

An assessment of the role of intradermal skin testing in the diagnosis of clinically relevant allergy to timothy grass

Harold S. Nelson, MD,^a John Oppenheimer, MD,^a Andrea Buchmeier,^a
Terance R. Kordash, MD,^b and Les L. Freshwater^c Denver, Colo.,
Spokane, Wash., and Elkhart, Ind.

Background: Immediate skin testing is generally the preferred method for establishing the presence of allergy in clinical practice. There is no agreement, however, as to whether intradermal testing should be routinely performed if skin prick test results are negative.

Purpose: The study was done to address the value of intradermal skin testing in the diagnosis of clinically significant sensitivity to grass pollen in patients exhibiting negative skin prick test responses to timothy extract.

Methods: Four groups were studied. Group I had a history of seasonal allergic rhinitis, negative skin prick test responses to timothy and Bermuda grass, but positive intradermal skin test responses to timothy grass. Group II had a history of seasonal allergic rhinitis and positive skin prick test responses to timothy grass. Group III had a history of seasonal allergic rhinitis but had negative responses to both prick and intradermal testing with timothy and Bermuda grass. Group IV had no history of rhinitis, had negative responses to skin testing with a panel of locally important allergens, as well as Bermuda and timothy grass, and had a serum IgE value of less than 20 IU/ml. Clinical sensitivity to grass was assessed by two methods: (1) nasal challenge with threefold increasing amounts of timothy pollen performed out of the pollen season and (2) correlation of subjects' daily symptom and medication scores with daily grass pollen counts during the grass pollen season.

Results: On the basis of nasal challenge with timothy grass, pollen allergic reactions were present in 11% of group I, 68% of group II, 11% of group III, and 0% of group IV. As determined by correlation of symptoms during the grass pollen season with grass pollen counts, 22% of group I, 64% of group II, 21% of group III, and 0% of group IV were considered allergic. If both criteria were required for a diagnosis of clinical allergy to grass, the percent positive was 0 for group I, 46 for group II, 0 for group III, and 0 for group IV.

Conclusion: Under the conditions of this study the presence of a positive intradermal skin test response to timothy grass (1000 AU/ml) in the presence of a negative skin prick test response to timothy grass (100,000 AU/ml) did not indicate the presence of clinically significant sensitivity to timothy grass, and by inference, to other cross-reacting grasses. (*J Allergy Clin Immunol* 1996;97:1193-201.)

Key words: Intradermal skin testing, timothy grass, skin prick test, seasonal allergic rhinitis, pollen

From ^athe Department of Medicine, National Jewish Center for Immunology and Respiratory Medicine, Denver; ^bMiles Inc., Allergy Products Division, Spokane; and ^cMiles Inc., Elkhart Area Site.

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Reprint requests: Harold S. Nelson, MD, National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson St., Denver, Colorado 80206.

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Immediate skin testing is the generally preferred method for establishing the presence of allergy in clinical practice. It is frequently recommended that the initial skin testing be performed by the percutaneous method because of its greater safety.¹ Although a common practice, there is no general agreement as to whether, in the absence of reactivity on percutaneous testing, intradermal skin testing should be routinely performed.² The poten-

Abbreviations used

AU:	Allergen unit
FAMC:	Fitzsimmons Army Medical Center
NJC:	National Jewish Center for Immunology and Respiratory Medicine
SPT:	Skin prick test

tial advantage of intradermal skin testing is its greater sensitivity; however, this procedure results in increased discomfort and cost.¹ Furthermore, there is the possibility that routine use of intradermal skin testing can lead to the institution of unnecessary and ineffective allergy immunotherapy if it leads to an overestimation of the presence of clinically significant allergy.

This study was designed to re-examine the value of intradermal skin testing in the diagnosis of clinically significant sensitivity to timothy and related grass pollens in patients exhibiting a negative percutaneous test response. To prove clinically relevant sensitivity to grass, we used two methods: nasal challenge with timothy pollen grains and examination of the correlation of each subject's daily symptom and medication scores with the daily grass pollen counts during the grass pollen season. The underlying assumption was that a subject with clinically significant allergy to grass should report increased symptom severity when exposed to grass pollen either in the laboratory or in the environment.

