THE OCCURRENCE OF ALLERGIC DISEASE IN PATIENTS WITH CUSHING'S SYNDROME

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THE concept of a relationship between adrenal cortical function and hypersensitivity reactions rests on studies linking these areas which have been recorded over many years.[1-3] More recently, extensive investigation of adrenal steroids and of adrenal corticotrophic hormone has been possible with observations of their effects on both naturally occurring allergic states and on experimentally induced hypersensitive states.[4, 5] That adrenal cortical steroids can influence allergic diseases has been well demonstrated. The clinical course of hay fever and of bronchial asthma has been measurably influenced by therapeutically administered cortisone.[6-8] The administration of ACTH, which induces secretion of endogenous adrenal cortical hormones, also favorably affects the allergic state.[9, 10]

Prednisone and prednisolone have been found to have comparable influences on the course of allergic diseases in therapeutic doses approximately one-fourth to one-fifth the effective dose of cortisone.[11, 12]

Additional steroid compounds differing in minor molecular configuration from cortisone are currently under investigation. Certain of these (for example, 9α-fluorohydrocortisone) have a greater influence on salt and water metabolism; others exhibit anti-inflammatory properties which appear to be correlated with effects on allergic states. Methylated derivatives of prednisolone and triamcinolone are being evaluated with respect to their influence on allergic diseases.[13, 14]

MATERIAL

We have studied the occurrence of allergic disease in a group of patients with Cushing's syndrome, which is primarily a disorder resulting from excessive secretion of cortisone-like hormones of the adrenal cortex. A series of 101 patients with this condition was studied at the Mayo Clinic. In each case unequivocal clinical evidence, and usually laboratory evidence as well, confirmed a diagnosis of Cushing's syndrome. Nineteen patients were observed to have tumors arising from the adrenal cortex, and eighty-two were found to have hyperplasia involving the adrenal cortex.[15] Five tumors were malignant and fourteen were benign adenomas. All patients were treated by either subtotal or total adrenalectomy.

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We have either examined and queried each patient concerning allergic diseases or reviewed his history for references to allergic disease in an effort to determine whether or not an association exists between the allergic state and Cushing's syndrome.

In those patients in whom Cushing's syndrome has developed, adrenal function has progressed from a state in which it was normal to one in which an excessive secretion of adrenal steroid has been manifest. After both total and subtotal adrenalectomy these patients have invariably been regarded as having potential or actual adrenal cortical insufficiency, and those undergoing total adrenalectomy have required maintenance doses of steroid preparations. After resection of a hyperfunctioning adrenal tumor, the remnant of adrenal cortex has been observed to be relatively hypoactive over periods of weeks to months, presumably as a consequence of the high preoperative titer of circulating adrenal corticosteroids.

RESULTS

We have found eight patients who presented allergic manifestations associated with Cushing's syndrome (Table I). Six of these had allergic reactions following the use of various drugs; the other two patients had bronchial asthma and allergic rhinitis which antedated the onset of Cushing's disease and which were present at the time that early manifestations of Cushing's syndrome developed.

TABLE I. THE OCCURRENCE OF ALLERGIC DISEASE IN PATIENTS WITH CUSHING'S SYNDROME

PATIENT	ALLERGIC MANIFESTATION	DRUG ANTIGEN	STATUS OF CUSHING'S SYNDROME AT TIME OF ALLERGIC REACTIONS	
			BEFORE OPERATION	AFTER OPERATION
1	Bronchial asthma; hay fever		See Fig. 1	See Fig. 1
2	Bronchial asthma; vasomotor rhinitis		See Fig. 2	See Fig. 2
3	Maculopapular drug rash	Potassium thiocyanate	Reaction	
4	Urticaria	Penicillin	Reaction	No reaction while receiving 50 to 200 mg. cortisone daily
5	Maculopapular drug rash	Dihydrostreptomycin		Reaction after first stage (no cortisone); no reaction after second stage (50 to 100 mg. cortisone daily)
6	Urticaria	Tetanus antitoxin; penicillin	Reaction	
7	Bullous dermatitis	Potassium iodide		Reaction while receiving 30 mg. of cortisone daily
8	Drug rash	Gantrisin		Reaction

Among those patients presenting drug allergy, sensitivity to several drugs was observed. The drugs included penicillin, dihydrostreptomycin, tetanus antitoxin, Gantrisin (3,4-dimethyl-5-sulfanilamido-isoxazole), potassium iodide, and potassium thiocyanate.

