

Immediate skin test reactivity to Food and Drug Administration-approved standardized extracts

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*In an effort to determine whether recently introduced Food and Drug Administration-approved standardized extracts produce clinically appropriate responses in a population, 200 subjects were skin prick tested (SPT). Thirteen extracts (10 pollens, two house dust (HD) mites and cat) were tested in three groups of subjects, 50 with a history of asthma or allergic rhinitis (AL), 50 without asthma or perennial or seasonal allergic rhinitis but with a positive immediate family history for these conditions (FAL), and 100 subjects without a personal or family history for these conditions (NAL). An SPT mean wheal diameter ≥ 3 mm was considered positive. Ninety percent (95% confidence interval [CI], 82% to 98%) of AL subjects had at least one positive SPT. Forty-six percent of FAL subjects (95% CI, 30% to 58%) and 29% of NAL subjects (95% CI, 20% to 38%) had at least one positive SPT. More FAL than NAL subjects had at least one SPT ($p < 0.05$), and FAL subjects had more positive SPTs than NAL subjects ($p < 0.05$), further supporting the genetic regulation of allergen-specific IgE production. Of the five AL subjects with no SPT wheal ≥ 3 mm, three subjects were available for intradermal tests. Thirteen nonstandardized allergens similar to allergens used for SPT were applied intradermally in each of these three subjects and were all negative. Compared with history, an SPT wheal ≥ 3 mm to cat produced a sensitivity of 0.90, a specificity of 0.90, and diagnostic accuracy of 0.90. Tenfold dilutions of pollens and cat reduced sensitivity without significantly improving specificity. Full-strength HD-mite extracts of *Dermatophagoides pteronyssinus* and *D. farinae* produced positive reactions in 17% and 12% of NAL subjects, respectively. The results suggest that full-strength Food and Drug Administration-approved extracts of pollens and cat are suitable for clinical diagnostic work. Full-strength HD-mite extracts (10,000 AU/ml) may be too concentrated for diagnostic skin testing. (J ALLERGY CLIN IMMUNOL 1990;86:766-74.)*

The use of immediate hypersensitivity skin testing as a diagnostic tool in clinical allergy dates to the studies on hay fever by Blackley in the 1860s.^{1,2} Since that time, it has become the standard clinical method for demonstrating the presence of allergen-specific IgE antibody in allergic diseases.³ The proper interpretation of skin tests, however, requires that extracts of allergens be of known composition and potency. Until recently, extract standardization has been based

Abbreviations used

SPT:	Skin prick test
AL:	"Allergy"
FAL:	"Family allergy"
NAL:	"No allergy"
FDA:	Food and Drug Administration
AU:	Allergy unit
SI:	Skin index
CI:	Confidence interval
HD:	House dust

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on measurements, such as the Noon unit, protein nitrogen unit, or weight/volume. The flaw in these methods is that correlation of biologic activity with the chemical analysis of these impure preparations is not evident.⁴ Additionally, the composition of commercially available extracts may vary greatly between manufacturers and within manufacturer from lot to

TABLE I. Subject demographics: Average size and number of positive SPTs per subject

	Group		
	AL	FAL	NAL
No. of subjects	50	50	100
Age (yr)	33.6 ± 5.5*	33.0 ± 8.3	33.2 ± 7.3
Age (range)	23-46	22-60	18-53
Sex (M/F)	12/38	9/41	34/66
Subjects with at least one SPT			
≥3 mm			
Wheal size of SPT (mm)	9.1 ± 6.1	8.1 ± 5.6	7.3 ± 4.5
No. SPT ≥10 mm erythema	6.2 ± 3.7†‡ (n = 45)	3.0 ± 2.0§ (n = 23)	1.9 ± 1.4 (n = 36)
No. SPT ≥3 mm wheal	5.7 ± 3.6†‡ (n = 45)	2.9 ± 1.8 (n = 22)	2.0 ± 1.2 (n = 29)
Histamine reaction (1 mg/ml) in all subjects skin tested			
Mean erythema diameter (mm)	16.5 ± 6.5	17.9 ± 6.4	16.4 ± 6.6
Mean wheal diameter (mm)	4.1 ± 1.9	3.8 ± 1.0	3.6 ± 1.4

*Mean ± SD.