METHODS

Subjects

Subjects 18 years of age or older, who met the inclusion and exclusion criteria, were recruited for one of four groups. None of the subjects reported a history of bronchial asthma or use of asthma medications. None of the subjects exhibited dermatographism. Immunotherapy had been administered to two subjects in group 1, six subjects in group 2, and four subjects in group 3; however, no subject had received this form of treatment more recently than 1982. No subject was known to have nasal polyps.

The subjects in group I had a history of symptoms of seasonal allergic rhinitis. They had a negative skin prick test (SPT) response to timothy grass (100,000 AU/ml) and to Bermuda grass (100,000 AU/ml). They exhibited a positive intradermal skin test response to timothy grass (1000 AU/ml).

The subjects in group II gave a history of seasonal allergic rhinitis symptoms. They had a positive SPT response to timothy grass (100,000 AU/ml).

The subjects in group III gave a history of symptoms of seasonal allergic rhinitis. They had negative SPT

(100,000 AU/ml) and intradermal test (1000 AU/ml) responses to both timothy and Bermuda grasses.

The subjects in group IV denied both personal and family history of symptoms of allergic rhinitis, had all negative skin test responses to a battery of 25 allergen extracts as determined by prick testing, negative responses to timothy and Bermuda grass as determined by intradermal testing at 1000 AU/ml, and a total serum IgE of less than 20 IU/ml.

Skin testing

Twenty-five extracts representing the predominant seasonal and perennial allergens in Colorado were used for skin prick testing. They included six trees, two grasses, six weeds, cockroaches, house dust mites, animal danders, and four fungi. Skin prick testing was performed with the most concentrated glycerinated extract available (all pollens, 1:20 wt/vol).

Skin prick testing was performed on the back with at least 5 cm distance between adjacent sites. A lancet (Miles, Inc., Allergy Products, West Haven, Conn.) was used for pricking. The lancet was pushed downward thorough a drop of extract into the skin at a 90-degree angle to the skin. This device has been shown to consistently produce a wheal of less than 3 mm in diameter when tested on the back with phenol-saline.³ In addition to the standard SPT test battery, timothy and Bermuda grass extracts were tested in duplicate—both at 100,000 AU/ml and timothy at 10,000 AU/ml.

Intradermal skin tests were performed with timothy and Bermuda grass extracts only in subjects with negative SPT responses. They were performed in duplicate with 1000 AU/ml concentrations on the upper outer arm by the injection of 0.02 ml of extract with a 1 ml disposable syringe and 27-gauge hypodermic needle. To blind the subjects to the results of their skin testing, patients with positive SPT responses to timothy grass had two additional intradermal skin tests with the histamine control solution. Therefore all subjects underwent the same total number of prick and intradermal skin tests.

Control skin tests were performed with 50% glycerin (prick) and 0.03% human serum albumin phenol-saline (intradermal) and with histamine phosphate 1.8 mg/ml histamine base (prick) and 0.0018 mg/ml histamine base (intradermal).

Criteria for positive SPT responses were a wheal of 3 mm or greater in diameter with erythema of at least 5 mm. Criteria for a positive intradermal skin test response were a wheal of 6 mm or greater with definite erythema. Histamine control skin tests were read at 10 minutes. Allergen and negative control skin tests were read at 15 minutes.

Allergen extracts

All extracts were obtained from Miles, Inc., Allergy Products. All nonstandardized extracts were in 50% glycerin. Freeze-dried standardized extracts were recon-

stituted in 50% glycerin for prick testing. Dilutions for intradermal skin testing were made with phenol-saline containing 0.03% human serum albumin. The same material was used for prick testing throughout the study. Fresh dilutions of extracts for intradermal testing were prepared weekly.

Pollen counts

Pollen counts were performed throughout the study (May 1, 1993 to July 15, 1993) at two sites, approximately 6 miles apart. Counts were performed at Fitzsimmons Army Medical Center (FAMC) Allergy Clinic by using a Rotoslide sampler (Aquebogue Machine and Repair Shop, Aquebogue, N.Y.). Slides were counted on the 5 weekdays, with counts for Saturday and Sunday estimated from the Friday count. Sampling at the National Jewish Center for Immunology and Respiratory Medicine (NJC) was performed with a Burkhard Spore Trap (Burkhard, Rickmansworth, Hertfordshire, England). Slides were counted 7 days per week at the NJC site. Counts from the two sites, one (NJC) representing the city of Denver and the other (FAMC) representing a suburban setting, were averaged to yield a daily grass pollen count.

