulphate he had used initially, probably accounted for the absence of corneal opacities.

DR. MCEWEN (*Melbourne*) said that if dosage was expressed in terms of chloroquine base it would eliminate the present confusion concerning preparations and dosage.

DR. R. M. MASON (*London*) said that his unit was studying placebo reactors in a current trial. They had also found that there were quite a proportion of patients in both groups who did not take the tablets and he thought that that might dilute the results.

PROF. J. H. KELLGREN (*Manchester*) wondered whether antimalarials might interfere directly with the sheep cell agglutination titre.

DR. J. BALL (*Manchester*) said that, at the plasma concentrations used, there was no effect *in vitro*.

DR. W. R. M. ALEXANDER (*Edinburgh*) asked whether other antimalarials, of different chemical composition, were being tried. Was the effect dependent on antimalarial action or chemical composition.

DR. POPERT replied that the 4-aminoquinolines, chloroquine and hydroxychloroquine, and also mepacrine, had mainly been used. Mepacrine bore some relation chemically to chloroquine, and could be regarded as a 4-aminoquinoline with an extra benzene ring attached to the quinoline nucleus. He did not think that the 8-aminoquinolines, such as pamaquine and primaquine, had been used, since they were considerably more toxic; nor had Proguanil, which had quite a different structure.

DR. A. FREEDMAN (*London*) observed that in a screening programme of the effects of many agents on the pleuropneumonia-like arthritis in rats, only three were found to have any effect. These were aureomycin, quinacrin, and gold.

Diphosphate de chloroquine dans l'arthrite rhumatismale. Un essai contrôlé

RÉSUMÉ

On rapporte les résultats d'un essai thérapeutique contrôlé (par la méthode de *double-blind*) et prolongé de la chloroquine chez 134 malades atteints d'arthrite rhumatismale.

Des malades pris alternativement, reçurent un comprimé (ou deux s'ils étaient hospitalisés) par jour, contenant 250 mg. de diphosphate de chloroquine pour les uns et 2,5 mg. pour les autres. De plus, tous les malades étaient soumis au traitement habituel; aucun ne reçut de sels d'or, mais 21 d'entre eux reçurent des corticosteroides.

Les résultats des examens médicaux, radiologiques et de laboratoire au début de l'essai ont été comparé à ceux obtenus après d'un à deux ans de traitement.

Les malades traités par les comprimés de 250 mg. ont accusé une amélioration appréciablement plus grande, du point de vue médical et analyse, que les témoins; le tableau radiologique était le même dans les deux groupes.

On nota une corrélation significative entre la baisse des titres d'agglutination des globules de mouton et l'amélioration physique.

Des symptômes attribuables à la toxicité de la chloroquine se sont manifestés chez treize malades traités activement et chez dix témoins; sept malades du groupe traité activement et un malade du groupe témoin ont abandonné la chloroquine au cours des six premières semaines en raison de ces symptômes.

On conclut que la chloroquine présente une certaine valeur comme adjuvant dans le traitement habituel de l'arthrite rheumatismale.

Difosfato de cloroquina en la artritis reumatoide

SUMARIO

Se relatan los resultados de una prueba ciega de tratamineto a largo plazo con cloroquina en 134 enfermos con artritis reumatoide.

Enfermos alternativos fueron tratados con una pastilla diaria (dos pastillas mientras estuvieron hospitalizados) conteniendo sea 250, sea 2,5 mg. de difosfato de cloroquina, como coadyuvante de un tratamiento conservativo; ninguno de los enfermos recibió sales de oro, pero 21 de ellos fueron tratados a la vez con corticosteroides.

Los resultados de las investigaciones clínicas, radiológicas y de laboratorio al principio de la prueba se compararon con los obtenidos después de uno a dos años de tratamiento.

Los enfermos tratados con pastillas de 250 mg. del fármaco presentaron una mejoría significativamente mayor, desde los puntos de vista clínico y de laboratorio, que los testigos; el mismo grado de progresión radiológia de la enfermedad apareció en ambos grupos.

Se registró una significativa correlación entre la disminución en los títulos de aglutinación de los eritrocitos de carnero y la mejoría clínica.

Síntomas atribuables a la toxicidad de la cloroquina aparecieron en trece de los enfermos tratados y en diez de los testigos; siete de los enfermos en tratamiento activo y uno del grupo de control abandonaron el tratamiento con cloroquina por dicha razón durante las seis primeras semanas.

Se concluye que la cloroquina puede ser de valor como coadyuvante del tratamiento conservativo de la artritis reumatoide.