CORTICOTROPHIN (ACTH) IN RHEUMATOID ARTHRITIS

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In the original investigation reported by Hench, Kendall, Slocumb, and Polley (1949), both cortisone and corticotrophin were found to suppress the inflammatory element of rheumatoid arthritis. Since then a large number of reports have been published on the effects of oral steroids in this disease, but only a few have described further experience with corticotrophin.

Corticotrophin has the disadvantage that it must be given by injection, and this is probably the main deterrent to its use in treatment. A further impediment may have been the consideration that the indirect action of corticotrophin through adrenal stimulation made the control of long-term corticosteroid therapy in rheumatoid arthritis and other chronic diseases unduly complicated. This indirect action may, however, be turned to advantage, since it is possible, by estimating the urinary steroid excretion, to measure the degree of adrenal stimulation produced and adjust the dose accordingly.

There appears to be one definite merit in corticotrophin as opposed to oral corticosteroid therapy. Symptoms of adrenal insufficiency (including fatigue, hypotension, dizziness, and muscular weakness) occur not uncommonly when oral steroids are withdrawn, after even a relatively short period of treatment. Although these symptoms are usually the result of an abrupt cessation, they may occur even with gradual withdrawal of the steroid, and whilst they are generally unpleasant rather than dangerous, severe adrenal insufficiency does occasionally occur. On the other hand, in our experience, even abrupt cessation of corticotrophin after prolonged administration is not followed by this type of adverse reaction.

Present Investigations

During the last 8 years we have studied patients with severe rheumatoid arthritis during the administration of either oral steroids or corticotrophin as

a long-term regime. The indication for the use of a corticosteroid or corticotrophin was severe active disease in which progress had not been checked by rest, salicylates, and, in most cases, gold. These patients were affected to the extent that they would have been unable to continue their occupations unless the disease could be suppressed, and most of them had already had to stop working.

Material.—The group treated with oral steroids comprises 104 cases and is being used only for comparison of the side-effects. The group treated with corticotrophin comprises 78 cases; the length of administration shown in Table I.

TABLE I
DURATION OF TREATMENT OF 78 PATIENTS

Duration of Treatment (yrs)	7	6	5	4	3	2	1	6-12 mths	Total
	1	2	5	3	4	19	21	23	78

Method.—In 58 of these cases regular estimations of urinary steroid excretion were carried out to try correlate the level of adrenal stimulation with the degree of suppression of the arthritis and with the occurrence of side-effects. Norymberski's method for estimating the excretion of 17-hydroxy-corticosteroids (17(OH)CS) was used (Appleby, Gibson, Norymberski, and Stubbs, 1955). While in hospital for the start of treatment, patients were taught in the biochemical laboratory to measure a 24-hr specimen and when they left hospital they were lent a litre-measuring cylinder and a number of 1-oz. (31-ml) containers with wooden cases which could be sent through the post. As they were nearly all working, they collected their specimens at the week-end, and used small plastic bottles for urine collection when they went out during the day. An aliquot of the well-mixed specimen with note of the 24-hr volume was sent by post to the laboratory each week. The accuracy of the 24-hr urine collection was checked by creatinine determinations.

We did not attempt to maintain any given level of adrenal stimulation, but regulated the dose of

corticotrophin primarily by the clinical response whilst observing 17(OH)CS excretion. We hoped thus to avoid over-stimulation and minimize side-effects.

The adreno-cortical response varies during treatment, and it is therefore important that the urinary steroid excretion should be checked at intervals. We do not know the reason for this variation, whether it is the activity of the disease, or some change in the cortex, but certain patterns of response have become familiar, and are discussed below.

Results of Treatment

In view of the difficulty of assessing the value of therapy in rheumatoid arthritis, especially over short periods of time without careful controls, this report is confined to the clinical response of a subgroup of forty cases in whom estimations of corticosteroid excretion and clinical assessments were carried out regularly from the start of treatment and were followed up for at least 2 years. This was the period of the Medical Research Council/Nuffield Cortisone-Aspirin Trial (1955), which, in the absence of a true control series, is here used for comparison. It should be noted, however, that the M.R.C./Nuffield trial included only early cases (3 to 9 months' duration) in which the prognosis would be expected to be more favourable than in our group.

