A Controlled Study of Chloroquine as an Antirheumatic Agent

By ALAN S. COHEN AND EVAN CALKINS

The use of a double-blind therapeutic study to determine the effects of chloroquine on rheumatoid arthritis demonstrated antirheumatic properties of this drug. The criteria of Lansbury were successfully combined with other objective measurements to provide data of statistical validity.

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THE QUEST for an effective and safe anti-inflammatory agent for use in the rheumatic diseases has centered, in recent years, chiefly around salicylates and corticoids, with some attention having been given to gold and phenylbutazone. Recently, clinical reports have suggested that the aminoquinoline compounds, heretofore known because of their usefulness in malaria, may also have antirheumatic potency.[1-10] This observation, if true, is of great importance not only because of immediate therapeutic implications, but also because study of these compounds, not related in any obvious fashion to the previously used agents, might provide important clues to the basic chemical properties of anti-inflammatory drugs.

Unfortunately, with one exception,[7] previous studies of the aminoquinolines in rheumatoid arthritis have not been conducted in a double-blind controlled fashion. Demonstration of beneficial action of a drug in rheumatoid arthritis is exceedingly difficult for two reasons. First, the chronic nature of the disease, with its tendency to exacerbations and remissions, necessitates prolonged and carefully controlled study. Second, the evaluation of the degree of activity of the disease, or of the inflammatory process, is difficult to estimate or quantify. Constitutional symptoms, joint discomfort and pain, and the physical appearance of joints are exceedingly difficult to evaluate in themselves; it is also difficult to determine how much weight to put on any one variable in assessing the over-all activity of the disease process.

In order to facilitate the evaluation of anti-inflammatory agents, two systems

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have been proposed which cite criteria by which the state of the disease can be calibrated. The American Rheumatism Association adopted a specific set of criteria in order to make appraisal of therapeutic results more uniform.[11,12] These criteria, however, make no attempt to quantify manifestations of disease activity.[13] Recently Lansbury has devised a system which attempts to isolate the various factors reflecting this systemic involvement by the disease and to place a numerical evaluation on them.[14]

The present study was undertaken with two purposes in mind: first, to determine in a controlled study whether or not antirheumatic activity is exhibited by chloroquine phosphate, a 4-aminoquinoline compound, and second, to compare the two sets of criteria for assessing disease activity which are mentioned above, and to evaluate, by statistical methods where possible, the validity of the variables considered in each.

Materials and Methods

Plan of Study

Twenty-two adult patients with active rheumatoid arthritis of at least eighteen months' duration were selected. All patients had at least two, and usually more, joints involved at the onset of the study. No patients receiving medication other than salicylates (in one case, Phenacetin) were accepted for study. All patients were on a program of physiotherapy, heat to affected joints and modified physical activity.

The study was controlled in a double-blind manner. The active preparation, chloroquine phosphate* in 0.25 gram tablets, and the placebo were identical in appearance. They were bottled in the pharmacy of the Massachusetts General Hospital and dispensed in such manner that no one of the direct participants in the study (patient, physician or secretary) was aware of the nature of the preparation that the patient was receiving.

The plan of study is outlined in figure 1. All patients were evaluated on their customary conservative therapy (see (1) in figure 1), and after a one week period on placebo with no aspirin (see (2) in figure 1). This was done to record the degree of inflammation (if any) that was being suppressed by the salicylates and to establish a test situation for comparing the validity of the proposed indices of disease activity. The patients by random selection were then placed on two study tablets per day, either chloroquine phosphate or placebo. They were instructed to resume aspirin, but to take it only in the doses needed. If the patients were not able to tolerate the test tablet in the full dosage, they were requested to take one tablet daily. The patients were re-evaluated, one, three, six and ten weeks later. Salicylates were again withdrawn for a one week period, while the patients remained on the study tablets. This concluded Phase I of the study. Following this, unknown to the patients, their tablets were switched. Those who had been taking chloroquine were put on placebo, and those who had been taking placebo were put on chloroquine. Salicylates were again taken as needed. After re-evaluation at two, four and eight weeks, the salicylates were withdrawn for a third time, and a final evaluation was performed. This concluded Phase II of the study.

All data were assessed and graded by means of an A.R.A. grade of improvement and a percentage change according to the systemic index of Lansbury, before it had been disclosed which patients had received chloroquine and which had received placebo during the respective phases of the study.

Except for the aspirin dosage, there was no change in the total program of hot applications, limited physical activity, and physical therapy being followed by each patient. Intercurrent illnesses were handled as usual; the test drug was continued unless a leukopenia

*Chloroquine phosphate (Aralen) was kindly supplied by Winthrop Laboratories, New York, N. Y.

below 3,000 white cells per cubic mm. occurred, or severe toxic manifestations became manifest.

Methods of Evaluation

At each evaluation visit, careful histories were obtained independently by two observers concerning the following: length and degree of morning stiffness, pain at rest, pain on motion (degree and location of pain and duration of activity which precipitated it), fatigue at rest and following activity degree of fatigue and duration of activity short of fatigue), intercurrent illness, emotional stress or environmental change and possible toxic effects of the medication. The number of aspirin tablets taken each day was tabulated from a daily log kept by the patient. The log was continued throughout the three periods of omission of salicylates. The patients also daily recorded the number of test tablets taken.