†AL versus FAL, $p \leq 0.05$.‡AL versus NAL, $p \leq 0.05$.§FAL versus NAL, $p \leq 0.05$.

lot. The lack of reliable extracts of known, consistent, allergenic potency has frustrated those involved in the clinical and research uses of these extracts.

Recently, specific criteria for the selection of reference extracts have been developed by the International Union of Immunological Societies under the auspices of the World Health Organization. In the United States, the Laboratory of Allergenic Products (FDA) provides criteria for the preparation and testing of reference extracts. Once the reference standard is selected for use, a bioassay method is used for assigning AUs.⁵ With this method, bioequivalence can be established, and relative potencies between extracts can be ensured.⁶

However, AUs are derived from subjects known to be exquisitely sensitive to the allergen tested, and the relevance of this standard has not been applied to a general population. With the introduction of standardized extracts, it is important for clinical interpretation of skin tests to determine the prevalence of positive skin tests with these allergens in clinically asymptomatic populations. Additionally, extracts need to be of adequate potency to identify allergic individuals. The purpose of this study therefore was to skin test a large group of allergic and nonallergic subjects to a variety of FDA-approved standardized extracts and to assess whether these extracts produce appropriate responses.

MATERIAL AND METHODS

Subjects

Two hundred adult subjects were recruited from hospital personnel and by advertisement. Consecutive responders were interviewed, and a questionnaire was administered to determine the presence or absence of a personal or immediate family history of atopic diseases⁷: (1) allergic rhinitis (itchy eyes or nose, sneezing, runny nose, or stopped up nose occurring in the same season each year [usually between March and September] or on exposure to specific allergens), (2) perennial rhinitis (year-round nasal symptoms most days, including runny nose or stopped up nose), (3) bronchial asthma (recurrent wheezing, tightness in the chest, and shortness of breath), and (4) atopic dermatitis (chronic, recurrent, dry, itchy rash of the inner aspects of the elbows or knees). Based on the results of this questionnaire, three groups of subjects were selected. The first group of 50 subjects had a personal history of seasonal or episodic allergic rhinitis or asthma (AL). The second group of 50 subjects had no personal allergic history but had at least one immediate family member (parent or sibling) with at least one of the four atopic diseases mentioned (FAL). The last group of 100 subjects had neither a personal nor immediate family history of any atopic disease (NAL). None of the subjects was receiving medications known to inhibit immediate hypersensitivity skin tests.^{8,9} The study was approved by the Institutional Review Board for the use of human subjects at National Jewish Center for Immunology and Respiratory Medicine, and all subjects gave informed consent before their participation.