Patients with nasal allergy and bronchial asthma have been observed to experience changes in the severity of these diseases with the occurrence of Cushing's syndrome. Striking remissions of nasal allergic disorders and bronchial asthma were correlated with the development of Cushing's syndrome. With surgical extirpation of a major part of the functioning adrenal cortex, allergic symptoms recurred. A less clear-cut relationship was observed concerning drug allergy among patients with Cushing's syndrome. Reports of the eight cases follow.

CASE REPORTS

Case 1.—A 16-year-old white girl presented herself at the Mayo Clinic on March 6, 1950. She related a history and presented findings of Cushing's syndrome then of eighteen months' duration.

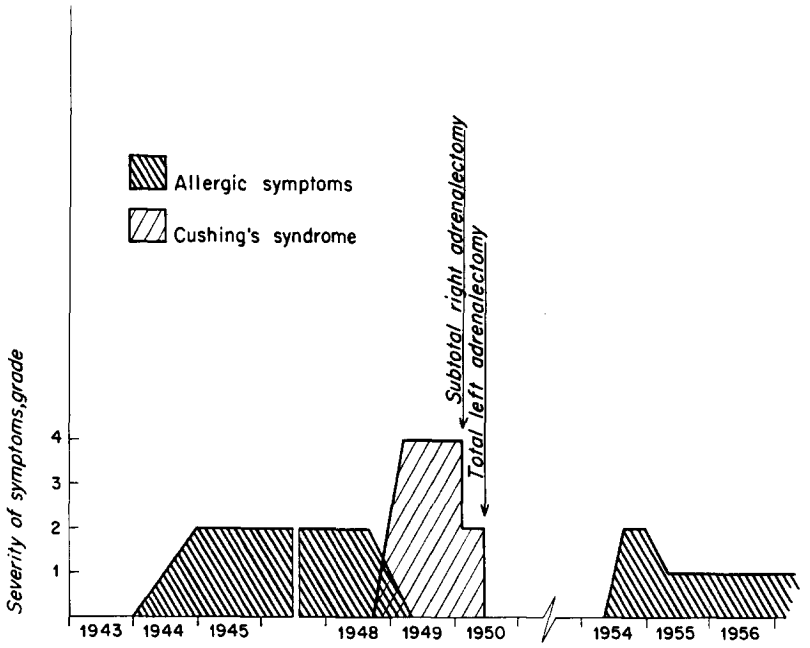

Fig. 1.—Allergic disease in Cushing's syndrome. Summary of data in Case 1.

On April 3, 1950, subtotal right adrenalectomy was performed and 6.5 grams, an estimated 90 per cent, of the adrenal gland was removed. The patient's convalescence following this operation was uneventful.

On June 24, 1950, exploration of the remnant of the right adrenal gland showed viable adrenal cortical tissue. Left total adrenalectomy was then done. The left adrenal gland weighed 11.6 grams and revealed cortical hyperplasia. Again, an uneventful convalescence followed operation. Although adrenal cortical extract was used during the early postoperative period, no maintenance program of steroid drug therapy was employed subsequently.

Three months after the second operative procedure there had been a striking remission in the manifestation of Cushing's syndrome.

The patient had a strongly positive family history of allergic disease. Her father had experienced eczema and asthma. An older sister was subject to eczema. A first cousin on the maternal side was asthmatic, as was a paternal uncle.

When the patient was 10 years of age, seasonal hay fever with both seasonal and perennial asthma had developed. She would experience exacerbations of asthma several times each year, usually following upper respiratory infections.

Six months after the insidious beginnings of Cushing's disease all allergic symptoms disappeared and were not manifested again during the period when Cushing's syndrome was present or for four years after its surgical correction; asthma then recurred. Asthma again developed after a severe upper respiratory infection and at a time when the patient was seven months pregnant. Subcutaneous injections of Adrenalin hydrochloride were required for symptomatic relief. Periodically since 1954 asthma has occurred in a mild form, particularly following respiratory infections, exertion, and breathing of cold air. The patient's seasonal hay fever recurred in 1956 (Fig. 1).