Nasal challenge

Nasal challenges were performed with the subjects blinded to the results of their skin tests. The challenge was performed first with lactose, then with 12 threefold serially increasing doses of timothy grass pollen (Miles, Inc., Allergy Products) mixed with lactose. The initial dose was 50 pollen grains, and the final dose was 885,350 grains. The pollen-lactose mix was placed in a capsule, and the selected dose was insufflated into one nostril with a Rhinochrom dispenser (Fisons Laboratories, Loughborough, England).

Throughout the nasal challenge, the subjects recorded symptoms, which were scored as follows⁴: sneezes (3 to 4 times, 1 point; 5 or more times, 3 points), rhinorrhea (anterior only, 1 point; posterior only, 1 point; both, 2 points; marked, 3 points), nasal blockage (breathing with difficulty, 1 point; one nostril blocked, 2 points; both nostrils blocked, 3 points), nasal itching (present, 1 point), palate or ear itching (present, 1 point), and conjunctivitis (present, 1 point). Doses were administered at 15-minute intervals until a total symptom score of 5 or greater was reached; this was considered the end point and indicated a positive challenge response.⁴

Nasal blockage index⁵ was performed before challenge and after an end point had been achieved. The data were used only in assessing borderline allergic reactions.

Medication exclusions

The following medications were discontinued for the indicated periods before nasal challenges and throughout the grass pollen season: oral decongestants, 1 day; antihistamines, 3 days; astemizole, 3 months; nasal and

oral steroids, 4 weeks; and nasal cromolyn and nedocromil, 4 weeks. Only 14 of the 68 subjects reported the use of nasal medication within 3 months of their initial enrollment. None of the subjects used topical decongestants or ipratropium, topical ocular medication, or injected corticosteroids within 3 months of or during the study. The nasal challenge was not performed if the subject had had symptoms of a viral respiratory tract infection within the preceding week.

Symptom diary

During the grass pollen season (May 1, 1993 to July 15, 1993) subjects maintained a symptom diary in which they recorded, twice daily, scores of 0 (none) to 3 (severe) for symptoms of itchy nose, runny nose, nasal obstruction, sneezing, and itchy eyes. Subjects were allowed to take terfenadine, 60 mg, as their only medication for symptoms of allergic rhinitis. On the basis of the degree of improvement in symptom scores reported in a double-blind study of terfenadine in seasonal allergic rhinitis,⁶ 2 points were added to the total daily symptom score for each terfenadine tablet used.

Statistical analysis

Symptoms from the subjects' diaries were analyzed in two ways: unadjusted, which included all data, and adjusted, which excluded days with high pollen counts other than grass pollen.

To compare a particular categorical feature among the groups, chi square analysis was used. The nasal challenge provocative dose was analyzed with the generalized Wilcoxon analysis for time to an event. Changes in symptom diary responses were compared among groups with a repeated-measures analysis of variance. The relationship of symptom severity with grass pollen counts was examined with Spearman's correlation coefficient and a within-subject *t* test. Analyses were deemed statistically significant if *p* was less than 0.05.

RESULTS

Subject characteristics

A total of 167 subjects were screened: 80 were enrolled, 74 completed nasal challenges, and 70 completed symptom and medication diaries. Complete data were available for both nasal challenge and symptom and medication diaries for 68 subjects, and the results reported here are restricted to this group. The original intention had been to recruit equal numbers for all groups, with a target of 23 subjects per group; however, only the timothy-positive control group was filled before the end of the recruitment period, which corresponded to the onset of the tree pollen season. This cutoff date was used to lessen the likelihood of nasal priming caused by aeroallergen exposure, which could affect the results of the nasal challenge. The subject group of greatest interest, those with a history of

TABLE I. Characteristics of the four subject groups

Group	No.	Age (yr)	IgE (IU/ml)	SAR in June	SAR in May but not June	SAR only in other months	PAR*
I	9	35 ± 11.3	109 ± 187.3	5	3	1	3
II	22	32 ± 6.6	165 ± 216.4	17	2	1	3
III	19	43 ± 13.3	32 ± 52.3	13	4	2	5
IV	18	35 ± 9.3	9 ± 3.8	0	0	0	0

SAR, Seasonal allergic rhinitis; PAR, perennial allergic rhinitis.