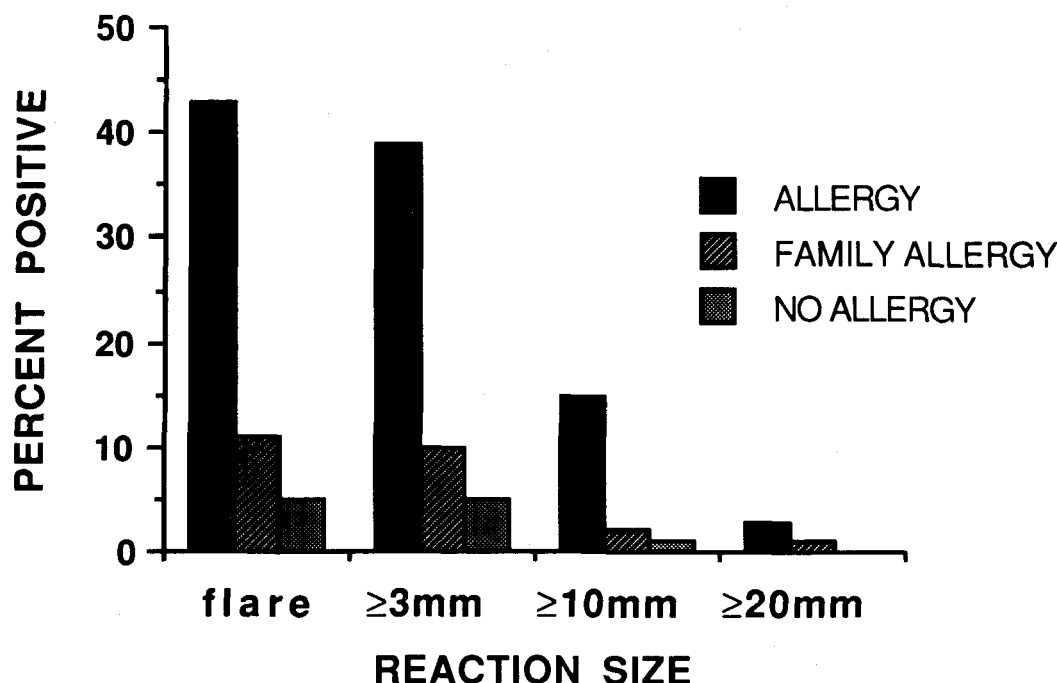


FIG. 1. Cumulative prevalence (percent) of all positive SPTs. Data include skin test reactions performed on all subjects; flare, 10 mm or greater mean erythema diameter; others are mean wheal diameters; AL, N = 650; FAL, N = 650; NAL, N = 1300.

Allergens for skin testing

Thirteen FDA-approved standardized aeroallergen extracts that were available in 1987 were used⁵: cat allergen (50,000 AU/ml), 10 common pollen extracts (100,000 AU/ml) at full strength concentrations and a 1:10 dilution, and two HD-mite extracts at full strength (10,000 AU/ml). Standardized extracts of timothy grass, short ragweed, and Russian thistle were purchased from Hollister-Stier Laboratories (Spokane, Wash.). Cat, American elm, box elder, Bermuda grass, and white oak were purchased from ALK America (Milford, Conn.). HD mites, *D. pteronyssinus* and *D. farinae*, were purchased from Berkeley Biological (Berkeley, Calif.), and American sycamore, common sagebrush, and red oak from 3M Diagnostic Systems (Mountain View, Calif.). Lyophilized extracts of cat and the pollens were reconstituted in 50% glycerine and stored at 4° C. The same lot number extract for each aeroallergen was used for all subjects. Each subject was also tested with histamine phosphate (1 and 10 mg/ml base) and compound 48/80 (45 and 450 mg/ml).

Skin testing method

Twenty-eight SPTs were performed on each subject's back with a template of seven horizontal rows and four vertical columns, with each test site 5 cm apart.¹⁰ Twenty-two of the sites tested 11 extracts (cat and 10 pollens) at full strength and a 1:10 dilution, two sites tested the mite extracts, and four sites tested the two dilutions of histamine and compound 48/80. The location of testing for the in-

dividual allergens and positive controls was rotated among the subjects to ensure equal distribution over the entire surface of the back and avoid possible variability as a result of different test sites.¹¹ SPT was performed with the Hollister-Stier smallpox needle, as previously described,¹² by either of two highly experienced technicians (D. M. R. or L. L. M.) who were not aware of the subjects' clinical history. In a previous study, no significant differences were found in skin test wheal responses to histamine between these two technicians.¹² After the skin test was performed, the drop of extract was removed.¹³ Histamine reactions were read 10 minutes after SPT; aeroallergens and compound 48/80 were read 15 minutes after SPT.¹⁴ Wheal-and-flare reactions were carefully outlined with a fine porous-tipped pen and tape transferred onto paper for a permanent record. The size of wheal-and-flare reactions was recorded in millimeters with the mean of the largest and midpoint orthogonal diameters. A mean wheal diameter of ≥ 3 mm was judged to represent a positive response,¹⁵ although wheal and erythema reactions of different sizes were also considered. SPT wheal diameters to cat allergen were also compared with wheal diameters to histamine, 1 mg/ml, on the same subject. An SI of the ratio of cat allergen:histamine was determined.¹⁶

Three of five AL subjects who had negative SPTs were available at a later date and were skin tested by the intradermal technique. Nonstandardized allergens, 1:1000 wt/vol, were injected with a 27-gauge needle to produce a bleb of 2 mm. Wheal and erythema reactions were measured