Two or more joints in each patient were evaluated on every visit for warmth, tenderness, fluid and swelling. They were graded according to the following scale: 0 = absent, 1+ = minimal, 2+ = moderate, 3+ = marked, 4+ = maximum. Large joint circumference was measured with a tape measure when possible. Finger-ring size (third and fourth fingers of

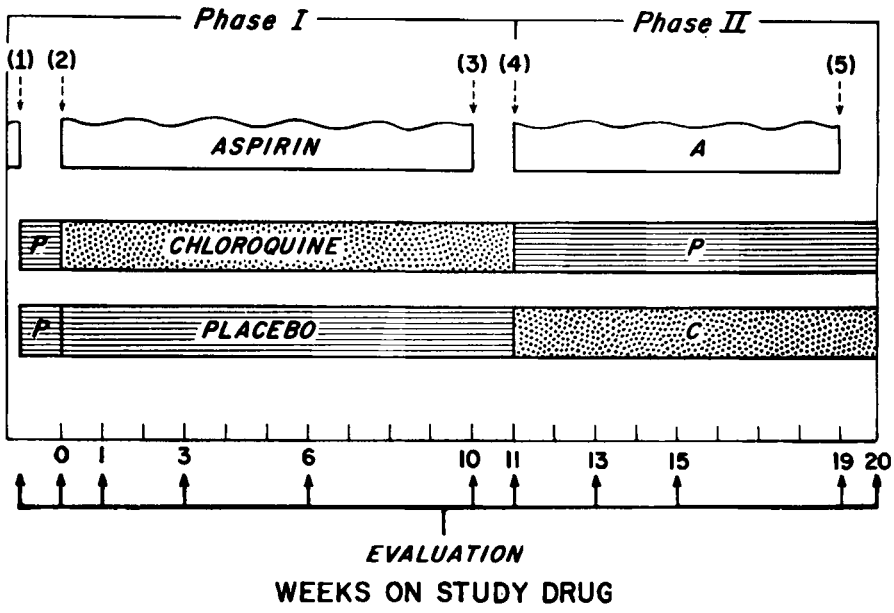

FIG. 1.—Plan of the double blindfold study. Points (1), (2), (3), (4) and (5) represent major evaluation visits, results of which are used in the detailed statistical analyses. A represents aspirin; P represents placebo; C represents chloroquine. Points designated by arrows on the bottom scale represent the weeks at which patients returned to the clinic for detailed medical and laboratory workup.

Thus, all patients were evaluated on customary therapy (1) and after a one week period on placebo without aspirin (2). Then they all resumed their usual program and took aspirin as needed. At the same time, patients were placed on two study tablets per day (either chloroquine or placebo) and re-evaluated one, three, six and ten weeks (3) later. Salicylates were again withdrawn for a one week period while the patients remained on the study tablets. Evaluation at the end of this week (4) concluded Phase I of the study.

Subsequently, unknown to the patients, their tablets were switched (i.e., those on placebo were changed to chloroquine and vice versa). Salicylates were again taken as needed. After re-evaluation at two, four and eight weeks (5), salicylates were withdrawn for a third time and a final evaluation was performed. This concluded Phase II of the study.

both hands) was determined by a standard set of rings, four measurements being obtained and averaged. Grip strength of each hand was measured by recording the manometric deflections following squeezing a sphygmomanometer cuff which had been rolled loosely into a ball and inflated to 20 mm. Hg. The average of three recordings on each hand was obtained. The range of motion of selected peripheral joints was measured by determining the distance between two points such as the insertion of the Achilles' tendon and the tuberosity of the ischium, first with the knee in the flexed and then in the extended position.

On each evaluation visit, blood was drawn for determination of white blood cell count, serum hemoglobin concentration, hematocrit and erythrocyte sedimentation rate (Rourke-Ernstene method), and a urinalysis was performed. At the onset and termination of the study, the cephalin flocculation and serum bilirubin concentrations were obtained. Lupus erythematosus cell preparations were performed by both heparin and clot technics prior to institution of the study. Sera were analyzed for the rheumatoid agglutination factor by the F-II precipitation test (Epstein), the latex fixation method (Plotz and Singer), and the Rh cell agglutination method (Vaughan).*

Characteristics of the patients studied.—At the completion of the study, after the code was broken, the characteristics of the patients in the two arbitrarily selected groups were reviewed. As shown in table 1, the groups were similar in nearly every respect.

Methods of Analysis

American Rheumatism Association Criteria.—All patients were classified at the beginning of therapy as to stage of their disease and the degree (class) of functional impairment in accordance with the American Rheumatism Association Criteria. Estimation of their response to treatment with the test tablets was based on changes in rheumatoid activity, i.e., Grade I response represented complete remission; Grade II, major improvement; Grade III, minor improvement, and Grade IV, no improvement.

