

Studies on the relationship between the level of specific IgE antibodies and the clinical expression of allergy: I. Definition of levels distinguishing patients with symptomatic from patients with asymptomatic allergy to common aeroallergens

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Background: The detection of specific IgE antibodies to environmental allergens does not always coincide with a diagnosis of clinically evident allergic disease, because some patients with positive skin and/or in vitro test results have no symptoms related to the allergen or allergens that induced the antibodies.

Objective: In a multicenter study the optimal cutoff values for specific IgE antibody levels and skin test results that could discriminate between patients with symptomatic and those with asymptomatic allergy were determined.

Methods: IgE antibodies specific for a panel of common aeroallergens were assayed with the Pharmacia CAP System (Pharmacia, Uppsala, Sweden) in two groups of patients, a group of 267 patients with symptomatic allergy and a group of 232 patients with asymptomatic allergy—both with positive skin prick test results—and in a group of 243 healthy, nonallergic control subjects. The cutoff values were established by receiver operating characteristic analysis.

Results: A significantly higher mean specific IgE antibody value was found in patients with symptomatic allergy compared with patients with asymptomatic allergy ($p < 0.001$) and in patients with symptomatic allergy compared with healthy control subjects ($p < 0.001$). The optimal CAP System cutoff value between patients with symptomatic and those with asymptomatic allergy was 11.7 kU/L, and when seasonal allergens were compared with perennial allergens, the cutoffs were 10.7 kU/L and 8.4 kU/L, respectively. The optimal cutoff value for the skin prick test was a wheal area of 32 mm² for seasonal allergens and 31 mm² for perennial allergens. The skin test had a lower diagnostic value (sum of sensitivity and specificity) than the CAP System.

Conclusions: Cutoff values for specific serum IgE antibody levels are likely to be useful in clinical practice to distinguish symptomatic from asymptomatic allergy in patients with positive skin test results. (*J ALLERGY CLIN IMMUNOL* 1995;96:580-7.)

Key words: Aeroallergens, specific IgE, symptomatic allergy, asymptomatic allergy, cutoff

The pathophysiology of allergic diseases depends on a series of factors such as the releasability of mast cells and basophils and the responsiveness

of target organs to mediators released from these cells. Still, the pivotal factor is undoubtedly the presence of specific IgE antibodies to environmental allergens.¹ The detection of these antibodies by in vivo or in vitro methods, nevertheless, merely

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Abbreviations used

ROC: Receiver operating characteristic

SPT: Skin prick test

indicates the existence of sensitization to given allergens; their presence does not always coincide with clinically significant allergic disease. Thus the diagnosis of allergic disease is usually based on a combination of information obtained from the medical history, which by itself cannot be considered as the "gold standard," with that obtained from in vivo and/or in vitro tests. The magnitude of the specific IgE response to a given allergen should theoretically be consistent with the clinical relevance of that allergen, but the correlation between the level of specific IgE antibodies and the clinical expression of an allergy has so far been unsatisfactory. In a series of studies that addressed this issue,² only a correlation between specific IgE level measured by RAST and severity of seasonal symptoms in patients allergic to ragweed has been reported.³ This is probably because until recently, sufficiently accurate quantitative assays for IgE antibodies were not available. The need for quantitative assays to "facilitate better definition of the relationship between quantity of IgE antibody and the symptoms or risk of disease" was underlined in a recent Position Statement by the American Academy of Allergy and Immunology.⁴

In the practice of allergy, the physician must often identify the allergen or allergens to which a patient is or is not clinically sensitive. For this, we usually depend on skin tests or serologic assays. Problems occur when the patient's history is not definitive, in which case in vivo and/or in vitro tests may be especially useful, and when the results of the tests do not correlate with the clinical picture. We therefore designed a study to determine whether, in patients with evidence of allergic sensitization, the quantitative results of the tests would allow us to distinguish those patients with clinically significant allergic disease from those who have no clinical symptoms.