*Perennial allergic rhinitis in addition to seasonal allergic rhinitis.

seasonal allergic rhinitis symptoms and a negative SPT response but a positive intradermal skin test response to timothy extract proved especially difficult to identify, suggesting that this is not a common clinical presentation.

The group characteristics are listed in Table I. The mean wheal diameters in response to timothy skin prick testing in group II were 14.2 ± 13.6 mm with 100,000 AU/ml and 11.7 ± 13.0 mm with 10,000 AU/ml. The mean erythema diameters in the same subjects were 44.7 ± 32.7 mm and 38.2 ± 30.3 mm, respectively. Two subjects with borderline SPT responses to 100,000 AU/ml had insignificant wheals with 10,000 AU/ml, and in one of these subjects, the erythema was also less than 10 mm in diameter.

The groups differed in the number sensitive to the tree pollens, which were present in the air in significant numbers at the beginning of the study. Positive SPT responses to ash, cottonwood, American elm, or Chinese elm were recorded in six of nine subjects in group I, 18 of 22 subjects in group II, seven of 19 subjects in group III, and no subjects in group IV. Of the subjects who reported perennial nasal symptoms, two of three in group I, three of three in group II, and two of five in group III had positive SPT responses to cat or dog. However, only one of the subjects (in group II) was known to be frequently exposed to the animal to which he or she was sensitive. Although most of the subjects with perennial symptoms in groups I and II were sensitive to house dust mites, house dust mites do not normally occur in significant numbers in the Denver area.⁷

Pollen counts

The pollens of ash, cottonwood, and elm were detected regularly during the first week of May but only rarely after the middle of May. Grass pollen was first detected on May 10 and began to rise to its peak in late May. The peak grass pollen counts were encountered from the sixth through the ninth weeks of the study (Fig. 1).

Nasal challenge

The proportions of subjects with positive nasal challenge results (subjects reporting a total score of at least 5 with any dose of timothy pollen) were: group I, 44%; group II, 91%; group III, 42%; and group IV, 11%. This proportion of positive challenge results was significantly different ($p < 0.0001$) for the four groups.

The above analysis ignores the fact that the positive reactions occurred at different timothy pollen doses (Fig. 2). The mean dose required for provocation was significantly less ($p < 0.05$) in group II compared with groups I and III. There was no significant difference in the mean provocative doses for groups I and III. Therefore a receiver operating characteristic curve analysis of the provocative doses was performed with group II for true-positive and group III for false-positive results. The largest difference in cumulative proportion of positive challenge results between the timothy SPT-positive control group (group II) and the timothy intradermal skin test-negative control group (group III) was at dose 4 where the percents positive were 64% and 5%, respectively. Therefore subjects with provocative doses of 4 or less were classified as exhibiting a true allergic reaction. Alternatively, the difference between group II and group III did not change after dose 6, and one subject in group IV reacted at dose 7. Therefore those with a provocative dose greater than 6 were classified as not exhibiting a true allergic reaction. Those with a provocative threshold at the fifth or sixth doses were considered borderline, and each subject was classified on an individual basis as allergic or nonallergic on the basis of symptom scores with the fourth dose and changes in the nasal blockage index. The results of this analysis are given in Table II.

Symptom diaries

Twenty-nine of the subjects required terfenadine during the period of diary recording. The median number of tablets used by these 29 subjects during the 10-week period was 4.