In thirteen of these forty cases, corticotrophin was discontinued before the end of the 2 years because the patients' response was unsatisfactory: in six because of side-effects, and in seven because a satisfactory level of adrenal stimulation could be maintained only with uneconomically large doses of corticotrophin. Since in these cases oral corticosteroid therapy was substituted, they have been excluded from the results given below.

In six of the remaining 27 cases, it was possible to withdraw corticotrophin before the end of 2 years because it was no longer required; the clinical

assessments were continued and are included in the results. The other 21 cases were still receiving corticotrophin at the end of the 2 years under review. These figures are summarized in Table II.

Clinical Assessments

In this study, clinical assessment was based on strength of grip and joint tenderness. The erythrocyte sedimentation rate has also been used as a measure of progress. Ability to carry out everyday actions, such as getting in and out of a bath unaided, has proved useful in assessing the progress of individual cases but cannot be summarized in the group results.

(a) *Strength of Grip*.—In most cases of rheumatoid arthritis, change in the strength of grip reflects closely the activity of the disease and forms the best single guide to progress. Strength of grip was measured by means of a sphygmomanometer cuff enclosed in a bag 6 in. long and 3 in. wide connected to a standard sphygmomanometer, so that 260 mm. Hg was the maximum recordable reading.

Table III (overleaf) shows the average readings of the sum of the grip of both hands in the 27 patients who completed the 2-year period of observation, together with the equivalent results in the M.R.C./Nuffield Trial.

Another mode of presentation of the results of tests of strength of grip, which was used in the M.R.C./Nuffield Trial, indicates the proportion of cases who showed given changes in their strength of grip during the 2-year period of study. Our results are compared with those of the M.R.C./Nuffield Trial in Table IV (overleaf).

(b) *Joint Tenderness*.—Joint tenderness to firm digital pressure is recorded in three grades, the average of the joints involved being taken as the index of joint tenderness. The results of the present study are shown in Table V (overleaf).

TABLE II
CASES OBSERVED FOR 2 YEARS
(with 17(OH)CS estimations from start of treatment)

Sex	Men	Women	Total
Corticotrophin Stopped			
Because of side-effects	—	6	6
Because of "resistance"	2	5	7
Because of favourable course of disease	2	4	6
Still having corticotrophin at end of 2 years	10	11	21
Total Patients	14	26	40

TABLE III
RESULTS OF TESTS OF STRENGTH OF GRIP

Trial	No. of Cases	Mean Age (yrs)	Mean Duration of Disease (yrs)	Means of Sum of Grip of Both Hands (mm. Hg)		
				At Start	After 1 year	After 2 years
Present Study	27	40.7	4.5	253	457	445
M.R.C./Nuffield (1955)	Cortisone	30	45	272	389	373
	Aspirin	28		227	330	322

TABLE IV
CHANGES IN STRENGTH OF GRIP AFTER 2 YEARS FROM START OF TREATMENT

Hand	Trial		No. of Cases	Change in Strength of Grip (mm. Hg)						
				Improved			None	Deteriorated		
				By 100 mm. Hg or More	By Less than 100 mm Hg	By Less than 100 mm. Hg		By 100 mm. Hg or More		
No.	Per cent.									
Right	Present Study		27	13	48	10	2	1	1	
	M.R.C./Nuffield	Cortisone	..	30	7	23	14	1	6	2
		Aspirin		28	4	14	15	3	6	—
Left	Present Study		27	16	59	9	2	—	—	
	M.R.C./Nuffield	Cortisone	..	30	11	37	12	1	5	1
		Aspirin		28	7	25	14	1	6	—

TABLE V
RESULTS OF ASSESSMENT OF AVERAGE JOINT TENDERNESS

Trial	No. of Cases	Mean Age (yrs)	Mean Duration of Disease (yrs)	Mean "Average" Joint Tenderness		
				At Start	After 1 Year	After 2 Years
Present Study	27	40.7	4.5	1.35	0.30	0.30
M.R.C./Nuffield	Cortisone	30	45	1.91	0.74	0.72
	Aspirin	28		1.89	0.76	0.58

