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A SUGGESTED QUANTITATIVE EVALUATION OF THE DEGREE OF SENSITIVITY OF PATIENTS WITH RAGWEED POLLINOSIS

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PROGRESS in the study of the therapy of allergy and changes in allergic status due to other causes has been hampered by the uncertainties of the usual subjective and objective measurements. It is true that ventilatory changes produced by asthma have been demonstrated.^{1, 2, 3} The maximum breathing capacity (m.b.c.), perhaps combined with vital capacity (v.c.) readings, gives considerable information about the presence or absence of bronchiolar constriction during an acute episode or experiment or over any extended time interval. But the bronchi are subject to numerous specific and nonspecific influences, and without controlling the allergenic cause a ventilatory determination at any one moment may be totally misleading. Neither the titer of the skin test response, the reaginic titer nor the amount of neutralizing antibody⁴ has any direct bearing on the severity of the clinical allergy or the therapeutic result from desensitization, ACTH, or cortisone.

It would seem reasonable, however, to presume that a diminution of symptoms referable to the respiratory tract would signify a lessened reactivity of the particular shock organ which should be demonstrable quantitatively. Attempts at testing the shock organ are by no means new. Blackley⁵ inhaled grass pollen to prove the etiology of his hay fever. Dunbar⁶ produced coryza by the application of pollen to the conjunctiva. Later, Noon and Cantab,⁷ using dilutions of grass pollen, followed the decrease in conjunctival sensitivity during a series of injections of grass extract. Duke⁸ suggested the application of substances to the ophthalmic and nasal mucosas as a diagnostic aid. He speculated on the idea that an inhalation test might be used to determine the cause of asthma. Vistreich, in a discussion of Blumstein's⁹ paper on nasal tests in diagnosis, suggested tests with serial dilutions of pollen solutions to prevent overdosage and to estimate sensitivity. Flamm, in the same

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discussion, proposed diluting the pollen with tale. Tuft and Blumstein¹⁰ used dry pollen diluted with an inert powder to determine the sensitivity of the nasal mucosa and to follow the course of clinical improvement from desensitizing injections. Stevens¹¹ used atomized extracts of various inhalants as a diagnostic measure, but abandoned the procedure after encountering delayed, severe asthmatic reactions lasting up to several days. All of these investigators found that normal subjects tolerated the largest doses given without developing typical hay fever or asthma.

The need for some quantitative assay became apparent in the investigation of the therapeutic effect of various procedures on hay fever and asthma. After a number of preliminary variations the following technique was adopted for the present.

METHOD

Antigen Titrations.—The present study is concerned only with ragweed extract in ragweed-sensitive patients. Undoubtedly, however, any inhalant substance could be used in a similar manner. Throughout the course of this investigation we employed the same lyophilized preparation of equal parts of giant and short ragweed extract. Prior to its use the 3 per cent lyophilized extract was redissolved in one-third of its original volume of saline (with phenol), thus making it a 9 per cent solution. Ten dilutions were prepared, ranging from 300 to 90,000 pollen (Noon) units per ml. The same solutions were used for all determinations of mucous membrane and skin sensitivities.

TABLE I

SOLUTION NUMBER	NUMBER OF POLLEN UNITS PER ML.
1	90,000
2	60,000
3	30,000 (1:33 or 3%)
4	20,000
5	10,000
6	5,000
7	3,000
8	1,000
9	500
10	300

Starting with Solution 10, a drop was placed in the inferior conjunctival sac. Every five minutes the concentration was increased until a reaction, consisting of itching, burning, and redness occurred. When this level was established the conjunctiva was flushed with normal saline containing 1:400 epinephrine. The opposite eye was used for control and comparison, and was either left untouched or was tested with the diluent.

Since nasolacrimal drainage often caused a reaction in the homolateral nostril, the nostril tested was on the opposite side from the eye subjected to the test. A spray of the extract was administered by seven compressions of the bulb of a DeVilbiss plastic nasal atomizer. The average delivery was 0.014 ml. with a range of 15 per cent variation. To minimize the inhalation of the spray into the bronchi the patient held his breath during the nasal adminis-

tration and at the completion of the spraying sniffed gently. Every five minutes the concentration was increased until a reaction was obtained, consisting of one or more of the following symptoms: itching, rhinorrhea, sneezing, and nasal blocking. The reaction was usually arrested by a spray of Pyribenzamine solution, with the addition of a 1:4000 epinephrine solution if necessary.

