FURTHER EXPERIENCES WITH PROLONGED TREATMENT OF RHEUMATOID ARTHRITIS WITH A.C.T.H. AND WITH GOLD*

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In an earlier report several problems concerning the long-term treatment of rheumatoid arthritis with A.C.T.H.† were discussed (Goslings *et al.*, 1950). Since that time relatively few authors have concerned themselves with this subject (Hench *et al.*, 1950; Boland, 1950). The conclusion reached from their work is that the general application of A.C.T.H. for the routine treatment of rheumatoid arthritis is not yet justified.

The investigations carried out at this centre on patients receiving prolonged treatment with A.C.T.H. have of late met with special difficulties in a group of patients who originally responded to therapy but later entered into what might be termed a refractory state. In this article several possible explanations of that failure are discussed.

Materials and Methods

The selection of patients was the same as that indicated in a previous communication. All patients were in hospital during the whole course of treatment and received the benefit of general symptomatic and physical therapy. Simultaneous treatment with gold was given during at least part of the A.C.T.H. therapy. Only patients who had failed to respond to gold therapy at an earlier stage of their disease, or who had received no previous treatment, were included in the series.

The methods used have been reported elsewhere (Querido *et al.*, 1951). The estimation of the excretion of the formaldehydogenic corticoids has been adapted from Daughaday's method (Daughaday, Jaffe, and Williams, 1948) as modified by Mason (personal communication, 1950). The ascorbic acid content of the urine was measured by titration with 2,6-dichlorophenolindophenol at pH 4.1. The classification of the rheumatoid process and the assessment of results have been adopted from the therapeutic criteria outlined by Steinbrocker *et al.* (1949).

Results

Table I gives the total number of patients included in this study, their period of treatment, time of follow-up,

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‡Unless otherwise stated, the pituitary hormone used throughout these studies was "cortrophine" (Organon). The dosages used are expressed in mg. Organon standard, which is equivalent to the provisional international A.C.T.H. standard.

and the maximal and minimal amounts of A.C.T.H. administered per patient.

TABLE I.—*Details of Patients Treated*

Number	20
Period of A.C.T.H. administration	1½–8 months
Follow-up after discontinuation of A.C.T.H.	1–14 months
Amount of A.C.T.H. per patient	1,150–6,570 mg

Two conclusions may be drawn from an analysis of the results of treatment with A.C.T.H. (Table II).

TABLE II.—*Results of Treatment with A.C.T.H.*

Result	Optimal Condition	Present Condition
Deterioration	0	3
No improvement	0	7
Minor improvement	3	4
Major improvement	6	5
Complete remission	11	1
Total	20	20

(1) Complete Remission not Always Obtained

It seems justifiable to suppose that a higher daily dosage might have improved these results. That 100% improvement cannot always be expected, however, is shown by the following case. One patient received six doses of 15 mg. a day without a total disappearance of signs and symptoms, in spite of a marked response with regard to the excretion of 17-ketosteroids. In this connexion it is considered important, when comparing the effects of different daily dosages of A.C.T.H., to state the number of injections daily as well as the total amount administered, divided doses producing a greater adrenal response than single ones (Querido *et al.*, 1951).

(2) Effect Maintained in a Relatively Small Minority of Cases

Deterioration occurred not only after the cessation of therapy but in the latter part of this study during the administration of the hormone in a dosage which was considered sufficient for an adequate adrenal response. Earlier experience had given an indication of the minimal effective dosage in six patients. In three this was found to be six doses of 2 mg. a day, these patients relapsing on six 1-mg. doses a day. Remission was sustained in a fourth patient with six 2-mg. doses daily. The two remaining patients required larger doses, but both had complicating diseases (nephrotic syndrome, psoriasis).

In sharp contrast with these results, the last patient of the series (No. 20, see below) relapsed in spite of a continued schedule of six doses of 7 mg. daily.

As a detailed description of the case histories would not assist in assessing the problems of long-term administration of the hormone, the most important facts are summarized in Table III.

So far, no correlation can be found between the severity of the disease and the results of therapy, nor between the maintenance of improvement and the total amount of A.C.T.H. given.

Illustrative Cases

In illustration of these divergent and often disappointing effects, the relevant data of two cases are presented. The first is an example of a highly satisfactory clinical response with sustained remission during prolonged low-dosage administration of A.C.T.H. The second demonstrates a complete relapse during the fourth week of treatment with A.C.T.H.