Systemic indices.—The systemic indices reported by Lansbury[14] include six factors: the erythrocyte sedimentation rate, pain on motion (quantitated by the number of aspirin tablets taken per day), muscle weakness (determined by compression of blood pressure cuff), length of morning stiffness, fatigability (hours after rising before fatigue was noted) and anemia. Statistical tables converting observed findings to percentile equivalents as used by Lansbury were employed. Each of the six measurements recorded at each clinic visit was converted to its percentile equivalent and the six were averaged. The activity would therefore range from 0 per cent to 260 per cent, as indicated by Lansbury. In order to express improvement numerically in a standard manner for comparison, the difference between the index of activity at the beginning of the phase of the study and at the end of the phase is expressed in this report as an absolute percentage improvement (or lack of improvement).

Example: At (1) on figure 1 = 200%
At (3) on figure 1 = 150%
50%

$$\frac{50\%}{200\%} = \frac{1}{4} = 25 \text{ per cent absolute improvement}$$

Arbitrarily, it was considered that any absolute improvement of 15 per cent or greater was clinically significant.

Statistical methods.—The nature of the experiment allowed two basic types of statistical comparisons to be made. First, the means of the various measurements obtained for the chloroquine-treated patients were compared to the means of the same measurements obtained from the placebo-treated group at various points in the study. The second type of comparison used each patient as his own control to determine whether or not the patient

*These serologic reactions were analyzed through the courtesy of Dr. H. G. Kunkel and associates, Rockefeller Institute for Medical Research, New York, N. Y.

TABLE 1.—*Characteristics of the Patients Studied*

		GROUP "A"*	GROUP "B"†	TOTAL
Number of patients		12	10	22
Number of female patients		8	7	15
Age in years (range)		30–78	34–69	30–78
Age in years (mean)		55.75	53.3	54.5
Duration of R.A. in years (range)		1.5–32	1.5–20	1.5–32
Duration of R.A. in years (mean)		11.0	8.1	9.75
Duration of continuous disease activity in years (range)		1.5–16	1.5–10	1.5–16
Duration of continuous disease activity in years (mean)		5.0	3.5	4.4
Positive L.E. test‡		0	0	0
Positive F-II precipitation test of Epstein		5§	6	11
Positive latex fixation test		7§	7	14
Positive Rh cell agglutination test		7§	7	14
Stage of Disease (A.R.A. classification)	I	1	0	1
	II	5	4	9
	III	4	3	7
	IV	2	3	5
Class of Disease (A.R.A. classification)	I	0	0	0
	II	8	5	13
	III	4	5	9
	IV	0	0	0

*Group "A" received chloroquine in Phase I, placebo in Phase II of the study.
†Group "B" received placebo in Phase I, chloroquine in Phase II of the study.
‡Both heparinized and clotted blood technics utilized.
§One patient not tested.

underwent significant changes coincident with shifts in the regimen (i.e., the method of matched samples).

When the first type of statistical test was carried out, the following points in the study were compared wherever the data were available.

A. Before and after cessation of aspirin (points (1) and (2) on figure 1).
B. Before and after the course of therapy with the initial study drug while on aspirin (points (1) and (3) on figure 1).
C. Before and after the course of therapy with the initial study drug when off aspirin for one week (points (2) and (4) on figure 1).
D. Before and after switch in study drug while on aspirin (points (3) and (5) on figure 1).

The comparisons were analyzed statistically by determining the significance of the differences of the means at the time particular points were being evaluated. A t test of significance was used to examine these differences.[15]

The second basic type of statistic used in the present study was designed to determine whether the same patient underwent significantly different changes when he or she was receiving different medications during the experiment (method of matching samples). According to this method of analysis, each patient acted as his own control. For these analyses only points (1), (3), and (5) in figure 1 were used. Although in the course of the study every patient who was observed until the end of the experiment had gone through one phase of the active and one of the inert drug, the two groups (the one receiving placebo first and the second receiving chloroquine first) were not combined in the analyses. They were kept separate, because one might expect chloroquine to have a lingering effect and

thereby make the patients on placebo during the last phase not comparable to those placed on the inert drug first.

In addition to the above analyses, the first change in the study, consisting of removing the patient from aspirin at the beginning of the experiment for one week, was analyzed. The statistical tests made here were for the purpose of determining which of the various symptoms, signs, laboratory tests or measurements investigated took a significant turn for the better or worse when the patient omitted aspirin for one week. The statistic used was for each attribute, the mean of the differences in the magnitude of the measurements taken before and after the patient was taken off aspirin. A t test of significance was used to examine the differences.[15]

For all the statistical tests carried out, if the observed value of the mean or of the proportion had a theoretical possibility, p, of occurrence of less than 5 in 1000 by chance, the event was considered highly significant, i.e.

$p = <0.005$ highly significant
$p = <0.01$ significant
$p = <0.025$
<0.05 possibly significant

All p values of more common occurrence were considered to be not significant.

Results

American Rheumatism Association Criteria.—When judged according to American Rheumatism Association criteria of improvement, ten of the twelve patients on chloroquine during Phase I improved, while no patient on placebo improved. As shown in table 2, the improvement was Grade I in one patient, Grade II in six, and Grade III in three.* In Phase II of the study, six of the eight patients who previously had been on placebo and now were on chloroquine showed improvement, three having Grade III response and three a Grade II response. In only one of the patients first on chloroquine, but now on placebo, did the improvement continue. Thus, cumulatively, 80 per cent (sixteen out of twenty patients evaluated) noted improvement on chloroquine therapy compared to 6 per cent (one out of seventeen) of the patients on placebo.

