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Research Article

OBSERVATIONS DURING ACTH AND CORTISONE ADMINISTRATION TO A PATIENT WITH LONGSTANDING PANHYPOPITUITARISM AND RHEUMATOID ARTHRITIS [1]

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The opportunity to observe the effect of administration of pituitary adrenocorticotrophic hormone (ACTH) and 11-dehydro-17-hydroxycorticosterone (cortisone) on the moderately active rheumatoid arthritis of a patient with panhypopituitarism was presented us. The clinical features (1, 2) of hypopituitarism are in essence those of hypo-function of the so-called "target" organs of the pituitary; the adrenal cortex, thyroid, and gonads. Sheehan and Summers (1) report "rheumatism of joints particularly of the knees" in 13 of 93 cases of panhypopituitarism, but elucidate no further on this clinical feature. The physiologic effects of ACTH and cortisone are well known (3, 4), and the dramatic response of patients with rheumatoid arthritis to these agents has been amply recorded (3, 5, 6). Forsham, Thorn, Prunty, and Hills (7) noted an absence of normal initial response after administration of ACTH in the majority of cases with severe hypopituitarism, although in one case, full adrenal cortical activity was noted after six days of ACTH administration. Knowlton, Jailer, Hamilton, and West (8) reported minimal metabolic effects after administration of ACTH for 12 days in a patient with longstanding hypopituitarism. An increase in excretion of 17-ketosteroids and uric acid and evidence of sodium and chloride retention were the observed effects.

This study was undertaken in order to observe the following:

1. What direct action, if any, ACTH might have on the clinical and laboratory findings of rheumatoid arthritis, inasmuch as adrenal cortical function was apparently absent.
2. Whether return of adrenal cortical activity would become apparent after ACTH administration.
3. The response to cortisone.

Case Report: LER, a 46 year old white woman, was first seen in the out-patient clinic at University Hospitals in 1945, complaining of intermittent attacks of swelling and tenderness of the shoulders, wrists, fingers, knees, and ankles. Recent attacks were associated with fever, anorexia, and weight loss. A vague history of increased heat tolerance was obtained. The husband described episodes that suggested hypoglycemia which had occurred intermittently during the preceding seven years. Menstrual and obstetrical history revealed that the only pregnancy, 27 years previously, had terminated with a prolonged labor, associated with excessive blood loss. Lactation was minimal, and ceased entirely after seven days. Menstrual function was not present after the pregnancy. Examination showed an asthenic, poorly nourished woman with dry skin. There was diminution of axillary and pubic hair. Blood pressure was 100/70 mm. Hg. Minimal joint signs were evident. Basal metabolic rates were -22% and -27%. Erythrocyte sedimentation rate was 86 mm./hour (Westergren). Clinical diagnoses of hypothyroidism and rheumatoid arthritis were made. The patient was discharged on thyroid substance 0.1 gm. daily.

There were four subsequent clinic visits, the final one being in August, 1946. Thyroid substance had been used only sporadically. On each occasion the patient complained of tachycardia. Little change was observed in the general appearance. The erythrocyte sedimentation rate remained elevated. On one occasion, a typical rheumatoid lesion of a metacarpal-phalyngeal joint was noted.

She was admitted to the medical service in January, 1949. During the previous 30 months she had experienced progressive asthenia and increasing periods of sleep. Her only medication had been 30 mg. of thyroid substance daily. In recent months progressive swelling and tenderness in the right knee and left ankle had been observed. Examination showed a very torpid and listless woman whose weight was 106 pounds. The skin had no increased pigmentation and was smooth and dry. Axillary and pubic hair were sparse. The breasts were atrophic. The heart was small. Blood pressure was 70/50. Pelvic examination revealed an atrophic uterus and senile vaginitis. Fusiform swelling of slight degree was evident at the interphalyngeal joints of the hands. The knees were limited in range of motion and marked

[1] This study was supported by the Trust Fund of the Department of Internal Medicine which permitted purchase of ACTH from Armour & Co. and cortisone from Merck & Co., Inc.

crepitation on motion was noted. There was thickening of the periarticular tissues.