TABLE III.—Results of A.C.T.H. and Gold on 20 Patients with Rheumatoid Arthritis

Case	Sex	Age	Duration of Disease Before A.C.T.H.	Stage of Disease	Functional Impairment	Duration of Administration of A.C.T.H.	Total Amount Administered in mg.	Degree of Improvement During Period of Optimal Condition	Degree of Improvement at End of A.C.T.H. Therapy	Period of Follow-up After A.C.T.H.	Degree of Improvement at the End of Follow-up Period
1 Sch.	F	36	7 yrs.	III	III	138 days	1,960	Complete	Complete	14 mths.	None
2 Swa.	M	42	10 "	IV	IV	102 "	3,170	Minor	None	4 "	+ Cachexia
3 Lis.	F	33	12 "	III	II	120 "	1,839	Complete	Complete	14 "	Major
4 Dri.	M	65	7 "	IV	IV	118 "	2,625	Minor	Minor	1 mth.	+ Uraemic
5 Gri.*	F	56	1 1/2 "	II	III	66 "	1,194	Complete	Complete	5 mths.	Major
6 Rij.†	M	32	2 1/2 "	IV	III	175 "	2,042	"	Major	14 "	"
7 Mas.	F	54	6 "	III	III	166 "	2,608	"	Complete	6 "	"
8 Pol.	M	50	1 1/2 "	II	III	110 "	1,839	Major	Major	7 "	+ Cortisone
9 Har.	F	28	6 "	II	II	247 "	4,535	Complete	Deterioration	8 mths.	Major
10 Dij.	F	37	10 "	III	IV	135 "	1,692	Major	Major	7 1/2 mths.	Minor
11 Bos.	F	48	15 "	IV	IV	90 "	1,512	Minor	None	4 1/2 "	Complete
12 Li.*	F	46	6 mths.	I	III	144 "	2,285	Complete	Complete	"	"
13 Me.	F	29	10 yrs.	III	IV	176 "	6,570	Major	None	Cortisone	"
14 Her.	F	40	4 "	III	II	73 "	2,146	Complete	"	"	"
15 Hen.	F	50	8 "	III	IV	103 "	2,390	"	"	"	"
16 Lat.	F	29	7 mths.	II	IV	127 "	2,284	Major	Minor	"	"
17 Lud.	M	59	1 yr.	II	III	55 "	2,123	Complete	"	"	"
18 Be.	M	55	3 mths.	III	IV	52 "	1,346	"	Deterioration	6 weeks	Deterioration
19 Lef.	F	43	7 yrs.	III	IV	89 "	1,959	Major	Minor	A.C.T.H. §	"
20 Ran.	F	50	11 "	II	III	55 "	2,130	"	Deterioration	3 weeks	"

* No previous therapy. † Ankylosing spondylitis, afterwards treated with amidopyrine. ‡ Now treated with cortisone. § Still on A.C.T.H. therapy. || Relapse occurred 10 months after discontinuation of A.C.T.H.

FIG. 1.—Case 12. Sustained remission after A.C.T.H. therapy, combined with gold treatment. Red. Lip.=reducing lipids. F.S.=formaldehyde steroids. Aurum=chrysotherapy started. The numbers in the lowest column refer to the batches of cortrophine used. The hatched areas represent the clinical condition of the patient, expressed in percentages of the pretreatment level (=100%).

Case 12 (Fig. 1).—A housewife 46 years old was admitted to hospital because of rheumatoid arthritis of six months' duration. The x-ray films of the affected joints were still normal, and no irreversible deformities had then developed. An attempt was made to arrest the active process at an early stage, and the normal course of treatment was begun. This consisted of six 7-mg. doses of A.C.T.H. daily until signs and symptoms had subsided, followed by a gradual reduction in dosage, first by decreasing the amount given at each injection and later by reducing the number of injections daily. A good adrenal and clinical response resulted. After a week, eosinophils reappeared in the peripheral blood without a change in the patient's condition. During the next nine weeks the patient remained in an excellent condition. On the seventy-fifth day she relapsed, the dosage at that moment being three 3-mg. doses daily. This demonstrates that A.C.T.H. alone was unable to produce a lasting remission in a case of recent origin.

A major improvement occurred when the daily dosage was raised to five of 6 mg., at which time gold therapy was begun. A temporary increase in the E.S.R. was observed from the ninety-fifth day of treatment onwards, probably due to the chrysotherapy. Such a phenomenon is often observed during the first weeks of this form of therapy. Four months after the last A.C.T.H. injection she was free from symptoms, the E.S.R. being 5–15 mm. (Westergren).