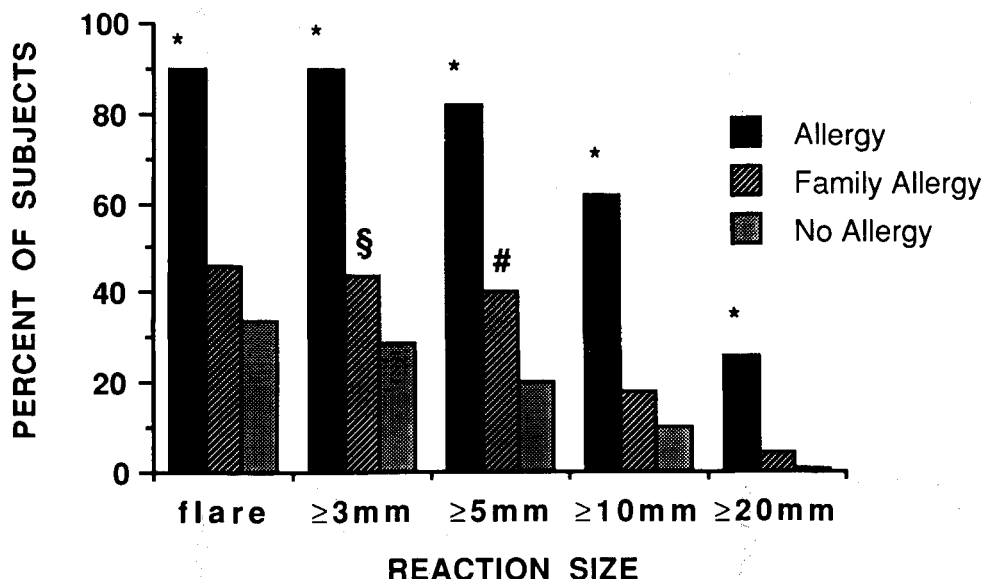


FIG. 2. Cumulative prevalence (percent) of subjects with positive SPTs by the size of the reactions; flare, 10 mm or greater mean erythema diameter; others are mean wheal diameters; AL, N = 650; FAL, N = 650; NAL, N = 1300; *AL versus FAL and NAL, $p < 0.001$; *FAL versus NAL, $p < 0.05$; \$FAL versus NAL, $p = 0.07$.

and recorded as described above. The intradermal tests were done after the prick tests and at a later time. Many of the standardized extracts were no longer commercially available and had previously been diluted in glycerine; therefore, they were not suitable for intradermal testing. In addition, doses for intradermal tests with standardized extracts have not yet been established.

In the calculations of sensitivity, specificity, and diagnostic accuracy, a "true positive" history was defined as direct cat exposure producing immediate (within 30 minutes) respiratory, ocular, or cutaneous symptoms suggestive of an immediate hypersensitivity reaction (e.g., pruritus, lacrimation, wheezing, or rhinitis).

Statistical analysis

Statistical analysis was performed with the StatView 512+ program (Brainpower, Inc., Calabasas, Calif.) on a Macintosh microcomputer (Apple Computer, Inc., Cupertino, Calif.). Comparisons between individual groups were performed by Student's paired t tests, one-way analysis of variance, and chi-square. When a one-way analysis of variance was used, a posthoc analysis for multiple comparisons with the Fischer protected least-significant test determined significance between individual groups. Ninety-five percent CIs on proportions were calculated.¹⁷ The sensitivity, specificity, and diagnostic accuracy of the cat-allergen SPT reactions were calculated (see Table II).

RESULTS

Two hundred subjects, 55 male and 145 female subjects (mean age, 33.2 years; ± 7.2 [SD]; range,

18 to 60 years), had 2800 skin tests applied. None of the subjects experienced a systemic reaction associated with the testing. Unless it is otherwise noted, all data discussed below apply to full-strength extracts.

The demographic data of the three groups of subjects are presented in Table I. There were no significant age or sex differences among these groups. The average size and number of positive SPTs observed in the three groups are presented in Table I. In subjects with at least one SPT wheal ≥ 3 mm, the mean wheal sizes obtained were not significantly different among the three groups, although there was a trend toward larger reactions in the AL group ($p = 0.06$). In subjects with at least one SPT wheal ≥ 3 mm, the number of SPT flares ≥ 10 mm and wheals ≥ 3 mm was significantly greater in the AL group ($p < 0.05$). The FAL group had more SPT flares ≥ 10 mm than the NAL group ($p < 0.05$). The mean wheal and erythema diameter reactions to histamine phosphate (1 mg/ml base) are also noted. No statistical differences between groups were found.