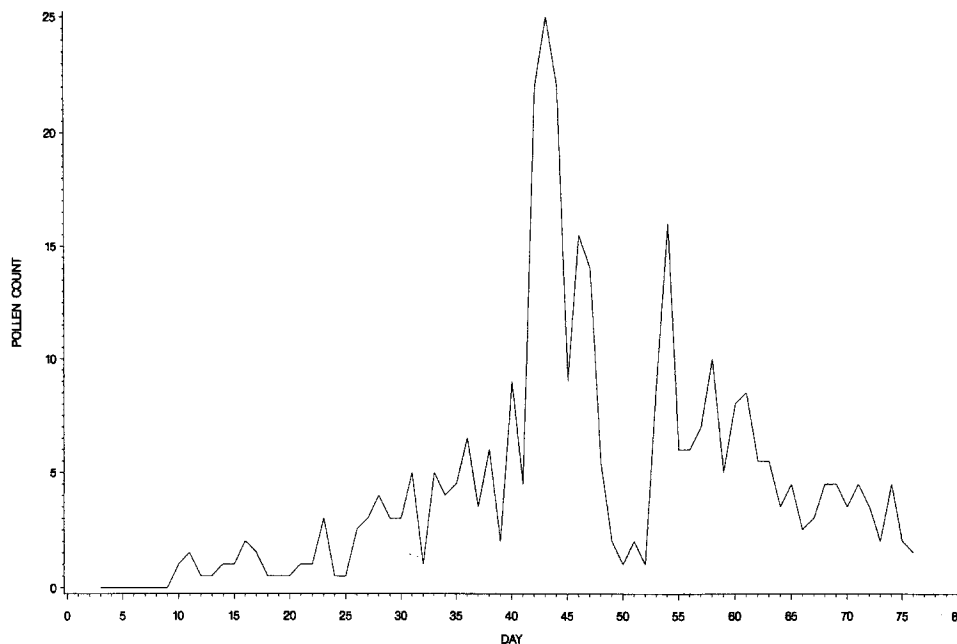


FIG. 1. Grass pollen counts in Denver in 1993. Day 1 is the first of May. Counts are the combined total of separate pollen counts performed at FAMC and the NJC.

The change in symptoms from week 1 of the study to weeks 6 through 9 (those with the highest grass pollen counts) was compared for each subject. The symptoms in group II increased significantly ($p < 0.05$) compared with those in groups I and III. The latter two groups did not differ significantly from each other (Table III).

To assess the relationship in individual subjects between symptoms and grass pollen exposure, three comparisons were made: (1) each subject's daily mean total symptom severity was correlated with the daily grass pollen count, (2) mean total symptom severity (both adjusted and nonadjusted) was compared for high and low grass pollen count days, and (3) mean worst symptom severity of the five symptoms recorded (both adjusted and nonadjusted) was compared for the high and low grass pollen count days. Subjects were considered allergic if at least one of these analyses was statistically significant and the remaining two indicated a positive trend. The numbers of subjects considered to have manifest allergic symptoms caused by grass pollen exposure as a result of this analysis were: group I, 22%; group II, 64%; group III, 21%; and group IV, 0%.

Overall assessment of clinical grass allergy

Subjects could be considered clinically allergic to grass on the basis of the nasal challenge with timothy or the correlation of diary symptoms and

grass pollen counts, or they could more conservatively be required to have positive responses to both criteria to be considered clinically allergic to grass. The results of these two approaches are given in Table IV.

DISCUSSION

In this study we have attempted to assess the value of a positive intradermal skin test response to timothy grass in patients with a negative SPT response to timothy grass in the diagnosis of clinical allergy to grass pollen. We compared the group of interest with two allergic control groups: a timothy SPT-positive "positive control" group and a timothy intradermal skin test-negative "negative control" group, as well as with a "nonallergic control" group. All three allergic groups reported symptoms consistent with allergic rhinitis, and the majority in each group reported increased symptoms during a period that included the grass pollen season.

We used timothy grass in this study because it has been demonstrated to be representative of the Northern pasture grasses, which produce the bulk of grass pollen in the Denver area.⁸

We skin tested patients with Bermuda grass as well and excluded patients who were more allergic to Bermuda grass extract than to timothy extract as determined by skin testing. We did this because although Bermuda grass is thought to not pollinate