To that end, three groups of subjects were recruited. Patients in the first group had a positive skin test response to one of five common aeroallergens and a clear history of rhinoconjunctivitis or asthma, those in the second group likewise had a positive skin test response but clearly had no symptoms related to the corresponding allergen,

and those in the third group were healthy nonallergic individuals. IgE antibody levels to the allergens being evaluated were quantitated with the Pharmacia CAP System assay (Pharmacia, Uppsala, Sweden), which has recently been reported to have excellent analytic sensitivity and specificity.⁵⁻⁷ For a group of three common seasonal allergens and for house dust mite allergen, optimal IgE antibody cutoff levels were obtained from receiver operating characteristic (ROC) curves. From these values, sensitivity, specificity, and diagnostic values for the antibody assays were then determined and compared with values obtained similarly for skin prick test (SPT) results.

METHODS

Patients

Subjects were recruited in 22 allergy consultation centers in Italy (listed in the Appendix). Each center was asked to select between 20 and 40 subjects who had positive skin test responses to one of five common aeroallergens (*Phleum pratense*, *Betula verrucosa*, *Parietaria judaica*, *Dermatophagoides pteronyssinus*, and *Felis domesticus*.) To determine the subject's clinical status, a detailed allergy history was obtained from each subject by a trained allergist. In addition, patients had to respond to a standardized questionnaire with items covering the kind of symptoms, their occurrence, and the subject's age at onset of these symptoms. Only symptoms that were definitely present or definitely absent were counted; suspected or possible symptoms were not considered as evidence.

Group 1 consisted of 267 patients with symptomatic allergy (170 female and 97 male subjects; mean age, 27.1 years; range 8 to 59 years). These subjects had to have a definite history of or current rhinoconjunctivitis, asthma, or both, with a clear association between the occurrence of allergic symptoms on exposure to the same allergen that induced a positive SPT reaction. Patients were excluded from the study if they had a history of asthma of more than 2 years' duration (to avoid cases in which established inflammation might influence the patient's clinical status), if they had been treated with any form of corticosteroid or other immunosuppressive therapy during the preceding 36 months, if they had an elevated IgE antibody level caused by another disease, or if they had ever received allergen immunotherapy.

Group 2 consisted of 232 patients with asymptomatic allergy (125 female and 107 male subjects; mean age, 31.1 years; range, 9 to 54 years). These subjects had to have a negative history of rhinoconjunctivitis and asthma caused by the aeroallergens that elicited the positive SPT reaction. In all cases, they had been referred to one of the participating allergy centers for evaluation of symptoms caused by noninhalant allergens (e.g., milk)

or by aeroallergens clearly unrelated to those being evaluated (e.g., pollens of trees such as olive or cypress, which have short and precisely limited pollination periods). Special care was taken to exclude symptoms caused by any of the five allergens included in this study. To rule out allergy to house dust mites, respiratory symptoms could not be elicited on exposure to house dust; to rule out allergy to cats, patients must not have had an allergic reaction, including urticaria, on contact with cats. In cases of allergy to mites or cats, patients must also not have ever had perennial symptoms; any respiratory symptom that the patient might report had to be of strictly seasonal nature. To be considered asymptotically allergic to the pollens, patients must not have had any respiratory symptom during the corresponding pollination period, that is, from February to April for birch trees, from April to June for the grasses, and from May to September for *Parietaria* species. Patients were also excluded from the study if they had been treated with any form of corticosteroid or other immunosuppressive therapy during the preceding 36 months or if they had ever received specific immunotherapy for the allergen eliciting a positive SPT reaction.

Control subjects

Group 3 consisted of 243 nonallergic subjects (150 female and 93 male subjects; mean age, 31.6 years; range, 9 to 59 years. These subjects were recruited in the same allergy consultation centers from the medical staff members and their siblings. They had to have a definitely negative history of hay fever, asthma, urticaria, atopic dermatitis, and any other significant immunologic disease. In addition to the above exclusion criteria for groups 1 and 2, all candidates for this group were screened for IgE antibodies with the Pharmacia Phadiatop test. This in vitro test detects specific IgE to a mixture of common aeroallergens and has been reported to be a useful method for confirming the absence of allergy in subjects with a negative allergy history.⁸ Subjects with a positive result were excluded from the study.

Diagnostic tests

All study subjects had the following in vivo and/or in vitro tests.