Case 2.—A 26-year-old white woman first presented herself at the clinic in 1940 with a history of asthma, then of five months' duration. It had occurred in the winter months and was associated with vasomotor rhinitis. An allergy survey revealed positive skin

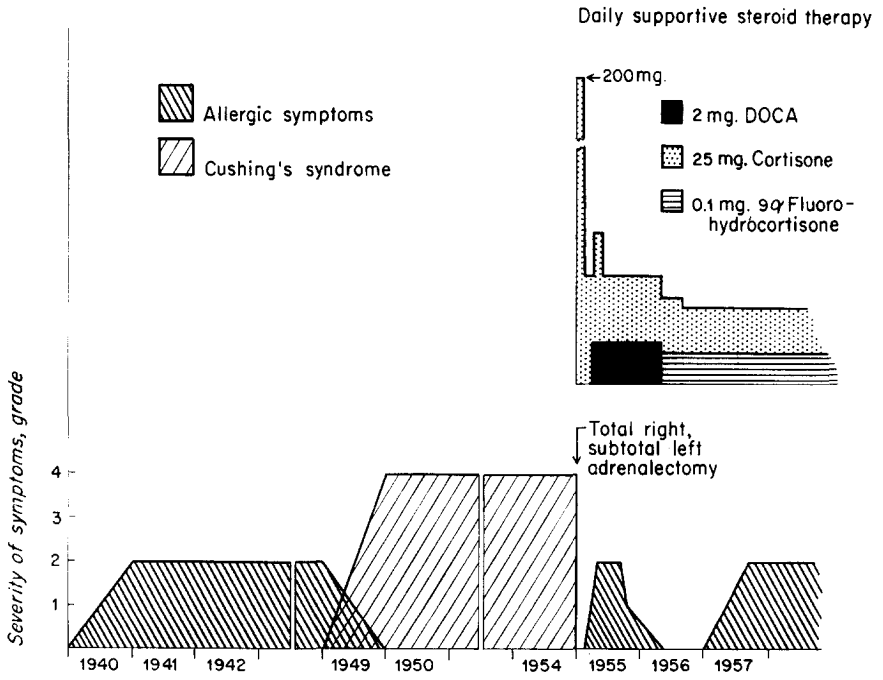

Fig. 2.—Allergic disease in Cushing's syndrome. Summary of data in Case 2.

reactions to dog and cattle hair, house dust, feathers, and certain ingestants. No other significant disease was observed in the course of studies on that occasion. Despite anti-allergic measures, the patient continued to have frequent exacerbations of bronchial asthma and vasomotor rhinitis, largely during the winter months.

In 1949, early symptoms of Cushing's syndrome developed. It is of considerable interest that with the onset of Cushing's syndrome the patient became entirely free from

bronchial asthma and vasomotor rhinitis and remained free for five years. At this time (December, 1954) she again came to the clinic and striking changes associated with Cushing's syndrome were apparent. On Jan. 3, 1955, the patient underwent total right adrenalectomy and subtotal left adrenalectomy. Her postoperative convalescence proved uneventful. Supportive measures included injections of cortisone in the early postoperative period and, later, 30 mg. daily of cortisone administered orally. For a short period in February, 1955, because of nausea, the daily dose of cortisone had been increased to 50 mg. with 2 mg. of Cortate being added to the regimen.

Progressive remission in symptoms and signs of Cushing's syndrome followed the surgical procedure (Fig. 2). Despite maintenance steroid therapy during the early postoperative course, however, a recurrence of moderately severe asthma developed within two months after surgical intervention. The asthma was of approximately the same degree of severity as that experienced prior to the onset of symptoms of Cushing's syndrome. It occurred in attacks requiring both ephedrine and injections of Adrenalin in oil for relief from nightly attacks.

The patient returned for postoperative evaluation of her Cushing's syndrome in April, 1955. An allergy survey undertaken to test her reaction to common inhalant allergens (miscellaneous substances, grasses, pollens, weeds, and molds prevalent in her community) revealed entirely negative skin reactions. A program of antiasthmatic measures was outlined in detail. These included precautions to avoid common inhalant allergens, abstinence from smoking, and measures to control bronchitis.

