

CORTISONE IN THE TREATMENT OF PATIENTS WITH RAGWEED
POLLINOSIS. DETERMINATION OF CHANGES IN SENSITIVITY
OF THE MUCOSA PRODUCED BY PRE- AND CO-SEASONAL
CORTISONE ADMINISTRATION

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THE clinical improvement of some allergic diseases during the use of cortisone can be questioned no longer. However, it has not been sufficiently established by objective measurements that cortisone increases tolerance to allergens. It has been shown^{1, 2} that the quantitative skin reaction to the specific allergen or to histamine remains unaltered. The primary object of the present investigation was to study the effect of cortisone on the reactivity of the shock organs to the specific allergen. Rose and associates³ and Grob and associates⁴ found that ACTH increased the tolerance of patients to inhaled allergens. In a previous paper, Feinberg, Stier, and Grater⁵ described a method using ragweed extract in a series of dilutions to determine quantitatively the sensitivity of the conjunctival, nasal, and bronchial mucosas. Using this procedure, observations were made on the changes in the level of sensitivity of the mucosa produced by cortisone given out of season and during the ragweed pollinating seasons.

METHOD

Fourteen patients were selected, ranging from 13 to 61 years of age, giving a history of hay fever or asthma during August and September, and showing a positive skin test to ragweed pollen extract. None of this group had diabetes, tuberculosis, infections, or hypertension. One patient gave a history of an episode of hypertension after bilateral oophorectomy but had a high normal blood pressure on examination. Four patients had hay fever and 10 had both asthma and hay fever. Six had been undergoing desensitization therapy for periods varying from eleven months to fourteen years; 8 either had never had injections or had taken treatment for less than six months. In all but one patient, treatment was discontinued in the spring of the year. Since 2 asthmatic patients dropped out shortly before the ragweed season, 2 substitute asthmatic patients were selected for seasonal treatment.

Increasing concentrations of ragweed extract ranging from 300 to 90,000 pollen units (Noon) per milliliter (p.u.) were used for all tests. The test dose was delivered as one drop to the conjunctiva, the spray from seven compres-

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sions of the bulb of a DeVilbiss No. 33 nasal atomizer to the nasal mucosa and the aerosol from ten compressions of the bulb of a Vaponephrin nebulizer by inhalation. The end points were as follows: for the conjunctiva—itching, burning, and redness; for the nasal mucosa—itching, rhinorrhea, and nasal blocking; for the bronchi—cough, wheezing, or dyspnea, accompanied by significant diminution in the maximum breathing capacity (m.b.c.). Each patient had at least one determination of mucosal sensitivity before the season and before any medication was given and 12 patients had two or more such base line studies. During administration of the hormone the level of sensitivity was determined once or twice a week. The mucosal sensitivity titrations were carried out between two and four hours after the morning dose of medication.

The weight, blood pressure, urinalysis, number of circulating eosinophils, and general condition of the patient were determined at least twice a week. Supervision of ventilatory tests and the determination of end points were always done by one individual (R. A. S.). The pollen extracts were always administered by the same person (M. W.) and the sensitivity levels obtained in each determination were not known to the other, until the end of each period. The results of each titration period were filed separately and not assembled until the period of hormone administration was over.

During the spring of the year each patient initially received a seven day course of oral cortisone,* consisting of 100 mg. daily, given in four doses of 25 mg. each. If no increase of pollen tolerance was manifest in one week, the same dose of cortisone was either continued or increased for another week. A significant increase in tolerance was obtained in 5 patients receiving 100 mg. daily for seven days, 6 for fourteen days, and 1 for twenty-one days. Two patients showed a fall in sensitivity only after 200 mg. daily for seven days, having previously shown no change after the seventh and fourteenth day with 100 mg. daily.

