CLINICAL TRIALS OF ACTH

Preliminary Report

By J. J. R. DUTHIE

In a recent Honyman Gillespie Lecture, Professor Davidson gave an account of the physiological and clinical effects of the adrenocorticotropic hormone of the pituitary gland and the steroid hormones of the adrenal cortex. He reviewed recent research in this field, and described the remarkable effects of these hormones in rheumatoid arthritis, rheumatic fever, gout and other diseases of the collagen group.

The purpose of the present communication is to describe the results of clinical trials of ACTH carried out in Edinburgh during the last four months. It was obvious from the outset that supplies of the hormone would be limited and that it would not be possible to use the high doses and prolonged courses given in American Clinics. It was felt, however, that a very useful purpose might be served by trials on a much more limited scale, which would provide first-hand experience of the clinical effects of ACTH, and it was also our hope that we might be fortunate enough to observe some clinical or metabolic result which had not as yet been fully described by workers in America. Admittedly our hopes were modest, because perusal of the ever-increasing number of papers covering the clinical, biochemical and metabolic effects of ACTH seemed to leave little scope for original work with the limited facilities available. However, the most generous support was received from all departments to whom application was made for advice or help. The clinical side of these trials represents the combined effort of a group of physicians working in the Department of Medicine and the Unit for Rheumatic Diseases in the Northern General Hospital.

In the time available it will only be possible to give a brief outline of the work done since supplies of ACTH were received four months ago. Certain lines of investigation are now being followed which may or may not shed some new light on the action of ACTH in rheumatic diseases, but much more work will have to be done before any conclusions can be reached.

First, the organisation of the trials will be described along with some of the methods of clinical assessment which have been evolved. It must be borne in mind that even four months ago very much less was known about the action of ACTH than is the case now, and this must be the excuse for certain errors of judgment and the failure to record information which experience has shown might have proved valuable.

A Honyman Gillespie Lecture delivered on 18th May 1950.

In view of the results obtained by Hench and his colleagues in cases of rheumatoid arthritis, it was decided to select patients suffering from this disease for trial in the first instance. They were chosen in accordance with the following criteria :—The disease must have been present for at least six months ; the small joints of the hands and feet must be involved ; the blood sedimentation rate must be at least 30 mm. in 1 hour (Westergren) ; and there must be radiological evidence of arthritis of the rheumatoid type in at least some of the affected joints. This had the effect of excluding cases in which any doubt existed as to the diagnosis.

It was decided that cases selected should be patients who had been under observation as in-patients for some weeks or months and in whom the disease had remained active in spite of rest in bed, full diet, splinting of the affected joints, and physiotherapy. These conditions were considered to be necessary for the trial of a new substance, as it is well known that in many cases these conservative methods of treatment will lead to complete relief of symptoms. It was also considered essential to precede and follow the administration of ACTH by a series of control injections of saline, to avoid confusion between the psychological effects of parenteral injections and the effects of ACTH. In the selected patients the basic regime of treatment was continued throughout the trial except for the withdrawal of analgesics some time before the trial began.

A great variety of methods of measuring clinical improvement in rheumatoid arthritis have been devised, but none are entirely reliable if used alone. It was decided to use a number of methods in the hope that it might be possible to select a group of tests which would be sufficiently sensitive to give an accurate picture of the daily variations in clinical condition before, during and after the administration of ACTH.

The degree of joint tenderness was measured by applying a uniform pressure to the affected joints. Four types of response were recorded :—

0 = No pain
1 = Slight pain
2 = Wincing
3 = Wincing and withdrawal

This method gave reasonably consistent results and provided a useful measure of the speed with which the inflammation in the joints subsided.

The time taken by the patient to perform certain simple tasks was measured daily—getting up and sitting down, walking a fixed distance. A questionnaire was used based on ward activities—the questions could be answered Yes or No—Did you get out of bed without help ? Did you dress yourself unaided ? and so on. These methods provided a rough measure of the speed with which functional improvement took place.

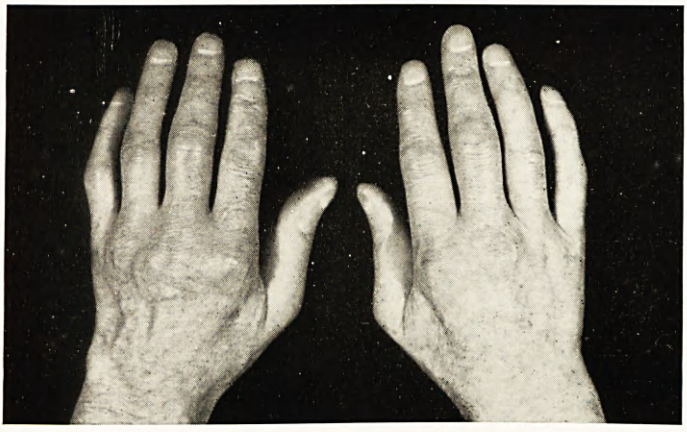

FIG. 1.

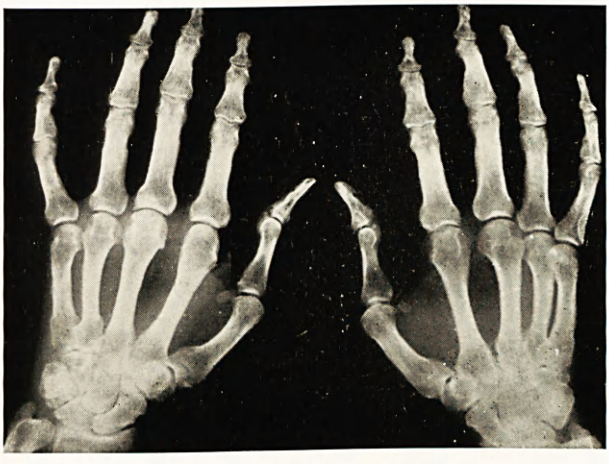

FIG. 2.

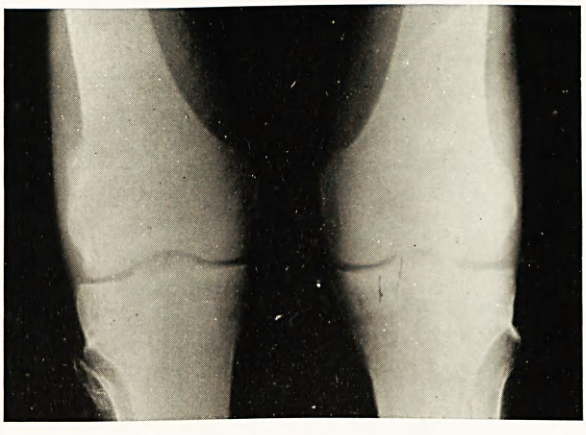

FIG. 3.

Power of grip was measured by asking the patient to squeeze the bulb of a sphygmomanometer and recording the average of three attempts in mm. of mercury.

Range of movement in the affected joints was measured daily, but found to be of limited value. Although movement increased during the administration of ACTH, this bore little relationship to the functional improvement.

Finally, in an attempt to assess any increase in functional capacity, a method was devised which measured the capacity for sustained effort of selected joint-muscle groups. A weight and pulley circuit was used, and the results expressed in foot-poundals, although strict mathematical interpretation of these figures is not justifiable.

These were some of the yardsticks devised to measure the clinical response to ACTH.

Hæmatological, Biochemical and Metabolic Studies

The blood sedimentation rate, hæmoglobin, packed cell volume, plasma proteins, blood sugar, blood cholesterol, uric acid, urea nitrogen, blood and urinary electrolytes, urinary 17-ketosteroids, and uric acid/creatinine ratio were measured at regular intervals throughout the control periods and during the administration of ACTH. Eosinophils in the peripheral blood were counted hourly on the first day of ACTH, and at four and eight hours thereafter. Where results have proved interesting, their possible significance will be discussed later on. It must be borne in mind that observations have been confined to the changes induced by short courses of ACTH. The longest period of administration in one patient has been thirteen days.

CASE 1.—The first case is that of a man aged 59 with a three years' history of pain and swelling in his joints. He had enjoyed excellent health before the onset of his symptoms. There was no history of preceding infection. He himself was of the opinion that repeated chilling at work had precipitated the onset of the disease. He had received two courses of gold, but developed dermatitis during the second. His condition had steadily deteriorated before his admission to hospital. He had had to give up his work, and had lost about 2 stones in weight. His hands, wrists, feet, ankles, knees, elbows and one shoulder had been affected. His B.S.R. was elevated on admission (100 mm. in 1 hour) and remained high throughout his stay in hospital. Many weeks of conservative treatment (splints, physiotherapy, etc.) did not lead to a material improvement in his condition. There was no evidence of organic disease in any other system. The changes in his hands are illustrated in Fig. 1, which shows slight spindling of the fingers and moderate swelling of the metacarpo-phalangeal joints. This patient was in an active phase of rheumatoid arthritis. His response to conservative measures was minimal, but X-rays (Figs. 2 and 3) showed that the changes in the joints were only of moderate degree, although function was markedly impaired. On these grounds he was considered a suitable case for trial with ACTH.

He received control injections of saline 8-hourly for 3 days, then 25 mg. ACTH 8-hourly for 5 days, followed by another 3 days of saline injections.

