

Methodologic aspects of the quantification of skin prick test responses: The EGEA study

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Background: The expression of responses of allergy skin prick tests is not standardized. Usual definitions of atopy are not quantitative.

Objective: We sought to perform a biometric analysis of responses to various allergens to propose synthetic, quantitative indices independent of the heterogeneity of responses to various allergens.

Methods: Adults (N = 1286) from the Epidemiological Study on the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness, and Atopy (EGEA) were included in the analysis. The first step, conducted for 678 subjects with at least 1 wheal >0, was to perform a standardization of wheal diameters to obtain comparable figures for 10 allergens through use of the means of the squares of wheal size as a scaling factor. The second step was a factor analysis of the standardized responses conducted not only for all subjects but also separately for asthmatic case and nonasthmatic control subjects. Finally, the strength of the link between various dichotomous and quantitative scores was assessed with multiRAST, total IgE, and asthma. Analyzed quantitative scores were based on the number of positive responses and on the nonstandardized and standardized sizes of the wheals.

Results: The standardization was efficient. Among asthmatic subjects but not other subjects, factor analysis evidenced a pattern with 3 factors, corresponding to outdoor, indoor, and mold allergens. The link study showed that all scores performed very similarly.

Conclusion: The number of positive tests is a quantitative score with valid biometric properties. It should be used more widely in clinical settings and in epidemiology to assess the severity of atopy. (*J Allergy Clin Immunol* 2003;111:750-6.)

Key words: Allergy, epidemiology, methods

There is no unanimously accepted way of expressing response to allergy skin prick tests. Usual definitions of atopy are based on a positive response to 1 or more allergens, often based on a wheal size 3 mm greater¹⁻⁴ than negative control, although 1 mm has also been considered.^{5,6} These thresholds were generally based on absolute terms, although some authors have used as a reference the positive histamine control.^{7,8} Erythema

Abbreviations used

ECRHS: European Community Respiratory Health Survey
EGEA: Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy
GM: Geometric mean
SPT: Skin prick test

response has also been considered.^{9,10} Besides dichotomous categorization, the total number of positive responses has been used,¹¹ and others have combined the number of positive tests and wheal sizes.^{4,12} Quantitative indices that use wheal size face the problem of the heterogeneity of wheal response according to the allergens. Simple summation or the averaging of wheal diameters mixes quantities of different magnitudes and produces values that might reflect the larger and mask the others.⁶ Therefore, semiquantitative scores that are based on wheal size classes¹³⁻¹⁵ or that take into account wheal size distributions of each allergen have been proposed.^{6,16} Independent of wheal size distribution, all methods ascribe the same weight to each allergen.

Associations between the responses to various allergens occur, for a variety of reasons related to the allergens, such as cross-reactivity (nature of allergens), simultaneous exposure (site of allergens), or the host (common sensitivity). Limited information, however, has been published for the rationale of the groupings that are commonly cited in the literature (outdoor, indoor, etc).^{11,17} Crude summation of the various responses does not take into account the pattern of response according to allergen type. Therefore, both dichotomizing the responses to various allergens in a single variable and considering all allergens in a similar way represent a potential loss of information, and no systematic methodologic work has addressed these questions.

With data from the Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness, and atopy (EGEA), the overall objective was to perform a biometric analysis of responses to various allergens to propose quantitative indices independent of the heterogeneity of responses to various allergens. Specific objectives were to (1) standardize the values of wheal diameters to obtain comparable figures with all the allergens; (2) define synthetic indices, by taking into account correlations between responses; and (3) assess the pertinence of standardization and factor analysis used

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to construct new scores by comparing the strengths of available dichotomous and quantitative scores on the relations with asthma, total immunoglobulin E (IgE) levels, and multiRAST.