The patient was again seen in July, 1955, at which time asthma persisted and she still required continuing medication for symptomatic relief. In October, 1955, she was having less asthma and required relatively little medication for its control. On subsequent visits in July and November, 1956, the patient was having virtually no trouble with asthma and required no medication for its relief. The asthma recurred, however, in October, 1957. Its pattern was similar to that experienced prior to the onset of Cushing's syndrome.

In the management of Cushing's syndrome she was ultimately able to effect a further reduction in maintenance steroid therapy, until she required only 15 mg. daily of cortisone and 0.1 mg. of 9α-fluorohydrocortisone daily.

Case 3.—A 51-year-old white woman presented herself at the clinic on Aug. 25, 1945. She was observed to have classic Cushing's syndrome.

In June, 1945, 3 grains of potassium thiocyanate three times daily for four days of each week had been prescribed. After 2 months a maculopapular rash had developed over a wide portion of her back. She had discontinued the medication one week before she was seen at the clinic. The rash was already subsiding. She was seen in consultation in the Section of Dermatology, where she was considered to have dermatitis medicamentosa resulting from the use of potassium thiocyanate. The concentration of cyanate in the blood had not been determined during the period when she had used the drug.

The patient underwent right adrenalectomy on Nov. 9, 1945, and partial left adrenalectomy on Jan. 26, 1946. At the time of the first operation the skin reaction had subsided, and it posed no problem then or later in the course of the patient's management.

Case 4.—A 47-year-old white woman presented herself at the clinic on Sept. 19, 1953. She related a history of urticaria that had developed after oral ingestion of penicillin tablets one month prior to the time of examination. Clinically the patient was observed to have symptoms of Cushing's syndrome. These had been present for at least four years. Urticaria was not present at the time of her examination at the Mayo Clinic.

Right adrenalectomy was done on Oct. 6, 1953, and a cortical adenoma that measured 3 by 3 by 2 cm. was removed. The patient's postoperative course was complicated by right pleural effusion which on two occasions necessitated thoracentesis. It was of interest that during two periods totaling seventeen days in the postoperative phase of her care, the patient received penicillin by injection and on a third occasion she received penicillin by aerosol.

Urticaria from penicillin did not develop during the postoperative period. During periods when penicillin was administered and tolerated, however, the patient was receiving cortisone orally in daily doses ranging from 50 to 200 mg.

Case 5.—A 23-year-old white woman presented herself at the clinic in November, 1951, with Cushing's disease then of ten years' duration.

On Dec. 4, 1951, the patient underwent left subtotal adrenalectomy and right total adrenalectomy. Small nodules were encountered in both adrenal glands. These were considered to be "nonfunctioning" adenomas.

The patient's convalescence proved uneventful, aside from a maculopapular eruption which developed ten days after operation, spreading diffusely over much of the body within four days. It was thought to result from the injection of dihydrostreptomycin. With discontinuation of the use of this medication, the rash faded and disappeared within several days. Cortisone was not being administered when the rash appeared.

The patient returned in November, 1953, relating a history of initial regression in all symptoms of Cushing's syndrome. In the six months prior to her readmission, however, the symptoms of Cushing's syndrome had recurred. The remnant of the left adrenal gland was removed. During the postoperative period the patient was given one brief course of dihydrostreptomycin by injection without any evidence of intolerance. At the same time she was also receiving supportive doses of cortisone intramuscularly in doses ranging from 50 to 200 mg. daily.

Case 6.—A 44-year-old white woman first presented herself at the clinic in January, 1951. She had symptoms of Cushing's syndrome which had developed insidiously, beginning three years prior to her registration. Two-stage bilateral adrenalectomy was performed.

One year prior to her registration at the clinic, at a time when Cushing's syndrome was already established, tetanus had developed. Tetanus antitoxin was administered, as was penicillin. An urticarial reaction had occurred after the administration of these medications employed in the management of tetanus. The reaction had abated, however, and was no problem at the time the patient registered at the clinic.

Case 7.—A 43-year-old white woman presented herself at the clinic in September, 1950. She related the history of an illness of six months' duration. A diagnosis of Cushing's syndrome was made. The patient declined exploration of the adrenal glands, however, and no definitive treatment was undertaken.