SPTs

Patients in groups 1 and 2 had SPTs with the five allergens mentioned previously (*P. pratense*, *B. verrucosa*, *P. judaica*, *D. pteronyssinus*, and *F. domesticus*) with the Phazet lancet (Pharmacia).⁹ This device was chosen for the study to reduce the influence of differences in the operator's SPT technique in different centers. The Phazet device, with preloaded allergen (no longer commercially available), was pressed at a 90-degree angle on the volar surface of the forearm

and kept there for 1 second. Each allergen was tested in duplicate. A negative diluent control and a positive control (histamine 10 mg/ml) were included in each series of tests. The outline of the resulting wheal was marked with a pencil, transferred onto a piece of cellophane and then onto the patient's record, from which the diameters were later measured and the areas calculated at the coordinating center. The SPT response was considered positive when a wheal of at least 3 mm in diameter and 7 mm² in area was elicited, according to recommendations of the European Academy of Allergy and Clinical Immunology.¹⁰

In vitro tests

For patients in groups 1 and 2, IgE antibody was assayed with the CAP System only for the causal allergen that had been identified by history and SPT (patients with symptoms) or by SPT alone (patients without symptoms). For subjects in group 3, all five allergen specificities were assayed with the CAP System. Twenty milliliters of venous blood was drawn from each subject and centrifuged; and serum samples were collected and stored at -20°C until assays were performed. Blood samples were obtained during the same periods from the two groups of patients to avoid possible differences in specific IgE levels caused by differences in exposure to the allergens (such as the seasonal rise of IgE antibody in pollen-sensitive patients). In spite of this precaution, this factor cannot be entirely excluded because of the different geographic locations of the participating centers.

All of the CAP System assays were performed at the same time by the same laboratory (Institute of Clinical Biochemistry, University of Padua, Italy, Dr. Plebani) according to a technique previously reported in detail.⁵ The immunoenzymatic method was used. Briefly, test sera were incubated with the solid phase, consisting of a flexible hydrophilic allergen carrier (polymer) encased in a capsule (the ImmunoCap [Pharmacia]). This carrier consists of a cyanogen bromide-activated cellulose derivative, which can bind at least 3 times more allergen than the corresponding paper disk used in RAST and up to 50 times more allergen than the amount adsorbed on a coated tube.⁵ An anti-human IgE (polyclonal and monoclonal) antibody mixture labeled with β -galactosidase (generating fluorescence) was then added. This reagent has high immunoreactivity and low background, allowing a wider range of measurement compared with RAST.⁵ Finally, the intensity of the resulting color was measured in a spectrophotometer. The entire procedure is automated. Results, expressed in kilounits per liter, were obtained by reference to a standard curve derived with serial dilutions of human IgE that was calibrated against the World Health Organization standard for IgE (standard WHO 75/502). One kilounit per liter corresponds to 2.4 ng of IgE per milliliter. A value greater than 0.35 kU/L is defined as a positive CAP System result.

TABLE I. Number of subjects with a positive CAP System assay result and total number of assays performed for each allergen (% positive*)

Allergen	Group 1	Group 2	Group 3
<i>P. pratense</i>	53/55 (96.3%)	35/39 (89.7%)	13/227 (5.7%)
<i>B. verrucosa</i>	41/42 (97.6%)	28/34 (80.8%)	5/206 (2.4%)
<i>P. judaica</i>	31/32 (96.8%)	22/22 (100%)	9/202 (4.4%)
<i>D. pteronyssinus</i>	125/134 (93.2%)	112/127 (88.1%)	21/243 (8.6%)
<i>F. domesticus</i>	4/4 (100%)	8/9 (88.8%)	5/230 (2.1%)