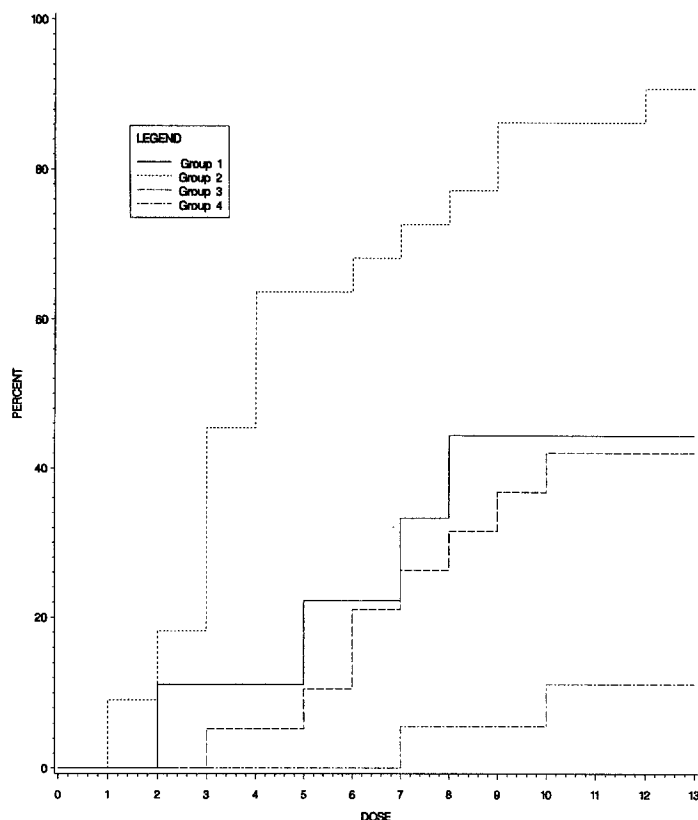


FIG. 2. Response to nasal challenge with progressively greater amounts of timothy grass pollen. Dose 1 contained 50 grains, and dose 13 contained 885,350 grains. Indicated is the percent of subjects in each of the four groups who had a symptom score of 5 or greater with that dose.

TABLE II. Classification of reaction to nasal challenge by group

Group	Allergic	Borderline allergic	Borderline nonallergic	Nonallergic	Percent allergic
I	1	0	1	7	11
II	14	1	0	7	68
III	1	1	2	15	11
IV	0	0	0	18	0

Allergic reactors had a symptom score of 5 or greater by dose 4. Nonallergic reactors did not have a score of 5 or greater by dose 6. Those subjects with a threshold at dose 5 or dose 6 were individually determined to be allergic or nonallergic reactors on the basis of their pattern or symptoms through dose 4 and changes in nasal blockage index.

in Denver, it cross-reacts with some native grasses,⁸ which may contribute a small but undetermined amount to the total grass pollen count in Denver.

We used two methods to determine clinical grass sensitivity. The first was intranasal challenge with timothy grass pollen mixed with lactose. This was administered in 12 incremental threefold increases in amount, allowing determination of a challenge threshold. These challenges were conducted before the onset of the tree pollen season to avoid, as much as possible, priming, which could have non-

specifically lowered the threshold for timothy grass pollen. With the exception of one patient in group II, the subjects had no exposure to perennial allergens to which they were sensitive. The method used for nasal challenge was that described by Bousquet et al.⁴ We selected this method because the threshold of sensitivity has been demonstrated to significantly correlate with symptom scores during natural pollen exposure.⁹ We used the scoring system described by Bousquet et al.⁴ and believe we had similar sensitivity because Bousquet et al.⁴ reported that 93% of their subjects allergic to grass

TABLE III. Change in diary symptoms from baseline to weeks of highest grass pollen counts

Group	Mean total daily symptom/medication scores*				
	Baseline	Change wk 6	Change wk 7	Change wk 8	Change wk 9
I	5.0	-1.0	-0.5	-1.0	-1.5
II	2.5	+1.5	+1.5	+1.5	+1.5
III	3.5	-0.5	0	-0.5	-0.5
IV	0.5	0	0	0	0

Indicated is the total symptom score for the first week of May and the change from this level during the weeks of highest grass pollen prevalence. Symptoms in group II increased significantly ($p < 0.05$) compared with groups I and III.

*Total scores for itchy nose, runny nose, nasal obstruction, sneezing and itchy eyes.

reacted at a threshold of 1215 grass pollen grains or less, and with our challenges 64% of the timothy SPT-positive group had positive results with the 1350 pollen grain dose.