Systemic indices of activity.—Similar results were obtained when the data were evaluated by the systemic indices of Lansbury. The absolute scale of improvement discussed earlier was utilized for these analyses. Arbitrarily, it was considered that any improvement of over 15 per cent by these indices was of significance. In Phase I, ten out of twelve patients on chloroquine had a 25 per cent improvement or better, including one who by A.R.A. criteria did not improve. In the other patients the improvement was less than 15 per cent. (One of these had exhibited a Grade III response by A.R.A. criteria.) No placebo-treated patient improved as much as 15 per cent.

In phase II, four of eight chloroquine-treated patients had an improvement of 15 per cent or greater. Of the four with a lesser response, three had improvement by A.R.A. criteria, while one with no improvement according to the latter analysis was better according to the systemic indices. In the placebo-treated group in Phase II, the same patient who had maintained improvement by

*In uncontrolled clinical observation, a Grade III response is not considered significant. In this study where the results are based on simultaneous observation of both treated and control groups of patients, a Grade III response is useful for comparison.

TABLE 2.—*Results of Therapy in Individual Patients According to the A.R.A. Criteria and Lansbury Systemic Indices*

Patient	PHASE I‡ CHLOROQUINE A.R.A. Grade	% of Improvement‖ (Systemic Index)	PHASE II§ PLACEBO A.R.A. Grade	% of Improvement (Systemic Index)
S.A.	III	+36.4	*	*
M.L.	II	+28.1	IV	−8.7
S.L.	II	+56.7	*	*
E.Mc.	I	+81.4	IV	−52.5
G.P.	IV	−27.0	IV	−6.3
P.R.	II	+55.4	*	*
E.S.	II	+48.7	II	+38.5
E.G.	III	+4.8	*	*
E.L.	IV	+27.5	IV	+10.8
E.N.	III	+37.8	IV	−20.3
J.P.	II	+40.7	IV	−19.4
B.R.	II	+27.4	*	*

	PLACEBO A.R.A. Grade	% of Improvement Index	CHLOROQUINE A.R.A. Grade	% of Improvement Index
W.B.	IV	+13.6	III	+22.1
C.B.	IV	−6.6	III	+16.9
E.C.	IV	0	III	+2.7
I.Mc.	IV	+10.5	II	+10.6
B.S.	IV	+6.4	†	†
K.A.	IV	+2.7	II	+8.5
M.C.	IV	+11.1	IV	+21.2
E.H.	IV	−32.7	II	+23.9
H.K.	IV	+11.5	IV	+9.2
J.R.	IV	+2.3	†	†

*Patient omitted from study during Phase I due to drug toxicity.

†Patient lost to follow-up.

‡Comparing the medical evaluation of the patient at points (1) and (3) on figure 1.

§Comparing the medical evaluation of the patient at points (3) and (5) on figure 1.

‖Determined on a 100% scale; see text.

A.R.A. criteria did so by the systemic indices. All the rest showed no further improvement. Thus, 70 per cent (fourteen out of twenty) of all patients treated with chloroquine improved according to the systemic index data, while only 6 per cent (one out of seventeen) of placebo-treated patients did so.

Improvement by either A.R.A. or Lansbury index was exhibited by 90 per cent of chloroquine-treated and 6 per cent of placebo-treated patients.

Statistical analyses of data.—(A) Effect of Omission of Aspirin. Each patient was evaluated by the various criteria both initially and then following one week on placebo without aspirin. These data gave information regarding the suppression of rheumatoid activity by the salicylates alone and provided figures for comparison with subsequent therapy. The data were separated into two groups: Group A, the patients subsequently treated with chloroquine in Phase I of the study and Group B, those subsequently given placebo in Phase I. Because of this separation, it was possible to compare the severity of symptoms being suppressed by aspirin in the groups and obtain further evidence

concerning whether the controls were comparable to the treated group of patients.

Ten modalities were statistically analyzed. When the significance of the difference of each modality was determined both before and after aspirin was withdrawn, the two groups gave similar results (table 3). Three modalities, i.e., grip strength, finger-ring size and length of morning stiffness significantly worsened in both groups. The joint warmth, amount of joint fluid, joint tenderness, circumference of large joints, length of time until fatigue set in and sedimentation rates showed no changes of significance.

The joint swelling of Group A increased off aspirin, while that of Group B did not. However, when these two groups were statistically compared with one another, no significant difference was found. When each modality was checked in this manner (thus checking the similarity of the groups by their inflammation off aspirin), all modalities but one showed no significant differences (table 4). The one that varied was joint tenderness.

(B) Individual Modalities Used in Determining Effect of Chloroquine (table 5). SYMPTOMS. The length of morning stiffness was significantly improved on chloroquine in both phases of the study, as measured by the significance of the difference of the means. The improvement was possibly significant by the method of matched samples. Fatigue was not significantly improved by either method of analysis with the exception of Phase II. The degree of lessening of pain in chloroquine-treated patients was highly significant in both phases. The method of matched samples showed a high level of significance in the patients on placebo first, possible significance in those on chloroquine first.

