ADRENOCORTICOTROPIC HORMONE (ACTH)
Its Effect in Bronchial Asthma and Ragweed Hay Fever

By
THERON G. RANDOLPH, M.D., F.A.C.A.
and
JOHN P. ROLLINS, M.D.
Chicago, Illinois

RELIEF of chronic bronchial asthma following the administration of adrenocorticotropic hormone (ACTH) was first observed by us in June, 1949; this occurred in a case of advanced rheumatoid arthritis complicated by bronchial asthma. The ability of ACTH to bring about improvement in chronic allergic symptoms was not surprising in view of its specific action in rheumatoid arthritis. Zeller recently reported clear-cut evidence that rheumatoid arthritis responds favorably to the elimination of specific food allergens and reviewed earlier contributions in respect to the allergic concept of this disease. Our clinical experience not only confirms the specific etiology of food allergens in arthritis, but we have also observed improvement in such cases following the specific diagnosis and treatment of inhalant allergy.

These preliminary observations led us to study the effects of ACTH in bronchial asthma and other allergic syndromes. Pilot observations were made on three patients with chronic asthma, preliminary observations of which have previously been reported. The clinical response of these three patients, whose histories are herewith reported in detail, prompted an evaluation of ACTH in the treatment of other allergic syndromes.

Patients with severe perennial bronchial asthma, refractory to conventional allergic management including prolonged periods of hospitalization, were selected for this study. They were hospitalized and the following determinations were made during a period of forty-eight hours prior to

Dr. Randolph is an instructor in internal medicine and Dr. Rollins is a research fellow in internal medicine, Northwestern University Medical School. The ACTH for this study was kindly furnished by Dr. John R. Mote, Armour Laboratories, Chicago. Presented at the Sixth Annual Meeting of the American College of Allergists, January 15-18, 1950, St. Louis, Missouri.
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during the interval of administration of ACTH, and for several days thereafter: (1) The average of three maximum expirations was taken as the vital capacity, charted in the forthcoming figures by the upper solid line. (2) The time required to exhale an arbitrarily selected volume of air, the amount being chosen in relation to the patient's vital capacity and measured in terms of the cubic centimeters of air expired per second, was designated the expiratory rate. This technique, modified after that originally described by Hamburger,3 will be described in detail elsewhere. The expiratory rate is plotted in the figures as the second (broken) line. (3) The absolute number of circulating eosinophils per cu. mm. of blood was determined by employing the direct counting chamber glycol stain technique previously described1; it is shown graphically by the lower solid line. (4) Individual food tests8,14 with known food allergens were performed within a three week period prior to hospitalization and repeated either during the course of or immediately following the administration of ACTH. (5) All epinephrine was discontinued for twenty-four hours immediately prior to the administration of ACTH, and aminophylline was administered as necessary for the relief of severe asthma.

Inspiratory and expiratory chest x-ray films were made prior and after the full therapeutic effect of ACTH had been obtained.

Case 1—C. P., unemployed male, aged forty-three, developed acute sinusitis in December, 1942, which continued throughout the winter. In March, 1943, he developed his initial attack of bronchial asthma which continued for a month until the onset of lobular pneumonia. During the period of and for a month following his pneumonic infection he remained free of asthmatic symptoms. Severe bronchial asthma recurred and has been present perennially to an incapacitating degree since the time except for temporary relief obtained during prolonged fasting. In 1945 all food was avoided for a twenty-one day period; after the eleventh day he remained completely free of asthma and rhinitis, was able to walk between two and five miles daily and lost a total of 21 pounds in weight. Three days after returning foods to his diet he had recurrence of his formerly severe rhinitis and asthma.

He has received many types of treatment, including repeated polyether chemotherapeutic and bilateral Caldwell-Luc operation, radium therapy of the sinuses, x-radiation of lungs, and repeated attempts to diagnose and treat inhalant and food allergy.

