

Quantitative inhalation bronchial challenge in ragweed hay fever patients: A comparison with ragweed-allergic asthmatics

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Fourteen ragweed hay fever nonasthmatic patients comparably sensitive to a group of ragweed-allergic asthmatics by skin test and leukocyte histamine release were tested by quantitative inhalation bronchial challenge with ragweed extract. The provocation dose of ragweed extract producing 35% decrease in airway conductance was determined and designated PD_{35} . PD_{35} values in the hay fever patients were not significantly different from PD_{35} values in the asthmatic group. These data suggest that carefully performed skin tests may be as diagnostically useful as bronchial challenge in routinely confirming the allergic etiology of seasonal asthma.

The responses of ragweed-allergic seasonal asthmatics to skin tests, bronchial challenge, and basophil histamine release with ragweed antigens were compared in a recent paper¹ and found to be quantitatively similar and significantly correlated. This leads one to question whether a laborious procedure such as bronchial challenge adds any diagnostic information to that more easily obtained with other diagnostic techniques dependent on specific IgE antibodies.

Our initial studies of ragweed-asthmatic patients revealed their level of sensitivity to ragweed extract as measured by skin test or leukocyte histamine release to be no greater than that observed earlier in hay fever patients. The fact that the asthmatic group suffers bronchial constriction during the ragweed season suggests that the sensitivity of their bronchi to ragweed pollen is greater than that of hay fever patients. This hypothesis was tested by comparing the bronchial sensitivity to ragweed extract in a group of hay fever patients with a

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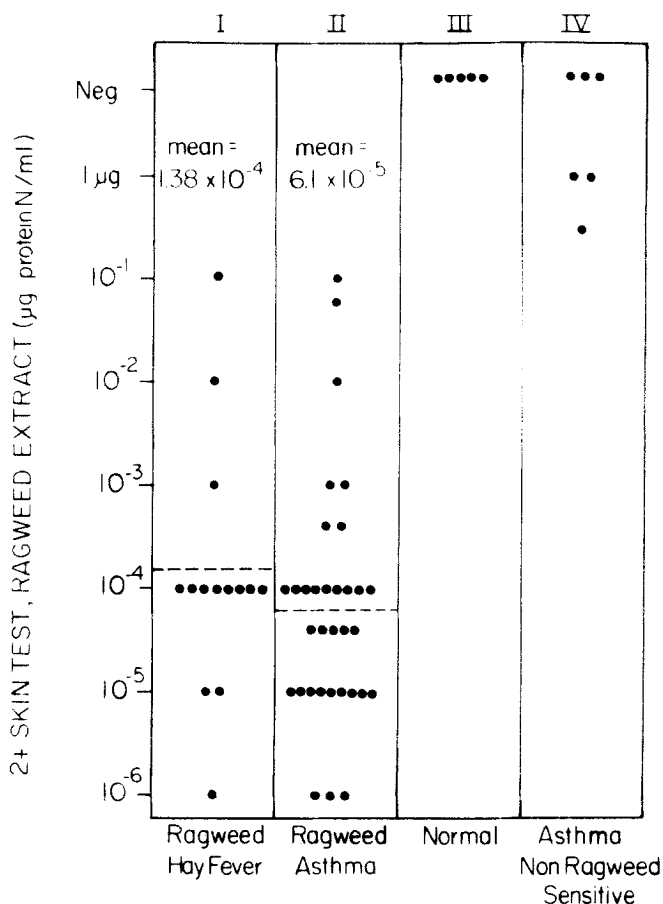


FIG. 1. 2+ skin response to ragweed extract in 4 groups of patients. For I vs II, $p > 0.3$.

group of asthma patients similar in skin and basophil sensitivity to ragweed extract.