OBJECTIVE MEASUREMENTS. *Grip strength* was not significantly improved. *Finger-ring size* in phase one was significantly improved in the chloroquine treated group, and though not altered in Phase II, did show by the method of matched samples a high level of significance in the group treated with placebo first.

TABLE 3.—*Effect of Abrupt Cessation of Aspirin in 22 Patients, Before Initial Administration of Chloroquine; Significance of Difference of Various Subjective and Objective Measurements Before and After Omission of Aspirin*

	Group "A" Treated with Chloroquine in Phase I		Group "B" Treated with Placebo in Phase I	
	p	t	p	t
(1) Grip strength	<0.025	−2.37	<0.005	−3.16
(2) Finger-ring size	<0.05	+2.08	<0.01	−2.98
(3) Morning stiffness	<0.05	+1.85	<0.05	+2.11
(4) Joint warmth	N.S.	+0.43	N.S.	+1.00
(5) Amount of joint fluid	N.S.	+1.40	N.S.	+1.68
(6) Joint tenderness	N.S.	+1.77	N.S.	−0.59
(7) Joint swelling	<0.05	+1.90	N.S.	+0.36
(8) Circumference of large joints	N.S.	+0.81	N.S.	+0.0014
(9) Sedimentation rate	N.S.	+0.65	N.S.	+0.89
(10) Fatigue	N.S.	−0.74	N.S.	−1.67

p = <0.005 = highly significant; p = <0.01 = significant; p = $\left.\begin{matrix}<0.025\\<0.05\end{matrix}\right)$ = possibly significant; N.S. = not significant.

TABLE 4.—*Significance of Difference Between Group A and Group B On and Off Aspirin*

	p	t
(1) Grip strength	N.S.	−1.26
(2) Finger-ring size	N.S.	1.16
(3) Morning stiffness	N.S.	0.638
(4) Joint warmth	N.S.	0.141
(5) Amount of joint fluid	N.S.	−0.44
(6) Joint tenderness	<0.05	1.79
(7) Joint swelling	N.S.	1.05
(8) Circumference of large joints	N.S.	0.07
(9) Sedimentation rate	N.S.	−0.268
(10) Fatigue	N.S.	0.21

p = <0.005 = highly significant; p = <0.01 = significant; p = $\left.\begin{matrix}<0.025\\<0.05\end{matrix}\right)$ = possibly significant; N.S. = not significant.

This table demonstrates that the chloroquine-treated group of patients was comparable, except for joint tenderness, to the placebo-treated patients, as determined by the response to withdrawal of aspirin.

TABLE 5.—*Statistical Comparison of Symptoms, Objective Measurements and Laboratory Findings in the Chloroquine-Treated and Placebo-Treated Patients*

	Significance of Differences of Means Chloroquine vs. Placebo Treated Patients				Matched Sample Analysis (Each patient as his own control)			
	Phase I On Aspirin (3) - (1)*		Phase II On Aspirin (5) - (3)*		Patients on Chloroquine First		Patients on Placebo First	
	p	t	p	t	p	t	p	t
Symptoms								
(1) Morning Stiffness	<0.01	−2.63	<0.01	+2.96	<0.05	−2.10	<0.05	−2.30
(2) Fatigue	N.S.	1.34	<0.05	−2.76	N.S.	+1.52	N.S.	+1.14
(3) Pain	<0.005	−5.69	<0.005	+6.63	<0.025	−2.70	<0.005	−5.63
Objective Measurements								
(1) Grip Strength	N.S.	−0.01	N.S.	+1.01	N.S.	−1.16	N.S.	+0.82
(2) Finger-ring Size	<0.01	−2.67	N.S.	+1.37	<0.005	−6.40	<0.025	−2.37
(3) Recorded Number of Aspirins per day	<0.005	−5.32	<0.05	+1.80	<0.01	−4.02	N.S.	−1.25
Specific Joint Measurements								
(1) Joint Warmth	<0.005	−4.20	<0.005	+7.07	N.S.	−1.64	<0.01	+3.04
(2) Joint Tenderness	<0.05	−1.75	N.S.	+1.28	N.S.	−1.35	N.S.	−0.71
(3) Joint Fluid	N.S.	−1.48	N.S.	+1.72	N.S.	−1.77	N.S.	−1.73
(4) Joint Swelling	<0.05	−2.06	<0.025	+2.19	N.S.	−1.27	N.S.	−1.80
(5) Large Joint Circumference	N.S.	−0.44	N.S.	−0.48	N.S.	+0.90	N.S.	+1.17
Laboratory Findings								
(1) Sedimentation Rate	<0.025	−2.19	N.S.	−0.78	N.S.	−1.78	N.S.	+0.86
(2) Hemoglobin	N.S.	+0.02	N.S.	+0.52	N.S.	−1.87	<0.005	+5.89
(3) White Blood Count	N.S.	−0.67	N.S.	+0.70	N.S.	−1.29	N.S.	0

p = <0.005 = highly significant; p = <0.01 = significant; p = $\left.\begin{matrix}<0.025\\<0.050\end{matrix}\right)$ = possibly significant; N.S. = not significant.

* = see figure 1.

The *decrease in the number of aspirins* used by the patients in phase I was highly significant, possibly significant in Phase II. It was significant by the method of matched samples in patients treated with chloroquine first and not significant in patients treated with placebo first.

