

# Successful initiation of alternate-day prednisone in chronic steroid-dependent asthmatic patients

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*Eleven chronic steroid-dependent asthmatic patients were successfully converted from daily to alternate-day prednisone. The status of the hypothalamic-pituitary-adrenal axis was studied before and after conversion to alternate-day prednisone. There was partial improvement of hypothalamic-pituitary function after 4 months of alternate day prednisone as indicated by the rise of plasma immunoreactive ACTH induced by insulin hypoglycemia. Adrenal function improved to a variable extent after 4 to 11 months of alternate-day prednisone. Clinical signs of hypercorticism remitted in most patients, even in those maintained on an increased total prednisone dose when it was given on alternate days.*

Corticosteroids are useful drugs for many diseases, including bronchial asthma. Severe bronchial asthma may require prolonged daily corticosteroid administration which itself may lead to untoward effects.<sup>1</sup> Attempts to discontinue corticosteroids in severe chronic asthmatic patients by gradual reduction of the daily dose has met with little success.<sup>2, 3</sup> Alternate-day prednisone is hypothalamic-pituitary-adrenal (HPA) axis sparing<sup>4</sup> and therefore preferable to daily therapy, but attempts to convert asthmatics from daily corticosteroids to alternate-day prednisone have had only variable success.<sup>5</sup>

Based on previous experience,<sup>4</sup> this study was designed to: (1) evaluate a protocol for conversion to alternate-day prednisone for asthmatic patients in whom previous attempts at conversion and a gradual reduction of the daily dose had failed, and (2) systematically follow the recovery of the HPA axis during conversion to alternate-day prednisone.

## **METHODS**

### **Patient selection**

Patients were selected from the L.B.V.A.H. Allergy Clinic and had been treated continuously by one of the authors (K. T.) for 0.7 to 7.0 years (mean 3.5). All 11 patients, ages 36 to 60 (mean 51), had perennial asthma but with definable "extrinsic" factors by both

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TABLE I. Design of study

| Studies                           | Time range (mo.)      |                                           |                                                              |   |                       |                          |   |   |   |
|-----------------------------------|-----------------------|-------------------------------------------|--------------------------------------------------------------|---|-----------------------|--------------------------|---|---|---|
|                                   | 0                     | 1                                         | 2                                                            | 3 | 4                     | 5                        | 6 | 7 | 8 |
| Alternate-day prednisone (q.a.d.) |                       |                                           |                                                              |   |                       |                          |   |   |   |
| Clinical                          | Daily prednisone      | 2 weeks of q.a.d. prednisone and ACTH gel | q.a.d. Prednisone with ACTH gel once/month (after ACTH test) |   |                       |                          |   |   |   |
| Hormonal                          | Insulin and ACTH test | Monthly ACTH tests                        |                                                              |   | Insulin and ACTH test | ACTH tests every 2-4 mo. |   |   |   |

history and skin testing. In each case a gradual reduction of daily prednisone and initiation of alternate-day prednisone had been tried unsuccessfully in the past. Only those patients were selected who were reliable and could maintain accurate and complete diaries. For the endocrine studies 7 asthmatic control subjects, ages 21 to 61 (mean 43.4), were selected who had never received corticosteroids or adrenocorticotrophic hormone (ACTH).

### Clinical studies

All patients were evaluated as needed *day or night* by the allergy staff (M. P. and/or K. T.) at least one to 2 times per week for the entire 8 month study. The patient diary was reviewed which included: symptoms, regular medications (i.e., prednisone, ACTH, oral bronchodilators), and supplemental medication (i.e., epinephrine, nebulized bronchodilator and aminophylline suppositories). Standard Veteran's Administration allergy extract injections were ordered by the physician at each visit.

*Procedure after preconversion insulin and ACTH tests.* After the preconversion insulin and ACTH tests were performed (see Hormonal studies), the previous daily dose of prednisone was doubled and taken on alternate days at 8:00 A.M. (Table I). On the "off" day (no prednisone), an intramuscular injection of 40 units of ACTH gel (Armour) was given for 7 doses (2 weeks). All other medication was continued as usual, i.e., bronchodilators, expectorants, antibiotics, and decongestants. If an exacerbation of asthma occurred, etiologic factors were eliminated if possible and treatment short of increased prednisone and/or ACTH was begun.

When asthma persisted requiring *double* the usual doses of nebulized bronchodilator, aminophylline suppositories, and/or epinephrine over a 48 hour period, additional amounts of prednisone and/or ACTH were prescribed. The dose and frequency given varied with the time of onset of the asthma as indicated: (1) During the initial 2 week phase of alternate-day ACTH gel and alternate-day prednisone: The alternate-day prednisone dose was increased by an additional 50 per cent and alternate-day ACTH was continued for 7 *more injections* (total of 14). (2) During the second to fourth weeks: Prednisone was increased by an additional 50 per cent, and 40 units of alternate-day ACTH gel was given for 3 *injections* (total of 10). (3) During the fourth to sixth weeks: *An injection* of 40 units of ACTH gel was given intramuscularly.