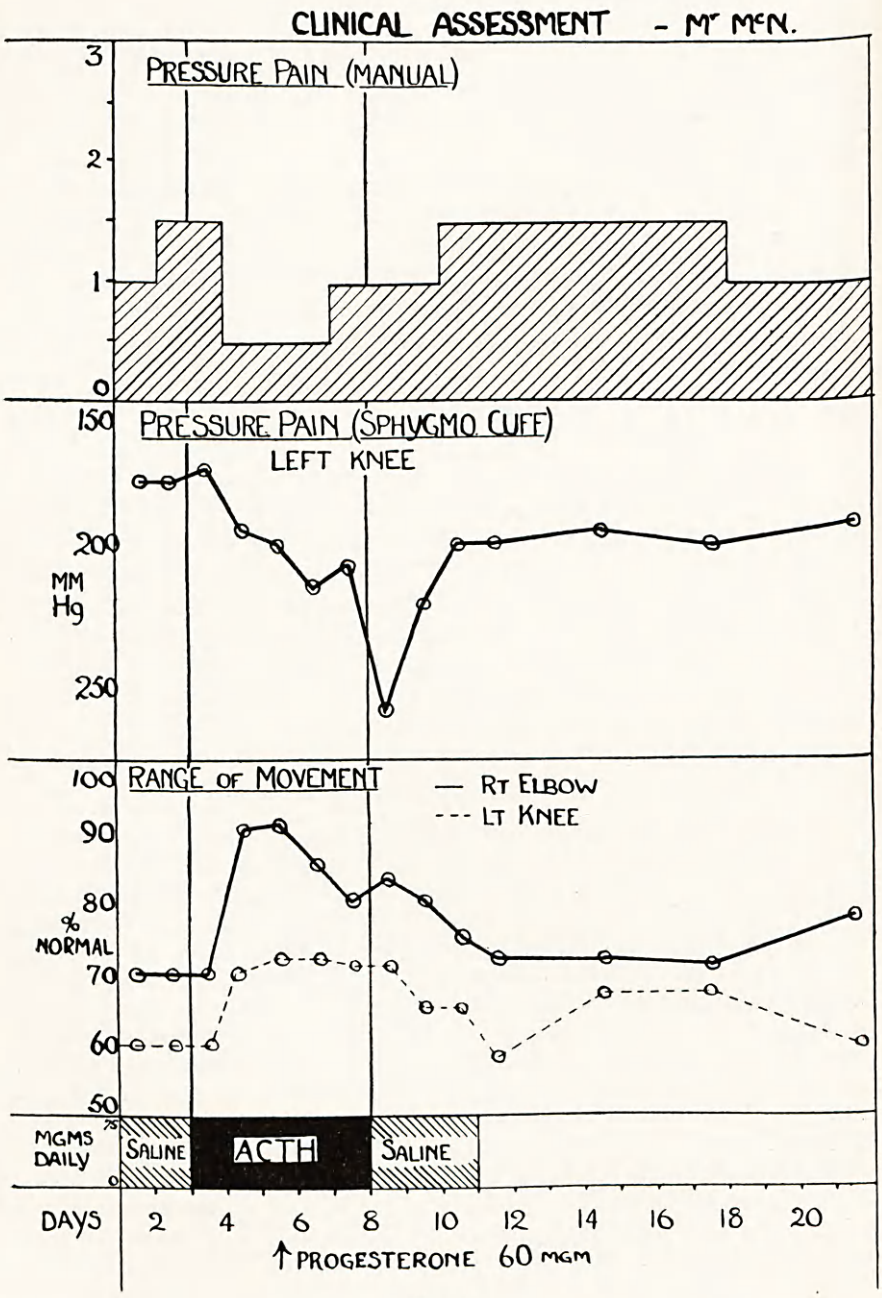
CLINICAL ASSESSMENT - Mr McN.
PRESSURE PAIN (MANUAL)
3
2
1
0
PRESSURE PAIN (SPHYGMO CUFF)
LEFT KNEE
150
200
250
MM Hg
RANGE OF MOVEMENT
— Rt Elbow
--- Lt Knee
100
90
80
70
60
50
% NORMAL
MGMS DAILY
SALINE
ACTH
SALINE
DAYS
2 4 6 8 10 12 14 16 18 20
↑PROGESTERONE 60 MGM

Fig. 4.

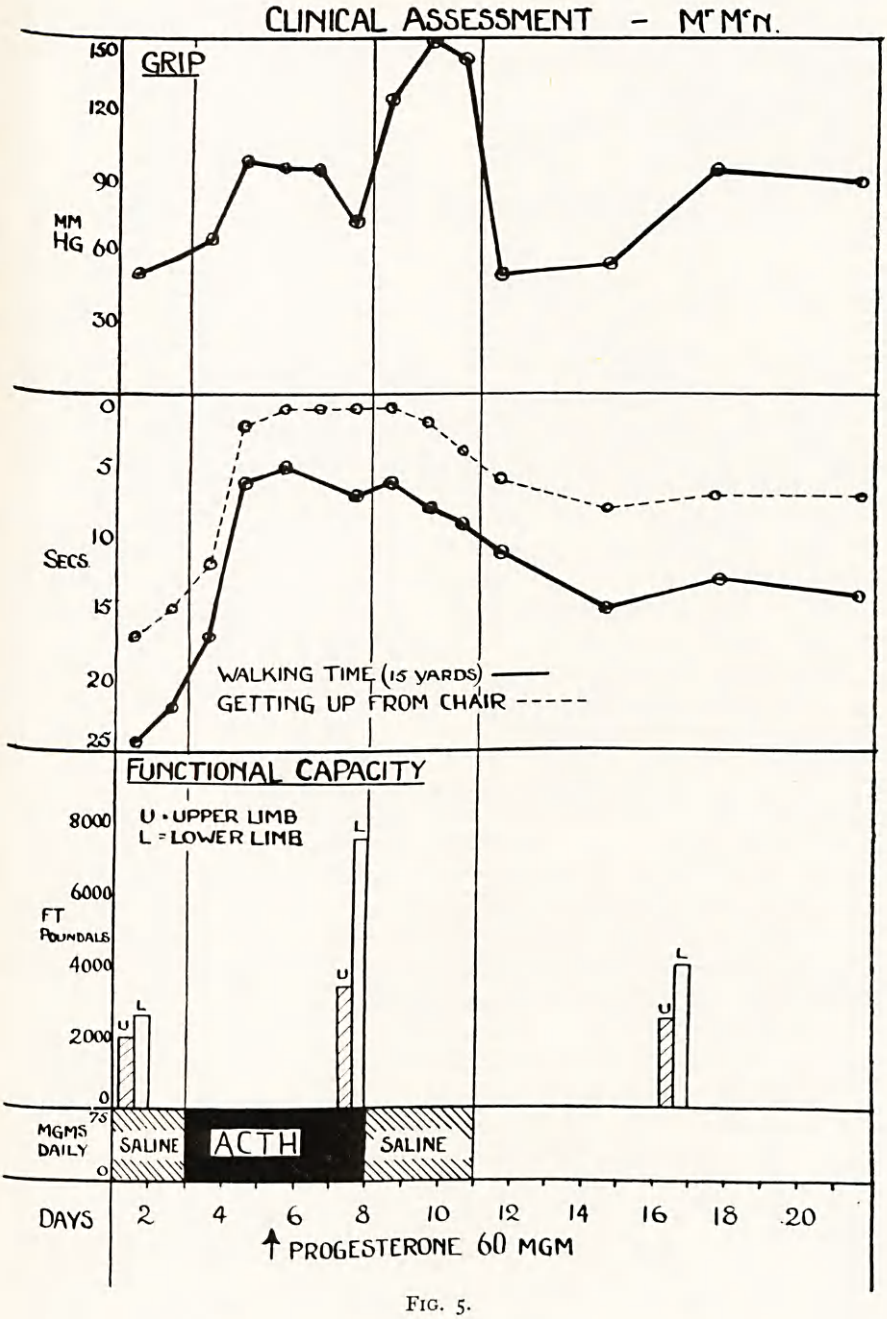
CLINICAL ASSESSMENT - Mr M'N.
GRIP
MM HG
150
120
90
60
30
SECS
0
5
10
15
20
25
WALKING TIME (15 YARDS)
GETTING UP FROM CHAIR
FUNCTIONAL CAPACITY
U = UPPER LIMB
L = LOWER LIMB
FT POUNDALS
8000
6000
4000
2000
0
MGMS DAILY
75
0
SALINE
ACTH
SALINE
DAYS
2
4
6
8
10
12
14
16
18
20
PROGESTERONE 60 MGM

FIG. 5.

A striking feature in this patient was the extreme degree of muscular stiffness. Without analgesics he was in continual pain.

The administration of ACTH induced a complete remission of symptoms. Pain rapidly diminished, and there was a striking improvement in functional capacity. Partial relapse occurred when ACTH was stopped, but in this case it was only partial.

Clinical Assessment

Figs. 4 and 5 show how these changes were measured by the methods described.

Pressure pain or joint tenderness diminished markedly, but was never completely absent in all the affected joints.

An attempt was made to obtain a more accurate measure of joint tenderness. A sphygmomanometer cuff was wrapped round the joint and inflated till pain was felt, and the pressure recorded. During ACTH the pressure required to elicit pain rose to 250 mm. Hg. Range of movement increased by 20 per cent. in the right elbow, and 12 per cent. in the left knee (Fig. 4). Grip improved markedly. Functional capacity, measured by the weight and pulley method, improved greatly in the lower limbs and less markedly in the arms. His walking speed increased greatly, and there was an equally striking improvement in the time taken to rise from a chair. The improvement was maintained to some extent after ACTH was stopped (Fig. 5).

The methods of assessment used seem to reflect reasonably accurately the dramatic improvement which took place.

Metabolic Effects of ACTH

In this case there was an initial retention of sodium, an increase in the excretion of potassium, and a sharp fall in urinary volume. Injection of progesterone, for a reason to be discussed later, appeared to cause a rise in urine volume and an increase in sodium and potassium output. When ACTH was stopped, urine volume rose, potassium output fell, and the sodium output rose further.

Urinary 17-ketosteroids were more than doubled during ACTH, and there was a rise in the uric acid/creatinine ratio (Fig. 6).

In another patient the response to ACTH was more clear-cut. Progesterone in this case did not appear to influence the electrolyte pattern in the urine. The uric acid/creatinine ratio rose more sharply (Fig. 7).

Effect of ACTH on Fasting Blood Sugar

ACTH induced a well-marked rise in fasting blood sugar. In this case there was no glycosuria. This observation—confirmed in other patients—substantiates the reports of the diabetogenic effect of ACTH (Fig. 8).

