adrenocortical response, and on occasion has been found to be more sensitive than the circulating eosinophil count. The test has proved of practical value in screening substances with a possible cortisone-like action. The connexion between these observations on capillary resistance and the ability of cortisone to suppress an inflammatory reaction is not at all clear. If it may be assumed that changes in the skin capillaries represent what is happening throughout the capillary bed, and if the inflammatory response is influenced by changes in the state of the capillaries, then these observations may provide a clue to the mode of action of cortisone in a wide variety of disease states.

Summary

Investigations have been continued in an attempt to establish the relationship between adrenocortical activity and changes in the resistance of skin capillaries (negative-pressure method).

Cases of hypopituitarism were found to have abnormally low capillary resistance. These patients did not respond to single injections of 25 mg. of A.C.T.H., but when repeated doses of the hormone were given a rise in resistance was obtained.

Distinct rises in resistance followed the administration of cortisone, either intramuscularly or orally, in a variety of disorders.

D.C.A. caused a fall in resistance, while progesterone, testosterone, oestradiol, and pregnenolone were without effect.

It is concluded from these and previous observations that rises in capillary resistance which follow non-specific stress are due to increased adrenocortical activity and increased output of glucocorticoid hormone. The test has been found to be a simple and sensitive index of adrenocortical response to stimuli.

During the period when this work was done the Rheumatic Unit, Northern General Hospital, was in receipt of grants from the Medical Research Council and the Nuffield Foundation. Part of the cortisone used was provided from a generous gift made jointly to the Medical Research Council and the Nuffield Foundation by Merck and Co., Inc. We should like to express our appreciation for much valuable assistance given by Dr. J. L. Potter, Elizabeth MacAdam Research Fellow.

REFERENCES

Le Vay, D., and Loxton, G. E. (1949). *Lancet*, **2**, 1134.

Lewin, E., and Wassen, E. (1949). Ibid., **2**, 993.

Pirani, C. L., Stepto, R. C., and Sutherland, K. (1951). *J. exp. Med.*, **93**, 217.

Robson, H. N. (1949). *Quart. J. Med.*, **18**, 279.

—— and Duthie, J. J. R. (1950). *British Medical Journal*, **2**, 971.

Scarborough, H. (1944). *Edinb. med. J.*, **51**, 335.

Selfter, J., Baeder, D. H., and Begany, A. J. (1949). *Proc. Soc. exp. Biol., N.Y.*, **72**, 277.

Emergency conditions in Egypt have as yet had no serious effect on the health of the troops in spite of the departure of many Egyptian labourers in the sanitary and antimalaria services. Labour has now been obtained from other sources, and there seems no reason to anticipate serious health difficulties when the hot weather arrives. About 20% of all admissions to hospital are accounted for by diseases of the skin, of which the majority are septic infections. Infections may be due to the combined effect on the skin of dry heat, dust, and sand. Scientific investigations are taking place. Bacillary dysentery and diarrhoea occur during the summer months and are certainly associated with the presence of flies. Extensive measures are taken to control fly breeding. Tonsillitis and pharyngitis form an important group of diseases twice as prevalent as in other tropical and subtropical commands, and on a level with experience at home. The possibility of an outbreak of enteric fever is always a source of some anxiety in the Middle East.

RESPONSIVENESS TO A.C.T.H. AND CORTISONE IN RHEUMATOID ARTHRITIS*

BY

J. H. KELLGREN, F.R.C.P., F.R.C.S.

O. JANUS, M.R.C.P.

R. MOORE, M.R.C.P.

AND

D. S. JACKSON, B.Sc.

(From the Rheumatism Research Centre, University of Manchester)

During some early investigations a few patients with rheumatoid arthritis were given courses of A.C.T.H. in a dosage of 12.5 mg. eight-hourly for periods of 10–14 days. The clinical and metabolic effects of these courses differed greatly in different patients : in one patient the symptoms and signs of rheumatoid arthritis were almost completely relieved, and this relief was accompanied by definite signs of hypercorticism such as oedema with marked sodium retention, decreased sugar tolerance, the development of " moon face " and striae, and a tenfold increase in urinary excretion of corticosteroids ; while another patient presenting a somewhat similar clinical picture failed to respond in any way to the A.C.T.H. The absence of response in the second patient was at first attributed to lack of potency in the second batch of A.C.T.H., but administration of some of the batch of A.C.T.H. which had given such good results in the first patient was equally ineffective in the second patient. This marked difference in responsiveness seemed to be of some practical and theoretical interest, and we therefore proceeded to investigate the possible variation in responsiveness of patients with rheumatoid arthritis to both A.C.T.H. and cortisone.