SPECIFIC JOINT MEASUREMENTS. The difference in the magnitude of *joint warmth* was highly significant demonstrating marked improvement in both

phases of the study. Matched sample analysis showed significant improvement when patients were on placebo first and no significance when they were given chloroquine first. The improvement in joint tenderness was of possible significance in Phase I, not significant in Phase II, and not significant by matched sample analysis. There was no significant change in the *amount of fluid* found in the joints, as estimated clinically. *Joint swelling* showed possibly significant improvement by the first type of analysis, none by the latter. *Large joint circumference* showed no significant change.

LABORATORY DATA. The *sedimentation rate* showed a possibly significant difference in phase one of the study, none in phase two and no change by matched samples analyses. The *blood hemoglobin level* showed improvement in the patients on placebo first by the matched sample analysis, but no change in the remainder of the analyses. There were no significant differences in the *white blood count* by either type of analysis.

Measurements of range of joint motion and of flexion deformity were carried out in a limited number of patients. These were too few to be evaluated in detail, but appeared to be consistent with the changes in the other indications of disease activity.

Systemic Index of Activity (table 6). A crude evaluation of the improvement of the patients by means of the previously noted modification of the index of activity to a 100 per cent scale was presented in an earlier section. When the index of activity figures were subjected to statistical analysis, it was found that the chloroquine-treated patients showed highly significant improvement in Phase I and significant improvement in Phase II as compared to the placebo-treated patients. The matched sample analysis showed possibly significant differences in the patients on chloroquine first and none in the patients on the placebo first.

The six factors constituting the systemic index have already been analyzed individually in the preceding paragraphs, but are regrouped in table 6.

Toxicity.—A list was prepared of known toxic manifestations of chloroquine.

TABLE 6.—*Statistical Analysis of Systemic Index of Activity*

	Significance of Differences Chloroquine vs. Placebo-Treated Patients				Matched Sample Analysis			
	Phase I On Aspirin (8) - (1)*		Phase II On Aspirin (5) - (3)*		Patients on Chloroquine First		Patients on Placebo First	
	p	t	p	t	p	t	p	t
Systemic Index of Activity of Lansbury	<0.005	−3.08	<0.01	+2.88	<0.025	−2.81	N.S.	−1.49
Morning Stiffness	<0.01	−2.62	<0.01	+2.96	<0.05	−2.10	<0.05	−2.30
Fatigue	N.S.	1.34	<0.05	−2.76	N.S.	+1.52	N.S.	+1.14
Number of Aspirins	<0.005	−5.32	<0.05	+1.80	<0.01	−4.02	N.S.	−1.25
Grip Strength	N.S.	−0.01	N.S.	+1.01	N.S.	−1.16	N.S.	+0.82
Hemoglobin	N.S.	+0.02	N.S.	+0.52	N.S.	−1.87	<0.005	+5.89
Sedimentation Rate	<0.025	−2.19	N.S.	−0.78	N.S.	−1.78	N.S.	+0.86

p = <0.005 = highly significant; p = <0.01 = significant; p = <0.025 / <0.050 = possibly significant; N.S. = not significant.

* = see figure 1.

These included skin rash, hair changes, headache, pruritus, visual disturbances, gastrointestinal complaints and neurologic complaints.[16,17] All patients in both phases of the study were asked about the presence of these symptoms at each study visit. They also were examined for the presence of rashes, hair changes and other possible toxic drug effects. Cephalin flocculation tests and serum bilirubins were carried out at the onset and termination of the study. White blood and differential leukocyte counts, hemoglobin and complete urinalyses were obtained at each clinic visit.

As shown in table 7 and figure 2, over half of the patients exhibited toxic manifestations during the chloroquine therapy, far more than due to the placebo therapy. In almost one-third (seven) of the patients, toxicity due to chloroquine was sufficiently severe to make stopping the drug advisable. In no placebo-treated patient was the drug omitted because of suspected toxicity.

In the chloroquine-treated patients, the most common severe complication was an epigastric burning sensation, associated with anorexia, and often with nausea and vomiting. This was usually not relieved by an antacid and belladonna; therefore, omission of the drug in four patients with these symptoms was advised. Roentgenograms of the upper gastrointestinal tract were taken in three patients. All were negative. The symptoms subsided following omission of the medication, but often only after a lapse of one to four weeks. The symptoms were accompanied in several cases by chilly or shaky sensations and by a slight tremor, which disappeared as soon as the drug was discontinued.

Chloroquine was discontinued in two patients because of a fall in the white blood count below 3,000 cells/cu. mm. In one case, the count was 2,800 and the other 2,600. The differential leukocyte counts remained normal. The white count in these patients did not fall abruptly but became lower over successive weekly visits. One of these two patients had severe gastrointestinal symptoms while the other was completely asymptomatic. The white blood count rose to normal within one week after the drug was discontinued. Chloroquine was discontinued in a seventh patient because of bizarre psychic manifestations. The patient, aged 78, developed auditory hallucinations, which disappeared when the drug was discontinued. The milder symptoms included blurred vision in three and telescoping vision in one patient. These effects disappeared several days after the dose was lowered.