Although we have been able to show by experimental individual food tests9,14 the ingestion of each of several major allergenic foods would cause a sharp exacerbation in his asthma and their complete avoidance would bring about some improvement, he has never obtained sufficient relief of asthma to be able to earn a livelihood. Although known to be dust sensitive clinically, each attempt to diagnose or treat his house dust allergy has resulted in an accentuation of symptoms, regardless of the exceedingly low levels at which therapy was instituted.

One week prior to hospitalization in August, 1949, an individual food test with orange was followed by a marked accentuation of his chronic asthma.

Figure 1 shows the serial observations of his ventilatory capacity and eosinophil levels prior to, during and following the administration of 225.0 mg. ACTH, given in 25.0 mg. doses every six hours. One should note the initial increase in eosinophils prior to starting treatment which occurred with the cessation of epinephrine administration. In order to keep these initial observations constant, he was maintained on his formerly restricted diet prior to and following therapy with ACTH. His smell of orange recurred, his nose became patent and he had complete relief of his rhinitis and asthma within twenty-four hours after starting therapy with this hormone. Although relative anosmia recurred after four days, he remained without troublesome allergic symptoms and required no symptomatic measures for their relief during a total period of three weeks. At the beginning of the fourth week from the time of starting therapy his asthma recurred, and in spite of the use of symptomatic measures it reached its former degree of severity within a week.

The experimental ingestion of orange failed to produce allergic symptoms when fed during the course of therapy and again when fed four days after the cessation of ACTH. There was no change in his skin test response to house dust as measured by serial dilution testing9,15 after ACTH therapy as compared with identical tests before treatment. Whereas intradermal skin testing with house dust extract (Endo) prior to the administration of ACTH had been followed by a constitutional reaction on each of three different occasions, repetition of the procedure failed to produce symptoms immediately after treatment with ACTH.

A month after the first course of ACTH he was again hospitalized at which time he was having asthma of the former degree of severity. He was given an identical course of ACTH and responded in a similar manner even though returned to a general, unrestricted diet immediately after the cessation of therapy. He remained

Fig. 1. Variations in the vital capacity, expiratory rate and peripheral blood eosinophils in C.P., a patient with bronchial asthma, following ACTH therapy.
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seated allergic rhinitis for the following three weeks, during which time aminophylline was not necessary and she was able to reduce materially the use of epinephrine.

Six additional patients with severe bronchial asthma but without pulmonary complications were also treated with Adrenocorticotropic hormone.

Two patients with seasonal ragweed asthma were relieved of all allergic symptoms for the remainder of the 1949 ragweed pollinating season; their cases will be summarized subsequently.

Case 7.—One male child, R. K., aged ten years, with a history of perennial bronchial asthma of four years' duration and known to be clinically sensitive to house dust, ragweed pollen, fungi and several major foods, received a total dose of 1400 mg. ACTH over a period of three days. This patient had immediate relief of asthma but had a moderate recurrence of wheezing for two days after returning to his home. He then remained entirely free of asthma for the following month, although in previous years this particular season had been his most troublesome period.

Case 8.—W. E., a man, aged sixty years, subject to perennial allergic rhinitis for ten years and bronchial asthma for one year, had complete relief of allergic symptoms for three weeks after receiving 300 mg. ACTH over a period of three days.

Case 9.—E. U., a man, aged fifty-two, developed perennial nasal allergy at the age of forty-seven which was subsequently complicated by nasal polypa. Within a few hours after his initial polypectomy at the age of forty-eight, he developed severe bronchial asthma which has been present constantly since except for a period of two and one-half months immediately following insulin shock therapy received as treatment for an acute toxic psychosis. An initial course of only 125 mg. ACTH was given because of progressive edema and gain in weight beginning after the fourth dose of 25.0 mg. Although he developed the expected degree of cosinopenia, there was no significant change in the severity of his asthma except for transient improvement during ACTH administration.

A second course of the same amount given three weeks later was followed by moderate improvement during the period of administration which persisted only for a four-day period. A comparable gain in weight and clinical edema again developed which prompted us to discontinue therapy.