Shortly after admission, she had a febrile episode associated with a urinary tract infection and lapsed into complete unresponsiveness with further drop in blood pressure. Treatment for Addisonian crisis was instituted and resulted in a satisfactory response. An unsuccessful attempt to stabilize the blood pressure, electrolyte, and endocrine metabolism on desoxycorticosterone and thyroid extract was made. Eventual maintenance medications were: *1*) Lipoadrenal Cortex (Upjohn), 2 ml. intramuscularly daily. *2*) Testosterone propionate, 20 mg. intramuscularly daily. *3*) Sodium chloride, 6 gm. daily.

Laboratory examination at the time of admission failed to demonstrate the presence of urinary gonadotropins, and 17-ketosteroid excretion was 0.84 mg./24 hours. Serum sodium was 290 mg./100 ml., potassium 29.3 mg./100 ml., and plasma chlorides 525 mg./100 ml. Blood urea nitrogen was 17 mg./100 ml. and the creatinine 1.0 mg./100 ml. X-rays revealed the lung fields to be clear. The cardiothoracic ratio was 0.38. X-rays of the abdomen demonstrated no calcification in the adrenal areas. Skull x-rays were normal. Roentgenograms of the hands demonstrated atrophic changes. A basal metabolic rate two weeks after admission was −16%. A plasma protein bound iodine in June, 1950, was 2.6 gamma/100 ml. A test for adrenal cortical insufficiency with 25 mg. ACTH as described by Thorn, Forsham, Prunty, and Hills (9) failed to demonstrate a significant drop in circulating eosinophils or change in urinary uric acid excretion. An intravenous glucose tolerance test produced a febrile reaction and drop in blood pressure which necessitated discontinuance of the test and use of supplementary adrenal cortical extract and intravenous saline.

METHODS

During the study the carbohydrate, fat, protein, and sodium in the diet were calculated since it was impossible to keep the diet constant. Blood pressure and weight were recorded daily at 7:00 a.m. Because of the mental status of the patient 24 hour urine and stool specimens were collected with some difficulty. Toluene was used as preservative in the urine specimens except on days when 17-ketosteroid and uric acid determinations were made. Eosinophil counts and leukocyte counts were done by the method of Randolph (10); erythrocyte sedimentation rates by the Westergren method; serum so-