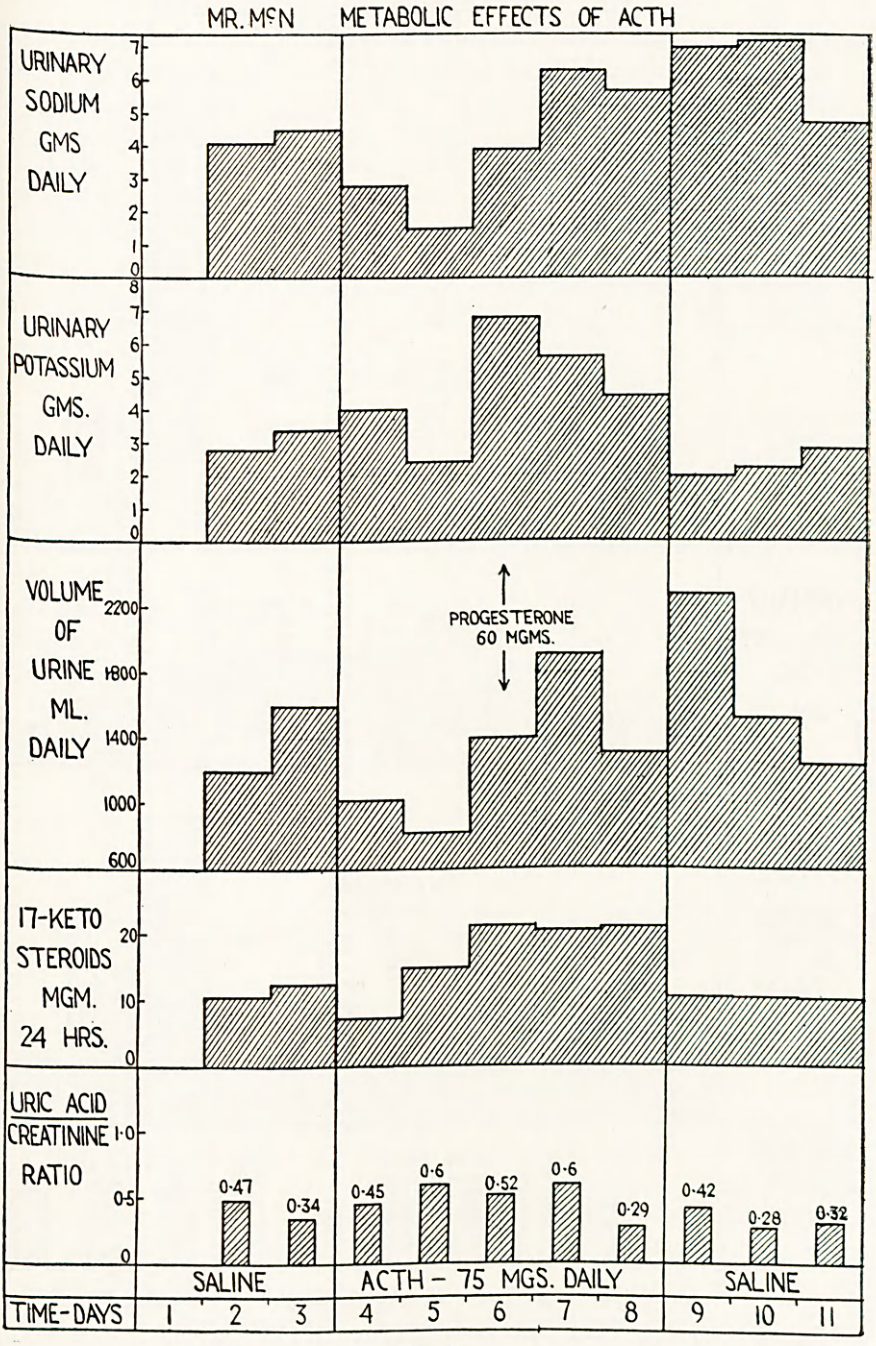
MR. McN METABOLIC EFFECTS OF ACTH
URINARY SODIUM GMS DAILY
URINARY POTASSIUM GMS. DAILY
VOLUME OF URINE ML. DAILY
PROGESTERONE 60 MGMS.
17-KETO STEROIDS MGM. 24 HRS.
URIC ACID CREATININE RATIO
0·47
0·34
0·45
0·6
0·52
0·6
0·29
0·42
0·28
0·32
SALINE
ACTH – 75 MGS. DAILY
SALINE
TIME-DAYS

FIG. 6.

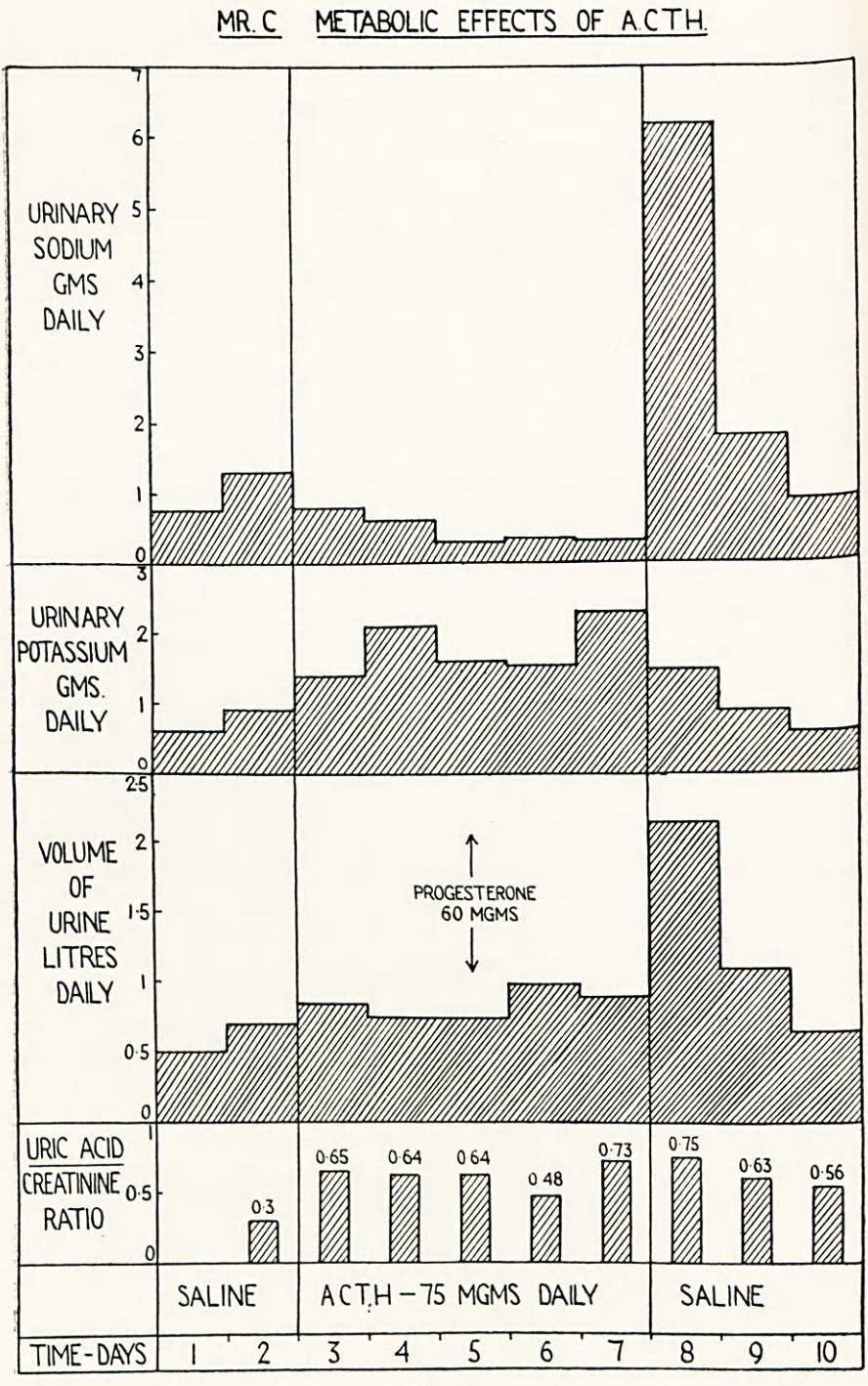
MR. C METABOLIC EFFECTS OF A.C.T.H.
URINARY SODIUM GMS DAILY
URINARY POTASSIUM GMS. DAILY
VOLUME OF URINE LITRES DAILY
PROGESTERONE 60 MGMS
URIC ACID CREATININE RATIO
0·3
0·65
0·64
0·64
0·48
0·73
0·75
0·63
0·56
SALINE
A.C.T.H – 75 MGMS DAILY
SALINE
TIME-DAYS
1 2 3 4 5 6 7 8 9 10

FIG. 7.

Hæmatology

There was no significant change in the packed cell volume or hæmoglobin percentage. Blood sedimentation rate fell from 84 to 50 mm. in 1 hour (Westergren), but before discharge from hospital had risen again to 87 mm. Eosinophils fell sharply and remained low throughout the administration of ACTH. They returned rapidly to their previous level on cessation of the hormone. There was a slight rise in plasma albumen and a fall in globulin—a reversion to a more normal pattern (Fig. 9).

This first patient conformed in every respect to the pattern of immediate clinical response described by Hench and his colleagues

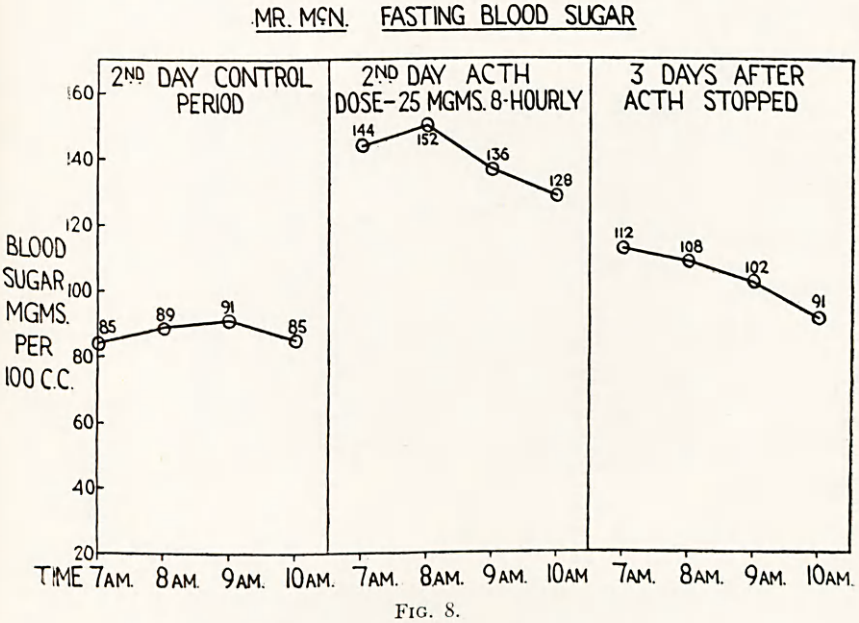

FIG. 8.

(1949). There was only a moderate and transitory drop in blood sedimentation rate, but the effect would probably have been more marked if the course of ACTH had been prolonged. The striking improvement suggests that the disabling effects of rheumatoid arthritis, in the earlier stages of the disease at least, are more directly due to inflammatory change in the soft tissues than to actual damage to the joint structures. ACTH appears to suppress rapidly this inflammatory component of the disease, with complete relief of pain and a marked improvement in function.