*A positive CAP System result is one greater than 0.35 kU/L

Data analysis

Differences in the levels of specific IgE among the three groups of subjects were analyzed by Student's *t* test. The cutoff levels of specific IgE discriminating patients with symptomatic allergy from those with asymptomatic allergy were determined by analysis of ROC curves.^{11, 12} The analysis was performed by using the computer program Labroc-1 (written by C. Metz et al., University of Chicago), a modified version of the program "Rscore II,"¹³ which establishes from the continuously distributed input data several operating points corresponding to a series of discriminator positions. Calculation and output of expected operating points are estimated on the fitted ROC curve together with asymmetric 95% confidence intervals for those points along the curve. The optimal cutoff was established by plotting the values of sensitivity (true positive results in patients with symptomatic allergy) and 1-specificity (1 - false-positive results in patients with asymptomatic allergy) obtained for each discriminator position and then determining the distance of the discriminator position from the ideal point represented by a sensitivity of 1 and a specificity of 1, that is, where 1-specificity equals 0. The optimal cutoff was obtained at the point of the curve at the minimal distance from the ideal point. For patients with symptomatic and asymptomatic allergy, the areas of SPT wheals were also analyzed by ROC curves. The diagnostic value, being the sum of the sensitivity and the specificity¹⁴ and ranging from a minimum of 0 to a maximum of 200, of each discriminator position for specific IgE and SPT area was also calculated.

RESULTS

Table I shows the number of allergen-specific CAP System assays performed and the rate of positivity in each group of subjects. SPTs were not included because the percent positive is 100 in groups 1 and 2 (because the positivity of SPT was the inclusion criterion), and they were not performed in group 3 (screened by Phadiatop test).

The mean concentration of specific IgE for all five allergens combined was 31.71 ± 11.42 kU/L in patients with symptomatic allergy, 8.57 ± 5.63 kU/L

in patients with asymptomatic allergy and 0.37 ± 0.06 kU/L in normal subjects. Both the difference between the specific IgE levels of patients with symptomatic and asymptomatic allergy and the difference between those of patients with symptomatic allergy and nonallergic subjects were highly significant ($p < 0.001$). Also, the difference between patients with asymptomatic allergy and nonallergic subjects was significant ($p < 0.01$).

The mean specific IgE values for the seasonal allergens (*P. pratense*, *B. verrucosa*, *P. judaica*) and the perennial allergens (*D. pteronyssinus* and *F. domesticus*) were then calculated for the two groups of patients with allergy. For the seasonal allergens the mean value for group 1 was 35.22 ± 10.81 kU/L, and for group 2 it was 8.83 ± 5.16 kU/L. For the perennial allergens the mean value for group 1 was 28.77 ± 12.02 kU/L, and for group 2 it was 8.39 ± 6.02 kU/L. In both cases the differences between the specific IgE levels for the two groups were significant ($p < 0.001$).

Figs. 1, 2, and 3 show ROC curves obtained by plotting sensitivity (true positive results in patients with symptomatic allergy) versus 1-specificity (1 - false-positive results in patients with asymptomatic allergy) from CAP System and SPT for the seasonal allergens plus *D. pteronyssinus* (*F. domesticus* was not included, because the number of patients was too small) (Fig. 1), for the seasonal allergens alone (Fig. 2), and for *D. pteronyssinus* (Fig. 3). The cutoff values were 11.7 kU/L for the IgE antibody and 32.2 mm² for the SPT for the four allergens, 10.7 and 32.4 for the seasonal allergens alone, and 8.4 kU/L and 31.2 mm² for *D. pteronyssinus*. The corresponding diagnostic values for the CAP System assays were 141.8 at 11.7 kU/L for the four allergens, 152 at 10.7 kU/L for seasonal allergens, and 134.4 at 8.4 kU/L for *D. pteronyssinus*. For SPT, the cutoff had a diagnostic value of 121.4 for the four allergens, 122.6 for seasonal allergens, and 121.9 for *D. pteronyssinus* (Table II).