The Investigation

During the first part of this investigation the limited material at our disposal led to the development of a technique for assessing the response to single intramuscular injections of A.C.T.H., using as indicators the depression of circulating eosinophils four and six hours after the injection and the changes in joint tenderness and power of grip occurring six hours after the injection (Janus, 1950).

Cortisone first became available at the beginning of 1951, and the effects of single injections of that substance were compared with single injections of A.C.T.H. ; but this was unsatisfactory, since the effects of A.C.T.H. reach a maximum about six hours after injection, while intramuscular cortisone is only slowly absorbed, and the effects of a single injection take as long as 24 hours to reach their maximum. Fortunately this difficulty could be overcome by giving cortisone by mouth, since the time relations of the effects of a single oral dose of cortisone resemble closely those of a single injection of A.C.T.H. (Boland and Headley, 1951 ; Kellgren and Janus, 1951). Our studies were therefore enlarged to include the effects of single oral doses of 50 mg. of cortisone, which were compared with single intramuscular injections of 25 mg. of A.C.T.H. in the same patient. Fourteen patients with rheumatoid arthritis were studied in this way, and these preliminary studies showed a great variation in individual responsiveness to both corti-

*This work was financed by a grant from the Oliver Bird Fund of the Nuffield Foundation.

sone and A.C.T.H. Thus five patients responded to both hormones, four responded to neither hormone, four responded to cortisone but not to A.C.T.H., and one responded to A.C.T.H. but not to cortisone.

The study of responses to single doses of these hormones is open to certain criticism. On the other hand, prolonged administration of either hormone might be expected to alter both the clinical and the endocrine status of the patients under investigation, thus rendering comparison between the effects of cortisone and A.C.T.H. impossible; we therefore compromised by studying the effects of three-day courses of A.C.T.H. and cortisone in standard dosage in 17 cases of rheumatoid arthritis.

Method of Study

All the patients studied were hospital in-patients suffering from active rheumatoid disease, and in the majority of cases the clinical signs of the disease were widespread and severe. After a preliminary period of observation on rest in bed, a course of A.C.T.H., consisting of 25 mg. intramuscularly six-hourly, was started at 12 noon and continued for 12 injections, making a total of 300 mg. After a rest period of at least four days a similar course of cortisone was given, using an oral dosage of 50 mg. of aqueous suspension six-hourly, making a total of 600 mg. The same lot of cortisone and the same batch of A.C.T.H. (Armour J.24410) were used throughout. Seven patients included in this series were subsequently given more prolonged courses of either or both hormones lasting from 3 to 12 weeks, though in most instances a lower daily dose was employed for these longer courses.

The clinical response to these courses was assessed by one of us (R. M.), who carried out a full clinical examination of the limbs each morning at the same time. The record included a detailed study of joint tenderness, range of movement, joint swelling, and general functional capacity, and also the power of grip in both hands. These observations were tabulated on specially constructed charts, and though no numerical precision is claimed for these clinical observations they allowed us to classify the patients' responses to the three-day courses into three broad categories: full (++), partial (+), and *nil* (0). A full response represents complete or almost complete relief of pain and joint tenderness and as much improvement of function as the anatomical changes in the limbs would permit, while a *nil* response was recorded when there was no demonstrable change.

Eosinophil counts were made daily at 10 a.m., using the technique previously described (Kellgren and Janus, 1951). A full (++) eosinopenic response was defined as a fall of more than 75% in the circulating eosinophils after the first day of treatment, and the response was classed as negative (0) when the fall was less than 50%. Intermediate responses were graded as partial (+).

In eight cases 24-hour specimens of urine were collected for the period immediately preceding each course and again during the final 24 hours of the course, and the corticosteroid excretion was estimated by the method of Bassil and Hain (1950). A full steroid response (++) was defined as at least a threefold increase in corticosteroid excretion, while a twofold to threefold increase was defined as partial (+). However, Marrian (1951) doubts the significance of such estimations, and in these experiments the excretion values never rose above the range of values (0–3 mg.) we have found in day-to-day estimation on normal subjects. Robinson and Norton (1951), using a different technique, only occasionally found significantly raised values in patients showing clinical signs of hypercorticism, and this agrees with our own experience of these estimations in over 100 cases. At the beginning of this study it was thought that the steroid excretion values would be important, and they have been included for completeness, but we now feel that their significance is somewhat doubtful.

The results in all 17 patients are summarized in the Table. The column headed "withdrawal response" indicates the patient's condition on the two days after each course relative to his pre-treatment condition. In this column + indicates a maintained improvement, 0 indicates a return to the pre-treatment status, and − indicates a deterioration below the pre-treatment level.

