

RAGWEED POLLEN DESENSITIZATION IN HAY FEVER
RELATIONSHIP TO SKIN TEST REACTION, DOSAGE, AND CLINICAL RESULTS

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IN A previous publication,¹ we discussed the question of the effect of specific pollen desensitization upon the skin test reaction. The responses to our questionnaire survey revealed a definite difference of opinion among practicing allergists concerning this point, similar to that contained in allergy textbooks² and in the literature. For example, most of those who responded felt that there was a distinct lessening of the skin test reaction; in fact, a few stated that they utilized the conversion of the reaction from positive to negative as an indication of remission or "cure" and based their cessation of treatment upon this finding. They agreed, therefore, with the opinions expressed in previous publications by Colmes³ and Vaughan,⁴ who likewise believed, from the results of their investigations, that cutaneous sensitiveness decreased considerably even from a single season's treatment and that this decrease could be utilized as a criterion of subsequent dosage.

A different opinion was expressed in other responses to the questionnaire by those who felt that pollen therapy had little or no effect upon the skin test reaction and that one should not depend upon this alteration to determine the clinical effect of treatment. This opinion was in accord with that expressed in previous publications by Markow and Spain⁵ and by Pearson,⁶ all of whom found, from their investigations, that treatment produced little change in skin test reactions and that even when a reduction took place, it was temporary. In view of the still prevalent difference of opinion among allergists, we attempted to provide more definite data by reviewing the case records of those ragweed hay fever patients who had received treatment regularly, both by the preseasonal method and by the perennial method, for periods of one to ten years or longer and who had been retested at varying intervals. These results were included in the report of our initial retest study in which we showed that pollen therapy apparently had little effect upon the skin test reaction except in those patients treated more than five years. In the latter group, there seemed to be definite reduction in a statistically significant proportion; however, the skin test became negative in only two patients in the entire series, and in both of them the reaction was reduced from slight to negative.

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In our first study we were concerned solely with changes in skin test reactions observed upon retesting, and therefore reported only the data which pertained to that phase. While we were reviewing this material, however, the opportunity presented itself to obtain more definite information regarding the effect of pollen therapy upon factors other than alteration in the skin test reaction, information which might interest the practicing allergist but about which, at least as indicated by a survey of the literature, difference of opinion still exists, perhaps because of a lack of more conclusive evidence. The present report contains the results of investigations of these factors. More specifically, we attempted to determine the following:

1. The effect of pollen therapy upon (a) the skin test reaction and (b) the clinical results.
2. The effect of dosage upon (a) the skin test reaction and (b) the clinical results.
3. The effect of the duration of treatment upon (a) the skin test reaction, (b) the clinical results, and (c) the dosage.
4. The effect of the method of treatment (perennial or pre-seasonal).

METHOD

As already indicated, we reviewed the case records of 200 patients with ragweed hay fever (referred to later as the "combined group"); 100 of these patients had received treatment each year by the preseasonal method, and the other 100 were treated perennially. The records were obtained from the private office files of the senior author (L. T.) and were selected by going through the file, starting with the letter "A" and continuing until 100 preseasonally treated and 100 perennially treated patients were obtained.

In making our selection, we tried, whenever possible, to choose patients with pure ragweed hay fever. However, clinical experience has shown that most hay fever patients have multiple sensitivities, both cutaneous and clinical. Thus, many have associated spring hay fever (grass and/or tree), others have perennial allergic rhinitis from sensitivity to allergens other than pollens (for example, inhalants or foods); and finally, some may have pollen asthma either associated with the hay fever or as the principal manifestation. When this is true, appropriate treatment is instituted in addition to ragweed pollen desensitization. These latter considerations apply to the 200 patients selected for study—in the majority, ragweed hay fever was the major manifestation but some had associated spring hay fever and/or perennial allergic rhinitis. A few had associated seasonal asthma, although none had pure pollen asthma. However, since most of our comparisons concerned only the sensitivity to ragweed and were made in the same patients, we felt that the presence of associated sensitivities or their treatment would not interfere significantly with the results obtained or with the statistical evaluation. This also was true of any comparisons between those treated preseasonally and those treated perennially, since the associated sensitivities other than ragweed in both groups were managed in the same manner.