The second method for determining the presence of clinical sensitivity to grass was to monitor the symptoms of allergic rhinitis twice daily throughout the period of grass pollination. We began this symptom monitoring at the end of the late spring tree pollen season and well before the first appearance of grass pollen. Diaries were continued for a total of 10 weeks, encompassing the peak (weeks 6 to 9) of the pollen season. The symptoms from these diaries were compared with the pollen counts on a daily basis, and on days with high and low grass pollen counts, with and without elimination of days with elevated tree pollen counts, in sensitive subjects. Both the mean total daily symptom score and the highest individual daily symptom score were used for these comparisons.

From these analyses, we drew the following conclusions.

First, subjects in the timothy SPT-positive control group (group II) indicated a significantly lower ($p < 0.05$) provocative dose on nasal challenge with timothy grass pollen than both the timothy intradermal skin test-negative control group (group III) and the timothy intradermal skin test-positive study group (group I). There was no significant difference in the provocative dose for groups I and III.

Second, subjects in the timothy SPT-positive control group (group II) indicated a significantly greater increase in symptom severity from baseline to the weeks of peak grass pollen counts (weeks 6 to 9) ($p < 0.05$) than those in the timothy intradermal skin test-negative control group (group III) or the timothy intradermal skin test-positive group (group I). There was no significant difference between groups I and III.

Third, sixty-eight percent of the subjects in the

TABLE IV. Overall assessment of clinical grass allergy

Group	No.	No. with allergy symptoms	
		One criterion	Both criteria
I	9	3 (33%)	0 (0%)
II	22	19 (86%)	10 (46%)
III	19	6 (32%)	0 (0%)
IV	18	0 (0%)	0 (0%)

Indicated is the number of subjects in each group who had allergy symptoms as determined by either one or both criteria: nasal challenge with timothy grass or significant correlation between diary symptoms and grass pollen counts during the grass pollen season.

timothy SPT-positive control group had a significant correlation between daily symptom scores and daily grass pollen counts or between symptom scores and high and low grass pollen days compared with 11% each in groups I and III.

Fourth, use of either a positive nasal challenge result or a correlation between diary symptoms and pollen counts provided a liberal interpretation of a subject's allergic sensitivity. According to this criterion 86% of the timothy SPT-positive group (group II) were allergic; however, 32% of the timothy intradermal skin test-negative group (group III) were also allergic. Use of the criterion that a subject must exhibit allergic symptoms by both nasal challenge and symptom correlation with pollen count provided a conservative assessment of a subject's allergic sensitivity. According to these criteria, only 46% of the subjects with positive SPT responses to timothy grass were considered to be allergic. However, none of the subjects in the timothy intradermal skin test-negative control group were considered clinically allergic to timothy grass. In each instance, the number in the timothy intradermal skin test-positive group was not significantly different from that in the timothy intra-

dermal skin test–negative control group (32%/33% and 0% for a single positive criterion or both positive criteria, respectively).

Fifth, regardless of the criteria used to identify a subject as allergic, the estimated positive predictive value of the timothy intradermal skin test–positive group I was nearly identical to that of the timothy intradermal skin test–negative control group (group III).

The results of this study are quite comparable to those of other studies, which have sought to evaluate the diagnostic usefulness of the intradermal skin test in clinical allergy.¹⁰⁻¹² In an epidemiologic study in Tucson, Arizona, the results of intradermal skin tests with 1:1000 wt/vol extracts of 13 allergens were compared in subjects with a history of allergic rhinitis or asthma (allergic) and those denying these conditions (nonallergic). In the presence of a negative SPT response to the same allergen, a positive intradermal skin test response was encountered more often in the nonallergic subjects than in the allergic subjects.¹⁰ In a study of patients with perennial rhinitis, those with positive SPT responses had positive results 63%, 89%, and 89% of the time, respectively on testing with the same allergen by RAST, leukocyte histamine release, and nasal challenge.¹¹ Subjects who had positive responses to the allergen only on intradermal testing invariably had negative responses as determined by RAST and leukocyte histamine release testing, and only one in 34 had a positive nasal challenge result. In one study in which intradermal testing did correlate with symptoms on natural exposure to ragweed,¹² a consistent correlation was observed only when the threshold skin test was with an extract of 1 protein nitrogen unit/ml or less. This would represent an extract one hundredth to one thousandth as concentrated as those used in our study, as well as in the negative studies reported above, and thus closer in sensitivity to the SPT than to the intradermal test, as customarily used.