*Difficulty during the first 6 weeks of alternate-day prednisone.* For any continuing difficulty in the first 6 weeks, the alternate-day prednisone dose was increased by another 50 per cent, and three additional doses of alternate-day ACTH gel were given.

*Subsequent treatment.* If no difficulty occurred by the sixth week, an ACTH test was performed (see Hormonal studies), with an additional intramuscular injection of 40 units of ACTH gel given upon completion of the test. The following day the prednisone dose was reduced by 20 mg. when alternate-day prednisone was greater than 40 mg., by 10 mg. when

alternate-day prednisone was 20 to 40 mg., or by 5 mg. when alternate-day prednisone was 20 mg. or less. The prednisone was thereafter reduced *monthly* following an ACTH test and a *monthly* injection of ACTH gel.

If difficulty occurred after reduction of alternate-day prednisone, etiologic factors were eliminated if possible and treatment short of additional prednisone or ACTH was begun. When the difficulty persisted for 48 hours and occurred in *2 weeks or less* after reduction in the dosage, a return to the prior alternate-day prednisone dose was instituted and an extra injection of 40 units of ACTH gel was given. When the difficulty persisted for 48 hours and occurred in *2 to 4 weeks* after the reduction in dosage, prednisone was increased to a dose halfway between the prior dose and current dose, and an extra injection of ACTH gel was given.

*Persistent asthma.* At any time during the study that asthma persisted despite increased alternate-day prednisone and additional ACTH, the patients were promptly hospitalized and treated with intravenous fluids, aminophylline, antibiotics, and a 5 to 10 day course of 40 to 120 mg. per day of prednisone. Then alternate-day prednisone was promptly resumed when the clinical status improved, minimizing prolonged daily prednisone.

### Hormonal studies

All patients were hospitalized and treated with oral bronchodilators, subcutaneous epinephrine and aminophylline as needed. Prednisone was withheld for 24 hours before each insulin and ACTH test. Intravenous saline solution was started the evening before, and the insulin test was performed at 8:00 A.M.<sup>6</sup> Basal levels of plasma glucose, cortisol, and immunoreactive ACTH and the response to 0.15 units of regular insulin per kilogram intravenously were determined at 30, 60, 90, and 120 minutes. Usual medications including prednisone were resumed following the test.

An ACTH test was performed 48 to 72 hours after the insulin test.<sup>7</sup> Resting and fasting cortisol levels and the 120 minute response to 40 units of intramuscular aqueous ACTH were estimated. Monthly ACTH tests were performed, and an insulin test was repeated after 4 months of treatment followed again in 48 to 72 hours by an ACTH test. Additional ACTH tests were done every 2 to 4 months on patients still suppressed at the 4 month follow-up or if further change in adrenal function was anticipated, i.e., after increased alternate-day prednisone and/or periodic daily courses of prednisone. Patients could be removed from the study at any time if medical judgement deemed this to be advisable.

### Laboratory methods

Blood samples were drawn before and after the administration of ACTH or of insulin at the above-stated intervals. Plasma was separated quickly and kept frozen at -20° C. until analysis. It was analyzed for glucose by the potassium ferrieyanide oxidation-reduction method adapted for the AutoAnalyzer,<sup>8</sup> for cortisol by the method of Mattingly,<sup>9</sup> and for plasma ACTH by a radioimmunoassay technique.<sup>10</sup>

## RESULTS

### Clinical

All 11 patients were successfully converted and maintained on alternate-day prednisone during the 8 month study (Table II). A temporary increase in alternate-day prednisone was needed in 6 patients (Patients 9, 10, 11, 12, 16, and 17). Therapeutic 5 to 10 day courses of ACTH and/or prednisone were required in 9 of 11 patients (except Patients 14 and 18), with return to alternate-day prednisone accomplished in all 11. After 4 months, one patient was off prednisone (Patient 18) and 5 patients were on reduced alternate-day prednisone doses (Patients 10, 13, 14, 17, and 19). Five patients were on the same or increased alternate-day prednisone dosage (Patients 9, 11, 12, 15, 16). By 8 months,

