Allergic Reactions to ACTH

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The use of adrenocorticotropic hormone (ACTH) has become established as an effective and generally safe method of therapy. Its value in allergic disorders is outstanding and we would find it difficult to practice without it. As with many effective drugs, however, there is a tendency toward overuse, and we are therefore reporting eight cases of allergic reactions to ACTH in an effort to re-emphasize the risks involved with its use.

The objectionable effects of ACTH therapy may be divided into three general categories. First, there are the usual side effects found especially in patients receiving large dosages for prolonged periods of time. Cushing's syndrome is a final phase of this problem but milder effects, e.g., weight gain and moon facies may occur even with small amounts. Next there are certain pre-existing diseases which may be aggravated by ACTH and other steroids, e.g., peptic ulcers, tuberculosis and diabetes. Finally, there are those conditions which are presumably on an antigen-antibody basis, characterized by urticaria, asthma, shock and sometimes death, unrelated to dosage or pre-existing diseases, and which may occur in patients who often demonstrate positive skin tests to the offending materials. We believe that the following cases fall into this last group.

Case Reports

Case 1: AG—This 59 year-old white man had a 25-year history of asthma and rhinitis, as well as a mild diabetes mellitus. He was first given ACTH gel (Armour) twice a day for about a week in December, 1955, and subsequently received seven more such injections at varying intervals with no apparent ill effects. On April 24, 1957, he was again given 40 units of ACTH-gel (Armour); 30 minutes later he became dyspneic, cyanotic, and developed severe wheezing and coughing. His blood pressure was unobtainable, but following emergency treatment with oxygen, epinephrine, intravenous aminophyllin and coramine he recovered rapidly. Electrocardiograms were unchanged. A month later scratch tests were read as follows:

| 0 | Lamb, beef, pork |
| 0 | Armour ACTH gel 80 units |
| 1 plus | Acthar HP 10 units (lyophylized) |
| 2 plus | Acthar HP 25 units (lyophylized) |
| 4 plus | Acthar HP 40 units (lyophylized) |
| 2 plus | Wilson ACTH gel 40 units |
| 1 plus | Corticotrophin zinc 40 units |

Case 2: Mrs. P. D.—This 45 year-old white housewife had a 25-year history of intermittent severe asthma and rhinitis. Because of the severity of symptoms she

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received ACTH both as a gel and an intravenous drip on several occasions between 1954 and 1957. In May, 1957, she was given 40 units of ACTH (Armour) "to pep up her adrenals" as she had been on prednisone for a year. She quickly developed generalized urticaria, angioneurotic edema of her left eye and ear lobes, and lost her voice. She recovered rapidly and uneventfully. Scratch tests gave the following results:

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<tbody>
<tr>
<td>0</td>
<td>10 units of ACTH gel (Armour)</td>
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<tr>
<td>2 plus</td>
<td>25 units ACTH gel (Armour)</td>
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<tr>
<td>4 plus</td>
<td>40 units ACTH gel (Armour) (lyophylized)</td>
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<tr>
<td>2 plus</td>
<td>80 units ACTH gel (Armour)</td>
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<tr>
<td>1 plus</td>
<td>Corticotrophin Zinc (Organon)</td>
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<tr>
<td>0</td>
<td>Control</td>
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<tr>
<td>0</td>
<td>Beef</td>
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<tr>
<td>1 plus</td>
<td>Pork</td>
</tr>
<tr>
<td>2 plus</td>
<td>Bovine ACTH (saline)—Armour</td>
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<tr>
<td>2 plus</td>
<td>Porcine ACTH (saline)—Armour</td>
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<td>0</td>
<td>Gelatin</td>
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Case 3: J.N.—This 67-year-old maintenance worker was first given ACTH in 1954 in an intravenous drip with aminophyllin because of intractable asthma. Six months later he was re-hospitalized and treated identically. During the second liter containing 20 units of ACTH and 20 cc. of aminophyllin he suddenly became dyspneic, confused, and developed convulsive movements of his extremities. His breathing was rapid and gasping, and his eyeballs rolled back. The attack lasted about two hours, after which he complained of pain in his left shoulder. X-ray films revealed an impacted fracture of the anatomical neck of the humerus, from which he recovered uneventfully. He has subsequently received aminophyllin on numerous occasions without difficulty. We were never able to skin-test the patient or identify the brand of soluble ACTH used in this patient.