METHODS

Population

The EGEA combines both a case-control study and a family study, and the protocol has been described in detail elsewhere.^{18,19} In brief, asthmatic probands were recruited in chest clinics from 6 clinical centers, and control subjects were population-based. Inclusion criteria were place of birth, area of residence, age, familial structure, and, for proband cases, a positive answer to 4 standardized questions ("Have you ever had attacks of breathlessness at rest with wheezing?" "Have you ever had asthma attacks?" "Was this diagnosis confirmed by a physician?" "Have you ever had an asthma attack in the last 12 months?"). The present analysis is based on adults (>18 years old) with skin prick tests to 10 allergens, ie, 1286 subjects, after exclusion of 1 outlier (subject with a *Cladosporium* wheal size of 20.5 mm).

Skin prick tests (SPTs), IgE, and MultiRAST

Allergens studied were cat, *Dermatophagoides pteronyssinus*, *Cladosporium herbarum*, *Alternaria tenuis*, timothy grass, olive, birch, *Parietaria judaica*, *Aspergillus*, and *Blattella germanica*. As in the European Community Respiratory Health Survey (ECRHS), SPTs were done with Phazets until 1994, ie, precoated lancets with lyophilized allergen extracts. Standard prick tests were performed with Stallergens extracts and Stallerpoint lancets for *Aspergillus* organisms and *Blattella germanica* and for all allergens (with the same specially prepared batch) for the 230 subjects examined after mid-1994, when the production of Phazets was stopped by the manufacturer. Wheal sizes were the mean of the 2 extreme diameters of the wheals. Responses were wheal size minus negative control. Observers were trained before the survey to follow the ECRHS protocol, and trained field workers were instructed that they should have a coefficient of variation of <30% for wheal size.

Total IgEs were measured by radioimmunoassay (Phadebas PRIST technique; Pharmacia Diagnostics, AB, France). Samples were tested for circulating specific IgE antibodies against common inhalant allergens with the use of the multiRAST Phadiatop (Pharmacia Diagnostics, AB, France). All analyses performed on log₁₀(total IgE) values were adjusted for age and sex, and results are expressed as geometric means.

Statistical methods

The first step of the analysis was standardization of wheal diameters to obtain comparable figures for 10 allergens in subjects with at least 1 wheal ≥ 1 mm. Using the ratio of the root mean square (RMS) of "cat wheal Stallergens" (taken as a reference) to the RMS for each allergen wheal size provides, without changing zero values, a standardization of both means and dispersions. This takes advantage of the roughly log-normal shape of the distributions of wheal sizes. Standardization by subtraction of the mean wheal size¹⁶ was also considered.

A standard factor analysis,²¹ with Varimax rotation, was performed to assess the value of the common grouping of allergens into indoor or outdoor groups. Analyses were based on log₁₀(standardized wheal size +1) because of the skewness of the distribution and the presence of zero values.

Finally, the strength of the relation with asthmatic status, log IgE, and positive MultiRAST of the various dichotomous and quantitative SPT scores (crude and transformed) were compared. Results

are expressed by Student *t* test values (derived from χ^2 for contingency tables) and by the test of the regression coefficient for quantitative variables. The purpose of that analysis was not to assess whether the relation was statistically significant, which was anticipated, but to compare the values of the *t* statistics.

RESULTS

Allergen test response

Among the 1286 subjects (15.3 to 70.9 years old), 678 had a positive response to at least 1 of the allergens (wheal size = 1 mm), with the greatest percentage of positive response for *D pteronyssinus* (Table I). As expected, asthmatic cases had markedly higher percentages of SPT+ and higher IgE values than did control subjects. Relatives of the asthmatic cases were in an intermediate position.

Efficiency of standardization of SPT wheal size

The value of the RMS for the cat allergen from Stallergens was 4.296. The standardization coefficients varied from 0.65 to 1.37 (Table II), which shows that the difference before and after standardization might reach 40%. The effect of standardization was not totally consistent between Phazets and Stallergens. For most of the allergens, standardization affected the values similarly for both brands, but for birch and *Alternaria*, standardization increased the values for Stallergens and decreased the values for Phazets.