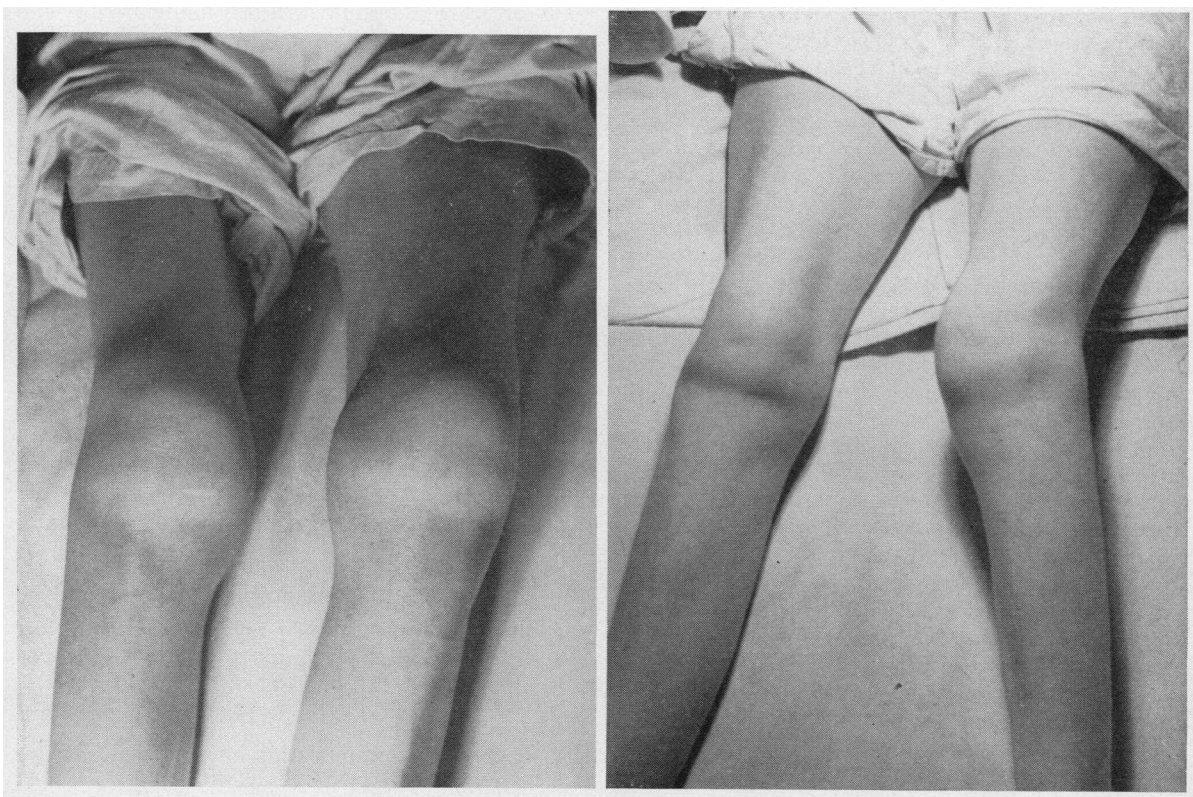

FIG. 1

A. PHOTOGRAPH OF THE KNEES TAKEN DURING THE INITIAL CONTROL PERIOD

B. PHOTOGRAPH AFTER THE SECOND COURSE OF CORTISONE, WITH DEFINITE DECREASE IN THE AMOUNT OF JOINT FLUID AND PERIARTICULAR SWELLING

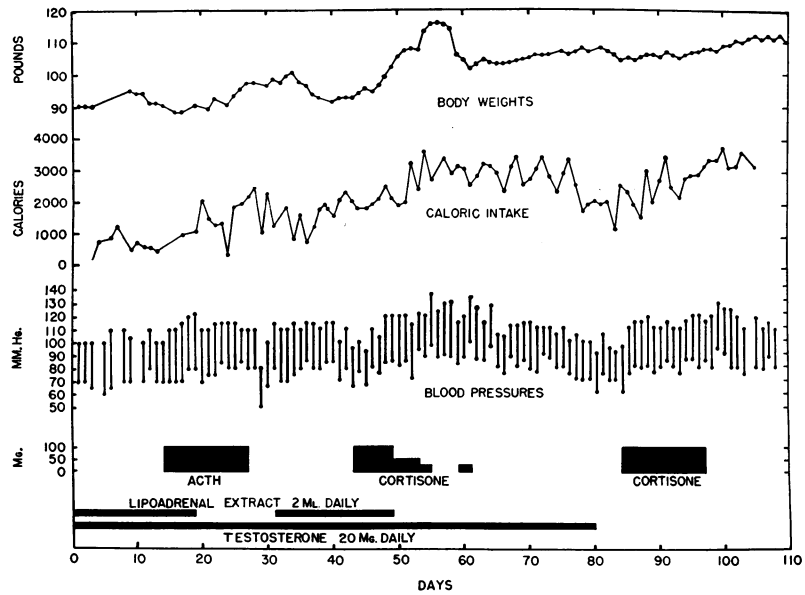

FIG. 2

dium by the method of Hoffman and Osgood (11); serum potassium according to Breh and Goebler (12); urine and blood uric acid by the method of Folin (13); 17-ketosteroids by the method of Robbie and Gibson (14). The patient was studied daily by two independent observers, and notations were made of changes in mental status, joint mobility, and general appearance. ACTH (Armour Standard LA-1-A Control J9801) freshly dissolved in saline was administered intramuscularly, 25 mg. every six hours. Cortisone acetate (Merck) was given every six hours intramuscularly (Figures 2, 3, 4).

Regimen (Figure 2): Function of the pituitary was thought to be so slight that to discontinue all medication at the start of ACTH administration was inadvisable. Lipoadrenal cortex was omitted after four days of ACTH, but testosterone was continued. Lipoadrenal cortex was again given at the termination of the course of ACTH when pneumonitis with fever and hypotension intervened. During the first period on cortisone, lipoadrenal cortex was discontinued when a sharp rise in weight and elevation of blood pressure occurred. Shortly thereafter cortisone was reduced and, later, discontinued when edema appeared. Added sodium chloride was also discontinued. Testosterone was discontinued before the second course of cortisone. At the completion of the second course of cortisone, no medications were given for 21 days. Fall in blood pressure necessitated resumption of therapy with lipoadrenal cortex.