CASE 2.—The next patient was a married woman of 39. She gave a ten months' history of pain and stiffness in her fingers, wrists, shoulders, knees, ankles and feet. The condition was rapidly progressive, and she had been confined to bed for five months prior to admission to hospital. She had lost some 2 stone in weight. Two courses of gold had been given, but she developed

dermatitis during the second course. Her father, paternal grandmother, and one paternal aunt also suffered from rheumatoid arthritis. She had been an active, healthy woman until the onset of the disease. On admission her joints were extremely painful, and flexion deformities had developed in both knees. Prolonged conservative treatment led to a considerable improvement

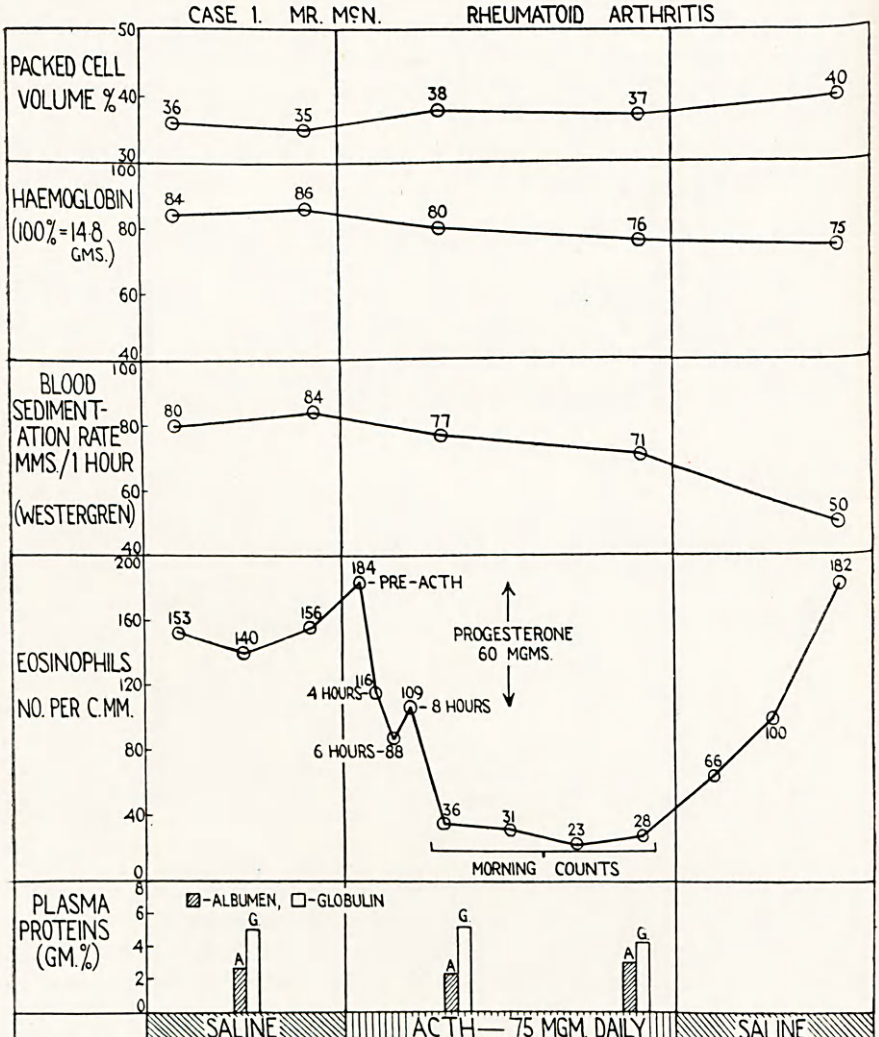

FIG. 9.

in her condition and she became ambulatory, although still very crippled. Her blood sedimentation rate was consistently elevated, and there was a moderate degree of anæmia resistant both to oral and intravenous iron. Movements in her knees, shoulders, and wrists remained markedly restricted, although X-rays showed only moderately advanced damage in these joints (Figs. 10, 11 and 12).

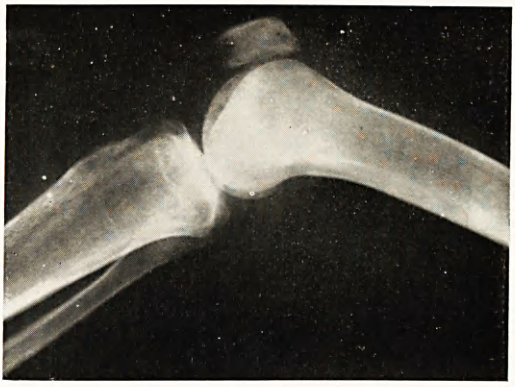

FIG. 10.

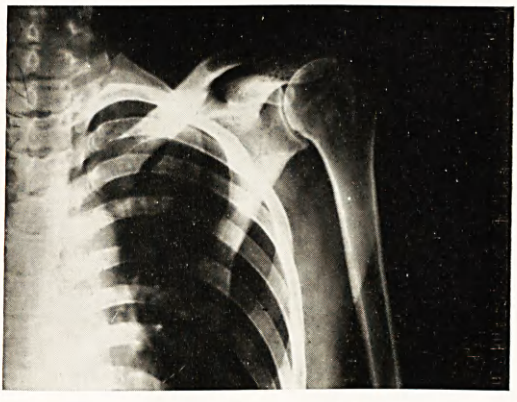

FIG. 11.

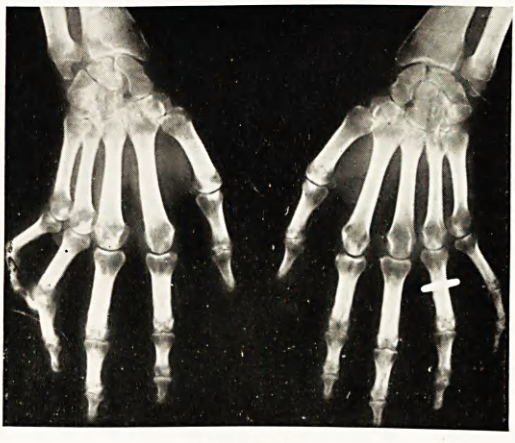

FIG. 12.

In view of the short history, limited response to conservative treatment, and evidence of continued activity, she was selected for trial with ACTH. Five days control saline was followed by 13 days of ACTH.

In this case, although there was a considerable improvement in function, there was no significant increase in range of movement in

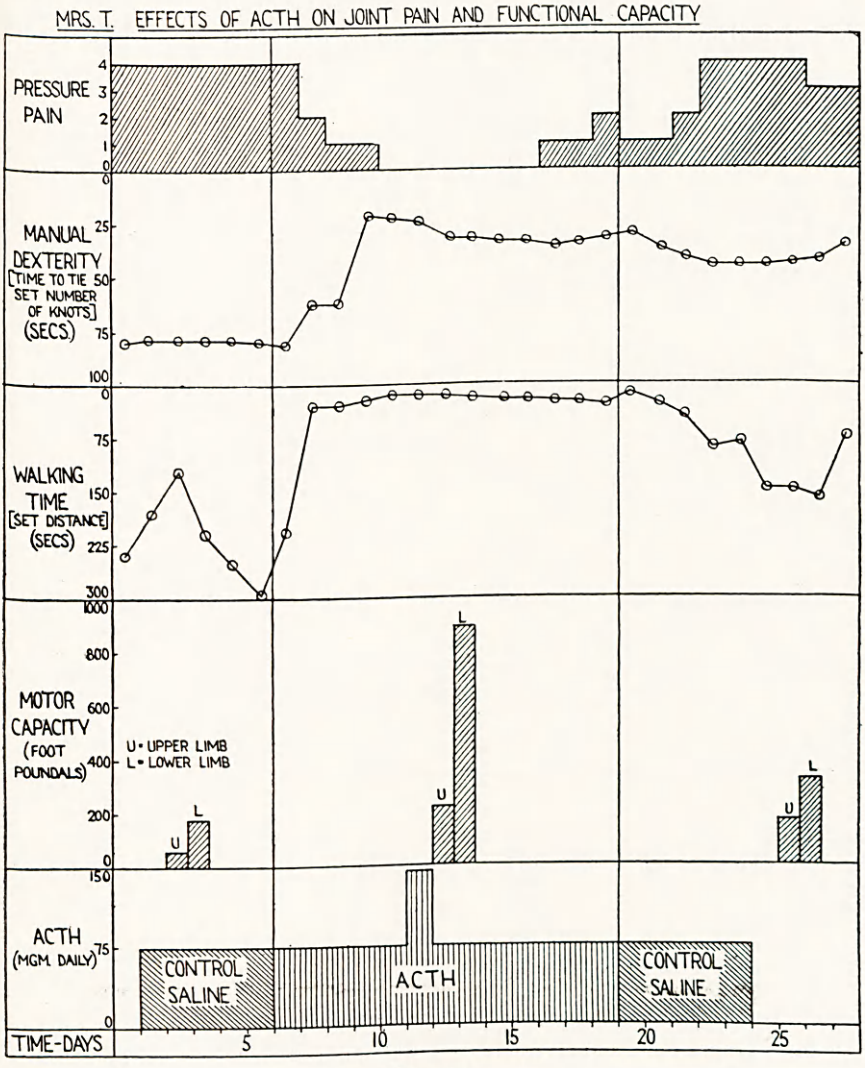

FIG. 13.

the knees or shoulders—the joints most markedly affected. As no gross disorder of joint architecture was revealed by X-ray examination, it must be accepted that the limitation in movement was due largely to adhesions and contractures in and around the joints. This would appear to place definite limits on the value of ACTH as a means of treatment. Active inflammation may be controlled, but pre-existing

damage, even if confined to the soft tissues in the form of capsular fibrosis, is unaltered. When a significant increase in range of movement does occur, it must be due to elimination of pain and muscular spasm. This was well illustrated in the first case.

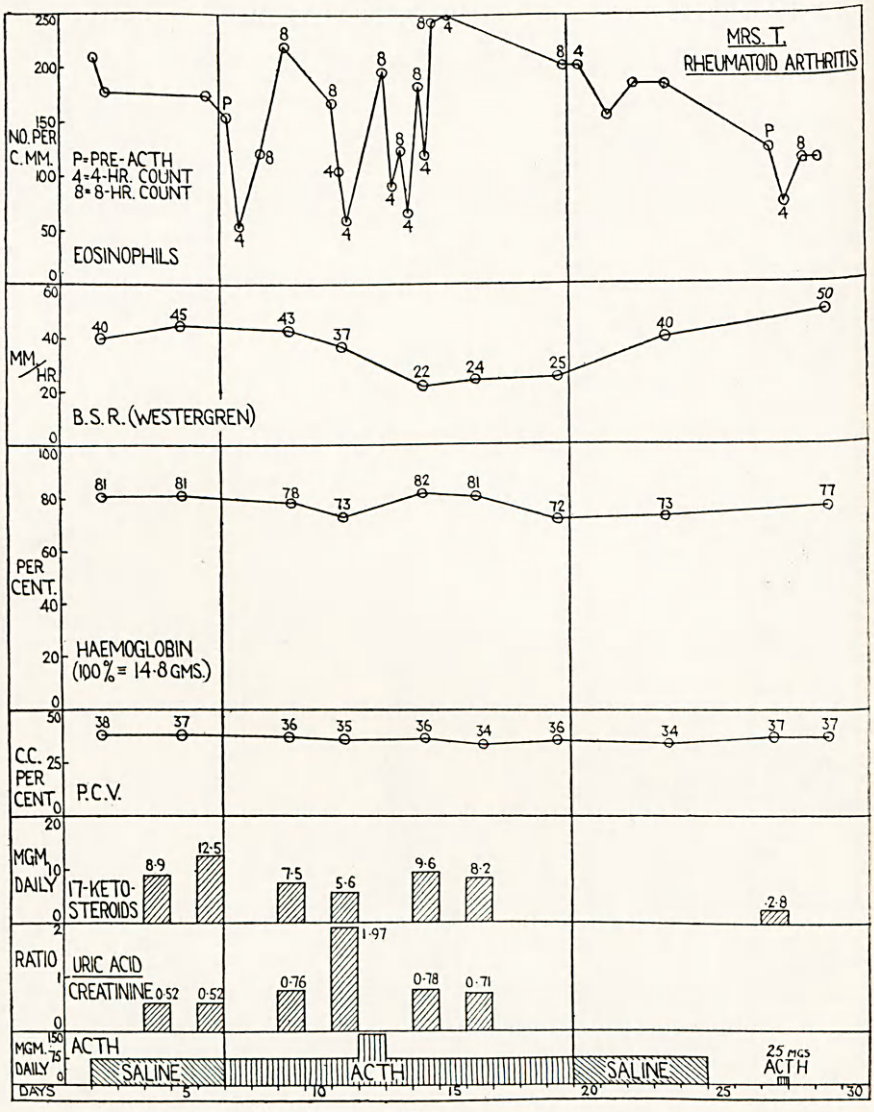

FIG. 14.