All patients were tested initially with increasing concentrations (0.0001, 0.001, 0.01, and 0.1 mg. N) of ragweed pollen extract (standardized by the total N method) until a marked reaction was obtained. Subsequent retests always were done with the same concentration which produced the largest reaction; thus, if R. 0.01 gave a marked reaction initially, the patient was retested with this concentration on subsequent visits. The ragweed pollen extract was prepared from a mixture of equal parts of giant and dwarf dry ragweed pollen extracted in the standard manner, according to the Coca method. Fresh extracts were prepared at least twice a year, so that the extracts used in the retests usually were fresh ones and similar in most respects to the extracts previously employed. Furthermore, the same extracts employed for the tests also were utilized in treatment.

Finally, all patients, regardless of the method of treatment (preseasonal or perennial), were given appropriate medication needed for relief of any active hay fever symptoms, but in no instance was drug therapy utilized as the sole or major form of treatment or was it sufficient to interfere with proper interpretation of the results obtained.

In addition, we were careful to obtain the following data: the duration of treatment, the skin test reaction at the time of the initial test (and especially of the final retest), the interval between these tests, the change in reaction (decrease, no change, or increase), the maximum dosage (in total N) of pollen extract that the patient was able to tolerate without inducing either a severe local or a constitutional reaction, and the clinical results of treatment (listed as poor, fair, or good). The latter was largely a subjective determination dependent upon the opinion of the patient but was supplemented by the notes contained in the patient's history record. Since all but three of the patients had been retested each year with the same concentration of pollen extract and by the same person (V. M. H.) for a period up to nine years (1945 to 1953, inclusive), we felt that any possible variation in symptoms resulting from yearly difference in pollen exposure thus would be corrected and a fair comparison assured. All the results were subjected to expert statistical analysis* under the supervision of Dr. H. Hamilton. The figures obtained were calculated and analyzed according to standard statistical methods using the chi-square formula and the law of probability (p). In recording our results, therefore, we use the term "significant" to indicate that the relationships obtained were not chance ones, whereas the figures for " p ," showing the level of confidence, are included in the tables.

RESULTS

Effect of Pollen Therapy.—

Upon skin test reactions: The data obtained are similar to those already included in our first report¹ and are shown in Table I. It will be observed that a significant number (51 per cent) of the combined group showed a decreased

*The authors are grateful to Miss Eileen Beier for her statistical analysis of our data and to Dr. H. Hamilton, Professor of Psychology, Temple University, Philadelphia, Pennsylvania, for his supervision.

skin test reaction as compared with the number showing an increase (17 per cent) or even those showing no change (32 per cent). On the basis of these results, we can conclude that a decrease in skin reaction is significantly more likely to occur than an increase. This is true regardless of whether the method of treatment employed is preseasonal or perennial.

Upon the clinical results: The data obtained are also shown in Table I. Inspection of the table (vertical column marked with †) shows that a significant number (73 per cent) of the 200 patients had good results as compared with 20.5 per cent who had fair results and only 6.5 per cent who had poor results. Similar results were obtained for both the preseasonally and the perennially treated groups, indicating that the method of treatment had little effect upon the results.

Further analysis was made concerning the relationship of the clinical results of treatment to the alteration in the skin test reaction. Analysis of our data (columns in Table I marked with *) indicates that in the combined group the percentage (40.5 per cent) of patients whose reactions decreased had good results was considerably larger than those whose reactions either remained the same (22.5 per cent) or increased (10.0 per cent). These results were the same regardless of whether the patients were treated perennially or preseasonally.

TABLE I. EFFECT OF POLLEN THERAPY UPON SKIN TEST REACTIONS AND UPON CLINICAL RESULTS

CLINICAL* RESULTS OF TREATMENT	COMBINED GROUPS				PRESEASONAL GROUP				PERENNIAL GROUP			
	SKIN TEST REACTIONS*				SKIN TEST REACTIONS				SKIN TEST REACTIONS			
	DE- CREASE	SAME	IN- CREASE	TO- TAL†	DE- CREASE	SAME	IN- CREASE	TO- TAL	DE- CREASE	SAME	IN- CREASE	TO- TAL
Good	40.5	22.5	10.0	73.0	38.0	25.0	9.0	72.0	43.0	20.0	11.0	74.0
Fair	7.0	7.5	6.0	20.5	6.0	8.0	7.0	21.0	8.0	7.0	5.0	20.0
Poor	3.5	2.0	1.0	6.5	4.0	2.0	1.0	7.0	3.0	2.0	1.0	6.0
Total†	51.0	32.0	17.0		48.0	35.0	17.0		54.0	29.0	17.0	

*p = between <.05 and >.02 (statistically significant).

†p = <0.001 (statistically significant).

‡p = <0.001 (statistically significant).

(Note: All figures represent percentages.)

