CLINICAL ASSESSMENT OF RAPIDLY ACTING AGENTS IN RHEUMATOID ARTHRITIS

BY

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The discovery by Hench, Kendall, Slocumb, and Polley (1949) of the therapeutic effects of cortisone in rheumatoid arthritis has stimulated the trial of many other steroids whose action might possibly be similar. Unfortunately the lack of cortisone in this country, with which such substances could be directly compared, has led to considerable difficulty in the interpretation of results. That many therapeutic trials have been carried out using unsatisfactory experimental methods has been strikingly illustrated by the recent controversy over the efficacy or otherwise of deoxycortone and ascorbic acid in rheumatoid arthritis. Some workers (Lewin and Wassén, 1949; LeVay and Loxton, 1950; and others) claim categorically that very remarkable results were being obtained; others (Kellgren, 1949; Spies *et al.*, 1949; Kersley *et al.*, 1950; Fletcher *et al.*, 1950; Copeman *et al.*, 1950) declare equally definitely that their results were negative. Similar claims, though less dramatic, are being made for other steroids lacking an oxygen atom at the 11 position—for example, “pregnenolone” (Davison *et al.*, 1950; Freeman *et al.*, 1950)—but, again, others have failed to confirm these results (Henderson *et al.*, 1950, who quote much unpublished work).

Clinical improvement has been the basis of most claims of therapeutic success. It is necessary, however, to support these claims by the demonstration that such improvement is real, and that it is due in fact to the particular substance administered. Quite apart from normal fluctuations occurring as part of the natural history of rheumatoid arthritis, the psychological effect of giving a new treatment may be considerable, especially as the dramatic effects of cortisone have become widely known. That such effects may be pronounced has been emphasized by Wolf (1950) in a paper entitled “The Effects of Suggestion and Conditioning on the Action of Chemical Agents—the Pharmacology of Placebos.”

Our aim has been to adopt methods of assessment of clinical improvement, with special reference to rheumatoid arthritis, which will show conclusively whether or not an apparently beneficial effect is due to the trial substance. A detailed description of the methods used is given. These have been applied to deoxycortone and ascorbic acid therapy as described by Lewin and Wassén (1949), since their claims were both dramatic and precise: improvement was said to occur within minutes of a single combined injection, and this therefore presented the problem of assessment in the simplest possible terms. It is, however, suggested that these methods might be capable of development and modification for other substances which may become available from time to time.

Experimental Methods

The method used involved the clinical assessment of patients suffering from rheumatoid arthritis before and after injection: it was designed to include the following precautions:

Adequate Numbers.—A sufficiently large number was treated to enable a satisfactory statistical analysis to be carried out where necessary.

Placebo Control.—All patients received both test substance and control injection on separate occasions. They were unaware that placebo injections were being used, and the order of injection was statistically randomized.

Observer Control.—The observer was unaware of the nature of the injection given when carrying out the assessment, nor did he have available any record of previous results.

In addition, care was taken to avoid psychological pressure in that patients were told they were not receiving cortisone or A.C.T.H., and that this was simply a scientific investigation into a substance whose effects were not known. It was made absolutely clear that this was an investigation in which they were being asked to co-operate and that it was not part of their treatment.

Since the full assessment of a case of rheumatoid arthritis is a long and tedious business it was necessary to select certain features which would reasonably be expected to be affected if an active agent were used. Such features were both subjective and objective. The subjective phenomena considered were pain and stiffness. Objective measurements were made of joint tenderness, muscle power as measured by the power of grip, range of movement as illustrated by the range of abduction of the shoulder-joint, and the speed of movement by the time taken to walk a distance of 8 yards (7.3 m.), including climbing some steps. While these are by no means complete—and experience will probably suggest other criteria—they cover most of the recognized features of the disability of rheumatoid arthritis.

Joint swelling as such was not measured. We have not established a satisfactory method of doing this, but it would seem reasonable to suppose that any significant reduction in swelling would be manifested by some change in the other features measured. Nor were pathological criteria included, since these have been the subject of careful investigation by others (Bywaters *et al.*, 1950; Dresner *et al.*, 1950), and, as has already been explained, the object was primarily to find out whether clinical improvement took place.