Discussion

Some degree of individual variation in responsiveness to drugs and hormones is a commonplace, but our observations suggest that with cortisone and A.C.T.H. great differences in responsiveness are commonly encountered in patients with rheumatoid arthritis. Thus among the 17 patients tested with three-day courses two showed obvious signs of hypercorticism such as oedema, "moon face," and euphoria, in addition to full suppression of rheumatoid symptoms. In Case 16 this resulted from cortisone and in Case 4 from A.C.T.H. On the other hand, in Cases 9 and 10 the same dosage had no effect whatsoever. In the dosage used a full clinical and eosinopenic response was obtained rather more often with cortisone than with A.C.T.H., and in Cases 3 and 7 there was practically no response to A.C.T.H. while the response to cortisone was excellent. On the other hand, Case 4, which gave the best response to A.C.T.H. of the whole group, gave a very indifferent response to cortisone.

In view of the arbitrary methods of assessment it is not surprising that there was no exact correspondence between the clinical and eosinopenic responses, but it will be noted that a full clinical response was not encountered in the absence of an eosinopenic response, and, conversely, all cases giving a full eosinopenic response showed some clinical response, so that the eosinopenic response may be used as a rough guide to clinical responsiveness. It may be

Response to A.C.T.H. and Cortisone in 17 Patients

Case No.	Sex	Disease Type	A.C.T.H.				Cortisone				
			Clinical Response	Eosinophil Response	Steroid Response	Withdrawal Response	Clinical Response	Eosinophil Response	Steroid Response	Withdrawal Response	
1	F	Severe generalized	++	++		+	++	++		+	
8	F	,, ,,	++	++	++	0	++	++	++	0	C
12	M	,, ,,	++	++	0	0	++	++	++	0	
16	F	,, ,,	++	++		−	++	++		−	
4	F	,, ,,	++	++	++	0	+	+	+	0	C
7	F	Moderate ,,	0	0	0	−	++	++	++	0	
3	F	Severe ,,	+	0		−	++	++		−	
17	F	Moderate ,,	+	++		0	+	++		0	
5	M	Severe ,,	+	++	0	0	+	++	0	0	C
6	M	,, ,,	++	+	+	+	++	+	0		C
2	F	,, ,,	+	+		−	+	+		−	
11	F	Moderate ,,	+	+	0	+	+	+	++	+	
14	F	,, ,,	0	+		0	+	+		0	
15	F	,, localized	0	+		0	0	+		0	
13	F	,, ,,	+	0	0	0	+	0		0	
9	F	Severe generalized	0	0		−	0	0		−	C
10	M	,, ,,	0	0	0	−	0	0	0	−	

In cases marked "C" in the last column the cortisone preceded the A.C.T.H.

argued that the three-day trial is not adequate and that more prolonged hormone administration would iron out these differences, but in the seven cases given more prolonged courses the degree of responsiveness did not seem to alter greatly, though there was a tendency for the more responsive patients to become somewhat less so.

A number of practical points arise from these observations. Thus the individual patient's responsiveness to cortisone and A.C.T.H. should be considered before embarking upon any programme of treatment with these hormones. and we suggest that the single-dose test may give a useful indication of this, though the three-day test would be more reliable. Furthermore, it seems unwise to state that a given syndrome in a given patient is unaffected by cortisone or A.C.T.H. unless enough hormone has been administered to produce signs of hypercorticism: a procedure not without danger. It is also clearly essential to assess the individual patient's responsiveness with cortisone or A.C.T.H. of known potency before attempting to assess the presence of similar activity in other substances or preparations by administering them to patients.

One of the most interesting findings in our series was the withdrawal deterioration which was sometimes observed in cases in which the administered hormone had no apparent effect, as in Cases 7, 9, and 10. According to Sayers (1950), tissue requirements of corticosteroids are greatly increased during stress, and the pituitary–adrenocortical system responds to these increased requirements by increased production of steroids, so maintaining a state of eucorticism; and no convincing evidence has as yet been produced to show that this mechanism is not working normally in rheumatoid disease. Although the response to cortisone or A.C.T.H. must be determined by many factors, such as the rates of absorption and destruction of the administered hormones, the degree of tissue responsiveness, tissue requirements, and so on, we suggest that the differing response of individual patients to administered cortisone and A.C.T.H. may be partly a reflection of the level of endogenous production. If the administered dose of hormone greatly exceeds endogenous production it causes some degree of hypercorticism, with eosinopenia and suppression of the inflammatory reaction, resulting in a clinical response; but if the administered dose is less than the amount produced endogenously the pituitary–adrenocortical system merely adjusts itself to a lower level of production and the net result is no change, though there may be a temporary withdrawal deterioration while endogenous production is getting under way again. Investigation of this hypothesis must, however, await accurate methods of assessing corticosteroid production in conditions of disease in which "utilization" is presumably high.