The bronchial tests were made with an aerosol obtained from a Vaponephrin nebulizer with a hand bulb. With care and practice a fairly constant rate of delivery of aerosol could be obtained from the ten bulb compressions used for each administration. The average delivery on each administration was 0.021 ml. with a variation of 8 per cent. A positive reaction occurred in one to three minutes and took various forms: oppression or tightness in the chest, wheezing, cough, or dyspnea. The attack of asthma thus precipitated was terminated, often only temporarily, by the inhalation of epinephrine or the use of some other sympathomimetic compound. Several hay fever patients who had no history of previous asthma developed a cough, itching of the throat, or chest discomfort, often severe, from strong concentrations of the extract; however, ventilation tests revealed little or no bronchiolar constriction. The production of pulmonary symptoms accompanied by significant diminution in the m.b.c. was taken as the end point for bronchial titration.

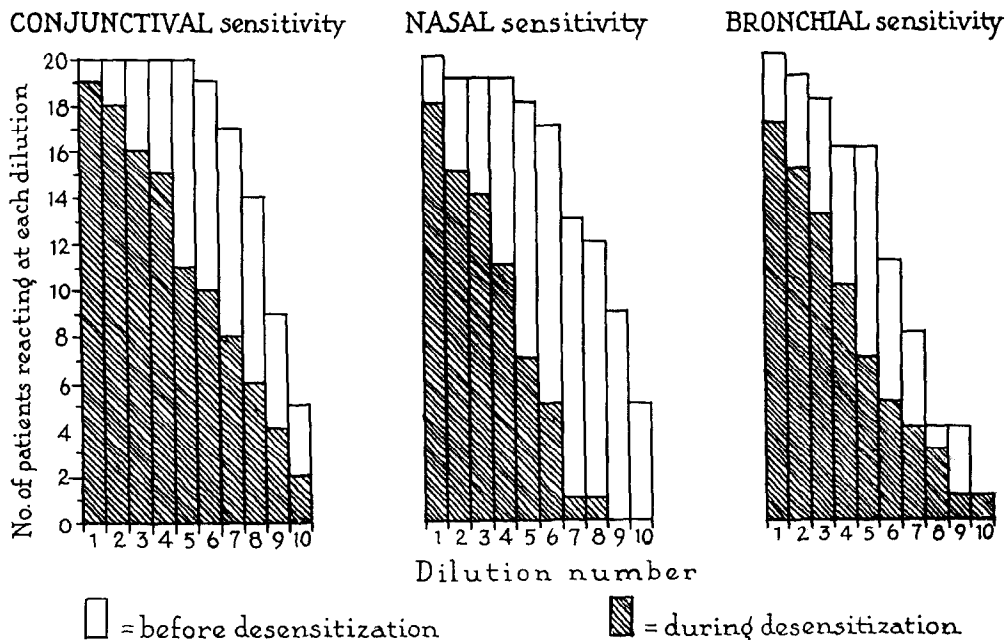
Ventilatory Function.—The vital capacity (v.c.) and maximum breathing capacity (m.b.c.) were determined at the beginning and at the completion of each set of mucous membrane titrations. The equipment consists of a rubber mouth piece, an inspiratory and expiratory high-velocity valve system, a Douglas bag, and a pocket-sized aneroid spirometer. This instrument has been shown by Cohen¹² to compare favorably in accuracy to the water bell type of spirometer. The vital capacity was determined at the beginning of the test period. While in the standing position, after a full inspiration, the patient exhaled completely into the spirometer. The best effort of at least three was recorded. Between administrations of bronchial test doses the v.c. was determined in order to detect any bronchial changes, according to the suggestions of Lowell and Schiller.¹³ After pulmonary symptoms were produced the best of at least three efforts was recorded.

Determination of the m.b.c., as has been pointed out by others,¹⁴ requires training of the subject. New patients were given adequate instruction, and then were shown the tests made on trained patients. Finally, after several short trials to get the feel, the test was performed. Since asthma attacks can be precipitated by this procedure, the test period was shortened from thirty to fifteen seconds. We found that the subject would select too shallow and rapid a level for maximum results if allowed to set his own volume. Consequently, the patient was instructed to make each breath about twice his tidal volume and to move this volume in and out as rapidly as possible. The timing was begun at the onset of the first expiration and the air was collected in the Douglas bag. The subject was encouraged and urged on during the test. At the end of fifteen seconds the bag was pinched shut and then emptied through the spirometer. This value multiplied by four gave the m.b.c.

At least twenty minutes must elapse between each performance of the test, otherwise fatigue plus alkalosis due to hyperventilation will diminish the effort expended by the patient. The best of several attempts was recorded at the beginning of the procedure and at the time when pulmonary symptoms had been induced.

RESULTS

This study is based on forty patients who underwent the testing procedure one or more times. There were twelve subjects whose symptoms consisted of hay fever only. Twenty-eight patients suffered from varying degrees of hay fever and asthma during the ragweed season. These 40 patients were evenly divided between those who had never had desensitization therapy or whose treatment was not over twelve months long in the aggregate and those who had had at least a year or more of intensive therapy. To illustrate the application of this method only one phase of the results is considered at this time.



