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ACTH and cortisone in the treatment of rheumatoid arthritis

Reuben David
University of Nebraska Medical Center

ACTH AND CORTISONE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Reuben David

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HISTORY

Thomas Addison in 1856 suggested that the adrenal cortex was essential to life and described a specific "deficiency syndrome" resulting from non-function or destruction of the adrenal gland in human beings. It is characterized by pigmentation, asthenia, and anorexia. He observed that these patients became suddenly and critically ill with extreme ease and often died with minor infection and stresses of various types. (2)

During the following seventy-five years, a vast amount of laboratory work was done on animals and was concerned with the physiological results of removing the adrenal gland in animals. Investigations during this period clarified and confirmed that adrenalectomized animals were in most respects the physiological counterpart of Addisonian disease in human beings. (2)

The existence of an extremely important relationship between the pituitary and the adrenal glands was first demonstrated by Smith who found that the hypophysectomy in experimental animals resulted in adrenal atrophy. (55) Twenty-five years ago, Evans, Houssay, and Collip showed that cell-free extracts of the anterior pituitary had a stimulating effect on the adrenal cortex of hypophysectomized animals, preventing atrophy, or even producing hypertrophy after prolonged administration. (11) (31) (7)

In 1936, Selye observed that animals subjected to extreme stresses as heat or cold, extreme fatigue, crushed muscle, poisoning with colchicine produced a stage of shock which was soon followed by recovery and increased resistence to the stimuli, but if the stress was continued long enough, death from exhaustion resulted.(43) The full implication of this phenomen in human diseas was get yet discovered even tho techniques had been evolved to reveal that it was the adrenal gland that allowed the animals to withstand the large variety of environmental stresses.

Investigation on the pituitary gland was carried out in the laboratories, and in 1933, Collip reported the isolation of ACTH in impure form. In 1943, several groups of investigators obtained it in pure form.(36)

Thorn was the first investigator to inject ACTH into human beings.(2) He observed that this compound stimulated the adrenal glands producing retention of sodium and chlorides, increased excretion of potassium and nitrogen, increased uric acid-creatinine ratio, decrease in the circulating eosinophils, and increased urinary excretion of 17-ketosteroids and 11-oxysteroids. These observations were confirmed during the next two years by Albright, Conn, Browne, Sayers, Burns, and McQuarrie.

At the same time that the pituitary gland was being investigated, increased interest was stimulated in the adrenal cortex. Dr. E. C. Kendall of Mayo Foundation succeeded in extracting several crystaline hormonal substances from the beef adrenal gland in 1941. He isolated one of the substances and called "compound E" which later became known as cortisone.(34) Its therapeutic potentialities were later investigated in 1948 by Hench, Slocumb, and Polley.(34)

The events which led to its therapeutic use on rheumatoid arthritic patients are interesting. Since 1929, Hench had been noting the beneficial effects of pregnancy and jaundice on rheumatoid arthritic patients. He had observed that of thirty patients with rheumatoid arthritis who had various types of intercurrent jaundice, complete remission of their arthritic symptoms were obtained in 83% of the patients.(25)(26)(27)(28)

Drs. Slocumb, Polley, and Hench recorded results of 150 rheumatoid pregnancies since 1938. They showed that most of the patients experienced a marked or complete recovery of their rheumatic symptoms during pregnancy. The relief was only temporary, however, and return of symptoms was noted after delivery.(25) A later report by Hench showed that pregnancy and jaundice relieved 60% to 90% of the patients of their arthritic symptoms.(43)

Prior to 1948 when ACTH and cortisone were first used on the rheumatic diseases, little more than the simple measures of bed rest, salicylates, physical therapy, fever and radiotherapy were advocated to change the final outcome of rheumatoid arthritis.(45) In attempts to reproduce the effect of pregnancy and jaundice, many measures were used such as blood transfusions from jaundiced persons, administration of female hormones from a pregnant woman, administration of various biliary products, and the induction of jaundice.(45)

General anesthesia and surgery treatment often caused remission of symptoms in rheumatoid patients. It had been previously shown that anesthesia and surgery stimulated the adrenal cortex.(24) It had also been shown that pregnancy caused hypertrophy of the adrenal cortex.(43) Finally, it was conjectured that the anti-rheumatic substance in jaundice, pregnancy, anesthesia, and surgery might be an adrenal hormone. This prompted Hench and the Mayo Foundation workers to investigate ACTH and the adrenal-cortical preparations in the treatment of rheumatoid arthritis.(24)

DEFINITION

Rheumatoid arthritis is a chronic constitutional disease of the joints characterized by inflammatory changes in the synovial membrane and periarticular structures, and by atrophy and rarefaction of the bones, In the earlier stages, the disease manifests itself as a migra-

tory swelling and stiffness of the joints; in the later stages by more or less deformity and ankylosis.(58)

ETIOLOGY

The etiology of rheumatoid arthritis (or rheumatoid disease, a name suggested lately with very good reason by Ellman and Ball, 1948) has not been finally determined. In spite, however, of the lack of knowledge concerning the exact cause of the disease, there are certain precipitating factors which are universally accepted as being conducive to its development; namely, severe physical or emotional shock, mental or physical fatigue, trauma and wounds, fractures of joints, sudden or repeated exposure to dampness, rain, or cold, and acute infections.