The cumulative prevalence of all positive SPT by size is illustrated in Fig. 1. As expected, a much greater number of SPT reactions occurred in the AL group. An intermediate number of SPT reactions were observed in the FAL compared to the NAL group. Thirty-seven percent (240 of 650) of the SPTs in the AL group produced a wheal of ≥ 3 mm, whereas only 10% (65 of 650) and 5% (77 of 1300) were of that size in the FAL and NAL groups, respectively. Only

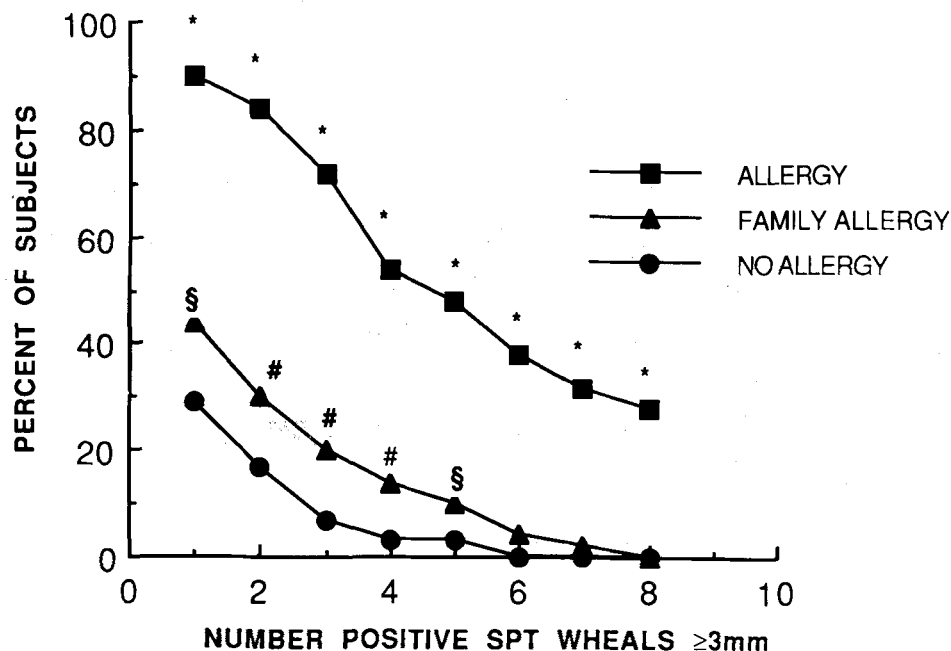


FIG. 3. Cumulative prevalence (percent) of subjects with SPT wheals ≥ 3 mm; *AL versus FAL and NAL, $p < 0.001$; #FAL versus NAL, $p < 0.05$; \$FAL versus NAL, $p = 0.07$.

1% of the SPT reactions in the NAL group were wheals ≥ 10 mm, compared to 15% in the AL group.

The number of subjects in each group with at least one positive SPT of different sized reactions is illustrated in Fig. 2. More AL subjects produced at least one positive SPT of any size than either of the other two groups ($p < 0.001$). Ninety percent (45/50; CI, 82% to 98%) of AL subjects had at least one SPT wheal ≥ 3 mm. Nevertheless, a substantial number of FAL subjects (46% [23/50]; CI, 30% to 58%) and NAL subjects (29% [29/100]; CI, 20% to 38%) had at least one positive SPT wheal ≥ 3 mm. There were twice as many subjects in the FAL as in the NAL group who demonstrated at least one SPT wheal ≥ 5 mm (40% versus 20%, respectively; $p < 0.05$) and a trend toward a greater number of reactions ≥ 3 mm wheal (44% versus 29%; $p = 0.07$). Of the five AL subjects with no SPT wheal ≥ 3 mm, three patients were available for intradermal tests. Thirteen nonstandardized extracts of the same allergens used for SPT were applied intradermally in each of these three subjects and were all negative.

The cumulative prevalence of subjects with SPT reactions producing a wheal diameter ≥ 3 mm is illustrated in Fig. 3. Significantly more subjects in the AL group had a greater number of positive SPTs than the other two groups ($p < 0.001$). More reactions were observed in the FAL than in the NAL group for two, three, and four positive SPTs ($p < 0.05$), and a

trend was observed for one and five positive SPTs ($p = 0.07$).