Details of Methods Used

Forty-three patients—33 female and 10 male—were selected for the trial at their routine visits for consultation or treatment. The diagnosis of rheumatoid arthritis was based on the presence of chronic progressive polyarthritis, largely symmetrical, tending to affect the peripheral joints early, with muscle-wasting, constitutional disturbance, and loss of weight, but with no evidence of any specific infective organism. The patients all fell into Stage 1, 2, or 3 of rheumatoid arthritis as defined by Steinbrocker *et al.* (1949). The age distribution, duration of symptoms, and sedimentation rate within three months of the trial are shown in Table I. It will be seen that no case with an E.S.R. below 15 mm. (Westergren) in the first hour was included. Radiographic changes characteristic of the disease were present in all 36 cases in which an x-ray examination had been carried out. The experimental nature of the treatment was made clear to all the patients, but few of those

TABLE I.—Age Distribution, Duration of Symptoms, and E.S.R.

Age		Duration of Symptoms		Sedimentation Rates (Westergren)	
Years	No. of Cases	Years	No. of Cases	Mm. in 1st Hour	No. of Cases
25- ..	3	1-	7	15-	9
35- ..	8	4-	9	25-	15
45- ..	14	7-	12	35-	6
55- ..	14	10-	6	45-	6
65 and over	4	13-	3	55-	5
		16 and over	6	65 and over	2
Total ..	43		43		43

asked refused to take part in the investigation. They were not told what drugs were being used or that control injections of an inert substance would also be given, but it was made clear that they were not receiving cortisone. They were asked not to take aspirin or other analgesics on the days of the injections.

Patients came up in groups of 10 to 12 to be tested and questioned individually by one of us. They were asked whether they had any pain and, if so, whether it was constant or only present on movement. They were also asked whether stiffness was present and, if so, which part of the body was chiefly affected.

In order to elicit joint tenderness, a swollen joint was squeezed between finger and thumb, maximal force being exerted. In the case of proximal interphalangeal joints, which were usually selected, pressure was applied to their lateral and medial aspects. The amount of joint tenderness was graded arbitrarily according to the patient's reaction to this procedure. If the patient said spontaneously or on questioning that the joint was tender, the amount of tenderness was graded as 1; if in addition he winced or grimaced, the grading was 2; if the reaction was more violent and accompanied by withdrawal of the hand, the grading was 3; if no tenderness could be elicited the grading was 0. This grading is rather similar to that used by Hench *et al.* (1950). They, however, describe some six grades of tenderness; our figures are therefore not comparable with theirs.

For testing grip a rolled sphygmomanometer cuff was used. The end of the cuff was sewn firmly to the roll so as to ensure a cylinder of constant size when inflated. The cuff was inflated until a pressure of 50 mm. Hg was registered on the sphygmomanometer. The diameter of the cylinder was then approximately 6 cm. The patient was told to put his elbow on the table with his forearm inclined to an angle of 45 degrees. The cuff was placed in his hand and he was told to squeeze it as hard as possible and maintain the pressure. The height of the mercury column could not be seen by the patient. The pressure which he was able to maintain for two or three seconds was then recorded, the grip being measured in the right and left hand alternately (Kellgren and Janus, 1950—personal communication). Three readings were taken from each hand, and subsequently the mean of these readings was calculated.

The patient was then asked to abduct his shoulder to the fullest possible extent. The arm was not allowed to move forwards, so that true abduction was carried out. The amount of abduction was recorded in degrees, and, though this is a visual estimate without instrumental aid, a considerable measure of accuracy can be obtained.

He was then asked to walk as quickly as possible from one end of the room to the other, some steps being placed in his path. The length of the room was 12 ft. 4 in. (3.76 m.) and the height of the steps 14 in. (35 cm.) (three

steps were involved of 6 in. (15 cm.), 8 in. (20 cm.), and 6 in. with no hand rail). The time taken to complete the course was measured with a stopwatch.

After being tested the patient received in a separate room his injection from whichever observer was not doing the assessing on that particular group (22 patients were injected by C. E. Q. and 21 by R. M. M.). Numbered envelopes had previously been prepared giving the order of injection, which was randomized. Each patient received a serial number, and the order in which his injections were to be given was determined by opening the corresponding envelope. The nature of the injection was thus concealed from the observer until the group he was assessing had completed the trial.