TABLE II. Summary of clinical data

| Patient No. | Age | Major sensitivities             | Preconversion daily prednisone (mg.) |        |                | Alternate-day prednisone (mg.) |       |       |
|-------------|-----|---------------------------------|--------------------------------------|--------|----------------|--------------------------------|-------|-------|
|             |     |                                 | Mean                                 | Range  | Duration (mo.) | Initial                        | 4 mo. | 8 mo. |
| 9           | 56  | Weeds, dust, and grasses        | 10                                   | 5 -15  | 31             | 20                             | 30    | 20    |
| 10          | 47  | Grasses, weeds, and dust        | 10                                   | 5 -25  | 60             | 10                             | 5     | 0*    |
| 11          | 56  | Weeds, dust, and grasses        | 20                                   | 15 -30 | 52             | 40                             | 40    | 20*   |
| 12          | 60  | Dust, mold, and grasses         | 10                                   | 5 -30  | 36             | 30                             | 40    | 20    |
| 13          | 58  | Dust and grasses                | 30                                   | 10 -40 | 78             | 60                             | 40    | 30    |
| 14          | 58  | Weeds, grasses, and dust        | 10                                   | 5 -15  | 18             | 20                             | 5     | 0*    |
| 15          | 55  | Grasses, weeds, and dust        | 10                                   | 5 -15  | 30             | 20                             | 20    | 10*   |
| 16          | 44  | Grasses, weeds, dust, and wheat | 15                                   | 5 -15  | 18             | 30                             | 40    | 20*   |
| 17          | 31  | Weeds, grass, and dust          | 10                                   | 7.5-20 | 12             | 15                             | 5     | 0*    |
| 18          | 36  | Dust and grasses                | 5                                    | 2.5-10 | 144            | 10                             | 0*    | 0     |
| 19          | 51  | Weeds and grasses               | 15                                   | 5 -30  | 78             | 30                             | 5     | 0*    |

\*Diminished hypercorticism.

5 patients were off prednisone (Patients 10, 14, 17, 18, 19), 5 were on reduced alternate-day prednisone (Patients 11, 12, 13, 15, and 16), and one (Patient 9) was on the same dose. By 8 months diminished signs of hypercorticism were observed in 8 patients. These included: decreased cushingoid facies (Patients 10, 11, 17, 18), diminished pedal edema (Patients 14, 15, 16, and 19), reduction of excess intraocular pressure (Patient 16), reduced hyperglycemia (Patients 14 and 18), and reduced excess weight (Patients 10, 17, 18).

## HORMONAL

### Insulin-induced hypoglycemia

*Plasma glucose.* No difference in plasma glucose values (basal and nadir) was found by t test analysis when the control group was compared to the patients (both initial and 4 month follow-up). No difference was found when the initial glucose values in patients were compared to values in the 4 month follow-up study. Adequate hypoglycemia was achieved in all patients except for Patients 7 and 13 at 4 months.<sup>6, 11</sup>

*Plasma cortisol.* A significant difference was observed at all time intervals when the mean levels in control asthmatic subjects were compared to those attained in the asthmatic patients treated with daily steroids (Tables III, IV, and VI). A trend toward improvement was observed after 4 months of alternate-day steroid treatment, although the increased responsiveness was not statistically significant (Tables IV and VI). Some patients who had a diminished response initially reached the range found in the control asthmatic subjects by 4 months (Patients 15, 17, 18, and 19).

*Plasma ACTH.* The mean basal level of plasma immunoreactive ACTH was significantly higher in the control asthmatic subjects than in the patients on daily prednisone (Tables III, IV, and VI). The levels of ACTH achieved with hypoglycemia at all time intervals sampled except 120 minutes were significantly higher in control asthmatic subjects than in the asthmatic patients on daily steroids (Table VI). Four months after the patients' conversions to alternate-day prednisone, the mean levels of plasma ACTH had increased significantly compared to the preconversion levels except for the 60 minute sample (Tables