Case 18 (Fig. 2).—A business manager, 55 years old, was also suffering from rheumatoid arthritis of recent origin. Most of his peripheral joints were affected, his sedimentation

rate was constantly higher than 100 mm., and his temperature fluctuated between 37.5° C. and 38.5° C. The severity of the process can be judged from the fact that during the three months of his illness distinct atrophy of his thenar muscles and ulnar deviation of the metacarpo-phalangeal joints had developed. His improvement was the most dramatic in the whole series of A.C.T.H.-treated patients. After four and a half weeks of therapy, however, when six doses of 4 mg. had been given daily for two and a half weeks, a total relapse occurred.

Discussion

It is always difficult to assess the results of therapy in a chronic illness with an irregular and changing course, such as rheumatoid arthritis. The literature makes it clear that 100% successes are never found with A.C.T.H. or cortisone. These considerations may partly

FIG. 2.—Case 18. Relapse of disease in fourth week of A.C.T.H. therapy. By that time the patient had received six doses of 4 mg. for a fortnight.

explain the variation in clinical response and the differences in dosages required, but cannot entirely account for the fact that, of late, patients constantly relapse after four to seven weeks' administration of the hormone, having initially shown satisfactory improvement. Below, attempts are made to account for the failures.

(a) Diminished Response to Cortisone-like Substances

One reason for failure may be a diminished response of the peripheral target organs to the cortisone-like substances produced by the adrenals under the influence of exogenous A.C.T.H. To test this hypothesis six patients who had become refractory to A.C.T.H.* were given

figures in Table IV prove that all four patients examined have a normal excretion pattern of I^{131} (Arnott *et al.*, 1949).

TABLE IV

	I^{131} Excretion After				Total I^{131} Excretion in 48 hrs.
	0-8 hrs.	8-12 hrs.	12-24 hrs.	24-48 hrs.	
♀ Her. (Case 14)	42.1	8.5	8.0	2.4	61.0
♀ Hen. (Case 15)	25.5	6.1	2.7	1.1	35.4
♀ Har. (Case 9)	45.6	6.5	5.4	1.5	59.0
♀ Me. (Case 13)	39.8	5.1	11.9	3.2	60.0
♀ Normal figures	27-44	4.4-10	3.8-11.6	1.7-9.4	49.5-62
Hypothyroidism			11-18	18-23	60-90

FIG. 3.—Case 15. Development of refractory state to A.C.T.H. after initial period of improvement. Satisfactory clinical reaction to usual amount of cortisone, indicating responsiveness of peripheral target-organs.

cortisone in normal quantities—for example, 200 mg. on the first day, 150 mg. on the second, and 100 mg. daily until at least a major improvement was obtained, followed by 50 to 75 mg. a day. All six responded favourably to this scheme of treatment. Case 15 is representative of this group (Fig. 3). In these cases a diminished response of the periphery could be excluded.

(b) Masked Corticogenic Hypothyroidism

Wolfson *et al.* (1950) suggest that the "possible existence of corticogenic hypothyroidism should be considered whenever a patient ceases to respond well to a daily dose of A.C.T.H. which previously was adequate for maintenance." This myxoedematous state can be discovered only with the help of the newer techniques for the investigation of thyroid deficiency, because of the opposing action of A.C.T.H. on the basal metabolic rate and the cholesterol level of the blood.

Tests of thyroid function with I^{131} were carried out in four patients who had failed to respond satisfactorily after an initial period of improvement on A.C.T.H. The

There is thus no evidence from these cases that the second hypothesis is correct.

(c) Failure of the Adrenals to Respond Adequately to the Corticotrophic Hormone

It is difficult to define what must be regarded as an adequate response. Has this to be judged by the satisfactory clinical effect or by the increased adreno-cortical activity according to laboratory data (fasting blood sugar, eosinophils, excretion of 17-ketosteroids and corticoids)?

Is a correlation between these two criteria obligatory or is one of them sufficient? Another difficulty is that present methods are insufficient to give an insight into the essential reactions of the adrenals to A.C.T.H.; qualitatively as well as quantitatively, the analyses of the adrenal response fail to meet the demands.