Clinical Assessment

Fig. 13 shows the details of clinical assessment. Joint tenderness rapidly diminished and finally disappeared, but returned towards the end of the course and increased rapidly when ACTH was stopped. Manual dexterity improved and walking speed also improved. Motor capacity increased in the legs ; less so in the arms.

Hæmatology (Fig. 14)

The most notable feature in this case was the rise in eosinophils between injections of ACTH and the eventual absence of any fall at all at four hours. The significance of this will be discussed later. The blood sedimentation rate dropped to 22 following a doubling of the dose for one day (150 mg.) and the hæmoglobin rose from 73 to 82 per cent. There was no significant change in the packed cell volume. Urinary 17-ketosteroids were only slightly increased, but the uric acid/creatinine ratio rose sharply—the rise was not maintained.

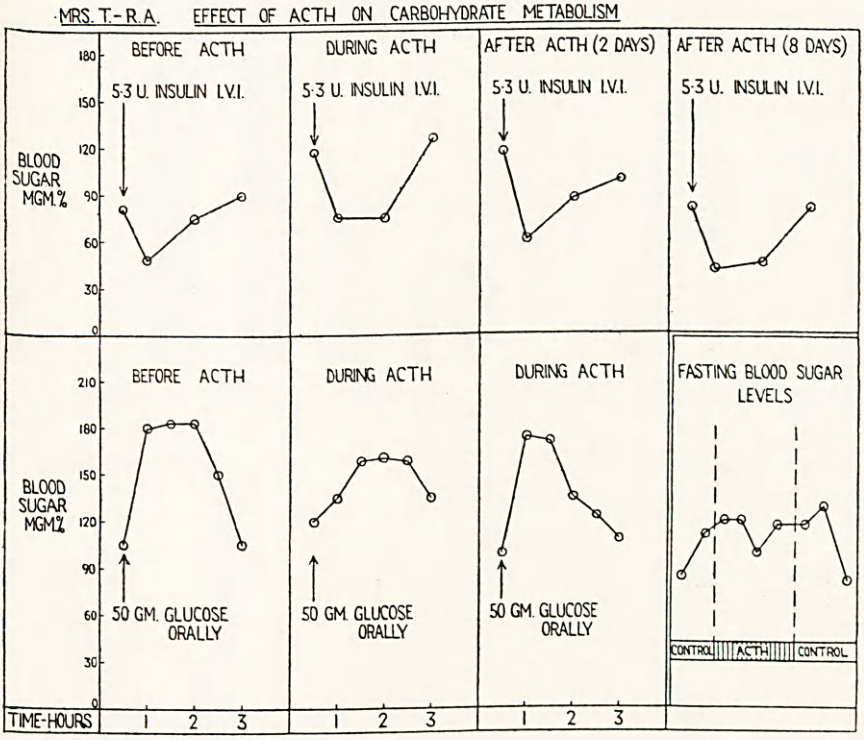

FIG. 15.

Effect on Carbohydrate Metabolism (Fig. 15)

Insulin resistance was significantly increased during ACTH, but rapidly returned to its previous level.

Glucose tolerance test gave a diabetic type of curve in this patient —a finding not infrequent in rheumatoid arthritis. ACTH significantly modified the shape of the curve.

Fasting blood sugar was raised throughout ACTH administration.

The effect of intravenous insulin (0·1 unit per kilo of body weight) on the eosinophil counts was recorded in the control period and during the administration of ACTH (Fig. 16). It was noted that the four-hour eosinophil count following injection of ACTH showed a steadily

diminishing response to ACTH—66 per cent. fall on 1st day, 55 and 47 per cent. on 7th day, 35 per cent. on 8th day, no fall at all at four hours on the 9th and 13th days. Intravenous insulin caused a 62 per cent. drop on the 10th day and a 50 per cent. fall 2 days after ACTH stopped. Insulin in the same dose was given 9 days after ACTH and caused a 72 per cent. fall. Twenty-five mg. ACTH on the following day caused only a 31 per cent. fall.

It would seem that in this woman insulin was capable of causing a fall in eosinophils when ACTH was no longer effective in this respect.

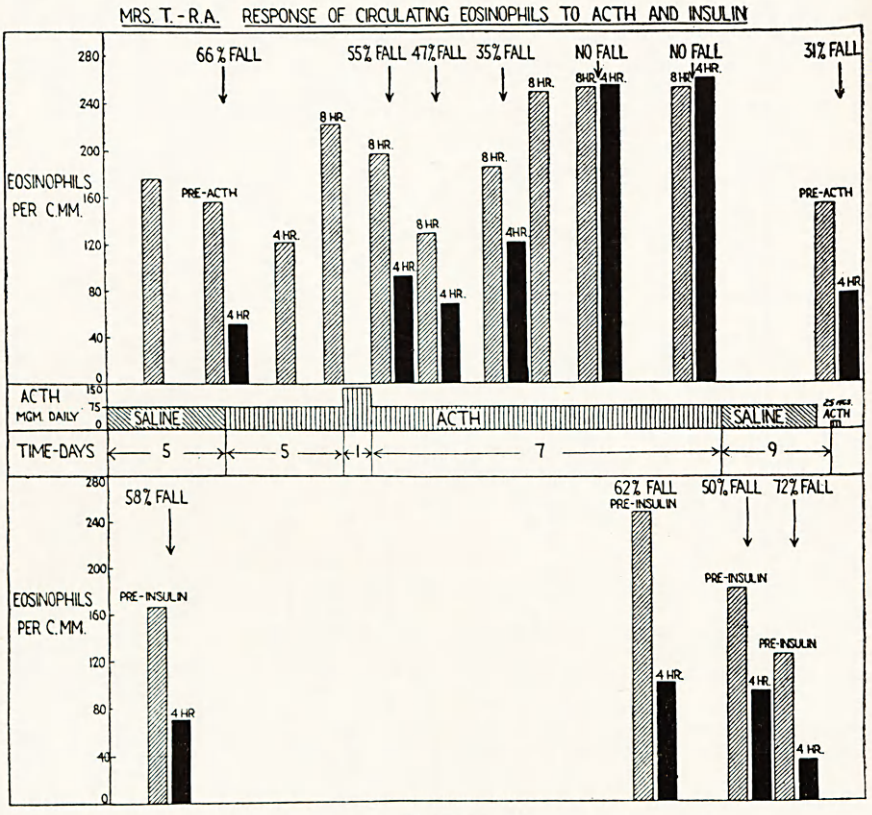

FIG. 16.

If eosinopenia is a reliable index of adrenal cortical response, then it is of considerable interest that insulin can cause a response when ACTH fails. This point was further investigated in this patient, and it was shown that the effect of insulin was dependent on the production of hypoglycæmia—insulin covered by glucose caused no fall in eosinophils. This would suggest that hypoglycæmia may stimulate the adrenal cortex directly and not through the pituitary gland, and this stimulus may be effective when the injection of ACTH is not. This patient relapsed after ACTH and has since been treated by daily insulin hypoglycæmia, with results equal to, if not rather

better than, ACTH. Insulin (30 units subcutaneously) caused a 60-70 per cent. fall in eosinophils. Godlowski (1949) has already reported on two cases treated by this method.

The effects on the eosinophil count of adrenalin, insulin and ACTH were investigated in a case of Simmonds disease (Fig. 17). While 25 mg. of ACTH caused no fall, insulin and adrenalin were both effective in this respect, though to a limited extent.

CASE 3.—This patient, a female aged 28, was admitted to the Royal Infirmary, Edinburgh, in October 1949. She had suffered from an arthritis of the rheumatoid type for eleven years. The condition slowly progressed for about two years. She then became pregnant and experienced a complete remission of symptoms. Her general health was excellent throughout her pregnancy, and she remained well during the following year. Joint

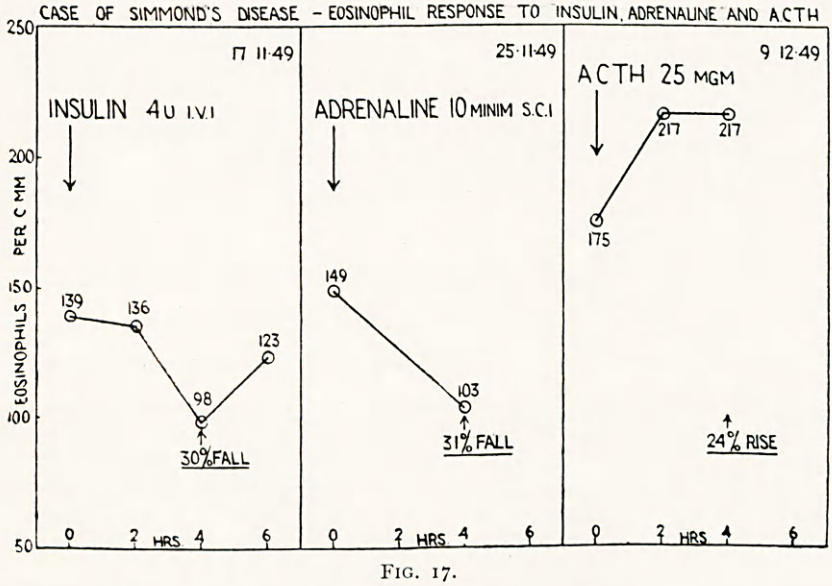

FIG. 17.

symptoms then returned, and slowly progressed with minor exacerbations and remissions until about two years ago, when pain became less, although stiffness and deformity persisted. During the last year her general health began to deteriorate. She lost weight steadily and she felt progressively more tired and ill. She became dyspnœic on effort, then dyspnœic at rest. About two months before admission to hospital she suffered a severe attack of vomiting and diarrhœa, and became feverish, with marked sweating. She developed a pain in her chest, aggravated by coughing. An itchy rash appeared on her abdomen, and a malar flush developed. She began to suffer from pain and frequency of micturition. On admission she was severely ill, with marked emaciation, persistent tachycardia, fever, orthopnœa and hoarseness. Examination revealed persistent hypertension, moderate albuminuria, cylinduria, anæmia, rapid B.S.R. and leucopenia. X-ray of her chest showed elevation of the diaphragm, but no pulmonary lesion in spite of persistent clicking crepitations at both bases and apices. ECG revealed flattened T waves in the three standard leads. A number of small erythematous lesions were

present on the abdomen. Her hair was falling out on brushing. Following three blood transfusions her general condition improved, but hypertension, tachycardia, albuminuria, leucopenia and the abdominal rash persisted.