Although Hench and his colleagues (Ward *et al.*, 1951) and other workers (Boland and Headley, 1951; Copeman *et al.*, 1952) claim satisfactory results with prolonged cortisone therapy in selected cases of rheumatoid arthritis, other workers (Freyberg *et al.*, 1951) are less enthusiastic, and from Duthie's (1952) review of up-to-date American experience it seems that such long-term therapy is unsatisfactory in most patients with rheumatoid disease. If we are not in fact restoring a state of eucorticism in the rheumatoid patient by administering a "clinically adequate" dosage of cortisone or A.C.T.H. but are merely producing a partial suppression of the inflammatory reaction by inducing a more or less subclinical state of hypercorticism, one would hardly expect the results to be uniformly good, and our own limited experience is certainly not encouraging. The proper evaluation of long-term cortisone or A.C.T.H. therapy in rheumatoid disease must, however, await the completion of controlled therapeutic trials.

Summary

Seventeen patients with rheumatoid arthritis were given standard three-day courses of 600 mg. of cortisone and 300 mg. of A.C.T.H. and their clinical and eosinopenic responses were studied in detail.

Four patients responded fully to both hormones, four gave no response with either hormone, four responded fully to cortisone but only partially or not at all to A.C.T.H., while one responded fully to A.C.T.H. and only partially to cortisone. The remainder gave only partial responses to either or both hormones.

The practical and theoretical implications of these findings are discussed, and it is suggested that the degree of response to a standard dose may to some extent be a reflection of the level of endogenous production.

The cortisone used in this work was provided from a generous gift made jointly to the Nuffield Foundation and the Medical Research Council by Merck and Co., Inc., and the A.C.T.H. was supplied by the Medical Research Council and Organon Laboratories Ltd.

REFERENCES

Bassil, G. T., and Hain, A. M. (1950). *Nature, Lond.*, **165**, 525.
Boland, E. W., and Headley, N. E. (1951). *J. Amer. med. Ass.*, **145**, 8.
Copeman, W. S. C., Savage, O., Bishop, P. M. F., Dodds, E. C., Kellie, A. E., Stewart, J. W., Glyn, J. H. H., Henly, A. A., and Tweed, J. M. (1952). *British Medical Journal*, **1**, 397.
Duthie, J. J. R. (1952). Ibid., **1**, 341.
Freyberg, R. H., Traeger, C. H., Patterson, M., Squires, W., Adams, C. H., and Stevenson, C. (1951). *J. Amer. med. Ass.*, **147**, 1538.
Janus, O. (1950). *British Medical Journal*, **2**, 1244.
Kellgren, J. H., and Janus, O. (1951). Ibid., **2**, 1183.
Marrian, G. F. (1951). *J. Endocrinol.*, **7**, lxix.
Robinson, A. M., and Norton, J. M. (1951). Ibid., **7**, 321.
Sayers, G. (1950). *Physiol. Rev.*, **30**, 241.
Ward, L. E., Slocumb, C. H., Polley, H. F., Lowman, E. W., and Hench, P. S. (1951). *Proc. Mayo Clin.*, **26**, 361.

EFFECT OF REPEATED INJECTIONS OF A.C.T.H. UPON THE BONE MARROW

BY

G. HUDSON, M.B., Ch.B., B.Sc.
Demonstrator in Anatomy

G. HERDAN, M.Sc., Ph.D., LL.D.
Lecturer in Statistics, Department of Preventive Medicine

AND

J. M. YOFFEY, M.D., D.Sc., F.R.C.S.
Professor of Anatomy
University of Bristol

In a previous paper (Yoffey *et al.*, 1951) the effects of a single administration of A.C.T.H. or of cortical extract ("eschatin") upon the bone marrow were reported. For the examination of the marrow a quantitative method was employed, and attention was directed more especially to the lymphocytes. It was then found that six hours after a single dose of eschatin a statistically significant increase occurred in the marrow lymphocytes, while six hours after a single injection of A.C.T.H. there was an increase in the marrow lymphocytes which almost reached significance level. Following these experiments it was thought that perhaps repeated administration of A.C.T.H. might produce a more decisive change in the marrow lymphocytes. Accordingly a number of guinea-pigs were given daily injections of A.C.T.H. for seven days, and the marrow was then examined. While these experiments have not yielded much further information about the marrow lymphocytes, they have served to direct attention to a possible stimulating action of A.C.T.H. on the bone marrow as a whole, and especially on erythropoiesis.