**TABLE III.** Response to insulin hypoglycemia and to ACTH stimulation in "control"†\* asthmatic patients

| Patient No. | Age  | Plasma analysis             | Insulin test |         |         |         |          | ACTH test |          |     |
|-------------|------|-----------------------------|--------------|---------|---------|---------|----------|-----------|----------|-----|
|             |      |                             | 0 min.       | 30 min. | 60 min. | 90 min. | 120 min. | 0 min.    | 120 min. | †   |
| 1           | 44   | Glucose (mg./100 ml.)       | 82           | 54      | 50      | 50      | 52       |           |          |     |
|             |      | Cortisol ( $\mu$ g/100 ml.) | 17           | 16      | 29      | 35      | 40       | 19        | 54       | 35  |
|             |      | ACTH ( $\mu$ g/ml.)         | 90           | 70      | 90      | 130     | 120      |           |          |     |
| 2           | 42   | Glucose                     | 70           | 30‡     | 74      | 56      | 72       |           |          |     |
|             |      | Cortisol                    | 13           | 25      | 25      | 31      | 31       | 14        | 33       | 19  |
|             |      | ACTH                        | 110          | 135     | 90      | 150     | 10       |           |          |     |
| 3           | 61   | Glucose                     | 80           | 20      | 20      | 50      | 64       |           |          |     |
|             |      | Cortisol                    | 23           | 32      | 32      | 38      | 48       | 13        | 26       | 13  |
|             |      | ACTH                        | Not Done     |         |         |         |          |           |          |     |
| 4           | 22   | Glucose                     | 80           | 44      | 46      | 70      | 86       |           |          |     |
|             |      | Cortisol                    | 24           | 18      | 42      | 28      | 25       |           |          |     |
|             |      | ACTH                        | 60           | 65      | 100     | 125     | 40       |           |          |     |
| 5           | 46   | Glucose                     | Not Done     |         |         |         |          |           |          |     |
|             |      | Cortisol                    | Not Done     |         |         |         |          | 10        | 28       | 18  |
|             |      | ACTH                        | Not Done     |         |         |         |          |           |          |     |
| 6           | 21   | Glucose                     | 80           | 20      | 28      | 50      | 74       |           |          |     |
|             |      | Cortisol                    | 17           | 15      | 22      | 29      | 21       | 25        | 58       | 33  |
|             |      | ACTH                        | Not Done     |         |         |         |          |           |          |     |
| 7           | 51   | Glucose                     | 102          | 60      | 58      | 78      | 94       |           |          |     |
|             |      | Cortisol                    | 21           | 23      | 32      | 30      | 30       | 7         | 30       | 23  |
|             |      | ACTH                        | 10           | 50      | 90      | 20      | 22       |           |          |     |
| 8           | 49   | Glucose                     | 96           | 40      | 34      | 56      | 68       |           |          |     |
|             |      | Cortisol                    | 17           | 13      | 19      | 29      | 26       | 13        | 30       | 17  |
|             |      | ACTH                        | Not Done     |         |         |         |          |           |          |     |
| Cortisol    | Mean |                             | 18           | 18      | 27      | 31      | 30       | 14        | 37       | 23  |
|             | SD   |                             | 3.5          | 4.3     | 7.8     | 2.9     | 6.9      | 5.9       | 13       | 8.5 |
| ACTH        | Mean |                             | 68           | 80      | 93      | 106     | 48       |           |          |     |
|             | SD   |                             | 43           | 38      | 5       | 59      | 25       |           |          |     |

\*Not previously treated with steroids.

†I = Increment (0 to 120 minutes).

‡Intravenous glucose, 15 Gm., at 45 minutes.

IV and VI). In Patients 12 and 19, a high basal plasma ACTH level was observed which decreased during insulin-induced hypoglycemia. Both patients had significant bronchospasm at the onset of the insulin test and plasma cortisol increased in both during hypoglycemia. Patient 11, after 4 months of alternate-day prednisone, had a normal basal ACTH level but had only a minimal increase in response to hypoglycemia. Unexplained are the nondetectable ACTH values observed in the initial test of Patient 14 and in Patient 18 in the 4 month follow-up test. These very low levels were found despite normal plasma cortisol responses to hypoglycemia in both (Table IV).

#### ACTH stimulation

A significantly greater mean response to ACTH administration occurred in the control asthmatic group compared to the responses in the asthmatics on daily prednisone (Tables III, V, and VI). Basal plasma cortisol levels did not

**TABLE IV.** Response to insulin hypoglycemia in asthmatic patients before and after conversion from daily to alternate-day steroid therapy