The evidence favoring acute infection as the exciting cause of the disease is considerable in view of the fact that the clinical course of the disease is strongly suggestive of infection, and the lesions in the joints are essentially inflammatory.

Group A Hemolytic Streptococci have been proposed by Ragan as the etiological agent.(45) He noted an interesting correlation between the serum agglutination of rheumatoid patients and the Group A Hemolytic Streptocco. He found that the agglutination of Group A hemolytic streptococci was positive in the first years of the disease in about 35% of the patients. After the first year,

the percentage was higher, being from 50% to 55% positive. The titre had no significance in the evaluation of the results. He found that in severe cases of the disease, the agglutinations were nearly always positive.

Guerra, Dry, Meyer, and Ragan postulated that pathogenic streptococci played a part in the etiology by producing an enzyme called hyaluronidase.(33) Hyaluronidase is a mucopolysaccharide which might be obtained from streptococci, staphlococci, pneumococci, and Clostridium welchii.(1) A speculative point is the possibility that during the initial infection, the hyaluronic acid in the capsul of the invading streptococci may act as a hapten and give rise to the formation in the patient of antibodies to the hyaluronic acid of the patient's own tissues.(1)

In considering the hyaluronidase as the etiological factor, we know that connective tissue contains hyaluronic acid and chondroitin-sulfuric acid,(33) and is dominantly affected in rheumatid diseases. It is also known that hyaluronic acid can be broken down by a number of agents, particularly certain tissue and bacterial enzymes so that its viscosity is reduced by depolarization.(33)(18) It might be quite logical to conclude that hyaluronidase is the enzyme which acts on the hyaluronic acid.

To support the hapten point of view, many workers suspect that rheumatoid patients become sensitized thru

some allergen and that they are in a state of allergy in which the most obvious manifestations are pathological reactions of mesenchymal tissues.(42)

Along the same line of reasoning, Seifter postulated a deficiency function of hyaluronic acid produced by hyaluronidase in patients "sensitive" to the enzyme, thus permitting exudate into the joints and leading eventually to rheumatoid arthritis.(18) However, hyaluronidase has not been demonstrated in the synovial fluid of rheumatoid patients.(18)

Jones feels that the literature up to the present time contains insufficient information to incriminate hyaluronidase as an important factor in the etiology of rheumatic diseases.(33) In spite of the fact that hyaluronidases may produce connective tissue lesions similar to those seen in the rheumatic diseases, Gardner advises extreme caution in assuming the causes to be identical.(18)

Selye proposed still another theory upon discovering that arthritis could be produced in the rat by removing both adrenal glands and one kidney.(34) This observation, together with the fact that rheumatoid arthritis is rarely seen in untreated patients with Addison's disease(59) suggests that adreno-cortical insufficiency is a prerequisite to the development of the rheumatic state.

Some workers believe that the adreno-cortical insufficiency is due to some suppressive action which prevents

the rapid and sufficient production of the adrenal hormone, or its utilization by the body tissues.(8) Conn believes that due to the wide spread distribution of nodules composed of lymphocytes and plasma cells in the rheumatoid patients, these are the result of thymus over-activity and that it is the thymus over-activity that suppresses the adrenal-cortical hormone.(8) It is generally known that adrenal-cortical extract produces a rapid dissolution of these lymphocytic accumulations.(43)

The fact that ACTH produces a rapid clinical improvement in the arthritic symptoms, and a marked decrease in eosinophiles indicates that the adrenal deficiency, if it is present, is not situated in the adrenal cortex, but at a higher level, namely, the hypophysis or diencephalon.(37)

PATHOLOGY

The basic lesion in rheumatoid arthritis, according to Klinge is fibrinoid degeneration or fibrinoid swelling.(1) The lesion involves the collagen bundles of mature fibrous tissue. The fibers swell and undergo a granular degeneration and fragmentation while at the same time there is exudation of fibrin-rich plasma into the tissue spaces.

Others have regarded the basic lesion to be a degeneration of the "ground-substance" of the mesenchyme.(1) Hyaluronic acid is an important constituent of this jelly-like substance.