Case 4: M.G.—This 25-year-old woman was first seen by us in January, 1954, because of urticaria present intermittently for one month despite treatment with antihistamines, cortisone, ACTH and diets. Two months previously she had been given a series of penicillin injections as well as penicillin inhalations for a sinus infection. She had a "mild attack of rheumatic fever" as a child. On examination there were many carious teeth, some suprapubic tenderness and an extremely tender urethra, but no cardiac abnormality was found. Treatment with chlorpheniramine maleate (Chlortrimeton), diphenhydramine hydrochloride (Benadryl) and elimination diets failed to produce improvements, so a series of five ACTH gel injections were given. Three months later she was hospitalized and given 20 units of ACTH gel (Armour). Thirty minutes later she had an epileptiform seizure following which she was weak, confused and vomited once. Her reflexes were brisk in the lower extremities, with a positive Babinski sign bilaterally and questionable ankle clonus on the left. All medication was stopped and her symptoms were treated with sodium amytal. Electroencephalograms revealed "mildly abnormal five second slowing bifrontally and bitemporally in the waking state." This was considered to be negative for epilepsy. She refused to have skin tests for ACTH. In the past six years she has had no further neurologic episodes. This patient stated that there was no previous history of epilepsy either in herself or in her family.

Case 5: J.F.—This 55-year-old salesman had a 17-year history of chronic asthma when he was first given ACTH in 1952. Subsequently he received ACTH both as the gel and in an intravenous drip on several occasions without incident until 1957 when he was restarted on a drip containing 20 units of Wilson's corticotropin in 1000 cc. 5 per cent glucose in water. Almost immediately he developed increasing dyspnea, generalized urticaria, and angioneurotic edema of the face and eyelids. The drip was stopped and epinephrine and Benadryl administered. The urticaria recurred intermittently for two to three months. We were never able to skin test this patient.

Case 6: M.Z.—This 44-year-old woman gave a six-year history of asthma requiring treatment with ACTH gel and drip on several occasions. She had numerous positive intradermal skin tests. In January, 1960, she was again treated with an intravenous drip of 5 per cent glucose in water containing 20 units of ACTH (brand unknown) 20 cc. (0.5 gm.) of aminophyllin and 1 cc. of 1:1000 epinephrine. Two hours later she developed generalized urticaria, followed by hoarseness and abdominal pain. Hydrocortisone was substituted for the ACTH in the drip, and Chlortrimeton administered. Symptoms subsided in four or five hours.

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Scratch tests revealed the following results:

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<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>+ + +</td>
<td>Organon purified corticotropin gel</td>
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<tr>
<td>+ +</td>
<td>Armour Acthar HP 80 units</td>
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<tr>
<td>+</td>
<td>Armour Foreline ACTH</td>
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<td></td>
<td>Armour Bovine ACTH</td>
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<tr>
<td>+ + +</td>
<td>Armour Acthar (lyophilized) 25 units</td>
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<td>+</td>
<td>Armour Acthar 40 units</td>
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<td>Beef</td>
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Case 7: M.K.—This 56-year-old woman had had asthma for 23 years, with symptoms almost constantly for the past two years. She had numerous positive intradermal skin tests. She was treated with intravenous drip ACTH in June, 1959, and had received ACTH three times without difficulty, when in April, 1960, she was again given an intravenous drip of ACTH (National) with aminophyllin and epinephrine because of intractable asthma. One and one half hours later she developed generalized urticaria which was treated successfully with Benadryl; hydrocortisone was substituted for ACTH in the intravenous drip. Scratch tests for ACTH were completely negative.