The prevalence of SPT reactions of ≥ 3 mm wheal to the different allergens is illustrated in Fig. 4. Sixty-two percent of AL subjects reacted to timothy grass, which produced the highest rate of reactions. The AL group had a higher prevalence of reactions to all of the 10 pollens and cat ($p < 0.001$) than either of the other two groups. Compared to the NAL group, the FAL group had a higher rate of reaction to many allergens: red oak, box elder, timothy, Bermuda, sage, and Russian thistle ($p < 0.05$). Interestingly, SPT reaction rates to *D. pteronyssinus* were not significantly different in the three groups ($p = 0.1$). Extracts of *D. pteronyssinus* and *D. farinae* produced positive SPT reactions in 17% and 12% of NAL subjects, respectively, a percentage much greater than reactions observed to pollens and cat. In the NAL group of subjects with at least one SPT wheal ≥ 3 mm, 59% (17/29) had an SPT wheal ≥ 3 mm to at least one of the dust mite species, and 47% (29/61) of all SPT wheals ≥ 3 mm were due to mite allergen in this group. In contrast, only 10% (25/254) and 13% (8/64) of SPT wheals ≥ 3 mm were caused by mites in the AL and FAL groups, respectively. When the results for mite reactions were analyzed with a cutoff criteria of ≥ 10 mm mean erythema diameter, similar findings were noted (data not presented).

The SPT results of extracts tested in a 1:10 dilution

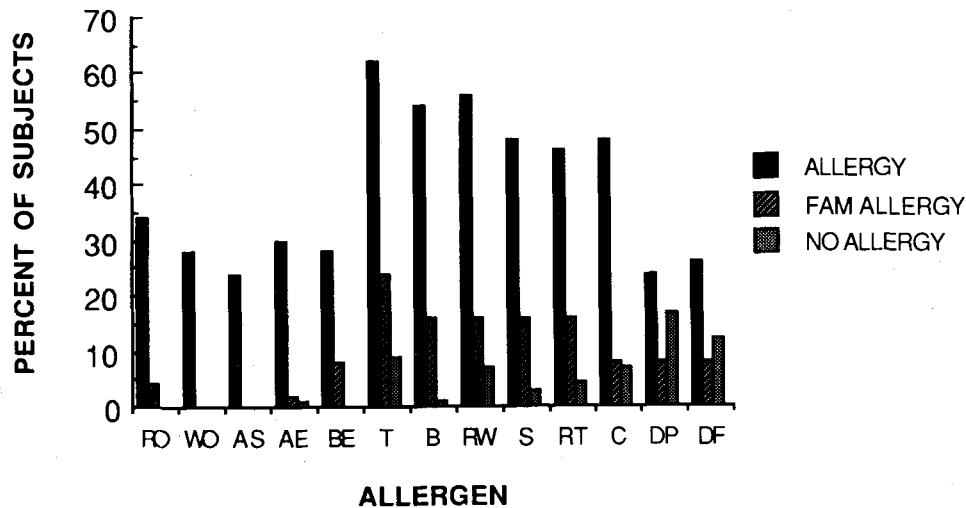


FIG. 4. Prevalence (percent) of subjects with SPT wheals ≥ 3 mm to the different allergens tested; RO, red oak; WO, white oak; AS, American sycamore; AE, American elm; BE, box elder; T, timothy; B, Bermuda; RW, ragweed; S, sage; RT, Russian thistle; C, cat; DP, *D. pteronyssinus*; DF, *D. farinae*.

TABLE II. Sensitivity, specificity, and accuracy of cat SPT tests of various sized reactions

	Sensitivity	Specificity	Accuracy
Erythema ≥ 10 mm	0.91 (20/22)	0.90 (159/177)	0.90
Wheal ≥ 3 mm	0.90 (19/22)	0.90 (160/178)	0.90
Wheal ≥ 5 mm	0.68 (15/22)	0.94 (168/178)	0.92
Cat SI $\geq 1.0^*$	0.82 (18/22)	0.88 (157/178)	0.86
Wheal ≥ 3 mm (1:10 dilution)	0.57 (12/21)	0.96 (172/179)	0.92
Wheal ≥ 5 mm (1:10 dilution)	0.33 (7/21)	0.98 (176/179)	0.92

TP, True positive; FP, false positive; FN, false negative; TN, true negative.