RESULTS

Clinical observations: Before the beginning of this study, the patient was lethargic, passive and intermittently hallucinated. During the first six days of ACTH administration, hallucination and agitation become extreme, requiring restraint and on one occasion tube feeding. The psychotic behavior became less pronounced when ACTH was continued. While on cortisone the patient became cooperative, and had long periods of lucid behavior. During administration of cortisone the skin remained dry and soft. The subcutaneous tissue of the face took on a loose, spongy consistency much like that seen in myxedema. A luxuriant growth of axillary and pubic hair appeared during cortisone therapy. This was accompanied by extreme modesty, which heretofore had been lacking completely. The activity of the rheumatoid arthritis was such that no dramatic change was observed. During the course of ACTH there was slight objective increase in range of motion of the knees, ankles and left elbow. After four days on ACTH the patient walked spontaneously for the first time during the entire period of hospitalization. The agitation and hallucination at this period, however, probably accounted for the apparent absence of pain on walking. In the interval between ACTH and cortisone administration there was a definite exacerbation of joint pain, swelling and local heat. Cortisone brought about definite objective and subjective improvement in the rheumatoid state (Figure 1). This occurred gradually during a seven day period. During the 22 day period be-

tween the courses of cortisone there was no exacerbation of joint signs or symptoms. Twenty-one days after completion of the second course of cortisone, both knees but especially the right, became painful, warm, and swollen. An accompanying systemic febrile response occurred.

A gain in body weight of nine pounds was noted after 10 days of ACTH administration (Figure 2). No edema was evident. This gain could not be followed accurately because pneumonitis necessitated the use of supplementary adrenal cortical extract three days after completion of ACTH administration. By the sixth day of the first course of cortisone, a weight gain of 10 pounds had occurred. Edema appeared and remained despite discontinuation of lipoadrenal cortex and sodium chloride. Cortisone was discontinued on the 12th day after her weight had risen from 93 to 115 pounds. It was believed that the appearance of edema was a manifestation of sodium retaining effect of cortisone (3), added to the effect of testosterone (15). After edema had disappeared her weight remained 10 pounds above the control level and represented an increase in body tissue. This gain was maintained in the 23 day interval between courses of cortisone. During the second period of cortisone her weight increased but 3 pounds. However, an additional gain of 5 pounds was noted in the 12 day interval subsequent to its administration. During the second period, when cortisone was the only drug being administered, no edema appeared.

Blood pressure was maintained slightly above control levels by ACTH after discontinuation of