Biopsy of one of the skin lesions showed perivascular lymphocytic infiltration and loss of collagen. On the basis of the presence of pathological changes in the joints, skin, kidneys, myocardium, and probably in the lungs, combined with a severe constitutional illness and persistent leucopenia, a diagnosis of acute disseminated lupus erythematosus was made, and it was decided to submit her to clinical trial with ACTH. Before this could be arranged, her condition suddenly deteriorated. Fever returned, her blood pressure rose, and albuminuria increased. Triple rhythm was noted, crepitations returned

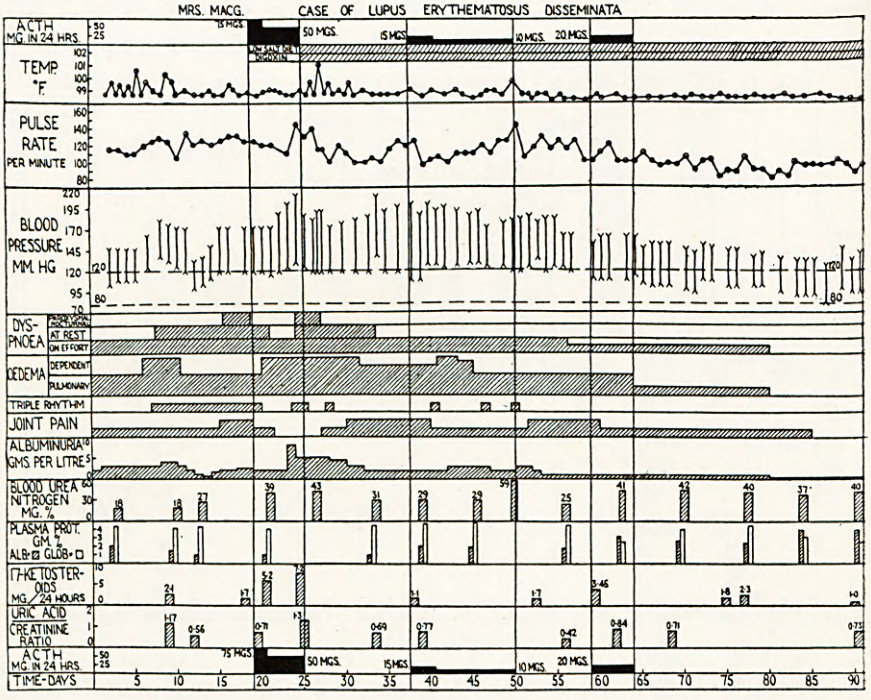

FIG. 18.

at both apices, and œdema of the back appeared. She became orthopnœic, and an erythematous rash developed on her face. Joint pain returned, and she suffered from attacks of paroxysmal nocturnal dyspnœa. Details of the clinical features and biochemical investigations are shown in Fig. 18.

ACTH was started on 14.12.49. Twenty-five mg. were given 8-hourly for 6 doses—a total of 150 mg. The dose was then reduced to 12½ mg. 6-hourly —50 mg. daily—for a further 4 days. There was a rapid improvement in her condition for the first 4 days. She experienced a marked sense of general well-being and improved greatly in appearance. Her appetite returned, joint pain disappeared, and movements improved. Dyspnœa became less marked, and the pulse rate fell. Blood pressure, albuminuria, and the abnormal plasma protein pattern were unaltered. There was a slight rise in the 17-ketosteroid excretion. On 19.12.49 the picture changed suddenly.

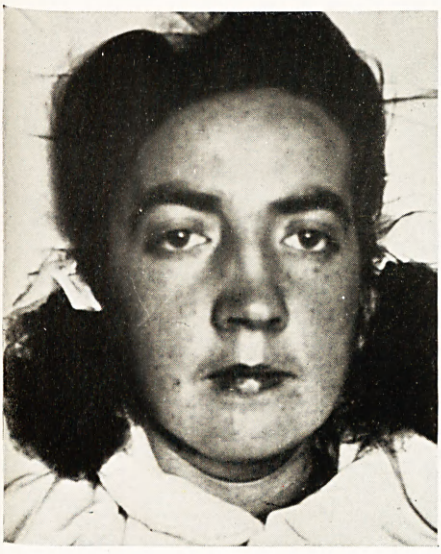

FIG. 19.

FIG. 20.

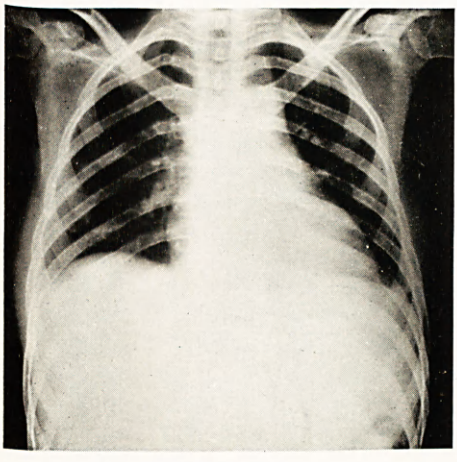

FIG. 21.

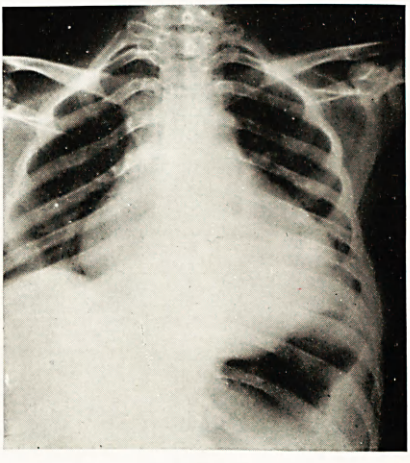

FIG. 22.

Fig. 19 shows her appearance before ACTH. Fig. 20 shows the marked rounding of her face, which appeared on the fifth day of ACTH.

Generalised œdema developed rapidly, breathlessness returned, diffuse crepitations were heard as high as the apices of both lungs, there was a sharp rise in blood pressure, albuminuria increased, and she became cyanosed. The picture was that of acute left ventricular failure. Fig. 21 shows the X-ray appearance of the chest before ACTH. Fig. 22 shows the appearance on the fifth day of ACTH. ACTH was stopped, as it was obvious that she had suddenly begun to retain fluid and that the increased load had precipitated cardiac failure. She was digitalised, and put on a salt-free diet. A moderate diuresis followed, and the signs of congestive failure rapidly diminished.

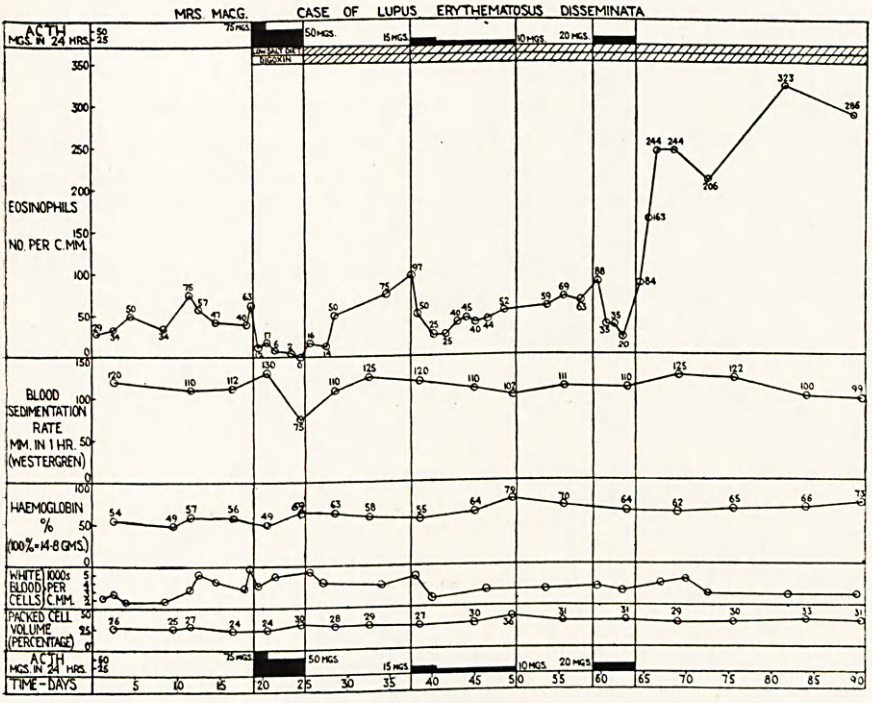

FIG. 23.

Joint pain returned and was more severe than on any previous occasion. Albuminuria decreased, and blood pressure fell slightly, and her general condition improved. This sudden emergency illustrates the dangers of ACTH in the presence of cardiac and renal disease.

On 2.1.50 ACTH was restarted in small doses—5 mg. 8-hourly. This was continued for 3 days, when rounding of the face returned. The dose was reduced to 10 mg. daily, and continued at this level for 10 days. There was a slow improvement in her general condition, a fall in blood sedimentation rate and a rise in hæmoglobin. ACTH was stopped, and she was put on glucose and peanut oil drip by stomach tube for 5 days. There was a fall in blood pressure, and ACTH was resumed at 20 mg. daily for 5 days. Following this last course, there was a sudden and spectacular rise in the eosinophils (Fig. 23), and from this time on there was a steady improvement in her condition—blood pressure and pulse rate fell steadily, albuminuria decreased,

plasma proteins tended to return to a normal pattern (Fig. 18), her appetite became ravenous, joint pain disappeared, and movements improved and weight rose. She eventually became fit to resume treatment for her joints and became fully ambulatory. A course of intravenous iron led to an improvement in her anæmia (hæmoglobin 78 per cent.) and the blood sedimentation rate fell to 54 mm. in 1 hour. There was still considerable evidence of renal damage—high blood urea nitrogen, impaired clearances, and fixed urinary specific gravity.

The conclusion reached in this case is that three short courses of ACTH had the effect of inducing a remission in the disease, which began after the third course and was signalled by the marked rise in eosinophils.

I should now like to discuss briefly certain special investigations which are still in progress.

Effect of ACTH on Progesterone Metabolism

Sommerville *et al.* (1950) have shown that in rheumatoid arthritis an abnormally high proportion of intramuscularly administered progesterone is excreted in the urine as pregnanediol when compared with normal controls.