One patient who received chloroquine for two weeks developed a severe

TABLE 7.—*Toxicity of Chloroquine*

	Total Number of Patients with Symptoms	Number of Patients in Whom Drug had to be Withdrawn Because of this Symptom
(1) Gastrointestinal	8	4
(2) Nonspecific Shakiness	5	0
(3) Visual	4	0
(4) Leukopenia	2	2
(5) Skin	1	0
(6) Mental	1	1

Total Patients Affected: 12 of 21

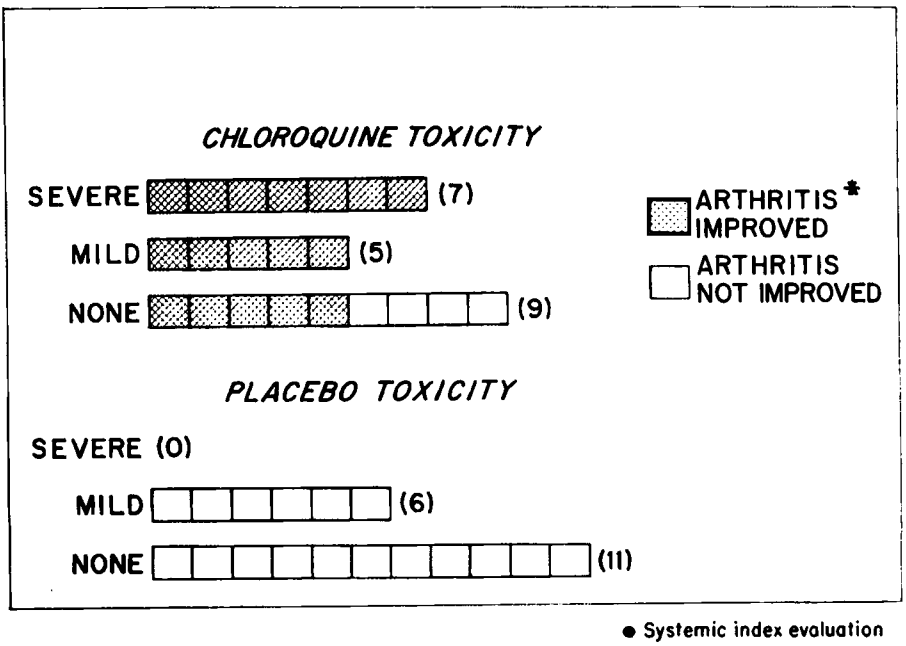

FIG. 2.—A total of 12 patients (of 21 eventually given chloroquine) had toxic symptoms. In seven the symptoms were severe enough to necessitate withdrawal of the drug. Although all patients who had side effects showed improvement (shaded squares), five patients with no side effects whatsoever were equally improved.

Six of the patients on placebo demonstrated side effects. In none were the side effects severe enough to warrant discontinuation of the drug.

maculopapular pruritic rash over her entire body. The patient was hospitalized and the drug discontinued. Since she was also on phenobarbital, and since she had no other side effects, it was difficult to know whether chloroquine was the responsible agent. The eruption subsided in three weeks, at which time the patient, under close observation, was given a test dose of 0.125 Gm. of chloroquine. Though no adverse response was noted, this suggestive test does not rule out the possibility that the eruption was caused by chloroquine. It is of interest that in the placebo-treated group, two patients had minor dermatologic complaints (pruritus, transient macular rash), and four had mild gastrointestinal upsets.

In conclusion, chloroquine in a dose schedule of 0.5 Gm. per day was associated with a high incidence of significant side effects. Reduction in dose to 0.25 Gm. per day which was attempted in all patients with side effects alleviated minor toxicity, but the severe side effects were unaffected until the drug was completely omitted.

DISCUSSION

In this short-term controlled study of antirheumatic effects of chloroquine in rheumatoid arthritis, administration of this agent resulted in improvement in a significant number of patients with active disease as compared to the control group.

The study was subject to several possible limitations. First, the number of patients studied, 22, was such that only a rather striking result would have any statistical validity. Despite this, considerable and significant differences between the control and treated groups were observed. Second, during the study, therapy had to be discontinued in seven patients because of toxicity and in two patients because of lack of follow-up. Fortunately each of these nine patients had at least three evaluation visits and had been on medication for at least three weeks; all the data on them were used in the analyses. Since previous reports of the results of chloroquine therapy indicate that the beneficial effects may not become apparent for as long as two months, these patients might have displayed greater improvement with more prolonged therapy. Finally, it should be noted that as a consequence of the time allotted for the study, Phase II consisted of eight weeks, compared to ten weeks for Phase I.

The statistical method of matched samples utilized each patient as his own control. If there were no variations in the disease with time, and if the first drug did not affect subsequent drug treatment, this type of analysis would be ideal. However, since rheumatoid arthritis does fluctuate with time, a paired control was felt to be more useful. In addition, the patient who was given chloroquine first and then switched to placebo would be expected (if the chloroquine were effective) to show the lingering effects of this drug in the second phase of the study. This indeed could appear to make the placebo more effective; therefore the patient could hardly serve as his own control. However, it was deemed that even with these limitations, the method was of value; if significant differences in the two groups were to appear here, one could feel doubly assured of a drug effect, while if none appeared, opinion would be reserved pending further study of a larger group.