It might be suggested that the criteria for clinical sensitivity used in this study are too strict, particularly because a positive response to both nasal challenge and natural pollen exposure was observed in only 46% of the subjects with positive SPT responses to timothy grass (group II). However, it is well recognized that positive SPT responses to potent pollen extracts can occur in many subjects who are free of symptoms.¹³ Therefore clinically irrelevant positive SPT results are probably common, further arguing against the need for the greater sensitivity of the intradermal test when potent allergen extracts are available.²

Further, only use of these strict criteria prevented making the diagnosis of clinically significant timothy grass allergy in the presence of a negative intradermal skin test reaction to timothy grass.

We also examined the SPT response to 10,000 AU/ml timothy grass in group II. Despite an overall small reduction in the mean wheal and erythema diameter between 100,000 AU/ml and 10,000 AU/ml, two subjects failed to meet the wheal criteria for a positive SPT response to timothy grass at the weaker concentration. One of these subjects also failed to meet the minimum requirement for erythema and thus would have been considered to have a negative SPT response. This subject who had a negative response to timothy grass extract (10,000 AU/ml) was positive for clinically significant sensitivity, both on nasal challenge and by correlation of symptoms with natural grass pollen exposure. This result emphasizes the need to use the most concentrated extracts available for allergy skin prick testing.

In summary we conclude that under the conditions of this study, the presence of a positive intradermal skin test response to timothy grass (1000 AU/ml) in the presence of a negative SPT response to timothy grass (100,000 AU/ml) does not indicate the presence of clinically significant sensitivity to timothy grass, and by inference, other cross-reacting grasses.⁸

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REFERENCES

1. Nelson HS. Clinical application of immediate skin testing. In: Spector SL, ed. *Provocation testing in clinical practice*. New York: Marcel Dekker, 1995:703-27.
2. Malling H-J. Methods of skin testing. *Allergy* 1993;48:55-6.
3. Nelson HS, Rosloniec DM, McCall LL, Iklé D. Comparative performance of five commercial prick skin test devices. *J Allergy Clin Immunol* 1993;92:750-6.
4. Bousquet J, Lebel B, Dhivert H, Bataille Y, Martinot B, Michel FB. Nasal challenge with pollen grains, skin-prick tests and specific IgE in patients with grass pollen allergy. *Clin Allergy* 1987;17:529-36.
5. Taylor G, Macneil AR, Freed DLJ. Assessing degree of nasal patency by measuring peak expiratory flow rate through the nose. *J Allergy Clin Immunol* 1973;52:193-8.
6. Kemp JP, Falliers CJ, Fox RW, Guill MF, Segal AT, Tsai TH, Sjoerdsma A. A multicenter, open study of the non-sedating antihistamine, terfenadine (Seldane), in the maintenance therapy of seasonal allergic rhinitis. *Ann Allergy* 1988;60:349-54.
7. Moyer DB, Nelson HS, Arlian LG. House dust mites in Colorado. *Ann Allergy* 1985;55:680-2.
8. Martin BG, Mansfield LE, Nelson HS. Cross-allergenicity among the grasses. *Ann Allergy* 1985;54:99-104.

9. Bousquet J, Maasch H, Martinot B, Hejjaoui A, Wahl R, Michel FB. Double-blind, placebo-controlled immunotherapy with mixed grass-pollen allergoids. *J Allergy Clin Immunol* 1988;82:439-46.
10. Brown WG, Halonen MJ, Kaltenborn WT, Barbee RA. The relationship of respiratory allergy, skin test reactivity, and serum IgE in a community population sample. *J Allergy Clin Immunol* 1979;63:328-35.
11. Reddy PM, Nagaya H, Pascual C, et al. Reappraisal of intracutaneous tests in the diagnosis of reaginic allergy. *J Allergy Clin Immunol* 1978;61:36-41.
12. Norman PS, Lichtenstein LM, Ishizaka K. Diagnostic tests in ragweed hay fever. A comparison of direct skin tests, IgE antibody measurements, and basophil histamine release. *J Allergy Clin Immunol* 1973;52:210-24.
13. Adinoff AD, Rosloniec DM, McCall LL, Nelson HS. Immediate skin test reactivity to Food and Drug Administration-approved standardized extracts. *J Allergy Clin Immunol* 1990;86:766-74.

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