Gardner believes that the basic lesion is similar to those found in other connective tissue disorders, and are primarily cellular in nature.(18) They are multiple, nodular, inflammatory lesions consisting of lymphocytes and plasma cells, and are widely distributed thruout connective tissue, being especially prominent in muscle and nerve tissue.(35)

There are surprisingly few chemical changes in the blood of rheumatoid arthritic patients.(58) "The blood urea and the non-protein nitrogen are well within normal figures. The carbon-dioxide combining power of the blood, the calcium of the circulating blood and the total fat and cholesterol of the fasting blood in arthrits are within normal limits. The basal metabolism is close to average normal level. Secondary microcytic anemia is present in the majority of the patients. A moderate leukocytosis is found in many patients, and the Schilling hemogram frequently shows increase of the immature cells, particularly in active cases. The sedimentation rate is increased in approximately 95% of the cases. The albumin-globulin ratio is reversed in the great majority of cases."

SUSCEPTABILITY TO TREATMENT

Rheumatoid arthritis involves two abnormal processes:(21) 1) pathologic physiology, which constitutes the "fire of the disease, and 2) pathologic anatomy, which constitutes the "ashes" of the disease.

The pathologic anatomy, of which we know something, is largely irreversible; but the pathologic physiology, of which we know almost nothing, is potentially and under certain circumstances, dramatically reversible. Thatmeans that it is susceptable to treatment if we can "put out the fire."

In addition to being potentially reversible, it is a chronic progressive disease.(58)(21) Success in treatment, therefore depends on the promptness and vigor with which it is instituted.

RESULTS FROM HORMONAL THERAPY

ACTH and Cortisone are the first natural agents by means of which it has been possible to demonstrate the potential reversibility of rheumatoid arthritis.(53)

Cortisone was first used on a 29 year old married woman who had severe rheumatoid arthritis for four and a half years. 100 mgs were given intra-gluteally on September 21, 1948. Daily doses of 100 mgs resulted in marked lessening of her symptoms. Eight days after the initial 100 mg dose, the dosage was reduced to 50 mg daily doses for four days, then 25 mgs for ten days. However, this latter dose was inadequate and the symptoms increased.(23)

Slocumb and his associates of Mayo Foundation reported on the treatment with ACTH of twenty-three

patients with severe, or moderately severe rheumatoid arthritis.[53] The anti-rheumatic effect was dramatic in thirteen, less dramatic in nine, and moderately in one. When either drug was discontinued, a relapse occurred, sometimes promptly, sometimes slowly. Eight patients maintained 60% to 90% of the improvement for seven to fourteen months, five patients maintained about 50% of the improvement. The other ten patients maintained little or none of the improvement.[53]

Hench, Kendall, and Slocumb report the results of administering 100 mg doses of ACTH for twelve days to two female patients with severe rheumatoid arthritis.[23] Marked clinical improvement essentially similar to that resulting from the use of Cortisone, occurred promptly. Within a few days, there was striking reduction of stiffness and pain on motion and articular tenderness. Sedimentation rates decreased even more promptly and steadily than when Cortisone was employed.

Ragan and his associates report on eight patients with rheumatoid arthritis who had been treated with ACTH.[47] All received the hormone intramuscularly in divided doses every six hours. In most of the patients the average daily dose was 40 mg. There was prompt remission of symptoms. After cessation of therapy, relapses occurred in seven of the eight patients.

Markson reports on treating two cases with ACTH (38) at the Wesley Memorial Hospital in Chicago, Illinois. The first case was a 55-year old white male who complained of swelling and tenderness in his left knee. He had fleeting acute attacks of redness, swelling, and severe pain in the 2nd phalangeal joint of the fingers, in the writs, and in the elbows, and at times in the shoulders. The fingers showed fusiform swelling of an old rheumatoid arthritis. Xray showed demineralization of bones in the right ankle joint. The bones had a "ground-glass" appearance.

On May 21, 1948, all medicine was discontinued except codiene. He was given 25 mg ACTH every 6 hours for a total of 100 mg in 24 hours. He continued this dose until June 5 when it was changed to 50 mg daily in three 8 hour intervals.

On June 30, the dose was changed to 15 mg at 12 hour intervals, for a total dose of 30 mg. daily. This dose was maintained until October 15. There occurred an almost complete remission of symptoms. Patient was able to walk up and down stairs. His posture was erect and he didn't have to use any support. No nervous reactions or untoward symptoms have been observed.

The second case treated with ACTH was another white male about 60 years old whose xrays showed a far advanced rheumatoid arthritis of the hands, elbows and shoulders.

The cervical vertebrae showed marginal lipping, and the left hip showed minimal hypertrophic arthritis. The knees showed decided narrowing of joint spaces with extensive osteoporosis.