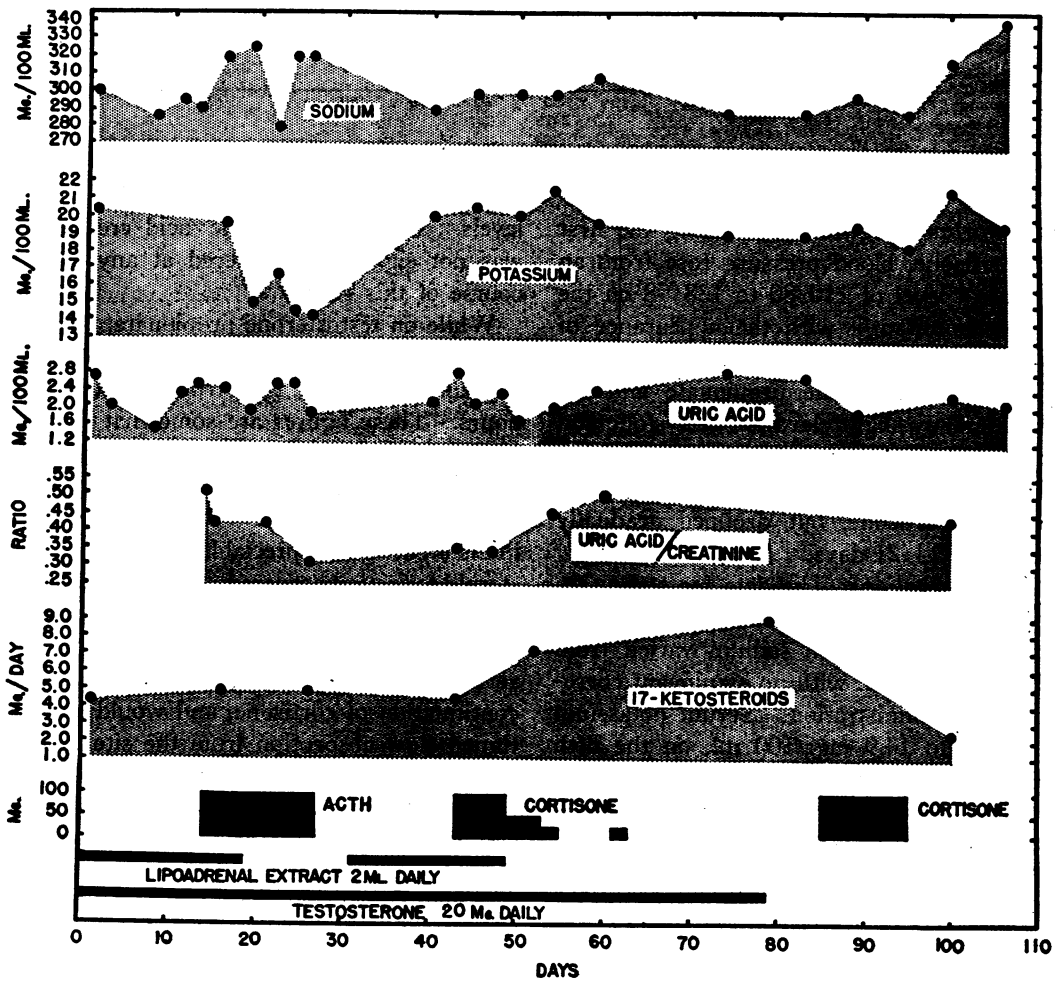

FIG. 3

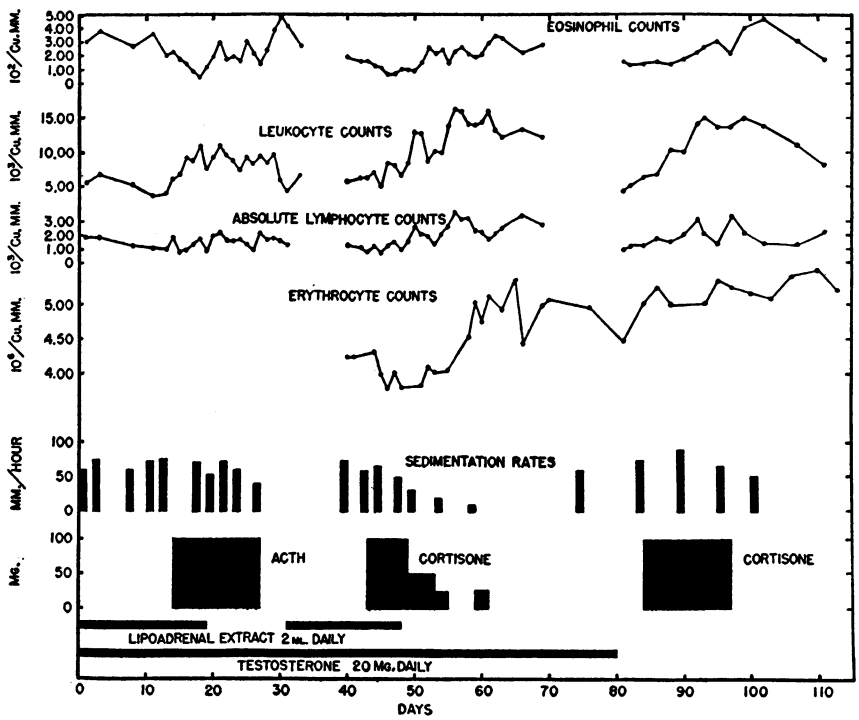

FIG. 4

lipoadrenal cortex (Figure 2). During the first course of cortisone, blood pressure rose from an average control level of 110/80 to 138/98 on the 12th day, concomitantly with the appearance of edema. When cortisone was given without lipoadrenal cortex, testosterone propionate and sodium chloride, only slight elevation of systolic and diastolic arterial tension was noted. Blood pressure did not return to control levels immediately after stopping cortisone, but dropped gradually over a period of 14–21 days.