The behavior of the standardization by a scaling factor instead of a shift is illustrated by the comparison of frequency curves obtained by the 2 methods for the 2 most contrasted allergens, *Cladosporium* and *D pteronyssinus* (Fig 1). Shifting the values to obtain a coincidence in means was not satisfactory (Fig 1, *B*), as the gap between curves remained large, except for a narrow "neighborhood" in the middle of the curves. The best standardization, ie, the closest curves, was obtained by a change of scale. The curves were closer for all values (Fig 1, *C*).

Considering the means before standardization, the ratio between extremes (timothy grass = 5.5 mm, *Cladosporium* = 2.8 mm) was 1.93 and became 1.05 after standardization. With the proposed scaling factor, the standardization was clearly efficient, but the question of its usefulness remained.

Research on common factors of SPT responses to various allergens

An analysis with 3 factors appropriately fitted the data. Three groups of allergens could be distinguished: an "outdoor" group with olive, birch, timothy, and *Parietaria* (with correlations between that factor and wheal sizes [loadings] in the range of 0.5 to 0.8), an "indoor" group with cat, *D pteronyssinus*, and *Blattella* (with loadings of 0.6 to 0.8), and a "mold" group with *Cladosporium* and *Aspergillus* (with loadings of 0.6 and 0.8). The values for the allergen *Alternaria* were between those of the indoor and outdoor groups (loadings of 0.4 and 0.5,