On June 20th, he was given 20 mg. ACTH every 6 hours, for a total dose of 80 mg. in 24 hours, and was continued until July 2, 1949 when the dose was changed to 20 mg. every 8 hours for 24 hour period. On Junly 26, the dose was changed to 45 mg. daily with 3 doses of 15 mg. each at 8 hour intervals. The patient had been maintained until October on two 20 mg. doses at 12 hour intervals. The patient was able to return to his work on a full time schedule after his discharge from the hospital. No untoward symptoms were noticed.

In both of the cases, the return to approximation of their original status was noted when the medicine was discontinued three days.

The effect of ACTH and Cortisone is best seen in patients with active inflammation in the joint. (48) Benefit is often apparent within the first twenty-four or forty-eight hours after treatment is begun. There is first a sense of "well-being" and often a sense of euphoria. The patient obtains marked improvement in his ability to use the joints without any convincing objective change in the joints. This suggests that there must be

a much greater element of muscular stiffness in the incapacitation produced by active rheumatoid arthritis than had previously been appreciated.

During the next few days, the patient usually finds objective improvement in the joints with relief of pain at rest, disappearance of tenderness over the joints, and of pain on motion. The joint effusions are generally decreased. Biopsies of affected joints (37)(29) before and during hormone treatment show a marked decrease in the inflammatory process and in the form of granulation tissue, but not a complete reversion to normal tissue structure. Freund (14) reported a striking reduction in the number of inflammatory cells in the joint fluid and a suggestive improvement in the quality of mucin. Bauer and his associates found that the number of leukocytes and the viscosity of the synovial fluid reach normal levels during treatment, altho in one case, histopathological examination of synovial tissue after three months of ACTH therapy was still consistent with the diagnosis of moderately active rheumatoid arthritis altho some improvement was shown.

Favorable results were reported in Denmark by Brochner-Mortensen and colleagues who tried ACTH and Cortisone on chronic rheumatoid patients. (5) The clinical effects closely resembled those reported in other countries: the articular swelling, pain and tenderness on motion,

rapidly diminished. The articular and muscle functions improved, the appetite improved, and the patient felt a real sense of well-being:

Not all results reported were as favorable as those just mentioned. Margolis and Caplan observed that in thirty-one out of fifty-six patients under continued administration of ACTH, either alone or with chrysotherapy, deteriation of improvement occurred.(39) Similarly, Elkinton, Hunt, and other workers reported recurrence of signs and symptoms of the disease despite increased dosage of ACTH.(12)

In contrast to the discouraging aspect of retrogression under long continued therapy in some patients, there were seven patients reported by Margolis and Caplan who had been under treatment for forty-seven to two-hundred and twenty-four days with varying doses of ACTH and chrysotherapy who have been able to discontinue use of the hormone and maintain the complete remission they had obtained during treatment.(12)

LABORATORY FINDINGS FOLLOWING THERAPY WITH ACTH AND CORTISONE

Laboratory findings in the blood of patients treated with either of the hormones were quite consistent in all of the reports reviewed. Sedimentation rate was reduced, usually becoming normal within 10-35 days.(2)(12)(39)(17) Hemoglobin tended to increase, occasionally as much as two

grams within a few weeks.[20] Red blood cells in patients who had become anemic, increased as much as one million red cells per cm. of blood in therapy of two weeks or longer.[20] Eosinophils in most instances showed a marked drop.[49][40][39][5][51][12] The decrease in lymphocytes was only about half as great as the decrease in eosinophils.[51] Serum proteins became elevated and reversed A/G ratios returned quite promptly to normal.[2]

METABOLIC FINDINGS FOLLOWING THERAPY WITH ACTH AND CORTISONE

Margolis and Caplan found that there was no consistent increase in urate and creatinine excretion, even when large doses of the hormone were administered.[39] Carlisle,[8] Brochner-Mortensen,[5] and Mach[37] found that there was increased urinary excretion of urates and creatinine.

Sodium excretion was low in all cases reported, in the initial period of administration of ACTH as observed by Forsham,[13] Thorn,[53] and others.[52] However, Carlisle found that retention of sodium and water, which occurred early in the treatment, was followed by a spontaneous diuresis which occasionally was so great as to cause the development of congestive heart failure with ascites, and pulmonary or peripheral edema.[6]

Potassium excretion was generally increased.[6] Mc Alphine, Venning, and others reported potassium retention in some patients and increased potassium excretion in other patients.[40] In cases of severe potassium excretion,

weakness, hypotension, alkalosis, and electro-cardiograph were noted.[6] The E.K.G. changes consisted of lowering of the T waves, depression of the S-T segments and S-T junction.