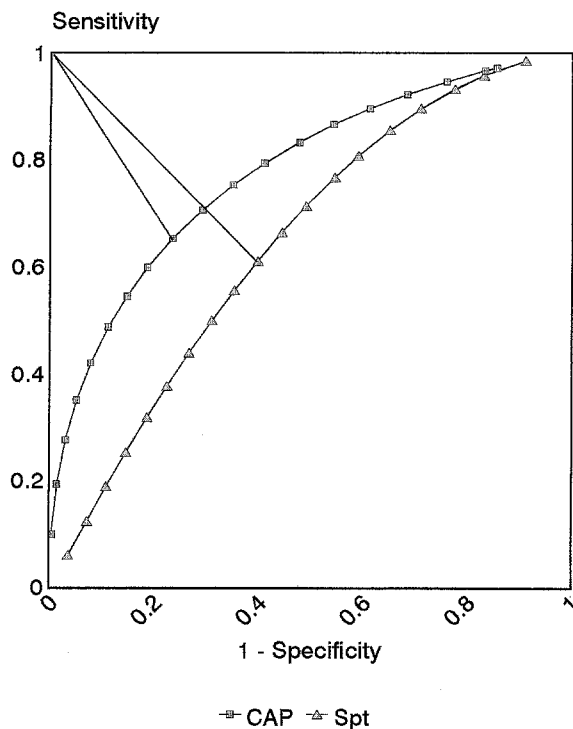


FIG. 1. ROC curve obtained with CAP System (squares) and SPT (triangles) by plotting sensitivity in patients with symptomatic versus 1-specificity in patients with asymptomatic allergy for all allergens.

DISCUSSION

In this study specific IgE antibodies were measured with a quantitative method in sera from two populations of patients with allergy, one with rhinoconjunctivitis and/or asthma caused by a common environmental allergen and another without symptoms of allergy to the same set of allergens, and from a large group of healthy, nonallergic control subjects. The mean antibody levels were significantly higher in the patients with symptomatic allergy compared with the patients with asymptomatic allergy, and a comparable difference was also observed between patients with symptomatic allergy and healthy control subjects. The mean antibody level in patients with asymptomatic allergy was also greater than the level in healthy control subjects, but to a lesser degree than it was for the patients with symptomatic allergy. These findings appear to be reliable because the three populations were defined according to very strict criteria, and confounding factors, such as when blood samples were taken, were also controlled.

A way to distinguish patients with symptomatic allergy from those with asymptomatic allergy is necessary in clinical practice because the simple presence of allergen-specific IgE antibodies to a

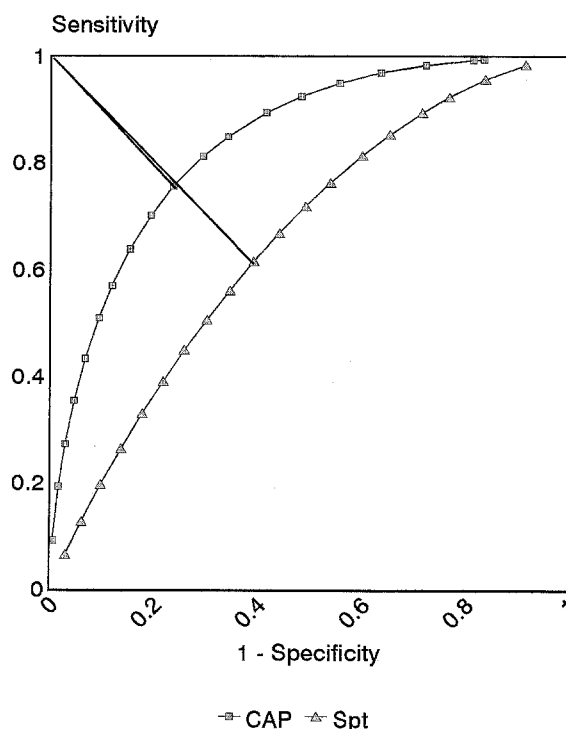


FIG. 2. ROC curve obtained with CAP System (squares) and SPT (triangles) by plotting sensitivity in patients with symptomatic allergy versus 1-specificity in patients with asymptomatic allergy for seasonal allergens.

particular environmental allergen does not mean that a patient has clinically significant symptoms when exposed to that allergen. It has long been recognized that a positive skin test response to an allergen in a patient who is free of symptoms cannot be regarded simply as a false-positive response because it is often possible to transfer the reaction passively to a nonallergic individual with the patient's serum.¹⁵ The significance of allergen-specific IgE antibody in an individual without symptoms remains uncertain. It is, at least, evidence of previous sensitization,¹⁶ and perhaps it is a marker of future allergic disease.¹⁷⁻¹⁹

The diagnosis of clinically relevant allergy depends, in the first instance, on a correlation between the clinical history and the results of skin tests. When a patient whose history is not definitive has positive skin test responses to multiple allergens, it is very difficult to distinguish clinically relevant allergens from those that are not relevant. One method that has been used in such cases is to challenge the target organ with the possibly relevant allergens.²⁰ Such tests are, however, risky and time-consuming. Moreover, their significance is not always different from that of the skin test, because the allergen doses commonly used in

challenge tests, which are usually much greater than those encountered during natural exposure, may elicit symptoms in subjects without apparent clinical sensitivity.