TABLE VI
RESULTS OF ERYTHROCYTE SEDIMENTATION RATE ESTIMATIONS (mm./hr)

Trial	No. of Cases	Mean Age (yrs)	Mean Duration of Disease (yrs)	Mean E.S.R. (mm./hr)		
				At Start	After 1 Year	After 2 Years
Present Study (Westergren)	27	40.7	4.5	43	13	18
M.R.C./Nuffield (Wintrobe)	Cortisone	30	45	42	27	29
	Aspirin	28		42	35	28

(c) *Erythrocyte Sedimentation Rate*.—The means obtained in this study (Westergren) are listed in Table VI with those of the M.R.C./Nuffield Trial (Wintrobe).

Persistence of Response to Corticotrophin

One of the difficulties in long-term treatment with oral steroids is the tendency for the suppression of the arthritis to lessen after a time. Higher dosage is then required, bringing with it an increased risk of severe side-effects. In an attempt to combat this diminishing effect, patients are often changed to one or other of the newer analogues of cortisone, but this again may only succeed for a short time. It appears that the original effectiveness of corticotrophin persists over long periods. Fig. 1 shows the means of the clinical assessments in the 27 cases who responded satisfactorily over a 2-year period,

including six in which the drug was withdrawn without relapse.

Relation of 17(OH)CS Excretion and Clinical Response

The large majority of normal values for 17(OH)CS excretion fall within the range of 5-15 mg./24 hrs (Moxham and Nabarro, 1956; Borth, Linder, and Riondel, 1957). In most cases of severe active rheumatoid arthritis, the excretion is nearer the lower level of these limits (about 5-10 mg./24 hrs). West (1957) has stated that, if the pre-treatment level of steroid excretion is doubled, there will be a measurable clinical response, and our experience agrees with this. Therefore, in some cases, it may not be

Fig. 1.—Means of clinical assessments in the 27 cases who responded satisfactorily for 2 years (including six “remissions”).

necessary to raise the excretion above 15 mg./24 hrs.

In most cases excellent clinical suppression as measured by increase in the strength of grip and abolition of tenderness, can be achieved with a 17(OH)CS excretion of around 20 mg./24 hrs.

Our usual starting dose is 20 units ACTH *per diem*, and as a rule the response is adequate, with a good increase (over 100 per cent.) in the steroid excretion. Occasionally we have had to increase

the dose to 30 units *per diem* before obtaining satisfactory adrenal stimulation. After the initial rise there is a marked fall in the steroid level, often to pre-treatment figures, as if the adrenal cortex had become temporarily exhausted. This is followed by a second rise of 17(OH)CS which flattens out. It is at this point that the maintenance dose may have to be adjusted to obtain a satisfactory continuing steroid excretion. Fig. 2 illustrates this point.

Fig. 2.—Initial rise in steroid excretion with corticotrophin, followed by a fall in excretion and then a secondary rise.

In some patients the steroid excretion remains steady on the same dose for months or years, as in Fig. 3, and no adjustment is necessary.

There are two types of variation which are rare but may occur at any time during treatment. The first is a sudden increase in adrenal response to a dose which has been giving a steady rate of excretion, as illustrated in Fig. 4 (overleaf). This patient, a girl aged 20, produced a sudden unexplained increased steroid excretion in the fourth month of treatment, accompanied by minor side-effects. The dose of corticotrophin had to be reduced rapidly before the 17(OH)CS excretion fell to a safe level. Such a variation will give rise to severe side-effects if it is

not recognized early and the dose reduced, and we suspect it to be due to a temporary lessening in the activity of the disease.

Occasionally the steroid excretion tends to diminish after a period on a regular dose of corticotrophin. This trend can usually be reversed by a moderate increase in the dose, but in some cases even doubling the original dose does not produce any rise in steroid excretion: West (1956) has reported this as acquired resistance to the hormone. We have, on occasion, been able to overcome this resistance by further increasing the amount of corticotrophin, but this has required very large doses,

Fig. 3.—Satisfactory degree of clinical suppression accompanied by a steady urinary steroid excretion after the initial adrenal stimulation.