Hyperglycemia and glycosuria occured in many of the patients who received large doses, or smaller doses over a long period of time. Browne found that hyperglycemia and glycosuria could be produced in a normal man with no rheumatic disease with a single large dose of ACTH.[31] Likewise, Conn, Lewis, and Wheeler reported producing hyperglycemia and glycosuria in normal individuals with intensive doses of ACTH over a period of days.[9] Altho this "diabetis" is generally observed to be temporary, returning to normal upon cessation of administration of ACTH or Cortisone, they indicate that there is some evidence that continued administration of ACTH might result in irreversible diabetis mellitus of a high insulin-resistant type.[9] Thorn, Boland, and Headley observed that patients taking ACTH or Cortisone need greater dosage of insulin if they are diabetic.[23]

17-ketosteroids and corticoid excretions in the urine are reported to be increased following ACTH or Cortisone therapy.[37][6][5][40] The significance of this increase has not been entirely understood. Thorn, Forsham, and other workers made a careful quantitative determination of the urinary excretion of 17-ketosteroids and 11-oxysteroids

in a normal patient who had been given large doses of ACTH and Cortisone.[57] They found that there was greater excretion of the steroids after the administration of ACTH than after Cortisone had been given. The excretion of the steroids shortly after the hormones had been administered, decreased to a level below the normal level that existed before the hormones had been administered. The results were interpreted as showing that both drugs cause depression of the pituitary, due perhaps to the increased endogenous production of adrenal steroids after ACTH administration, and to the steroid itself after the cortisone had been administered. Following the cessation of the hormone administration, the delayed return of the hypoactive pituitary function to normal, temporarily deprived the hypertrophied adrenal hypofunction as measured by the decrease in steroid excretion.

Freund and his associates failed to observe any detectable rise in ketosteroid excretion in human beings following the administration of large amounts of cortisone.[15]

DOSAGE

The therapeutic effective dose of ACTH and Cortisone in rheumatoid arthritis varies widely. When using ACTH, Robinson advises as a general principle, to start the patient on 10-12 mg every 6 hours so that a total of 40-50 mg. per day is given.[48] The patient is

kept on this dose for several days to ascertain if the therapeutic effect is being obtained. If no effect after several days is obtained, increase the dose to 15 mg. every 6 hours, and if after a few days no response is obtained, then increase the dose to 20 mg. every 6 hours for a total of 80 mg. a day.

If the maximal clinical effect from the smallest daily dose is required, the daily dose should be divided into four injections six hours apart. The possibility of prolonging the action of ACTH is being investigated and it seems likely that preparations having effectiveness for 24 hours will be available in the future. At present, the clinical and physiological effects of a given dose of ACTH are likely to be worn off in about 6 hours.

If a full clinical laboratory remission is obtained, the dose of ACTH should be decreased to find the minimal dose which is effective in maintaining the remission. In general, the 6 hour dosage schedule should be maintained until each individual injection is of the order of 5-10 mg. per injection. The next daily dosage decrease may be accomplished by giving at 8 hour intervals the same individual dose that was used in the 6 hour schedule. If this is successful, the injection may be spaced at 12 hour intervals. In some patients, remission can be maintained on a single injection every 24 hours.

The dosage of ACTH and Cortisone in children does

not appear to be proportional to body size, age, or surface area. The required dose to produce a remission is about the same as is needed in adults and appears to vary with the severity of the disease process rather than any other single factor.

Carlisle agrees that altho the dosage for children has not been established, it seems to be more nearly proportional to the severity of the disease than to body size.(6) It is his opinion that frquently an adult dose is needed and is often well tolerated.

All that has been said as to the beneficial effects of ACTH applies to Cortisone given in doses of 25-50 mg. every 6 hours. According to Robinson, 1 mg of ACTH releases the biological equivalent of 2-3 mg. of Cortisone.(48) 100 mg. "E" acetate is the chemical equivalent of 89 mg. Cortisone (compound E).(23)

A rest period of not less than three or four weeks sould be allowed between courses of treatment with cortisone to allow recovery of adrenal activity.(6) A "course" at full therapeutic dosage is generally considered to extend over a period of two to six weeks and the total dosage per course should not be over three or four grams.

UNFAVORABLE REACTIONS

In contrast to the many favorable responses to ACTH and Cortisone, there are several unfavorable "side-effects" which occur mainly when large doses of 200 mg. or more

are administered, or when doses of 100 mg. are prolonged over a period of several months. Menopausal women and teen-aged children are the most susceptable, and men are the least susceptable.(53)

The Mayo Foundation workers offer the suggestion that these several undesirable effects ought not to be regarded as "side-effects" or toxic reactions, but preferably should be regarded as "physiologic reactions." In other words, they represent the effects of the biological activities involved.

