THE ROLE OF ACTH AND CORTISONE IN THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

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The steroids ACTH and cortisone have now been used in the treatment of systemic lupus erythematosus for over five years. Several reports on the results of treatment are available (Haserick, 1953; Dubois *et al.*, 1952; Soffer and Bader, 1952; Harvey *et al.*, 1954). There are few publications in the British literature in which the results of treatment are recorded. (Cohen and Cadman, 1953; Gold and Gowing, 1953; Richards, 1954.)

This report is an attempt to assess the results in a further 12 cases treated over the period, 1950 to 1954.

The main clinical features of these 12 patients are recorded in Table 1, and the main haematological features in Table 2. Differential plasma protein analysis showed an abnormal albumin-globulin ratio, at some stage of the disease, in eight cases (Fig 1). The clinical features and laboratory findings in this group permit little doubt that these patients were suffering from systemic lupus erythematosus.

Before attempting to assess the value of any therapeutic measure in this disease, the prognosis in the untreated case must be considered. Dubois *et al.* (1952) quote a mean expectation of life of 22 months, but Bundick and Ellis (1951) record the figure of four and a half years. It is to be noted that in these groups the diagnosis in most cases lacked the confirmation of a positive L.E. cell test. This criticism does not apply to a series of ten patients seen by Haserick in the year 1948-49, all of whom showed a positive L.E. cell test. None received steroid therapy and at the time of his report in 1953 (Haserick, 1953), one remained alive.

In the present series the patients have been under observation from 1 to 58 months, following or during treatment. This group, therefore, provides material for an assessment of short term results in all cases, but an evaluation of the long term results of treatment is rather more limited.

Treatment

The dose and method of administration of ACTH and cortisone have varied in this series, but are in accord with the generally accepted practice in this country.

TABLE 1

MAJOR CLINICAL MANIFESTATIONS IN 12 CASES OF SYSTEMIC LUPUS ERYTHEMATOSUS

Symptom sign	No. of cases
Rash	10
Fever	12
Arthralgia: Arthritis	10
Pleurisy: Pneumonitis	11
Pericarditis: Endocarditis	2
Cardiac failure	5
Proteinuria	10
Retinitis: Cytoid bodies	3
C.N.S. involvement	4
Reynaud's phenomenon	2

Initial Therapy. This phase of treatment is considered to be that period from the start of treatment until a remission has been successfully induced, during which time high doses of ACTH or cortisone are usually employed. This period ranged from 18 days to 42 days in this group, with an average of 22 days.

Corticotrophin was used for the initial phase of therapy in eight patients. In seven instances it was given by the intramuscular route in doses ranging from 25 mg. to 200 mg. daily, and two patients received intravenous corticotrophin in doses of up to 50 mg. daily.

Cortisone, given orally in daily doses of 100 mg. to 300 mg., was used in three cases. One patient received both ACTH and cortisone (table 3).

Maintenance Therapy. Continuous steroid therapy was maintained in six cases. In two patients treatment was discontinued for a short period after the initial course, but was resumed because of a severe recrudescence of symptoms, and it is notable that in neither case was the second course effective. In the remaining four patients hormonal therapy was discontinued after the initial course either by design or because of complications.

Intramuscular ACTH gel was used for maintenance treatment in two cases, the dose varying from 15 mg. to 25 mg. daily. Oral cortisone, in amounts ranging from 50 mg. to 75 mg. daily, was given to four patients (Table 3).

TABLE 2
HAEMATOLOGY

Case	Sex	Age	Hb (g.)	W.B.C.	E.S.R.	L.E. cells	Platelets
1	F	57	11.0	6,000	32	+	220,000
2	F	39	7.0	1,700	70	+	Nil
3	F	30	8.4	1,000	120	+	64,000
4	F	39	6.36	3,000	140	+	Normal
5	F	57	7.4	2,500	121	+	Normal
6	F	23	9.2	4,000	50	+	110,000
7	F	44	10.4	6,500	50	+	——
8	F	14	13.0	3,400	62	——	——
9	F	56	11.4	5,000	50	+	——
10	M	22	9.5	4,000	63	+	Normal
11	F	34	11.4	2,000	39	+	Normal
12	F	50	11.5	1,800	31	±	Normal