80 units twice daily in one case. Fig. 5 (opposite) illustrates this temporary resistance in a girl aged 17, which was accompanied by clinical relapse during the twelfth month of treatment. It was eventually overcome by doubling the dose for a short period. Once this refractory state has subsided, we have often been able to reduce the dose again quite rapidly to the previous maintenance level. In a few cases it appeared that prolonged high dosage would be necessary to maintain an adequate response and corticotrophin was withdrawn on this account. In the majority of patients, however, little change has been needed over prolonged periods.

Side-Effects

The main difficulty in the long-term treatment of severe rheumatoid arthritis, with either oral steroids or corticotrophin, is the occurrence of severe side-effects. We were anxious to find out if there was any difference between those produced by oral steroids and those produced by corticotrophin in long-term treatment.

Table VII (overleaf) gives a comparison of two groups observed during the last 8 years, and shows some interesting differences:

- (1) Dyspepsia and peptic ulceration are much

Fig. 4.—Increase in steroid excretion at the fourth month, accompanied by minor side-effects, only corrected by drastic dose reduction.

more common with an oral hormone, which lends support to the theory that this side-effect is due to the local action on the gastric mucosa.

(2) As would be expected, the pituitary hormone is more likely to cause skin trouble such as acne and pigmentation. With corticotrophin acne may be severe, covering the face, chest, and back, and particularly in young women it has been serious enough on a few occasions to necessitate withdrawal or change of the hormone. Pigmentation with corticotrophin has not been a problem and has merely consisted in retention during most of the winter months of sunburn gained in the summer.

(3) Hypertension is more common with corticotrophin. This has been severe enough to cause us to withdraw or change the drug in only six cases.

Correlation of Side-Effects with Level of Adrenal Stimulation

During the last 4 years we have been able to correlate in 58 patients the degree of adrenal stimulation with the occurrence of side-effects.

Hypertension.—There is disagreement whether or not hypotension constitutes a clinical feature of rheumatoid arthritis. Whereas the Empire Rheumatism Council Report (Lewis-Faning, 1950) and Short, Bauer, and

Fig. 5.—Temporary resistance developing in the 12th month of treatment accompanied by clinical relapse. This was overcome by doubling the dose for a short time.

TABLE VII
INCIDENCE OF SIDE-EFFECTS

Therapy					Oral Steroids 104		Corticotrophin 78	
No. of Cases					No.	Per cent.	No.	Per cent.
Side-Effects	Weight Increase				29	27.9	24	30.7
	Moon Facies				54	51.9	42	53.8
	Oedema				34	32.7	23	29.4
	Dyspepsia				49	47.1	12	15.3
	Peptic Ulceration (or Erosion) ..				12	11.5	2	2.5
	Glycosuria				5	4.8	10	12.8
	Acne				7	6.7	25	32.0
	Hirsuties				20	19.2	17	21.7
	Pigmentation				1	0.96	17	21.7
	Chemosis				3	2.9	6	7.6
	Menstrual Irregularity				11/76	14.3	13/50	26.0
	Hypertension				18	17.3	26	33.3
	Osteoporosis				6	5.8	4	5.1
	Mental Disturbance				2	1.9	3	3.8

Reynolds (1957) were unable to show this, Turner and Lansbury (1954) found a low blood pressure in 320 patients, and in the small group of severe cases reported here it has been quite evident.

All patients have shown some rise of blood pressure when the 17(OH)CS excretion has risen significantly above the normal range. When the excretion has been between 25 and 35 mg./24 hrs, about 15 per cent. of patients have shown a rise in the diastolic pressure to 100 mm. Hg, and when the excretion has exceeded 40 mg./24 hrs, the proportion has risen to about 45 per cent. As a rule these rises in blood pressure are transient and closely parallel the corticosteroid excretion. We have not seen chronic hypertension arise in this way, but, in a few cases, when a high corticosteroid excretion has been maintained for 2 to 3 weeks, the hypertension has persisted after a reduction in dose of corticotrophin has brought the 17(OH)CS down to a lower level, and the blood pressure has then fallen only gradually over a period of weeks or months.