At the onset of the pollen season, the patients were allowed to develop symptoms for several days before starting cortisone orally. Most patients began taking the drug August 21 to 23. Three began on August 28 and 3 on August 30. If symptoms persisted after two or three days the dosage was increased. As soon as two or three days had elapsed without symptoms the dosage was decreased. Thereafter, the minimal dosage of cortisone was used to maintain the patients with minimal symptoms. The first estimation of mucosal sensitivity was made while the patient was on the maximum dosage of cortisone. Subsequent estimations usually were made after the subject's medication had been decreased.

An attempt was made to determine the effect of cortisone on the absorption from the connective tissue^{6, 7} by estimating the time of disappearance of intracutaneous wheals produced by 0.2 ml. of various saline solutions consisting of histamine, histamine plus hyaluronidase, hyaluronidase in concentrations varying from 200 to 10 turbidity reducing units per ml., and saline solu-

*Cortone by Merck.

tion. The histamine used was a 1:1,500 dilution calculated as the free base. Initially fluorescein was incorporated in the solutions and the time for disappearance of fluorescence was estimated using a Wood's lamp. However, it was observed that fluorescein absorption did not parallel the fluid absorption. Thereafter, the end point was taken as the time when the skin over the injection site, when pinched up between the fingers, was no longer palpably thicker than the uninjected skin over the same area of the opposite forearm.

RESULTS

Clinical.—All of the patients obtained considerable relief under cortisone therapy. Asthmatic symptoms were more readily relieved than were hay fever symptoms. Table I indicates the effect of maximum doses of cortisone on the symptoms.

TABLE I

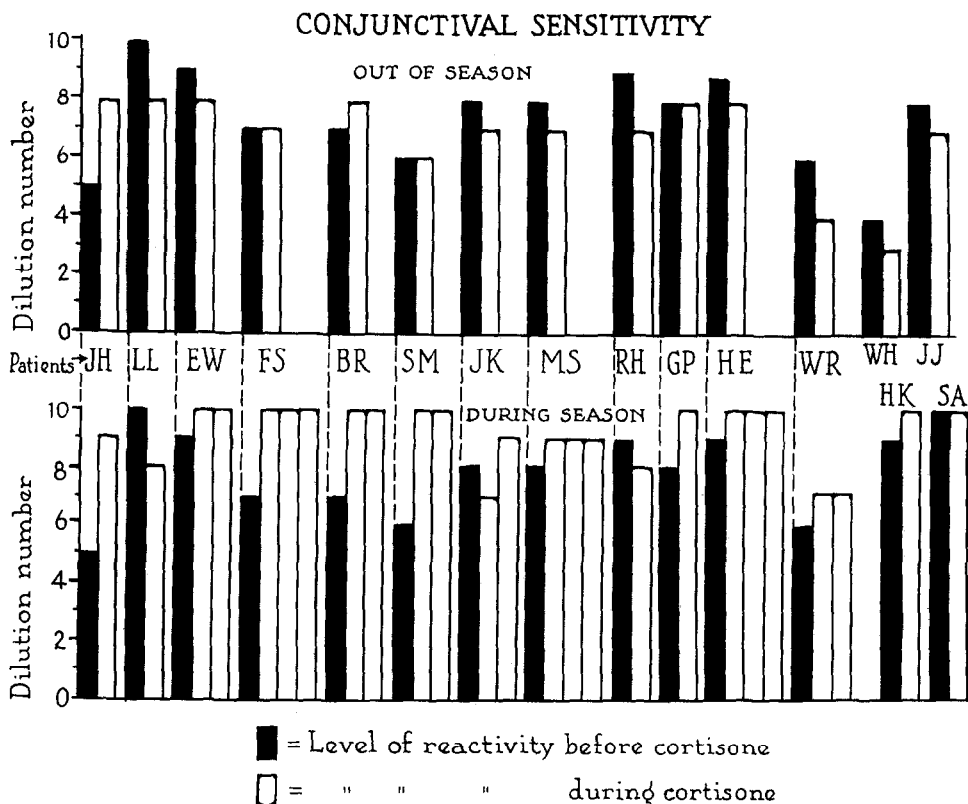
	HAY FEVER SYMPTOMS	ASTHMA SYMPTOMS
No relief	0	0
Partial relief	10	2
Complete relief	4	8