Case 8: A.C.—This 68-year-old man had asthma for 12 years. Skin tests were almost negative and "P pulmonale" was present on his electrocardiogram. Between 1948 and 1959 he received ACTH on several occasions, both as the gel and in an intravenous drip. In November, 1959, he was restarted on the drip because of severe asthma. About two hours later he suddenly became maniacal with shouting, jerking, disorientation, tremors, confusion and urinary incontinence. The entire episode lasted only five minutes, being relieved by 75 mg. of meperidine hydrochloride (Demerol) and discontinuance of the intravenous drip. Subsequently neuologic examination revealed only minimal non-specific changes, a lumbar puncture (bloody tap) failed to show increased pressure, and an electroencephalogram was read as "much disorganization of the basic frequencies, but not epileptic."

Skin tests to ACTH were completely negative, and he has had no further neurologic difficulties.

Discussion

Allergic reactions apparently due to ACTH may be caused by sensitivity to any of the following:

1. ACTH itself.
2. The vehicle or preservative injected with the ACTH, e.g., gelatin.
3. The animal source from which the ACTH was derived, e.g., pork or beef.
4. A contaminant introduced by the manufacturer, or
5. A contaminant in the syringe, e.g., penicillin.

Our reactions occurred to Armour, Wilson and National Drug Company material so contamination by any one manufacturer can be ruled out. Those patients who exhibited positive skin tests to the materials, invariably reacted to various types of ACTH but not to the gelatin, pork or beef. Five of the eight patients had their allergic reactions to the ACTH intravenous drip so it is unlikely that any contamination of tubing or syringes could have taken place in them. Also, once a syringe has been used for penicillin in our office, it is never used for anything else.

About 1957 we abandoned the use of intermittent injections of ACTH to "pep up" the adrenals of patients on long-term steroid therapy, as it was shown to be probably ineffective for this purpose. We feel, however, that the intravenous drip of ACTH in status asthmaticus is so effective that it is more than worth the risks involved. This is why our later patients reacted to the drip—we rarely used the gel.

Allergic reactions to ACTH have been reported by numerous investigators since 1950, and symptoms ranging from urticaria to death. Some observers feel that there is a definite relationship between ACTH therapy and convulsions, and suggest that ACTH may induce convulsions in predisposed (occult) epileptics, just as it might precipitate diabetes in susceptible individuals. Dorfman reported status epilepticus with subsequent brain damage in three of 40 rheumatic children treated with ACTH, in the absence of associated hypertension or electrolyte imbalance. Hofer and Glaser discuss electroencephalographic abnormalities under such circumstances, while Wayne describes four of 43 patients who had convulsions from ACTH. Bonham had a patient die from convulsions following treatment with ACTH and cortisone, no specific abnormality being found at autopsy.

If these convulsions were on an allergic basis, the patients might have positive skin tests to ACTH, as do many patients who have had hives, asthma or shock following the drug. On the other hand, if the reactions were due to a predisposition to epilepsy,
no such skin reactions would be expected. It is unfortunate that we were able to skin
test only one of our three patients with cerebral manifestations; his tests were
negative.

Anaphylactic shock was reported from an ACTH drip by Anderson10 and by Wilson,11
but Wilson later gave one of his patients ACTH gel unexpectedly. Anaphylaxis occurred
in seven patients described by Brown and Hollander,6 and Fisalo12 had a patient expire
within 15 minutes of an injection. Others have also reported such severe reactions.13-16

Skin testing with ACTH has been performed by several investigators with varying
results. Perkoff et al.14 showed that in individuals sensitive to corticotrophin, positive
reactions may be restricted to preparations from a particular species or may extend
to ACTH derived from many different animals (sheep, pig, horse, and whale pituitary).
Their patients' serum was found to retain passively transferrable, reagin-like anti-
bodies to several corticotrophin preparations for at least 16 months after the anaphy-
lactic reaction.

The cases reported by Swift16 and Feinberg et al.3 showed skin sensitivity to several
species of ACTH. On the other hand, several of the patients reported by Brown and
Hollander6 were later able to tolerate a beef gland preparation instead of the usual
carcass pork product.