Sensitivity: the ability to detect a condition if it is present = $\frac{TP}{TP + FN}$

Specificity: the ability to detect the absence of a condition if it is absent = $\frac{TN}{TN + FP}$

Accuracy: patients correctly diagnosed = $\frac{TP + TN}{TP + TN + FP + FN}$

*SI = $\frac{\text{Cat wheal reaction}}{\text{Histamine wheal reaction}}$

were also examined. Only full-strength extracts of timothy, ragweed, and cat produced positive SPT reactions (wheals ≥ 3 mm) in $>5\%$ of NAL subjects, and discussion is limited to those allergens. A tenfold dilution of ragweed and cat extract induced a slightly lower prevalence of positive SPT reactions in the AL and NAL groups, although the differences were not statistically important. However, a tenfold dilution of timothy induced significantly fewer positive SPT reactions in the AL group (42% versus 62%; $p = 0.04$)

and a nonsignificant reduction in the prevalence of positive reactions in the NAL group (4% versus 9%; $p = 0.1$). A large number of the NAL group had positive SPT reactions to both HD-mite species. This result was not anticipated, and unfortunately, the study design did not test 1:10 dilutions of these extracts.

The sensitivity, specificity, and diagnostic accuracy of standardized cat extract are presented Table II. An SPT wheal of ≥ 3 mm with full-strength extract produced the best overall sensitivity and specificity. The

diagnostic accuracy of 1:10 dilutions was slightly better than that of the full-strength extracts, although the sensitivity was markedly reduced.

DISCUSSION

The purpose of this study was to assess the immediate skin reaction in a large group of allergic and nonallergic subjects to a variety of FDA-approved standardized extracts to determine whether these extracts produce appropriate responses for clinical diagnostic use. In this group of subjects, 90% of those subjects with allergic rhinitis or asthma had at least one positive SPT (wheal ≥ 3 mm) to the 13 allergens tested. Those subjects without a personal history of atopy but an immediate family member with one of these conditions had an intermediate prevalence of reactions. Not surprisingly, the AL group also demonstrated more positive reactions. Interestingly, there were no significant differences in the mean size of SPT wheals between the individual groups, and many NAL subjects produced very large reactions. Therefore, skin testing with these extracts identified the overwhelming majority of allergic subjects who frequently reacted to multiple antigens. Those subjects with no history of an atopic disease not infrequently had at least one positive reaction, but multiple positive tests were relatively uncommon.

Other studies have assessed the prevalence of immediate skin test reactions in populations of subjects with unstandardized extracts. In general, skin test reactivity in the range of 20% to 49% has been found for the general population.^{18, 22} Studies of nonallergic populations reveal wide prevalence ranges of 5% to 64%.^{18, 23-29} Unfortunately, most of these studies did not include the allergic history of immediate family members. The absence of this information might explain the wide ranges reported. For example, Curran and Goldman²⁴ found 50% of nonallergic individuals with a positive family history of atopy had positive skin tests to aeroallergens, compared to only 9% of subjects with a negative family history. The range of prevalence estimates for positive skin tests in allergic populations has been reported to be 50% to 95%.^{18, 20, 24-26, 28-30} The differences in these studies is due in part to the methods and criteria of patient selection, the types and numbers of allergens used, and the varying criteria used for a positive reaction.

The results of our study with FDA-approved standardized extracts approximate results found previously. The prevalence rates with these extracts are, for the AL group, generally higher than the mean of previous studies with nonstandardized extracts; prevalence rates for the NAL group are generally lower. The prevalence rate of 44% for the FAL group is quite

similar to that of Curran and Goldman²⁴ (50%). To our knowledge, this study is the only other skin test prevalence study to assess nonallergic subjects with positive family histories. Therefore, these data suggest that full-strength FDA-approved extracts produce a degree of sensitivity and specificity (for populations) generally similar to that obtained with the nonstandardized commercial extracts. Two preliminary studies have suggested that FDA-approved standardized extracts offer no diagnostic advantage over nonstandardized extracts when FDA-approved extracts are used for study in individual subjects.^{31, 32} Nevertheless, the results strongly support the suitability of these standardized extracts for use in clinical diagnostic work. They offer the potential advantage of reproducibility and comparability of diagnostic skin testing performed over time.