She returned for further consideration on Jan. 28, 1952. On Feb. 19, 1952, bilateral total adrenalectomy was performed, after which the symptoms of Cushing's disease regressed. Bronchitis developed, however, as a sequel to an upper respiratory infection approximately two and one-half years later. An iodide expectorant was administered. In two days large, clear blebs developed on the skin; these were considered to be a manifestation of bullous dermatitis medicamentosa resulting from the use of iodides. With cessation of medication with iodides, the reaction promptly subsided. At that time the patient was being maintained on 30 mg. daily of cortisone.

Case 8.—A 20-year-old white woman was admitted to the clinic on June 14, 1954, with classic Cushing's syndrome. Symptoms were then of two years' duration.

On June 24, 1954, an adrenal cortical adenoma was removed with part of the left adrenal gland. The patient's convalescence proved essentially uneventful. In the course of her postoperative care, however, Gantrisin was administered because of a low-grade urinary tract infection. Following the use of this drug for two days (July 20 and 21), a skin rash developed which abated after discontinuation of the medication. The patient was not receiving any maintenance steroid therapy at the time the rash appeared.

COMMENT

The effect of adrenal cortical hormones on the hypersensitive state has been well established. It would appear that adrenal cortical compounds having

an "anti-inflammatory" activity are more effective in influencing the hypersensitive state than are substances directed primarily toward salt-and-water metabolism. The dosage of these hormones required to influence the hypersensitive state differs considerably. Steroids elaborated by the adrenal cortex are known to undergo many changes in the course of their intermediary metabolism, particularly within the liver. Individual variations in the intermediary metabolism of these substances may well exist. Disease processes may alter the pattern of these intermediary processes, thereby leading to an altered steroid structure. Perhaps the basis for the so-called allergic diathesis may lie within such congenital or acquired metabolic defects.

As yet, studies of the adrenal cortex have been concerned primarily with the quantitative aspect of adrenal cortical function. A consideration of qualitative changes as induced by various disease entities on hormones elaborated by the adrenal cortex is less well understood. Additional information may be derived from further study of patients having adrenal disease, by further study of altered steroid metabolism induced by other disease processes, and through further chemical separation or synthesis of steroid compounds. As the steroid preparations become available, their functions are being reviewed for possible influences on the allergic state.

It would appear quite possible that, as yet, we remain on the periphery of the problem of adrenal cortical disease and its relationship to the ephemeral "allergic state." It is possible that those adrenal cortical steroids already tested are effective only generally and not as specifically as other still unknown substances. Through studies correlating adrenal and allergic disease, the adrenal facet of the allergic state may be defined further.

SUMMARY AND CONCLUSIONS

At the Mayo Clinic eight of 101 patients with Cushing's syndrome were found to have histories or findings of allergic diseases. Among the patients having Cushing's syndrome were nineteen who had hyperfunctioning tumors of the adrenal cortex; five of the tumors were malignant. The remainder of the patients presented adrenal cortical hyperplasia. Of the eight patients presenting histories of allergic disease, six had experienced untoward reactions following the use of medications. Two patients presented histories of asthma and hay fever. An analysis of the course of the allergic disease during periods of relatively normal, increased, and decreased adrenal cortical function has been made.

It would appear that drug allergy may occur in patients manifesting either excessive or deficient adrenal cortical function. The occurrence of drug allergy was insufficiently frequent to warrant conclusions as to the possible effect of adrenal cortical functions on its course. Allergic reactions occurred both before and after the surgical correction of Cushing's syndrome by extirpation of the adrenal glands. However, large doses of cortisone administered during postoperative care effectively suppressed drug allergy when drugs which had previously elicited allergic reactions were given.

In patients having nasal allergy and bronchial asthma a study was made concerning the severity of allergic symptoms during periods of relatively normal, excessive, and deficient adrenal cortical function. These states existed prior to the onset of Cushing's syndrome, during the time the disease was active, and after the surgical removal of all or part of both adrenal glands or of adrenal cortical tumors. It would appear, from a review of the cases of two patients concerning whom extensive data were available, that the allergic state is ameliorated at times when Cushing's syndrome is active. Conversely, it would appear that surgical treatment for Cushing's syndrome by extirpation of much or all of the functioning adrenal cortical tissue is followed by a return of symptoms arising from allergic disease.

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