EFFECT of DESENSITIZATION in RAGWEED POLLINOSIS PATIENTS

Fig. 1.

Fig. 1 shows the effect of desensitization upon the mucous membrane sensitivity. The 20 untreated patients were compared as a group with the 20 who had received desensitization therapy. Patients have not yet been followed long enough to compare the changes in the readings of individual subjects as a result of hyposensitization. In the treated group there was a definite decrease in the number of patients reacting at each dilution. This decrease was somewhat more marked in the titration of nasal sensitivity. Some patients in the treated group failed to react to two administrations of the most concentrated extract but none of these failed to react in more than one site tested.

The number of patients examined by this procedure is as yet too small to justify a more detailed presentation. However, certain trends have become manifest. There seems to be an indication that a shock organ specificity exists. The hay fever patients, while reacting to high dilutions in the nose, tolerate strong concentrations of extract by aerosol before developing symptoms. So far no hay fever patient without a history of asthma has reacted to an aerosol of a dilution weaker than number 6. The asthmatic patients react to much higher dilutions of aerosolized extract. Several asthmatic persons have been encountered, who tolerate strong solutions in the nose but are very sensitive to the inhaled aerosols.

Considerable variability from one titration to the next was encountered in some patients. Others were fairly consistent in their reaction levels when tested before or well after the ragweed season. Twelve patients who had no complicating sensitivities were repeatedly tested out of season with ragweed pollen extract and fairly consistent results were obtained. Out of a total of 96 determinations of mucosal sensitivity only eleven individual tests varied as much as two dilutions:

TABLE I

M. S.	<i>Eye</i> 9, 9, 9, 9;	<i>Nose</i> 10, 8, 10, 8;	<i>Bronchi</i> 5, 6, 5
E. W.	<i>Eye</i> 9, 10, 10, 10;	<i>Nose</i> 10, 10, 9, 10;	<i>Bronchi</i> 7, 8, 8
L. L.	<i>Eye</i> 10, 8, 8;	<i>Nose</i> 10, 8, 10;	<i>Bronchi</i> 9, 8, 9
H. E.	<i>Eye</i> 9, 7;	<i>Nose</i> 7, 9;	<i>Bronchi</i> 7, 7
R. H.	<i>Eye</i> 9, 8, 8;	<i>Nose</i> 3, 4, 4;	<i>Bronchi</i> 7, 6, 6
L. Van O.	<i>Eye</i> 10, 10;	<i>Nose</i> 8, 8;	<i>Bronchi</i> 6, 6
G. S.	<i>Eye</i> 5, 7;	<i>Nose</i> 1, 1;	<i>Bronchi</i> 2, 3
J. K.	<i>Eye</i> 8, 8, 7;	<i>Nose</i> 5, 5, 6;	<i>Bronchi</i> 2, 2, 2
B. R.	<i>Eye</i> 7, 8, 8;	<i>Nose</i> 8, 7, 8;	<i>Bronchi</i> 4, 4, 5
J. J.	<i>Eye</i> 8, 7;	<i>Nose</i> 3, 3;	<i>Bronchi</i> 0, 0
A. D.	<i>Eye</i> 10, 10;	<i>Nose</i> 5, 5;	<i>Bronchi</i> 9, 8
F. S.	<i>Eye</i> 7, 7, 7;	<i>Nose</i> 8, 6, 8;	<i>Bronchi</i> 6, 6, 6

A number of other patients tested repeatedly showed considerable variability. In many instances an unexpected high sensitivity could be explained by the presence of a high count of atmospheric grass pollen or mold spores and the fact that the patient was known to be sensitive to these antigens. One patient was consistent for three titrations until the winter when her sensitivity greatly increased. She was markedly sensitive to house dust and apparently had been having rhinitis from it. Another patient was tested shortly after a bout of infectious bronchitis and found to have a markedly increased bronchial sensitivity.

DISCUSSION

The level of reactivity of the mucosas of the eyes, nose, and bronchi of 40 patients is reported to illustrate the method. Generally, conjunctival reactions occurred in a larger per cent of patients than did nasal or bronchial reactions. The eyes are probably not more sensitive than either the nose or bronchi but with our technique received a greater dosage per unit of surface. It would appear that the conjunctival sensitivity could serve as a reference point for comparison of nasal and bronchial reactions and in a general manner reflects the over-all sensitivity of the contiguous respiratory mucosa. Thus, it seems

that earlier workers utilizing the conjunctiva for diagnostic and therapeutic testing^{6, 7, 15} may have had a valid basis for the estimation of clinical sensitivity. There also appears to be a correlation of the relative titer of sensitivity of each organ with the primary clinical picture of the patient. The hay fever sufferers manifest a high nasal sensitivity with low bronchial reactivity. The asthmatic patients have a high bronchial sensitivity with variable but generally high nasal sensitivity. This supports the clinical impression that the syndromes recognized as hay fever and asthma are determined at least in one respect by a difference in the relative sensitivity of the two "shock organs," the nasal and bronchial mucosa.