Six patients completely relieved of their asthma continued to have minimal to moderate hay fever. Of the four patients having hay fever symptoms only one obtained complete relief on 100 mg. daily; the others required 150, 200, and 200 mg. daily, respectively, and obtained only incomplete relief. One asthmatic patient obtained relief from asthma on 300 mg. daily but moderate rhinitis continued. Another asthmatic patient had incomplete relief of both hay fever and asthmatic symptoms on 100 mg. daily and probably received an inadequate dosage. The third asthmatic patient was incompletely relieved on 200 mg. daily and continued to be awakened each morning by mild asthma. His hay fever was promptly relieved by cortisone and did not recur. His was the longest period of treatment, 71 days, as well as the largest total dosage, 6.6 Gm., due to the marked postseasonal prolongation of asthmatic symptoms.

All patients required 100 mg. or more of cortisone daily to obtain their initial maximum relief. Four required 100 mg., one 150 mg., eight 200 mg., and one 300 mg. daily. The duration of treatment varied from eight to seventy-one days with 12 patients treated from thirteen to thirty-one days. The total cortisone dosage varied from 700 mg. to 6,600 mg. Ten patients received 2,200 to 2,875 mg. of the hormone.

Abrupt discontinuance of cortisone in the latter part of the season precipitated severe recurrence of rhinitis, often within six to eight hours and always within twenty-four hours. Asthmatic symptoms usually returned within twenty-four hours but were delayed two or three days in some cases. In contradistinction gradually decreasing doses over a period of ten to fourteen days tided the patients over the declining days of the season without any exacerbations upon cessation of hormone therapy. Late in the season some patients reported that moderate morning or evening symptoms were relieved

by 25 to 50 mg. of cortisone. However, since such symptoms are usually temporary and resolve spontaneously, it is doubtful whether these infrequent small doses were effective.



EFFECT of CORTISONE on RAGWEED POLLINOSIS PATIENTS

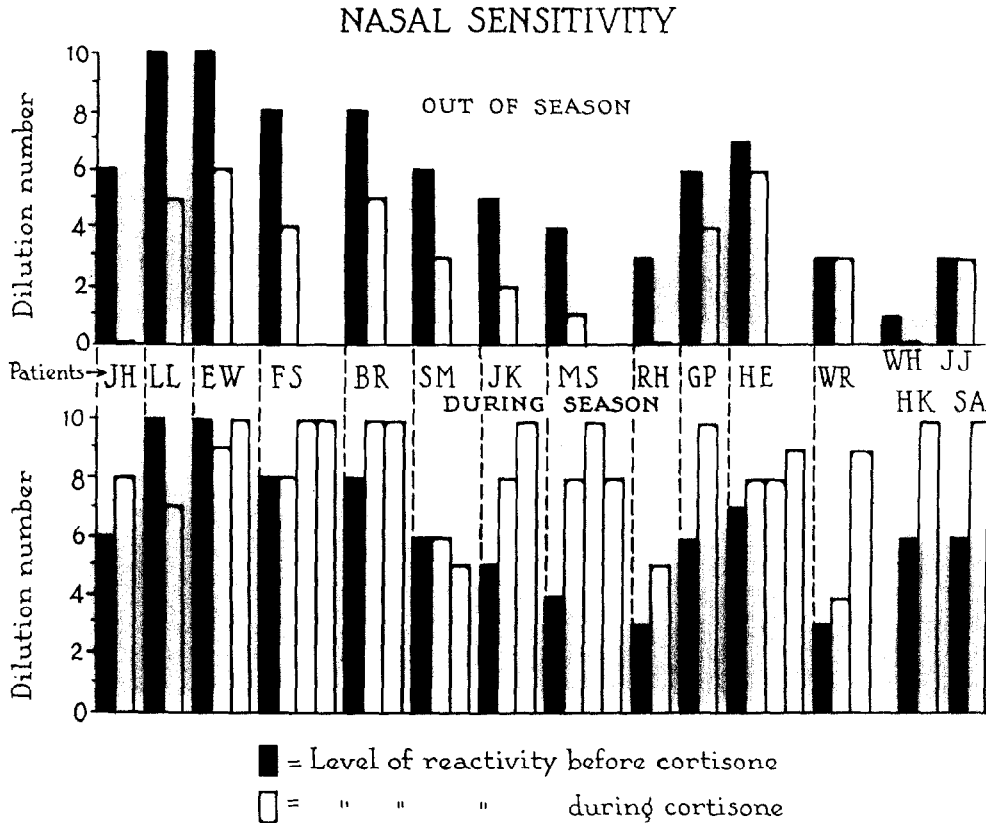
Fig. 1.