Fig. 24 shows the results in 9 postmenopausal women and 4 men suffering from rheumatoid arthritis, and 6 normal postmenopausal women and 4 normal men. This abnormality in the metabolism of

	Normal	Rheumatoid arthritic
Men	9·3	21·7
	10·0	23·8
	12·2	26·1
	14·7	27·4
Postmenopausal women	12·1	19·0
	13·7	20·7
	15·2	22·0
	15·6	25·1
	15·6	25·7
	16·0	26·8
		31·0
		35·0
		36·4

FIG. 24.

progesterone, a steroid structurally not unlike cortisone, suggests that the metabolism of cortisone itself may be abnormal in this disease. It was felt that it would be of considerable interest to investigate the effect of ACTH in cases where a high pregnanediol excretion had already been demonstrated. If pregnanediol excretion returned to normal levels during the administration of ACTH, it would be reasonable to conclude that it does not reflect an analogous abnormality in cortisone metabolism. If, on the other hand, it remains high, this would favour the original hypothesis that there might be an associated abnormality in the metabolism of cortisone in the affected tissues, rather than a deficient secretion of the hormone by the adrenal cortex. This hypothesis would also go some way towards explaining the

necessity for the high doses of cortisone—100 mg. daily—required to produce a response in rheumatoid arthritis. Recent work has shown that 20-40 mg. daily are sufficient to maintain a case of Addison's disease.

Five-day courses of ACTH—75 mg. daily—were given to four patients showing high levels of pregnanediol in the urine following a test dose of progesterone in the control period. On the third day

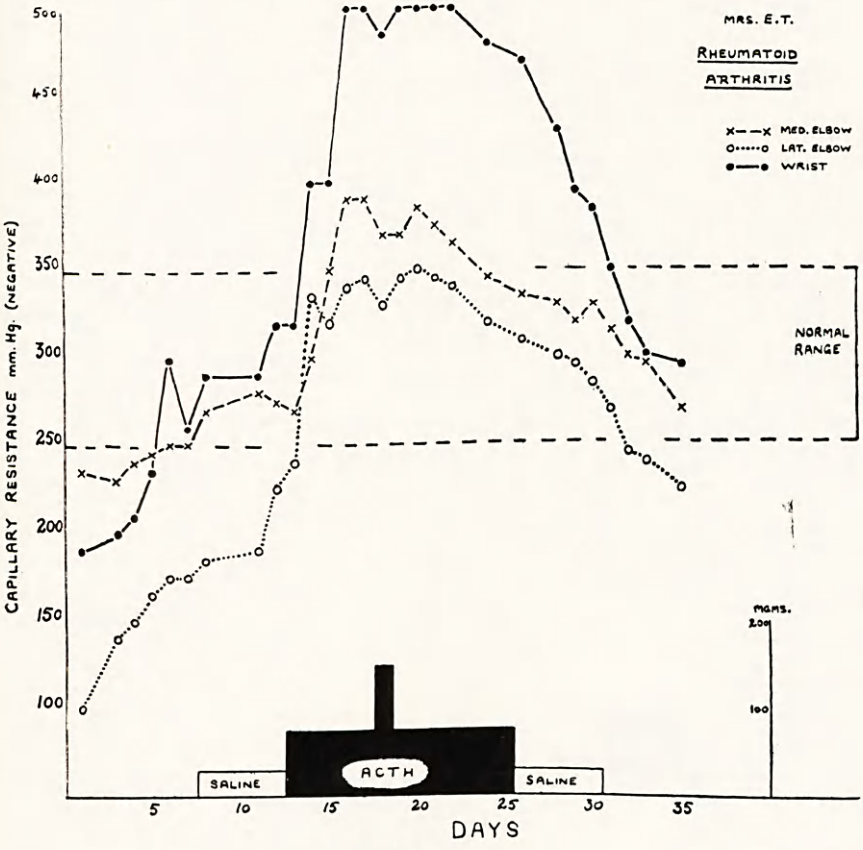

FIG. 25.

of the ACTH course, a further 60 mg. progesterone was injected. Although there are certain difficulties in interpreting the results, since ACTH alone appears to stimulate the excretion of pregnanediol-like substances in the urine, it appears that ACTH does not correct the abnormal metabolism of the administered progesterone.

The persistence of the abnormality in steroid metabolism during ACTH-induced remissions goes some way towards substantiating the theory of the existence of a similar abnormality in the metabolism of the adrenal steroids, but no more can be said until it becomes possible to investigate the metabolism of cortisone itself.

The Effect of ACTH on Capillary Resistance

Dr Robson, Department of Medicine, has been investigating capillary resistance in a variety of conditions, using the method originally devised by Dalldorf (1933) and later modified by Scarborough (1941). He became particularly interested in the rapid rise in capillary resistance to levels well above normal following splenectomy in cases of thrombocytopenic purpura. He felt it necessary to control this observation by observing the changes following other surgical procedures, and found that similar rises in resistance followed any major operation.

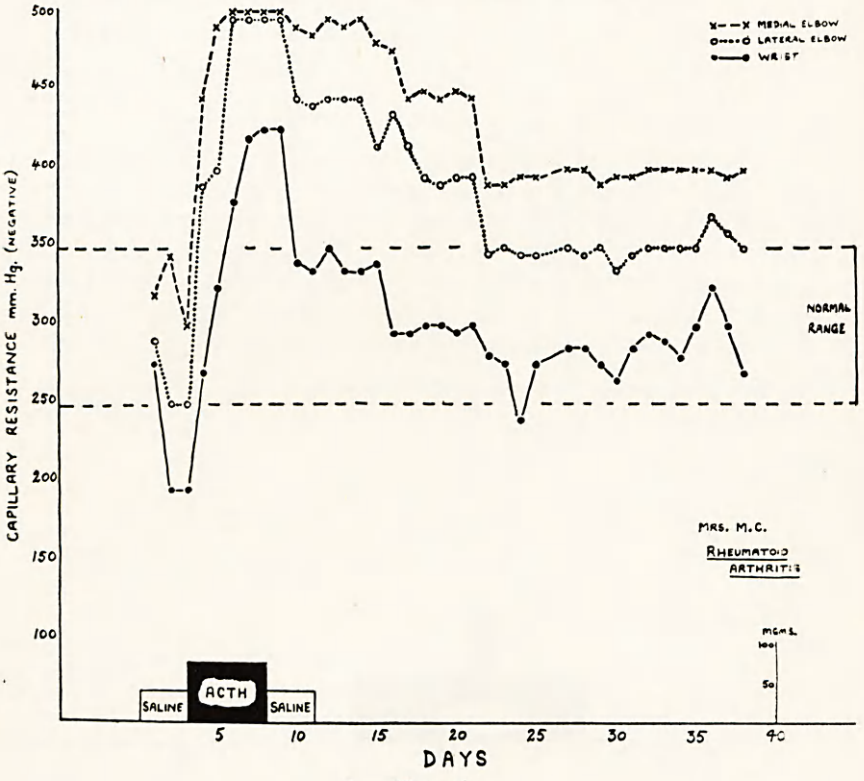

FIG. 26.

To decide whether this phenomenon was the result of tissue damage, he measured capillary resistance in patients receiving radiotherapy for malignant disease. Again sharp increases were recorded. Was tissue damage an essential factor, or might some other mechanism be at work? Injections of T.A.B. and insulin produced the same effect. Could the common factor be adrenalin? Adrenalin infusions caused a sharp rise in resistance. About this stage in Dr Robson's researches, the first reports on ACTH appeared, and, as all the conditions investigated fell into the category of possible activators of the pituitary-adrenal mechanism, the obvious step was to observe the effect of ACTH on capillary resistance. The answer was clear cut, as is shown in Figs. 25, 26 and 27.

Capillary resistance rises very rapidly and falls more slowly to normal levels on cessation of ACTH. The one case in which this did not happen is perhaps even more illuminating. This was a case of acute disseminated lupus erythematosus in a girl of 15 who showed

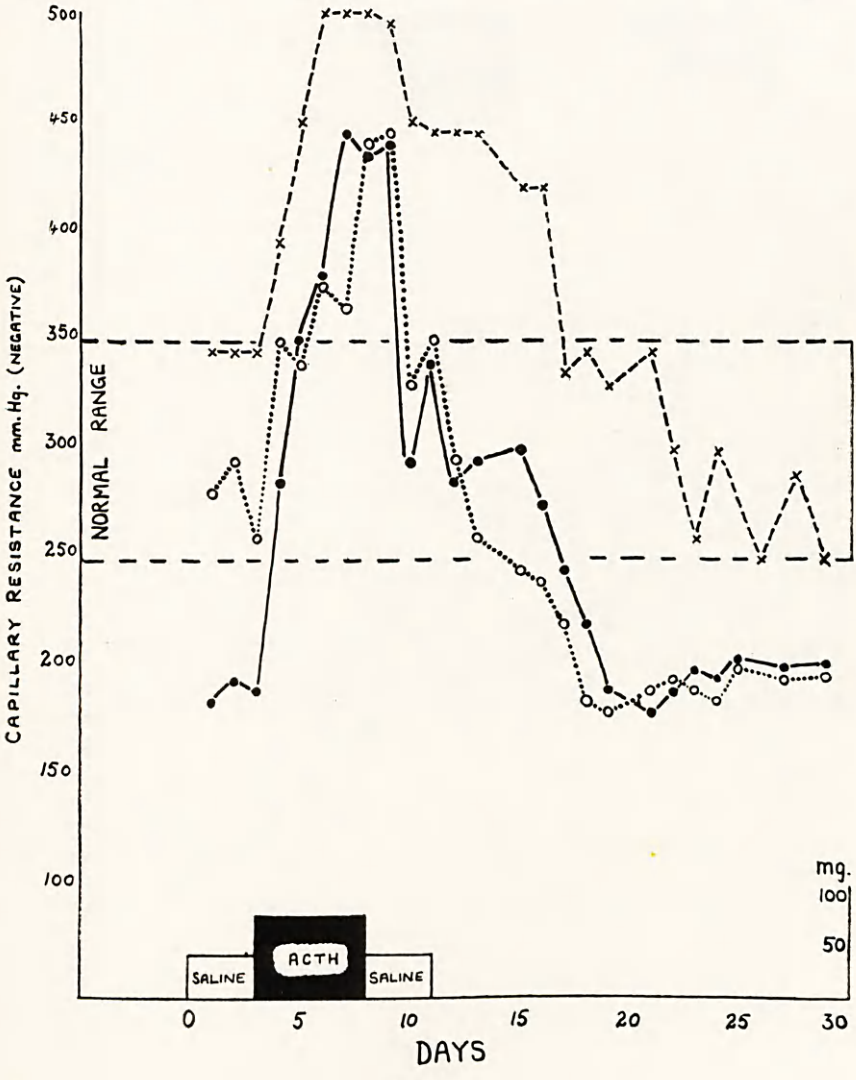

FIG. 27.

little or no improvement following two courses of ACTH. The capillary resistance fell steadily, and the patient finally developed epileptiform seizures and died in coma (Fig. 28).