| Patient No. | Age  | Plasma analysis              | Insulin test            |         |         |         |          |                                            |         |         |         |          |
|-------------|------|------------------------------|-------------------------|---------|---------|---------|----------|--------------------------------------------|---------|---------|---------|----------|
|             |      |                              | While on daily steroids |         |         |         |          | After 4 months of alternate-day prednisone |         |         |         |          |
|             |      |                              | 0 min.                  | 30 min. | 60 min. | 90 min. | 120 min. | 0 min.                                     | 30 min. | 60 min. | 90 min. | 120 min. |
| 9           | 56   | Glucose (mg./100 ml.)        | 94                      | 26      | 41      | 52      | 70       | 90                                         | 38      | 52      | 68      | 86       |
|             |      | Cortisol ( $\mu$ g./100 ml.) | 19                      | 18      | 25      | 34      | 23       | 15                                         | 12      | 20      | 35      | 34       |
|             |      | ACTH ( $\mu$ g/ml.)          | 20                      | 10      | 55      | 7       | ND*      | ND                                         | ND      | ND      | 10      | 5        |
| 10          | 47   | Glucose                      | 82                      | 30      | 32      | 40      | 48       | 150                                        | 44      | 24      | 50      | 52       |
|             |      | Cortisol                     | 11                      | 12      | 19      | 21      | 25       | 7.4                                        | 12      | 16      | 16      | 15       |
|             |      | ACTH                         | Not done                |         |         |         |          | 95                                         | 86      | 130     | 150     | 73       |
| 11          | 56   | Glucose                      | 72                      | 10      | 22      | 60      | 60       | 90                                         | 32      | 40      | 66      | 86       |
|             |      | Cortisol                     | 4.5                     | 0.6     | 1.9     | 9.6     | 1.9      | 3.4                                        | 3.0     | 4.3     | 4.3     | 3.4      |
|             |      | ACTH                         | ND                      | ND      | ND      | ND      | ND       | 62                                         | 81      | 78      | 71      | 63       |
| 12          | 60   | Glucose                      | 90                      | 26†     | 110     | 68      | 78       | 104                                        | 44      | 58      | 94      | 90       |
|             |      | Cortisol                     | 8.9                     | 4.1     | 9.8     | 8.9     | 13       | 6.8                                        | 9.1     | 12      | 15      | 12       |
|             |      | ACTH                         | ND                      | ND      | ND      | ND      | ND       | 90                                         | 45      | 30      | 70      | 85       |
| 13          | 58   | Glucose                      | 78                      | 32      | 34      | 66      | 78       | 118                                        | 66      | 80      | 106     | 114      |
|             |      | Cortisol                     | 2.6                     | 1.0     | 2.8     | 7.5     | 5.7      | 6.3                                        | 8.9     | 5.8     | 13      | 5.4      |
|             |      | ACTH                         | 22                      | 21      | 28      | 24      | 19       | 10                                         | ND      | ND      | 15      | 25       |
| 14          | 58   | Glucose                      | 106                     | 40      | 48      | 70      | 82       | 76                                         | 22      | 50      | 56      | 78       |
|             |      | Cortisol                     | 15.0                    | 19      | 18      | 33      | 24       | 6.8                                        | 21      | 29      | 21      | 35       |
|             |      | ACTH                         | ND                      | ND      | ND      | ND      | ND       | 17                                         | 24      | 85      | 110     | 88       |
| 15          | 55   | Glucose                      | 80                      | 28      | 30      | 54      | 62       | 10                                         | 14      | 31      | 24      | 21       |
|             |      | Cortisol                     | 7.5                     | 16      | 7.5     | 9.0     | 15       |                                            |         |         |         |          |
|             |      | ACTH                         | Not done                |         |         |         |          |                                            |         |         |         |          |
| 16          | 44   | Glucose                      | 75                      | 28      | 60      | 76      | 96       | 100                                        | 40      | 52      | 64      | 76       |
|             |      | Cortisol                     | 19                      | 15      | 19      | 14      | 14       | 9.3                                        | 10      | 11      | 16      | 14       |
|             |      | ACTH                         | 15                      | 13      | 17      | 22      | 17       | ND                                         | 20      | 18      | 70      | 90       |
| 17          | 31   | Glucose                      | 90                      | 34      | 56      | 68      | 90       | 86                                         | 30      | 46      | 66      | 88       |
|             |      | Cortisol                     | 9.2                     | 9.9     | 17      | 13      | 20       | 8.8                                        | 30      | 37      | 38      | 38       |
|             |      | ACTH                         | Lost                    | 35      | 50      | 38      | 40       | 45                                         | 90      | 50      | 100     | 80       |
| 18          | 36   | Glucose                      | 148                     | 74      | 50      | 84      | 86       | 110                                        | 48      | 50      | 62      | 78       |
|             |      | Cortisol                     | 11                      | 16      | 9.6     | 13      | 16       | 14                                         | 12      | 28      | 34      | 31       |
|             |      | ACTH                         | 10.5                    | 21      | 17      | 17      | 11       | ND                                         | ND      | ND      | ND      | ND       |
| 19          | 51   | Glucose                      | 108                     | 40      | 50      | 54      | 66       | 80                                         | 38      | 46      | 50      | 52       |
|             |      | Cortisol                     | 16                      | 15      | 22      | 27      | 20       | 17                                         | 23      | 29      | 24      | 35       |
|             |      | ACTH                         | ND                      | ND      | ND      | ND      | ND       | 110                                        | 65      | 54      | 41      | 52       |
| Cortisol    | Mean |                              | 11                      | 11      | 14      | 17      | 16       | 9.5                                        | 12      | 20      | 22      | 23       |
|             | SD   |                              | 5.6                     | 6.7     | 7.8     | 9.9     | 7.4      | 4.2                                        | 5.8     | 11      | 10      | 12       |
| ACTH        | Mean |                              | 7.6                     | 11      | 19      | 12      | 9.7      | 43                                         | 41      | 45      | 64      | 54       |
|             | SD   |                              | 9.5                     | 13      | 22      | 14      | 14       | 44                                         | 37      | 44      | 48      | 35       |

\*ND = Not detectable.