A third course two weeks later, consisting of 50 mg. daily in divided doses for three days, failed to produce edema or to cause any improvement in his asthma. Subsequently, this patient was diagnosed specifically and found sensitive to milk. The removal of milk and wheat from his diet has been more effective in controlling his asthma than ACTH administration in the dosage schedules employed. Although the cumulative addition of wheat was tolerated, each attempt to reintroduce milk has resulted in acute abdominal cramps and diarrhea.

Case 10.—J. S., aged fifty-eight, and previously reported by Markson, had been subject to rheumatoid arthritis for twelve years and mild perennial bronchial asthma for one year prior to starting ACTH therapy June 20, 1949. He has received a daily dosage of ACTH sufficient to control his rheumatoid arthritis since. While he was treated for his arthritis, we noted a gradual improvement in his asthma during the first twelve days of therapy; this was based on clinical evidence as well as a change in his expiratory rate from 800 to 1,700 c.c. per second.

Although undiagnosed and untreated from the allergic standpoint, he continued without troublesome asthma since this time, except for periods beginning four months.
after the institution of therapy when attempts were made to reduce the amount of ACTH to a minimum dose capable of relieving his arthritic pain. During the periods when receiving 125 mg. ACTH daily, his asthma recurred in its former severity.

Three patients with acute ragweed hay fever were hospitalized between the dates of August 30 and September 5, 1949; they were placed in one room with open windows. The ragweed pollen count remained over 30 per day throughout the period during which the following observations were made.

The number of times per twenty-four hours that each patient sneezed, sniffled, coughed or blew her nose was recorded for forty-eight hours prior to, during the course of, and for four days following the completion of ACTH therapy. Eosinophils, total leukocyte, myeloid and mononuclear cells were determined by the method previously described. Pre- and post-treatment skin tests, skin biopsies and passive transfer studies were made; these will be reported in a subsequent article.

Case II.—H. D., a woman, aged fifty, had been subject to yearly hay fever from mid-August to the second week of October since 1944. She had received pre-seasonal specific therapy since the onset of her ragweed symptoms. She also had been subject to typical rheumatoid arthritis of twelve years' duration.

She received 225 mg. ACTH in divided doses over a period of forty-eight hours. Evidence of improvement in her nasal symptoms, first noticed thirty minutes following the initial injection of 25.0 mg., progressed to complete relief of hay fever at the end of six hours. Aside from mild sneezing in the afternoon of the third day, she had no further hay fever throughout the remainder of the ragweed hay fever season. Her arthritic symptoms also improved but recurred ten days after the cessation of ACTH therapy. Variations of the blood elements and a summary of the clinical data are shown in Figure 4.

Case II.—B. H., a woman, aged thirty-eight, had been subject to perennial nasal allergy with superimposed severe ragweed hay fever for the past sixteen years, complicated by seasonal bronchial asthma for the past twelve years. As may be noted in Figure 5, she developed leukocytosis and eosinopenia immediately after
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Fig. 6. Variations in the cellular elements of the peripheral blood as determined by hemocytometer counting chamber differential technique and the symptom response in M.A., a patient with allergic rhinitis, ragweed hay fever and bronchial asthma, following ACTH therapy.

Table 1

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<td>500 mg</td>
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injection of 0.5 c.c. epinephrine which had been given in order to control some asthma developing immediately following skin testing with ragweed extract.

She received 25 mg of ACTH during a period of forty-eight hours. Her respiratory symptoms began to improve thirty minutes after the first dose of 25 mg and were completely relieved at the end of forty-eight hours. Repeated tests at this time failed to produce any symptoms. She had no further hay fever or asthma for the remainder of the pollen season, and her perennial rhinitis remained 50 per cent improved for the following four months compared with the severity of her symptoms during a comparable period in previous years.