MATERIALS AND METHODS

Fourteen ragweed hay fever patients who denied having ever experienced symptoms of asthma (group I), 33 ragweed-allergic seasonal asthmatics (group II), 5 normal subjects (group III), and 6 nonragweed-sensitive seasonal asthmatics (group IV) were included in this study. The patients were tested with serial dilutions of crude ragweed pollen extract (Center Laboratories, lyophilized Lot No. 16608FD) to determine the highest dilution required for a 2+ skin response (10-mm wheal and 20-30 mm erythema measured in 2 dimensions).^{1, 2} Skin tests were called negative if a 1- μ g protein nitrogen per milliliter concentration of ragweed extract did not induce a reaction.

Leukocyte histamine release with ragweed antigen E was performed using May's modification³ of the technique described by Lichtenstein and Osler.⁴ The concentration of antigen E producing 50% histamine release was interpolated from dose-response curves. Patients whose leukocytes released less than 50% of their cellular histamine are included in the data depicted in the figures but are not used for the statistical compilations.

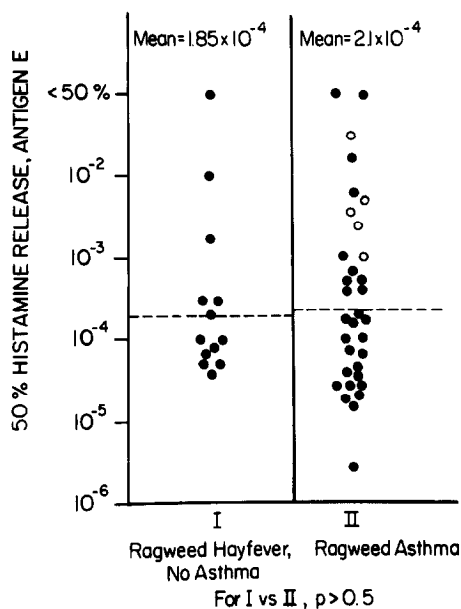


FIG. 2. 50% leukocyte histamine release to antigen E. Open circles indicate patients who initially were low histamine releasers (<50%), but who subsequently released 50% of their histamine.

Inhalation bronchial challenge tests were performed using a variable pressure body plethysmograph to determine specific airway conductance (S_{GAW}), as previously described.^{1, 5} The cumulative provocation dose of antigen producing a 35% decrease in airway conductance (S_{GAW}) was designated the PD_{35} . Antigen dose is expressed in units, with one unit defined as one breath of a 1- μ g protein nitrogen per milliliter ragweed extract solution. As reported previously,^{1, 5} there is a tenfold variation in bronchoprovocation results using the previously described method.

RESULTS

Fig. 1 represents the skin test data obtained from the 4 groups of patients. The concentration of ragweed extract required to produce a 2+ skin response in both ragweed-sensitive groups, hay fever patients and asthmatics, ranged from 10⁻⁶ to 10⁻¹ μ g protein nitrogen per milliliter. No significant difference was observed between these two groups. Three of the seasonal asthmatics from group IV with negative inhalation challenges at 1,000 U did have positive skin tests to ragweed, but only at concentrations as high as 0.3 or 1 μ g protein nitrogen per ml.

Fig. 2 shows the concentration of antigen E required for 50% leukocyte histamine release in the ragweed hay fever, nonasthmatic patients and the ragweed-asthmatic patients. One hay fever patient and 2 asthmatic patients released less than 50% of their cellular histamine to a concentration of 1 μ g/ml of antigen E. Five asthmatics represented by open circles in Fig. 2 initially were low histamine releasers, but on subsequent testing did release 50% of their cellular histamine to antigen E. The mean antigen E concentration required for 50%