†Intravenous glucose, 10 Gm., given at 50 minutes.

**TABLE V.** ACTH stimulation tests in asthmatic patients before and after conversion from daily to

| Patient No. | While on daily steroids |          |     | After  |          |     |        |          |     |
|-------------|-------------------------|----------|-----|--------|----------|-----|--------|----------|-----|
|             |                         |          |     | 1 mo.  |          |     | 2 mo.  |          |     |
|             | 0 min.                  | 120 min. | I*  | 0 min. | 120 min. | I   | 0 min. | 120 min. | I   |
| 9           | 19†                     | 40       | 21  | 18     | 35       | 17  | 5      | 23       | 18  |
| 10          | 9                       | 20       | 11  | —      | —        | —   | 13     | 23       | 10  |
| 11          | 1                       | 6        | 5   | —      | —        | —   | 4      | 11       | 7   |
| 12          | 3                       | 17       | 14  | —      | —        | —   | 11     | 27       | 16  |
| 13          | 1                       | 8        | 7   | 3      | 16       | 13  | 9      | 19       | 10  |
| 14          | 15                      | 28       | 13  | 22     | 37       | 15  | 16     | 27       | 11  |
| 15          | 17                      | 23       | 6   | —      | —        | —   | —      | —        | —   |
| 16          | 13                      | 25       | 12  | —      | —        | —   | 6      | 26       | 20  |
| 17          | 15                      | 21       | 6   | —      | —        | —   | 12     | 24       | 12  |
| 18          | 13                      | 30       | 17  | 12     | 37       | 25  | 14     | 31       | 17  |
| 19          | 19                      | 40       | 21  | 17     | 34       | 17  | 16     | 36       | 20  |
| Mean        | 11                      | 24       | 13  | 14     | 32       | 18  | 11     | 25       | 14  |
| SD          | 6.8                     | 11       | 5.9 | 7.2    | 8.8      | 4.5 | 4.5    | 6.8      | 4.8 |

\*I = Increment (0 to 120 minutes).

†Plasma cortisol micrograms per 100 ml.

**TABLE VI.** Comparison of mean responses to ACTH stimulation and insulin hypoglycemia

|                                           | Control patients | p Value* control vs. daily steroids | Asthmatics on daily steroids | p Value daily steroids vs. 4 mo. alternate-day prednisone | 4 mo. alternate-day prednisone |
|-------------------------------------------|------------------|-------------------------------------|------------------------------|-----------------------------------------------------------|--------------------------------|
| ACTH stimulation                          |                  |                                     |                              |                                                           |                                |
| Cortisol ( $\mu\text{g}/100\text{ ml.}$ ) |                  |                                     |                              |                                                           |                                |
| 0 min.                                    | 14               | NS†                                 | 11                           | NS                                                        | 9.7                            |
| 120 min.                                  | 37               | 0.02                                | 24                           | NS                                                        | 24                             |
| Insulin hypoglycemia                      |                  |                                     |                              |                                                           |                                |
| Cortisol ( $\mu\text{g}/100\text{ ml.}$ ) |                  |                                     |                              |                                                           |                                |
| 0 min.                                    | 18               | < 0.01                              | 11                           | NS                                                        | 9.5                            |
| 30 min.                                   | 18               | 0.02                                | 11                           | NS                                                        | 12                             |
| 60 min.                                   | 27               | < 0.01                              | 14                           | NS                                                        | 20                             |
| 90 min.                                   | 31               | < 0.001                             | 17                           | NS                                                        | 23                             |
| 120 min.                                  | 30               | < 0.001                             | 16                           | NS                                                        | 23                             |
| ACTH ( $\mu\text{g}/\text{ml.}$ )         |                  |                                     |                              |                                                           |                                |
| 0 min.                                    | 63               | 0.02                                | 7.6                          | 0.05                                                      | 43                             |
| 30 min.                                   | 80               | 0.01                                | 11                           | 0.05                                                      | 41                             |
| 60 min.                                   | 93               | 0.01                                | 19                           | NS                                                        | 45                             |
| 90 min.                                   | 106              | 0.01                                | 12                           | 0.01                                                      | 64                             |
| 120 min.                                  | 48               | NS                                  | 9.7                          | 0.01                                                      | 54                             |

\*Probability that the mean values compared do not differ significantly.