Chemical observations: The data for serum sodium, potassium, uric acid, and 17-ketosteroids are given in Figure 3. Serum sodium varied from 280 to 335 mg./100 ml. with no significant correlation to drug administration. Serum potassium levels dropped to 14.9 mg./100 ml. on the fifth day of ACTH and remained below control levels during the entire course. This was interpreted as suggestive evidence of adrenal cortical activity inasmuch as potassium diuresis had been an observed effect of ACTH administration (3, 7, 8). No alteration of significance occurred during cortisone administration. Neither ACTH nor cortisone significantly altered the blood uric acid levels. The urinary uric acid/creatinine ratio was not significantly altered at any time in the course of this study.

While on testosterone propionate, 20 mg. daily, before and during the control period, 17-ketosteroid excretion ranged from 4.4 to 6.6 mg./24 hours. These figures are somewhat less than the percentage excretion of administered testosterone observed by Fraser, Forbes, Albright, Sulkowitch and Reifenstein (16). While ACTH was administered, no appreciable change in 17-ketosteroid excretion occurred. During the first course of cortisone, while testosterone was continued, an increased excretion of 17-ketosteroids was observed. This effect was noted 20 days after discontinuation of cortisone, and would suggest continued slow absorption from the site of injection, an observation previously made by Sprague, Power, Mason and Cluxton (17). Following the second course of cortisone during which no testosterone was given, the 17-ketosteroid excretion was maintained near the control level by cortisone.

Alteration in tolerance of carbohydrate was not evidenced by fasting and post-prandial blood sugar determinations.

Hematologic observations: Values for erythrocyte sedimentation rate, circulating eosinophils, total leukocytes, absolute lymphocytes, and erythrocytes are plotted in Figure 4. The erythrocyte sedimentation rate decreased from an average control value of 68 mm./hour at the termination of ACTH administration to 40 mm./hour. Significant decrease to 10 mm./hour occurred 16 days after initiation of cortisone therapy. During the second course of cortisone a significant decrease in sedimentation rates failed to occur. Total circulating eosinophils dropped from an average control level of 290/cu. mm. to 44/cu. mm. on the fourth day of ACTH therapy. A gradual return to essentially control level by the seventh day of treatment was noted. A similar decrease in circulating eosinophils was observed during the first course on cortisone, while no definite trend occurred during its second exhibition. The total leukocytes rose from an average control value of 5000/cu. mm. to average treatment values of 9000/cu. mm. on ACTH. A pronounced increase in total leukocyte count occurred after six days of cortisone and continued for eight days after its discontinuation. A similar increase was observed during the second course of cortisone. There was very little change in absolute lymphocyte counts during the entire study.

The erythrocyte count rose from control levels of 4,300,000/cu. mm. to 5,980,000/cu. mm. at the completion of the second course of cortisone.

DISCUSSION

Because this patient had clinical signs of hypothyroidism and a low basal metabolic rate, she was treated with small amounts of thyroid substance on four occasions. The response was adverse and each time the therapy had to be discontinued. The symptoms which caused the latest admission to the hospital suggested adrenal insufficiency, and although she was hypokinetic and her skin was dry the signs of myxedema were not outstanding. ACTH caused no alteration in the relationship of the clinical signs of adrenal insufficiency to those of hypothyroidism, but when the hypoadrenalism was controlled with cortisone, striking signs of myxedema occurred. Clinically it seemed that partial control of either adrenal or thyroid insufficiency enhanced signs of the untreated endocrine deficiency. That there is a relationship between adrenal and thyroid function has been demonstrated by Soffer, Gabrilove, and Jailer (18). Evidence that this relationship is more than relative is not apparent from our study.

The observations set forth in this study of an unusual clinical combination of rheumatoid arthritis and hypofunction of the adrenal cortex secondary to hypopituitarism are in keeping with the rapidly accumulating data in this field (3–6, 8). In our patient there was clinical and laboratory evidence that some bit of adrenal cortex remained and was responsive to stimulation by ACTH. This response mediated through the adrenal glands was shorter and less intense than the general response to substituted cortisone. Generalizations from this series of studies are not warranted.

SUMMARY

1. ACTH and cortisone were administered to a patient with longstanding panhypopituitarism and rheumatoid arthritis.

2. Partial adrenal cortical activity was demonstrated during ACTH administration.

3. The effect on the arthritis was equivocal after administration of ACTH, but was definite after administration of cortisone.

4. Clinical, chemical and hematologic data are in agreement with present conceptions of the metabolic and therapeutic properties of ACTH and cortisone.

ACKNOWLEDGMENTS

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