The technique of injection was as follows: 5 mg. of deoxycortone in 1 ml. of oil or 1 ml. of saline was injected into the muscles of the outer side of the thigh, followed in one or two minutes by 1 g. of ascorbic acid in 10 ml. of aqueous solution or 10 ml. of saline intravenously.

One hour after injection the patient was asked whether his pain was better, unchanged, or worse, and whether his stiffness was less, unchanged, or greater. When the patient reported improvement or deterioration, its extent was graded as "slight," "moderate," or "marked" according to the impression made by his statement. Any other effects from the injections were noted and the tests previously described were then repeated. The assessor was not allowed to see the results of any previous tests when making his assessment. Finally, one week later we noted any improvement or deterioration which had occurred and, in particular, whether the arthritis was better or worse than before the injection.

Results

Subjective Changes.—An analysis of the subjective impressions of the patients following injection is shown in Tables II, III, and IV. In Table II the overall

TABLE II.—Overall Assessment (Subjective)

Condition After Treatment Relative to Condition Before	No. of Cases			
	1 Hour After Injection		1 Week After Injection	
	Da/asc.	Saline	Da/asc.	Saline
Better	24	24	18	16
Unchanged	16	18	19	18
Worse	3	1	5	8
Total	43	43	42	42

One patient did not return for assessment after final injection and has been excluded from comparison one week after.

Da/asc. = deoxycortone and ascorbic acid.

TABLE III.—Pain

Pain 1 Hour After Treatment Relative to Pain Before	No. of Cases	
	Da/asc.	Saline
Better { Marked	1	1
Moderate	12	11
Slight	5	5
Unchanged	23	26
Worse	2	—
Total	43	43

Da/asc. = Deoxycortone and ascorbic acid.

improvement or deterioration, whether affecting pain or stiffness, is recorded. Pain and stiffness are considered separately in Tables III and IV, and the grading of the responses is shown. It is clear from these tables that there was subjective improvement in many patients, no less than 58% claiming this to be the case one hour after either

TABLE IV.—Stiffness

Stiffness 1 Hour After Treatment Relative to Stiffness Before	No. of Cases	
	Da/asc.	Saline
Better { Marked	11 } 19	6 } 19
Moderate		
Slight		
Unchanged	23	22
Worse	1	2
Total	43	43

Da/asc. = Deoxycortone and ascorbic acid.

injection. It is also clear from the tables that the test substance was no more effective than saline in this respect. Only one patient showed marked subjective improvement, and this occurred after each injection. One hour after the first injection (deoxycortone and ascorbic acid) he said there was a dramatic relief of his pain and considerable diminution of stiffness. At the end of a week he said that some days he "had been better, some days worse," but, on the whole, slight improvement had occurred. He was then given his control injection of saline, and one hour later said that "almost immediately after the injection there was a glow and complete relief of pain—it was dramatic." The pain had "gone completely" from his hands, and this time a marked relief of stiffness had also occurred. A week later he said that his improvement had been maintained for four days and that he had then relapsed, although not quite to his pre-injection level.

Joint Tenderness.—The degree of joint tenderness of the selected joint at the first assessment was as follows: 4 cases showed grade 1 tenderness only, 26 cases grade 2, and 13 cases grade 3. The wrist-joint was used in 4 cases, a metacarpo-phalangeal joint in 1 case, and a proximal interphalangeal joint in 38 cases. As can be seen from Table V, the numbers of those improved after injection were relatively small and the difference between the effects

TABLE V.—Joint Tenderness

Tenderness 1 Hour After Treatment Relative to Tenderness Before	No. of Cases	
	Da/asc.	Saline
Better by 1 point on scale ..	8	7
Unchanged	34	32
Worse by 1 point on scale ..	1	4
Total	43	43

Joint tenderness was measured on a scale: 0 = no pain; 1 = slight pain; 2 = wincing; 3 = wincing and withdrawal.
Da/asc = Deoxycortone and ascorbic acid.

of deoxycortone/ascorbic acid and saline is negligible. No formal tests of significance are required to stress the similarity between the figures.