Figs. 1, 2, and 3.—Each graph represents the reactivity of the conjunctiva, nose or bronchi in individual patients before and after cortisone therapy. The height of a column designates the weakest dilution producing a response. The numbers indicate the strength of the solution, the weakest dilution being No. 10. The dark column is the level of reactivity before cortisone, the light after cortisone. The upper portion of each graph shows the values obtained when cortisone was administered out of season. The light columns in the lower portion of each graph indicate the values obtained after cortisone was administered during the hay fever season.

A high incidence of unpleasant side reactions was encountered. Ten or 71 per cent of the patients developed untoward symptoms that cleared when the hormone was discontinued or drastically reduced. Of these, individual minor complications were: insomnia, 5; transient glycosuria (with a blood sugar under 100 mg. per cent), 3; dysuria and polyuria, 2; rounding of the face, 1; headache, 1; nausea, 1; ankle edema, 1; and acne, 1.

The minor reactions that occurred in 8 (57 per cent) of the cases were present during maximum dosages of hormone and cleared up when the dosage was reduced. The insomnia began with euphoria, harder and longer periods of work, and inability to relax. The patients slept fitfully or not at all, even after taking barbiturates. In a few days they felt lethargic, worn out, and

depressed. Mild dysuria and polyuria in two women were not accounted for by abnormal findings in the urine and the symptoms cleared when the drug was decreased. Three patients experienced a gain of six to eleven pounds while on cortisone, but in each the weight gain was probably due to the voracious appetite. One of these patients had a transient ankle edema that disappeared while still on the hormone.



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Fig. 2.—For explanation, see Fig. 1.

Three patients developed such major reactions that the hormone had to be discontinued. One 18-year-old girl, on 200 mg. of cortisone daily, developed acneform pustules, one of which on her forehead went on to marked inflammation. When seen after twenty-four hours there was a rapidly spreading edema of her forehead. She had no fever, erythema, or local heat but the upper cervical lymph nodes were markedly swollen and exquisitely tender. She was hospitalized and given antibiotics with recession of the swellings. Subsequently, she tolerated 100 mg. of cortisone daily with incomplete relief of the rhinitis.

A 30-year-old woman required 300 mg. of cortisone daily for relief of asthma. She did not sleep for two days and became extremely weak and depressed to the degree of psychosis. Two days after stopping the drug she had recovered from her depression but again had severe hay fever and asthma.

The third patient, a 37-year-old woman, had previously received estrogens for a transient hypertension after bilateral oophorectomy. The highest blood pressure recorded before the season and during preseasonal cortisone was 150/90. Partial relief of her hay fever was obtained with 200 mg. of cortisone daily but she developed insomnia followed by a severe headache with blurring vision. Her blood pressure rose to 208/136. The headache and insomnia disappeared when the cortisone was stopped, but a blood pressure of around 216/122 persisted until estrogens were given again.