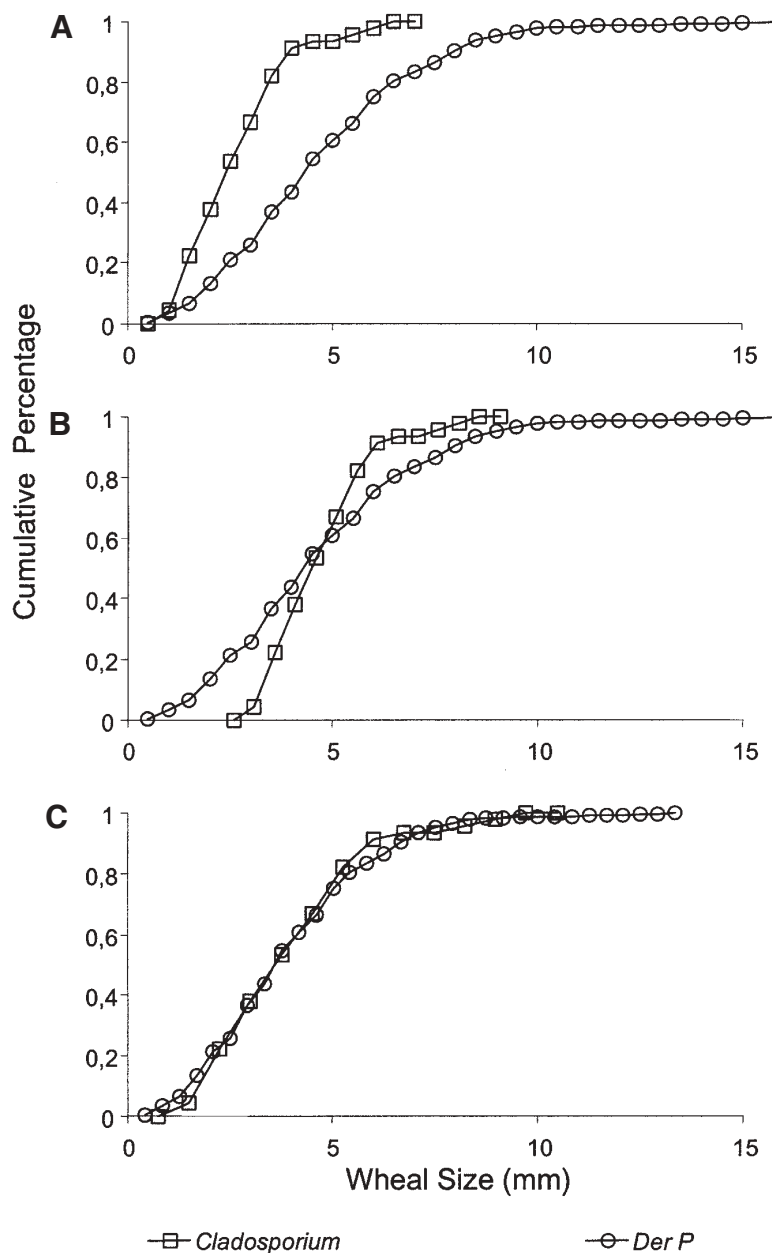


FIG 1. Distribution of SPT responses according to different methods of standardization. Shown are the results for allergens with the smallest (*Cladosporium*, represented by squares) and the largest (*D pteronyssinus*, represented by circles) values. **A**, Raw data. **B**, Standardization that equates the means. **C**, Standardization that equates the RMSs.

respectively) and were subsequently included in the outdoor group. All other loadings were notably lower, ranging from 0.03 to 0.40.

The same analysis was then performed on 2 contrasted subsets of subjects (asthmatic cases and nonasthmatic control subjects) to assess whether the grouping evidence held. The cases exhibited the same pattern as the overall sample, with *Alternaria* belonging clearly to the outdoor group. By contrast, for nonasthmatic control subjects, the grouping did not fit the indoor/outdoor/mold partition.

Assessment of the relation of SPT scores with phenotypes

The relation of various dichotomous and quantitative scores was assessed by computing *t*-test statistics between groups of subjects with various atopy-related status (multiRAST, total IgE; Table III) and asthma (Table IV). Quantitative scores analyzed were based on the number of positive responses and on the sizes of the wheals before and after standardization. The

TABLE I. Characteristics of the population

	All	Cases	Relatives of cases	Spouses of cases	Control subjects
N/n	1286	204	665	118	299
Age (y): mean $\pm$ SD	39.5 $\pm$ 13.0	38.7 $\pm$ 14.5	37.0 $\pm$ 12.4	48.4 $\pm$ 8.6	42.1 $\pm$ 12.7
Male (%)	49.0	51.5	48.6	46.6	49.2
Asthma (%)	31.8*	100	23.9	4.3	12.2
SPT response: wheal size = 1 mm (%)					
Any of 10 allergens	52.6	76.0	54.9	28.0	41.1
Cat	16.2	32.8	15.5	6.8	10.0
<i>Cladosporium herbarum</i>	5.6	12.3	5.0	1.7	4.0
<i>Aspergillus</i>	10.0	15.7	10.1	8.5	6.4
Olive	10.3	18.6	10.1	2.5	8.4
Birch	7.2	9.3	8.7	3.4	4.0
<i>D pteronyssinus</i>	30.4	49.0	31.9	15.3	20.4
<i>Alternaria tenuis</i>	10.0	19.6	9.8	2.5	7.0
Timothy grass	21.2	31.4	22.6	8.5	16.4
<i>Blattella germanica</i>	18.0	24.0	18.7	11.0	15.1
<i>Parietaria judaica</i>	4.2	6.4	3.8	4.2	3.7
No. of positive responses					
0	47.3	23.5	45.0	72.0	58.9
1	17.3	19.1	19.7	12.7	12.7
2	14.2	16.7	15.2	6.8	13.4
3	9.2	14.7	9.0	1.7	8.7
≥ 4	12.0	26.0	11.1	6.8	6.3
Total and specific IgE, N/n tested	1231	196	639	116	280
Total IgE GM (IU/mL)	60	186	61	32	33
95% CI	2.2-1676	11-3091	2.4-1591	1.4-740	1.5-754
MultiRAST+ (%)	38.2	70.9	38.2	15.8	24.9

*For 1250 subjects with documented asthma status.