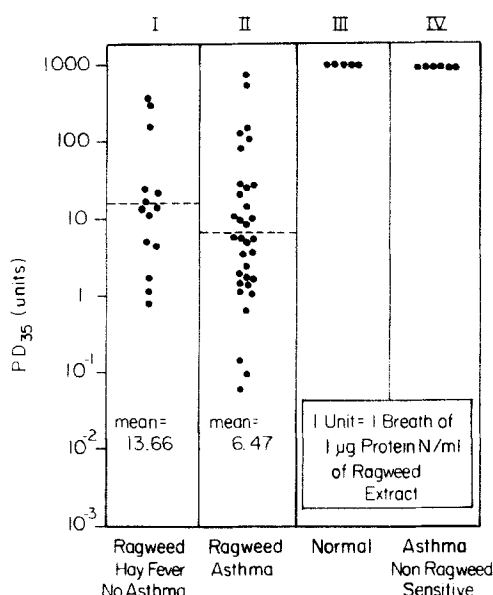


FIG. 3. Provocation dose (PD₃₅) of ragweed extract causing 35% decrease in airway conductance in 4 groups of patients. For I vs II, $p > 0.3$.

histamine release in the patients with only hay fever is 1.85×10^{-4} µg/ml, and in the ragweed asthma group is 2.1×10^{-4} µg/ml. This difference in basophil sensitivity to antigen E is not significant.

Fig. 3 summarizes the PD₃₅ values of all four groups of patients. The PD₃₅ range in the ragweed hay fever group is from 8×10^{-1} U to 350 U (mean = 13.66 U). In the ragweed asthma group the PD₃₅ range is from 6×10^{-2} U to 770 U (mean = 6.47 U). Although the mean PD₃₅ in the hay fever group is slightly more than twice that of the asthmatic group, the difference in the PD₃₅ values between the two groups is not significant. Neither the normal control subjects nor the nonragweed-sensitive asthmatic patients showed a positive response to inhalation challenge with ragweed extract. Marsh and associates⁶ estimate the actual annual dosage of antigen E in Baltimore to be in the range of a few nanograms per year. Therefore, the theoretical dose of antigen E delivered to a patient reaching a cumulative antigen dose of 1,000 U on bronchoprovocation is at least 500-fold greater than he would receive annually from natural exposure. We assume the pollen counts from our suburban Baltimore Rotoslide sampler to be representative of natural exposure since we have shown previously that symptom scores of highly sensitive ragweed hay fever patients correlate significantly with pollen counts, whereas symptom scores of poorly sensitive patients do not correlate with pollen counts.² The report by Busse, Reed, and Hoehne⁷ showed that there may be twice as much ragweed antigen present in the air in amorphous particles from ragweed plants than in ragweed pollen grains. These amorphous particles are smaller in size than ragweed pollen grains and are capable of reaching the bronchi. Even with the calculated