Since these severe reactions occurred on the thirteenth or fourteenth day the dose of hormone given in the first fourteen days could be compared with that for the other patients. The first 2 patients discussed above received the highest doses given in this fourteen day period, 2235 and 2200 mg. The third patient received 1600 mg. and ranked seventh in the amount given.

TABLE II

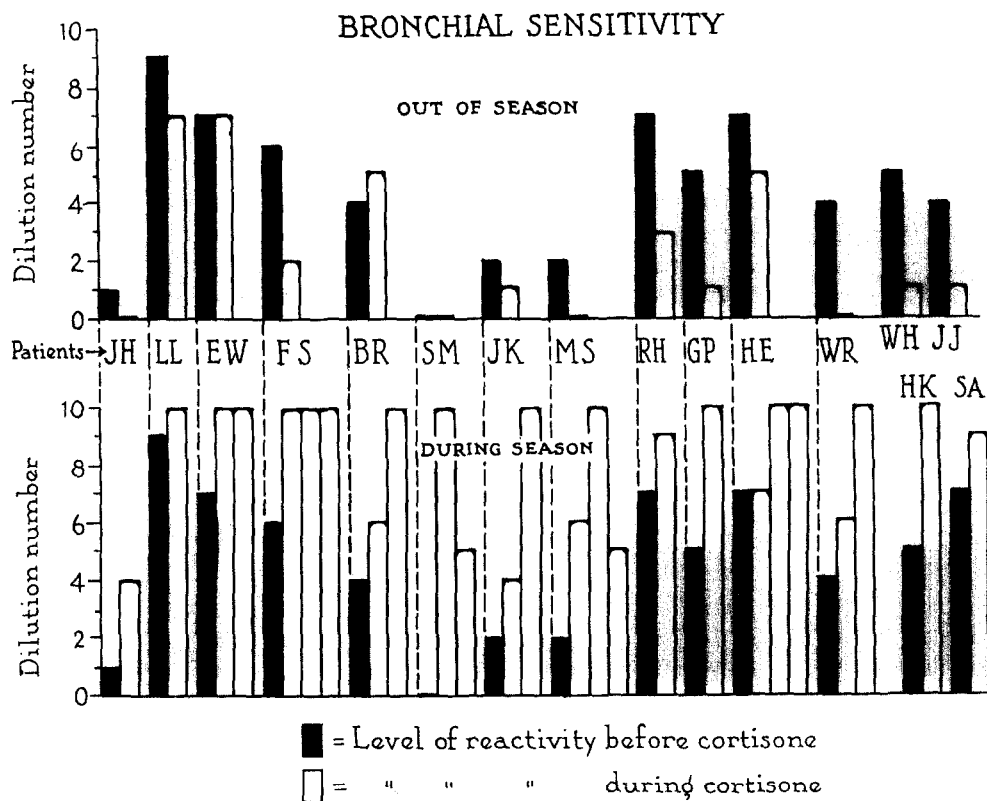
POLLEN UNITS (NOON) MIXED RAGWEED EXTRACT PER MILLILITER	REFERENCE NUMBER ASSIGNED EACH DILUTION
90,000	1
60,000	2
30,000 (1:33)	3
20,000	4
10,000	5
5,000	6
3,000	7
1,000	8
500	9
300	10

Experimental Studies.—Table II lists the concentrations of the ragweed extract dilutions and the reference numbers used in Figs. 1 to 3. In the upper portion of graphs, Figs. 1, 2, and 3, the changes in mucosal reaction levels before and during cortisone out of season are charted for each patient. The least change occurred in the ophthalmic sensitivity. Ten patients showed changes of one dilution or none at all. Three showed a decrease in sensitivity of two dilutions and one an increase of three during cortisone therapy.