In regard to in vitro titration of allergen-specific IgE, the studies reported to date have considered the sensitivity, specificity, and efficiency of the available tests, comparing results obtained in allergic and nonallergic subjects. To our knowledge, there has not yet been a study aimed at discriminating patients with asymptomatic allergy from those with symptomatic allergy on the basis of their IgE antibody levels. In this study we used a quantitative assay, which has been reported to have very good diagnostic capabilities, to measure specific IgE.⁵⁻⁷ In fact, this assay has greater sensitivity than the RAST, especially for allergens such as house dust mites and cat (which were included in our panel), with no decrease in specificity.^{6,21} We determined the optimal cutoff levels of the CAP System and the SPT from ROC curves. This approach is based on information theory¹¹ and has been used increasingly in medicine in recent years. It has also been used recently to determine cutoff values for SPTs,²² for in vitro tests,²³ and for both of these.²⁴

By ROC analysis, we found that the cutoff value between patients with symptomatic allergy and those with asymptomatic allergy was 10.7 kU/L for seasonal allergens and 8.4 kU/L for *D. pteronyssinus*. These cutoff values appear to be more useful than the cutoff values for SPT, because they have a greater diagnostic value (the sum of sensitivity and specificity): 152 for seasonal allergens and 134.4 for the perennial allergen with the CAP System and 122.6 and 121.9, respectively, for the SPT. This may seem surprising, because since the introduction of the RAST,²⁵ in vitro tests have always been found less sensitive than skin tests. This lower sensitivity was also confirmed in a recent study that compared three in vitro IgE antibody assays, including the CAP System, with skin tests.²⁴ Our results, however, cannot be compared with those of these other studies because we studied patients with positive skin test results with and without symptoms of allergy. Moreover, in our study the sensitivity of SPT (at least, for the first discriminator positions) was higher than that of the CAP System, but this was counterbalanced by the much lower specificity (i.e., greater number of false-positive results) of the SPT. The relative lack of specificity of the SPT accounts for the lower diagnostic value at the optimal cutoff value for the SPT.

The cutoff levels for the CAP System found in

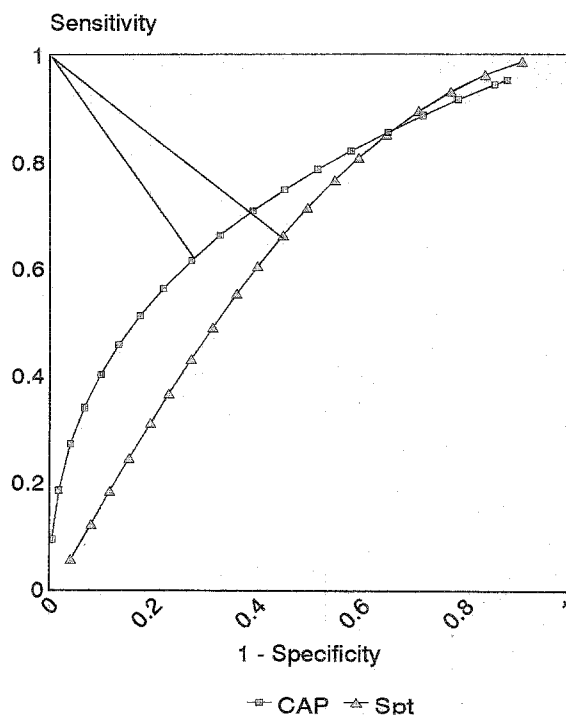


FIG. 3. ROC curve obtained with CAP System (squares) and SPT (triangles) by plotting sensitivity in patients with symptomatic allergy versus 1-specificity in patients with asymptomatic allergy for *D. pteronyssinus*.