We may conclude, therefore, that pollen therapy in hay fever patients generally will produce good clinical results, especially in those whose skin test reactions decrease following treatment.

Effect of Dosage.—

Upon skin test reaction: Analysis of these data (Table II) showed that alteration in the skin test reaction was significantly related to dosage in the combined group. Inspection of the results obtained reveals, in the first place, that a majority (79.5 per cent) of the 200 patients were able to take pollen extract in dosages of 0.01 N or greater. In the latter group of patients, as indicated in the table, a higher proportion (43.5 per cent) of subjects with dosage of 0.01 N or over (vertical column marked with *) were more likely to have a decreased skin test reaction than either no change (24.5 per cent) or an increase (11.5 per cent), in contrast to those patients who received less

than 0.01 N in whom no similar relationship existed. This is even more apparent and significant in those patients who received a dosage of 0.1 N or over (vertical column marked with †), 11.5 per cent of whom showed a decreased skin test reaction compared with 2.5 per cent who showed no change and 0.5 per cent who had an increase.

TABLE II. EFFECT OF DOSAGE ON SKIN TEST REACTION (COMBINED GROUPS)

EFFECT ON REACTION	LESS THAN 0.01 N*	0.01 N AND OVER*	LESS THAN 0.1 N†	0.1 N AND OVER†
Decrease	7.5	43.5	39.5	11.5
Same	7.5	24.5	29.5	2.5
Increase	5.5	11.5	16.5	0.5
Total	20.5	79.5	85.5	14.5

*p = <0.05 >0.02 (statistically significant).

†p = <0.001 (statistically significant).

(Note: All figures represent percentages.)

These results suggest that the size of the dose reached apparently is related to the change in skin test reaction; that is, the larger the dose, the more likely is a reduction in skin test reaction to occur.

Upon clinical results: The data pertaining to the effect of dosage upon clinical results in the combined group are shown in Table III. Analysis of the

TABLE III. EFFECT OF DOSAGE ON CLINICAL RESULTS OF TREATMENT (COMBINED GROUPS)

CLINICAL RESULTS OF TREATMENT	LESS THAN 0.01 N	0.01 N AND OVER	LESS THAN 0.1 N*	0.1 N AND OVER
Good	12.5	60.5	59.5	13.5
Fair	5.5	15.0	20.0	0.5
Poor	2.5	4.0	6.0	0.5
Total	20.5	79.5	85.5	14.5

*p = <0.01 >0.001 (statistically significant).

(Note: All figures represent percentages.)

results obtained again reveals that pollen therapy, regardless of the dose, is more likely to bring about good results than either fair or poor results. But, in addition, the results obtained definitely show that the higher the dosage, the better are the results likely to be. Thus, as indicated in Table III, a significant percentage (13.5 per cent) of patients getting a dosage of 0.1 N or over (vertical column marked with *) had good results, compared to a total of 1.0 per cent having fair or poor results. This is a larger ratio (13.5 to 1) than patients getting a dosage of less than 0.1 N, in whom 59.5 per cent had good results compared to 26.0 per cent having fair and poor results. This would seem to indicate that the results of treatment in hay fever patients are influenced favorably by high dosages.

Effect of Duration of Treatment.—

Upon the skin test reaction: Since the length of treatment for patients in the combined group varied from one year to ten years or more, the data for different periods of time were analyzed. The results obtained are shown in Table IV. Inspection of the latter shows that the longer the patient is treated,

the more likely is the skin test reaction to decrease. This is particularly true of patients treated for one to five years, representing the majority (56 per cent), compared with those treated for more than five years (44 per cent).

TABLE IV. EFFECT OF DURATION OF TREATMENT ON SKIN TEST REACTION (COMBINED GROUPS)

EFFECT ON REACTION	1 YEAR	2 YEARS AND OVER	1 TO 5 YEARS*	6 YEARS AND OVER*	1 TO 10 YEARS	11 YEARS AND OVER
Decrease	4.0	47.0	24.5	26.5	43.5	7.5
Same	4.5	27.5	22.5	9.5	31.0	1.0
Increase	1.5	15.5	9.0	8.0	15.5	1.5
Total	10.0	90.0	56.0	44.0	90.0	10.0

*p = <0.02 >0.01 (statistically significant).

(Note: All figures represent percentages.)