As this study has been concentrated on low-dosage schemes from the start, it has repeatedly been observed that during periods of low dosage the various laboratory criteria for adreno-cortical activity fail to indicate a positive response to the pituitary hormone used, with persistence of the clinical improvement (Fig. 1, second month of treatment). After discontinuation of this small maintenance dose a relapse may occur. On the other hand, the laboratory data in a few instances have

*"Refractory to A.C.T.H." indicates that a patient's clinical condition deteriorated in spite of the administration of a dosage which had previously caused improvement and/or maintained this improved condition. In this situation it might be possible to bring about a favourable response with higher doses. "Relatively refractory" might be a more appropriate description.

indicated a quantitatively satisfactory response, whereas the patients have shown unmistakable signs and symptoms of the recurrence of the disease. One example (Case 20) is given graphically in Fig. 4.

FIG. 4.—Case 20. Relapse of disease in eighth week of A.C.T.H. therapy, in spite of six doses of 7 mg. daily.

This 50-year-old schoolteacher had been in the rheumatism wards for more than a year. She reacted only partially to routine therapy. For seven weeks she received six doses of 7 mg. daily. She relapsed on the forty-eighth day of treatment, and after a few days was worse than before the initiation of A.C.T.H. therapy. At the time of her relapse the excretion of 17-ketosteroids was 13.4 mg., compared with a pre-treatment level of 4.2 and 4.6 mg. per 24 hours. It is obvious that there is no correlation between the clinical and laboratory criteria. It is possible that laboratory methods which give a more thorough analysis of the adrenal response would indicate a shift in the hormone production and show a relative insufficiency.

FIG. 5.—Case 13. (See Table III.) During the 10-day period indicated, a daily amount of 1 g. of ascorbic acid was administered intravenously. The vitamin C content of the diet was kept as low as possible by eliminating fresh fruit and vegetables. No effect was observed on the criteria of adrenocortical activity or on the clinical condition.

At the moment we are unable to come to a conclusion regarding this possibility.

It is known that stress and exogenous A.C.T.H. cause an ascorbic acid depletion of the adrenals; the most widely used assay for pituitary adrenocorticotrophic hormone is based on this observation (Sayers *et al.*, 1948). It might be supposed that long-continued treatment with A.C.T.H. might lead to ascorbic acid deficiency, and that this deficiency was the cause of the diminished response. If this assumption were correct extra supplies of vitamin C should enable the adrenals to react normally again.

Unfortunately, experiments made in this direction lead to entirely negative results. There was no sign of increased adreno-cortical activity or clinical effect in spite of the intravenous administration of 1 g. of ascorbic acid daily (Fig. 5).

During these studies literature pertinent to this possibility appeared (Hyman *et al.*, 1950; Treager *et al.*, 1950), indicating that even in clinical scurvy there is an adequate adrenal response to A.C.T.H.

(d) Decreased Activity of the Adrenocorticotrophic Hormone

Different batches may vary in therapeutic activity in spite of an almost identical assay, which, being biological, is subject to certain variability. A few patients were therefore treated with one batch, and during a relapse this was replaced with the same amount of a Danish preparation of A.C.T.H. (Roskilde) or in one patient A.C.T.H. (Armour), for a period of six days. Daily examination of the eosinophils, fasting blood sugar, excretion of 17-ketosteroids, sedimentation rate, and clinical condition lent no support to the supposition that the cortrophine preparation had diminished in potency.

The one and a half years' study has emphasized the similarity of the therapeutic response of all the different batches of A.C.T.H. used during the initial period of treatment. However, with the batches which are available at present it appears impossible to maintain with reduced dosage the improvement brought about by the higher initial dosage, as was possible in the first group of patients. A relapse is now found to occur with less or even without reduction of the dosage, but it is presumably of greater significance that this relapse always occurs after four to seven weeks of treatment, more or less independently of the dosage used (see Figs. 2 and 4).

One patient, however, who was treated in the later period of this investigation, sustained a remission during prolonged therapy with low doses. It seems worth noting that she had received one of the old batches of A.C.T.H. which had been used in the earlier studies. Her case history has been mentioned above (Case 12, Fig. 1).

These observations suggest the possibility of the development of neutralizing antibodies against the particular batches of pituitary hormone which have been available during the last months.

Recent literature reveals that others have encountered similar difficulties. The experiences of Wolfson *et al.* (1950) have already been mentioned. Margolis and Caplan (1951), in a review of their results of prolonged treatment with A.C.T.H., describe the normal variation of the direct effect of the agent. They also mention a deterioration in the degree of improvement with long-continued administration of A.C.T.H.