Thus, in our discussion of the usefulness of the measurements, we accepted improvement (as of statistical significance), if the analysis by the differences of the means was upheld by the matched sample analyses; we placed in a "to be investigated further" category those that were not upheld by matched sample analysis or those that were significant by matched sample analysis alone; and we considered all other results as not significant in separating the chloroquine and placebo groups. There appeared to be a high degree of correlation between the usefulness of the American Rheumatism Association criteria of improvement, which are largely dependent upon the articular manifestations of disease, and the indices of activity of Lansbury, dependent upon systemic factors. Both were useful and indeed supplementary tools in evaluating the results of therapy.

Under the circumstances noted above the systemic indices of activity appear to demonstrate significant differences between the placebo-treated and chloroquine-treated groups (table 6). However, in this series of patients, of the six parts that constitute the total index only the morning stiffness and number of aspirins taken per day appear to be of individual significance.

When one considers all the parameters measured and analyzed, morning stiffness and pain were the symptomatic manifestations that were of notable

value. This correlates with generally held clinical impressions. The time until fatigue set in was not consistently useful in this study.

In the joint examination, the degree of warmth was of value. Tenderness and swelling of the larger joints were difficult to assess, and the results were not reproducible. The clinical estimation of the amount of joint fluid also showed no significant changes, and measurements of the circumference of large joints by means of the tape measure proved to be of no value. Measurements of finger-ring size, however, were a very useful determinant of the therapeutic efficacy of the drug. Grip strength was surprisingly ineffective in determining therapeutic result. Among the laboratory tests, hemoglobin and white blood count showed no significant variations. The sedimentation rate was only of suggestive value.

The value of these particular modalities is emphasized by the fact that during the study of the effect of aspirin withdrawal on all 22 patients prior to chloroquine or placebo treatment, measurements of finger-ring size and the patient's estimation of the duration of morning stiffness showed significant differences on and off aspirin treatment. In this portion of the study, the changes in grip strength were also significant.

Chloroquine has been in use as an antimalarial for a number of years, but has been given largely to healthy young adult males and administered in lower and less prolonged dosage schedules than suggested in rheumatoid diseases. The results of this study emphasize that chloroquine is a toxic drug. In one-third of the patients the drug had to be discontinued because of toxic effects; two-thirds of the patients complained of toxic manifestations of some degree. This incidence of toxicity is higher than in other reported studies.[7-10]

Relatively few studies of the toxicity of chloroquine in rheumatoid arthritis have been reported. Freedman,[7] in his carefully controlled study of 69 patients, observed no toxicity of significance over a four month period; yet one of his patients on chloroquine developed delusions and euphoria after six weeks. Although this was not reversed on omission of the medication, and though the patient was elderly, the symptoms were remarkably similar to those observed in one of the present patients whose mental aberrations cleared on omission of the drug. Bagnall[8] observed reactions in over 50 per cent of the patients on 250 mg. of chloroquine daily and had to omit the drug in 10 per cent of his series of 125 patients. Haydu[4] found no toxicity in 28 patients given 500 mg. of chloroquine three times a week for six months. Scherbel[10] reported that six of 25 patients could not tolerate the medication. Rinehart[9] made no mention of side effects in 33 patients.

The fact that our patients were specifically questioned concerning the known toxic manifestations of this drug may have contributed to the higher incidence of minor symptoms. Indeed, six patients on placebo had minor side effects usually consisting of nonspecific gastrointestinal complaints. None of the patients complained of severe toxic symptoms during the period of placebo therapy, however, when they were similarly questioned. When severe toxicity to chloroquine did appear it was serious enough to warrant hos-

pitalization in four cases, and almost daily follow-up in the other three. More detailed long-term studies must be carried out in chronically ill patients receiving large doses of the drug, before a true assessment of the toxicity of this agent can be achieved.

These results serve to highlight the difficulties encountered in an attempt to evaluate antirheumatic and anti-inflammatory effects in rheumatoid arthritis. Without carefully worked out controls, it would not be possible to make *any* definite comparisons. With the controls, certain modalities stand out as being highly useful measurements and others as of questionable value. Despite the indication that chloroquine does possess antirheumatic activity, more extensive and prolonged clinical evaluation will be necessary before the beneficial effects of antimalarial agents can be considered proven, their mechanism understood and their possible place in the total therapy of the patient appreciated.

Summary

1. A short-term double blind controlled study was carried out in 22 patients in order to obtain evidence concerning possible antirheumatic effects of chloroquine. Antirheumatic activity was observed in 70 per cent to 80 per cent of the patients (depending on criteria of improvement) as opposed to 6 per cent of the controls.

2. Chloroquine toxicity in this study was significant. In seven patients, medication had to be omitted: in four because of gastrointestinal effects, in two because of leukopenia, and in one due to hallucinations.

3. Detailed statistical analyses of the data were carried out to determine the usefulness of general and individual comparisons. The A.R.A. criteria of improvement correlated closely with evaluation by means of the systemic indices of activity. Among the individual modalities, morning stiffness, articular pain, number of aspirins taken per day, and finger-ring size were most useful.

4. Further long-term carefully controlled studies are needed before the place of chloroquine in our therapeutic armamentarium is established.

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