Glycosuria.—As with the blood pressure responses, some patients have shown transient glycosuria when corticosteroid excretion has been high. One patient developed a true "steroid diabetes"; this was a man who showed evidence of marked adrenal stimulation when he was given what proved to be a very potent batch of corticotrophin. Despite rapid reduction of the dose, his 17(OH)CS excretion rose from 40 to 105 mg./24 hrs over a period of 5 weeks. It then fell to about 80 mg., but after a further 3 weeks he developed glycosuria, with polyuria and thirst, and a glucose-tolerance test showed a diabetic type of curve; corticotrophin was withdrawn, and with the fall in 17(OH)CS excretion the

glucose tolerance gradually reverted to normal, although there was a significant time-lag. Characteristically, until no time was ketonuria detected.

Fluid Retention and Weight Increase.—All patients have put on some weight while having corticotrophin, but many of them were underweight when treatment was started, and we have taken an increase of 7 lb. (3.2 kg.) or more above their normal weight as being excessive. Improvement in appetite almost always follows effective corticotrophin administration, and such patients have to be warned to check their weight. The majority are able to maintain a normal weight without any drastic dietary restriction, but in about 20 per cent. strict measures are necessary and on the whole it is this group which shows a tendency to fluid retention. These side-effects appear to be due to individual susceptibility rather than adrenal over-stimulation, and frequently become apparent when the 17(OH)CS excretion rises above 15 mg./24 hrs.

Androgenic Side-Effects.—Acne, hirsuties, and menstrual disturbances were quite common in the younger women. They were rarely severe and often occurred when the 17(OH)CS was raised only slightly above the normal range, that is to 15-25 mg./24 hrs. They appeared to be an individual susceptibility in this respect and as a rule androgenic side-effects were not apparent until the patient had received an effective dose of corticotrophin for at least 3 weeks.

It appears, after studying the correlation between side-effects and the level of adrenal stimulation, that the severe disturbances due to overstimulation occur

when the level of 17(OH)CS excretion rises above 30 mg./24 hrs. These side-effects take some weeks to appear and are reversible, though there may be a considerable time-lag between the lowering of the dose and their consequent disappearance.

Discussion

After 8 years' experience, it is clear that a daily self-administered injection of corticotrophin is a practical long-term method of suppressing the activity of severe rheumatoid arthritis. The majority of the patients who were crippled before this treatment have returned to, and remained at, their occupations, and some 46,000 injections have been given without local complications. Suppression of the arthritis can be maintained and the effect of adrenal stimulation does not become less over long periods.

In an earlier report (Savage, Davis, Chapman, Popert, Robertson, and Copeman, 1957), we pointed out the variability of different batches of the drug, and this has now been corrected by the firms whose material we have used in this series.

The corticotrophin has been withdrawn in 46 of the 78 cases started on a long-term regime. It is interesting to examine the reasons for these withdrawals. In fifteen cases the drug was stopped because the patients were able to lead normal lives without it, requiring only occasional aspirin for pain and stiffness. These patients had previously been incapacitated, but were able to return to work while receiving treatment with corticotrophin. After a few months, as progress was satisfactory, the dose was slowly lowered and in this particular group, as no relapse occurred, the corticotrophin was stopped. During the very active stage of the arthritis corticotrophin had suppressed the disease, and as remission occurred it was found possible to withdraw the drug.

These fifteen cases have been followed up for an average of 3 years, and in only one has there been a significant relapse: a woman aged 25, in whom severe arthritis returned at the fifth month of pregnancy 1 year after the drug had been withdrawn. The previous duration of the arthritis in these fifteen cases varied from 6 months to 13 years. The average length of corticotrophin administration was 9 months, and we could discover no common factor in the pattern of steroid response. In only four of these patients can we consider the disease to be in complete remission. In the remaining eleven there are periods of mild activity and the erythrocyte sedimentation rate remains raised, but salicylates are sufficient to enable them to lead normal lives. In the comparable series of 104

similar patients on oral steroids, we have been able to discontinue the hormone in only two cases.