An SPT wheal ≥ 3 mm or erythema ≥ 10 mm was found to be very sensitive and specific in identifying cat-allergic individuals. An SPT wheal ≥ 5 mm improved somewhat the overall diagnostic accuracy of the test, but the significant loss in sensitivity would appear to outweigh this slight advantage. The use of the SI, in which the size of the reaction to 1.0 mg/ml of histamine was used as the threshold for a significant SPT, did not enhance the accuracy of the test. The use of a 1:10 dilution of extract caused marked reduction in the sensitivity of the test and therefore appears not to be appropriate for diagnostic use. The sensitivity and specificity of the ≥ 3 mm wheal are quite similar to the results found by Vanto¹⁶ in his studies with dog extract. In his study, a "true positive" was considered only if the patients had a suggestive history, positive RAST, and positive bronchial or conjunctival provocation challenge. Since we estimated "true positive" reactions on the basis of history alone, it is reasonable to assume that we would have overestimated the prevalence of these reactions (compared with the addition of provocation challenge and RAST). Nevertheless, marked similarities in diagnostic accuracies were found. A more recent study estimated the accuracy of cat SPT with a "true positive" based on history alone.³³ The sensitivity and specificity were only 0.76 and 0.83, respectively, with unstandardized extracts. That we found a sensitivity and specificity of 0.90 and 0.90 using an FDA-approved standardized cat extract suggests an enhanced ability for clinicians to identify accurately cat-allergic patients.

Testing with a tenfold dilution of pollen extracts did not appear to offer any advantage over testing with the full strength. Because it appears most important to identify the maximum number of "true" responders (increased sensitivity), it is our opinion that some

sacrifice in specificity should be acceptable, and subjects considered "false" responders could be identified by history. As discussed above, no apparent advantage to the 1:10 dilution of cat extract could be found as well.

Reactions to HD mite were much more common than to pollens and cat in the NAL group, accounting for 47% of all positive SPTs in that group. SPT reaction rates to *D. pteronyssinus* were not significantly different among the three groups ($p = 0.1$). The rates of SPT reactions within the AL subjects were similar to rates with tree pollens. However, since most AL subjects had only seasonal allergic rhinitis and the study was conducted in an area of low mite prevalence,^{34, 35} reactions to HD mites would not be expected to be as common as to pollens. These results were not anticipated, and unfortunately, the study design did not test 1:10 dilutions of these extracts. Nevertheless, the observations that AL and NAL subjects both had higher rates of reactions than expected suggest that full-strength (10,000 AU/ml) HD-mite extracts may be too concentrated for diagnostic testing. Further evaluations should be performed.

The SPT prevalence rates of the FAL group demonstrate that asymptomatic subjects whose first-degree family members have an atopic disease have a higher rate of SPT reactions than subjects without a family history. To our knowledge, only one previous study has examined this question, and the findings were similar to our findings.²⁴ It is possible that many of these asymptomatic SPT-positive subjects will develop allergic disorders in the future.³⁶

Five of the 50 AL subjects had negative SPTs. Three of these five subjects who were available for intradermal testing with nonstandardized extracts of the same allergens also had negative responses. Since only 75% to 85% of patients with asthma have positive skin tests³⁷⁻³⁹ and since entry criteria for the AL subjects could have included only asthma, it is possible that this may have accounted for the negative skin tests. However, all five of these subjects provided a history of seasonal symptoms suggesting allergic rhinitis, and four of the five subjects had at least one first-degree relative with an atopic disease. The reason for the negative reactions in these subjects is not clear. None of the subjects were receiving medications known to inhibit immediate hypersensitivity skin tests,^{8, 9} and all subjects had appropriate responses to histamine and compound 48/80. None were currently receiving immunotherapy or had received it within the previous 2 years. It is possible that testing with a larger number of allergens might have elicited positive responses. The concept of "localized allergy" to explain observations in patients who appear to have clinical

allergy, but in whom no skin reaction can be found, was suggested in 1927⁴⁰ and supported by other investigators.⁴¹⁻⁴³

In conclusion, FDA-approved standardized extracts of pollens and cat in full strength appear to be suitable for use in SPTs for clinical diagnostic work and will allow reproducibility and comparability over time. It is our belief that extracts should be of a potency to maximize sensitivity (i.e., identify true responders). It would appear appropriate to allow some sacrifice in specificity (i.e., "false positives") since these patients would be identified by the clinical history. FDA-approved extracts of HD mite may be too concentrated at full strength for diagnostic skin testing, since they yield an appreciable percent of positive reactions in asymptomatic subjects. Positive tests to these antigens must be interpreted with consideration of this high rate of clinical false positive reactions. FAL subjects demonstrated an intermediate rate of reaction, further supporting the genetic regulation of allergen-specific IgE production.

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