†Not significant ( $p > 0.05$ ).

differ significantly in these patients when retested after conversion to alternate-day prednisone (Tables V and VI). Patients who had normal ACTH tests after 4 months were no longer tested (Patients 14, 16, 17, and 18). After the fourth month, the other patients were tested every 2 to 4 months. Although there was no significant change in the increment or the 120 minute cortisol at 4 months, a trend is apparent if one compares the initial and last ACTH tests (Table V): (1) The smallest increment in plasma cortisol response to ACTH in the control group of asthmatic patients was 13  $\mu\text{g}$  per 100 ml. If the study group is divided on the basis of whether their initial test increment while on daily steroids was

## alternate-day steroid therapy

## alternate-day prednisone for:

| 3 mo.  |          |     | 4 mo.  |          |     | 7-11 mo. |          |    |
|--------|----------|-----|--------|----------|-----|----------|----------|----|
| 0 min. | 120 min. | I   | 0 min. | 120 min. | I   | 0 min.   | 120 min. | I  |
| —      | —        | —   | 19     | 30       | 11  | 18       | 23       | 5  |
| 14     | 33       | 19  | 10     | 24       | 14  | 1        | 18       | 17 |
| 1      | 13       | 12  | 4      | 9        | 5   | 15       | 28       | 13 |
| —      | —        | —   | 5      | 16       | 11  | —        | —        | —  |
| 1      | 12       | 11  | 4      | 13       | 9   | 3        | 15       | 12 |
| 15     | 34       | 19  | 15     | 34       | 19  | —        | —        | —  |
| —      | —        | —   | 6      | 21       | 15  | 14       | 33       | 19 |
| 3      | 22       | 19  | 7      | 36       | 29  | —        | —        | —  |
| 13     | 27       | 14  | 12     | 30       | 18  | —        | —        | —  |
| —      | —        | —   | 19     | 40       | 21  | —        | —        | —  |
| 18     | 38       | 20  | 12     | 24       | 12  | 15       | 38       | 23 |
| 9      | 26       | 17  | 10     | 24       | 14  | 11       | 26       | 15 |
| 7.1    | 10       | 3.7 | 5.7    | 10       | 6.8 | 6.9      | 8.7      | 6  |

either 13  $\mu\text{g}$  per 100 ml. or above (Patients 9, 12, 14, 18, and 19) or below 13  $\mu\text{g}$  per 100 ml. (Patients 10, 11, 13, 15, 16, and 17), the mean increments for the groups are 17  $\mu\text{g}$  and 8  $\mu\text{g}$  per 100 ml., respectively. In comparison, the mean increments calculated from the last ACTH test available on each patient are 16  $\mu\text{g}$  and 18  $\mu\text{g}$  per 100 ml. for the respective groups. The rise in the initially "low" group's mean increment suggests an improved adrenal response in those patients initially most suppressed. (2) Patient 9 had just completed a 10 day course of daily prednisone, which may explain the reduced responsiveness observed at 8 months. If the most current ACTH stimulation results (excluding those from Patient 9) are compared with the preconversion responses, there was significantly increased responsiveness with alternate-day prednisone as evaluated by the mean increment in plasma cortisol (18  $\mu\text{g}$  per 100 ml. compared to 11  $\mu\text{g}$  per 100 ml., respectively, with  $p$  less than 0.01).

## DISCUSSION

### Clinical studies

This study demonstrated that chronically steroid dependent asthmatic patients can be converted to alternate-day prednisone. During this 8 month study a temporary increase in alternate-day prednisone with daily courses of prednisone and/or ACTH was usually required. However, a decrease in steroid requirement was eventually accomplished, with 10 of 11 patients being off prednisone or on diminished alternate-day doses. A decrease in clinical manifestations of hypercorticism was observed in 8 of 11 patients.

It is difficult to explain the apparent success of this study compared to other attempts at alternate-day prednisone conversion<sup>4</sup> and/or daily dosage reduction in asthmatic patients.<sup>2,3</sup> Possible explanations include: (1) patient selection differed; (2) the patient's "conservative" allergy care was handled differently; (3) the protocol design allowed the initiation and maintenance of alternate-day prednisone.

The first possibility may be a factor in that most of the series reported have included both intrinsic and extrinsic asthmatic patients or have dealt with intrinsic asthmatic patients alone.<sup>2-4</sup> Our patients were clearly steroid-dependent asthmatic patients in whom attempts to reduce the daily dose and to initiate alternate-day prednisone had failed in the past. They *all*, however, had definable *extrinsic* factors and were already on injections of allergy extract at the onset of the study.