Summary

Twenty patients with rheumatoid arthritis have been treated with A.C.T.H. during periods of one and a half to eight months. Invariably a relapse occurred when the administration of A.C.T.H. was discontinued or when the dosage was too low. In a few cases the improvement obtained with A.C.T.H. could be maintained by concomitant chrysotherapy.

A previous report from this centre gave the first results of A.C.T.H. therapy in rheumatoid arthritis. In four cases the minimal effective dosage was found to be six doses of 2 mg. daily.

In a group of patients studied since then an initial period of striking improvement has been followed by the onset of

a refractory state. This failure of adequate response is not only seen with low dosage but may develop in spite of continued high initial dosage, usually appearing after four to eight weeks of treatment.

Attempts to explain these failures have so far been unsuccessful. The following possibilities have been excluded by special study: masked corticogenic hypothyroidism; diminished response of the peripheral target-organs; vitamin C deficiency; and decreased activity of the pituitary hormone preparations.

Investigations into the possible development of neutralizing antibodies or a shift in the hormone production of the adrenals appear to be indicated.

The administration of A.C.T.H. in cases of rheumatoid arthritis should still be regarded as worthy of investigation.

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B.C.G. VACCINATION IN THE NEWBORN

PRELIMINARY REPORT

BY

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No one can rest satisfied with the results of treating tuberculous meningitis with streptomycin. Even the best figures so far reported show a mortality of some 40–50% (Debré *et al.*, 1949; Smith and Vollum, 1950). The residua, too, in the recovered cases are by no means negligible.

Tuberculous meningitis takes its heaviest toll in the early months of life—that is, in the first two years, when the chances of close contact with heavy and often continual exposure are maximal and the source of such contact is all too often undiagnosed till it is too late to save the infant.

Because of the enormous number of people with active tuberculosis at large—140,000 in England and Wales, according to a recent report (Heaf, 1950)—the risk of infants' being exposed and contracting the disease is a very real one. Indeed, guaranteed freedom from exposure is virtually impossible, and it would seem, therefore, that active immunization offers the greatest hope of success in abolishing tuberculous meningitis in infancy. Such an immunization would protect simul-

taneously against bovine tuberculosis, and thus the risk of infection from imperfectly treated milk would also be removed.

It has for long been held that newborn infants do not react to immunization, or do so most inadequately; and on these grounds active immunization procedures have commonly been delayed till the fourth month of life or later, and a similar recommendation might be expected to apply to vaccination against tuberculosis.

Early Immunization

If any proposed immunization programme is to be fully satisfactory it must start as soon after birth as possible, so that protection may be given against the earliest exposure. There is no placentally transferred immunity to tuberculosis as there is, or may be, to diphtheria in the early months of life.

It is now known that newborn infants can and do respond reasonably well to immunization, though in general their powers of antibody production are probably less than they are at six months of age and thereafter. Wallgren (1950) has commented on the remarkable insensitivity of newborn infants to B.C.G., and has recommended that for their vaccination larger doses should be given (twice the adult dose) and that the development of tuberculin sensitivity should not be expected till a longer time afterwards (10–12 weeks, as against 4–6 weeks in childhood).

Where segregation of the infant is necessary because of a tuberculous milieu in the home to which he would return, it is obviously desirable for administrative reasons, if for no other, that the period of segregation should be as short as possible. Any place of isolation, whether it be a cubicle in a hospital, a residential nursery, or a foster-home, should be free from the risk of exposure of the infant to any cross-infection, for manifestly it would militate against the success of any immunization regime if, in the process of protection against tuberculosis, death were to result from some intercurrent infection. The minimal period of isolation is therefore a matter of some practical importance.

Procedure

As part of the child health programme it was decided to immunize infants born in St. Mary's Maternity Hospital, Manchester, with B.C.G. during the first week of life. All parents are invited to have their infants thus immunized; approximately 50% avail themselves of the offer. The aim of this project is the abolition of tuberculous meningitis in infancy, and this paper is therefore obviously only a preliminary report of what will be, in the first place, a five-year follow-up study.

Attached to the department of child health is a welfare centre, open daily, to which any mother delivered at St. Mary's Hospital, or on the district, may bring her infant. It is thus hoped to be able to follow closely and at frequent and regular intervals the progress of immunized infants.

The immediate questions to which answers were desired were: (a) What dose of B.C.G. is necessary for effective vaccination in the newborn? (b) What is the minimal time in which conversion can occur? (c) What are the dangers of overdosage if it be found that the answer to (b) varies with the dose of vaccine given? (d) In the event of complications, what is the best treatment for them?