Nearly all of the unfavorable effects resemble Cushing's Syndrome and hyper-adrenalism. Many patients experienced a fluctuation in weight and diuresis, and a few had edema. The edema occurred with or without the use of a low salt diet or diuretics.(53) In most cases the face became fuller,(6) but a real "moonface" as occurs in Cushing's Syndrome has not been observed.(19)

In many cases there was pigmentation of the skin, either diffuse or well localized in freckles in the folds of the skin.(19)(24)

Mild hirsuitism with increase of hair on the cheeks, upper lip, and on the extremeties was occasionally seen in the female patients.(19)(24)(56)

Delayed wound healing was a point of controversy. Carlisle reported that studies showed that wound-healing was retarded because of inhibition to granulation tissue and fibrous formation.(6) This was also reported by Ragan,

House, Clotz.[46] Plotz, however, was unable to duplicate the delayed effects of wound healing as observed by Ragan and associates.[44]

Hypertension as the result of hyper-cortical adrenalism has been mentioned by some writers.[24][6][53] However, Elkinton, Hunt, Godfrey, McCrory, Rogerson, and Stokes[12] report that no significant hypertension has been observed as occuring with the hyper-adrenal syndrome produced by ACTH. Carlisle[6] offers the suggestion that it is probably the retention of sodium and water that is responsible for a slight elevation of blood pressure. Kersley[34] suggests that the slight elevation if present, may be due to contamination of the ACTH with pitressin.

A variety of mental states have been observed with prolonged treatment.[1] Mental states varying from a general feeling of "well-being" to an exaggerated response of euphoria have been recorded. Occasionally in a few cases, there was a mild depression or a manic state; and in a few rare instances, a pre-existent or latent mental derangement such as schizophrenia seemed to be intensified or precipitated.

PRECAUTIONS AND GENERAL CONSIDERATIONS

Since unfavorable reactions do occasionally take place when ACTH and Cortisone therapy is used, special precautions and considerations should be taken to prevent the unpleasant reactions.[6] Carlisle has listed some of the precautions and considerations to be taken:

1. The relative contra-indications should be evaluated

before ACTH or Cortisone is used. Some of the contra-indications that he lists are as follows:

a. diminished cardiac reserve.

b. latent or over psychotic tendencies.

c. diabetis mellitus.

d. uremia.

e. senescence.

f. debility accompanying advanced cachetic states.

2. The dietary NaCl intake should be restricted. Fluid output and intake should be measured, and the patient should be weighed daily.

3. Hypopotassemia should be corrected by giving supplementary KCl.

4. Hyperglycemia in diabetics should be controlled by increasing the amount of insulin.

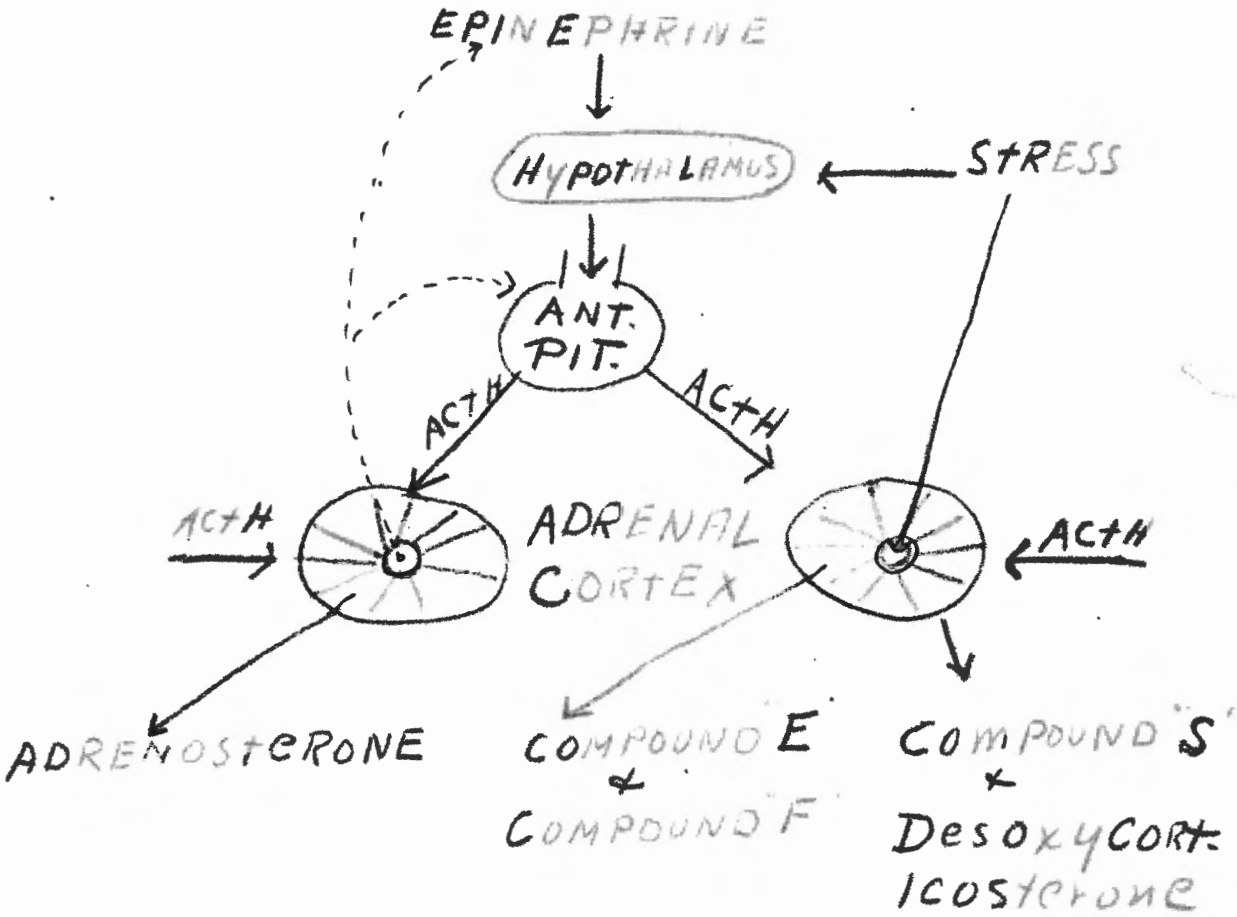
5. Early psychotic tendencies can often be detected. The premonitory symptoms are marked swings of mood, severe insomnia, bad dreams, and increased psychomotor activity.