The second possibility seems unlikely, although the increased personal attention afforded by only one or two attending physicians may have been a factor. Standard Veteran's Administration allergy extracts were utilized along with bronchodilators, expectorants, and antibiotics.

The third possibility appears to be the most likely factor accounting for the successful conversion of the patients to alternate-day prednisone. A review<sup>3</sup> of 538 asthmatic patients revealed that only 75 (14 per cent) could be successfully weaned off corticosteroids. In the management of these patients there was no uniform method of handling the corticosteroids, and gradual reduction of the daily dose was generally the approach. In 1958, alternate-day therapy was proposed.<sup>12</sup> Subsequent studies have suggested variable pituitary-adrenal axis suppression with the use of alternate-day dexamethasone,<sup>13</sup> betamethasone,<sup>14</sup> and triamcinolone.<sup>15</sup> More recent studies with the use of short-acting corticosteroids have supported the efficacy of alternate-day prednisone in asthma and other inflammatory of diseases.<sup>1, 11, 16-19</sup> Freedman<sup>5</sup> has reported that alternate-day prednisone does not adequately control symptoms in a majority of adult intrinsic asthmatic patients. In contrast, others have observed that both intrinsic and extrinsic asthmatic children can usually be converted to alternate-day prednisone.<sup>20, 21</sup>

This study was designed to convert patients to alternate-day prednisone with the use of supplemental ACTH injections, while limiting daily prednisone and/or ACTH courses to 5 to 10 days where possible. Increased alternate-day prednisone was considered preferable to daily prednisone and was required in 5 patients (see Results). Of special interest are those patients who required increased total prednisone dosage and were maintained on 40 to 80 mg. of *alternate-day prednisone* (Patients 11, 12, and 16). After 4 months of alternate-day prednisone, despite the increased average dosage the responses to hypoglycemia in these patients had improved. Concomitantly, there was diminished clinical evidence of hypercorticism. The value of this protocol, as compared to previous methods of "weaning" from daily steroid administration, is that the disease can be controlled and the HPA axis recovery may occur even in patients who required increased amounts of steroid. The use of supplemental ACTH in this study was based on previous experience.<sup>4</sup> The present study does not clearly delineate the role of supplemental ACTH injections in conjunction with alternate-day prednisone, as properly controlled patients converted to alternate-day prednisone but not given ACTH injections were not studied.

The insulin and the intramuscular ACTH stimulation tests of HPA function have been widely used.<sup>1, 6, 7, 11, 14</sup> This is the first report in asthmatic patients of the plasma ACTH response to insulin-induced hypoglycemia. Prior studies

have suggested that chronic corticosteroid therapy initially leads to hypothalamic-pituitary suppression followed by adrenal suppression.<sup>15, 22, 23</sup> Measurement of plasma ACTH in addition to plasma cortisol permits hypothalamic-pituitary function to be studied independently of adrenal function. Plasma ACTH thus defines the hypothalamic-pituitary arm of the hypothalamic-pituitary-adrenal axis, and the plasma cortisol response to exogenous ACTH delineates the adrenal component. Prior to initiation of alternate-day prednisone, when a clear-cut difference in the functional state of the hypothalamic-pituitary versus the adrenal component was discernible the hypothalamic-pituitary component was more suppressed than was the adrenal (Patients 9, 12, 16, 18, and 19; Tables III and IV).

Graber and associates<sup>24</sup> studied HPA axis recovery in patients after abrupt cessation of therapeutic corticosteroids or after adrenalectomy. Hypothalamic-pituitary function appeared to return in 2 to 5 months, with the adrenal recovering by 5 to 9 months. Single plasma ACTH (bioassayable) and cortisol measurements were reported in their study. Our data support the conclusions of Graber and associates. Hypothalamic-pituitary-adrenal axis improvement occurred in asthmatic patients after conversion from daily steroids to alternate-day prednisone. Improvement in hypothalamic-pituitary function was demonstrable 4 months after conversion to alternate-day prednisone, with adrenal recovery more variable but usually occurring between 4 and 11 months.

Berson and Yalow<sup>25</sup> reported that stress, such as hypoglycemia, would rapidly release ACTH and that frequent plasma determinations were necessary for accurate assessment of hypothalamic-pituitary function. The superiority of a stress test with frequent sampling compared to basal values alone was illustrated by Patient 16 whose postconversion basal ACTH was nondetectable but in whom hypoglycemia evoked a brisk rise (Table IV). Had only basal ACTH been measured, improved hypothalamic-pituitary function would have been missed. Similarly, had only a postconversion basal ACTH been measured in Patient 11, the hypothalamic-pituitary function would have been considered normal. Yet hypoglycemia produced only a minimal increment in ACTH levels, indicating residual impairment of hypothalamic-pituitary function not detected by the single basal determination.

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