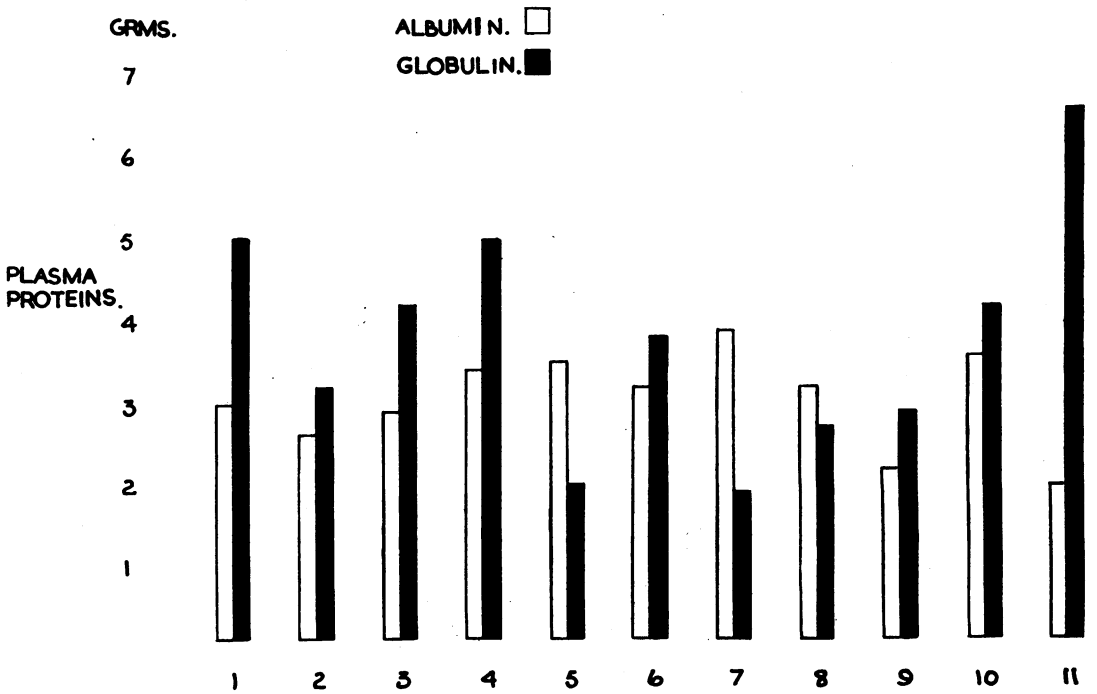

FIG. 1.

TABLE 3

Case	Age	Sex	Treatment				Results	Period (Months from start of treatment)
			Initial	Mg./day	Maintenance	Mg./day		
1	57	F	ACTH	25—30	None	—	Remission	54
2	39	F	ACTH	25—50	Cortisone*	50—150	Died	5
3	30	F	Cortisone	100—300	None	—	Died	27
4	39	F	Cortisone	100	Cortisone	50—75	Died	21
5	57	F	Cortisone	100—150	Cortisone	50	Died	5
6	23	F	ACTH	50	ACTH*	50—200	Died	7
7	44	F	ACTH	50—100	Cortisone	75	Died	8
8	14	F	ACTH	200	None	—	Remission	30
9	56	F	ACTH Cortisone	50 100—200	Cortisone	100	Remission	1
10	22	M	ACTH	40	ACTH	15	Relapse	3
11	34	F	ACTH	50—100	ACTH	25	Relapse	30
12	50	F	ACTH	50—75	None	—	Relapse	26

*In cases 2 and 6 this represents a second ' initial ' course

TABLE 4

RESULTS OF TREATMENT—ACTH AND CORTISONE

Case	Sex	Age	W.B.C.		E.S.R.		L.E. cells	
			Before	After	Before	After	Before	After
1	F	57	7,000	5,000	39	44	+	+
2	F	39	4,500	5,100	73	56	+	—
3	F	30	1,000	1,900	101	102	+	+
4	F	39	3,000	5,000	100	123	+	+
5	F	57	4,000	4,000	127	121	+	+
6	F	23	8,000	4,000	40	62	+	+
7	F	44	6,500	8,000	14	50	+	+
8	F	14	4,000	1,000	59	51	—	—
9	F	56	5,000	8,000	50	23	+	+
10	M	22	4,000	4,900	62	62	Negative	+
11	F	34	3,000	6,000	63	61	+	+
12	F	50	1,800	—	31	45	+	+

Results

The efficacy of these hormones in the treatment of systemic lupus erythematosus may best be judged by their effect on the two phases of the disease, namely, the acute state, or 'lupus crises,' and the subacute phase.

It is now well documented that they frequently exert a dramatic effect on the acute stage, and may appear life saving (Cary *et al.*, 1950; Soffer *et al.*, 1950; Haserick *et al.*, 1951; and Dubois *et al.*, 1952; Harvey *et al.*, 1954). In this series fever was controlled, at least initially, in all except one case, usually within the first 48 hours. In six patients fever recurred within the first ten days of treatment. Disseminated skin lesions present in nine patients cleared within about ten days of the start of treatment. Patients with arthritis or arthralgia claimed relief as a result of treatment, and there was often an objective reduction in periarticular swelling. For two reasons it is difficult to assess the effect of ACTH or cortisone on the pleuro-pulmonary lesions. Firstly, it is not easy to distinguish, clinically or radiologically, between a secondary infective process, and the 'specific' pulmonary lesions described by Rakov and Taylor (1942) and Thorell (1952). Secondly, the almost invariable use of antibiotics in this group makes any evaluation of steroid therapy unreliable. In this series, four patients developed extensive pulmonary changes only after treatment had commenced. As noted by Ragan (1952) two patients with significant renal involvement responded poorly to steroid therapy, and in only one case in the group was there an appreciable reduction in albuminuria following treatment.