Here it would appear that the adrenal cortex was exhausted and no longer capable of responding to ACTH. The capillary resistance would appear, therefore, to be a sensitive test of the activity of the adrenal cortex, and a steady fall such as occurred in this case is of

grave prognostic significance. It is of considerable interest in this connection that no eosinophils were present in the peripheral blood throughout this patient's illness.

An opportunity arose at this time to test the effect of ACTH on a

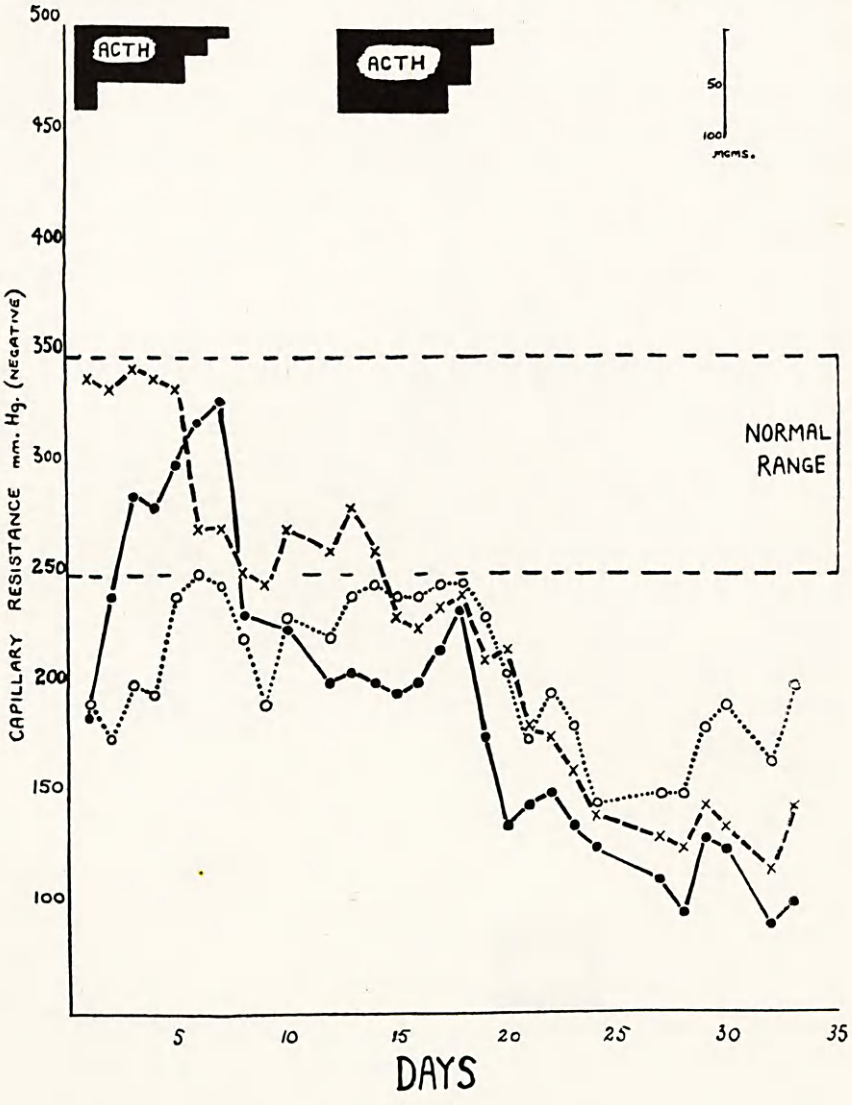

FIG. 28.

case of idiopathic thrombocytopenic purpura in which low capillary resistance is a striking feature. This case first developed signs of the disease in the form of recurrent petechial rashes, ecchymosis and thrombocytopenia in 1946, which continued without remission till 1948, when spontaneous improvement occurred. Signs recurred in 1949 on the twelfth day of the puerperium following a normal pregnancy.

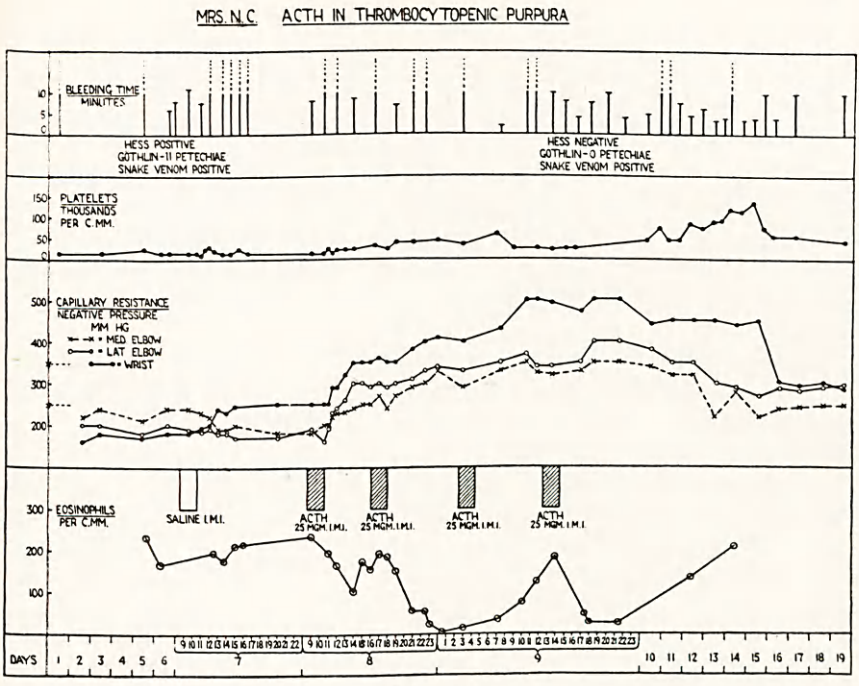
MRS. N.C. ACTH IN THROMBOCYTOPENIC PURPURA
BLEEDING TIME MINUTES
HESS POSITIVE
GOTHLIN-II PETECHIAE
SNAKE VENOM POSITIVE
HESS NEGATIVE
GOTHLIN-0 PETECHIAE
SNAKE VENOM POSITIVE
PLATELETS THOUSANDS PER C.MM.
CAPILLARY RESISTANCE NEGATIVE PRESSURE MM HG
MED ELBOW
LAT ELBOW
WRIST
EOSINOPHILS PER C.MM.
SALINE I.M.I.
ACTH 25 MGM I.M.I.
ACTH 25 MGM I.M.I.
ACTH 25 MGM I.M.I.
ACTH 25 MGM I.M.I.
DAYS

FIG. 29.

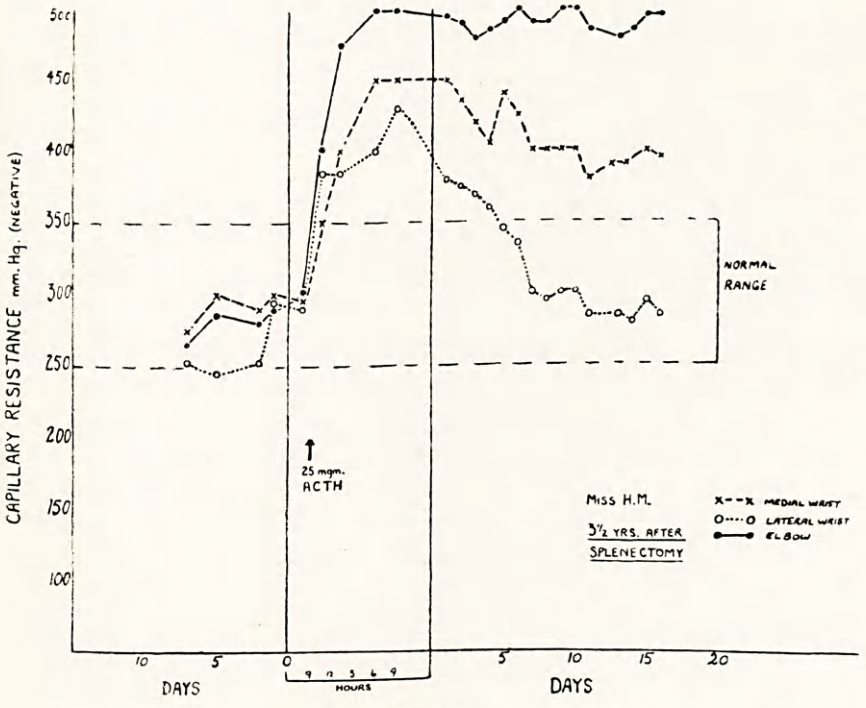
CAPILLARY RESISTANCE mm. Hg. (NEGATIVE)
NORMAL RANGE
25 mgm. ACTH
MISS H.M.
3½ YRS. AFTER SPLENECTOMY
X--X MEDIAL WRIST
O····O LATERAL WRIST
ELBOW
DAYS
HOURS
DAYS

FIG. 30.

There were no signs of remission until she received ACTH. Only four doses of 25 mg. were given—a total of 100 mg. (Fig. 29). Capillary resistance arose, and all signs of hæmorrhage disappeared. The remission has continued up to date, although platelets and capillary resistance have returned to subnormal levels.

A single dose of 25 mg. of ACTH was given to a patient who had her spleen removed on account of thrombocytopenic purpura three years ago. The rise in capillary resistance in this instance was extremely rapid (Fig. 30). Resistance reached the 500 level within a few hours. In other cases this level was not reached until the second day of ACTH.

It would appear possible that in certain circumstances the spleen secretes a substance or substances which antagonise the action of adrenal steroids. More cannot be said at the present time, but further research may well prove fruitful.

This technique may also prove to be of considerable value in screening new substances with cortisone-like activity, and may well replace the much more tedious and time-consuming method of counting eosinophils in the peripheral blood.

Conclusions

In this preliminary report on the clinical, biochemical and metabolic effects of ACTH, an account has been given of the work done during the four months since supplies of the hormone became available in Edinburgh. Certain lines of research have opened up which may eventually prove fruitful, but much more information is required about the mode of action of ACTH and the adrenal steroids whose production it stimulates before any final decision can be reached as to its value as a means of treatment.

We should like to record our sincere appreciation to Professor Davidson, Department of Medicine; Professor Marrian, Department of Biochemistry; Professor Gaddum, Department of Pharmacology, and Dr Stewart, Department of Clinical Biochemistry, for invaluable advice and technical assistance given throughout these trials.

The trials were made possible by the generosity of the manufacturers of ACTH, Armour Laboratories, Chicago, and Organon Laboratories Ltd., London, to whom we are indebted for supplies of the hormone.

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