The nasal sensitivity revealed the greatest change, with a decrease of two to six dilutions in 10 patients. Two patients showed a decrease of one dilution, 2 were unchanged, and 3 patients showed no reaction of the nasal mucosa from two applications of the most concentrated extract.

The bronchial sensitivity was also decreased by cortisone. The 4 patients with uncomplicated hay fever showed no reaction to pollen extract weaker than dilution No. 2 (60,000 p.u.), and in 2 there was an abolition of the bronchial reaction to the strongest concentration during cortisone treatment. These were patients J. H., S. M., J. K., and M. S. Ten had a decrease of from one to four dilutions. One was unchanged and one increased one dilution in sensitivity.

In the lower portion of Figs. 1, 2, and 3 the mucosal reactions determined before the season and before cortisone treatment are compared with the levels of reaction at the point of maximum cortisone dosage during the season. In addition, 8 patients received one or two more tests while on lower cortisone dosages. In nearly every patient there was a moderately to markedly increased sensitivity of each shock organ. The only significant decrease, two dilutions in the ophthalmic reactivity and three dilutions in the nasal test, occurred in patient L.L. while on 300 mg. of cortisone daily. The 4 patients with uncomplicated hay fever showed a marked rise in the level at which symptoms of tightness in the chest and cough could be produced. Auscultation of the chest never revealed wheezing at this time and the m.b.c. was diminished very little if at all.



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Fig. 3.—For explanation, see Fig. 1.

Patients needing the largest doses of cortisone to produce a decreased mucosal response before the season required 200 mg. a day or more of cortisone at the peak of the season. The best clinical relief was obtained in those patients showing the greatest decrease in sensitivity during preseasonal administration of cortisone. However, there was no significant correlation between the pre-seasonal dose and that required during the season.

During the preseasonal period of cortisone administration the level of circulating eosinophils was diminished by more than 50 per cent of the initial level in all but 3 patients. Nevertheless, these 3 patients showed a significant decrease in their mucosal sensitivity. With an increase in the dose of cortisone a further decrease in sensitivity occurred, but one patient still failed to show a fall in eosinophils. During the seasonal treatment with cortisone every patient showed a fall in eosinophils of over 50 per cent at the period of maximum dosage. There was no correlation between the degree of fall of eosinophils and the degree of symptomatic improvement. The first eosinophil determination after two days on a constant dose of cortisone was the lowest.

There was considerable variation in the time of absorption of fluid injected intracutaneously but in most instances a delay was observed. The wheals produced by normal saline disappeared in 15 to 120 minutes while on cortisone therapy, as compared to 13 to 85 minutes before treatment. The disappearance time of wheals produced by histamine before and during treatment paralleled but was somewhat longer than those for the normal saline—10 to 105 minutes before treatment and 16 to longer than 120 minutes during cortisone administration. The wheals from varying dilutions of hyaluronidase from 200 to 10 turbidity reducing units per ml. disappeared in half a minute to eighteen minutes with prolongation of the disappearance time during cortisone up to forty-five minutes; this was especially marked in concentrations below 50 units per ml. The skin underwent a different type of local reaction to hyaluronidase during cortisone administration. The erythema about the wheal was much more intense. Shortly after the swelling disappeared, it reappeared and persisted for an additional ten to thirty-five minutes longer. The phenomenon of recurrence was most marked at higher concentrations.

In 8 patients, reagin and thermostable antibody titers were determined before the ragweed season and shortly after the height of pollination while on cortisone therapy. There was considerable variation in the individual reagin titers, but no titer change was observed during treatment. Five patients had been receiving ragweed injections for over a year prior to May of 1951. Two of these, and one patient who had not received injections, showed thermostable antibody but no appreciable change in titer was detected during seasonal treatment with cortisone.