On the administration of strong concentrations of pollen extract the hay fever patient developed symptoms of cough, itching, and chest discomfort which often were quite troublesome, yet the m.b.c. was little if any diminished; whereas the act of extreme inspiration was accompanied by such distress and urge to cough that the v.c. was considerably diminished. Such a vital capacity determination cannot, however, be regarded as a true indication of the functional capacity of the lungs.

A phenomenon noted some time ago by Stevens¹¹ was encountered here also. After the bronchial symptoms were produced, patients were given an aerosol of some sympathomimetic agent for relief. Many also were given moderate doses of antihistamines to take during the next 12-24 hours. Nevertheless, several patients reported that upon retiring that night they noted a mild recurrence of the asthma. This symptom at times would occur for three or four subsequent evenings.

If such a "shock organ" specificity exists, it conceivably could involve any general region of the respiratory mucosa aside from the nasal and bronchial regions. We did find apparent tracheal and perhaps pharyngeal reactions in some patients. The sensations experienced at that time duplicated the patients' subjective experience during the season. These people did not manifest bronchoconstriction, so apparently the bronchi were not involved. Similarly the conjunctival mucosa could become a primary shock organ and perhaps such a condition exists in seasonal catarrhal conjunctivitis. However, the group tested did not include such a patient.

Of the 40 patients examined, 20 were untreated (or had minimal treatment) and 20 had had over a year of perennial desensitization. The general level of reactivity was definitely decreased in the treated group. The decrease in the level of nasal reactivity after treatment somewhat exceeds the decrease in the bronchial sensitivity. This might suggest that asthmatic symptoms are more difficult to control by desensitization than are hay fever symptoms. The experience of allergists is to the contrary. Several possibilities suggest themselves to explain this apparent discrepancy. The treated asthmatic patients included several subjects who had much higher bronchial than nasal sensitivity. Their bronchi then were the primary shock organ. These cases would weight the results in the treated group. It is also possible that naso-tracheo-bronchial

leakage had added to the dose of extract reaching the bronchi by aerosol. We are at present administering the bronchial aerosol before the nasal spray in order to evaluate this factor as a possible source of error.

As experienced by Tuft and Blumstein,¹⁰ we found considerable variation from titration to titration on individual patients. It is our impression that this variability is not a fault of the method but rather reflects the shifting reactivity of the respiratory mucosa in response to numerous and diverse factors. If grass pollen or mold spores were present in the air, patients sensitive to mold, grass, and ragweed pollen would require less ragweed extract to produce a reaction, even though at the time of the titration they were symptom-free. The presence of infection or other disease of the respiratory tract may lessen the amount of extract necessary to produce symptoms. By use of a room in which the amount of pollen in the air could be controlled, Holmes, Treuting, and Wolff¹⁶ demonstrated the influence that the emotional status and life situation have upon the threshold of mucosal reactivity. The variability present in these mucosal titrations reflects then the additive insult necessary to bring mucosal changes to their symptomatic threshold. Thus the greatest value of these titrations is not so much their absolute titers but rather in the changes they undergo in response to varying situations.

Many applications of this technique suggest themselves. Among these are the evaluation of the relative efficacy of various modifications of desensitization therapy, the determination of a level at which it is safe to discontinue treatment, the influence of drugs, and the effect of stress, emotion, pregnancy, and other nonspecific factors. Some of these studies are already under way, but more data and time will be required to arrive at any opinions. In a paper to be published¹⁷ our results with this technique in patients treated with cortisone will be described. This procedure is applicable to the use of any inhalant, and the results with other causative agents might prove informative, especially with respect to the effect of one factor upon the patient's response to another.

SUMMARY

1. A quantitative method is presented whereby the response of the eye, nose, and bronchi to a specific antigen can be determined.
2. Twenty patients with ragweed pollinosis without desensitization therapy showed a greater sensitivity than that found in another group of 20 ragweed sensitive patients who had had more than one year of such treatment.
3. There was correlation between the history of clinical symptoms in a particular shock organ and the degree of sensitivity as shown by quantitative tests in the various tissues.
4. The methods, or future modifications of it, should be applicable to the study of various factors. Among these are variations in procedures in desensitization therapy, modified allergens, the effect of various nonspecific factors and nonspecific therapy and the establishment of safe levels at which to discontinue treatment.

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