this study are proposed to be used as decisional levels in clinical practice when it is necessary to resolve the question of the relevance of a positive skin test response or, as is often the case, of multiple positive skin test responses, when there is no clear-cut clinical history of symptoms on exposure to the allergen or allergens that elicit positive responses. This is as yet only clear for aeroallergens. Other allergens, such as foods or Hymenoptera venoms, require further investigation. Furthermore, the decisional levels that we have proposed could be useful when a diagnosis of allergy is based only on in vitro test results, as in the so-called "remote practice of allergy." Such a practice, although criticized by the American Academy of Allergy and Immunology,²⁶ is being done increasingly and can lead to much unnecessary allergen immunotherapy.⁴

In conclusion, we found a significant difference in the levels of allergen-specific IgE antibodies measured with the CAP System between two populations of subjects sensitized to common aeroallergens, and the levels were significantly lower in patients with asymptomatic allergy compared with those with symptomatic allergy. A cutoff level of 10.7 kU/L for seasonal allergens and 8.4 kU/L for

TABLE II. Cutoff values, sensitivity, specificity, and diagnostic values for CAP System and SPT

	Cutoff value		Sensitivity		Specificity		Diagnostic values	
	CAP (kU/L)	SPT (mm ²)	CAP (kU/L)	SPT (mm ²)	CAP (kU/L)	SPT (mm ²)	CAP (kU/L)	SPT (mm ²)
All allergens	11.7	32.2	65.2%	61.1%	76.6%	60.3%	141.8	121.4
Seasonal allergens	10.7	32.4	75.5%	61.6%	76.5%	61.0%	152.0	122.6
<i>D. pteronyssinus</i>	8.4	31.2	61.6%	66.3%	72.8%	55.6%	134.4	121.9

D. pteronyssinus was found to discriminate between these two groups of patients. The cutoff levels for SPT were, respectively, 32.4 mm² for seasonal allergens and 31.2 mm² for *D. pteronyssinus*, but their diagnostic value was lower than that of the *in vitro* assay.