Case 13—M. A., physician's wife, aged thirty-seven, had been subject to perennial asthma and severe incapacitating headaches since childhood. These symptoms had been relieved for a period of two years as a result of dust therapy and the avoidance of several major allergenic foods. An intractable cough which began in April 1949, was controlled by the avoidance of beet and cane sugar. In each instance, individual food tests with cane sugar and with beet sugar were followed by a ten minutes by the onset of violent coughing. Similarly, the accidental or inadvertent ingestion of one of these sugars had been followed by the precipitation of coughing.

Her initial hay fever and bronchial asthma developed while on a visit to the high school season, necessitating her return to the hospital September 5, 1949. During the twenty-four-hour period prior to ACTH therapy she sneezed, sniffled, coughed or blew her nose 640 times. She was maintained on a formerly restricted diet during the course of administration of 125 mg ACTH. A decrease in the incidence and severity of sneezing occurred forty minutes after the initial intramuscular injection of 25.0 mg.

Fifteen minutes after each injection of 25.0 mg ACTH this patient experienced a transient vasoconstriction with pallor and coldness of her extremities but with no significant change in her blood pressure. These manifestations were attributed to the small quantity of posterior pituitary fraction present in this material. Two hours after the initial injection she complained of bilateral deep pelvic pain which radiated caudally and anteriorly into the groin. She remarked that this pain was identical in character to premenstrual pain present prior to surgical removal of the left ovary and x-ray castration of the right ovary four and three years previously.

Discussion

With the exception of the two cases of seasonal ragweed asthma, the other asthmatics selected for this study of the effectiveness of adrenocorticotropic hormone in bronchial asthma were perennial advanced cases of this disease. As judged from the age of the onset of asthma, the majority of these patients would qualify for the designation of “intrinsic asthma” as described by Rackemann. Furthermore, several of the cases were complicated by nasal polypi and aspirin sensitivity, a combination which has been striking in respect to the difficulty in the management of bronchial asthma from the standpoint of specific allergic diagnosis and therapy. It should be re-emphasized that the patients chosen for the administration of ACTH were not a random sample of bronchial asthma but represented the most difficult diagnostic and therapeutic problems gleaned from a private practice of allergy.

Ten of the eleven asthmatics to whom a short course of ACTH had been administered obtained a marked degree of relief of their chronic symptoms. The duration of relief varied from a week to as long as five months following a single course of therapy, ranging in total dosage of ACTH from 125.0 to 325.0 mg. One case, E. U., developed evidence of fluid retention early in the course of each of two attempts to treat him with ACTH in a manner found effective in the other asthmatics. Although he failed to develop edema in the third course of ACTH at a lower dosage level, he also failed to show a significant degree of improvement in his allergic symptoms when treated for a period of time found to be effective in other cases.

We have had the opportunity of observing only one patient, J. S., treated with continuous ACTH therapy. This arthritic patient with mild...
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complicating bronchial asthma has received a dosage varying from 12.0 to 75.0 mg. daily for the past eight months. As previously stated, his asthma recurred when treated for several days at the lower level of dosage although he remained free of arthritic pain. With a further reduction in dosage his arthritic pain also recurred.

In general, prolonged continuous therapy for the treatment of bronchial asthma does not seem to be indicated in view of the response obtained from short intermittent courses of therapy.

The degree of relief of asthma in the ten cases showing a favorable response varied from complete to approximately 50 per cent. By complete relief is meant an absence of rhinorrhea as detected on repeated chest examinations, the maintenance of normal vital capacities in respect to the individual's surface area and the ability to lead normal lives without obvious wheezing in the absence of taking medications for the relief of asthmatic symptoms. In general, the most striking results were obtained in those cases uncomplicated by other pulmonary pathology. ACTH was least effective in the asthmatics shown by x-ray and clinical evidence to have pulmonary emphysema, extensive scarring resulting from pleurisy and empyema. Our experience has shown that in most instances the greater the degree of pulmonary emphysema the less satisfactory was the clinical response to ACTH administration. The outstanding exception to this statement is the case of E. O.