In Table 4, details of the total white count, E.S.R., and L.E. cell tests immediately before, and after four to six weeks' treatment are presented. It will be seen that of the seven cases with a leukopaenia immediately before the start of treatment, four showed an increase in total white count; the small numbers involved and the known spontaneous variation in white cell counts in this disease make this an observation of doubtful significance. In only one case was the sedimentation rate reduced during treatment, and in many the rate actually increased, a feature noted previously by Thorn *et al.* (1950) and Dubois *et al.* (1952). The L.E. cell phenomenon persisted throughout this period of observation in eight patients, although fading in intensity towards the end of the period.

Table 5 records the plasma protein analysis immediately before, and after four to six weeks' treatment, and it is apparent that there is no tendency for the abnormal protein pattern to return to normal within this period. In fact in only one case did the high globulin level fall, whereas in three cases there was an increase in the globulin level together with a reversal of the A:G ratio after treatment. This is not in agreement with the observations of Soffer and Bader (1952) or of Cohen and Cadman (1953) but these authors do not state their period of observation. It is possible that a more detailed analysis of the globulin sub-fractions would have shown a different trend.

TABLE 5

RESULTS OF TREATMENT—ACTH AND CORTISONE PLASMA PROTEINS

Case	Sex	Age	Before	After
1	F	59	A = 3.8 G = 2.7	A = 4.0 G = 2.8
2	F	39	A = 2.3 G = 4.3	A = 2.9 G = 4.2
3	F	30	A = 4.0 G = 2.7	A = 2.9 G = 4.2
4	F	39	A = 3.4 G = 5.0	A = 2.4 G = 4.7
5	F	57	A = 3.2 G = 1.9	A = 3.2 G = 2.0
6	F	23	A = 3.3 G = 3.8	A = 3.2 G = 3.8
7	F	44	A = 3.9 G = 1.9	A = 5.2 G = 1.7
8	F	14	A = G =	A = G =
9	F	56	A = 3.2 G = 2.7	A = G =
10	M	22	A = 2.4 G = 2.0	A = 2.8 G = 2.9
11	F	34	A = 2.8 G = 2.5	A = 3.2 G = 3.3
12	F	44	A = 2.0 G = 6.7	A = 1.5 G = 3.6

As already stated, this group does not allow of a long term study, but it should be noted that of the 12 cases treated with ACTH and cortisone since 1950, half have died. The average duration of life after commencement of treatment in the six who have succumbed was 12 months. The impression gained from the close follow-up of five patients on long-term maintenance therapy has been that these steroids merely modify and subdue the inevitable progress of the disease. At no time after the start of treatment was there enough evidence to suggest that the pathological changes characteristic of systemic lupus erythematosus had been arrested.

Of the six patients who remain, three were in

hospital in relapse at the time of this report. Three patients are in remission, two of whom no longer receive maintenance treatment.

Side effects produced by corticotrophin and cortisone have been prominent in this group. Familiar complications such as hypertension with fits, hypokalaemia, steroid diabetes, and acute mania have been encountered. Two patients have developed miliary tuberculosis during the course of treatment, and in neither case was a tuberculous focus suspected before the commencement of treatment; this potential hazard has been recorded previously (Harris-Jones and Pein, 1952; Walker, 1952).

Discussion

This group of patients has been studied and presented because the results of treatment differ from some previously reported (Cohen and Cadman, 1953; Rishards, 1954). In their study of a group comparable to the present one, Soffer and Bader (1952) quote a mortality of 33 per cent. In a recent survey of 62 cases treated with ACTH and cortisone, Harvey *et al.* (1954) record a mortality of 29 per cent.; in 26 per cent. the disease appeared inactive following a single course of steroid therapy; 18 per cent. required continuous maintenance therapy.

The impression gained from the present study, is that although these hormones may induce a remission, particularly in the acute phase, they have little influence on the subsequent course of the disease. Their effect on the pulmonary lesions is unpredictable, and in this respect their use may be hazardous. The thrombocytopaenic state appears uninfluenced by treatment. When the haematological and biochemical results of treatment are set against the clinical response, it seems difficult to conceive that the fundamental pathological process is being arrested. It appears more likely that ACTH and cortisone merely modify the hyper-immune state, and minimize the antigen-antibody reactions presumably responsible for the disease process. Despite their obvious limitations however, these steroids remain the most valuable weapons yet available for the treatment of systemic lupus erythematosus.

Summary

The results of the treatment of 12 cases of systemic lupus erythematosus with ACTH and cortisone are recorded. An evaluation of these results has been attempted, and from this it has been concluded that although these steroids modify the acute phase of the disease, there is less evidence that they influence its subsequent course.

It is a pleasure to record my gratitude for the great help and encouragement I have received from the physicians and dermatologists of the Royal Hospital, and Royal Infirmary, Sheffield, under whose care the patients were admitted. I would also like to express my thanks to Professor C. H. Stuart-Harris for his helpful criticisms of this paper.

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