DISCUSSION

The therapeutic scheme of increasing the dose to parallel increasing symptoms and amounts of pollen in the air resulted in the largest dosage at the end of the first fourteen day period. It is possible that this scheme by favoring greater pituitary suppression, necessitated larger amounts for maximum effect than would be required if larger doses were used at the beginning of therapy. The increased amounts of hormone administered gave increased opportunity for the production of adverse reactions. Glycosuria without hyperglycemia appearing early in cortisone therapy and disappearing spontaneously was probably a result of increased glomerular filtration, as indicated by Earle and associates.⁹

Cortisone is not satisfactory as the sole treatment for most cases of seasonal allergy. Several patients requested a return to desensitization therapy in preference to suffering the same unpleasant reactions. The majority of patients felt they had experienced fewer hay fever symptoms with cortisone than they had had since developing their allergy. Although increasing and high cumulative doses are inadvisable, cortisone would seem to be of value for brief periods of time at the peak of the pollen season. Relief may be afforded those patients who obtain unsatisfactory results from desensitization therapy or who cannot reach sufficiently large doses of extract because of local or systemic reactions. The results of the titrations described suggest that cortisone exerts its effect most intensely on those tissues which constitute the specific shock organ rather than equally on all the mucous membranes. In other words, cortisone produces the greatest change where apparently the greatest abnormality exists. It is unlikely that cortisone should be selective in itself. Therefore, the alterations taking place in specifically sensitized tissues are reversible by the nonspecific ability of cortisone to alter the reactivity of all tissues.

An attempt was made to determine the mucosal sensitivity of the first 4 patients who presented themselves for cortisone treatment at the beginning of the ragweed pollinating season. A prompt and intense injection of the conjunctivas and paroxysms of sneezing or nasal blocking occurred in response to the greatest dilution of extract. After these exaggerated reactions all 4 patients declined to inhale the aerosol of the extract. Because of this experience, pretreatment assays during the season were abandoned. A study of the data comparing the sensitivity during the pollen season with that of the base line obtained before the season might lead one to conclude that cortisone caused no increase in tolerance. Actually cortisone increased the patient's tolerance sufficiently so that the airborne pollen produced only mild or no symptoms. This discrepancy between the results of the assays and clinical results is probably explained by the consideration that although cortisone diminishes the reactivity of the tissues to pollen, the dose to which the patient is exposed during the assay is the sum of the pollen applied artificially and that encountered naturally.

The patients with hay fever also showed a marked decrease in the tolerance of the bronchial mucosa during the pollen season. Symptoms were produced, often by the very dilute solutions, but there was little or no decrease in the m.b.c. The symptoms of cough and chest discomfort could have arisen from irritation of sensory nerve endings in the larynx, trachea, bronchi or bronchioles since apparently no diminution in the caliber of the bronchioles occurred. One patient with a history of a single stormy hay fever season consistently showed a slight decrease in m.b.c. during the season. The possibility of true asthmatic involvement is to be considered in this patient.

Asthmatic patients quite often would experience a recurrence of asthma about twelve hours after the estimation of bronchial sensitivity. Sometimes this would last for several days. Only a few patients on seasonal cortisone therapy noted transient and mild recurrences of chest tightness after the bronchial titration. It is known that patients suffering from pollinosis often

continue to have symptoms for some time after pollen disappears from the air. It is possible that seasonal cortisone therapy given such patients would decrease the severity of persistent bronchiolar changes.

The delay in the absorption of intracutaneously injected saline and of saline and histamine may indicate that cortisone impairs the absorptive mechanism. The ability of hyaluronidase to increase diffusion in connective tissue was diminished by cortisone. A reappearance of swelling after disappearance of the wheal produced by hyaluronidase was unexpected but may have a plausible explanation. Cortisone, by delaying the diffusion of hyaluronidase, causes a local retention of the enzyme in a higher concentration. The effect is an alteration of the ground substance of the local blood vessels permitting engorgement and exudation of fluid which results in a local recurrence of swelling. The increased erythema which was noted indicates some changes in the vascular response.