TABLE II. Standardization of wheal size for 678 subjects with at least 1 wheal diameter larger than control

Allergen	n	Subjects tested with Stallergens† (n = 139)			Subjects tested with Phazet (n =539)		
		Mean wheal size (mm)	Maximum wheal size (mm)	Standard-ization coefficient*	Mean wheal size (mm)	Maximum wheal size (mm)	Standard-ization coefficient*
Cat	208	3.95	9.5	1 (reference)	4.20	11.5	0.90
<i>Cladosporium herbarum</i>	72	2.91	6.0	1.37	2.81	6.5	1.40
<i>Aspergillus</i>	128	3.31	8.0	1.18	—	—	—
Olive	133	4.92	14.0	0.76	4.41	16.0	0.87
Birch	93	3.27	6.5	1.16	4.15	13.5	0.90
<i>D pteronyssinus</i>	391	5.14	12.5	0.75	4.91	16.0	0.78
<i>Alternaria tenuis</i>	129	3.66	10.5	1.05	4.42	11.5	0.86
Timothy grass	273	4.52	12.5	0.83	5.77	18.5	0.65
<i>Blattella germanica</i>	231	3.61	12.0	1.08	—	—	—
<i>Parietaria judaica</i>	54	3.44	8.0	1.10	3.30	8.5	1.13

*Standardization coefficient is defined as the ratio of the RMSs of the Stallergens cat allergen wheal response to the RMS of the considered allergen.

†For all allergens but *Aspergillus* and *Blattella germanica*, for which all subjects were tested with Stallergens extracts.

analysis was also performed for the 3 scores based on the mean of standardized wheal sizes for each group exhibited previously in the factor analysis (indoor, outdoor, mold).

As expected, *t* statistics were greater for MultiRAST than for total IgE, which were greater than those for asthma (and nearly all were highly significant). The behavior of the various scores based on the responses to all allergens was very close, whereas the outdoor and mold scores were less related, even sometimes missing statistical significance for the last one.

These results do not support the hypothesis that standardization should enhance the dependence; if anything, the *t* values for standardized values were always smaller than those for scores based on raw values (eg, *t* statistics were 23.2, versus 25.6 in the analysis based on the whole sample). Scores based on the average of wheal sizes, the number of wheals ≥ 3 mm than the control, or even the existence/nonexistence of any wheal ≥ 3 mm than control were of similar interest, at least in an epidemiologic context. The simplest way to quantitatively assess the severity of atopy might be the number of positive responses.

Asthma, rhinitis,
other respiratory
diseases

TABLE III. Dependence of various SPT scores on positive MultiRAST and total IgE, stratified according to personal and familial history of asthma

	MultiRAST					Total IgE				
	Asthmatic		Nonasthmatic			Asthmatic		Nonasthmatic		
	All subjects	Cases	Relatives of cases	Relatives of cases	Control subjects	All subjects	Cases	Relatives of cases	Relatives of cases	Controls
N/n	1209	189	143	464	236	1231	196	145	468	243
MultiRAST (% positive)	38.2	70.9	70.6	28.5	21.2	—	—	—	—	—
Total IgE (IU/mL)	—	—	—	—	—	60	186	117	50	31
Dichotomous SPT variables										
Any wheal ≥ 1 mm	20.9*	8.6	6.6	11.6	7.6	15.6	2.3	6.6	7.7	5.2
Any wheal ≥ 3 mm	22.7	9.1	7.1	12.7	8.5	15.2	2.5	6.5	7.5	6.0
Semiquantitative SPT scores										
Number of wheals ≥ 1 mm	22.0	7.1	6.0	11.8	8.7	14.6	3.2	5.3	7.2	6.2
Number of wheals ≥ 3 mm	24.0	7.8	6.8	12.6	9.4	14.2	3.1	5.3	7.5	6.1
Continuous SPT scores										
Mean of raw wheal sizes	25.6	8.4	6.6	14.2	11.7	15.0	3.2	5.0	8.1	6.9
Mean of standardized wheal sizes	23.2	7.7	6.2	12.5	10.2	14.3	3.0	4.9	7.5	6.7
Continuous SPT scores based on response pattern										
Mean of standardized wheal sizes for outdoor allergens	17.3	5.0	4.0	11.2	10.4	9.4	1.4	2.6	6.2	4.9
Mean of standardized wheal sizes for indoor allergens	22.9	8.0	6.1	12.2	8.1	15.2	3.6	5.6	8.0	6.1
Mean of standardized wheal sizes for molds	3.5	1.5	1.6	1.6	1.2	3.9	0.6	1.3	1.2	2.0