6. It is essential that supervision of the patient follows the discontinuation of ACTH or Cortisone because these hormones may continue to act for some time after the last injection; or there may be reappearance of severe manifestations of the disease. In occasional cases there may be a temporary hypoadrenal state if treatment is withdrawn too rapidly. (48)(53) Therefore, the withdrawal should be preceded by a tapering off, especially if large doses of ACTH

have been given.

MECHANISM OF THERAPEUTIC EFFECT

It seems probable but is not definitely established, that the favorable response of rheumatoid arthritic patients to ACTH is due to the production of hyperadrenalism and a subsequent suppression of the mesenchymal tissue.(47) The known mechanism of adrenal-cortical stimulation as presented in the New England Journal of Medicine by Thorn and his associates is diagramed below.(56) In addition, some suggestions were included from a diagram by Carlisle in the British Medical Journal.(6)



The mechanisms presented in the diagram explain the "alarm reaction" and "adaptation syndrome" proposed by Selye. This is in harmony with what Long (58) emphasizes as the common denominator in the various stress situations, namely, the stimulation of the autonomic nervous system with subsequent release of epinephrine. Sayers and Sayers (50) agree with this emphasis. Injections of epinephrine, or stimuli which cause secretion of epinephrine, lead to the output of ACTH and thus to increased output of adrenal-cortical hormones. (36)(52)(49)(56)

The fact that ACTH produces a rapid clinical improvement and a decrease in eosinophiles indicates that in Rheumatoid Arthritis, the endocrine deficiency, if it exists, is not situated in the adrenal cortex but at the level of the hypophysis or diencephelon. (37) Hume has shown that an intact hypothalamus is necessary for normal release of ACTH. (36)

Li has worked on the ACTH molecule in an endeavor to find out what part of it possess the physiological activity. (54) He reported that after partial hydrolysis of pituitary ACTH to the peptide stage, fragments were obtained which retained their biological activity. These fragments had an average chain length of eight amino-acids.

Recently Brink, Meisenger, and Folkers reported that ACTH derived from pig pituitaries was subject to peptic

digestion. The digestion products of molecular weight small enough to be dialyzable, kept rheumatoid arthritis in remission in two patients who had previously been treated with ACTH. In addition, this dialysis product was clinically active in a third patient. The effect of these degradation products was equivalent to the intact ACTH. On further hydrolysis, these active fragments were found by paper-strip chromatography to contain at least seven or eight of the common amino acids.(54)

Treatment with ACTH, in contrast to Cortisone, presupposes the capacity of the patient's own adrenal glands to produce large quantities of hormone for prolonged periods of time.(56) It is to be anticipated that under certain circumstances adrenocortical reserve might be low and ACTH therapy hence would be relatively innefective.(56)

A given quantity of ACTH may elicit a variable increase in adrenal steroid output, depending on the status of the adrenal cortex at the time that therapy is instituted. Thus a quiescent gland may respond minimally to a standard dose of ACTH where a very active gland may show a tremendous absolute increase in hormone output.(57)

Several tests are recorded as having special value in determining the reserve status of the adrenal cortex.