As shown in the table (vertical columns marked with *), skin test reactions in subjects treated for more than five years are significantly more likely to decrease (26.5 per cent) than to remain the same (9.5 per cent) or increase (8 per cent), as compared with subjects treated for one to five years in whom 24.5 per cent show a decrease while 22.5 per cent remain the same and 9.0 per cent show an increase. Evidently, therefore, the longer the treatment is continued, the more likely is the skin test reaction to decrease.

Upon clinical results: The data pertaining to the effect of duration of treatment upon clinical results, analyzed for varying periods of time,* are shown in Table V. It will be observed at once that the longer treatment is

TABLE V. EFFECT OF DURATION OF TREATMENT ON CLINICAL RESULTS OF TREATMENT (COMBINED GROUPS)

EFFECT ON CLINICAL RESULTS	1 YEAR*	2 YEARS AND OVER*	1 TO 5 YEARS	6 YEARS AND OVER	1 TO 10 YEARS	11 YEARS AND OVER
Good	6.5	66.5	39.5	33.5	65.5	7.5
Fair	1.5	19.0	12.5	8.0	18.5	2.0
Poor	2.0	4.5	4.0	2.5	6.0	0.5
Total	10.0	90.0	56.0	44.0	90.0	10.0

*p = <0.05 >0.02 (statistically significant).

(Note: All figures represent percentages.)

continued, the better are the results likely to be. Thus, patients treated for two years or more are significantly (vertical column marked with *) more likely to have good (66.5 per cent) or fair (19.0 per cent), rather than poor results (4.5 per cent) than is true of those getting treatment for one year only. By the time patients have been treated for five years or longer, the results of treatment generally are good and they become increasingly better because fewer patients have either fair or poor results. This suggests, therefore, that the longer treatment is continued, the better are the clinical results.

Upon dosage: The data pertaining to dosage, analyzed for varying periods of time, are shown in Table VI. Inspection of the latter shows that the longer

*The authors realize that hay fever patients who obtain satisfactory results are more likely to persist in treatment than those who do not, but this contingency has been considered in the statistical evaluation by comparing the results for single years (for example, one year, two years, etc.). For the sake of brevity, these detailed figures have been omitted.

the patient is treated, the more likely is the dosage to be 0.01 N or over. This is especially true when comparing subjects treated for one to five years, representing the majority (56 per cent), with those treated for more than five years (44.0 per cent). As shown in the table, patients treated for more than five years are significantly (vertical column, Table VI, marked with *) more likely (38.5 per cent) to have a dosage of 0.01 N or greater than less than 0.01 N (5.5 per cent) as compared with patients treated for one to five years (41 per cent compared with 15 per cent).

TABLE VI. EFFECT OF DURATION OF TREATMENT ON DOSAGE (COMBINED GROUPS)

EFFECT ON DOSAGE	1 YEAR	2 YEARS AND OVER	1 TO 5 YEARS*	6 YEARS AND OVER*	1 TO 10 YEARS	11 YEARS AND OVER
0.01 N and over	5.5	74.0	41.0	38.5	71.0	8.5
Less than 0.01 N	4.5	16.0	15.0	5.5	19.0	1.5
Total	10.0	90.0	56.0	44.0	90.0	10.0

*p = <0.02 >0.01 (statistically significant).
(Note: All figures represent percentages.)

From the analysis of the data relating to the duration of treatment, we may conclude that longer treatment brings higher dosage, better clinical results, and eventual decrease in the skin test reaction.

Effect of Method of Treatment (Preseasonal or Perennial).—While some of the data pertaining to the method of treatment employed already have been included or mentioned in our previous analyses, we felt that it might be of clinical interest to summarize these observations separately. In the first place, we found that the method of treatment apparently has no influence upon the change in skin test reaction, although a decrease in reaction is significantly more likely than an increase, regardless of the method of treatment. Likewise, little significant difference was noted in the results of treatment, regardless of whether the patient was treated preseasonally or perennially. However, the dosage distribution was different for the two groups. Thus, the proportion of cases receiving dosages larger than 0.01 N was significantly higher for the perennial than for the preseasonal group.

These results indicate, therefore, that there is no significant difference in the relationship of the method of treatment to the change in skin test reaction or to the clinical results obtained, but the pollen dosage is likely to be higher in the perennial group.