Not only is adrenocorticotropic hormone effective in relieving temporarily the symptoms of severe, long sustained bronchial asthma, but it also changes the reactivity of allergic individuals known to be specifically sensitized to food and inhalant allergens. In several instances foods known to produce acute accentuations in bronchial asthma prior to the administration of ACTH were tolerated without evidence of symptoms during the course of and for a period of time following ACTH therapy. Similarly, test procedures with house dust and ragweed pollen which produced constitutional reactions prior to therapy failed to do so during or immediately following treatment with adrenocorticotropic hormone. It should be emphasized, however, that ACTH seems capable of producing only a transient refractoriness to known allergenic offenders.

With the recurrence of bronchial asthma following a course of ACTH therapy, symptoms are readily relieved following the inhalation of a small amount of epinephrine spray. This is in decided contrast to the ability of epinephrine to relieve symptoms of similar severity prior to the administration of ACTH. Whereas an individual might have found it necessary to inhale 1:100 epinephrine eight to ten times prior to hormone therapy to obtain relief from an attack of asthma, literally a "whiff" of the 1:100 concentration effects prompt relief of asthma of comparable severity after ACTH therapy. This change in the effectiveness of epinephrine is only temporary.

ACTH appears to be a remarkably effective agent in bringing about complete relief of ragweed hay fever as evidenced by the striking results in three patients treated during the height of the 1949 ragweed hay fever season. Not only did this therapy eradicate all evidences of clinical hay fever but protected the three individuals so treated for the remainder of the current ragweed pollinating season. The effect on the skin tests and passive transfers of these patients to ragweed pollen extracts will be presented in another publication.19

In addition to the relief of asthma and rhinitis as a result of ACTH treatment, these patients usually experienced marked general improvement, in that they noted an increased warmth of their extremities, an apparent increased vascularity of the nail beds and skin; they claimed to feel less tense and apprehensive, more relaxed and tranquil. That improvement in these symptoms as well as the asthma was not due to suggestion is attested by the fact that in many instances the patients were unaware of the exact time at which ACTH therapy started, placebos containing a small amount of propylene glycol in saline having been administered intramuscularly for several doses prior to the administration of ACTH with the patient understanding that he was receiving potent preparations. In no instance did evidence of clinical improvement occur under such circumstances.

Variations in the blood elements following ACTH therapy has been discussed in previous publications.7-12 In general, these consist of an initial decrease in the total leukocyte count, followed by a leukocytosis and eosinopenia.

We have not observed any deleterious effects from ACTH in allergic individuals treated with short-term intermittent courses of therapy as outlined in this communication. Neither has there been any unpleasant side effects with the exception of the so-called pelvic cramps in the case of M. A. We wonder if these symptoms may have been the result of stretching of the adrenal capsule as a consequence of transient enlargement of the gland, or possibly as the result of hemorrhages in the adrenal cortex.

In our experience in treating allergic individuals with ACTH, we have learned to watch for the following course of sequential events: The dosage of ACTH is started at 25.0 mg. intramuscularly every six hours with the aim of obtaining a prompt and maximum glanular stimulation of short duration. It is continued at this level even though the eosinophils markedly diminish or disappear from the peripheral blood; this usually occurs within twenty-four hours from the time of the first dose. We observe the patient’s fluid intake and output as well as the daily weight for, as a rule, the dosage is reduced 50 per cent in the event of a definite oliguria or a gain in weight of 2 to 3 pounds in twenty-four hours. Most adult patients and some children, particularly those with eczema, tolerate ACTH therapy at a dosage of 25.0 mg. every six hours for a total of nine doses without hazard even though there is no deliberate attempt made to regulate the electrolyte balance.

It should be emphasized, finally, that dangers said to be associated with
ACTH therapy pertain to long-continued treatment and thus far in our experience have not been observed in therapy consisting of short intensive courses followed by relatively long rest periods as employed in this study.

REFERENCES

17. Rollins, J. P., and Randolph, T. G.: The expiratory rate as a measurement of the severity of bronchial asthma. (Submitted for publication).