Grip Test.—The average power of grip in each hand before and after injection, measured in mm. Hg over and above the 50 mm. Hg to which the cuff was inflated, is shown in Table VI, together with the average increase

TABLE VI.—Grip Test. Average of Three Readings (mm. Hg)

	Right hand			Left hand		
	Before Injection	After Injection	Difference	Before Injection	After Injection	Difference
Da/asc. ..	50	55	+5	47	52	+5
Saline ..	51	55	+4	48	52	+4

Da/asc. = Deoxycortone and ascorbic acid.

in grip after injection. Table VII gives the frequency distribution of the range of improvement or deterioration. Taking both hands together (86 hands, 43 patients), an increased grip was recorded in 65 after deoxycortone/

ascorbic acid and in 56 after saline. It will be seen from Table VI that the difference in the average increase in grip after test substance as compared with control amounted to 5–4=1 mm. Hg in favour of the test substance for each hand. Such differences are of no practical significance even if they were technically so. Using a significance test, however, for right hands $t=0.433$, $P>0.6$, and for left hands $t=0.757$, $P>0.4$. Evidently in this experiment the effect of deoxycortone/ascorbic acid on the power of grip was not significantly different from that of saline.

TABLE VII.—Grip Test

Difference between Grip 1 Hour After Injection and Grip Before Injection (mm. Hg)	No. of Cases					
	Right Hand		Left Hand		Both Hands	
	Da/asc.	Saline	Da/asc.	Saline	Da/asc.	Saline
Better by more than 10 ..	9	11	9	11	18	22
" 5-1-10 ..	10	9	13	5	23	14
" 0-1-5-0 ..	14	8	10	12	24	20
Worse by 0-0-4-9 ..	5	8	8	8	13	16
" 5-0-9-9 ..	3	4	1	5	4	9
" more than 9-9 ..	2	3	2	2	4	5
Total	43	43	43	43	86	86

Da/asc. = Deoxycortone and ascorbic acid.

Shoulder Abduction.—Patients with a full range of abduction of the shoulders had to be excluded from the analysis of this test since the only change possible would have been a deterioration. Only 24 right shoulders and 26 left shoulders were therefore available in our cases. The average range of abduction of the shoulder-joint in these cases, measured in degrees, is shown in Table VIII.

TABLE VIII.—Average Shoulder-joint Abduction in Degrees

	Right Shoulder			Left Shoulder		
	Before Injection	After Injection	Difference	Before Injection	After Injection	Difference
Da/asc. ..	109	112	+3	100	106	+6
Saline ..	102	108	+6	100	105	+5

Da/asc = Deoxycortone and ascorbic acid.

The difference in response for right shoulders was 6–3=3 degrees in favour of saline, and for left shoulders 6–5=1 degree in favour of deoxycortone/ascorbic acid. As already described, these measurements were made without instrumental aid, and such changes are, of course, well within the experimental error of the method. In any case, such differences are of no practical importance and technically not significant (right $P>0.4$, left $P>0.8$). Table IX shows the frequency distribution of the range

TABLE IX.—Shoulder Abduction

Difference between Abduction 1 Hour After Injection and Abduction Before Injection (Degrees)	No. of Cases					
	Right Shoulder		Left Shoulder		Both Shoulders	
	Da/asc.	Saline	Da/asc.	Saline	Da/asc.	Saline
Improvement:						
20 and over ..	4	3	4	3	8	6
15 ..	—	2	2	2	2	4
10 ..	5	5	3	4	8	9
5 ..	3	1	3	—	6	1
No change ..	7	10	10	13	17	23
Deterioration:						
10 ..	—	1	—	1	—	2
5 ..	2	1	—	3	2	4
15 ..	—	—	2	—	2	—
20 and over ..	3	1	2	—	5	1
Total	24	24	26	26	50	50

Da/asc. = Deoxycortone and ascorbic acid.
Patients who had a maximum range (180 degrees) before injection of either Da/asc. or saline were excluded from this tabulation. Abduction was measured to the nearest 5 degrees, and the scale of differences therefore is discrete.

of improvement or deterioration, and it reveals that where improvements of 15 degrees or better are considered the figures for deoxycortone/ascorbic acid and saline, taking right and left shoulders together, are identical, in each case 10 shoulders showing this amount of improvement. Again, therefore, the test substance has been shown to be without benefit.