*Unless otherwise specified, values are *t* statistics. For example, 20.9 is the *t*-test value (corresponding to a *P* value $<10^{-4}$), which is the square root of the χ^2 contingency table of MultiRAST (negative versus positive) and SPT+ to any allergen (no versus yes) in all subjects and 8.6 when the analysis is restricted to the 189 asthmatic cases.

TABLE IV. Dependence of various SPT scores on asthma

	All subjects with and without asthma	Cases vs nonasthmatic control subjects	Relatives of cases with and without asthma	Controls with and without asthma
No. of asthmatic/nonasthmatic subjects	397/853	204/258	152/485	36/258
Dichotomous SPT variables				
Any wheal ≥ 1 mm	11.5	8.4	7.3	3.2
Any wheal ≥ 3 mm	12.6	8.1	8.3	4.0
Semiquantitative SPT scores				
Number of wheals ≥ 1 mm	11.0	8.1	6.8	3.5
Number of wheals ≥ 3 mm	11.2	7.4	7.1	4.2
Continuous SPT scores				
Mean of raw wheal sizes	11.1	8.0	7.1	3.9
Mean of standardized wheal sizes	10.7	7.8	6.7	3.6
Continuous SPT scores based on response pattern				
Mean of standardized wheal sizes for outdoor allergens	7.4	4.4	5.4	2.8
Mean of standardized wheal sizes for indoor allergens	10.9	7.7	6.9	3.5
Mean of standardized wheal sizes for molds	3.2	3.7	0.9	0.0

Values are *t* statistics. For example, 11.5 is the square root of the χ^2 of the contingency table of SPT+ to any allergen with asthma.

DISCUSSION

Quantification of response to allergens

The availability of quantitative measures to assess the severity of atopy through the SPT is a challenge. The responses to various allergens are different because of the differences in allergens and environmental exposures,

insufficient standardization of allergen extracts, and interactions of genetic and environmental factors. Responses to various allergens are correlated because of cross-reactivity between allergens, potential contamination during the procedure, genetic factors leading to an overall pattern of response, and common exposures to allergens belonging to close reservoirs. The present work aimed at tackling the

biometric aspect of the problem, first, by standardizing wheal size with the response to cat as the reference and then constructing various quantitative indices based on the number and size of the responses, with and without wheal size standardization. Finally, performance of the scores was assessed by their link with 3 related phenotypes, whose strengths of relation to the SPT response were different: MultiRAST, total IgE, and asthma. All analyses were based on data collected in the EGEA and allowed us to compare the results from subjects who differed by their personal and familial histories of asthma.

All scores (dichotomous and semiquantitative, based on the number of positive wheals, and continuous, based on the mean of wheal sizes before and after standardization) behaved similarly. The number of positive test results therefore appeared as a quantitative index with good biometric properties and might be used to assess the severity of atopy. A factor analysis, performed to understand what the responses to various allergens have in common, in asthmatics showed a clear pattern with 3 groups: indoor, outdoor, and molds. This pattern was not so clear in other subjects, suggesting that asthma status plays a role in the response pattern. Scores based on indoor allergens only had a behavior close to those based on all allergens, regardless of the category of subjects.