Thorn's test makes use of the fact that the levels of circulating eosinophils are intimately related to the activity of the adrenal cortex.(49) The measurement of the fall of circulating eosinophiles four hours after the

injection of ACTH or epinephrine subcutaneously, forms the basis of the test for adreno-cortical and pituitary adreno-cortical reserves respectively.

The inability of ACTH to produce lymphocytopenia if there is poor cortical reserve may be taken as a test since it has been reported that ACTH will not produce a lymphocytopenia in adrenalectomized animals or in patients with Addison's disease.(51) Futher additional proof should be submitted before it is used as a confirmatory test.

Steroid excretion in the urine has been proposed as a test for adrenal cortical reserve. However, since some reports indicate increases, and others indicate decreases in the excretion following ACTH therapy, this would prove to be a very unreliable test.

Also, in evaluating the effects to be expected from ACTH or Cortisone therapy, one must bear in mind that whereas Cortisone administration adds directly to the level of adrenal steroids in the body fluids, it suppresses the endogenous steroids by prohibiting ACTH production. For this reason the more active the adrenal gland, the less effective will be a given quantity of cortisone. Thus a 50-100 mg dose of cortisone administered to a patient with very active adrenal cortex would actually result in overall decrease in the circulating adrenal hormone.(57)

SUMMARY

The trend of events which led to the use of ACTH and Cortisone in treating rheumatoid arthritis began when Thomas Addison made his suggestion that the adrenal cortex was essential to life. Since then, investigators have been busy on the problem of isolating the extracts of the pituitary and adrenal cortex and noting their physiological function. The observation that pregnancy, jaundice, anesthesia, surgery, and other types of stress all produced hypertrophy of the adrenal cortex and gave some relief in many cases of rheumatoid arthritis, led men like Hench and his associates to use the hormones on rheumatoid arthritic patients.

The etiology of the disease, altho not finally determined, is very possibly due to streptococci infection, altho studies show that streptococci infection of the upper respiratory tract occur only slightly more frequent in patients with rheumatoid arthritis than in normal persons. It is believed there is some evidence to show that the streptococci exert an enzymatic action against the hyaluronic acid component of connective tissue, or that they initiate a sort of an allergic response to "sensitized persons." Another factor that might be an etiological agent is over-activity of the thymus.

The basic lesions produced in the disease are in the "ground-substance" of the mesenchyme, or in the cellular

elements, or are a combination of these. They are similar to lesions found in other connective-tissue diseases. Few, if any, changes occur in the blood except anemia, leukocytosis, and increased sedimentation rate, and reversed albumin-globulin ratio.

Rheumatoid arthritis is susceptable to therapy, especially if treated early while in the inflammatory stage. The greatest degree of improvement is obtained in patients with early, mild or moderately severe arthritis , without serious capsular contractures or deformities, who require relatively small doses of the hormone and for whom the dose can eventually be reduced to practically minute amounts and for some entirely discontinued. Optimum results were observed when administration occurred at six hour intervals.

Unfavorable "side effects" appeared to be few. The most significant side reactions were edema, a tendency toward development of a diabetogenic state, hirsuitism, and weakness and fatigue due to potassium loss. The development of hypertension was controversial. Relatively infrequent psychic abnormalities apparently represented an accentuation of the patient's basic personality difficulty.

ACTH and Cortisone was very effective when given alone, but the relief from symptoms usually lasted only

as long as the hormone was administered, relapses developing either immediately or shortly after cessation of treatment. Only in a few cases was there continued remission of symptoms.

There appeared to be a tendency toward deterioration in the degree of improvement with long-continued administration. The fact of long continued usage of the drug, and the increased tendency of side effects with long usage creates a serious problem. The possibility of using some other form of therapy such as chrysotherapy after regression of symptoms has begun with ACTH or Cortisone might be a solution to the problem. Also the production of smaller molecular products which are able to retain their action for longer than six hours duration may help to solve the problem. The mechanism of these drugs is to stimulate the production of cortical steroids, or to supply them if the adrenal cortex is unable to synthesize them.

Treatment with ACTH in contrast to Cortisone, requires that functional adrenal cortical tissue be present in the patient. Also in evaluating the effects to be expected from ACTH or Cortisone therapy, the state of activity of the adrenal gland must be borne in mind. Several tests are recorded in the literature as having value in determining the potential activity or reserve of the adrenal cortex.

From the cases reviewed in the literature, it seems quite evident that ACTH and Cortisone give equally good results in the regression of symptoms in rheumatoid arthritis.

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