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REFERENCES

1. Siraganian RP. Mechanism of IgE-mediated hypersensitivity. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds. Allergy: principles and practice. 4th ed. St Louis: Mosby, 1993:105-34.
2. Ownby DR. Clinical significance of IgE. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds. Allergy: principles and practice. 4th ed. St Louis: Mosby, 1993:1059-76.
3. Norman PS, Lichtenstein LM, Ishizaka K. Comparison of specific IgE antibodies, leukocyte sensitivity by histamine release, direct skin tests, and symptoms in hay fever. In: Goodfriend L, Schon A, Orange R, eds. Mechanisms in allergy: reagin-mediated hypersensitivity. New York: Marcel Dekker, 1973:151-62.
4. Executive Committee of the American Academy of Allergy and Immunology. The use of *in vitro* tests for IgE antibody in the specific diagnosis of IgE-mediated disorders and in the formulation of allergen immunotherapy [Position statement]. J ALLERGY CLIN IMMUNOL 1992;90:263-7.
5. Ewan PW, Coote D. Evaluation of a capsulated hydrophilic carrier polymer (the immuno CAP) for measurement of specific IgE antibodies. Allergy 1990;45:22-9.
6. Bousquet J, Chanez P, Chanal I, Michel FB. Comparison between RAST and Pharmacia CAP System, a new automated specific IgE assay. J ALLERGY CLIN IMMUNOL 1990;85:1039-43.
7. Pastorello EA, Incorvaia C, Pravettoni V, et al. A multicentric study on sensitivity and specificity of a new *in vitro* test for measurement of IgE antibodies. Ann Allergy 1991;67:365-70.
8. Eriksson NE. Allergy screening with Phadiatop[®] and CAP Phadiatop[®] in combination with a questionnaire in adults with asthma and rhinitis. Allergy 1990;45:285-92.
9. Holgersson M, Stahlenheim G, Dreborg S. The precision of skin prick test with Phazet[™], the Osterballe needle and the bifurcated needle. Allergy 1985;40:64-6.
10. Dreborg S, ed. Skin tests used in type I allergy testing. Position paper of the European Academy of Allergology and Clinical Immunology. Allergy 1989;44(suppl 10):27-8.
11. McNeil BJ, Hanley JA. Statistical approaches to the analysis of receiver operating characteristic (ROC) curves. Med Decis Making 1984;4:137-50.
12. Gerhardt W, Keller H. Evaluation of test data from clinical studies. I. Terminology, graphic interpretation, diagnostic strategies and selection of sample groups. Scand J Clin Lab Invest 1986;46(suppl 181):5-42.
13. Swets JA, Pickett RM. Evaluation of diagnostic systems: methods from signal detection theory. New York: Academic Press, 1982.
14. Armitage P, Berry G. Statistical methods in medical research. 2nd ed. Oxford: Blackwell Scientific, 1987.
15. Lindblad JH, Farr RS. The incidence of positive intradermal reactions and the demonstration of skin sensitizing antibody to extracts of ragweed and house dust in humans without history of rhinitis or asthma. J Allergy 1961;32:392-401.
16. Yunginger JW. Diagnostic tests, total IgE levels and specific IgE antibody levels. In: Kaplan AP, ed. Allergy. New York: Churchill Livingstone, 1985:112-23.
17. Chambers VV, Glaser J. The incidence of subsequent ragweed pollinosis in symptom-free persons having positive reactions to ragweed-pollen extract. J Allergy 1958;29:249-57.
18. Hagy GW, Settupane GA. Risk factors for developing asthma and allergic rhinitis. J ALLERGY CLIN IMMUNOL 1976;58:330-6.
19. Horak F. Manifestation of allergic rhinitis in latent-sensitized patients. A prospective study. Arch Otorhinolaryngol 1985;242:224-39.
20. Naclerio RM, Norman PS, Fish JE. *In vivo* methods for the study of allergy. Mucosal tests, techniques, and interpretations. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds. Allergy: principles and practice. 4th ed. St Louis: Mosby, 1993:595-627.
21. Pastorello EA, Incorvaia C, Pravettoni V, Marelli A, Farioli L, Ghezzi M. Clinical evaluation of CAP System and RAST in the measurement of specific IgE. Allergy 1992;47:463-6.
22. Ollier S, Osman J, Hordle DA, Amin N, Overell B, Davies R. Skin prick test preparation of *Dermatophagoides pteronyssinus* for prediction of a positive response to provocation testing. Clin Exp Allergy 1989;19:457-62.
23. de Blay F, Zana H, Offner M, Verot A, Velten M, Pauli G. Receiver Operating Characteristic analysis: a useful method for a comparison of the clinical relevance of two *in vitro* IgE tests. J ALLERGY CLIN IMMUNOL 1993;92:255-63.
24. Williams PB, Dolen WK, Koepke JW, Selner JC. Comparison of skin testing and three *in vitro* assays for specific IgE

- in the clinical evaluation of immediate hypersensitivity. *Ann Allergy* 1992;68:35-45.
25. Berg TLO, Johansson SGO. Allergy diagnosis with the radioallergisorbent test: a comparison with the results of skin and provocation tests in an unselected group of children with asthma and hay fever. *J ALLERGY CLIN IMMUNOL* 1974;54:209-21.
26. American Academy of Allergy and Immunology. The remote practice of allergy [Position statement]. *J ALLERGY CLIN IMMUNOL* 1986;77:651-2.
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APPENDIX

Centers participating in the study

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Ospedale Ascoli Tomaselli, Catania (N. Crimi)
Ospedale Civile, Cagliari (G. S. Del Giacco)
Ospedale Civile, Novara (M. Galimberti)
Policlinico Gazzi, Messina (G. Girbino)
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Coordinating Centers

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Bizzozzero Division of General Medicine, Niguarda Cà Granda Hospital, Milan
Andrea Cesalpino Foundation, First Department of Internal Medicine, University "La Sapienza," Rome
Allergy and Clinical Immunology Center, Scientific Department of Internal Medicine, University of Genoa
Department of Allergy and Clinical Immunology, University of Florence
Department of Allergy and Clinical Immunology, University of Bari