Arnoldsson12 states, "In ten cases with manifest reactions to ACTH, intradermal
tests have been made at regular intervals. It has been demonstrated that the skin
reactions weaken in a number of cases after a period of six to 12 months. In these
latter cases, we have again been able to administer ACTH without complications." He
believes that his cases were due to a specific hypersensitivity to the hormone. In our
cases we reached a similar conclusion, but would avoid using ACTH under any circum-
stances in a patient who has reacted adversely to it.

SUMMARY

1. Sensitization to ACTH is becoming more frequent; symptoms may include urti-
caria, angio-edema, convulsions, shock and death.
2. Eight reactions are reported including three with cerebral manifestations and one
   with shock.
3. Convulsions may be due to either an allergy or a predisposition to epilepsy. We
   were unable to determine which of the two was present in our three patients.
4. Our reactions were probably due to ACTH itself, rather than to any contam-
   inating antigen.
5. ACTH remains a valuable drug, but should be used only when indicated. Once a
   patient has reacted to it, he should not receive it again.

RESUMEN

1. La sensibilización al ACTH se está haciendo más frecuente; los síntomas pueden
   incluir urticaria, angioedema, convulsiones, shock y muerte.
2. Se relatan ocho reacciones, comprendiendo tres con manifestaciones cerebrales
   y una con shock.
3. Las convulsiones pueden deberse ya sea a la alergia o a la predisposición a la
   epilepsia. No podemos determinar de cuál de esas causas se debía en nuestros tres
   enfermos.
4. Las reacciones que observamos se debieron probablemente al ACTH mismo y no
   a ningún otro antígeno contaminante.
5. El ACTH sigue siendo una droga valiosa pero debe usarse cuando está indicada.
   Una vez que el enfermo ha reaccionado a ella ya no debe volver a usarse.

ZUSAMMENFASSUNG

1. Sensibilisierung gegenüber ACTH wird häufiger; ihre Symptome können sich
   erstrecken auf Urtikaria, Gefäßödeme, Krämpfe, Schock und Tod.
2. Bericht über 8 Reaktionen einschließlich 3 mit cerebralen Manifestationen und
   einem mit Schock.
3. Krämpfe können entweder die Folge einer Allergie sein oder einer Prädisposition
   zu Epilepsie. Es war uns nicht möglich, zu bestimmen, welcher dieser beiden Momente
   bei unseren 3 Kranken vorlag.
4. Unsere Reaktionen waren wahrscheinlich eher dem ACTH selbst zu zuschreiben
   als irgend einem verurteilenden Antigen.
5. ACTH bleibt ein wertvolles Arzneimittel, sollte aber nur dann angewandt werden,
   wenn es indiziert ist. Hat einmal ein Kranke darauf ungünstig reagiert, sollte man
   es ihm nie wieder geben.

REFERENCES

REGULATORY MECHANISMS OF PULMONARY PRESSURE
IN CONGESTIVE HEART DISEASES

The most important factors which participate in the regulation of the pulmonary pressure in congenital heart diseases with left to right shunts (patent ductus arteriosus, atrial septal defect and ventricular septal defect) were studied.

The main factors responsible for pulmonary hypertension in these types of heart disease are essentially of a functional nature.

A probable reduction in the partial pressure of oxygen in the blood of the pulmonary veins causes a reflex vasoconstriction of the precapillary arterioles of the lung. The reduction of a PaO₂ is due both to a low partial oxygen pressure in the air at altitudes above 1,500 meters and to impaired blood oxygenation relative to a pulmonary hypervolemia. Although the reflex vasoconstriction is not the main factor, it is an important one in the regulation of pulmonary pressure. Other factors include the increased energy of contraction of the right ventricle, the transmission of the systemic pressure to the pulmonary circulation, and the "pseudomitral syndrome." When the last two mechanisms are lacking, as in the case of atrial septal defect, pulmonary hypertension is uncommon.

All of these factors are susceptible to being reduced or eliminated with the surgical treatment of the malformation.