Step Test.—From Table X it can be seen that after deoxycortone/ascorbic acid 30 patients showed an improvement on their time, and after saline 29. One patient had

TABLE X.—Step Test

Difference Between Time 1 Hour After Injection and Time Before Injection (Seconds)	No. of Cases	
	Da/asc.	Saline
Better by more than 6.0	—	3
" 4.1-6.0	4	4
" 2.1-4.0	9	6
" 0.1-2.0	17	16
Worse by 0.0-1.9	12	12
" 2.0-3.9	—	—
" 4.0-5.9	—	1
Total	42	42

Da/asc. = Deoxycortone and ascorbic acid.
One patient who was unable to complete the test before saline injection has been excluded from the comparison.

to be excluded as she could not satisfactorily complete the test before her first injection. The average improvement in the times taken following injection (Table XI) was

TABLE XI.—Step Test

	Average Time Taken in Seconds		
	Before Injection	After Injection	Difference
Da/asc.	14.7	13.4	-1.3
Saline	14.9	13.3	-1.6

Da/asc. = Deoxycortone and ascorbic acid.

1.3 seconds after test substance and 1.6 seconds after control injection, giving an advantage of 0.3 second to saline. This difference is again without practical or technical significance ($t=0.573$, $P>0.5$).

Discussion

As Bywaters *et al.* (1950) have pointed out, the presentation of statistically negative results such as we have shown in the objective tests described does not necessarily prove that the particular treatment is without effect, since the wrong criteria may have been chosen for measurement. However, in this investigation no difference could be detected in the subjective responses to deoxycortone/ascorbic acid as compared with saline: and, in fact, there is a marked similarity between the effects of control and test substances in this connexion.

It has already been shown by Kellgren (1949), Spies *et al.* (1949), and Bywaters *et al.* (1950) on small series of in-patients that deoxycortone/ascorbic acid therapy is without effect in rheumatoid arthritis, but the finding that no less than 58% of the 43 out-patients treated by us showed subjective improvement is of considerable interest. It emphasizes the fact that the strictest control methods are necessary to demonstrate that this is not in fact due to the test substance. It was possible to do this by proper randomization of the control injections, combined with the other precautions described, and it seems probable that these effects are simply due to the psychological effect on the patient of the administration of a new treatment. This may also explain the good results which have been claimed for this treatment.

Conclusions

This investigation indicates that the intramuscular injection of 5 mg. of deoxycortone followed immediately by the intravenous administration of 1 g. of ascorbic acid has no specific therapeutic effect on out-patients suffering from rheumatoid arthritis. This applies to subjective effects as well as the degree of joint tenderness, power of grip, range of shoulder abduction, and speed of walking. It also suggests that the injection of any substance of no therapeutic value whatever may produce a transient subjective improvement in approximately two-thirds of cases of rheumatoid arthritis.

Summary

Forty-three patients with active rheumatoid arthritis have been treated with deoxycortone and ascorbic acid, with saline controls.

Subjective improvement occurred to an equal extent after both test and control injections.

No significant difference could be detected when the results of objective tests with control injections were compared with those in which the test substance was used.

The methods of control and assessment used are described.

Our thanks are due to Dr. W. S. C. Copeman, Professor A. Bradford Hill, and Dr. Oswald Savage for their advice and encouragement, and to the physicians of the Arthur Stanley Institute for allowing us to use their cases. We are also much indebted to Mrs. A. E. White for her help with the injections.

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The report of the first session of the Joint I.L.O./W.H.O. Committee on the Hygiene of Seafarers has just been published as No. 20 in the Technical Report Series of the World Health Organization. The committee reviewed some of the main problems affecting the health of seafarers, including such subjects as medical examinations, medicine chests on board ship, accommodation and food supplies on board, hospital treatment on board and in foreign ports, rehabilitation, and social welfare. It was decided that W.H.O. should be asked to investigate the means whereby seamen might be medically examined with a view to preventing the employment of those suffering from active pulmonary tuberculosis. Suggestions were also invited for devising a practical procedure for the medical examination of all new entrants into the service and for ensuring regular periodical examinations thereafter. On the important subject of venereal disease the committee recommended that the attention of Governments be drawn to the importance of maritime nations adhering to the Brussels Agreement of 1924 as an interim measure until a broader instrument, in the form of international health regulations for venereal-disease control, may be established.