Although several quantitative indices have been proposed,^{6,13-16} none is generally accepted in the epidemiologic or clinical literature, likely because of the lack of a formal biometric study of various scores. To our knowledge, the present study is the first attempt to address the pertinence of quantitative indices for assessing the severity of atopy from a biometric point of view.

The issue of wheal size

Our standardization was based on the idea that null responses have a specific meaning and that the nonnull responses have quite a log-normal distribution, as suggested in the literature^{6,16} and confirmed in the present data set. The whole distribution is then zero-inflated. This inflation is known to produce positive biases on variance estimations, and therefore, standardization factors need to be computed among the nonnull responses. The use of a scaling factor instead of a shift¹⁶ appeared more appropriate for log-normally distributed values and automatically maintained zero values for individuals, whereas Barbee et al,⁶ using a more complicated procedure, achieved this at a group level only. The method presented herein, ie, scaling by RMSs, might be useful with other data or samples. The generality of the actual standardization coefficients needs confirmation from other studies, but it is a reassuring fact that they worked satisfactorily with a mixture of 2 brands of allergens.

Scores based on standardized wheal sizes never perform better than those based on crude data. Although the standardization removed irrelevant variation between allergens, it might also have removed pertinent information. Some information seems to hold in wheal size, which is not currently captured by the available indices. From preliminary results (data not shown), differences in

environmental conditions were not associated with wheal size in the present data set (eg, for *D pteronyssinus*). Wheal sizes have been reported to be associated with bronchial hyperresponsiveness²² and to FEV₁ decline,²³ but those studies did not systematically compare various indices. Wheal size could be more strongly associated than other indices for other traits, such as the severity of disease or inflammation, but it was chosen for the present biometric analysis to consider 3 well-defined traits only. From a practical point of view, it should be emphasized that the present results do not suggest that consideration of wheal size, with or without adjustment, yields interesting information compared with the number of responses.

The issue of the number of responses

The number of responses is a classic index, generally not used quantitatively. Usually, polysensitization is considered versus monosensitization. Results are consistent with the associations between asthma and the number of positive test results.^{10,11} Results show that this simple index (especially with a cutoff of 3 mm) has good biometric properties, and we suggest that it be used more widely, particularly in epidemiologic studies. Obviously, the interest of such a quantitative index is dependent on the number of allergens tested in a given setting.

The issue of correlations between responses

The factor pattern was dependent on the asthma status of the subjects. A clear pattern that separated the responses to indoor, outdoor, and mold allergens was evidenced among the asthmatic subjects, whereas this pattern was less clear in other subjects. These results support the classic distinction of indoor and outdoor allergens used in clinical settings, but interesting questions remain regarding the reasons for the difference in pattern observed in various groups of subjects. Simultaneous cutaneous reactivity toward several allergenic extracts might reflect various factors. Genetic factors might lead to preferential transmission in the ability to become sensitized toward a specific allergen. Environmental factors might favor the development of allergens for which survival conditions are similar. Proliferation of dust mites and cockroaches depends on the relative humidity of ambient air, and numerous patients exhibit sensitization to both allergens.²⁴ Immunologic characteristics of the allergens might lead to true "cross-reactivity" related to common epitopes in 2 plant species that are botanically close.²⁵⁻²⁷ Combined reactions might also be related to the presence of a panallergen in species which are not botanically close.²⁸ Regarding indoor allergens, true cross-reactivity is also observed between dust mites and cockroaches because of the presence of tropomyosin,²⁹ between dogs and cats through albumin,^{30,31} and through major animal allergens.^{32,33} Among the previous reasons for correlations between responses, those related to the characteristics of allergens cannot explain differences between asthmatic and nonasthmatic subjects. Therefore, the results suggest that the differences in pattern might

depend on the nature of the relation of asthma to atopy.^{34,35} Because the pattern was clear in asthmatic subjects, further work could address whether some types of allergens are related specifically to asthma characteristics, such as the occurrence of asthma in subjects with a familial history or the severity of disease.

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