COMMENT

Pollen desensitization in seasonal hay fever long has been such a well-established and relatively unchanged procedure that allergists have only a rather general impression as to the effects of pollen therapy and its relationship to such factors as skin test reactions, dosage, and clinical results. However to the novice or beginner devoid of such experience, or to the questioning patient, definite information about these factors is lacking. Recourse to the

literature or to allergy textbooks provides conflicting opinion and only generalizations based on clinical experience. This uncertainty was especially evident in the answers furnished by allergists to our questionnaire survey. Therefore, when either the patient or the physician asks about the effect of pollen therapy, especially about the length of time it must be carried out and the expected clinical results, the answers often are indefinite because they depend mostly upon impressions gained from the clinical experience of the attending physician or allergist. We believe that the results of the investigations herein reported supply more definite answers to some of these questions and help to clarify existing uncertainty.

First, for example, let us consider the question of the effect of pollen desensitization upon the skin test reaction. The belief that pollen therapy causes a progressive decrease in the skin test reaction¹ was verified. However, the reaction seldom becomes negative; furthermore, such a decrease is more likely to take place in patients who have had long-continued treatment (more than five years), and in those patients who can take high doses of pollen extract. On the basis of these findings, one can conclude that a decrease in the skin test reaction is likely, but it would be unwise to use either this decrease as a criterion of subsequent dosage or the reduction to negative as a basis for the discontinuance of treatment.

Another observation resulting from our studies relates to the effect of pollen desensitization upon the final clinical results. From their accumulated clinical experience, allergists generally have agreed with the statements contained in publications by Walker⁷ and Vander Veer and Clarke,⁸ showing that pollen therapy generally is effective, especially if continued long enough. Our studies support these findings, since we have shown that the longer patients are treated, the better are the results, especially in patients who also showed decrease in their skin test reactions and in those who tolerated higher dosages of pollen extract (0.01 N or more). That this was true, regardless of whether treatment was perennial or preseasonal, is of interest because of the widely held belief, exemplified by statements in the allergy literature⁹ and textbooks, that somewhat better results are to be expected after perennial treatment than after preseasonal treatment. In justification of the latter belief, however, it is our observation that a higher dosage level was reached by more patients in the perennial group than in the preseasonal group. This may be more apparent than real since, if the allergist finds that the patient cannot take higher dosages without an ensuing reaction, he usually will not recommend perennial treatment. The perennial group thus becomes a somewhat selective group of patients who can tolerate higher dosages; and, since they can do so usually for longer periods, the results in the perennial cases generally should be better. However, despite the general impression that results are better in the perennially treated cases, our studies show that the clinical results in both groups are about equal; therefore, so long as the

patient can take a high dosage and is treated for periods longer than five years, it makes little difference whether he is treated preseasonally or perennially.

Our observation that the duration of pollen desensitization favorably influences the clinical results is of interest in relation not only to pollen desensitization, but also to desensitization with other allergenic extracts (for example, molds, house dust, etc.) in conditions other than hay fever. Allergists sometimes find it difficult to decide how long they should continue desensitizing injections in patients who are feeling well and who are receiving their maximum tolerated dose, even at longer intervals. At times the patient settles it by discontinuing treatment, but in those willing to continue there is considerable uncertainty as to how long the injections should be continued or whether their continuance will bring about better results. There is uncertainty also as to how effective any type of desensitization is, whether in hay fever, asthma, or other allergic conditions. The results of our studies with pollen extracts lend further support to the clinical impression that long-term desensitization with allergenic extracts can be an effective therapeutic procedure.

Finally, our demonstration of the beneficial effect of high dosage also is of special clinical interest. While allergists generally try to administer the largest dose of pollen extract that the patient can tolerate, it sometimes is stated that the size of the dose does not necessarily influence the clinical result. That is, a patient could have a good clinical result even though his dosage is not high. While this may be true in some patients, our studies indicate that most patients do better with higher dosage.

SUMMARY AND CONCLUSIONS

A review of the case records of 200 ragweed hay fever patients who had been receiving treatment regularly, both preseasonally and perennially, and who had been retested at frequent intervals permits the following conclusions:

1. A decrease in the skin test reaction may follow pollen desensitization, but it is more likely in patients getting high pollen dosage and in those treated for more than five years, regardless of the method employed. It seldom becomes negative.

2. Pollen therapy in hay fever usually will produce good results, but this is more likely in patients whose skin test reactions decrease and also in patients who can take high doses of pollen extract.

3. The longer treatment is continued, the better the clinical results are likely to be.

4. The method of treatment, whether perennial or preseasonal, does not significantly influence the results obtained or the change in skin test reaction, although the dosage of pollen extract is likely to be higher in patients receiving perennial treatment because they are especially chosen for that group.

5. Our findings in these investigations of hay fever patients are helpful in relation to desensitization not only with pollen extract, but also with other allergenic extracts employed in allergic conditions other than hay fever.

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