In the remaining 31 cases corticotrophin was withdrawn either because of side-effects (18 cases) or because of the development of a "resistance" to the drug (13 cases). It might have been possible to overcome the resistance by increasing the dosage, as shown in Fig. 5, but at that time not enough corticotrophin was available for this.

In the 31 cases in which the drug was withdrawn because of side-effects, we found that there was too small a margin between the level of adrenal stimulation needed to achieve worthwhile suppression of the arthritis and that at which side-effects occurred, so that continuing treatment with corticotrophin did not seem practicable. The majority of these patients were transferred to oral steroids.

During this study the value of biochemical control has become evident. With this method of control it is possible to check the degree of adrenal stimulation and, when it appears insufficient or excessive, to adjust the dose accordingly.

During the earlier part of our 8-year study of corticosteroid therapy in severe rheumatoid arthritis, the choice between oral steroids and corticotrophin was determined by supplies. Our preference was for oral steroids when available. It is our current practice, however, to use corticotrophin when long-term steroid treatment is indicated, unless the hands remain too crippled for self-injection to be practicable.

Summary

(1) During the last 8 years, 78 cases of severe rheumatoid arthritis have been studied during the self-administration of corticotrophin by subcutaneous injection.

(2) In 58 cases, regular estimations of urinary 17-hydroxy-corticosteroid levels have been carried out by Norymberski's method.

(3) In 27 cases which responded satisfactorily for over 2 years, the clinical measurements have been compared with the groups of cases of early rheumatoid arthritis reported in the Medical Research Council-Nuffield trial for a similar period.

(4) The majority of these patients have been able to return to their occupations and in fifteen of the 78 the corticotrophin has been withdrawn without relapse of the arthritis.

(5) Side-effects have been correlated with the levels of adrenal stimulation and compared with those in a group of patients receiving oral steroids.

This work has been aided by grants from the Dan Mason Research Foundation of the West London Hospital Medical School; the Empire Rheumatism Council; and the Endowment Funds of the West London Hospital.

The corticotrophin used in this study was provided partly by the Ministry of Health and partly by Crookes Laboratories Ltd. of England, and the Armour Laboratories and Wilson Laboratories of the United States of America.

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Corticotrophine (ACTH) dans l'arthrite rhumatismale

RÉSUMÉ

(1) Pendant les dernières 8 années on étudia 78 malades atteints d'arthrite rhumatismale sévère qui s'administraient de la corticotrophine par voie sous-cutanée.

(2) Dans 58 cas on détermina régulièrement les taux des 17-hydroxy-corticostéroïdes par la méthode de Norymberski.

(3) Dans 27 cas qui réagirent d'une manière satis-

faisante pendant plus de 2 ans, on compara les données cliniques à celles rapportées par *Medical Research Council-Nuffield*, concernant des groupes de cas d'arthrite rhumatismale précoce traités pendant une période similaire.

(4) La majorité de ces malades purent retourner à leurs métiers et chez 15 sur 78 la corticotrophine fut interrompue sans provoquer une rechute de l'arthrite.

(5) On détermina la corrélation entre les effets secondaires et le degré de la stimulation surrénale et on les compara aux effets secondaires dans un groupe de malades recevant des stéroïdes par voie orale.

Corticotrofina (ACTH) en la artritis reumatoide

SUMARIO

(1) Durante los últimos 8 años se estudiaron 78 enfermos con artritis reumatoide grave que se administraban a sí mismos corticotrofina por vía subcutánea.

(2) En 58 casos se determinó regularmente la concentración de los 17-hidroxi-corticoesteroides por el método de Norymberski.

(3) En 27 casos que respondieron satisfactoriamente durante más de dos años, se compararon los datos clínicos a los contenidos en el informe de las investigaciones de *Medical Research Council-Nuffield* sobre grupos de casos de artritis reumatoide precoz tratados durante un período similar.

(4) La mayoría de estos enfermos pudieron volver a sus ocupaciones y en 15 de los 78 enfermos la administración de corticotrofina fue interrumpida sin provocar una recaída de la artritis.

(5) Se determinó la correlación entre los efectos secundarios y el grado de estimulación suprarrenal, y se compararon estos efectos a los en un grupo de enfermos recibiendo esteroides por vía oral.