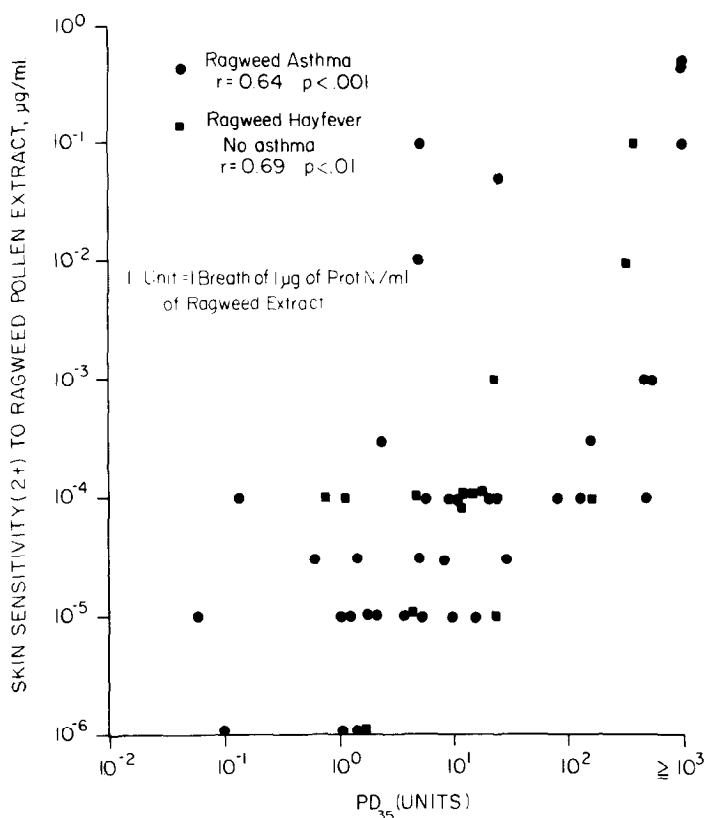


FIG. 4. Provocation dose (PD₃₅) of ragweed extract causing 35% decrease in airway conductance (abscissa) vs 2+ skin test response to ragweed pollen extract (ordinate) in ragweed asthmatic patients (closed circles) and ragweed hay fever, nonasthmatic patients (closed square symbols).

increased annual dosage of ragweed antigen from amorphous particles, however, the bronchoprovocation dose of antigen E at 1,000 U of ragweed extract is approximately 200-fold greater than the dosage with natural exposure. Therefore, patients with a negative challenge at 1,000 U are called nonragweed-sensitive.

Fig. 4 shows the relationship between the concentration of crude ragweed extract required for a 2+ skin response and the provocation dose of ragweed causing a 35% decrease in airway conductance in both ragweed asthmatics and ragweed hay fever, nonasthmatic patients. As we previously reported for ragweed asthmatics,¹ the correlation coefficient, r , is 0.64 ($p < 0.001$) when comparing 2+ skin response with PD₃₅. For the group with only ragweed hay fever, these tests correlate similarly ($r = 0.69$, $p < 0.01$).

DISCUSSION

Positive inhalation challenge tests in patients with hay fever, but without asthma, have been reported previously.⁸⁻¹² Townley, Dennis, and Itkin¹⁰ stress that on the average patients with asthma are 4 times more sensitive to inhalation

with pollen extracts than hay fever patients.¹⁰ However, their two groups of patients do not appear to be selected to be comparably sensitive by skin test. Moreover, hay fever and asthma patients were not necessarily tested with the same extracts since a variety of pollen sensitivities were present in their two groups. The difference in sensitivity to allergen challenge was not nearly as great as that observed with methacholine or histamine challenge.

Our data, obtained from ragweed hay fever and ragweed-asthmatic patients comparably sensitive by skin test and leukocyte histamine release, show no significant difference in mean PD₃₅ values in the two groups. This finding suggests that patients allergic to ragweed have IgE antibody on lung mast cells as well as skin mast cells and circulating basophils whether or not they manifest symptoms of asthma during natural exposure. Moreover, the failure of quantitative bronchial challenge with pollen extracts to differentiate ragweed asthmatics from patients with only ragweed hay fever suggests that bronchial challenge by this method is not specific for clinical asthma. In our studies so far, we have confined ourselves to measurement of airway conductance in the body plethysmograph, a technique that principally registers large airway responses. Qualitative differences in the responses of asthmatic and nonasthmatic patients may, however, be revealed when methods sensitive to changes in smaller or peripheral airways are employed. Studies of this possibility have been initiated. Nevertheless, the significant correlation between skin tests and quantitative bronchial challenge in these patients indicates that carefully performed skin tests are as diagnostically useful as bronchial challenge in confirming the allergic etiology of seasonal asthma.

It is important to note that these results are from studies of a single allergen in seasonal allergic asthmatic and hay fever patients in whom the diagnosis is not in question. Whether the relationships observed for ragweed-sensitive patients will be found in patients sensitive to other allergens remains to be seen.

In this study we have investigated mainly patients with positive skin tests. It is possible that some asthmatic patients with negative or very low skin tests to ragweed extract might respond to a bronchial challenge in a way that is diagnostically positive. However, 6 such patients reported here showed no response with challenges up to 1,000 U of ragweed extract. As already noted, this amount of ragweed is greater than the natural seasonal exposure to ragweed pollen.

Although we feel the correlation we have observed between skin and bronchial sensitivity in ragweed-allergic patients raises questions about according bronchial challenge a special place in the routine diagnosis of allergic asthma, the latter technique remains useful for research studies and drug evaluations.

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