The symptomatic and objective improvement brought about by cortisone was not associated with any change in the circulating reagin or the thermostable blocking antibody. These findings are in conformity with the observations of other workers.^{1, 2, 10, 11}

SUMMARY

1. Fourteen patients having hay fever or a combination of hay fever and asthma due to ragweed were given oral cortisone. The hormone was administered for a short time several months before the ragweed season and again during the pollinating season. Changes in the mucous membrane sensitivity of the eye, nose, and bronchi were determined quantitatively during both periods.

2. Symptoms of hay fever were more difficult to control than were those of asthma.

3. Ten patients developed untoward reactions. Cortisone had to be discontinued in 3 patients because of severe complications. Reasons for this high rate of side reactions are suggested.

4. Cortisone given out of season decreased the sensitivity of the mucosa to ragweed extract. The greatest change occurred in the organs primarily affected.

5. After obtaining relief from cortisone administered during the pollinating season, a dilution of pollen weaker than that required prior to the season produced a reaction of the mucosa.

6. The time of disappearance of intracutaneously injected saline or histamine was somewhat lengthened by cortisone. The disappearance time of hyaluronidase was markedly prolonged. The altered reaction to hyaluronidase is discussed.

7. There was no detectable change in the titers of the skin sensitizing antibody or the thermostable antibody in the patients treated with cortisone.

REFERENCES

1. Leith, W., Graham, M. J., and Burrage, W. S.: Effect of ACTH on the Immediate Skin Reaction and Passive Transfer Test in Man, *J. ALLERGY* **22**: 99, 1951.

2. Feinberg, S. M., Dannenberg, T. B., and Malkiel, S.: ACTH and Cortisone in Allergic Manifestations. Therapeutic Results and Studies on Immunological and Tissue Reactivity, *J. ALLERGY* **22**: 195, 1951.
3. Rose, B., Pare, J. A. P., Pump, K., and Stanford, R. L.: Preliminary Report of ACTH in Asthma, *Canad. M. A. J.* **62**: 6, 1950.
4. Grob, D., Schoenrick, E. H., Winkenwerder, W. C., and Harvey, A. McG.: The Influence of ACTH on the Reactivity of the Bronchial Tree, Skin and Secretory Glands to Specific Antigens, Histamine and Mecholyl in Bronchial Asthma, *Proc. Second Clin. ACTH Conf.* **1**: 499, 1951, The Blakiston Co.
5. Feinberg, S. M., Stier, R. A., and Grater, W. C.: A Suggested Quantitative Evaluation of the Degree of Sensitivity of Patients With Ragweed Pollinosis, *J. ALLERGY* **23**: 387, 1952.
6. Opsahl, J. C.: The Role of Certain Steroids in the Adrenal Hyaluronidase Relationship, *Yale J. Biol. Med.* **22**: 115, 1949.
7. Forbes, G. B., Deisher, R. W., Perley, A. M., and Hartman, A. F.: Effect of Hyaluronidase on the Subcutaneous Absorption of Electrolytes in Humans, *Science* **111**: 177, 1950.
8. Earle, D. P., Alexander, J. D., Farber, S. J., and Pellegrine, E. D.: Observations on the Relation of Renal Function Changes to the Electrolyte and Glycosuric Effects of ACTH, *Proc. Second Clin. Conference* **1**: 139, 1951, The Blakiston Co.
9. Loveless, M. H.: The Influence of ACTH on the Sensitizing and Immunizing Antibodies of Inhalant Allergy, *Bull. N. Y. Acad. Med.* **27**: 496, 1951.
10. Cooke, R. A., Sherman, W. B., Menzel, A. E. D., Chapin, H. B., Howell, C. M., Scott, R. B., Myers, P. A., and Downing, L. M.: ACTH and Cortisone in Allergic Diseases; Clinical, Serologic (Electro-phoretic), and Immunologic Studies, *J. ALLERGY* **22**: 211, 1951.